CHAPTER 7

Higher FIT cut-off levels: lower positivity rates but still acceptable detection rates for early stage colorectal cancers


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Abstract

Background: Adjusting the threshold for positivity of quantitative Fecal Immunochemical Tests (FITs) allows for controlling the number of follow-up colonoscopies in a screening program. However, it is unknown to what extent higher cut-off levels affect detection rates of screen relevant neoplasia. This study aimed to assess the effect of higher cut-off levels of a quantitative FIT on test positivity rate and detection rate of early stage colorectal cancers (CRCs).

Methods: Subjects >40 years old scheduled for colonoscopy in 5 hospitals were asked to sample a single FIT (OC sensor®) before colonoscopy. Screen relevant neoplasia were defined as advanced adenoma or early stage cancer (stage I and II). Positivity rate, sensitivity and specificity were evaluated at increasing cut-off levels of 50-200 ng/ml.

Results: In 2,145 individuals who underwent total colonoscopy, 79 patients were diagnosed with CRC, 38 of which with early stage disease. Advanced adenomas were found in 236 patients. When varying cut-off levels from >50 to >200 ng/ml, positivity rates ranged from 16.5% to 10.2%. With increasing cut-off levels, sensitivity for early stage CRCs and for screen relevant neoplasia ranged from 84.2%–78.9% and 47.1%–37.2%, respectively.

Conclusions: Higher FIT cut-off levels substantially decrease test positivity rates with only limited effects on detection rates of early stage CRCs. However, spectrum bias resulting in higher estimates of sensitivity than would be expected in a screening population may be present.

Impact: Higher cut-off levels can reduce strain on colonoscopy capacity with only a modest decrease in sensitivity for curable cancers.

Introduction

Screening for colorectal cancer (CRC) using guaiac-based fecal occult blood tests (G-FOBT) has been shown to reduce CRC-related mortality (1-3). In recent years, a growing body of literature lends support to the notion that fecal immunochemical tests (FITs) are superior to G-FOBT in CRC screening (4-8). This superiority does not only imply higher participation rates and sensitivity for advanced neoplasia, but also better reproducibility and quality control due to the automated analysis and quantitative test output (9). The quantitative test output allows for adjusting the threshold for the definition of a positive test. This is important since several recent studies comparing G-FOBT and FIT have reported a lower specificity of FIT when a cut-off level of 50-100 nanogram hemoglobin per milliliter was used (5-8). Once this test is applied in a CRC screening program, a lower cut-off level will result in more screenees being referred for colonoscopy, and due to lower specificity, a higher number of futile colonoscopies. Higher FIT cut-off levels will decrease strain on colonoscopy resources, but might also be associated with more curable CRCs being undetected. To test this hypothesis, a study design is needed in which all FIT negative individuals undergo the reference test, i.e. complete colonoscopy. However, in most population-based screening studies, only FIT-positive individuals undergo colonoscopy (4-7,10,11). Although these screening studies reflect the target population for screening, sensitivity cannot be calculated. Specificity can be calculated, but only indirectly and based on less accurate rare disease assumptions (6). Moreover, these studies often have a low yield of CRCs, which restricts the power to stratify these cancers by stage (6,7,12,13). When aiming at CRC mortality reduction, detection of early stage cancers is much more relevant than detecting late stage cancers. In a referral population, like in the present study, a higher prevalence of CRC and its precursors will allow for stratification of quantitative FIT results for different phases of the natural history of the disease. We therefore assessed the effect of a higher cut-off level of a quantitative FIT on positivity rates and on detection rates of curable, early stage CRCs and advanced adenomas in a colonoscopy-controlled population.

Patients and Methods

Study population and study design
Details of study design and of most materials and methods relevant for this study have been published previously in a report on the direct comparison of a FIT and a g-FOBT (8). All ambulatory subjects over the age of 40 years scheduled to undergo elective colonoscopy from June 2006 to January 2009 at one of the five participating hospitals, were invited to participate in this study. Invitation was either in person by the referring gastroenterologist or through telephone by one of five research workers stationed at each of the participating centers. Once subjects consented in participation, they received an envelop containing...
background information on the study, the FIT with extensive instructions and an informed consent form. When an individual could not be reached by telephone, the same package was sent but with an additional explanatory letter. Two of these five participating hospitals are situated in rural areas, another two are large teaching hospitals with an urban population. One of the centers is an academic medical center with a predominantly urban population. In all centers, local Medical Ethics Review Board approval was obtained prior to the start of the study. All eligible individuals were asked to sample one FIT on stool from a bowel movement on the day prior to colonoscopy. Patients with a documented history of inflammatory bowel disease (IBD), subjects who failed to complete the test and subjects in whom no written informed consent was obtained were excluded from further analysis. We also excluded subjects with incomplete colonoscopies and subjects with inadequate bowel cleansing, as judged by the endoscopist.

**Fecal Immunochemical Tests**

The FIT used in the present study is the automated quantitative OC-sensor® test (Eiken Chemical Co., Tokyo, Japan). The FIT was sampled from stool produced the day before colonoscopy and before bowel preparation had started. Subjects were excluded when the FIT was sampled after initiation of bowel preparation. Illustrated instructions guided the participants to sample their stool ensuring that contact with water and urine was prevented. No restrictions were made with regard to diet during the week in which the stool sample was taken (14). Participants were asked to discontinue anticoagulants and NSAIDs 5 days prior to colonoscopy. On the day of colonoscopy, the completed test and the signed informed consent form were handed over to the nursing staff at the endoscopy department. All FITs were stored at minus 5 degrees Celsius on arrival. Tests were analyzed using the OC sensor MICRO desktop analyser (Eiken Chemical Co., Tokyo, Japan) according to the manufacturers instructions (15). Tests were analyzed within one week by one of two experienced technicians who were unaware of the clinical data. Both technicians received special training for analyzing the tests.

**Standards of reference**

Colonoscopy was the standard of reference for the presence, size and location of colorectal neoplasia. Colonoscopies were performed or supervised by experienced gastroenterologists. Endoscopists were blinded to the FIT result. Conscious sedation using Midazolam was offered to all patients. A complete colonoscopy was defined as intubation of the cecum with identification of the ileocecal valve or appendiceal orifice, or intubation up to an obstructing neoplasm. The results of histopathological analysis of tissue samples obtained during colonoscopy were the standard of reference for the diagnosis of adenoma or cancer. Surgical resection specimens were used for the standard of reference for CRC staging. If no surgical resection had been performed, the results of histopathological biopsy specimens were used instead. Adenomas ≥1.0 cm, with any villous features (i.e. tubulovillous or villous adenoma) or high-grade dysplasia, were considered advanced adenomas (16,17). Advanced neoplasia included all cases of CRC and all advanced adenomas. Colorectal carcinomas were staged according to the AJCC cancer staging manual (18). Early stage CRC was defined as AJCC stage I or II, whereas late stage CRC was defined as AJCC stage III or IV. Since the ultimate goal of screening is the detection of early stages of diseases, we defined screen relevant neoplasia as one or more advanced adenoma(s) or early stage CRC (8,19). If multiple lesions were present, classification was based on the most advanced lesion found.

**Statistical analysis**

Taking colonoscopy as the reference test, sensitivities and specificities of FIT at six cut-off levels were calculated for the following colonoscopy outcomes 1) the presence of CRC; 2) the presence of early stage CRC; 3) the presence of advanced adenoma; 4) the presence of screen relevant neoplasia and 5) the presence of advanced neoplasia. The sensitivity is calculated as the proportion of positive test results in patients with an outcome less severe than the colonoscopy outcome under consideration. The specificity is calculated as the proportion of negative test results in patients with an outcome less severe than the colonoscopy outcome under consideration. Note that, therefore, the same specificity results from choosing either outcome 1 (all stages of CRC) or outcome 2 (early stage CRC), and from choosing either outcome 3, 4, or 5. For dichotomizing the FIT results, we used cut-off levels of 50, 75, 100, 125, 150 and 200 ng hemoglobin per ml, which are levels frequently used in FIT studies (7,20,21). The calculations were repeated for the subgroup of patients that are considered at low risk for colonic neoplasia (procedure indications: abdominal pain, constipation and screening colonoscopy in average risk individuals) as well as for the high-risk subgroup separately.

We used receiver operator characteristic (ROC) curve analysis, including calculation of the area under the curve (AUC) with 95% confidence intervals to evaluate the relation between the quantitative FIT outcome and 1) the presence of CRC; 2) the presence of early stage CRC; 3) the presence of advanced adenoma and 4) the presence of screen relevant neoplasia. All analyses were performed with SPSS for Windows Version 15 (SPSS Inc., Chicago, Illinois).

**Results**

**Characteristics of the study population**

Overall 2,525 individuals who underwent colonoscopy sampled a FIT. In total 380 individuals were excluded (Figure 1). The mean age of the 2,145 individuals that were included for final analysis was 61.8 years (range 40-89 years) and 53.8% of these were female. Colonoscopy was performed because of gastrointestinal symptoms in 1,109 individuals (51.7%), whereas screening or surveillance for CRC was the indication for colonoscopy in 955 asymptomatic individuals (44.5%). Of 81 individuals (3.8%) the primary indication remained unspecified (Table I).
Patients scheduled for elective colonoscopy in 5 participating hospitals who performed the FIT (n = 2,525)

Exclusion:
- Documented history of IBD (n = 22)
- FIT inadequately sampled (n = 3)
- Age < 40 years (n = 165)

Patients undergoing colonoscopy (n = 2,335)

Exclusion:
- Incomplete colonoscopy (n = 168)
- Insufficient bowel lavage (n = 13)
- Colostomy (n = 7)

Patients with a total colonoscopy and sufficient bowel cleansing (n = 2,147)

Exclusion:
- No histopathological diagnosis (n = 2)

Patients included for final analysis (n = 2,145)

FIT results

The overall FIT positivity rates at the different cut-off levels varied from 16.5% (n = 354 at cut off >50 ng/ml) to 10.2% (n = 218 at cut off >200 ng/ml). Table II shows the test characteristics of FIT at different cut-off levels to detect CRC, early stage CRC, late stage CRC, advanced neoplasia, screen relevant neoplasia and advanced adenomas. Table III summarizes the sensitivities and positivity rates for early stage CRC and for screen relevant neoplasia.

Table 1: Primary indications for colonoscopy among 2,145 consecutive patients in five hospitals in the Amsterdam area enrolled in a study comparing detection rates for early stage colorectal cancers at different FIT cut-off levels.

<table>
<thead>
<tr>
<th>Indication Group</th>
<th>Indication for colonoscopy</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic/suspect</td>
<td>Weight loss</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Clinical suspicion of diverticulitis</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Clinical suspicion of IBD</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>297</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Haematochezia</td>
<td>237</td>
</tr>
<tr>
<td></td>
<td>Altered bowel habits</td>
<td>253</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Clinical suspicion of CRC (inconclusive histology)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy for polypectomy</td>
<td>49</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,109</td>
</tr>
</tbody>
</table>

Screening & Surveillance

<table>
<thead>
<tr>
<th>Indication for colonoscopy</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average risk</td>
<td>42</td>
</tr>
<tr>
<td>Familial history of CRC</td>
<td>319</td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>24</td>
</tr>
<tr>
<td>Polyp surveillance</td>
<td>396</td>
</tr>
<tr>
<td>Post CRC surveillance</td>
<td>147</td>
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<tr>
<td>Radiological suspicion of malignancy</td>
<td>25</td>
</tr>
<tr>
<td>Screening for CRC in celiac disease</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>955</td>
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</table>

Other

<table>
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<tr>
<th>Indication for colonoscopy</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Not specified</td>
<td>81</td>
</tr>
</tbody>
</table>

Grand total 2,145

Colonoscopy results

CRCs were found in 79 individuals (3.7%). Of these CRCs, 38 (48.1%) were classified as early stage (AJCC stage I or II) and 36 (45.6%) were classified late stage (AJCC stage III or IV). For five rectal cancers (6.3%) stage could not be determined accurately due to the effects of neo-adjuvant radiotherapy. In 236 individuals (11.0%) at least one advanced adenoma was found. This resulted in 315 individuals with advanced neoplasia (either advanced adenoma or CRC) and 274 individuals with screen relevant neoplasia (either advanced adenoma or early stage CRC).
Receiver-operating characteristic (ROC) curves for FIT
The AUC of the ROC curve for the detection of CRC (n = 79) was 0.93 (95% CI, 0.89-0.96). For the detection of early stage CRC (n = 38), an AUC of 0.89 was found (95% CI, 0.82-0.95). When all screen relevant neoplasia were considered (n = 274), the AUC was 0.72 (95% CI, 0.68-0.76). The AUC for the detection of advanced adenomas separately (n = 236) was 0.69 (95% CI, 0.65-0.73).

Sensitivities in high versus low risk populations
Sensitivities of FIT for CRC, early stage CRC and screen relevant neoplasia were compared between indication groups that were considered at low risk for colon neoplasia versus at high risk. Patients with procedure indications like abdominal pain, constipation and screening colonoscopy in average risk individuals were considered to belong to a low risk population (n = 374). The remaining procedure indications were considered to reflect a high risk population (n = 1771) (Table I). Sensitivity and the yield of screen relevant lesions in these two populations are shown in Table IV.

Discussion
In the present study, test performance of one of the most commonly used fecal immunochemical tests was evaluated at different cut-off levels in a large cohort of individuals undergoing colonoscopy. It was found that by increasing the cut-off level specificity increased substantially, whereas the effects on detection rates of curable, early stage, colorectal cancers were only limited. Although many other aspects have to be taken into account when deciding on the most suitting cut-off level, this study has its focus on sensitivity and specificity. In general, the FIT showed to have good test characteristics for detecting both CRC and early stage CRC, as reflected by the ROC in the current study. Adjusting the cut-off level from >50 ng/ml to >200 ng/ml resulted in a substantial decrease in the number of positive tests (16.5% to 7.7%). Compared to a cut-off level of >50 ng/ml, two early stage cancers would have been missed at a cut-off level of >200 ng/ml. In fact, from a cut-off level of >125 ng/ml upwards, no further decrease in sensitivity was found. Specificity, however, increased from 86.4% to 92.8% with increasing cut-off levels. Focusing on all screen relevant neoplasia, 47.1% were detected with the lowest cut-off level of >50 ng/ml, while the highest cut-off level of >200 ng/ml yielded only 37.2% of all screen relevant lesions.

Consequences of these findings depend on the setting in which FIT is applied. The choice for a higher FIT threshold may be particularly relevant when a screening program is to be implemented, like is planned for the Netherlands (22). The Dutch Health Council advised to start screening at a cut-off level of 75ng/ml, even though using 50ng/ml might be more cost-effective (22). However, current colonoscopy capacity is insufficient to cope with positive screenees at this cut-off level. A higher FIT cut-off level will limit the number of colonoscopy referrals. In the first round of a screening program both early and late stage CRCs, so called prevalent cancers, will be detected in a range consistent with their respective prevalences.
The colonoscopy-controlled referral population used in the present study has two advantages compared to a screening population. Firstly, in most FIT studies to date, only individuals with a positive test underwent subsequent colonoscopy. This precluded the determination of sensitivity, false negative rates and thus specificity of the investigated tests. The present study design provides accurate data on direct sensitivity of the FIT at different cut-off levels.

Secondly, the referral population contained a higher number of individuals with CRC or advanced adenomas compared to an average risk screening population. Consequently, FIT results could be stratified by stage of the disease. More precise data on sensitivity and specificity in high risk populations are necessary but were not available to this study.

The colonoscopy-controlled referral population has two advantages. Firstly, in most FIT studies to date, only individuals with a positive test underwent subsequent colonoscopy. This precluded the determination of sensitivity, false negative rates and thus specificity of the investigated tests. The present study design provides accurate data on direct sensitivity of the FIT at different cut-off levels.

in a screening-naïve population. So, in the first round, yield and thus strain on the healthcare system, will be inflated by the prevalent advanced stage CRCs. In later rounds of screening, however, less advanced CRCs will be left in the population and the performance characteristics of the screening program will largely depend on the potential to detect early stage CRCs, i.e. incident cancers. In this respect, it is highly relevant to know that increasing the cut-off level to >200 ng/ml has a relatively small effect on the sensitivity to detect early stage cancers when starting a CRC screening program. The lower positivity rate and the higher specificity will result in less referrals for colonoscopy with an acceptable decrease in detection rates. When the prevalence of target lesions would decrease in later screening rounds, cut-off levels can easily be adjusted to lower values in order to achieve a more sensitive program. The miss rate for advanced adenomas at a higher cut-off level is somewhat higher (70% at >200 ng/ml versus 65% at >150 ng/ml), given the natural history of the disease, an advanced adenoma that would easily be adjusted to lower values in order to achieve a more sensitive program. The miss rate for advanced adenomas at a higher cut-off level is somewhat higher (70% at >200 ng/ml versus 65% at >150 ng/ml), given the natural history of the disease, an advanced adenoma that would be missed in the initial screening round would have multiple opportunities to be detected in a consecutive round, either still at the stage of an advanced adenoma or as an early stage cancer.

Table 3: Positivity rates and sensitivity for early stage CRCs and screen relevant neoplasia at different cut-off levels of FIT in a consecutive series of 2,145 patients referred for colonoscopy.

<table>
<thead>
<tr>
<th>Cut-off Level (ng/ml)</th>
<th>≥ 50 ng/ml</th>
<th>≥ 75 ng/ml</th>
<th>≥ 100 ng/ml</th>
<th>≥ 125 ng/ml</th>
<th>≥ 150 ng/ml</th>
<th>≥ 200 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positivity rate (%)</td>
<td>16.5%</td>
<td>14.3%</td>
<td>13.0%</td>
<td>12.1%</td>
<td>11.1%</td>
<td>10.2%</td>
</tr>
<tr>
<td>N (2,145)</td>
<td>354</td>
<td>307</td>
<td>279</td>
<td>259</td>
<td>239</td>
<td>218</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>84.2%</td>
<td>81.6%</td>
<td>81.6%</td>
<td>78.9%</td>
<td>78.9%</td>
<td>78.9%</td>
</tr>
<tr>
<td>N (38)</td>
<td>32</td>
<td>31</td>
<td>31</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>47.1%</td>
<td>45.3%</td>
<td>43.4%</td>
<td>42.0%</td>
<td>40.1%</td>
<td>37.2%</td>
</tr>
<tr>
<td>N (274)</td>
<td>129</td>
<td>124</td>
<td>119</td>
<td>115</td>
<td>110</td>
<td>102</td>
</tr>
</tbody>
</table>

* Early stage CRC is defined as AJCC stage I or II
† Screen relevant neoplasia is defined as either one or more advanced adenoma(s) or an early stage carcinoma (AJCC stage I or II)
** Note: Of five rectal cancers the oncological stage of disease at diagnosis could not be assessed due to the effects of neo-adjuvant radiotherapy.

Table 4: Sensitivity of FIT (OC-sensor®) for colorectal cancer (CRC), early stage CRC and screen relevant neoplasia in a low risk versus high risk population based on procedure indication in a consecutive series of 2,145 patients referred for colonoscopy.

<table>
<thead>
<tr>
<th>Cut-off Level (ng/ml)</th>
<th>≥ 50 ng/ml</th>
<th>≥ 75 ng/ml</th>
<th>≥ 100 ng/ml</th>
<th>≥ 125 ng/ml</th>
<th>≥ 150 ng/ml</th>
<th>≥ 200 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>85.7%</td>
<td>85.7%</td>
<td>85.7%</td>
<td>71.4%</td>
<td>71.4%</td>
<td>71.4%</td>
</tr>
<tr>
<td>N (4,681)</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
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<tr>
<td>(95% CI)</td>
<td>(42.1–99.6)</td>
<td>(42.1–99.6)</td>
<td>(42.1–99.6)</td>
<td>(29.0–96.3)</td>
<td>(29.0–96.3)</td>
<td>(29.0–96.3)</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>75.0%</td>
<td>75.0%</td>
<td>75.0%</td>
<td>75.0%</td>
<td>75.0%</td>
<td>75.0%</td>
</tr>
<tr>
<td>N (34)</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
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</tr>
<tr>
<td>(95% CI)</td>
<td>(19.4–99.4)</td>
<td>(19.4–99.4)</td>
<td>(19.4–99.4)</td>
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</tr>
<tr>
<td>Sensitivity (%)</td>
<td>44.7%</td>
<td>44.7%</td>
<td>42.1%</td>
<td>42.1%</td>
<td>42.1%</td>
<td>36.8%</td>
</tr>
<tr>
<td>N (274)</td>
<td>17</td>
<td>17</td>
<td>16</td>
<td>16</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(28.6–61.7)</td>
<td>(28.6–61.7)</td>
<td>(26.3–59.2)</td>
<td>(26.3–59.2)</td>
<td>(21.8–54.0)</td>
<td>(21.8–54.0)</td>
</tr>
</tbody>
</table>

High risk population was defined as subjects undergoing colonoscopy for any procedure indication but abdominal pain, constipation or average risk screening.

* Early stage CRC is defined as AJCC stage I or II
† High risk population was defined as subjects undergoing colonoscopy for any procedure indication but abdominal pain, constipation or average risk screening
§ Screen relevant neoplasia is defined as either one or more advanced adenoma(s) or an early stage carcinoma (AJCC stage I or II)

Note: Of five rectal cancers the oncological stage of disease at diagnosis could not be assessed due to the effects of neo-adjuvant radiotherapy.

Secondly, the referral population contained a higher number of individuals with CRC or advanced adenomas compared to an average risk screening population. Consequently, FIT results could be stratified by stage of the disease. More precise data on sensitivity and specificity, i.e. with smaller confidence intervals than data from screening studies in which there is a lower prevalence of target lesions, could be calculated (4.6, 7.20, 23). In screening studies,
Three other lines of evidence provide indications that the effect of spectrum bias in the present study may be limited. Firstly, when comparing sensitivities of FIT for screen relevant neoplasia in patients from the present study population who could be considered to have a low risk for colonic neoplasia to those that would be at higher risk, only minor differences in sensitivity were found (29,30). Secondly, spectrum bias could also be explained by a different tumor stage distribution in the referral population compared to those in a screening population. A comparison of CRCs from a referral and a screening population indeed revealed a higher prevalence of advanced cancers. After stratifying for T-stage, however, no differences in FIT results were found between the screening and referral population (31). Thirdly, test characteristics found in screening studies remain debatable, as 70% of screen detected CRCs in the British NHS National Bowel Cancer Screening Program appeared to be symptomatic (32). In conclusion, in the present study higher cut-off levels turned out to result in only a 5.3% decrease in detection rate for early stage colorectal cancer, while at the same time substantially reducing the number of positive FITs with 6.3%. Overestimation of sensitivity, however, due to potential spectrum bias cannot be ruled out completely. When a higher cut-off level would be used as a first step preceding colonoscopy in a CRC screening program, lower numbers of colonoscopies would be required. This may facilitate the appropriate allocation of available resources. The lower detection rates of advanced adenomas may be overcome by the fact that these lesions are likely to be detected in a later screening round while probably still being at a stage of disease at which death from CRC can be prevented.

The higher positivity rate of the FIT and higher prevalence of advanced neoplasia in the present referral population make it impossible to extrapolate the positive and negative predictive values (PPV and NPV) of this study to a screening population. However, by applying Bayes' theorem, the sensitivity and specificity from this study can be combined with observed prevalences of CRC and advanced adenomas found in the general population in order to estimate the NPV and PPV in the general population (26). Although these computed values for NPV and PPV should be interpreted with caution, it allows us to explore the effect of increasing cut-off levels. The prevalence of CRC found in Dutch screening studies is 0.8% and advanced adenomas are found in 6.7% (22). In the time period 2003-2007, 54% of all newly diagnosed CRC patients presented with early stage disease (27). Increasing the cut-off level of FIT from >50 ng/ml to >200 ng/ml hardly affected NPV for early stage CRC (99.9%). The PPV for detection of early stage cancer, however, increases substantially from 2.6% to 4.5%. The number needed to scope reduced significantly by increasing the cut-off level to >200 ng/ml, resulting in a 42% decrease in required colonoscopies and only a 6% reduction in detection rates of early stage CRCs.

An important issue is whether the present findings can be generalized to a screening population. The use of a referral population to evaluate a screening test carries the risk of introducing spectrum bias. Spectrum bias refers to the situation that the spectrum of the disease phenotype differs from that in the population in which the test ultimately will be applied (28). This might lead to overestimation of sensitivity. An ultimate answer to this question can only come from a colonoscopy-controlled screening population. To accrue a similar number of cancers in such a study design as in the present study would require a very large sample size which might frustrate such a study design. According to the number of CRCs found in the two large screening trials in The Netherlands, such a study should invite 30,275 average risk individuals for FIT screening to obtain the same CRC yield as in the present study (6,7). This sample size is based on the assumption of a 60-62% participation rate for FIT and 84-95% compliance to colonoscopy after a positive FIT (6,7).
Reference list:


