

RISK OF ADVANCED PROXIMAL NEOPLASMS IN ASYMPTOMATIC ADULTS ACCORDING TO THE DISTAL COLORECTAL FINDINGS

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ABSTRACT

Background and Methods The clinical significance of a distal colorectal polyp is uncertain. We determined the risk of advanced proximal neoplasia, defined as a polyp with villous features, a polyp with high-grade dysplasia, or cancer, among persons with distal hyperplastic or neoplastic polyps as compared with the risk among persons with no distal polyps. We analyzed data from 1994 consecutive asymptomatic adults (age, 50 years or older) who underwent colonoscopic screening for the first time between September 1995 and December 1998 as part of a program sponsored by an employer. The location and histologic features of all polyps were recorded. Colonoscopy to the level of the cecum was completed in 97.0 percent of the patients.

Results Sixty-one patients (3.1 percent) had advanced lesions in the distal colon, including 5 with cancer, and 50 (2.5 percent) had advanced proximal lesions, including 7 with cancer. Twenty-three patients with advanced proximal neoplasms (46 percent) had no distal polyps. The prevalence of advanced proximal neoplasia among patients with no distal polyps was 1.5 percent (23 cases among 1564 persons; 95 percent confidence interval, 0.9 to 2.1 percent). Among patients with distal hyperplastic polyps, those with distal tubular adenomas, and those with advanced distal polyps, the prevalence of advanced proximal neoplasia was 4.0 percent (8 cases among 201 patients), 7.1 percent (12 cases among 168 patients), and 11.5 percent (7 cases among 61 patients), respectively. The relative risk of advanced proximal neoplasia, adjusted for age and sex, was 2.6 for patients with distal hyperplastic polyps, 4.0 for those with distal tubular adenomas, and 6.7 for those with advanced distal polyps, as compared with patients who had no distal polyps. Older age and male sex were associated with an increased risk of advanced proximal neoplasia (relative risk, 1.3 for every five years of age and 3.3 for male sex).

Conclusions Asymptomatic persons 50 years of age or older who have polyps in the distal colon are more likely to have advanced proximal neoplasia than are persons without distal polyps. However, if colonoscopic screening is performed only in persons with distal polyps, about half the cases of advanced proximal neoplasia will not be detected. (N Engl J Med 2000;343:169-74.)

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THE clinical significance of distal colorectal polyps depends on two factors: whether the polyps are associated with advanced proximal neoplasms, and whether polyps with histologic features of advanced neoplasia (e.g., villous features) are clinically important. Although Stryker et al. reported that large polyps (>10 mm in diameter) left intact progress to colorectal cancer at a rate of about 1 percent per year,¹ it is unclear whether smaller polyps with histologic features of advanced neoplasia have a similar natural history. If early detection of such lesions is desirable, then the ability to estimate the risk of advanced proximal neoplasia with precision may be important both for deciding which patients should undergo examination of the proximal colon after sigmoidoscopic screening and for evaluating other screening strategies.

Previous studies of the association between polyps in the distal colon and advanced proximal neoplasia have lacked control groups of persons with no distal abnormalities,²⁻⁵ making it difficult to identify risk factors for advanced proximal neoplasia. Furthermore, these studies have varied with respect to features that can affect the outcome, including the sample size and the criteria for classifying distal lesions (i.e., according to their size, number, location, or histologic features). Differences in reported risks have led to conflicting recommendations for the use of colonoscopy according to distal findings, particularly for patients with distal tubular adenomas, with important implications for the case of individual patients as well as for guidelines for colorectal-cancer screening.²⁻⁵

We analyzed data from a large cohort of persons at average risk who underwent colonoscopic screening for colorectal cancer. Our primary objective was to determine the relative risk of advanced proximal neoplasia in patients with distal polyps, either hyperplastic or neoplastic, as compared with persons with no distal polyps. A secondary objective was to determine the risk of large proximal neoplasms (≥ 10 mm in diameter) according to the distal findings.

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METHODS

Study Design

We performed a cross-sectional analysis of consecutive asymptomatic adults, 50 years of age or older, who underwent colonoscopic screening for the first time between September 1995 and December 1998. The study was approved by the institutional review board of Indiana University at Indianapolis.

Screening Program

In September 1995, Eli Lilly, which has its own health insurance plan for employees, retirees, and their dependents, began providing colonoscopic screening as a benefit. Persons 40 years of age or older receive a brochure about the screening program and are encouraged to call a toll-free number for more information or to make an appointment to be screened. A telephone interview is used to establish that persons who call to make an appointment for screening are asymptomatic (e.g., they report no visible rectal bleeding, no recent change in bowel habits, and no recent or current lower abdominal pain) and have no personal history of colorectal cancer, colorectal polyps, or inflammatory bowel disease. Thirty-six board-certified gastroenterologists and colorectal surgeons practicing in central Indiana participate in the screening program.

Study Procedures and Definitions

Polyethylene glycol lavage solution was used for bowel preparation. Fecal occult-blood testing was not performed before colonoscopic screening, and information on the presence or absence of a family history of colorectal cancer and the results of prior screening or diagnostic colorectal evaluations was not available, since such information is not routinely recorded.

During colonoscopy, the location and size of all polyps were determined before they were removed. Pathological specimens were evaluated by one of three board-certified pathologists, who classified polyps according to the criteria established by the World Health Organization.⁶

For the purpose of our analysis, the boundary between the proximal colon and the distal colon was defined as the junction of the splenic flexure and the descending colon, as assessed by the endoscopist. In the case of patients with more than one polyp in either the proximal or distal segment of the colon, the most advanced lesion in that segment was included in the analysis. The size of the polyp was estimated either with the use of open-biopsy forceps or on the basis of clinical judgment.

Distal and proximal findings were categorized as indicating normal mucosa (no polyps), hyperplastic polyps, tubular adenomas, or advanced neoplasms. An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer. Findings such as lipomas, lymphoid aggregates, chronic nonspecific inflammation, and inflammatory or juvenile polyps were categorized as indicating normal mucosa. No specimens were considered to be nondiagnostic.

Statistical Analysis

The prevalence of both advanced proximal neoplasms and large proximal neoplasms was calculated on the basis of the distal colorectal findings. The unadjusted relative risk of each distal and proximal finding was calculated for men as compared with women.⁷ Multivariate logistic-regression analysis was used to estimate the adjusted relative risk of advanced proximal neoplasia and large proximal neoplasms (≥ 10 mm in diameter), with the use of age, sex, and distal colorectal findings as independent variables.⁸ For each distal finding, the "number needed to screen" was determined. Conceptually similar to the "number needed to treat,"⁹ the number needed to screen is the number of persons with a particular distal finding who would have to undergo colonoscopy in order to detect one advanced proximal neoplasm. Analyses were performed with SPSS for Windows software (version 9.0, SPSS, Chicago).

RESULTS

From September 1995 through December 1998, a total of 2686 persons underwent colonoscopic screen-

ing. We excluded from the analysis 692 persons who were less than 50 years old. The study cohort thus consisted of 1994 persons. Their mean (\pm SD) age was 59.8 ± 8.3 years, and 58.9 percent were men (mean age, 59.6 ± 8.3 years). The mean age of the women was 60.1 ± 8.4 years. Colonoscopy to the cecum was performed in 97.0 percent of patients.

A total of 12 cancers were detected: 8 in men and 4 in women; their mean age was 69.8 ± 10.0 years. Seven patients had cancers in the proximal portion of the colon; in three of the seven, there were associated distal lesions (adenomas in two patients and a hyperplastic polyp in one). Five of the 12 patients had carcinoma in situ, 1 had a Dukes' stage A lesion, 4 had Dukes' stage B lesions, and 2 had Dukes' stage C lesions.¹⁰ There were no deaths related to colonoscopy. One patient had a colonic perforation that was managed medically. Three patients who had bleeding after polypectomy went to an urgent care center or emergency room for evaluation; none required transfusion or surgery.

Distal and proximal findings are shown in Table 1. No polyps were present in the distal colon in 78.4 percent of the patients (mean age, 60.0 ± 8.3 years). Hyperplastic polyps, tubular adenomas, and advanced neoplasms were present in the distal colon in 10.1 percent, 8.4 percent, and 3.1 percent of the patients, respectively. Men were more likely than women to have hyperplastic polyps (unadjusted relative risk, 1.49; 95 percent confidence interval, 1.12 to 1.97), tubular adenomas (unadjusted relative risk, 1.54; 95 percent confidence interval, 1.13 to 2.11), and advanced neoplasms (unadjusted relative risk, 2.39; 95 percent confidence interval, 1.32 to 4.31).

No polyps were present in the proximal colon in 84.6 percent of the cohort (mean age, 59.8 ± 8.2 years) (Table 1). Hyperplastic polyps were present in 3.6 percent, tubular adenomas in 9.3 percent, and advanced neoplasms in 2.5 percent. Men were more likely than women to have tubular adenomas (unadjusted relative risk, 2.3; 95 percent confidence interval, 1.7 to 3.2) and advanced neoplasms (unadjusted relative risk, 3.7; 95 percent confidence interval, 1.8 to 8.0).

The prevalence of advanced proximal neoplasia according to the findings in the distal colon is shown in Table 2. Among the 1564 persons with no distal polyps, the prevalence of proximal neoplasia was 1.5 percent (95 percent confidence interval, 0.9 to 2.1 percent), and the prevalence increased linearly among persons with distal hyperplastic polyps (4.0 percent), tubular adenomas (7.1 percent), and advanced neoplasms (11.5 percent). The proportions were essentially the same when advanced proximal neoplasms and large proximal neoplasms were considered together. Twenty-three of the 50 patients with advanced proximal neoplasia (46.0 percent) had no polyps in the distal colon. Had these 23 patients undergone screening sigmoidoscopy, their proximal neoplasms would not have been detected, because of the absence of distal polyps.

TABLE 1. FINDINGS IN THE DISTAL AND PROXIMAL COLON IN THE COHORT OF 1994 PATIENTS.*

| FINDING | DISTAL COLON | | PROXIMAL COLON | |
|--------------------|--------------|----------|----------------|----------|
| | PATIENTS | AGE | PATIENTS | AGE |
| | no. (%) | yr | no. (%) | yr |
| No polyp | 1564 (78.4) | 60.0±8.3 | 1686 (84.6) | 59.8±8.2 |
| Hyperplastic polyp | 201 (10.1) | 59.3±7.4 | 72 (3.6) | 60.6±9.5 |
| Tubular adenoma | 168 (8.4) | 62.0±9.4 | 186 (9.3) | 62.1±8.8 |
| Advanced neoplasm† | 61 (3.1) | 62.2±8.0 | 50 (2.5) | 64.4±8.9 |

*Plus-minus values are means ±SD.

†An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer.

Table 2 also shows the relative risk of advanced proximal neoplasia, adjusted for age and sex, according to the distal findings, with patients who had no distal polyps serving as the reference group. The magnitude of the risk was related to the histologic features of the distal lesion.

The size of a distal adenoma alone was unrelated to the risk of advanced proximal neoplasia. Thirteen of 124 patients with distal adenomas that were 1 to 5 mm in diameter had advanced proximal neoplasia (10.5 percent; 95 percent confidence interval, 5.7 to 17.3 percent). Advanced proximal lesions were detected in 2 of 72 patients with adenomas that were 6 to 9 mm in diameter (2.8 percent; 95 percent confidence interval, 0.3 to 6.6 percent) and in 4 of 26 with distal adenomas that were 10 mm or more in diameter (15.4 percent; 95 percent confidence interval, 4.4 to 34.9 percent), respectively.

The prevalence of large proximal neoplasms according to the distal findings is shown in Table 3. Despite the small number of patients with large le-

sions, the risk of a large proximal neoplasm was significantly associated with the histologic stage of the distal lesion (two-tailed P value for trend, 0.02). The confidence intervals for the proportions indicate that the risk of large proximal neoplasms was greater for patients with distal tubular adenomas or advanced neoplasms than for those with distal hyperplastic polyps or no distal polyps. Table 3 also shows the adjusted relative risk of a large proximal neoplasm according to the distal findings, with persons who had no distal polyps serving as the reference group. The presence of distal neoplasia increased the age- and sex-adjusted relative risk of a large proximal neoplasm.

Multivariate analysis showed that after adjustment for sex and distal findings, age was significantly associated with the risk of advanced proximal neoplasia, with a relative risk of 1.3 (95 percent confidence interval, 1.3 to 1.4) for every successive five-year interval between the ages of 50 and 80 years. Likewise, male sex, adjusted for age and distal findings, increased the risk of advanced proximal neoplasia by 3.3 (95 percent confidence interval, 1.5 to 7.1).

DISCUSSION

If there were a reliable distal marker for clinically important proximal neoplasia (i.e., a sentinel lesion) or if normal findings in the distal colon were a reliable marker for the absence of clinically important proximal neoplasia, then sigmoidoscopic examination of the distal colon and rectum would help determine which persons should undergo examination of the proximal colon.

In our study, a polyp of any size or type in the distal colon was associated with an increased risk of histologically advanced proximal neoplasia. The magnitude of the risk was proportional to the histologic features of the distal lesion. The risk of a large proximal neoplasm was similarly related to the histologic features of polyps in the distal colon.

TABLE 2. PREVALENCE OF ADVANCED PROXIMAL NEOPLASMS ACCORDING TO THE DISTAL FINDINGS.*

| DISTAL FINDING | TOTAL | ADVANCED PROXIMAL NEOPLASM | | ADJUSTED RELATIVE RISK (95% CI)† |
|--------------------|---------------------|----------------------------|-----------------|----------------------------------|
| | no. of patients (%) | no. of patients | % (95% CI) | |
| No polyp | 1564 (78.4) | 23 | 1.5 (0.9–2.1) | 1.0 |
| Hyperplastic polyp | 201 (10.1) | 8 | 4.0 (1.3–6.7) | 2.6 (1.1–5.9) |
| Tubular adenoma | 168 (8.4) | 12 | 7.1 (3.3–11.0) | 4.0 (1.9–8.3) |
| Advanced neoplasm | 61 (3.1) | 7 | 11.5 (3.4–19.5) | 6.7 (3.2–16.6) |

*An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer. CI denotes confidence interval.

†The relative risk was adjusted for age and sex. The group of patients with no distal polyps was the reference group.

TABLE 3. PREVALENCE OF LARGE PROXIMAL NEOPLASMS ACCORDING TO THE DISTAL FINDINGS.*

| DISTAL FINDING | TOTAL | LARGE PROXIMAL NEOPLASM | | ADJUSTED RELATIVE RISK (95% CI)† |
|--------------------|-----------------|-------------------------|----------------|----------------------------------|
| | no. of patients | no. of patients | % (95% CI) | |
| No polyp | 1564 | 17 | 1.1 (0.6–1.6) | 1.0 |
| Hyperplastic polyp | 201 | 4 | 2.0 (0.5–5.0) | 1.8 (0.6–5.5) |
| Tubular adenoma | 168 | 7 | 4.2 (1.7–8.4) | 2.9 (1.1–7.2) |
| Advanced neoplasm | 61 | 3 | 4.0 (1.0–13.7) | 3.5 (1.0–13.0) |

*A large neoplasm was defined as a lesion that was 10 mm or more in diameter. An advanced neoplasm was defined as a polyp or polypoid lesion with villous features, a polyp or polypoid lesion with high-grade dysplasia, or cancer. CI denotes confidence interval.

†The relative risk was adjusted for age and sex. The group of patients with no distal polyps was the reference group.

Because previous research has suggested that the histologic features of distal polyps may be a better marker for advanced proximal neoplasia than their size¹¹ and because the measurement of a polyp through the endoscope may be inaccurate,¹² we defined an advanced neoplasm on the basis of histologic findings instead of size. To make our findings comparable with those of other studies, however,²⁻⁵ we also considered the relation between distal polyps and the combination of histologically advanced neoplasms and large tubular adenomas (≥ 10 mm in diameter) in the proximal colon. Because this relation was no different from that between distal polyps and histologically advanced proximal neoplasms alone, we have presented the results only for the definition of advanced neoplasm that we consider to be the more reliable of the two definitions.

In addition to distal polyps, we found that age was an important predictor of risk. For every five-year interval between the ages of 50 and 80 years, the risk of advanced proximal neoplasia increased by 32 percent. Few data are available to assess age as an independent risk factor for advanced proximal neoplasia. Levin and colleagues found that an age of more than 65 years was an independent risk factor for advanced proximal neoplasia.⁵ In a study of colonoscopic screening among 621 asymptomatic persons who were 50 to 75 years old and who had negative fecal occult-blood tests, Rex and colleagues found that each five-year increase in age increased the odds of colonic neoplasia of any kind by 1.36.¹³

In our study, men were more likely than women to have both proximal and distal neoplasms and were more than three times as likely to have advanced proximal neoplasms, after adjustment for age and distal findings. Although men are known to be at increased risk for colorectal neoplasia, the effect of sex apart from age and distal findings has been uncertain.^{11,14}

The prevalence of advanced proximal neoplasia in our patients with distal hyperplastic polyps was 4.0 percent (95 percent confidence interval, 1.3 to 6.7 percent). Although the 95 percent confidence interval for this estimate overlaps that for persons with no distal polyps, the relative risk of advanced proximal neoplasia, adjusted for age and sex, in patients with distal hyperplastic polyps as compared with the patients who had no distal polyps was 2.6 (95 percent confidence interval, 1.1 to 5.9). In part because of small samples, studies of the risk of proximal neoplasia in asymptomatic persons with distal hyperplastic polyps have had inconsistent findings. The risk of a proximal neoplasm of any size has ranged from 15 to 32 percent.¹⁵⁻¹⁸ More important, the risk of advanced proximal neoplasia and the risk of large proximal neoplastic polyps have not been assessed. Otori and colleagues found *K-ras* mutations in 47 percent of hyperplastic polyps, suggesting that they could be precursors of neoplasia.¹⁹ In the light of practice guidelines suggesting that hyperplastic polyps are not important^{20,21} and the need to consider previous findings in the process of interpreting new data,²² the importance of hyperplastic polyps remains uncertain and must be clarified by further research.

The efficiency of sigmoidoscopic screening in detecting proximal lesions can be assessed by calculating the number needed to screen — that is, the number of persons who would have to undergo sigmoidoscopic screening in order to detect one advanced proximal neoplasm. As the criterion for performing colonoscopy is relaxed (i.e., from the most stringent criterion of an advanced distal neoplasm to the criteria of a distal tubular adenoma or advanced neoplasm, any distal polyp, and finally, no polyp), the number needed to screen increases substantially (Table 4). However, the proportion of patients with advanced proximal neoplasia also increases. Further-

TABLE 4. NUMBER NEEDED TO SCREEN ACCORDING TO THE DISTAL FINDING USED AS A CRITERION FOR COLONOSCOPY.*

| DISTAL FINDING AS CRITERION FOR COLONOSCOPY | ADVANCED PROXIMAL NEOPLASM DETECTED (N=50) | NO. NEEDED TO SCREEN (95% CI) | NO. SCREENED |
|---|--|-------------------------------|--------------|
| | no. of patients (%) | | |
| Advanced neoplasm | 7 (14) | 9 (5–25) | 61 |
| Tubular adenoma or advanced neoplasm | 19 (38) | 12 (8–21) | 229 |
| Hyperplastic polyp, tubular adenoma, or advanced neoplasm | 27 (54) | 15 (12–25) | 430 |
| No polyp, hyperplastic polyp, tubular adenoma, or advanced neoplasm | 50 (100) | 40 (31–55) | 1994 |

*The number needed to screen is the number of patients who would have to undergo colonoscopic screening in order to identify one patient with advanced proximal neoplasia. CI denotes confidence interval.

more, even when colonoscopy is performed for any distal polyp, nearly half the cases of advanced proximal neoplasia are missed. These data indicate that a substantial proportion of advanced proximal neoplasms are not associated with any distal sentinel lesion. Physicians and policy makers could use this information to determine the appropriate threshold for performing a full colonoscopic examination. Although our data may be useful for deciding which screening techniques are best, other information is also important, such as the expense and complications of colonoscopy, the need for and frequency of repeated examinations, coexisting disease in patients undergoing screening, and the natural history of histologically advanced neoplasms.

The limitations of our study require comment. Despite the colonoscopic screening of 1994 persons, only 50 advanced proximal neoplasms were found. The small number of advanced and large proximal neoplasms precluded certain subgroup analyses. This limitation is not unique to our study. Some investigators have suggested that the size and number of distal tubular adenomas may affect the risk of proximal neoplasia.²⁻⁴ In our study, only 12 of the 168 persons with distal tubular adenomas had advanced proximal neoplasms. The small size of this subgroup precluded the detection of any but the largest differences. Furthermore, we did not find a significant association between the risk of advanced proximal neoplasia and the size of a distal adenoma, in contrast to the results reported by Read and colleagues.² Yet because the two studies had small numbers of patients, with overlapping confidence intervals for each category of lesions, the results of the two analyses are not statistically different. Wide confidence intervals as a result of the small numbers of advanced proximal lesions account at least in part for the paradox of qualitatively different yet statistically similar findings among studies.

Both in our study and in previous studies, limited clinical information was available to supplement the endoscopic information provided by the screening examinations. Individual risk estimates for advanced proximal neoplasia might be derived from such information as race, body-mass index, the presence or absence of a family history of colorectal neoplasia, and the results of any previous colorectal screening and diagnostic tests. Although several groups have investigated the risk of proximal neoplasia on the basis of distal findings alone,^{2-5,23-26} future studies should evaluate the risk by incorporating additional clinical information.

In summary, we found that increasing age, male sex, and the presence of polyps in the distal colon were independent risk factors for advanced proximal neoplasms in persons who were 50 years of age or older. Although our results are consistent with those of other studies with respect to the importance of advanced distal neoplasms as a marker of proximal neoplasia, our findings raise questions about the possible additional importance of hyperplastic polyps. Like other investigators,^{27,28} we found that almost half the patients with advanced proximal neoplasms had no distal lesions. The current strategy of deciding who should undergo colonoscopy solely according to the findings in the distal colon should be reconsidered.

Supported in part by grants from the Walther Cancer Institute, Indianapolis, and the National Institute of Diabetes and Digestive and Kidney Diseases (K24 DK02756-02).

We are indebted to the following members of the Lilly Colorectal Cancer Prevention Program: Kathy Anderson, R.N., David Bash, M.D., Diane Batza, R.N., Jeffery Bilotta, M.D., Robert Bishop, M.D., Gary Bolinger, M.D., Lawrence Born, M.D., E. David Brown, M.D., Galantin Bryan, J. Scott Buckley, M.D., Janet Burson, R.N., Robert Callon, M.D., Gene Chiao, M.D., Charles Cline, M.D., Sue Corneliuss, R.N., Michael Elmore, M.D., William Erdel, M.D., Paul Frederick, M.D., John Geneczko, M.D., Elizabeth Glowinski, R.N.,

Debra Helper, M.D., David Hollander, M.D., James Jacob, M.D., Olaf Johansen, M.D., Joseph Katz, M.D., Paul Kvo, M.D., Frederick Lane, M.D., Gregory Lemmel, M.D., Margaret Lockard, R.N., Mark Lybik, M.D., Stephen Mahoney, M.D., Michael Manbeck, M.D., James McGill, M.D., Donald McGovern, Jr., M.D., Becky Mellon, R.N., Janet Miller, R.N., Katherine O'Conner, M.D., Thomas O'Conner, M.D., Patrick Park, M.D., Scott Pittman, M.D., David Pound, M.D., Phyllis Quintana, Douglas Rex, M.D., Donald Shook, M.D., William Sobat, M.D., Daniel Stanley, M.D., Frank Troiano, M.D., Benjamin Upchurch, M.D., Max Warner, M.D., and Maurits Wiersema, M.D.

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