Hereditary & familial colorectal cancer
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Citation for published version (APA):

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ADDING FAMILY HISTORY TO FAECAL IMMUNOCHEMICAL TESTING INCREASES THE DETECTION OF ADVANCED NEOPLASIA IN A COLORECTAL CANCER SCREENING PROGRAMME


Alimentary Pharmacology & Therapeutics 2016;44(1):88-96
ABSTRACT

Background

Faecal immunochemical testing (FIT) for colorectal cancer (CRC) screening has suboptimal sensitivity for detecting advanced neoplasia. To increase its performance, FIT could be combined with other risk factors.

Aim

To evaluate the incremental yield of a screening programme using a positive FIT or a CRC family history, to offer a diagnostic colonoscopy.

Methods

For this post hoc analysis, data were collected in the colonoscopy arm of a colonoscopy or colonography for screening study. In this study, 6600 randomly selected, asymptomatic men and women (50-75 years) were invited for screening colonoscopy. 1112 Participants completed a FIT and a questionnaire prior to colonoscopy. We compared the yield of FIT-only and FIT combined with CRC family history, defined as having one or more first-degree relatives with CRC.

Results

At a 10 µg Hb/g faeces FIT-positivity threshold the combined strategy would increase the yield from 36 (3.2%; CI: 2.4-4.5%) to 53 (4.8%; CI: 3.7-6.2%) cases of advanced neoplasia, at the expense of 148 additional negative colonoscopies. Sensitivity in detecting advanced neoplasia would increase from 36% (CI: 26-46%) to 52% (CI: 42-63%), whereas specificity would decrease from 93% (CI: 92-95%) to 79% (CI: 76-81%). The strategy will be preferred if one accepts 8.8 false positives for every additional participant in whom advanced neoplasia can be detected.

Conclusions

Offering colonoscopy to those with a positive FIT or CRC family history increases the yield of a FIT-based screening programme. Depending on the number of negative colonoscopies one accepts, this combined approach can be considered for improving CRC screening.
INTRODUCTION

Colorectal cancer (CRC) is the second most prevalent type of cancer in the Netherlands. CRC originates from precursor lesions, mostly adenomatous polyps. Progression of adenomas into cancer takes 10-15 years thereby offering a long window of opportunity to intervene. Early detection and treatment of advanced adenomas and cancer (together referred to as advanced neoplasia) by colonoscopy can reduce both the incidence and mortality of CRC.

Several countries now offer colonoscopy screening to age-selected inhabitants. As this procedure is invasive, burdensome and costly, a number of countries rely on faecal immunochemical testing (FIT) for triaging screening participants to undergo colonoscopy. The European Union confirmed that FIT fulfils the requirements for primary CRC screening. Accordingly, FIT-based screening was introduced in the Netherlands in 2014 for persons aged 55-75 years.

FIT screening results in participation rates of around sixty per cent, which is high compared to other screening methods such as primary sigmoidoscopy screening. However, its diagnostic performance is limited.

To further optimise the triaging of screening participants, targeting those at highest risk of having advanced neoplasia, FIT could be combined with other risk factors. One of those risk factors is having a first-degree relative with CRC, regardless of age. In most countries, many of these family members go unrecognised; they do not receive regular surveillance colonoscopies, but are invited for the regular population-based screening programme. Several reports showed that nearly a quarter of those with a false-negative FIT result have a first-degree relative with CRC, compared to one-tenth of participants with a true-negative FIT result.

The aim of this analysis was to evaluate the performance of a combined CRC screening strategy by offering colonoscopy to those with a positive FIT as well as to those with one or more first-degree relatives with CRC. We evaluated the incremental yield of this combined strategy relative to FIT-only screening, in terms of number of cases with advanced neoplasia detected in screening participants, in a post hoc analysis of data collected previously in a colonoscopy screening trial.

MATERIALS AND METHODS

Study population

Data collected in the Colonoscopy or Colonography for Screening (COCOS) trial were used for this analysis. The COCOS trial is a multicentre population-based randomised screening trial performed in the Netherlands between June 2009 and July 2010. Its primary aim was to
compare participation and yield between colonoscopy and CT colonography in a CRC screening programme. For the current analysis, only data from participants in the colonoscopy arm of the COCOS trial were included, as data on family history were only collected in that arm and colonoscopy is considered the reference standard for detecting advanced neoplasia.

The trial, which was performed before the introduction of the national FIT-based screening programme for CRC in the Netherlands, has been described elsewhere. In that trial 6600 asymptomatic men and women, aged between 50 and 75 years, were randomly selected and invited for primary colonoscopy. Screening participants provided written informed consent. Ethical approval was obtained from the Dutch National Health Council. The trial was registered in the Dutch Trial Register (NTR1829).

FIT

All invitees willing to undergo colonoscopy were asked to complete a one sample FIT within 48 h before their colonoscopy and before starting bowel preparation (OC-Sensor; Eiken chemical, Tokyo, Japan).

Colonoscopy

All participants underwent colonoscopy, regardless their FIT result. Colonoscopies were performed at one of the two participating screening centres (Academic Medical Center Amsterdam, Erasmus Medical Center Rotterdam) by experienced gastroenterologists, according to current quality indicators.

Pathology

One of two expert gastrointestinal pathologists assessed all removed and biopsied lesions. Vienna criteria were used to define histological results. Advanced neoplastic lesions are defined as CRC and advanced adenomas; an advanced adenoma was defined as an adenoma ≥10 mm, an adenoma with villous histology (>25% villous), and/or an adenoma with high-grade dysplasia.

Family history

Data on family history were collected using a paper questionnaire with three questions, based on a previously validated questionnaire. In case of incomplete or unclear data, these were complemented with family history information collected during the intake visit scheduled prior to colonoscopy.
Statistical analyses

We compared the yield of a combined approach, hypothetically selecting participants for colonoscopy based on FIT and family history, to that of selection based on FIT-only. Screening participants would only be invited for colonoscopy if they had a positive FIT and/or a positive family history. We used FIT-positivity cut-off values of 10, 15 and 20 µg Hb/g faeces (corresponding to 50, 75 and 100 ng/mL faeces), as these thresholds are most commonly used in screening studies.\textsuperscript{36, 37, 36}

A CRC family history was defined as reporting one or more first-degree relatives with CRC (parents, siblings, children), regardless their age. In an additional sensitivity analysis, the definition of a CRC family history was restricted to those with a first-degree relative with CRC younger than 60 years and those with at least two first-degree relatives with CRC, regardless their age. The latter definition was based on international colonoscopy surveillance guidelines.\textsuperscript{37-39}

In addition to changes in yield, we evaluated the performance in terms of the number of additional true positives with the combined strategy, relative to a FIT-only strategy, the additional false positives, and the corresponding changes in sensitivity, specificity and number needed to scope. We were able to calculate the accuracy statistics for both strategies since all participants in the COCOS trial underwent colonoscopy, regardless their FIT result or family history. In these analyses, colonoscopy was the reference standard and advanced neoplasia was the target condition.

With the combination of two factors for selection – FIT and family history – there will never be fewer participants selected for colonoscopy, compared to a FIT-only based selection, only more. As such, the sensitivity of combining FIT with family history will never be lower than that of FIT-only screening, and specificity will never be higher. This means that a simple test of a difference in sensitivity and specificity will be misleading. For this reason, we used the approach as formulated by Macaskill and colleagues to evaluate the differences.\textsuperscript{40} In summary, Macaskill relied on likelihood ratios to compare the performance of a combined testing strategy to that of one of its components: a single test. The combined strategy has superior performance compared to FIT-only, if the negative likelihood ratio of the combination is significantly smaller than the negative likelihood ratio of FIT-only and, simultaneously, the positive likelihood ratio of the combination is significantly larger than the positive likelihood ratio of FIT-only. In that case, the increase in true positives far outweighs the increase in false positives.

We would reject the combined approach if the corresponding negative likelihood ratio was larger than the negative likelihood ratio of the FIT-only selection and the positive likelihood ratio smaller than that of FIT-only. If neither of these situations holds true, the decision to use the combination depends on the trade-off of the expected additional false positives against
the incremental number of true positives. Selecting this trade-off can be guided by considering the benefits, harms and costs of extra colonoscopies, as well as logistic considerations.

Results of the above comparison of likelihood ratios are shown both statistically and graphically. In the graphical approach regions are identified, based on likelihood ratios, where a clear choice can be made between the single and the combined strategy or where trade-off occurs.

All statistical analyses were performed using SPSS statistics version 20.

RESULTS

Study group

Of the 6600 invited, 1426 (22%) agreed to undergo colonoscopy. Family history data were available for 1236 (87%); 1112 (90%) of these also completed a FIT (Figure 1). Their data were

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**Figure 1.** Study flow. For the FIT-only strategy, a positive test was defined as a positive FIT result (results shown for a cut-off value of 10 µg Hb/g faeces). For the combined strategy, a positive test-result was defined as a positive FIT or a CRC family history.
included in the analyses. The mean age of these 1112 participants was 60.6 (s.d. 6.2) years; 543 (49%) were female. Advanced neoplasia was detected in 101 (9.1%), including 7 (0.6%) with cancer and 94 (8.5%) with one or more advanced adenomas.

**Yield of FIT**

The performance of FIT has been reported previously. At a cut-off value of 10 µg Hb/g faeces, 102 (9.2%) in 1112 participants had a positive FIT; 36 (3.2%; 95% CI: 2.4-4.5%) of these had advanced neoplasia at colonoscopy. In 1010 persons with a negative FIT, advanced neoplasia would have been missed in 65 (5.8%; 95% CI: 4.6-7.4%), including one with CRC. This results in a sensitivity in detecting advanced neoplasia of 36% (95% CI: 26-46%) at a specificity of 93% (95% CI: 92-95%). Results for other cut-off values can be found in Tables 1 and 2. At cut-off values of 15 and 20 µg Hb/g faeces, the missed advanced lesions included two CRCs for each cut-off value.

**Yield of CRC family history**

A family history of CRC was found in 185 participants (17%); the median number of affected first-degree relatives in these was 1 (range 1-3). In this subgroup, 27 had advanced neoplasia at colonoscopy (15%; 95% CI: 10-20%; including two with CRC), vs 74 in the 927 participants without a family history of CRC (8.0%; 95% CI: 6.4-9.9%). This results in a sensitivity of family history in detecting advanced neoplasia of 27% (95% CI: 18-36%) at a specificity of 84% (95% CI: 82-87%).

**Table 1. Advanced neoplasia among persons with a negative FIT result, stratified for FIT cut-off value and CRC family history**

<table>
<thead>
<tr>
<th>FIT-negative results per FIT cut-off (µg Hb/g faeces)</th>
<th>Family history of CRC</th>
<th>Total</th>
<th>Advanced neoplasia</th>
<th>No advanced neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>+</td>
<td>165 (16%)</td>
<td>17 (10%)</td>
<td>148 (90%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>845 (84%)</td>
<td>48 (6%)</td>
<td>797 (94%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1010</td>
<td>65</td>
<td>945</td>
</tr>
<tr>
<td>15</td>
<td>+</td>
<td>169 (16%)</td>
<td>19 (11%)</td>
<td>150 (89%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>869 (84%)</td>
<td>52 (6%)</td>
<td>817 (94%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1038</td>
<td>71</td>
<td>967</td>
</tr>
<tr>
<td>20</td>
<td>+</td>
<td>171 (16%)</td>
<td>19 (11%)</td>
<td>152 (89%)</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>883 (84%)</td>
<td>54 (6%)</td>
<td>829 (94%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1054</td>
<td>73</td>
<td>981</td>
</tr>
</tbody>
</table>

FIT, faecal immunochemical testing; CRC, colorectal cancer
Table 2. Performance in detecting advanced neoplasia of FIT-only vs FIT combined with CRC family history, N=1112 participants

<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>FIT-only</th>
<th>FIT &amp; family history of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Positives</td>
<td>102 (9.2%)</td>
<td>74 (6.7%)</td>
</tr>
<tr>
<td>False positives</td>
<td>66 (5.9%)</td>
<td>44 (4.0%)</td>
</tr>
<tr>
<td>Missed AN cases</td>
<td>65 (5.8%)</td>
<td>71 (6.4%)</td>
</tr>
<tr>
<td>Detected AN cases</td>
<td>36 (3.2%)</td>
<td>30 (2.7%)</td>
</tr>
<tr>
<td>Sensitivity FIT % (95% CI)</td>
<td>36 (26-46)</td>
<td>30 (21-40)</td>
</tr>
<tr>
<td>Specificity FIT % (95% CI)</td>
<td>93 (92-95)</td>
<td>96 (94-97)</td>
</tr>
<tr>
<td>PLR (95% CI: PLR FIT&amp;FH/FIT†)</td>
<td>5.46 (-)</td>
<td>6.82 (-)</td>
</tr>
<tr>
<td>NLR (95% CI: NLR FIT&amp;FH/FIT†)</td>
<td>0.69 (-)</td>
<td>0.73 (-)</td>
</tr>
<tr>
<td>Yield % (95% CI)</td>
<td>3.2 (2.4-4.5)</td>
<td>2.7 (1.9-3.8)</td>
</tr>
<tr>
<td>Number needed to scope to detect AN (95% CI)</td>
<td>2.8 (2.2-3.7)</td>
<td>2.5 (1.9-3.3)</td>
</tr>
</tbody>
</table>

AN, advanced neoplasia; PLR, positive likelihood ratio; NLR, negative likelihood ratio; CRC, colorectal cancer; FIT, faecal immunochemical testing; FH, family history.
* Including one of the two missed CRCs in the FIT-only strategy.
† 95% confidence interval of the positive likelihood ratio or negative likelihood ratio of the ratio of the combined strategy and FIT-only.
Yield of the combined strategy

The incremental yield of relying on family history for selecting additional screening participants to colonoscopy will be generated by those with a false-negative FIT result (Figure 1). Table 1 shows endoscopic findings among participants with a negative FIT result, stratified for FIT cut-off value and CRC family history. Among the 1010 FIT negatives (at a cut-off value of 10 µg Hb/g faeces), 165 (16%) had a CRC family history, of whom 17 (10%) had advanced neoplasia.

In addition, inviting the 165 FIT negatives with a CRC family history for colonoscopy would increase the number of detected cases of advanced neoplasia from 36 (3.2%; 95% CI: 2.4-4.5%) to 53 (4.8%; 95% CI: 3.7-6.2%) in the 1112 participants, at the expense of 148 additional negative colonoscopies. The corresponding number needed to scope to detect one case with advanced neoplasia would increase from 2.8 (95% CI: 2.2-3.7) participants for FIT-only to 5.0 (95% CI: 4.0-6.4) for the combined strategy. Results for other FIT cut-off values can be found in Tables 1 and 2.

At a FIT cut-off value of 10 µg Hb/g faeces, sensitivity in detecting advanced neoplasia increased to 52% (95% CI: 42-63%) for the combined strategy, while specificity decreased to 79% (95% CI: 76-81%). Similar changes in performance for other FIT cut-off values were observed (Table 2).

Figure 2 shows the incremental changes in performance when adding family history of CRC to FIT in ROC space. The changes in positive likelihood ratio were statistically significant, whereas the changes in negative likelihood ratio were not (Table 2), so the combination is not unconditionally superior. The decision to use the combined strategy depends on the number of additional false positives one is prepared to accept relative to the number of additional true positives. Using the Macaskill approach, the threshold is estimated at 8.8, based on a prevalence of advanced neoplasia of 9%, as observed in this study. This means that the combination is preferred if one accepts at least 8.8 additional false positives for each additional true positive, at a FIT cut-off value of 10 µg Hb/g faeces. For a FIT cut-off value of 15 µg Hb/g faeces, this ratio would be 8.0, and 8.1 at 20 µg Hb/g faeces.

Sensitivity analysis

When restricting the definition of a family history of CRC to only those individuals with a first-degree relative with CRC at an age younger than 60 years or at least two first-degree relatives with CRC regardless their age, the yield would change from 36 (3.2%; 95% CI: 2.4-4.5%) to 42 (3.8%; 95% CI: 2.8-5.1%) detected cases of advanced neoplasia at a FIT cut-off value of 10 µg Hb/g faeces. This would be at the expense of 49 additional negative colonoscopies. The corresponding number needed to scope to detect one case with advanced neoplasia would increase from 2.8 (95% CI: 2.2-3.7) to 3.7 (95% CI: 2.9-4.9) participants. Sensitivity in detecting advanced neoplasia increased to 42% (95% CI: 32-52%), while specificity decreased
Figure 2. Critical regions for likelihood ratios in ROC space for different cut-off values of FIT. The slope of the line from (0; 0) that passes through the point representing the accuracy of FIT gives the positive likelihood ratio (PLR) for FIT. The slope of the line from (1; 1) that passes through the same point gives the negative likelihood ratio (NLR) for FIT. The shaded area represents the area for possible values of the sensitivity and specificity of the combined strategy (FIT and CRC family history, FH). The two lines divide the shaded area into three regions. The combined strategy is preferred if found in region (a) (far more additional true positives than false positives). FIT-only is preferred if the combined strategy is found in region (c) (far more additional false positives than true positives). In region (b) a trade-off has to be made, depending on the relative value of additional true positives vs. the value of false positives.

to 89% (95% CI: 86-90%). Compared to the nonrestricted definition of CRC family history, the combination is preferred if one accepts at least 8.2 (instead of 8.8) additional false positives for each additional true positive.
**DISCUSSION**

Using FIT as a triage test in a colorectal screening programme does not detect all persons with advanced neoplasia. Our analyses show that relying on a combination of CRC family history and FIT in selecting participants in CRC screening for colonoscopy increases sensitivity of the screening programme, at the expense of specificity. At a 10 µg Hb/g faeces FIT-positivity threshold, the yield of advanced neoplasia per 1112 participants would increase from 3.2% to 4.8%, whereas the number needed to scope to detect one subject with advanced neoplasia would increase from 2.8 to 5.0. The combined strategy would be preferred if one accepts 8.8 more false positives for every additional participant in whom advanced neoplasia can be detected.

In the COCOS trial, all screening participants underwent colonoscopy, regardless their FIT result or family history, which allowed us to calculate estimates of the yield of FIT-only and FIT combined with CRC family history. The COCOS invitees were a random sample from an average risk population in the Netherlands, although participation in this colonoscopy screening trial was substantially lower than with FIT-based screening. Moreover, the number of detected advanced neoplastic lesions was relatively small, resulting in a wide range in confidence intervals for sensitivity analyses.

A number of other potential limitations of our study deserve discussion. Our analysis was a post hoc evaluation of collected data; we do not know if the adherence to the invitation to undergo colonoscopy would be affected by the basis for that invitation; adherence could differ for referrals based on the FIT test vs. those based on family history, or the number of family members affected, and their age.

We only included those who performed both FIT and a questionnaire in order to demonstrate how family history could increase the detection of advanced neoplasia among those with a false-negative FIT. In a future prospective study, participants should be recommended to perform both tests, but if only one test is performed, and either FIT or family history is positive, the corresponding participants would still be invited for a colonoscopy.

We acknowledge that our definition of a CRC family history is relatively broad, and that we did not consider the number and age of CRC affected relatives. We selected this definition for reasons of feasibility in a screening setting, based on the previously reported finding that the risk of having advanced neoplasia is higher when one has one or more first-degree relatives with CRC, regardless their age. An alternative approach for collecting family data would be to restrict the definition of a CRC family history, as we did in our sensitivity analysis.

At present, many persons at increased risk of familial CRC syndromes, such as Lynch syndrome, are still unidentified and might participate in population-based screening programmes.
may be beneficial to specify the definition of a family history of CRC such that these invitees could meet the Amsterdam, Bethesda or familial CRC criteria, thereby also taking into account Lynch syndrome associated extra-colonic tumours. As such, all persons detected by the questionnaire would qualify for a colonoscopy surveillance programme, instead of a population screening programme. A more detailed questionnaire was recently validated by our research group. This questionnaire also asks for the number of nonaffected relatives, as this influences the odds of having a CRC family history. Yet, we do not know whether collecting more detailed data would affect participation in FIT-based screening programmes.

We observed that offering colonoscopy to those with a positive FIT as well as those with a family history of CRC, would identify more persons with advanced neoplasia compared to a FIT-only strategy. Two Asian studies have confirmed the possibility of detecting advanced neoplasia among FIT negatives with a family history of CRC. A retrospective analysis in a small Korean study, reported by Cha et al., reported an odds ratio of 7.33 for detecting advanced neoplasia in FIT negatives with a first-degree relative with CRC. Another study reported that 3.6% of 513 FIT negatives with a first-degree relative with CRC had advanced neoplasia, compared to 3.3% of 3534 participants without a CRC family history. These numbers are lower than ours, which could be a result of the low prevalence of advanced neoplasia in their study population and the low number of participants with a family history of CRC (12.6%). Although the prevalence of a family history of CRC was relatively high in our population, this is in line with previous Western studies.

Several previous studies have evaluated the effect of combining FIT with other CRC risk factors in building risk models, but studies evaluating the effect of combining FIT with family history are scarce. Such a combined approach seems easier and more feasible than working with a multivariable risk model. It could be a first step in improving FIT-based screening programmes, which are used across the world, by simply adding one test: if either one is positive, participants qualify for colonoscopy. Long-term effects of such an approach were recently shown by Goede et al. They estimated, using microsimulation modelling, that 9-14% more CRC related deaths would be prevented over a 30 year period when using a comparable combined approach in consecutive screening rounds. These authors also took participation rates and several FIT cut-off values into account and estimated that 33-55% additional colonoscopies would have to be performed.

As we evaluated the incremental yield of a once-only FIT and family history collection, we cannot analyse the effects of this strategy in repeated screening rounds. Offering both FIT and a family history questionnaire in repeated screening round could be beneficial, as family history can change over time, thereby possibly creating new indications for colonoscopy. A biannual collection of family history information, as is usual for FIT screening, may be too frequent for
this purpose. In any case, those persons identified with a family history of CRC could be offered surveillance colonoscopies instead of participating in the combined screening strategy.

Other ways exist for increasing detection in FIT-based CRC screening programmes. Lowering the cut-off value of FIT or combining two FITs will also lead to increased sensitivity, at the expense of a decrease in specificity.16, 17, 51 Although changes in test performance seem to be less dramatic in those approaches, they will not lead to a detection of persons with familial CRC syndromes.

Our analyses, based on previously collected data, show the potential of combining FIT with family history in CRC screening programmes. Future prospective studies could evaluate actual participation rates, performance, effectiveness and cost-effectiveness of combined approaches, possibly and preferably in consecutive screening rounds. In all cases, it is likely that the implementation of such combined approaches will be guided by the incremental costs and the harms-benefit balance of inviting more screening participants for colonoscopy, a decision that should be informed both by societal, clinical and personal considerations.

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