CHAPTER 8

Colorectal cancer surveillance in high-risk asymptomatic patients: can surveillance intervals be increased after a negative faecal immunochemical test?


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Abstract

Introduction: The purpose of surveillance programs is to detect adenomas before malignant transformation. Given the increasing burden on colonoscopy capacity, it has been suggested that faecal immunochemical test (FIT) results could guide surveillance colonoscopy intervals.

Aim: The aim was to verify whether surveillance of asymptomatic high-risk individuals can be based on FIT sampling, with colonoscopy referral only in case of a positive FIT result. Therefore, we studied the miss rate of advanced neoplasia by using FIT prior to colonoscopy.

Methods: Prospective cohort study of ambulatory asymptomatic high-risk patients (personal history of adenomas/CRC or family history of CRC), who sampled a FIT (OC sensor) before elective colonoscopy. Test characteristics of FIT for detection of CRC and advanced adenomas were determined (cut-off level 50ng/ml).

Results: In total, 1,041 subjects were included and sampled a FIT (516 personal history of adenomas, 172 personal history of CRC and 353 family history of CRC). Five CRCs (0.5%) and 101 advanced adenomas (9.7%) were detected by colonoscopy. Single FIT sampling resulted in a sensitivity, specificity, PPV and NPV for CRC of 80%, 89%, 3% and 99.9%, respectively, and for advanced adenoma of 28%, 91%, 24% and 92%, respectively. Simulation of multiple screening rounds indicated that sensitivity of FIT for advanced adenoma may be as high as 81% after 5 screening rounds.

Conclusions: In once-only FIT sampling before colonoscopy, 70% of advanced neoplasia were missed. A simulation approach indicates that multiple screening rounds may be more promising in detecting advanced neoplasia and could potentially alleviate endoscopic burden.

Introduction

Colorectal cancer (CRC) is a major health problem with over 500,000 deaths per year worldwide (1,2). The use of colonoscopy to evaluate patients for the presence of CRC has increased substantially in the past decade (3-5). This concerns both high-risk asymptomatic individuals and patients with signs or symptoms suggestive of CRC. At present, 22% of colonoscopies in the United States are performed for a family history of CRC and another 22% for surveillance after polypectomy or resection of CRC (6). These patients are considered to be at higher risk for the presence of colorectal neoplasia. In The Netherlands, these percentages are somewhat lower but still 33% of colonoscopies are performed for a personal history of adenomas or CRC or a family history of CRC (7). With the intended introduction of a CRC screening program in the near future, not only the number of screening colonoscopies, but also the number of surveillance colonoscopies because of a personal history of colorectal neoplasia will increase (8). Since the burden on endoscopic capacity is already high in some countries, it has been proposed to use faecal immunochemical tests (FITs) to postpone elective colonoscopy in asymptomatic high-risk subjects (9,10). Previous studies on guaiac-based fecal occult blood tests (g-FOBTs) have shown that the clinical use of this strategy was hampered by its relatively low sensitivity for advanced adenomas (11). For that reason, high-risk subjects are recommended not to rely on g-FOBT screening, but to undergo colonoscopic evaluation at predetermined intervals (12-14). FIT, however, has been proven to be superior to g-FOBTs in detecting advanced adenomas and CRC (15-22). The higher sensitivity of FIT for advanced adenomas is particularly relevant since the goal of a surveillance program is to detect advanced adenomas before malignant transformation and in this way prevent CRC related death. A recent study in asymptomatic high-risk patients, showed sensitivities of 100% and 65% for the detection of CRC and all advanced neoplasia, respectively (9). These results need confirmation in a different set of patients, preferably with a larger sample size and higher yield of advanced neoplasia, before contemplating on its use in surveillance programs. We calculated the miss rate of CRC and advanced adenomas of single and double FIT sampling performed before elective colonoscopy in order to evaluate whether FIT may be used to triage asymptomatic high-risk individuals for immediate colonoscopy referral versus repeated FIT testing and postponed colonoscopy surveillance.

Material and Methods

Study population and study design
Details of the study design and of most materials and methods relevant for this study have been published previously in a report on the direct comparison of FIT and g-FOBT (18). All ambulatory subjects (>18 years) scheduled for elective colonoscopy from June 2006 to
Patients scheduled for elective colonoscopy in 5 participating hospitals who performed the FIT (n = 3,721)

Exclusion:
- Symptomatic patients or patients at average risk (n = 2,419)
- Surveillance in longstanding IBD (n = 113)
- Surveillance for hereditary syndromes (n = 54)
- FIT inadequately sampled (n = 3)

Asymptomatic high risk patients undergoing colonoscopy (n = 1,132)

Exclusion:
- Incomplete colonoscopy (n = 47)
- Insufficient bowel lavage (n = 5)

Patients with a total colonoscopy and sufficient bowel cleansing (n = 1,080)

Exclusion:
- No histopathological diagnosis (n = 39)

Patients included for final analysis (n = 1,041)

Figure 1: Study flow diagram

October 2009 at one of the five participating hospitals, were invited to participate in our initial study (18). Invitation to participate in the initial study was irrespective of their indication for colonoscopy (i.e. screening, surveillance, or presence of symptoms). For the purpose of the present study, only asymptomatic patients with a personal history of adenomas/CRC or asymptomatic individuals with a family history of CRC were included. In addition to the original study protocol in which subjects were asked to sample one FIT, we extended the protocol by asking for a second FIT sample before colonoscopy in the final 15 months of inclusion (June 2008 to October 2009).

Once patients 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 with an additional explanatory letter. In all centres, local Medical Ethics Review Board approval was obtained prior to the start of the study.

All eligible individuals were asked to sample one or two FITs on stool from one or two bowel movements, respectively, prior to colonoscopy. Exclusion criteria were: symptomatic patients or patients at average risk, surveillance in inflammatory bowel disease (IBD), surveillance for hereditary syndromes, age below 18 years, inadequate FIT sampling, absence of informed consent or patients in which no histopathological diagnosis was obtained. In addition, patients with incomplete colonoscopies and patients with inadequate bowel cleansing, as judged by the endoscopist, were excluded (see Figure 1).

All medical files were assessed to evaluate the time interval since prior colonoscopy, previous presence of advanced neoplasia, cumulative number, size and histology of polyps detected at previous colonoscopies, and a two-generation family history of CRC. Family history of CRC was stratified into two groups, using accepted criteria (23). A significant family history of CRC was defined as one first-degree relative with CRC diagnosis under the age of 60 years or with more than one first-degree relative with CRC of any age (group 1). A non-significant family history was defined as one first-degree relative older than 60 years with a CRC diagnosis or second-degree relatives with a CRC diagnosis (group 2).

**Faecal Immunochemical Test**

The FIT used in the present study is the automated OC-sensor test (Eiken Chemical Co., Tokyo, Japan), which has a quantitative outcome. The baseline FIT was sampled on a bowel movement one day before colonoscopy (t = -1), whereas the additional FIT for double sampling was performed on stool obtained two days prior to colonoscopy (t = -2; see figure 2).

Both FITs were sampled before bowel preparation had started. Patients who sampled the FIT after starting bowel preparation were excluded. 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 (24). Participants were asked to discontinue anticoagulants and NSAIDs 5 days prior to
Figure 2: Flowchart of invitation and FIT sampling

Patients for elective colonoscopy
Participating Centers (n=5)

Invitation by telephone

Tests sent by mail

FIT

Bowel Lavage

Colonoscopy

\( t = 0 \)

\( t = -1 \) or

\( t = -1 \) and -2 day

FIT = faecal immunochemical test

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 analyzer (Eiken Chemical Co., Tokyo, Japan) according to the manufacturers instructions (25). For single FIT sampling a cut-off level of 50 ng/ml was used. For double FIT sampling, we considered the FIT positive when the cut-off level exceeded 50 ng/ml in at least one out of two samples. In general, 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. In case tests could not be analyzed within one week, the tests were deep frozen at minus 20 degrees Celsius.

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 CRC. The results of histopathological analysis of tissue samples obtained during colonoscopy were the standard of reference for the diagnosis of adenoma or cancer. Adenomas ≥1.0 cm, with any villous features (i.e. tubulovillous or villous adenoma) or high-grade dysplasia, were considered advanced adenomas (26,27). Advanced neoplasia included all cases of CRC and all advanced adenomas. If multiple lesions were present, classification was based on the most advanced lesion found.

Statistical analysis

Taking colonoscopy as the reference test, sensitivity specificity, positive and negative predictive value (PPV and NPV) of FIT were calculated for the following colonoscopy outcomes: 1) the presence of CRC; 2) the presence of advanced adenoma; and 3) the presence of advanced neoplasia. Sensitivity is calculated as the proportion of positive test results in patients with the colonoscopy outcome under consideration. 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 2 or 3. For dichotomizing the FIT results, a cut-off level of 50 ng/ml was used, which is considered the most sensitive cut-off level for the OC-sensor. The 95% confidence intervals (CI) were calculated using the exact method (www.measuringusability.com/wald.htm). To study confounding in the relationship between presence of advanced neoplasia and FIT result, a logistic regression analysis was carried out and, where necessary, corrected for confounding factors. Age, gender, procedure indication, adequacy of bowel cleansing, time interval to prior colonoscopy, previous presence of advanced neoplasia, cumulative number of > 3 adenomas detected at prior colonoscopies and a significant family history of CRC were considered as potential clinical confounders.

The Chi-square test was used for the comparison of proportions. A two sided P-value of < 0.05 was considered statistically significant. All analyses were performed with SPSS for Windows Version 15 (SPSS Inc., Chicago, Illinois).

Results

Characteristics of the study population

Overall, 1,041 asymptomatic high-risk subjects who underwent surveillance colonoscopy sampled one FIT. In addition, a subgroup of 43% of these patients sampled two FITs (n = 451). The mean age of all patients was 60.7 years (range 27-87 years) and 50.1% of these were male. Colonoscopy was performed because of a personal history of adenomas in 516 patients (49.6%). In 172 patients (16.5%) and 353 patients (33.9%), colonoscopy was performed because of a personal history of CRC and a family history of CRC, respectively.

In 249/1041 patients (23.9%) a significant family history of CRC was observed. The date and findings of the last colonoscopy prior to FIT sampling were known for 872/1041 patients (84%). In 305 patients the previous colonoscopy was within two years of the current colonoscopy and FIT. A total of 386 patients had a colonoscopy more than two years prior to their current colonoscopy and FIT. In 181 patients, all with a family history of CRC, the current colonoscopy was their first colonoscopy.
Colonscopy results

CRC was found in five patients (0.5%). Of these, three were found in patients with a personal history of CRC, one in a patient with a family history of CRC and one in a patient with a personal history of adenomas. Early stage CRC (AJCC stage I/II) was found in 3/5 patients (60%). In 3/5 patients diagnosed with CRC, only limited data on findings and interval of prior colonoscopy could be retrieved. Two patients with recurrent CRC had a previous colonoscopy two years before. In one case, the first CRC diagnosis was obtained from that particular colonoscopy and in the other case only two small adenomas were found during previous colonoscopy. In 101 patients (9.7%) at least one advanced adenoma was found. Of these, 19 (19%) were found in patients with a personal history of CRC, 23 (23%) in patients with a family history of CRC and 59 (58%) in patients with a personal history of adenomas. Of all advanced adenomas, 42% had ≥3 adenomas diagnosed on previous colonoscopies, 67% (n = 68) were sized >10 mm, 28% (n = 28) had villous histology and 5% (n = 5) had high grade dysplasia. Advanced neoplasia (CRC and advanced adenoma together) were found in 106 patients (10.2%). The yield of advanced neoplasia per indication group is shown in Table I. The yield of advanced neoplasia was significantly higher in patients with a personal history of CRC than in patients with a family history of CRC (12.8%; n = 22/172 versus 6.8%; n = 24/353; p = 0.02). The same result was found when comparing the yield in patients with a personal history of adenomas to patients with a family history of CRC (11.6%; n = 60/516 versus 6.8%; n = 24/353; p = 0.02). The yield of advanced neoplasia was not significantly different between patients with a personal history of CRC and patients with a personal history of adenomas (p = 0.68). The quality of bowel preparation was rated “good” in 77% (n = 805) of colonoscopies and was rated “fair” in 23% (n = 236) of colonoscopies. No procedure related complications were observed.

FIT results

The overall FIT positivity rate in single FIT sampling was 11% (115/1041 patients). The positivity rate for the subgroup of patients that sampled two FITs was 19% (87/451 patients). Single FIT sampling resulted in a sensitivity, specificity, PPV and NPV for CRC of 80%, 89%, 3% and 99.9%, respectively. Sensitivity, specificity, PPV and NPV of FIT for advanced adenomas was 28%, 91%, 24% and 92%, respectively. Table II summarizes the test characteristics of single and double FIT sampling for the presence of CRC and advanced adenomas. The overall sensitivity for CRC and advanced neoplasia in the total population was 80% and 30% respectively, missing 1 out of 5 cancers and 74 out of 106 advanced neoplasia. Double FIT sampling resulted in a sensitivity of 33% for advanced neoplasia, missing 28 out of 42 advanced neoplasia.

The positivity rates and test characteristics of single FIT sampling for the presence of all advanced neoplasia in the three indication groups separately are shown in Table III. The positivity rate was significantly higher both in patients with a personal history of CRC and patients with a personal history of adenomas compared to patients with a family history of CRC (12%; n = 21/172 and 14%; n = 70/516 versus 6.8%; n = 24/353; p = 0.04 and p = 0.002). Regarding all test characteristics, only specificity for CRC and specificity for advanced adenoma differed significantly between the patients with a personal history of colorectal neoplasia and patients with a family history of CRC (specificity for CRC is 87.1%; n = 596/684 versus 93.5%; n = 59/684).
n = 329/352; p = 0.002; specificity for advanced adenoma is 89.4%; n = 542/606 versus 94.2%; n = 310/329; p = 0.014). No significant differences in specificity for CRC or advanced adenomas were found when separating personal history of neoplasia in personal history of CRC and personal history of adenomas. No significant differences in sensitivity, PPV and NPV for either CRC or advanced adenoma were found between these three groups. Sensitivity of FIT for detecting all advanced neoplasia was not significantly higher in patients with a significant family history for CRC compared to patients with a non-significant family history of CRC (33.3%; n = 5/15 versus 29.7%; n = 27/91; p = 0.78).

Logistic regression analysis

A positive FIT result was highly predictive for the presence of advanced neoplasia in the total group of patients (odds ratio (OR) 4.44; 95% confidence interval (CI) 2.77 - 7.12; p<0.0001). Selecting only those patients who had had at least one previous colonoscopy in combination with a cumulative number of > 3 adenomas detected at prior colonoscopies led to a somewhat lower OR of 3.79 (95% CI 2.19 - 6.57; p<0.0001). Correction for the selection of possible confounders in a logistic regression model had only a minor effect on this OR (OR=3.56, 95% CI 2.01 to 6.33; p<0.0001). More specifically, age, procedure indication, time interval to prior colonoscopy, cumulative number of > 3 adenomas detected at prior colonoscopies, and a significant family history of CRC were all variables that were independently associated with the presence of advanced neoplasia in univariate regression analysis. In a multivariate logistic regression model, using backward selection, only procedure indication (personal history of colorectal neoplasia), a short time interval to prior colonoscopy and cumulative number of > 3 adenomas detected at prior colonoscopies, were significant independent predictors.

Discussion

In the present study, test performance of one of the most commonly used faecal immunochemical tests was evaluated in a large cohort of asymptomatic, high-risk individuals undergoing colonoscopy surveillance. It was found that 20% of CRCs and 72% of advanced adenomas were missed when using a single FIT sampling strategy at the lowest cut-off level. Moreover, sampling a second FIT preceding colonoscopy did not result in a significant increase in sensitivity since still only 33% of all advanced neoplasia was detected. When the indication groups were separated into patients with a personal history of CRC, a personal history of adenomas and patients with a family history of CRC, a higher FIT positivity rate and a higher yield of advanced neoplasia was observed in the first two groups. Sensitivity, however, did not significantly differ between these three indication groups, showing that a once-only FIT sampling strategy is inaccurate in detecting advanced neoplasia in either group of high-risk, asymptomatic individuals.

Limited data are available on the performance of FITs in asymptomatic high-risk patients. Three studies have assessed the efficacy of a first generation, qualitative FIT (OC light and Hemeselect) in volunteer first-degree relatives of patients with CRC, where sensitivities ranged from 50-83% for detection of advanced neoplasia (10,28,29). In these studies, sample sizes were small and numbers of target lesions were very limited, which hampers the generalization of these results. In patients with a personal history of CRC, one study showed a 100% sensitivity for detecting 9 recurrent CRCs (30). These results were obtained from stools sampled with digital examination and therefore not representative for at home FIT sampling. Moreover, test characteristics for advanced adenomas were not available. Another study, using a qualitative FIT in a larger population, showed sensitivities of 70% and 44% for detecting CRC and advanced adenoma, respectively (31). However, incorrect criteria for the definition of advanced adenoma were used in this study. In general, test characteristics from qualitative FITs should be interpreted with caution since the test performance can vary greatly between the different qualitative FITs, indicating that quality assurance is an issue (32). The most promising results were shown in a recent study, sampling three FITs preceding colonoscopy in asymptomatic high-risk patients (9). Sensitivities of 100% and 65% for the detection of CRC and all advanced neoplasia, respectively, were found using the same type of FIT as was used in the present study at the

| Table 3: Positivity rates and test characteristics for advanced neoplasia of single FIT sampling in three different indication groups in 1041 asymptomatic, high risk subjects referred for colonoscopy. |
|--------------------------|-------------------------------|-------------------|------------------|-----------------|-----------------|
|                          | Personal history of adenomas (n = 516) | Personal history of CRCs (n = 172) | Family history of CRCs (n = 353) | Total (n = 1041) |
| Positivity rate N        | 14% 70/516                      | 12% 21/172        | 7% 24/353        | 11% 115/1041    |
| Sensitivity              | 32% 19/60 (20-45)               | 36% 8/22 (17-59)  | 21% 5/24 (7-42)  | 30% 32/106 (22-40) |
| Specificity              | 89% 405/456 (86-92)             | 91% 137/150 (86-95) | 94% 310/329 (91-96) | 91% 852/935 (89-93) |
| PPV*                    | 27% 19/70 (17-39)               | 38% 8/21 (18-62)  | 21% 5/24 (7-42)  | 28% 32/115 (20-37) |
| NPV†                    | 91% 405/446 (88-93)             | 94% 137/151 (85-95) | 94% 310/329 (91-96) | 92% 852/926 (90-94) |

† Advanced neoplasia is defined as either one or more advanced adenoma(s) or a CRC
*PPV: positive predictive value
† NPV: negative predictive value
§ CRC: colorectal cancer
same cut-off level (9). Unfortunately, we were not able to confirm these promising findings in our study with a comparable sample size and a larger number of target lesions. Multiplicity of testing (three versus two FIT samples) and different prevalences of advanced adenomas (higher in the present study) may partly explain the differences between the two studies in FIT performance.

Periodically performing non-invasive FIT sampling in the surveillance of high-risk individuals in order to triage individuals for invasive colonoscopy sounds appealing, as this could lead to a better utilization of colonoscopy as both a diagnostic and therapeutic procedure. However, when considering such an alternative surveillance scheme, a high sensitivity of FIT is important. Specificity is less of a concern, because at present colonoscopy is performed in all these patients. Even at the lowest and most sensitive cut-off level of 50 ng/ml in single and double FIT sampling, the majority of advanced neoplasia was missed in the present study. On the one hand it is debatable whether missing advanced adenomas is clinically relevant, since they could be detected in subsequent surveillance rounds (either with FIT or colonoscopy) while still being in a curable stage. On the other hand, a delay in detecting CRC can result in progression into advanced stage disease. Yet, the risk of progression from adenoma to carcinoma in the majority of patients with a family history of CRC and in the majority of patients with a personal history of adenomas may be limited and comparable to the risk in the general population (12,33,34). Particularly in patients with only a few small tubular adenomas in the past or a non-significant family history of CRC, a window of opportunity exists and multiple rounds of FIT sampling may be a good alternative to colonoscopic surveillance. The present study was not designed to provide information on interval FIT testing in a surveillance program. Recent data from Australia showed that multiple rounds of FIT sampling within an existing surveillance program aided the detection of advanced neoplasia (35). In that particular study, it was clearly demonstrated that repeated testing results in a compounding of sensitivity. It was also shown that in those patients who returned a negative FIT in multiple rounds of testing, the chance of finding advanced neoplasia was significantly reduced (35). When we model cumulative detection in the same manner (assuming unbiased detection each time testing is done), it can be calculated that a once-only FIT sensitivity of 80% for CRC compounds to 99.2% with 3 rounds of testing (1-1-sensitivity)^3 (9,35). Similarly for advanced adenoma detection, modelling a 28% once-only sensitivity compounds over 3 rounds of testing to 63%, and over 5 rounds of testing to 81%, which may be acceptable for the detection of an advanced adenoma. Although these computed sensitivities should be interpreted with caution, it allows us to explore the effect of multiple rounds of testing. Such a strategy of repeated FIT sampling in selected individuals may hold potential to postpone invasive colonoscopy and create more colonoscopic capacity. The effects of earlier diagnosis, particularly of advanced adenomas, on survival remain elusive and might only be clarified in a long-term prospective randomized trial. Since the yield of CRC is generally low in surveillance programs, it is questionable if such a study is feasible.

There are some concerns that need to be addressed for proper interpretation of our results. Firstly, the majority of all patients was asked to discontinue their NSAIDs and anticoagulants before colonoscopy. Recent reports have indicated that sensitivity is higher without substantial loss of specificity while continuing these drugs in a screening population (36,37). This warrants further investigation in a high risk surveillance population and may have led to an underestimation of sensitivity in the present study. Secondly, the number of target lesions is relatively low. Although this study has a large sample size and the percentage of target lesions is higher than in most other studies, the absolute number of cancers is low (9,10,28-31). Potential explanations for the low number of CRCs may be overconsumption of colonoscopy surveillance for lower risk patients and inappropriate colonoscopy referral for patients with a non-significant family history of CRC. Elaborating on this latter suggestion, the present study showed a relatively low percentage of patients that actually met the criteria for a significant family history (24%). This is probably due to the increasing awareness for CRC and the low threshold for referring patients with any affected family member for colonoscopy. Definitions of significant family history of CRC vary substantially among different gastroenterology societies. Recent UK guidelines for CRC screening in familial CRC are more stringent than Israeli and Australian guidelines, making it difficult to compare the outcomes of FIT sampling in different populations (23,38,39).

In the present study, we first assessed the FIT characteristics in all patients with any affected family member, as it is known that there is an excess risk for advanced neoplasia in these people (relative risk 2.24) (40). Then, we compared the sensitivity of FIT for patients with a significant family of CRC to patients with a non-significant history of CRC. No significant difference was observed. In conclusion, the present study of high-risk individuals for colorectal neoplasia, shows that 67-70% of all advanced neoplasia are not detected by single or double FIT sampling before colonoscopy. Recent reports have indicated that sensitivity is higher without substantial loss of specificity. The effects of earlier diagnosis, particularly of advanced adenomas, on survival remain elusive and might only be clarified in a long-term prospective randomized trial. Since the yield of CRC is generally low in surveillance programs, it is questionable if such a study is feasible.
References


