Risk profiling and screening for colorectal cancer
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Participation, yield and interval carcinomas in three rounds of biennial FIT-based CRC screening

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Submitted
Abstract

Background
The effectiveness of FIT-based colorectal cancer screening programs is not only influenced by the initial participation rate but also by program adherence during consecutive screening rounds. We aimed to evaluate the participation rate, yield and interval cancers in a third round of biennial CRC screening using FIT.

Methods
Four years after the first screening round and two years after the second round, 10,050 average risk individuals (50 to 75 years of age) were invited to participate in a third round of biennial FIT-based CRC screening. These persons received an invitation via postal mail, which included a FIT-test, an information leaflet, and a return envelope. All FIT-positives without contra-indications were recommended to undergo a colonoscopy. Colonoscopy findings were classified as advanced neoplasia (CRC or advanced adenoma) or other. We merged our data with the national cancer registry in the Netherlands to identify all non-screen detected cancers in our cohort. We calculated participation rates, FIT positivity rate and FIT positive predictive value, and compared it with the results of the first two screening rounds.

Results
5,671 invitees (56%) returned the FIT in this third screening round, compared to 52% in the second round and 56% in the first round (p<0.001). Overall, 377 of the third round participants (6.6%) had a positive FIT result, versus 8.0% in the second round and 8.1% in the first round (p=0.05). Of all FIT positives, 318 (84%) underwent colonoscopy. Within this group, 105 persons had advanced neoplasia, of which 16 had cancer. The FIT positive predictive value for advanced neoplasia was 30%, compared to 44% in the second round and 55% in the first round, a significant decline (p<0.01). Carcinomas detected during the third round of screening were significantly lower in staging than those found in non-participants (P=0.006)

Conclusion
In a FIT-based screening program, participation rates remained stable over consecutive biennial screening rounds, while the FIT positivity rate and its positive predictive value for advanced neoplasia gradually decline. Cancers in non-participants are significantly higher in staging than cancers in participants. Interval cancers were not significantly different in stage from those detected during screening or in non-participants.
Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer related death\textsuperscript{13}. The prognosis of patients is largely determined by the clinical and pathological stage of the colorectal cancer at the time of diagnosis. Population screening by guiac fecal occult blood testing and sigmoidoscopy has been shown to reduce CRC-related mortality rate.\textsuperscript{4,5,6,7} More recent studies used the fecal Imunochemical test (FIT), a quantitative test for the detection of advanced neoplasia.

In FIT-screening all individuals with a positive FIT test are recommended to undergo colonoscopy. A major advantage of a FIT-based screening program is the relatively high participation-rate.\textsuperscript{1,8} However, the effectiveness of FIT-based CRC screening programs is not only influenced by the initial participation rate but also by program adherence over consecutive screening rounds. The downside of this type of screening is the limited accuracy of the FIT. Approximately one quarter of cancers is missed in a single round of FIT screening.\textsuperscript{15,9} By repeating the screening invitation, e.g. biannually, program sensitivity will increase.

Several fecal occult blood based screening trials have been conducted. A study in Scotland reported a reduction in colorectal cancer mortality in a third round of biannual guiac FOBT-based screening.\textsuperscript{7,9}

In Italy participation rates in a FIT based biannual colorectal cancer screening program were high (60%). Positive predictive value of FIT was 40% in the first round compared to 33% in the later rounds.\textsuperscript{10,11} In the second round of the biannual pilot screening program in the Netherlands, FIT positive predictive value for advanced neoplasia was lower than in the first round, and fewer advanced neoplasia were detected.\textsuperscript{1,12}

Despite the documented mortality reduction we know that screening is not perfect. Interval carcinomas, defined as carcinomas detected between two consecutive screening rounds, can occur. These cancers can be missed by either the primary screening test or during colonoscopy after a positive primary test, but they can also develop rapidly between consecutive screening rounds. Understanding the incidence of these interval cancers can help to improve the quality and the impact of a screening program. Besides, appropriate data on the chances of having an interval cancer in the screening program may be relevant information for invitees.

In the Netherlands, a FIT based nationwide screening program will be introduced in 2013. To investigate the effectiveness and efficiency of such a screening program we designed a pilot population-screening program in the Amsterdam region. We aimed to evaluate the participation rate and yield of a third round of CRC screening using FIT, and to study the occurrence of interval cancers between the rounds.
Methods
Three consecutive rounds of FIT based screening have been organized in Amsterdam, the Netherlands. In the first round 10,054 individuals had been randomized to receive a guaiac FOBT or a FIT test. Since the yield and participation were more favorable in participants receiving FIT, only the FIT test was used in consecutive rounds. The methods and results for the first two rounds have been reported in detail elsewhere. Below we report on the third round.

Population and design
Randomly selected individuals between 50 and 75 years of age living in the same postal codes of the Amsterdam region as in round 1 and 2 were invited to participate in this third round of biennial FIT-screening. This study was designed as a dynamic cohort study. All individuals included in the first and the second round were re-invited, as well as individuals who had moved into the target area and those who had reached the target age. Individuals who had moved out of the area or passed the upper age limit were not re-invited. Cohort members were identified using the electronic database of the regional municipal administration registration.

Institutionalized people were excluded from participation. Participants who had tested positive in a previous round were not invited again. The invitation letter indicated that invitees with rectal blood loss and or a change in bowel habits should not participate in screening, but contact their general practitioner instead.

Invitation
Invitations for the third round were sent out by the Foundation of Population Screening Mid-West using the same centralized invitation program as in previous screening rounds (ICOLON). Invitees received a pre-announcement, followed by an invitation kit two weeks later by postal mail. This invitation kit contained an invitation letter, an information leaflet, a FIT, testing instructions, and a card with frequently asked questions. A reminder was sent two and eight weeks after the initial invitation.

Stool tests
In all consecutive rounds of this study, the OC-Sensor FIT (Eiken Chemical Co, Tokyo, Japan) was used. It provides a quantitative measurement of fecal human hemoglobin. The FIT consists of a probe attached to a cap, which fits a collection tube containing hemoglobin-stabilizing buffer. Participants were instructed to collect one stool, to sweep the tip of the probe several times through the feces, and to insert the probe into the tube. No diet restrictions were specified. In the specialized laboratory of the Academic Medical Center,
returned FITs were processed using the OC-Sensor automated instrument (OC-sensor; Eiken Chemical Co, Tokyo, Japan). In parallel with the definition used in previous screening rounds, a test result was considered positive if it exceeded the cut-off level of 50 ng hemoglobin per milliliter feces. 1-3,6,7

Colonoscopy
All participants with a positive FIT result were invited for a consultation at one of the screening centers. During this consultation, the implications of the positive test were explained and the medical history was discussed. If no contraindications were present, a colonoscopy was advised, and the procedure itself and instructions for bowel preparation were discussed with the participant. For bowel preparation we used a PEG solution (Moviprep, 2 liters) combined with 10 mg bisacodyl. Colonoscopies were scheduled within two weeks after the consultation.

Colonoscopy quality indicators were recorded on a case record form. In case of polyps, endoscopic removal of the lesions was attempted during the same procedure. If cancer was suspected or if endoscopic removal was not possible, biopsies were obtained and histopathological assessment provided a definitive diagnosis used for further treatment strategies.

Colorectal lesions
For all lesions exact data on location, size, macroscopic aspect, morphology, removal and endoscopic assessment of radical resection were recorded during colonoscopy.

All lesions were evaluated by an experienced gastrointestinal pathologist according to the Vienna criteria.14 All lesions were classified as adenocarcinoma, adenoma (tubular, tubulovillous, villous), hyperplastic, sessile serrated adenoma, traditional serrated adenoma, or miscellaneous. Dysplasia was defined as either low-grade or high-grade. Advanced adenoma was defined as any adenoma >10 mm or an adenoma with a villous component >25% or with high-grade dysplasia. Cancers were staged according to the 7th edition of the American Joint Committee on Cancer classification.1-3,6,7

Non-screen detected carcinomas
Interval cancers were defined as cancers detected in screening participants after a negative screening examination, but before the next invitation to screening. To identify the number of interval carcinomas detected between the three consecutive screening rounds and the number of cancers in non-participants, data from all invitees were linked to the Netherlands Cancer Registry, which is a nearly complete national database containing data on all new cancer patients, including tumor type, date of diagnosis and stage.15,8
Data analysis
We evaluated participation, yield and interval carcinomas in the third round of FIT-based screening and compared it to the two previous rounds. The participation rate was defined as the number of invitees returning a FIT relative to the number of all eligible invitees. We estimated FIT positivity and its positive predictive value for advanced neoplasia (cancer and advanced adenoma). FIT positivity was defined as the proportion of participants with a positive FIT test result. Positive predictive value was defined as the number of participants with advanced neoplasia and a positive test relative to all participants with a positive test result.

We evaluated the number and stage of interval cancers. Screen detected carcinomas were defined as cancers detected during the screening. Cancers not detected during screening could be either those detected in participants (interval carcinoma) or in non-participants. Chi-square test statistics were used to test for differences in the distribution of cancer stage and location between screen detected, non-screen detected and interval cancers.

All authors had access to the study data and have reviewed and approved the final manuscript.

Results
Participation
In total 5,671 of 10,050 invited individuals (56%) participated in the third round of FIT based screening. Baseline characteristics of the participants in all three rounds are summarized in Table 1. Figure 1 shows the flow of participants.

Yield
Of all participants in the third round, 377 (6.6%) had a positive FIT. The FIT positivity rate was significant lower than the first and the second round (8.1% and 8.0% respectively, \(p=0.001\)). Three hundred and eighteen FIT-positives underwent colonoscopy (84%). Of those not undergoing colonoscopy, 31 (8.2%) did not have a colonoscopy for medical reasons (unfit or comorbidity with estimated life-expectancy of < 5 yrs); 28 (7.4%) did not want to undergo the procedure. Advanced neoplasia were detected during colonoscopy in 105 participants: one or more advanced adenoma in 89 (28%); colorectal cancer in 16 (5.4%). Table 2 shows the location and morphology of the advanced adenomas. The FIT positive predictive value was 33%, which was significant lower than in the first and the second round \(p=0.03\).
Figure 1 Flowchart *Only the FIT arm of the first screening round is discussed in this paper.*
### Table 1: Characteristics of screening participants

<table>
<thead>
<tr>
<th></th>
<th>First round* (N=5038)</th>
<th>Second round (N=10,265)</th>
<th>Third round (N=10,050)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>2871 (57%)</td>
<td>5367 (52%)</td>
<td>5671 (57%)</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>59 (6.8)</td>
<td>60 (6.8)</td>
<td>61 (6.5)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1463 (46%)</td>
<td>2376 (44%)</td>
<td>2505 (44%)</td>
</tr>
</tbody>
</table>

*FIT arm of the study.

### Table 2: Yield in 3 consecutive rounds of FIT-based screening

<table>
<thead>
<tr>
<th></th>
<th>First round (N= 5038) *</th>
<th>Second round (N=10,265)</th>
<th>Third round (N=10,050)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation</td>
<td>2871 (57%)</td>
<td>5367 (52%)</td>
<td>5671 (56%)</td>
</tr>
<tr>
<td>FIT positivity</td>
<td>233 (8.1%)</td>
<td>430 (8.0%)</td>
<td>377 (6.6%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>196 (80%)</td>
<td>373 (87%)</td>
<td>318 (84%)</td>
</tr>
<tr>
<td>Advanced neoplasia**</td>
<td>100 (54%)</td>
<td>164 (38%)</td>
<td>105 (33%)</td>
</tr>
<tr>
<td>Location of advanced neoplasia***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>24 (27%)</td>
<td>44 (29%)</td>
<td>36 (34%)</td>
</tr>
<tr>
<td>Distal</td>
<td>64 (73%)</td>
<td>104 (69%)</td>
<td>58 (55%)</td>
</tr>
<tr>
<td>Type of advanced neoplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>12 (12%)</td>
<td>11 (7.0%)</td>
<td>16 (15%)</td>
</tr>
<tr>
<td>Advanced adenoma</td>
<td>88 (88%)</td>
<td>153 (93%)</td>
<td>89 (85%)</td>
</tr>
<tr>
<td>Size of advanced adenoma****</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10 mm</td>
<td>66 (75%)</td>
<td>120 (75%)</td>
<td>35 (40%)</td>
</tr>
<tr>
<td>6-9 mm</td>
<td>12 (14%)</td>
<td>9 (6.0%)</td>
<td>18 (20%)</td>
</tr>
<tr>
<td>1-5 mm</td>
<td>10 (11%)</td>
<td>10 (15%)</td>
<td>34 (39%)</td>
</tr>
</tbody>
</table>

*FIT arm of the study.

**At least one advanced neoplasia detected during colonoscopy.

***For 3 adenomas in the second and eleven adenomas in the third round location was unknown.

****For one adenoma in the second and one adenoma in the third round size was unknown.
Interval Cancers

We compared the number of carcinomas between rounds and between interval periods. In the first round of screening 20 carcinomas were detected in 5038 participants (0.4%); in the second round 11 carcinomas were detected in 5367 participants (0.2%), a significant decline (p=0.05). Nine interval carcinomas were detected after the first screening round (0.2%), 15 after the second screening round (0.3%), a non-significant difference (p=0.14). The difference in carcinomas detected in non-participants did not significantly change between rounds, with 28 carcinomas in 5,012 (0.6%) non-participants in the first round and 27 carcinomas in 4,898 non-participants (0.6%) in the second round (p=0.48).

Table 3 shows the numbers of the several types of cancer detected. There were no significant differences in age and sex for cancers between the respective groups. Table 3 displays the stages and location of interval cancers. Carcinomas found in first round participants were significantly lower in staging than carcinomas found in non-participants (p=0.05); Carcinomas detected during the second round of screening were also significantly staged lower than those found in non-participants (P=0.006). Of the interval cancers found between the first and the second round, seven participants had tested negative on the FIT test; two participants had a positive FIT test and had undergone colonoscopy, which was negative. For the interval cancers found between round two and three eleven participants had a negative FIT test; four participants had undergone colonoscopy. Interval cancers were not significantly different in staging from those detected during screening or in non-participants.
### Table 3  Stage and location of cancers detected during screening, interval cancers and cancers in non-participants

<table>
<thead>
<tr>
<th></th>
<th>First Round (N=20)*</th>
<th>Second Round (N=11)</th>
<th>Third Round (N=16)</th>
<th>Interval Cancers after first round (N=9)</th>
<th>Interval Cancers after second round (N=15)</th>
<th>Non participants first round (N=28)</th>
<th>Non participants second round (N=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Missing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Distal **</td>
<td>8</td>
<td>10</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Proximal***</td>
<td>12</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

*FIT and Guaic arm of the study together.
** Descending colon, sigmoid colon or rectum.
*** Cecum, ascending colon, hepatic flexure, transverse colon or splenic flexure.
Discussion

In the third round of a FIT-based screening study in the Netherlands we observed a stable participation-rate, at around 55%, and a significant decrease in FIT-positivity and FIT positive predictive value compared to the first and the second round. Cancers in non-participants are significantly higher in staging than cancers detected during the screening process.

An important strength of our study is the possibility to merge our data with the cancer registry in the Netherlands, which enabled us to generate information about interval cancers and cancers in non-participants. Some limitations to this study need to be discussed. We were not able to obtain sensitivity estimates because colonoscopies were not done in individuals with a negative FIT-result. Although the positive predictive value for advanced neoplasia was high, it is known that sensitivity in FIT based screening is limited.7,9

Participation rates in three consecutive rounds of screening did not significantly change. Participation rates were lower than the 61% and 63% participation-rates of a first and second round pilot-program in another Dutch region10,11 and are comparable to that of the third round of the Scottish guaic FOBT screening cohort.12 In the first round of this screening project screening guiac fobt was compared with FIT. The participation rate in that round was significantly lower in the guiac group (47% for guiac and 60% for FIT) while the detection rate for advanced neoplasia was higher in the FIT group.4,13

The yield of biannual FIT-based screening declines over rounds. In this third round of screening, advanced neoplasia were detected in one third of FIT-positive participants undergoing colonoscopy, which is a significant decrease from earlier rounds. This is in line with the results of earlier studies. The Scottish guiac FOBT-based screening cohort shows a decline in yield for the first two rounds, but no significant decrease in the third round.22 A Danish study showed a decrease in positive predictive value in guiac based screening until the fifth round of screening.15 In our study FIT positivity and positive predictive value were significantly lower in the third round compared to earlier rounds. Based on the experience in FOBT-screening5, we expect that FIT-positivity and positive predictive value of FIT in our cohort will reach a plateau after several screening rounds, but we have not yet observed this plateauing after three rounds.

In FIT-based colorectal cancer screening cancers and advanced adenomas can be missed either by the FIT or during colonoscopy after a positive FIT. Both leave patients behind with false reassurance. Steele et al investigated interval cancers in a screening program using guiac-FOBT.20 They concluded that there is a substantial number of interval cancers in this type of screening, and that those cancers are associated with a better prognosis.
than cancers in non-screened individuals. The number of non-screen detected cancers are a good indicator of the effectiveness of a screening program. Gill et al. compared screen detected and interval cancers in the Bowel Cancer Screening Program. In their study no significant differences in staging were found between interval and screen detected cancers.16 Morris et al showed that screen detected cancers have a better prognosis than tumors suggested outside screening in non-participants. 17In our study the differences between screen detected and interval cancers were not significant in staging but we cannot make statements about prognosis for patients detected with cancer in our cohort. The histology of interval cancers will be assessed in a follow up study.

In conclusion, in a third round of biennial FIT-based screening for CRC in the Netherlands, participation was stable but FIT-positivity and positive predictive value declined. Detected cancers had lower stages than cancers in non-participants. There were no differences for staging in interval cancers and cancers detected during screening. FIT based biannual pilot screening studies should be continued in order to assess the course of FIT-based screening over the years.
References


