USE OF COLONOSCOPY TO SCREEN ASYMPTOMATIC ADULTS FOR COLORECTAL CANCER

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ABSTRACT

Background and Methods The role of colonoscopy in screening for colorectal cancer is uncertain. At 13 Veterans Affairs medical centers, we performed colonoscopy to determine the prevalence and location of advanced colonic neoplasms and the risk of advanced proximal neoplasia in asymptomatic patients (age range, 50 to 75 years) with or without distal neoplasia. Advanced colonic neoplasia was defined as an adenoma that was 10 mm or more in diameter, a villous adenoma, an adenoma with high-grade dysplasia, or invasive cancer. In patients with more than one neoplastic lesion, classification was based on the most advanced lesion.

Results Of 17,732 patients screened for enrollment, 3196 were enrolled; 3121 of the enrolled patients (97.7 percent) underwent complete examination of the colon. The mean age of the patients was 62.9 years, and 96.8 percent were men. Colonoscopic examination showed one or more neoplastic lesions in 37.5 percent of the patients, an adenoma with a diameter of at least 10 mm or a villous adenoma in 7.9 percent, an adenoma with high-grade dysplasia in 1.6 percent, and invasive cancer in 1.0 percent. Of the 1765 patients with no polyps in the portion of the colon that was distal to the splenic flexure, 48 (2.7 percent) had advanced proximal neoplasms. Patients with large adenomas (≥10 mm) or small adenomas (<10 mm) in the distal colon were more likely to have advanced proximal neoplasia than were patients with no distal adenomas (odds ratios, 3.4 [95 percent confidence interval, 1.8 to 6.5] and 2.6 [95 percent confidence interval, 1.7 to 4.1], respectively). However, 52 percent of the 128 patients with advanced proximal neoplasia had no distal adenomas.

Conclusions Colonoscopic screening can detect advanced colonic neoplasms in asymptomatic adults. Many of these neoplasms would not be detected with sigmoidoscopy. (N Engl J Med 2000;343:162-8.)

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polypoid lesions were removed and evaluated histologically. The purpose of the study was to determine the prevalence and location of colonic neoplasia in asymptomatic patients, the risk of proximal advanced neoplasia in patients with and in those without neoplasia in the distal colon, and the likelihood that advanced proximal neoplasia would be detected on the basis of the presence of an adenoma in the distal colon.

**METHODS**

**Patients**

The study protocol was approved by a central human-rights committee and by the corresponding committee at each participating center. Patients were enrolled in the study between February 1994 and January 1997. They were recruited from 13 Veterans Affairs medical centers, representing each major region of the United States. Patients were recruited in one of three ways: by random selection from the center’s clinic list on the basis of age, by the selection of asymptomatic patients referred for screening sigmoidoscopy, and by advertisement for patients with a family history of colorectal cancer. Oversampling for patients who had one or more first-degree relatives with colorectal cancer was performed in order to have an adequate number of patients with a family history in the sample. A study nurse asked each patient to complete a brief questionnaire designed to determine eligibility for the study. Patients were excluded if they reported symptoms of lower gastrointestinal tract disease, 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 medical evaluation. Other exclusion criteria were current participation in other studies, a history of disease of the colon (colitis, polyps, or cancer) or colonic surgery, a colonic examination within the previous 10 years (sigmoidoscopy, colonoscopy, or barium enema), a medical condition that could increase the risk associated with colonoscopy (active cardiac or pulmonary disease or other serious disease) or that would preclude a benefit from colonoscopic screening (cancer or any terminal illness), a prosthetic heart valve, anticoagulant therapy, nonmedical problems (psychiatric disorders, lack of transportation, homelessness or lack of support at home, or excessive use of alcohol), and a need for special precautions in performing colonoscopy (i.e., antibiotic prophylaxis). In addition, women of childbearing potential were excluded.

**Study Protocol**

Eligible persons who provided informed consent completed detailed questionnaires that covered diet, physical activity, drug use, and family history of cancer. A physical examination was performed, and laboratory studies were ordered to evaluate coagulation. The patients received a polyethylene glycol–based electrolyte solution for bowel preparation, along with instructions for use. A complete colonoscopic examination was performed while the patients were under conscious sedation with an intravenous agent. All examinations were performed at the participating centers by the study investigators, who were selected because of their extensive experience with colonoscopy. During the examination, the location and size of all polypoid lesions were noted by study nurses. The size of each polyp was estimated with the use of an open-biopsy forceps, which is 7 mm in diameter. Investigators were required to provide photographic documentation of cecal landmarks and of all polyps and other important lesions.

If the colonoscopic examination was incomplete because of problems with bowel preparation or failure to reach the cecum, the patient was asked to return for a second attempt. If a complete examination was performed within six months after the first attempt, a complete examination was reported, and the combined results of the two examinations were included in the analysis. If the second examination was also incomplete, the results were excluded from the analysis. If the patient underwent surgery within six months after the initial examination and if the resected specimen could be evaluated, then a complete examination was reported, and the results were included in the analysis.

**Histologic Evaluation**

All retrieved polypoid lesions were sent to local pathology laboratories for histologic evaluation. Slides were sent to a designated expert in pathology at the Veterans Affairs Medical Center in Hines, Illinois, for an independent, blinded review. When there was agreement between the local pathologist and the pathologist at the coordinating center, a final pathological classification was made. When there was disagreement, the slides were sent to a pathologist at the Veterans Affairs Medical Center in Minneapolis or in Portland, Oregon. The results of the third review were used to classify the lesion. Patients were classified on the basis of their most advanced lesion in order to determine the prevalence of pathological features. For example, a patient 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. Patients were classified separately according to the number of adenomas in the distal colon and the number in the entire colon. The distal colon was defined as the rectum, sigmoid, and descending colon up to but not including the splenic flexure. The proximal colon was defined as the splenic flexure and other, more proximal portions of the colon. The risk of proximal neoplasia associated with distal colonic lesions was determined.

Advanced colonic neoplasia was defined as an adenoma with a diameter of 10 mm or more, a villous adenoma (i.e., at least 25% villous), an adenoma with high-grade dysplasia, or invasive cancer. Patients with intramusosal carcinoma or carcinoma in situ were classified as having high-grade dysplasia. Cancer was defined as the invasion of malignant cells beyond the muscularis mucosa.

**Statistical Analysis**

Data-base management and all statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.). Rates and proportions were calculated for categorical data, and means and standard errors for continuous data. In addition, standard logistic-regression methods were used to calculate odds ratios for advanced neoplasia, with 95 percent confidence intervals. Odds ratios were adjusted for age and family history of cancer in analyses of the risk of advanced neoplasia in the distal and proximal colon.

**RESULTS**

A total of 17,732 patients were screened for enrollment in the study, and 3196 eligible patients were enrolled. Selected demographic characteristics of the study population are shown in Table 1. The proportion of patients who were recruited by random selection from clinic lists was 48.8 percent; 45.0 percent of the patients had been referred for sigmoidoscopy, and 6.2 percent had responded to the advertisement for patients with a family history of colorectal cancer. The prevalence of a family history of colorectal cancer (one or more affected first-degree relatives) was 13.9 percent in the final study population but 8.2 percent in the overall group of patients who were randomly selected from clinic patients, with the difference due to oversampling. The most frequently reported reasons for exclusion are shown in Table 2. A total of 1463 patients met the criteria for enrollment but declined to participate.

Colonoscopy was completed to the cecum in 3121 of the 3196 patients (97.7 percent). In 14 patients,
more than one procedure was required to complete the examination. Patients were classified on the basis of the most advanced lesion found in the colon (Table 3). A total of 1441 patients (46.2 percent) had no polypoid lesions. In the other 1680 patients (53.8 percent), a total of 5218 polyps were removed. In 391 patients (12.5 percent), the most advanced lesions were hyperplastic polyps. In 118 patients (3.8 percent), biopsy of what appeared to be a polyp revealed either normal mucosa or nonpolypoid, miscellaneous findings. In all, 62.5 percent of the patients had no evidence of neoplasia.

A total of 1171 patients had one or more adenomas of any type or invasive cancer (37.5 percent). In 842 patients, the most important finding was a tubular adenoma that was less than 10 mm in diameter. Of these patients, 687 had one or two adenomas, 112 had three or four, and 43 had five or more.

Advanced disease (defined as an adenoma with a diameter of at least 10 mm, or villous features, high-grade dysplasia, or invasive cancer) was present in 329 patients (10.5 percent). In 155 patients (5.0 percent), the most advanced lesions were large tubular adenomas (>10 mm). Ninety-three patients (3.0 percent) had adenomas with villous features, 51 (1.6 percent) had adenomas with high-grade dysplasia, and 30 (1.0 percent) had invasive cancer. Among the patients with cancer, the stage was T1N0 in nine patients, T2N0 in six, and T3N0 in seven; six patients had nodal involvement (N1 or N2), and two had metastatic disease.

The most advanced lesions in the distal colon and in the proximal colon were identified separately for each patient (Table 4). In the primary analysis, the distal colon was defined as the rectum and the sigmoid and descending colon. According to this definition, 228 patients (7.5 percent) had advanced disease in the distal colon (i.e., distal to the splenic flexure) and 128 (4.1 percent) had advanced disease in the proximal colon. We also determined the prevalence of advanced disease in the distal colon defined as only the rectum.
and sigmoid colon. With the more restricted definition, 188 (6.0 percent) had advanced disease in the distal colon, and 169 (5.4 percent) had advanced disease in the proximal colon.

The likelihood that advanced proximal neoplasia would be detected on examination of the distal colon was determined by noting the presence or absence of an adenoma in the portion of the colon that was distal to the splenic flexure (Table 4). Among the patients with advanced proximal neoplasia, 48.4 percent (62 of 128) had at least one adenoma in the distal colon, and 14.1 percent (18 of 128) had large adenomas (>10 mm in diameter) in the distal colon. With the distal colon defined as the rectum plus the sigmoid colon, only 37.9 percent of the patients with advanced proximal neoplasia (64 of 169) had a distal adenoma.

Among the patients with no adenomas distal to the splenic flexure, 2.7 percent had advanced proximal neoplasia. These patients served as the reference group in an analysis of the risk of advanced proximal neoplasia according to the distal findings. The odds ratios (with 95 percent confidence intervals), adjusted for age and the presence or absence of a family history of colorectal cancer, are shown in Table 5, according to the two definitions of the distal colon. The patients with distal hyperplastic polyps did not have a higher risk of advanced proximal neoplasia than the patients without distal polyps. However, the patients with small or large adenomas in the distal colon had a significantly increased risk of advanced proximal neoplasia: odds ratio for patients with small adenomas, 2.6 (95 percent confidence interval, 1.7 to 4.1); odds ratio for patients with large adenomas, 3.4 (95 percent confidence interval, 1.8 to 6.5). Among patients with small tubular adenomas (<10 mm in diameter) in the distal colon, the presence of one or two adenomas was significantly associated with an elevated risk of proximal advanced neoplasia, but the presence of a larger number of adenomas did not further increase the risk. When the distal colon was defined as the rectum and sigmoid colon, the presence of distal adenomas, whether small or large, was still associated with an increased risk of advanced proximal neoplasia. The odds ratio for proximal advanced neoplasia was higher for the patients with distal villous adenomas (4.7; 95 percent confidence interval, 2.1 to 10.4) than for the patients with distal tubular adenomas (2.6; 95 percent confidence interval, 1.7 to 4.0), but the difference was not statistically significant.

The effect of age on the prevalence of advanced neoplasia was assessed as an independent variable. The prevalence of advanced neoplasia increased from 5.7 percent in the youngest patients (50 to 59 years old) to 13 percent in the oldest patients (70 to 75 years old). There was a trend toward an increased prevalence of advanced proximal neoplasia with age (P<0.001): the prevalence was 2 percent for patients who were 50 to 59 years old, 4.9 percent for those 60 to 69 years old, and 5.9 percent for those 70 to 75 years old.

There were no differences in the rates of advanced neoplasia according to the method used to recruit patients (P=0.32). Patients with a family history of colorectal cancer who were recruited by any of the three methods had a higher age-adjusted risk of advanced neoplasia than patients with no family history (14.3 percent vs. 9.9 percent; odds ratio, 1.5; 95 percent confidence interval, 1.1 to 2.0).

Ten patients (0.3 percent) had serious complications during or immediately after colonoscopy: six patients had gastrointestinal bleeding that required hospitalization, and one each had a myocardial infarction, a cerebrovascular accident, Fornier’s gangrene that required hospitalization, and thrombophlebitis. Three patients died within 30 days after colonoscopy; none of the deaths were directly related to the procedure. There were no perforations.

DISCUSSION

We evaluated the use of colonoscopy as a primary screening procedure in a large number of asymptomatic adults. The combined prevalence of invasive

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**Table 4. Prevalence and Location of Advanced Neoplasia.**

<table>
<thead>
<tr>
<th>Definition of Distal Colon</th>
<th>Advanced Neoplasia</th>
<th>Advanced Neoplasia with Distal Adenoma</th>
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<tbody>
<tr>
<td></td>
<td>Distal</td>
<td>Proximal</td>
</tr>
<tr>
<td></td>
<td>no. of patients</td>
<td>total no. (%)</td>
</tr>
<tr>
<td>Rectum and sigmoid colon</td>
<td>188/3121 (6.0)</td>
<td>169/3121 (5.4)</td>
</tr>
<tr>
<td>Rectum and sigmoid and descending colon</td>
<td>228/3121 (7.3)</td>
<td>128/3121 (4.1)</td>
</tr>
</tbody>
</table>

*Total refers to all patients with advanced neoplasia who had adenomas in the distal colon.
†Proximal refers to all patients with advanced proximal neoplasia who had adenomas in the distal colon.
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The prevalence of advanced proximal neoplasia was 2.6 percent. Most of the patients with cancer (73.3 percent) were identified before there was nodal involvement or distal spread and were therefore candidates for curative treatment. These data suggest that screening with colonoscopy in asymptomatic men can detect early and potentially curable advanced neoplasia. In the National Polyp Study, patients who underwent colonoscopy, with the removal of all polyps, had a lower incidence of colorectal cancer during six years of follow-up than did the reference populations. Although our study was not designed to determine whether colonoscopic screening would reduce the rate of mortality from colorectal cancer, the results indicate that many cases of advanced neoplasia would be detected as part of a colonoscopic screening program.

Our findings can be used to determine the yield of a screening examination limited to the distal colon. There has been controversy about the importance of detecting small adenomas (<10 mm in diameter) in the distal colon. In our study, all patients were asymptomatic and underwent full colonoscopy, irrespective of the findings in the distal colon. Patients with no polyps of any kind in the rectum or sigmoid or descending colon had a risk of advanced proximal neoplasia of 2.7 percent. Among patients with no polyps in the rectum or sigmoid colon, the prevalence of advanced proximal neoplasia was 3.7 percent. The risk of proximal advanced neoplasia increased significantly with age. Patients with distal hyperplastic polyps had a risk of advanced proximal neoplasia that was similar to the risk among patients with no polyps. However, patients with distal adenomas of any size had a higher risk of advanced proximal neoplasia than patients with no distal adenomas.

We determined the prevalence of advanced proxi-
nal neoplasia in asymptomatic patients and the likelihood that such patients would have any adenomas in the distal colon (Table 4). When the distal colon was defined as the rectum and the sigmoid and descending colon, 48.4 percent of the patients with advanced proximal neoplasia had adenomas in the distal colon. When the distal colon was defined as the rectum and sigmoid colon, only 37.9 percent of the patients with proximal advanced neoplasia had distal advanced neoplasia. Therefore, the majority of advanced proximal neoplasms would not have been detected if the distal colon had been examined either to the junction of the sigmoid colon and the descending colon or to the splenic flexure.

These data can be interpreted in two ways. Examination of the distal colon to the splenic flexure, followed by full colonoscopy if an adenoma of any size had been found, would have identified the 79.9 percent of patients with advanced neoplasia. However, if the distal colon had been examined only to the junction of the descending colon and the sigmoid colon, then the advanced neoplasia in 31.9 percent of the patients would not have been detected. Failure to detect advanced neoplasia may be more likely in older patients than in younger patients, since the prevalence of advanced proximal disease increases with age.

Our study population included a disproportionately large number of patients who had one or more first-degree relatives with colorectal cancer. These patients had an increased age-adjusted risk of advanced neoplasia, a finding that is consistent with the results of other studies.20 22 These data support the recommendation of an expert panel that colonoscopy be offered to such patients.7

Our study has several important limitations. First, the results are applicable only to men. There is considerable evidence that men have higher age-adjusted rates of cancer than women.23 In addition, a definition of the distal colon that includes the left colon to the splenic flexure may not reflect the actual depth of insertion of a sigmoidoscope. Therefore, we determined the yield of an examination that reached the junction of the sigmoid colon and the descending colon. Our data demonstrate that a more extensive examination of the colon leads to a higher rate of detection of advanced neoplasia. Finally, the effectiveness of colonoscopy depends on the expertise of the endoscopist.24 In our study, all the endoscopists had substantial experience with colonoscopy, as reflected by the high rate of successful cecal intubation. The results of examinations performed by less experienced endoscopists may be different.

We believe that the use of colonoscopy to screen asymptomatic men for colorectal cancer is feasible and that such screening can identify patients with advanced neoplasia who may benefit from the detection and removal of the lesions. The majority of advanced lesions are distal to the splenic flexure. However, our data show that more than half the cases of advanced proximal neoplasia would not be detected with sigmoidoscopy to the splenic flexure. Patients with distal adenomas of any size have a higher risk of advanced proximal neoplasia than patients with no distal adenomas. In the group of patients in our study who had no distal adenomas, 2.7 percent had advanced proximal lesions, which would not have been detected with sigmoidoscopy alone. It remains to be determined whether a full colonoscopic examination will lead to a greater reduction in the rate of mortality from colorectal cancer than other methods of screening.
16. Read TE, Read JD, Butterly LF. Importance of adenomas 5 mm or less in diameter that are detected by sigmoidoscopy. N Engl J Med 1997; 336:8-12.