

## IMPORTANCE OF ADENOMAS 5 mm OR LESS IN DIAMETER THAT ARE DETECTED BY SIGMOIDOSCOPY

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### ABSTRACT

**Background** The need for colonoscopy in patients with adenomas 5 mm or less in diameter that are detected by sigmoidoscopy is controversial.

**Methods** We prospectively determined the prevalence of proximal colonic neoplasms in asymptomatic patients at average risk for colorectal cancer, each of whose index lesion on screening fiberoptic sigmoidoscopy was a benign adenoma. Polyps found on sigmoidoscopy underwent biopsy, and colonoscopy was recommended to all patients with neoplastic polyps. Rectosigmoid adenomas were classified as diminutive ( $\leq 5$  mm in diameter), small (6 to 10 mm in diameter), or large ( $\geq 11$  mm in diameter).

**Results** Of 3496 consecutive patients referred for sigmoidoscopy, 311 had neoplastic rectosigmoid polyps; 108 of these patients were excluded from the analysis because of a history of colonic neoplasia, symptoms, prior colonic evaluation, or incomplete follow-up data. The remaining 203 patients made up the study group, and all underwent colonoscopy. Neoplasms were found in the proximal colon in 40 of 137 patients (29 percent) with diminutive index polyps, 15 of 52 patients (29 percent) with small index polyps, and 8 of 14 patients (57 percent) with large index polyps. Advanced neoplasms (adenomas  $\geq 10$  mm in diameter, adenomas with a villous component or moderate-to-severe dysplasia, carcinoma in situ, or frank carcinoma) were found in 8 patients (6 percent), 5 patients (10 percent), and 4 patients (29 percent), respectively. Two patients with diminutive index polyps had proximal carcinoma in situ, and two had proximal stage I carcinomas; one patient with a large index polyp had proximal stage III carcinoma.

**Conclusions** The substantial prevalence of proximal colonic neoplasms, including advanced lesions, in asymptomatic average-risk patients with rectosigmoid adenomas  $\leq 5$  mm in diameter warrants colonoscopy in these patients. (N Engl J Med 1997;336:8-12.)

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**I**NCREASED use of flexible sigmoidoscopy as a screening examination for colorectal carcinoma has led to increased detection of benign adenomatous polyps  $\leq 5$  mm in diameter (referred to as diminutive) in the rectosigmoid of asymptomatic patients.<sup>1,2</sup> Although adenomas are neoplastic lesions that are considered to be the precursors of most colorectal cancers,<sup>3,4</sup> the clinical importance of diminutive adenomas that are found on screening sigmoidoscopy has been the subject of considerable debate.<sup>2,3,5-22</sup> Some believe that adenomas of the rec-

tosigmoid, no matter what their size, are markers of neoplastic change throughout the colon and thus recommend colonoscopy for patients with such adenomas.<sup>2,8,9,11,12,14,15,20-22</sup> Others believe that the probability of discovering an advanced proximal neoplasm is low (1 to 4 percent), and therefore, colonoscopy is not indicated.<sup>5-7,10,16,17,19</sup> No consensus has been reached.<sup>3</sup> Studies in which it was concluded that colonoscopy is unnecessary have been retrospective,<sup>17,19</sup> have relied on follow-up of patients by means of national cancer registries<sup>6</sup> or autopsy records,<sup>17</sup> or have based their conclusions on the low prevalence of advanced proximal neoplasms, despite finding a substantial prevalence of smaller proximal neoplastic polyps.<sup>5,10,19</sup> Studies advocating colonoscopy could be criticized for including symptomatic patients or patients at risk for colorectal neoplasms<sup>9,12,15</sup> or for having only a small group of patients available for analysis.<sup>8,11,12,21</sup>

We prospectively determined the prevalence of proximal colonic neoplasms in a large group of asymptomatic patients at average risk for colorectal cancer who were found to have diminutive benign adenomatous polyps on screening flexible sigmoidoscopy. Because the definition of diminutive polyps in the literature has ranged from  $\leq 5$  mm to  $\leq 10$  mm in diameter, we classified polyps  $\leq 5$  mm as diminutive and those 6 to 10 mm as small. We also compared patients with diminutive or small polyps with a group of patients whose index rectosigmoid polyps were large ( $\geq 11$  mm).

### METHODS

Data were collected prospectively on 3496 consecutive patients referred for screening flexible sigmoidoscopy at the Lahey-Hitchcock Medical Center between May 1992 and April 1995. In preparation for sigmoidoscopy, patients were instructed to take 10 oz (300 ml) of magnesium citrate (Cumberland-Swan, Smyrna, Tenn.), 3 bisacodyl tablets (Dulcolax, Ciba, Woodbridge, N.J.), and only clear liquids on the day before examination and to use a Fleet enema (C.B. Fleet, Lynchburg, Va.) on the day of the examination. Sigmoidoscopy was performed with a 60-cm flexible fiberoptic instrument (Pentax, Orangeburg, N.Y.). All polyps identified by sigmoidoscopy underwent biopsy. Colonoscopy was recommended to all patients in whom adenomatous polyps were found. All colonoscopies were performed within one year of sig-

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moidoscopy (usually within three months). In preparation for colonoscopy, patients underwent whole-gut lavage with polyethylene glycol–electrolyte solution (Colyte, Reed and Carrick, Jersey City, N.J.). Colonoscopy was performed with a video colonoscope (Pentax). All polyps found at colonoscopy were removed. Patients who had an incomplete colonoscopic examination were referred for air–contrast barium enema. The size and location of the lesions were obtained from the endoscopy report. The examiner used biopsy forceps as a visual guide to estimate the size of the polyps. The histologic characteristics of the polyps were obtained from the pathology report. Advanced neoplasms were defined as adenomas  $\geq 10$  mm in diameter, adenomas with a villous component or moderate-to-severe dysplasia, carcinoma in situ, or frank carcinoma.

To obtain an asymptomatic, average-risk study population, we excluded patients from the analysis if they had a history of colon cancer, neoplastic polyps, or inflammatory bowel disease; had a positive fecal occult-blood test (Hemoccult); had a first-degree relative with colon cancer; had rectal bleeding; had anemia; had a recent change in bowel habits; or had undergone colonoscopy or enema with contrast medium within five years before flexible sigmoidoscopy. Patients were also excluded if they did not undergo colonoscopy at our institution, declined to undergo colonoscopy, or had an incomplete colonoscopy and then did not have a subsequent air–contrast barium enema.

Statistical comparisons between groups were calculated with Fisher's exact test (two-tailed).

RESULTS

Polypoid lesions were found on 768 of the 3496 screening flexible-sigmoidoscopic examinations (22 percent). The histologic characteristics of the most advanced (index) lesion identified are shown in Table 1. Ninety of the 311 patients with neoplastic rectosigmoid polyps were excluded from the analysis because of a history of colonic neoplasia, symptoms, or prior colonic evaluation. Eighteen additional patients were excluded from the analysis because of incomplete follow-up data: seven had undergone colonoscopy elsewhere; five declined to undergo colonoscopy; one had not yet undergone colonoscopy; two had had incomplete colonoscopy and had not subsequently had an air–contrast enema; and three had had an air–contrast enema that was not preceded by colonoscopy.

The study population was thus composed of 203 asymptomatic, average-risk patients in whom benign neoplastic polyps were identified by screening flexible sigmoidoscopy, and who then underwent colonoscopy at our institution. Colonoscopy to the cecum was achieved in 189 of the 203 patients (93 percent). The 14 patients in whom cecal intubation was not confirmed underwent air–contrast barium enema examinations, all of which showed no mass lesions. Patients were divided into three groups on the basis of the size of their index rectosigmoid neoplasms: 137 patients had diminutive index polyps ( $\leq 5$  mm in diameter), 52 patients had small index polyps (6–10 mm in diameter), and 14 patients had large index polyps ( $\geq 11$  mm in diameter). The histologic characteristics of the index rectosigmoid neoplasms are shown in Table 2.

Among the 137 patients with diminutive index le-

TABLE 1. HISTOLOGIC CHARACTERISTICS OF INDEX LESIONS FOUND AT FLEXIBLE SIGMOIDOSCOPY.

CHARACTERISTIC	NO. OF PATIENTS	% OF TOTAL
Hyperplastic polyp	391	50.9
Neoplastic polyp	311	40.5
Normal mucosa	52	6.8
Unknown*	8	1.0
Inflammation	4	0.5
Lipoma	1	0.1
Hamartoma	1	0.1
Total	768	

\*The histologic characteristics of the index lesion could not be determined in eight patients for the following reasons: anticoagulation at the time of flexible sigmoidoscopy (no biopsy) and subsequent negative findings on air–contrast barium enema (two patients); diminutive polyp and no pathology report (three patients); polyp seen at flexible sigmoidoscopy (no biopsy) and not seen at subsequent colonoscopy (one patient); polyp seen at flexible sigmoidoscopy (no biopsy), and patient declined to undergo colonoscopy (one patient); and polyp seen at flexible sigmoidoscopy (no biopsy) and not recovered at subsequent colonoscopy (one patient).

TABLE 2. HISTOLOGIC CHARACTERISTICS OF INDEX NEOPLASTIC LESIONS FOUND AT FLEXIBLE SIGMOIDOSCOPY IN 203 ASYMPTOMATIC AVERAGE-RISK PATIENTS.

CHARACTERISTIC	RECTOSIGMOID ADENOMA $\leq 5$ mm IN DIAMETER (N = 137)	RECTOSIGMOID ADENOMA 6–10 mm IN DIAMETER (N = 52)	RECTOSIGMOID ADENOMA $\geq 11$ mm IN DIAMETER (N = 14)
	no. of patients (%)		
Tubular adenoma	129 (94)	41 (79)	9 (64)
Tubulovillous adenoma	3 (2)	8 (15)	3 (21)
Villous adenoma	1 (1)	0	1 (7)
Adenoma with moderate-to-severe dysplasia	4 (3)	3 (6)	1 (7)

sions (mean [ $\pm$ SD] age,  $60.7 \pm 6.7$  years), the mean size of the rectosigmoid polyps was  $3.4 \pm 1.7$  mm and the index neoplasm was solitary in 128 (93 percent). Proximal neoplasms were found in 29 percent at colonoscopy (Table 3), and advanced proximal neoplasms were found in 6 percent, including three tubular adenomas  $\geq 10$  mm in diameter, one tubulovillous adenoma, two adenomas with carcinoma in situ, and two frank carcinomas. The two patients with frank carcinoma had stage I lesions (T2N0M0 according to the tumor–node–metastasis system of staging), and both underwent colectomy. As of Oc-

**TABLE 3.** HISTOLOGIC CHARACTERISTICS AND SIZE OF THE MOST ADVANCED PROXIMAL NEOPLASM FOUND AT COLONOSCOPY IN 203 ASYMPTOMATIC AVERAGE-RISK PATIENTS WITH BENIGN RECTOSIGMOID ADENOMAS, ACCORDING TO THE SIZE OF THE INDEX LESIONS.

VARIABLE	RECTOSIGMOID ADENOMA $\leq 5$ mm IN DIAMETER (N = 137)	RECTOSIGMOID ADENOMA 6–10 mm IN DIAMETER (N = 52)	RECTOSIGMOID ADENOMA $\geq 11$ mm IN DIAMETER (N = 14)
	no. of patients (%)		
Patients with proximal neoplasms	40 (29)	15 (29)	8 (57)
Histologic characterization of most advanced proximal neoplasm			
Tubular adenoma	35	13	6
Tubulovillous adenoma	1	2	1
Carcinoma in situ	2	0	0
Carcinoma	2	0	1
Size of most advanced proximal neoplasm			
$\leq 5$ mm	25	5	0
6–10 mm	8	5	4
$\geq 11$ mm	7	5	4

tober 1996, both were free of disease. The presence of multiple diminutive rectosigmoid adenomas was not predictive of advanced proximal neoplasia: four of the nine patients with more than one adenoma at flexible sigmoidoscopy had proximal neoplasms, but none had advanced proximal neoplasms.

Among the 52 patients with small index lesions (age,  $61.7 \pm 7.2$  years), the mean size of the rectosigmoid polyps was  $6.3 \pm 2.4$  mm and the index lesion was solitary in 44 (85 percent). The prevalence of proximal neoplastic lesions (29 percent) and advanced proximal neoplasms (10 percent) was similar to the prevalence in patients with diminutive rectosigmoid adenomas (Table 3). Advanced proximal neoplasms included three tubular adenomas  $\geq 10$  mm in diameter and two tubulovillous adenomas (35 mm and 15 mm in diameter). As in the group with diminutive index lesions, the presence of multiple small rectosigmoid adenomas was not predictive of advanced proximal neoplasia: three of the eight patients with more than one adenoma at flexible sigmoidoscopy had proximal neoplasms, but none had advanced proximal neoplasms.

Among the 14 patients with large index lesions (age,  $63.7 \pm 5.2$  years), the mean size of the rectosigmoid polyps was  $13.3 \pm 6.5$  mm and the index lesion was solitary in 10 (71 percent). Proximal neoplasms were discovered on colonoscopy in 8 of the 14 patients (57 percent): four tubular adenomas 6 to 10 mm in diameter and four neoplasms  $\geq 11$  mm, including one tubulovillous adenoma and one stage III carcinoma (T3N1M0) (Table 3). Thus, 4 of 14 patients (29 percent) had advanced proximal neoplasms in this group.

Increased size of the index rectosigmoid neoplasm did not correlate with the prevalence of proximal

neoplasia ( $P = 0.11$ ), but it did correlate with the prevalence of advanced proximal neoplasia ( $P = 0.02$ ). Age was not a significant variable. Of the 203 patients in the study population, 29 percent of the 143 patients under 65 years of age had proximal neoplasms, as compared with 35 percent of the 60 patients over 65. Advanced neoplasms were found in 7 percent of those under 65, as compared with 12 percent of those over 65.

## DISCUSSION

We found that asymptomatic, average-risk patients with diminutive or small rectosigmoid adenomas on screening flexible sigmoidoscopy have a 29 percent prevalence of proximal neoplasms at colonoscopy. Our data are consistent with those of prior studies that used similar methods, which demonstrated a 26 to 42 percent prevalence of proximal neoplasms in patients with diminutive rectosigmoid adenomas.<sup>8,10-12,15,19,21</sup> However, some of these studies included symptomatic patients or patients with established risk factors for the development of colorectal carcinoma.<sup>9,12,15</sup> We used strict exclusion criteria to avoid such biases.

We also found that patients with diminutive or small rectosigmoid adenomas have a substantial prevalence of advanced proximal neoplasms — 6 percent and 10 percent, respectively. Most striking were the four patients whose diminutive rectosigmoid adenomas prompted the discovery of early-stage proximal carcinomas. Although the prevalence of advanced neoplasms in prior studies has varied somewhat (1 to 13 percent),<sup>5,10,15,21</sup> our values are within this range and are higher than those expected in the general population (3 percent), as estimated by Grossman et al. in their age-adjusted analysis of autopsy data.<sup>10</sup>

The substantial prevalence of proximal colonic neoplasms in our patients with diminutive rectosigmoid adenomas suggests that neoplastic change in the distal colon may be a marker for neoplastic change in the proximal colon. Since we did not perform colonoscopy in a control group of patients who had no neoplasms at sigmoidoscopy, this association remains unproved. The prevalence of proximal neoplasia in asymptomatic, average-risk patients without neoplastic polyps in the rectosigmoid has ranged from 13 to 28 percent in the literature,<sup>8,14,21,23</sup> although the largest of these studies, by Rex et al. (422 patients), had only a 15 percent prevalence of proximal neoplasia.<sup>14</sup>

Some have argued that diminutive rectosigmoid adenomas are not markers for proximal neoplasia<sup>10,19</sup> because of autopsy data demonstrating adenomatous colorectal polyps in 23 to 46 percent of American and Western European adults.<sup>24-27</sup> However, the average age of patients in autopsy studies is about 10 years older<sup>24-27</sup> than in our series, and the prevalence of adenomatous polyps has been shown to increase with age, by about 7.5 percent per decade.<sup>24,25,28,29</sup> Autopsy series do not exclude symptomatic patients or patients at high risk for colon carcinoma, which may result in a higher prevalence of colonic neoplasia than is seen in asymptomatic patients at average risk.

Some studies of patients with diminutive rectosigmoid adenomas have demonstrated a low prevalence (1 to 3 percent) of advanced proximal neoplasms.<sup>5,10</sup> However, our study and others<sup>15,21</sup> have found a substantially higher prevalence (6 to 13 percent). Furthermore, a paucity of advanced proximal neoplasms should not be reassuring, since a small, benign adenoma will not necessarily remain small and benign. Untreated polyps have been shown to grow and undergo malignant change,<sup>18</sup> and autopsy studies have shown that polyp size increases with increasing age,<sup>28</sup> suggesting that polyps grow over time. Carcinoma can exist in small polyps; 15 percent of malignant polyps removed in a study of colonoscopic polypectomies were less than 10 mm in diameter.<sup>22</sup> Data from the National Polyp Study suggest that the removal of even diminutive colorectal adenomas may prevent the development of colorectal carcinoma.<sup>4</sup>

The decision to proceed with colonoscopy in patients with rectosigmoid adenomas should ideally be based on the reduction in the risk of colorectal carcinoma afforded by colonoscopic polypectomy of proximal lesions. It is difficult to estimate this risk because colorectal cancers grow slowly and are relatively uncommon as compared with benign polyps. Atkin et al. found a low incidence of subsequent colon cancer in patients who had had small ( $\leq 10$  mm) rectosigmoid adenomas removed by rigid sigmoidoscopy and were not subsequently monitored by colonoscopy.<sup>6</sup> Spencer et al. found no increase in the risk

of subsequent colon carcinoma in patients who had small ( $\leq 10$  mm) rectosigmoid polyps observed or fulgurated without biopsy.<sup>17</sup> It is difficult to draw firm conclusions from their data, however. Follow-up of patients through the National Health Service Central Register,<sup>6</sup> medical records, or autopsy<sup>17</sup> may be inaccurate. Many patients in the study by Atkin et al. did in fact undergo colonic evaluation, resulting in polypectomies, which may have reduced the risk of colon carcinoma.<sup>6</sup> The study by Spencer et al. was retrospective, and selection bias was introduced by the exclusion of 227 patients who did undergo biopsy of their polyps and had unfavorable histologic characteristics, and by the inclusion of the 68 percent of patients who underwent barium enema before entering the study.<sup>17</sup> In addition, since no biopsies were performed, many of these polyps may have been non-neoplastic polyps, which are not associated with an increased risk of proximal neoplasia.<sup>14,21</sup>

Given the difficulties of evaluating the subsequent risk of carcinoma, we believe that the prognostic value of neoplastic rectosigmoid polyps is best estimated by their association with proximal colonic neoplasia. Advanced rectosigmoid neoplasms are clearly associated with advanced proximal neoplasms. In addition, our data show that patients with diminutive or small adenomas on screening sigmoidoscopy have a substantial risk of having proximal colonic neoplasms, many of which are advanced lesions. It may ultimately be more cost effective to decrease the frequency of subsequent colonoscopies than to abandon evaluation of the proximal colon.

Our study did not address the issue of proximal neoplasms in asymptomatic patients with negative fecal occult-blood tests who do not have rectosigmoid neoplasms and who would thus be missed with the current screening strategy. Screening colonoscopy has been advocated by some because of its ability to detect proximal neoplasms in the absence of distal neoplasms.<sup>23,30</sup> However, the great cost has deterred most centers from adopting such a program.<sup>13</sup> Since flexible sigmoidoscopy remains the recommended endoscopic screening procedure for colorectal cancer in asymptomatic, average-risk patients,<sup>31,32</sup> findings at sigmoidoscopy will thus dictate the need for subsequent colonoscopy. We believe the substantial prevalence of proximal neoplasms and advanced proximal neoplasms in patients with diminutive and small rectosigmoid adenomas clearly warrants colonoscopy.

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