Lower Risk of Advanced Neoplasia Among Patients With a Previous Negative Result From a Fecal Test for Colorectal Cancer

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See Alquist DA et al on page 272 in *CGH*; see editorial on page 422.

BACKGROUND & AIMS: Consecutive rounds of fecal occult blood tests (FOBTs) are used to screen for colorectal cancer (CRC); they detect precursor lesions and early-stage disease. We assessed whether the positivity rate and the positive predictive values (PPVs) for advanced neoplasia and CRC decrease with repeated testing by using fecal immunochemical tests (FITs). **METHODS:** Data were collected from 2 rounds of screening. In the first round, average-risk persons (50 to 74 years old) were randomly assigned to groups that received the guaiac FOBT or FIT. In the second round, the subjects received only FIT (1594 received FIT after guaiac FOBT and 2022 received FIT after FIT). The positivity rate and PPV for advanced neoplasia and CRC were compared between second-round participants with a previous negative test result (FIT after guaiac FOBT or FIT after FIT) and first-round participants (guaiac FOBT or FIT). **RESULTS:** The rate of positive results from FIT was 7.4% in the FIT-after-FIT group, compared with 8.1% in the first-round FIT group (P = .34). A significant decrease was observed in the PPV for advanced neoplasia between the first and second round from 55% (132/239) to 44% (112/252; P = .017). The PPV for CRC was 8% (20/239) in the first round versus 4% (9/252) in the second round (P = .024). Ten interval cancers were diagnosed. There were no significant differences in stages of cancers detected in the first and second round or the interval cancers. **CONCLUSIONS: The rate of positive results from FIT does not decrease after repeated CRC screening, but the PPVs of FIT for advanced neoplasia and for CRC are significantly lower among second-round participants who tested negative in the first round.**

Keywords: Diagnostic Yield; Average-Risk Population; Colon Cancer Screening; Efficacy.

Mass screening programs for colorectal cancer (CRC) are aimed at decreasing the mortality and morbidity of CRC. Several methods of screening for CRC are available, including fecal occult blood tests (FOBTs), flexible sigmoidoscopy, and colonoscopy. To date, only 2-step screening programs such as FOBT-based screening and sigmoidoscopy screening have a documented effectiveness in reducing disease-specific mortality.[1–4]

The efficiency of any 2-step screening program depends on the ability of the initial screening test to detect target lesions. A good initial screening test should have a small number of false-positive test results and, even more importantly, a small number of false-negative test results in patients with CRC. Both the guaiac FOBT and the fecal immunochemical test (FIT) have a high sensitivity for CRC but are less well able to detect advanced adenomas.[2,3,5–9]

Most data on the performance of FOBT-based screening programs stem from randomized controlled trials that used the guaiac test only.[2–4] Two studies in an asymptomatic population in which all participants underwent colonoscopy reported a sensitivity of the guaiac test for cancer of 13% and 25%. This is in line with the results of a study of Graser et al, who found a sensitivity of 20% for the guaiac test.[10] Specificities for cancer were 95% and 80%.[11,12]

It has recently been shown that the FIT, which uses enzyme immunoassays detecting human hemoglobin, has better test characteristics and is associated with a higher participation rate.[13–16] The gain in sensitivity compared with the guaiac FOBT seems higher for advanced adenomas than for cancers.[17,18] The FIT has other advantages over the older guaiac FOBT, such as the absence of dietary restrictions and the quantitative nature of the test, with the ability to vary the positivity threshold. Little is known, however, about the performance of FIT in consecutive screening rounds.

The aim of the study reported here was to evaluate the performance of FIT in a second round of CRC screening. We recently completed 2 rounds of a Dutch FOBT-based screening pilot in asymptomatic persons aged 50 to 74 years. During the first round, invitees were randomized to receive either a guaiac FOBT or a FIT.[15] In the second round, only the FIT was used. We hypothesized that the positivity rate would be lower in the second round and

Abbreviations used in this paper: CRC, colorectal cancer; FIT, fecal immunochemical test; FOBT, fecal occult blood test; PPV, positive predictive value.

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that fewer cases of CRC and advanced neoplasia would be detected in second-round FIT-positive participants who had tested negative in the first round compared with first-round test-positive participants. We expected a more pronounced decrease for cancers than for advanced adenomas.

Subjects and Methods

Two consecutive screening rounds have been completed in a fecal test–based CRC pilot screening program in the Amsterdam region of The Netherlands. The first round was conducted in 2006. In this first round, 10,054 invitees were randomized to receive either a guaiac FOBT or a FIT. The second round used FIT only and was performed among 10,258 persons in 2008 (trial registration no. NTR1327). Ethical approval was provided by the Dutch Health Council (2005/03WBO, The Hague, The Netherlands). The study designs of the first and second rounds have been reported in detail elsewhere.[15,19] A summary is given in the following text.

Population and Design

Asymptomatic persons aged 50 to 74 years and living in the catchment area of the pilot program were eligible for invitation to the screening program. Symptomatic persons were advised not to participate in the program but to contact their general physician. The catchment area comprised 3 postal code areas within the surroundings of Amsterdam.

A file containing all eligible persons based on birth date and postal code was extracted by the municipalities from the population database. A random sample of this file was invited through an invitation letter by postal mail. Invitations were coordinated by the regional Comprehensive Cancer Center Amsterdam, an organization that is also responsible for the logistics of the nationwide breast and cervical cancer screening programs in The Netherlands.

Persons with a positive test result in the first round were excluded from participation in the second round. In case of adenomas, these test-positive persons were enrolled in a surveillance program according to the Dutch guidelines.[20] In case of CRC, they were referred to the departments of oncology and/or surgery of our hospital for treatment. Other individuals who no longer fulfilled eligibility criteria at the start of the second round did not receive an invitation for the second round. This concerned persons older than 74 years or persons who had moved out of the catchment area.

Invitation Procedure

An invitation kit with the stool test was sent by postal mail. The invitation letter was signed by the principal investigator. In addition to the invitation letter, the kit also contained a detailed information brochure, a test instruction leaflet, and a postage-free return envelope. Participants could perform the test at home and return it by postal mail. A signed informed consent form had to be enclosed in the return envelope. A reminder letter was sent to nonresponders at 6 weeks and at 3 months.

Stool Tests

Guaiac FOBT. The guaiac FOBT used in the first round was the Hemoccult II (Beckman Coulter Inc, Fullerton, CA). No dietary instructions were given. Persons were instructed to collect 2 samples of 3 consecutive bowel movements. Cards were developed and read by 2 trained laboratory technicians. Cards were not rehydrated. A test result was considered positive if one or more of the 6 samples showed a blue discoloration.

FIT. The FIT that was used in both rounds was the OC-Sensor by Eiken (Tokyo, Japan). After arrival at the laboratory, tests were stored at 4°C and processed in batches by using an automated clinical analyzer (OC-Sensor Micro; Eiken). A single test was used on one occasion, and a hemoglobin value of 50 ngHb/mL was used as the threshold for test positivity.

Colonoscopy

All participants with a positive test result received a mailed invitation for a consultation at the screening center. During this consultation, the positive test result was explained and, in the absence of contraindications, a colonoscopy was advised. Contraindications for colonoscopy were imaging of the colon within the past 2 years (colonoscopy or computed tomographic colonography), a life expectancy of less than 5 years, or severe comorbidity. The cost of colonoscopy was covered by the participants' health insurance company.

Colonoscopies were scheduled within 2 weeks after the consultation and were performed by experienced endoscopists. All persons were routinely offered conscious sedation using intravenous midazolam 0.5 mg and/or fentanyl 0.01 mg. Polyethylene glycol solution (2 L; MoviPrep(r), Salix Pharmaceuticals, Morrisville, NC) combined with bisacodyl 10 mg orally was used for bowel preparation. During the procedures, a research assistant was present to record key performance indicators. Size, location, and type of treatment were recorded for all lesions. Lesion size was estimated by using a 7-mm open biopsy forceps. Location was considered distal if the lesion was located distal from the splenic flexure. Indigo carmine staining and/or scopolamine 20 mg were used on endoscopists' request only. All lesions were preferably removed endoscopically during the first procedure and reviewed histopathologically.

Pathology

All biopsy specimens, polyps, and excision specimens were examined by one experienced pathologist. Histology, grade of dysplasia, and involvement of margins were reported for all lesions. An advanced adenoma was defined as any adenoma $\geq$10 mm or an adenoma with a villous component $>$20% or with high-grade dysplasia. Cancer was defined as CRC with invasion beyond the muscularis mucosa. Cancers were staged according to the 5th edition of the American Joint Committee on Cancer classification.[21] Formerly used categories such as carcinoma in situ and intramucosal carcinoma were classified as high-grade dysplasia. Sessile serrated and traditional serrated lesions were classified as adenomas. Nonneoplastic lesions included hyperplastic polyps and inflammatory polyps.

Data Analysis

In this analysis, we evaluated the accuracy of FIT in second-round participants who had also participated in the first round. This means that only data from second-round participants with a negative test result in the first round were included. The accuracy results in this group were compared with the accuracy estimates for the FIT and for the guaiac FOBT obtained in all first-round screening participants. Primary outcome measures were the positivity rate, the positive predictive value (PPV) for CRC, and the PPV for advanced adenomas and CRC combined (hereafter referred to as advanced neoplasia).

The positivity rate was calculated as the number of positive test results relative to the number of tests returned. The PPV was