Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population

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Background & Aims: Despite poor performance, guaiac-based fecal occult blood tests (G-FOBT) are most frequently implemented for colorectal cancer screening. Immunochemical fecal occult blood tests (I-FOBT) are claimed to perform better, without randomized comparison in screening populations. Our aim was to randomly compare G-FOBT with I-FOBT in a screening population.

Methods: We conducted a population-based study on a random sample of 20,623 individuals 50–75 years of age, randomized to either G-FOBT (Hemoccult-II) or I-FOBT (OC-Sensor). Tests and invitations were sent together. For I-FOBT, the standard cutoff of 100 ng/ml was used. Positive FOBTs were verified with colonoscopy. Advanced adenomas were defined as ≥10 mm, high-grade dysplasia, or ≥20% villous component.

Results: There were 10,993 tests returned: 4836 (46.9%) G-FOBTs and 6157 (59.6%) I-FOBTs. The participation rate difference was 12.7% (P < .01). Of G-FOBTs, 117 (2.4%) were positive versus 339 (5.5%) of I-FOBTs. The positivity rate difference was 3.1% (P < .01). Cancer and advanced adenomas were found, respectively, in 11 and 48 of G-FOBTs and in 24 and 121 of I-FOBTs. Differences in positive predictive value for cancer and advanced adenomas and cancer were, respectively, 2.1% (P = .4) and −3.6% (P = .5). Differences in specificities favor G-FOBT and were, respectively, 2.3% (P < .01) and −1.3% (P < .01).

Differences in intention-to-screen detection rates favor I-FOBT and were, respectively, 0.1% (P < .05) and 0.9% (P < .01). Conclusions: The number-to-scope to find 1 cancer was comparable between the tests. However, participation and detection rates for advanced adenomas and cancer were significantly higher for I-FOBT. G-FOBT significantly underestimates the prevalence of advanced adenomas and cancer in the screening population compared with I-FOBT.

More than 30 years ago, guaiac-based fecal occult blood tests (G-FOBT) to screen for colorectal cancer (CRC) were introduced.1,2 A G-FOBT is a relatively inexpensive test, easy to use that can be carried out at home. However, G-FOBTs are not specific for human blood and quality control on the evaluation of the tests is hardly possible.3 Despite these disadvantages, the G-FOBT is still the most implemented test for CRC screening.4–9

A promising alternative is the immunochemical fecal occult blood test (I-FOBT). I-FOBTs are also inexpensive and noninvasive; in addition, these tests are often easier to carry out than G-FOBTs. Another advantage of I-FOBTs is that they are specific for human blood. The most prominent advantage is that many I-FOBTs make quality control possible. At least in theory, they also promise better diagnostic performance than G-FOBTs. In several studies I-FOBTs, seem to have higher specificity compared with G-FOBTs.10–14

To demonstrate that I-FOBTs have improved diagnostic performance, the tests should be compared with G-FOBTs in a randomized design in a general screening population. Up to now, direct comparison has only been performed in subjects at higher risk for CRC, like subjects with a positive G-FOBT, symptomatic patients, or patients already diagnosed with CRC.15–19 Also, some studies focused on test performance parameters of both G-FOBT and I-FOBT by asking people to perform both tests at the same time, but such an approach may have negative impact on participation rates.20–23 Another study comparing G-FOBT with I-FOBT was performed in a non-randomized design and the specific I-FOBT used (Inform) was not semiquantitative, did not allow quality control, and had to be performed on 2 days with separate bowel movements.10 In the present study, we aimed to randomly compare the test performance parameters of the Hemoccult II G-FOBT (Beckman Coulter, Fullerton, CA) with the OC-sensor I-FOBT (Eiken Chemical Co, Tokyo, Japan) in a screening population.

Abbreviations used in this paper: 95% CI, 95% confidence interval; CRC, colorectal cancer; FOBT, fecal occult blood test; G-FOBT, guaiac-based fecal occult blood test; I-FOBT, immunochemical fecal occult blood test; Negatives, FOBT-negative patients; Positives, FOBT-positive patients; PPV, positive predictive value.
Methods

Population

The population in this prospective study was a random selection of the general Dutch population between 50 and 75 years of age in Nijmegen, Amsterdam, and surrounding areas. Population data with respect to date of birth, gender, and postal area were provided by the civil service of the municipalities and updated every 8 weeks to keep the database up to date with respect to moving, age, and death. Institutionalized and symptomatic people were excluded. Symptomatic people were advised to contact their physician.

Randomization, Invitation, and Participation

From the municipal databases, random samples were taken according to postal address and randomized to receive a G-FOBT or an I-FOBT. If >1 individual was listed at the same address they received the same test to ensure relative blinding to the alternative test. Deviation from an equal distribution of the test allocation was prevented by an especially designed randomization program. From June 2006 to February 2007, randomized individuals received the allocated test, immediately with the invitation, an information brochure, a consent form, and a freepost envelope. The information brochure was designed in accordance with brochures used in other countries and provided concise background information for CRC screening and follow-up examination in case of a positive FOBT. Phone numbers to help desks in the 2 screening areas were given as well as links to informative websites. The only intervention to raise participation was a single written reminder 2 weeks after the initial invitation. The time for adherence—the time between invitation and returning the test—was unrestricted. Time for adherence was only restricted by closing of the study at May 1, 2007, after which time only follow-up was completed.

FOBTs

In this study 2 FOBTs were compared. The most commonly implemented G-FOBT, Hemoccult II (Beckman Coulter) was used. For the I-FOBT an automated semiquantitative I-FOBT: OC-sensor (Eiken Chemical Co) was chosen to allow quality control. No diet instructions were given and people were instructed to prevent contact of feces with toilet bowl water and urine and not to perform the test if visible blood was present. Illustrations as well as written instructions and examples aided in fecal sampling. To ensure consistent testing quality, 2 specially trained laboratory workers analyzed all FOBTs in 1 gastroenterology research laboratory in Nijmegen.

A complete Hemoccult II test consists of 3 separate cards. With that 6 applicator sticks, a collecting envelope, and written instructions were sent. Each card should be used on a consecutive day with defecation and on each card 2 samples of different parts of the defecation should be applied with a separate applicator stick. People were instructed to put all 3 test cards in a supplied collecting envelope and to return it as freepost. The cards were not rehydrated.24 If the test was performed incorrectly or <3 cards were returned, new test cards were sent with a letter explaining how to perform the test correctly. Incomplete tests were rare and almost always due to applying the stool on the wrong side of the card. Positivity was defined as blue discoloration of any of the 6 stool samples within 30–60 seconds after applying the developing solution. Ninety-nine percent of the tests were developed within 6 days. Tests were stored according to manufacturer instructions.

The OC-Sensor test consisted of a single sampling tube and written instructions. The sampling tube, filled with stabilizing buffer, had an integrated fecal probe. Participants were instructed to scrape different parts of the surface of their defecation with the probe. The amount of feces that can be inserted into the sample bottle is regulated to approximately 10 mg.14 Participants were instructed to return the test as soon as possible because lasting exposition to room temperature might result in degradation of hemoglobin in the sampling solution.13 If the test could not be returned immediately, storage in a refrigerator was advised. In the laboratory, tests were immediately developed or stored at 4°C. Of the tests, 75% were developed within 2 days and 99.6% within 6 days. Samples were processed by the OC-Micro instrument (Eiken Chemical Co).14 All patients with an I-FOBT ≥50 ng hemoglobin per milliliter sample solution (ng/mL) were invited for colonoscopy. Because the manufacturer recommends a cutoff of 100 ng/mL (corresponding to ±20 µg hemoglobin per gram of feces14) and because this cut-off value has been applied in several studies,25–30 we decided beforehand to use the 100 ng/mL cut-off level in the analysis of this study.

Colonoscopy and Lesions

Colonoscopy was offered to all FOBT-positive patients (Positives). All colonoscopies were performed by experienced gastroenterologists using conscious sedation with midazolam. If the cecum could not be reached at the initial colonoscopy, the procedure was repeated using propofol anesthesia, and occasionally a computed tomographic colonoscopy was performed followed by a second colonoscopy, if necessary. If possible, all observed neoplasias were removed, and other lesions were biopsied, if necessary. Lesions were classified as pedunculated or sessile polyps, carcinoma, or other and recorded in number, size (≤25, 6–9, or ≥10 mm), and location (proximal [cecum to splenic flexure] or distal [descending colon to rectum]). Histology was evaluated by an experienced pathologist and graded as carcinoma, tubular adenoma, tubulovillous adenoma, villous adenoma, serrated adenoma, hyperplastic polyp, or miscellaneous. Polyp size was measured by the endoscopist. Advanced adenomas
were defined as adenomas $\geq 10$ mm, with high-grade dysplasia or with a villous component $\geq 20\%$. All early and late complications of colonoscopy were recorded. All colonoscopies were completed in May 2007.

**Data Analysis**

The participation rate was calculated as the number of persons returning an FOBT relative to the number of invitations sent. The positivity rate was calculated as the number of persons with a positive FOBT (Positives) relative to the number of persons returning an FOBT. In screening studies usually only the detection rate of true positives relative to the number of persons actually participating by returning an FOBT are presented, that is, the detection rate according to per-protocol analysis. We also present the detection rate according to the intent-to-screen analysis, or the number of true positives relative to the number of invited persons. By determining the intent-to-screen detection rate, the difference in participation and performance are combined in 1 overall rate. The number needed to screen to find 1 true positive was calculated as the number of invited persons relative to the number of true positives followed up with colonoscopy. The number needed to scope to find 1 true positive was calculated as the number of endoscopies relative to the number of true positives.

The specificity was calculated under the rare disease assumption, as 1 minus the number of false positives relative to the total number of participants reduced by the number of true positives, disregarding the number of false FOBT-negative patients (Negatives). In relatively rare diseases, the overestimation of the specificity owing to disregarding the number of false negatives, is limited to the confidence interval of the true specificity. A small decrease in specificity in mass screening can be clinically relevant because this would result in many more colonoscopies. Therefore, we only present the specificity for advanced adenomas and cancer; we discuss the precision of the estimation in the Discussion.

Rates and rate differences of participation, positivity, detection, PPV, and specificity were calculated and all percentages were reported with 95% confidence intervals (95% CI). Rate differences are statistically significant if the confidence interval does not include zero. Statistically significant differences are supplemented with $P$-values. In the tables, statistically significant differences are bolded. If $>1$ lesion was present, a patient was classified by the most advanced lesion from more to less severe: from carcinoma, to $\geq 1$ adenoma $\geq 10$ mm, to high-grade dysplasia, to villous component $\geq 20\%$, to minor neoplasia. With adjusted logistic regression analysis, the influence of gender and age on the performance of the tests was evaluated. Statistical analysis and randomization were performed with SAS system for windows, software version 8.02 (SAS Institute Inc, Cary, NC).

Power was based on the lowest expected difference of all subgroups, namely, the difference in detection rate, for CRC between FOBTs. Based on literature data, a minimal difference of 0.3% in CRC detection was expected. With a sample size of 6083 in each group, a 2-group $\chi^2$ test with a 0.05 2-sided significance level would have 80% power to detect a 0.3% difference between FOBTs, assuming detection rates of 0.2% for G-FOBT and 0.5% for I-FOBT. A sample size of 10,000 in each group was considered to be sufficient.

**Ethical Approval and Consent**

The study was reviewed and approved by the Dutch Health Council (2005/03WBO, The Hague, The Netherlands). All participants gave written informed consent for the FOBT and, if positive, for colonoscopy.

**Results**

**Population**

Overall 20,623 individuals were invited; 10,301 received a G-FOBT and 10,322 an I-FOBT (Figure 1). The mean age of the invited individuals was 60.7 $\pm$ 7.1 years (mean $\pm$ SD) and was not different between the FOBT groups. More women than men were randomly selected.

![Flow chart from invitation to detection with numbers, percentages, and 95% confidence intervals between brackets.](image)
with a difference of 3.4% (95% CI, 2.5–4.4; \( P < .01 \)). After test allocation, gender differences were equal for both tests (Table 1).

Tests were returned by 10,993 individuals, 4836 (46.9%) in the G-FOBT group and 6157 (59.6%) in the I-FOBT group. The difference of 12.7% (95% CI, 11.3–14.1; \( P < .01 \)) was statistically significant. Time for adherence, after correction for 3-day testing for G-FOBT and 1-day testing for I-FOBT, was on average longer for G-FOBT (21 days) than for I-FOBT (19 days; \( P < .01 \)). For 75% of the participants, time for adherence was within 28 and 23 days, respectively (\( P < .01 \)) and for <1% of both FOBTs >100 days (\( P = .2 \)).

Of the G-FOBT participants 117 (2.4%) tested positive and 339 (6.1%) of the I-FOBT participants, with a difference of 3.4% (95% CI, 2.5–4.4; \( P < .01 \)). The age of 1 woman I-FOBT participant was unknown. Age and gender were equally distributed over both FOBTs.

**Colonoscopy Results**

To evaluate the outcome in the 456 FOBT Positives, a colonoscopy was performed in 383 (84%) patients. The cecum was reached in 358 patients (94%). In patients in whom the cecum was not reached during the initial colonoscopy, a successful second colonoscopy was performed under propofol anesthesia. In the 383 patients endoscoped, a total of 35 cancers and 899 polyps were found (Table 2).

Cancer was found in 11 of the G-FOBTs and in 24 of the I-FOBTs. Advanced adenomas were found in 46 of the G-FOBTs and in 121 of the I-FOBTs. The intention-to-screen detection rates of the I-FOBT were significantly higher than the intention-to-screen detection rates of the G-FOBT (Table 3). The difference in intention-to-screen detection rates for all patients with advanced adenomas and cancer was 0.9% (95% CI, 0.6–1.1; \( P < .01 \)) and for all patients with cancer 0.1% (95% CI, 0.0–0.2; \( P < .05 \)). The number needed to screen according to intention to screen to find an advanced adenoma or carcinoma was 181 for G-FOBT and 71 for I-FOBT, and to find 1 cancer was 936 for G-FOBT and 430 for I-FOBT.

None of the differences in PPVs (Table 3) between G-FOBT and I-FOBT were statistically significant; the difference in PPV for advanced adenomas and cancer was estimated to be –3.6% (95% CI, –14.8 to 7.7; \( P = .5 \)), and for cancer was estimated to be –2.1% (95% CI, –8.6 to 4.4; \( P = .4 \)), which was lower for I-FOBT. The number needed to scope to find 1 person with an advanced adenoma or cancer was <2 for both FOBTs. The esti-

### Table 1. Characteristics of Invited Persons and Participants According to Test With 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>G-FOBT (n = 10,301)</th>
<th>I-FOBT (n = 10,322)</th>
<th>G-FOBT (n = 4836)</th>
<th>I-FOBT (n = 6157)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% 95% CI</td>
<td>% 95% CI</td>
<td>% 95% CI</td>
<td>% 95% CI</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.6 (47.8–48.8)</td>
<td>48.3 (47.8–49.7)</td>
<td>43.2 (41.8–44.6)</td>
<td>45.8 (44.6–47.0)</td>
</tr>
<tr>
<td>Female</td>
<td>52.2 (51.2–53.2)</td>
<td>51.2 (50.3–52.2)</td>
<td>56.8 (55.4–58.2)</td>
<td>54.2 (53.0–55.4)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>50.4 (49.4–51.4)</td>
<td>51.7 (50.7–52.7)</td>
<td>47.5 (46.0–48.9)</td>
<td>51.0 (49.7–52.2)</td>
</tr>
<tr>
<td>≥60</td>
<td>49.2 (48.5–50.6)</td>
<td>48.3 (47.3–49.3)</td>
<td>52.5 (51.1–54.0)</td>
<td>49.0 (47.8–50.3)</td>
</tr>
</tbody>
</table>

### Table 2. Number of Colonoscopies and Number of Polyps and Cancer per Test, With Subdivisions for Kind of Polyp, Kind of Adenoma, and Size of Polyps

<table>
<thead>
<tr>
<th></th>
<th>G-FOBT</th>
<th></th>
<th>I-FOBT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of colonoscopies</td>
<td>103</td>
<td>280</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of polyps and cancera</td>
<td>231</td>
<td>703</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>11</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyps</td>
<td>220</td>
<td>679</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdivision of polypsb</td>
<td>220</td>
<td>679</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenomas</td>
<td>154</td>
<td>470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperplastic polyps</td>
<td>62</td>
<td>163</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serrated polyps</td>
<td>2</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other polyps</td>
<td>2</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subdivision of all adenomasd</td>
<td>154</td>
<td>470</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular</td>
<td>93</td>
<td>295</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubulovillous</td>
<td>42</td>
<td>138</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villous</td>
<td>12</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclassified</td>
<td>7</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of all polyps (mm)d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>60</td>
<td>155</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–9</td>
<td>43</td>
<td>125</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>117</td>
<td>399</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aThe number of lesions was higher than the number of colonoscopies because >1 lesion per colonoscopy is possible.
bPolyps were subdivided in adenomatous, hyperplastic, serrated, or other polyps.
cAdenomas were subdivided in tubular, villous, tubulovillous, or unclassified adenomas.
dAll polyps were subdivided by size in ≥10, 6–9, and ≤5 mm.
mated specificity of the I-FOBT was statistically significantly lower, but only −1.3% (95% CI, −1.8 to −0.8; \( P < .05 \)) for advanced adenomas and cancer and −2.3% (95% CI, −2.9 to −1.6; \( P < .01 \)) for cancer.

Age and gender were randomized equally over the FOBTs, but as known risk factors for advanced adenomas and cancer we studied the differences between FOBTs for age and gender (Table 4). The detection rates for women and younger participants were lower, but the differences between FOBTs were consistent. The unadjusted, and for gender- and age-adjusted odds ratios for the intention-to-screen detection rates of advanced adenomas and cancer for FOBTs were both 0.4 (95% CI, 0.3–0.5; \( P < .01 \)).

### Discussion

In this population study, we randomly compared the performance of a G-FOBT with an I-FOBT in a previously screening naïve population. Another study
comparing G-FOBT (Hemoccult-II) with I-FOBT was not randomized, included far fewer persons, and used a different I-FOBT. This I-FOBT (Infor) was not quantitative, making quality control less adequate.10 Despite these drawbacks, the results of this study were in line with ours.

Other studies evaluating I-FOBTs included far less subjects and did not focus on a screening population, but investigated high-risk groups, like symptomatic patients, patients with a positive G-FOBT, or even patients with CRC.15–19 Other studies were indeed designed for a screening population, but fewer subjects were included and asked to perform both the G-FOBT and the I-FOBT at the same time, which might induce selection bias in favor of highly motivated participants.20–23

Our study revealed several interesting results. First, direct comparison of the tests demonstrated a significantly higher participation rate for the I-FOBT. The reasons for this difference are not apparent and presently under investigation. Second, the specificity of the I-FOBT for advanced adenomas and cancer was significantly lower compared with the G-FOBT, but the detection rate for advanced adenomas and cancer with the I-FOBT was significantly higher. Consequently, 3 times as many subjects tested with the I-FOBT are referred for a negative colonoscopy. On the other hand, 3 times as many patients with advanced adenomas and cancer were left undetected in the G-FOBT group compared with the I-FOBT group, ultimately resulting in comparable PPVs for both tests.
cancer between 0.3% and 1.0%. In our study, including all participants, the detection rate of advanced adenomas and cancer was on average 1.9%, and for cancer 0.3%. However, in 56% of the participants with a positive FOBT, advanced adenomas and cancer were found and cancer alone in 8.6%.

What is the meaning of our findings for a general screening population? In 2004 a total of 410,000 endoscopies including gastroduodenoscopies, endoscopic retrograde cholangiopancreatographies, and colonoscopies were performed in Dutch endoscopy centers. In our country, 4.5 million people between 50 and 75 years are potential candidates for screening. This implies that, in a G-FOBT based screening program, 42,500 additional colonoscopies have to be performed to detect almost 4500 cancers and 20,000 advanced adenomas. In an I-FOBT–based screening program, almost 125,000 additional colonoscopies have to be performed to detect almost 11,000 cancers and 55,000 advanced adenomas. If the population at risk will primarily be screened by colonoscopy, about 1.2 million colonoscopies have to be performed to detect about 9700 cancers and 75,000 advanced adenomas presuming that, according to Segnan et al, 26.5% of the population will participate in such a screening program, that 0.8% of these subjects will have cancer, and 6.3% advanced adenomas. Thus, the number to scope to find 1 cancer or 1 advanced adenoma are comparable between G-FOBT– and I-FOBT–based screening programs. Compared with FOBT-based screening programs, the number to scope to find 1 cancer in a colonoscopy based screening program is 13 times higher and the number to find 1 advanced adenoma is 7 times higher.

Another major advantage of the I-FOBT we used is that the test is semiquantitative. This allows shifting the cut-off value of the test. When resources are limited and the prevalence of CRC in the population is expected to be low, one could consider increasing the cut-off value of the test and vice versa. In addition, the I-FOBT does not have dietary restrictions, because it is specific for human blood. In contrast, extensive dietary restrictions are advised for the G-FOBT to avoid false-positive test results, although others question this. In our study, we did not advise dietary measures for subjects receiving the G-FOBT, because this would make comparison unfairly biased in favor of the I-FOBT.

Despite written and verbal information about colonoscopy before and after performing an FOBT, 16% of subjects with a positive test refused this follow-up examination. This was comparable to other FOBT-based screening studies. The majority of the subjects ultimately refused colonoscopy because of anxiety. Increased adherence positively influences detection rates and the precision of the confidence intervals for both tests, but the conclusions of our study will not change, because adherence was not dependent on the kind of FOBT.

Advanced adenomas and cancer were found more often in men than in women, despite the fact that more women than men participated in the study. In addition, advanced adenomas and cancer were also more often detected in older persons. This is in line with other studies. Thus, the diagnostic yield increases with age. This finding may help to narrow the age range for screening in different populations, depending on resources and prevalence of advanced adenomas and cancer. Male preponderance for advanced adenomas and cancer may be attributed to sex hormones; it has been hypothesized that estrogens may have protective effects on the development of CRC, or to gender differences in exposure to environmental factors, like smoking, dietary fiber, or exercise. There was no difference between FOBTs concerning the preponderance of males and older individuals having advanced adenomas or cancer.

Several previous studies dealt with the diagnostic performance of FOBTs. Most of these studies reported comparable results to our data. Although some studies reported lower diagnostic performance for G-FOBTs, others showed somewhat better results for I-FOBTs. Up to now, a randomized comparison between G-FOBT and I-FOBT in a screening population was lacking. There can be several reasons for the observed differences between these studies. One of the most important variables is the definition of advanced adenomas, which varies between studies. It remains unclear which lesions ultimately will develop into cancer and in what timeframe. Therefore, we were conservative in defining advanced adenomas. We also provided subgroup analyses to make comparisons between studies more feasible.

There is a small difference in specificity between G-FOBT and I-FOBT. However, even small differences in specificity result in high absolute numbers of false positives, increasing costs and work load for endoscopy units. The method we used for estimating specificity slightly overestimates the true specificity especially for more prevalent lesions and more sensitive tests. In turn, the difference in specificity is slightly underestimated up to at most 0.2% for advanced adenomas and cancer, increasing the difference in favor of the G-FOBT. Overall, the conclusions about statistical significance and clinical relevance therefore do not change by the systematic error of the specificity estimation.

In conclusion, direct comparison between a G-FOBT and an I-FOBT revealed that the number to scope to find 1 CRC is not different between G-FOBT and I-FOBT. However, participation and detection rates for advanced adenomas and cancer were significantly higher in the group tested with I-FOBT. By result, 2.5 times more advanced adenomas and cancer and 2.2 times more cancers were detected with I-FOBT compared with G-FOBT. Therefore, G-FOBT significantly underestimates the prevalence of advanced adenomas and cancer compared with I-FOBT in a screening population.
References


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