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ONE-TIME SCREENING FOR COLORECTAL CANCER WITH COMBINED FECAL OCCULT-BLOOD TESTING AND EXAMINATION OF THE DISTAL COLON

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ABSTRACT

Background Fecal occult-blood testing and sigmoidoscopy have been recommended for screening for colorectal cancer, but the sensitivity of such combined testing for detecting neoplasia is uncertain. At 13 Veterans Affairs medical centers, we performed colonoscopy to determine the prevalence of neoplasia and the sensitivity of one-time screening with a fecal occult-blood test plus sigmoidoscopy.

Methods Asymptomatic subjects (age range, 50 to 75 years) provided stool specimens on cards from three consecutive days for fecal occult-blood testing, which were rehydrated for interpretation. They then underwent colonoscopy. Sigmoidoscopy was defined as examination of the rectum and sigmoid colon during colonoscopy, and sensitivity was estimated by determining how many patients with advanced neoplasia had an adenoma in the rectum or sigmoid colon. Advanced colonic neoplasia was defined as an adenoma 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer.

Results A total of 2885 subjects returned the three specimen cards for fecal occult-blood testing and underwent a complete colonoscopic examination. A total of 23.9 percent of subjects with advanced neoplasia had a positive test for fecal occult blood. As compared with subjects who had a negative test for fecal occult blood, the relative risk of advanced neoplasia in subjects who had a positive test was 3.47 (95 percent confidence interval, 2.76 to 4.35). Sigmoidoscopy identified 70.3 percent of all subjects with advanced neoplasia. Combined one-time screening with a fecal occult-blood test and sigmoidoscopy identified 75.8 percent of subjects with advanced neoplasia.

Conclusions One-time screening with both a fecal occult-blood test with rehydration and sigmoidoscopy fails to detect advanced colonic neoplasia in 24 percent of subjects with the condition. (N Engl J Med 2001;345:555-60.)

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SCREENING of populations who are over 50 years of age, have no symptoms of colorectal cancer, and are at average risk for the disease has been advocated by many organizations and expert panels.[1-5] There is evidence that screening persons who have no symptoms with the use of a fecal occult-blood test or sigmoidoscopy can reduce mortality from colorectal cancer.[6-10] Several expert panels[2-5] have recommended combined screening with sigmoidoscopy and a fecal occult-blood test. Proponents of combined screening argue that advanced neoplasia could be detected in more patients by combined screening than by one test. However, few studies have evaluated combined screening.[11-13] In a nonrandomized study, the group that underwent fecal occult-blood testing plus sigmoidoscopy had longer survival after detection of colorectal cancer than the group that underwent only sigmoidoscopy.[11] In two randomized studies, rates of detection of advanced neoplasia were higher among subjects offered both tests than among subjects who were offered fecal occult-blood testing alone,[12,13] although many of the patients offered both tests did not actually undergo sigmoidoscopy.

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*Participants in the study group are listed in the Appendix.

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Our group previously reported the results of screening with colonoscopy in asymptomatic subjects.[14] The purpose of the prior study was to determine the prevalence and location of advanced neoplasia and the rate at which examination of the distal colon detects such tumors. All participants were given guaiac-impregnated cards for the collection of two stool samples on each of three consecutive days. These tests were completed before the colonoscopy. We now report the sensitivity, specificity, and positive or negative predictive value of a one-time fecal occult-blood test for detecting advanced neoplasia and examine whether combining such a test with an examination of the distal colon increases the rate of detection of advanced neoplasia.

METHODS

Study Subjects

The study protocol was approved by a central human-rights committee and by committees at each participating center. Enrollment was conducted from February 1994 to January 1997. Participants were recruited from 13 Veterans Affairs medical centers, as previously described[14]; this paper reports additional analysis of a subgroup of the same study cohort. Subjects were excluded if they reported symptoms of disease of the lower gastrointestinal tract, including rectal bleeding on more than one occasion in the previous six months, a marked change in bowel habits, or lower abdominal pain that would normally require a medical evaluation. Other exclusion criteria were prior disease of the colon (colitis, polyps, cancer, or a condition requiring surgery), examination of the colon within the previous 10 years (including sigmoidoscopy, colonoscopy, and barium enema), serious medical conditions that could increase the risk associated with colonoscopy or were so severe that screening would have no benefit, a need for special precautions in performing colonoscopy (including anticoagulation and antibiotic prophylaxis), and childbearing potential. Subjects with psychiatric disorders, unstable living conditions, or lack of transportation were also excluded. Other criteria for exclusion have been described previously.[14]

Study Procedures

Eligible subjects, who provided written informed consent, underwent a complete physical examination and received a polyethylene glycol–based electrolyte solution for bowel preparation. Subjects were given guaiac-impregnated cards (Hemoccult II, SmithKline Diagnostics, Palo Alto, Calif.) for the collection of two stool samples on each of three consecutive days before bowel preparation. The cards were returned on the day of the colonoscopy. After a drop of water was added (rehydration), the developer solution was applied. The method of rehydration was based on a previous study of fecal occult-blood testing.[6] The developed cards were interpreted by trained study nurses. In most cases, the endoscopist was not aware of the results of the fecal occult-blood test. Subjects who did not submit test cards were excluded from the analysis.

Colonoscopy was performed as described previously.[14] The location and size of all polypoid lesions were recorded by study nurses. Subjects were excluded from analysis if examination of the colon was not completed in one or two procedures within six months of the first attempt. Examination of the rectum and sigmoid colon during colonoscopy was defined as a surrogate for sigmoidoscopy.

Histologic Evaluation

All retrieved polypoid lesions were sent to local pathology laboratories for processing. Interpretation of the histopathological features was performed by the local pathologist, a central pathologist, and, when there was disagreement, a third reviewing pathologist. None of the pathologists were aware of the other interpretations.

Classification of tumors was based on the most advanced lesion. For example, a subject who had a villous adenoma and a tubular adenoma was classified as having a villous adenoma. The most advanced lesions in the entire colon, distal colon, and proximal colon were determined. The distal colon was defined as the sigmoid colon and rectum. The proximal colon included the descending colon and all proximal portions of the colon.

The diagnosis of advanced colonic neoplasia was made when an adenoma was 10 mm or more in diameter, was at least 25 percent villous, had high-grade dysplasia, or was classified as an invasive cancer. Intramucosal carcinoma and carcinoma in situ were classified as high-grade dysplasia. The criterion for a diagnosis of cancer was an invasion of malignant cells beyond the muscularis mucosa.

Statistical Analysis

All data were sent to the coordinating center of the Veterans Affairs Cooperative Study Program in Perry Point, Md., for analysis. Management of the study data base and all statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). Descriptive statistical analyses included the calculation of rates and proportions for categorical data and means and standard errors for continuous data.

RESULTS

Of the 17,732 persons who were screened for inclusion in the study, 3196 met the criteria for enrollment. A complete examination of the colon to the cecum was performed in 3121 eligible persons, 2885 of whom (92.4 percent) returned their test cards before colonoscopy and are the subjects of our analysis. The mean age of the group was 63.0 years; 96.8 percent of the subjects were men, and 14.2 percent reported having a first-degree relative with colorectal cancer.

Among the 2885 subjects, 1319 (45.7 percent) had no polypoid lesions. In 472 (16.4 percent), the most advanced lesions were hyperplastic polyps or nonadenomatous polyps, and in 788 (27.3 percent), the most advanced finding was one or more tubular adenomas less than 10 mm in diameter.

Advanced neoplasia was detected in 306 subjects (10.6 percent): 182 had advanced neoplasia in the distal colon and 150 in the proximal colon (some patients had advanced lesions in both regions), 143 had one or more large tubular adenomas (10 mm or more in diameter), 90 had an adenoma with villous features, 49 had an adenoma with high-grade dysplasia, and 24 had invasive cancer.

At least one test card was positive for fecal occult blood in the case of 239 subjects (8.3 percent). Among all 306 subjects with advanced neoplasia, 73 (23.9 percent) had a positive test for fecal occult blood (Table 1). The sensitivity of the test for detecting cancer or high-grade dysplasia was 35.6 percent. The false positive rate (a positive result in the absence of any neoplasia) was 6.2 percent. The positive predictive value of the test (the probability that a person with a positive test has advanced neoplasia)

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TABLE 1. SENSITIVITY AND SPECIFICITY OF THE FECAL OCCULT-BLOOD TEST.*

VARIABLE	SUBJECTS WITH A NEGATIVE TEST (N=2646)	SUBJECTS WITH A POSITIVE TEST (N=239)	ALL SUBJECTS (N=2885)
No neoplasia			
No polypoid lesions — no. (%)	1235	84 (6.4)	1319
Nonadenomatous polyps — no. (%)	23	1 (4.2)	24
Normal biopsy specimen — no. (%)	79	5 (6.0)	84
Hyperplastic polyps — no. (%)	343	21 (5.8)	364
Total — no. (%)	1680	111 (6.2)	1791
Specificity — %	—	93.8	—
Neoplasia			
Tubular adenoma <10 mm — no. (%)	733	55 (7.0)	788
Advanced neoplasia — no. (%)			
Tubular adenoma ≥10 mm	118	25 (17.5)	143
Villous adenoma	68	22 (24.4)	90
High-grade dysplasia	35	14 (28.6)	49
Cancer	12	12 (50.0)	24
Total — no. (%)	966	128 (11.7)	1094
Sensitivity for advanced neoplasia — %	—	23.9	—
Negative predictive value†	—	87.8	—
Positive predictive value†	—	39.7	—
Sensitivity for any neoplasia — %	—	11.7	—
Negative predictive value	—	63.5	—
Positive predictive value	—	53.6	—

*The specificity is calculated as the number of subjects with a negative test divided by the total number of subjects with no neoplasia (1680/1791). The sensitivity is calculated as the number of subjects with neoplasia and a positive test divided by the total number of subjects with neoplasia (73/306 for advanced neoplasia and 128/1094 for any neoplasia). The negative predictive value is calculated as the number of subjects with a true negative test divided by the number with a true negative test plus the number with a false negative test (1680/1913 for advanced neoplasia and 1680/2646 for any neoplasia). The positive predictive value is calculated as the number of subjects with a true positive test divided by the number with a true positive test plus the number with a false positive test (73/184 for advanced neoplasia and 128/239 for any neoplasia).

†The negative group was defined as subjects having no neoplasia. Subjects with small tubular adenomas were excluded from this calculation.

was 39.7 percent, and the negative predictive value (the probability that a person with a negative test does not have advanced neoplasia) was 87.8 percent. As compared with subjects with a negative test, those with a positive test had a significant risk of having advanced neoplasia (relative risk, 3.47; 95 percent confidence interval, 2.76 to 4.35). The test was positive in 24.2 percent of subjects with distal advanced neoplasia and in 23.3 percent of subjects with proximal advanced neoplasia. There was a strong association between the number of test cards with positive results and the likelihood of advanced neoplasia ($P<0.001$) (Table 2).

TABLE 2. RISK OF ADVANCED NEOPLASIA BASED ON THE NUMBER OF CARDS WITH POSITIVE TESTS FOR FECAL OCCULT BLOOD.*

NO. OF POSITIVE CARDS	TOTAL NO. OF SUBJECTS	NO. OF SUBJECTS WITH ADVANCED NEOPLASIA (%)
0 of 3	2646	233 (8.8)
1 of 3	132	30 (22.7)
2 of 3	69	23 (33.3)
3 of 3	38	20 (52.6)

*With an increasing number of positive cards, the rate of advanced neoplasia increases ($P<0.001$).

Table 3 shows the diagnostic sensitivity of one-time screening with sigmoidoscopy alone, fecal occult-blood testing alone, or combined testing. We assumed that if sigmoidoscopy detected an adenoma, or if a fecal occult-blood test was positive, the subject would undergo colonoscopy. If sigmoidoscopy was performed alone, the total number of endoscopic examinations (sigmoidoscopy plus colonoscopy) in our population of 2885 subjects would be 3451, the rate of detection of advanced neoplasia would be 70.3 percent (95 percent confidence interval, 65.2 to 75.4), and the number of colonoscopic examinations needed to identify 1 subject with advanced neoplasia would be 2.6. If a fecal occult-blood test was performed alone, the total number of endoscopic examinations would be 239, the rate of detection of ad-

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TABLE 3. SENSITIVITY OF THE SCREENING PROGRAMS AND NUMBER OF ENDOSCOPIC PROCEDURES IN THE 2885 STUDY SUBJECTS.

SCREENING PROGRAM	NO. WITH A POSITIVE TEST	NO. OF PROCEDURES*	SENSITIVITY FOR ADVANCED NEOPLASIA
			% (no. with a positive test/total no. with advanced neoplasia)
Single test			
Fecal occult-blood test alone†	239	239	23.9 (73/306)
Sigmoidoscopy alone‡	566	3451	70.3 (215/306)
Combined tests			
Sigmoidoscopy first, then fecal occult-blood test	719	3604	75.8 (232/306)
Fecal occult-blood test first, then sigmoidoscopy	719	3365	75.8 (232/306)

*The total represents flexible sigmoidoscopies plus colonoscopies.

†Colonoscopy was performed if the fecal occult-blood test was positive.

‡A positive test was defined as the finding of any adenoma; colonoscopy was performed if the results of sigmoidoscopy were positive.

vanced neoplasia would be 23.9 percent, and the number of colonoscopic examinations needed to detect advanced neoplasia in one subject would be 3.3. Combined screening with a fecal occult-blood test and sigmoidoscopy would identify 75.8 percent of subjects with advanced neoplasia (95 percent confidence interval, 71.0 to 80.6), a small and statistically insignificant increase in the rate of detection as compared with sigmoidoscopy alone. Among all patients with proximal advanced neoplasia, combined testing would identify 76 out of 150 patients (50.7 percent).

Table 3 also shows the effect of the order of testing in combined screening. The analysis assumed that if the first test had a positive result, a colonoscopy would be performed and the second test would not be conducted. We found that when subjects underwent the fecal occult-blood test first, fewer total endoscopic procedures (sigmoidoscopy plus colonoscopy) would be performed than when subjects underwent sigmoidoscopy first (3365 vs. 3604 endoscopic examinations). The addition of the fecal occult-blood test to sigmoidoscopy slightly reduced the total number of endoscopies as compared with sigmoidoscopy alone (3365 vs. 3451 examinations).

The sensitivity of screening programs was assessed in relation to the age of the subjects (Table 4). There was no correlation between age and the frequency of positive tests for fecal occult blood ($P=0.14$ for trend) or age and the rate of detection of advanced neoplasia with a combined screening program ($P=0.16$ for trend). In the group of subjects with no adenoma in the distal colon but an advanced neoplasm in the proximal colon, which would not be detected with sigmoidoscopy, the sensitivity of the fecal occult-blood test declined with age from 35.3 percent in subjects 50 to 59 years of age to 19.6 percent in patients 60 to 69 years of age and 4.3 percent in subjects 70 to 75 years of age ($P=0.02$).

DISCUSSION

Screening asymptomatic persons for colorectal cancer can reduce mortality from the disease.[2] Screening with the fecal occult-blood test, sigmoidoscopy, or both has been recommended by expert panels.[1-5] This study evaluated the sensitivity of each screening test, both alone and in combination, in a cohort of persons without symptoms who were undergoing complete colonoscopy.

The result of the fecal occult-blood test was positive in 6.4 percent of subjects with no polyps, as compared with 7.0 percent of subjects with only small tubular adenomas ($P=0.584$). Therefore, one-time fecal occult-blood testing is not useful in identifying patients with small tubular adenomas. In contrast, one-time screening identified 23.9 percent of subjects with advanced neoplasia and 35.6 percent of subjects with cancer or adenomas with high-grade dysplasia. Prior studies have found that the one-time fecal occult-blood test has a sensitivity of 33 to 50 percent for invasive cancer, results similar to ours.[15,16] With annual testing, the sensitivity of a rehydrated fecal occult-blood test for detecting cancer is reported to be as high as 90 percent.[6] However, in clinical practice, many persons who enroll in screening programs that test for fecal occult blood do not undergo more than one test.[17] We used a fecal occult-blood test with rehydration, which increases the sensitivity of the test,[6] but current guidelines from the American College of Physicians argue against the use of rehydration[18] and other expert panels have not specified a preference.[1-5] Our results for the diagnostic sensitivity of the one-time fecal occult-blood test are likely to be equal to or better than results with nonrehydrated tests.[6]

In our study, 30.5 percent of the subjects with a positive test for fecal occult blood had advanced neoplasia, as compared with 8.8 percent of those with a negative test (relative risk, 3.47; 95 percent confidence interval, 2.76 to 4.35). These data reinforce all existing recommendations for colonoscopy in patients with a positive test for fecal occult blood.

Testing with one-time sigmoidoscopy alone would detect 70.3 percent (95 percent confidence interval, 65.2 to 75.4) of patients with advanced neoplasia, assuming that all patients with an adenoma in the distal colon subsequently undergo complete colonoscopy. The addition of the rehydrated fecal occult-blood test to sigmoidoscopy did not increase the rate of detection of advanced neoplasia significantly. One-time combined testing would fail to identify 24

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TABLE 4. RELATION BETWEEN AGE AND THE LIKELIHOOD OF POSITIVE SCREENING TESTS.

VARIABLE	ALL SUBJECTS (N=2885)	SUBJECTS 50–59 YEARS OLD (N=953)	SUBJECTS 60–69 YEARS OLD (N=1375)	SUBJECTS >69 YEARS OLD (N=557)
Prevalence of advanced neoplasia (%)	10.6	5.7	12.9	13.3
Results of fecal occult-blood test (%)*				
Rate of positive results	8.3	6.4	9.5	8.6
Sensitivity	23.9	25.9	24.7	20.3
Specificity	93.8	94.8	92.6	94.9
Results of combined fecal occult-blood test and sigmoidoscopy (%)				
Rate of detection of advanced neoplasia†	75.8	79.6	77.0	70.3
Positive fecal occult-blood test in patients with advanced neoplasia and no distal adenoma‡	18.7	35.3	19.6	4.3

*The rate of positive results for fecal occult-blood testing is calculated as the number of subjects with a positive test divided by the total number of subjects (239/2885 for all ages, 61/953 for 50 to 59 years, 130/1375 for 60 to 69, and 48/557 for over 69). Sensitivity is calculated as the number of subjects with advanced neoplasia and a positive test divided by the total number of subjects with advanced neoplasia (73/306 for all ages, 14/54 for 50 to 59, 44/178 for 60 to 69, and 15/74 for over 69). Specificity is calculated as the number of subjects without neoplasia and with a negative test divided by the total number of subjects without neoplasia (1680/1791 for all ages, 603/636 for 50 to 59, 760/821 for 60 to 69, and 317/334 for over 69).

†The detection rate for advanced neoplasia for combined testing was calculated as the number detected divided by the total number of subjects with advanced neoplasia (232/306 for all ages, 43/54 for 50 to 59, 137/178 for 60 to 69, and 52/74 for over 69). If any adenoma was found in the distal colon, full colonoscopy was performed.

‡The rate of positive fecal occult-blood tests was calculated as the number of subjects with positive tests divided by the total number of subjects (17/91 for all ages, 6/17 for 50 to 59, 10/51 for 60 to 69, and 1/23 for over 69). With increasing age, the rate of positive tests declined significantly (P=0.02).

percent of patients with advanced neoplasia. We speculate that repeated testing with a fecal occult-blood test, sigmoidoscopy, or both at recommended intervals would improve the rate of detection.

We found that if a fecal occult-blood test is performed first, fewer total endoscopic examinations are performed than if sigmoidoscopy is performed first. Clearly, performing a fecal occult-blood test before sigmoidoscopy is a cost-effective practice.

In older patients, advanced neoplasia is more likely to occur in the proximal colon, frequently without adenomas in the distal colon.[14,19] For such patients, a fecal occult-blood test could be useful. The trend toward an age-related decline in the rate of detection of advanced neoplasia with combined screening was not statistically significant (P=0.16). However, we found that rates of positive one-time tests for fecal occult blood in subjects with advanced proximal neoplasia and no distal adenoma decline with age (P=0.02).

Our study has several important limitations. First, the results can be generalized only to men. Since men have a higher age-adjusted incidence of cancer than women,[20] the results of combined screening may differ for women. We defined examination of the distal colon, including the left colon up to the junction of the sigmoid and the descending colon, as a surrogate for sigmoidoscopy; this definition may not reflect the actual depth of insertion of a sigmoidoscope and may overestimate the sensitivity of sigmoidoscopy. Finally, the accuracy of colonoscopy depends on the expertise of the endoscopist.[21] In our study, all the endoscopists had substantial experience with colonoscopy. The actual rate of detection of advanced neoplasia in patients with positive results of fecal occult-blood testing or sigmoidoscopy may be different if the tests are performed by less experienced endoscopists.

We found that one-time screening of asymptomatic subjects with the fecal occult-blood test plus sigmoidoscopy fails to identify about one quarter of subjects with advanced neoplasia and one half of subjects with advanced proximal neoplasia. Therefore, clinicians should not be confident that advanced neoplasia has been ruled out when the results of one-time combined testing are negative. Screening programs that use fecal occult-blood tests and sigmoidoscopy may be more effective if the tests are repeated at appropriate intervals. Health policy experts will need to consider these data when developing recommendations for screening for colorectal cancer.

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APPENDIX

The following persons participated in Veterans Affairs Study Group 380: *Data Monitoring Board* — B. Levin (chairperson), C.R. Boland, M. Brown, R. Burt, R.B. D'Agostino, and D.K. Rex; *Executive Committee* — S. Prindiville (special consultant, Denver), A. Schatzkin (Bethesda, Md.),

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