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CLINICAL RESEARCH STUDY

Risk of proximal colorectal neoplasia among asymptomatic patients with distal hyperplastic polyps

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ABSTRACT

PURPOSE: Many guidelines on colorectal cancer screening do not consider distal hyperplastic polyps to be a marker for proximal neoplasia. However, 11 of 17 published studies have shown an increased risk of proximal neoplasia in patients with distal hyperplastic polyps. Our goal is to assess the risk of proximal neoplasia in asymptomatic patients with distal hyperplastic polyps, compared to those with distal tubular adenomas or no distal polyps.

METHODS: We assessed proximal (cecum, ascending, transverse colon and splenic flexure) and distal polyps in patients undergoing screening colonoscopy, classifying them into 3 groups: distal hyperplastic polyps only; distal adenomas with or without hyperplastic polyps; no distal polyps. The prevalence of proximal neoplasia and advanced neoplasia (polyps ≥1 cm, villous adenomas, or cancer) was compared among these groups.

RESULTS: Of 2357 patients, 427 (18%) had neoplasia, including 103 (4%) with advanced neoplasia. Proximal neoplasia occurred in 175 (9%) of 1896 patients with no distal polyps, compared with 28 (12%) of 237 with distal hyperplastic polyps ($P = 0.20$) and 64 (29%) of 224 with distal adenomas ($P < 0.0001$). Proximal advanced neoplasia occurred in 39 (2%) patients with no distal polyps, compared with 4 (2%) with distal hyperplastic polyps ($P = 0.70$) and 9 (4%) with distal adenomas ($P = 0.13$).

CONCLUSIONS: Patients with distal hyperplastic polyps, unlike those with distal adenomas, do not exhibit an increased risk for proximal neoplasia or proximal advanced neoplasia compared to those with no distal polyps. The discovery of hyperplastic polyps on screening sigmoidoscopy should not prompt colonoscopy.

Although colonoscopic screening in asymptomatic patients aged ≥50 years is becoming more popular, many patients are still screened by sigmoidoscopy.[1] A distal adenoma is regarded as a marker for proximal neoplasia.[2] However, the importance of distal hyperplastic polyps is unclear. Most screening guidelines do not consider distal hyperplastic polyps to be markers for proximal neoplasia.[3-5] These guidelines are supported by studies showing that the prevalence of proximal neoplasia in patients with distal hyperplastic polyps is similar to those with no distal polyps and lower than those with distal adenomas.[6-11] However, numerous studies have reported opposite results.[12-22] These discrepancies may be due to limitations in study design and patient selection.

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The purpose of our study is to assess the risk of proximal neoplasia in asymptomatic screening patients with distal hyperplastic polyps, as compared to those with distal adenomas or no distal polyps. The results will help determine whether or not patients with hyperplastic polyps found on sigmoidoscopy should be referred for colonoscopy.

Methods

This study protocol was approved by the Institutional Review Board of Virginia Mason Medical Center, Seattle.

Subject recruitment

Between July 2001 and October 2003, we enrolled consecutive adults participating in our screening colonoscopy clinic. In this clinic, one-time colonoscopy was performed on asymptomatic patients. Most participants were referred from local primary care providers. Patients were screened by a nurse using a standard questionnaire to verify that they did not have gastrointestinal symptoms, including bleeding, persistent or severe diarrhea, changes in bowel habits, or abdominal pain. We also confirmed that patients had not had a positive fecal occult blood test within the past 6 months. Additional exclusion criteria included a history of colorectal cancer or adenomas, inflammatory bowel disease, hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis syndromes, incomplete colonoscopy, suboptimal bowel preparation, or age younger than 40 years. We analyzed our entire study cohort as well as the subgroup of patients aged ≥50 years. Ten board-certified gastroenterologists performed all colonoscopies.

Screening procedures

Bowel preparation was done with phospho-soda laxative solution (CB Fleet, Lynchburg, Va) or polyethylene glycol lavage (Schwarz Pharma, Milwaukee, Wis) using the same protocol as that used for diagnostic colonoscopy. Fecal occult blood testing was not routinely performed before the procedure. During colonoscopy, the size and location of all polyps were recorded and the polyps were removed if possible. Polyp specimens were classified according to criteria established by the World Health Organization. Specimens with nonspecific inflammation, lymphoid hyperplasia, or hamartomatous features were considered to be "normal" tissue for the purposes of this study.

For our study, we defined the proximal colon to include the cecum, ascending colon, transverse colon, and splenic flexure. However, because the sigmoidoscope may reach the splenic flexure during unsedated procedures, a secondary analysis was done using an alternative definition of the demarcation—the descending and sigmoid colon junction. An "advanced" neoplastic lesion was defined as a polyp with villous, highly dysplastic, or malignant features, or ≥1 cm in size.

Data analysis

All data was collected in a customized Access XP database (Microsoft, Redmond, Wash). The prevalence of proximal neoplasia and proximal advanced neoplasia was calculated for each of 3 groups: those with distal hyperplastic polyps but no distal adenomas, those with distal adenomas with or without distal hyperplastic polyps, and those with no distal polyps. All polyps were confirmed histologically. In the case of patients with multiple types of polyps, the patient was classified according to the most advanced precancerous lesion, eg, a patient with both adenomas and hyperplastic polyps was included in the adenoma group. Age- and sex-adjusted risk ratios (RR) were calculated, with the risk of patients without distal polyps being set at 1.0. P values <0.05 were considered significant.

The risk of proximal neoplasia was also assessed in subgroups with distal nonadvanced neoplasia or rectal hyperplastic polyps. Multivariate logistic regression analysis was performed, with proximal neoplasia or proximal advanced neoplasia as the dependent variable, and age, sex, family history of colorectal cancer, and distal colorectal findings as the independent variables. Data analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, Ill).

Results

During the study period, 2427 patients underwent screening colonoscopy. Twenty-two patients were excluded because they were younger than 40 years, and 48 were excluded because colonoscopy was incomplete or the bowel preparation was suboptimal. This left a study cohort of 2357 patients aged ≥40 years and 2188 patients ≥50 years. The mean age, prevalence of smoking or nonsteroidal anti-inflammatory agent use and family history of colon cancer did not differ between the 3 comparison groups, but patients with distal adenomas had a higher proportion of men (Table 1).

Overall findings

Overall, 427 (18%) patients had at least one neoplastic lesion, including 103 (4%) with at least one advanced neoplasm. The prevalence of neoplasia and advanced neoplasia increased with advancing age and male sex (Table 2). A total of 9 cancers were detected (0.4%); 5 were proximal to the splenic flexure. All patients were treated with surgical resection and are still alive at the time of this publication. There were no procedure-related deaths or complications except for a post-polypectomy bleed and a perforation requiring partial colectomy. This corresponded to a complication rate of 0.1%.

Table 1 Clinical and demographic charactersitics of study patients; the demarcation between proximal and distal colon is assumed to be at the splenic flexure

		Subgroups based on distal findings		
	Overall (N = 2357)	No polyp (n = 1896)	Hyperplastic polyp (n = 237)	Adenoma (n = 224)
Characteristic	Number (%) or Mean ± SD			
Age (years)	58.8 ± 9	58.6 ± 9	58.9 ± 8	60.2 ± 10
Male sex	1167 (50%)	914 (48%)	118 (50%)	146 (65%)
Aspirin or nonsteroidal anti-inflammatory drug use*	141 (6%)	114 (6%)	17 (7%)	12 (5%)
Family history of colon cancer†	455 (19%)	362 (19%)	46 (19%)	47 (21%)
Smoking history‡	189 (8%)	152 (8%)	21 (9%)	18 (8%)

*Regular use is defined as taking at least 1 unit of either aspirin or a nonsteroidal anti-inflammatory agent more than once every 2 days, on average, during the past 6 months.

†Positive family history is defined as having at least one case of colorectal cancer in a first- or second-degree relative.

‡Positive smoking history is defined as being a current smoker or having a ≥20 pack-year smoking history.

SD = standard deviation.

Risk of proximal neoplasia

The prevalence of proximal neoplasia and proximal advanced neoplasia varied according to distal colon findings (Table 3). For both definitions of the demarcation, the risk of proximal neoplasia in the distal hyperplastic polyp group was similar to that of the no distal polyp group and significantly lower than that of the distal adenoma group. Analogous results were obtained when we restricted our analysis to patients aged ≥50 years (Table 4). The risk of proximal advanced neoplasia was not statistically different among the 3 comparison groups.

We found no differences in the risk of proximal neoplasia or proximal advanced neoplasia in patients with rectal hyperplastic polyps versus those with sigmoid or descending colon hyperplastic polyps (Tables 3 and 4). When patients with distal advanced neoplasia were excluded, patients with nonadvanced distal neoplasia still had a significantly increased risk of proximal neoplasia. For example, amongst patients aged ≥40 years, 45 of 168 patients with distal nonadvanced neoplasia had proximal neoplasia, resulting in a relative risk of 2.9 (95% confidence interval [CI] 2.0 to 4.2) when compared to those with no distal polyps.

Number-needed-to-screen

The estimated numbers of patients aged ≥40 years who would need to undergo colonoscopy to detect one proximal neoplasm were 10.9 for patients with no distal polyps, 8.5 for those with distal hyperplastic polyps, and 3.5 for those with distal adenomas. Among those aged ≥50 years, the numbers were 10.8 for patients with no distal polyps, 8.0 for those with distal hyperplastic polyps, and 3.4 for those with distal adenomas.

The estimated numbers of patients aged ≥40 years who would need to undergo colonoscopy to detect one proximal advanced neoplasm were 48 for patients with no distal

Table 2 Overall findings stratified by sex and age

	Age 40-49 years	Age 50-59 years	Age 60-69 years	Age 70+ years
Most advanced finding in colon*	Number (%)			
Men	n = 86	n = 635	n = 281	n = 166
No polyp	69 (80%)	426 (67%)	174 (62%)	88 (53%)
Hyperplastic polyp	7 (8%)	77 (12%)	32 (11%)	16 (10%)
Adenoma	8 (9%)	108 (17%)	56 (20%)	44 (27%)
Advanced neoplasia†	2 (2%)	24 (4%)	19 (7%)	18 (11%)
Women	n = 83	n = 623	n = 326	n = 157
No polyp	63 (74%)	479 (77%)	237 (73%)	113 (73%)
Hyperplastic polyp	12 (15%)	75 (12%)	47 (14%)	15 (10%)
Adenoma	7 (8%)	56 (9%)	28 (9%)	17 (11%)
Advanced neoplasia†	1 (1%)	13 (2%)	14 (4%)	12 (8%)

*In the case of patients with multiple types of polyps, the patient was classified according to the most advanced precancerous lesion.

†An "advanced" neoplasm was defined as a polyp with villous, highly dysplastic or malignant features, or ≥1 cm in size.

Table 3 Prevalence of proximal neoplasia and proximal advanced neoplasia according to the most advanced lesion in the distal colon in patients ≥40 years of age

		Risk for proximal neoplasia			Risk for proximal advanced neoplasia*		
Most advanced distal polyp	Total patients	Patients with proximal neoplasia Number (%)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Patients with proximal advanced pneoplasia Number (%)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)
Assuming demarcation between the proximal and distal colon is at the splenic flexure							
No polyp	1896	175 (9%)	1.0	1.0	39 (2%)	1.0	1.0
Hyperplastic polyp	237	28 (12%)	1.3 (0.8-2.0)	1.3 (0.8-1.9)	4 (2%)	0.8 (0.3-2.3)	0.8 (0.3-2.3)
Rectal	122	15 (12%)	1.3 (0.8-2.3)	–	2 (2%)	0.8 (0.2-3.3)	–
Distal colon‡	115	13 (11%)	1.2 (0.7-2.2)	–	2 (2%)	0.9 (0.2-3.6)	–
Adenoma	224	64 (29%)	3.1 (2.2-4.3)	2.8 (2.0-3.9)	9 (4%)	2.0 (0.9-4.1)	1.8 (0.9-3.7)
Assuming demarcation between the proximal and distal colon is at the descending-sigmoid junction							
No polyp	1978	225 (11%)	1.0	1.0	48 (2%)	1.0	1.0
Hyperplastic polyp	206	26 (13%)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	5 (2%)	1.0 (0.4-2.5)	1.0 (0.4-2.5)
Rectal	122	14 (12%)	1.2 (0.7-2.2)	–	3 (3%)	1.0 (0.3-3.3)	–
Distal colon‡	84	12 (14%)	1.6 (0.8-2.9)	–	2 (2%)	1.0 (0.2-4.1)	–
Adenoma	173	54 (31%)	2.7 (2.0-3.8)	2.5 (1.8-3.5)	8 (5%)	1.9 (0.9-4.1)	1.7 (0.8-3.7)

RR = relative risk; CI = confidence interval.

*An "advanced" neoplasm was defined as a polyp with villous, highly dysplastic or malignant features, or ≥1 cm in size.

†Relative risk is adjusted for sex and age.

‡Distal colon is defined as the colon distal to the demarcation, excluding the rectum.

Table 4 Prevalence of proximal neoplasia and proximal advanced neoplasia according to the most advanced lesion in the distal colon in patients ≥50 years of age

		Risk for proximal neoplasia			Risk for proximal advanced neoplasia*		
Most advanced distal polyp	Total patients	Patients with proximal neoplasia n (%)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)	Patients with proximal advanced neoplasia Number (%)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)
Assuming demarcation between the proximal and distal colon is at the splenic flexure							
No polyp	1755	163 (9%)	1.0	1.0	37 (2%)	1.0	1.0
Hyperplastic polyp	225	28 (12%)	1.3 (0.9-2.0)	1.3 (0.9-2.0)	4 (2%)	0.9 (0.3-2.4)	0.9 (0.3-2.4)
Rectal	118	15 (13%)	1.4 (0.8-2.4)	–	2 (2%)	0.8 (0.2-3.4)	–
Distal colon‡	107	13 (12%)	1.3 (0.7-2.4)	–	2 (2%)	0.9 (0.2-3.7)	–
Adenoma	208	62 (30%)	3.2 (2.3-4.5)	2.9 (2.1-4.1)	9 (4%)	2.1 (1.0-4.3)	1.9 (0.9-3.9)
Assuming demarcation between the proximal and distal colon is at the descending-sigmoid junction							
No polyp	1832	208 (11%)	1.0	1.0	45 (3%)	1.0	1.0
Hyperplastic polyp	194	26 (13%)	1.2 (0.8-1.8)	1.1 (0.7-1.6)	5 (3%)	1.0 (0.4-2.7)	1.0 (0.4-2.6)
Rectal	118	14 (12%)	1.0 (0.6-1.9)	–	3 (3%)	1.0 (0.3-3.4)	–
Distal colon‡	76	12 (16%)	1.4 (0.7-2.6)	–	2 (3%)	1.1 (2.6-4.5)	–
Adenoma	162	52 (32%)	2.8 (2.0-4.0)	2.6 (1.8-3.6)	6 (4%)	1.5 (0.6-3.6)	2.0 (0.6-3.3)

RR = relative risk; CI = confidence interval.

*An "advanced" neoplasm was defined as a polyp with villous, highly dysplastic or malignant features, or ≥1 cm in size.

†Relative risk is adjusted for sex and age.

‡Distal colon is defined as the colon distal to the demarcation, excluding the rectum.

polyps, 59 for those with distal hyperplastic polyps, and 25 for those with distal adenomas. Among those aged ≥50 years, the numbers were 47 for patients with no distal polyps, 56 for those with distal hyperplastic polyps, and 23 for those with distal adenomas.

Multivariate logistic regression

In multivariate models, age (odds ratio [OR] 1.4 per 10 years; 95% CI: 1.1 to 1.8), male sex (OR 1.9; CI: 1.7 to 2.2) and distal neoplasia (OR 3.5; CI: 2.8 to 4.5) were independent risk factors for proximal neoplasia. Family history (OR 1.5; CI: 0.9 to 2.4) and distal hyperplastic polyp (OR 1.3; CI: 0.9 to 1.9) were not significant. For proximal advanced neoplasia, male sex (OR 2.2; CI: 1.2 to 3.6) was a risk factor, whereas age (OR 1.3 per 10 years; CI: 0.9 to 1.9), family history (OR 1.4; CI: 0.6 to 2.9), distal hyperplastic polyp (OR 0.9; CI: 0.4 to 2.3), and distal neoplasia (OR 1.6; CI: 0.8 to 2.8) were not. Distal neoplasm was still an independent predictor (OR 2.2; CI 1.3 to 3.6) for proximal neoplasia even when patients with advanced distal neoplasia and multiple distal neoplasia were excluded.

Discussion

Most guidelines do not recommend colonoscopy for patients with only hyperplastic polyps in the distal colon.[3-5] Of the 17 published studies assessing the relationship between distal hyperplastic polyps and the risk for proximal neoplasia, 6 showed that the risk in patients with distal hyperplastic polyps is similar to those with no distal polyps or lower than those with distal adenomas.[6-11] In contrast, 11 studies have reported opposite results.[12-22] A recent study on mixed polyps did not find any association with proximal neoplasia.[23]

These heterogeneous results can be explained by differences in study design. For example, some studies enrolled only screening patients whereas others included symptomatic patients undergoing diagnostic colonoscopy. Upon stratification, we find that only 6 of 11 studies on screening patients[12,15-17,21,22] concluded that hyperplastic polyps were markers for proximal neoplasia, in contrast to 5 of 6 studies on symptomatic patients.[13,14,18-20] Because the importance of distal hyperplastic polyps is mainly applicable to asymptomatic patients, screening studies are more likely to give valid answers to our study question.

In some studies, colonoscopy was performed on all enrolled patients (so-called "universal colonoscopy" design), whereas in others, patients first underwent sigmoidoscopy, with colonoscopy occurring only in those found to have distal colon polyps of any type ("nonuniversal colonoscopy" design). In most of this latter group, biopsy of the distal polyp was not done until the time of colonoscopy. On stratification, only 5 of 11 studies with the "universal colonoscopy" design[13,14,19,20,22] found that hyperplastic polyps were markers for proximal neoplasia, whereas all 6 studies with the "nonuniversal colonoscopy" design concluded that hyperplastic polyps were markers.[12,15-18,21] Several factors may account for these discrepancies. In "nonuniversal colonoscopy" studies, the "no distal polyp" group often consists of patients whose distal polyps were of "normal" histology, therefore there is no true control group. Furthermore, in such studies, the distal polyp biopsied on colonoscopy may not be the same as the one that was seen on the initial sigmoidoscopy; for example, a patient with a small distal adenoma may be misclassified because the adenoma was missed on follow-up colonoscopy.

It should also be noted that small studies comparing patients with distal adenomas versus those with distal hyperplastic polyps may suffer from inadequate statistical power and be vulnerable to a type 2 error, whereas studies comparing patients with no distal polyps versus those with distal hyperplastic polyps may demonstrate that the risk in the distal hyperplastic polyp group is significantly higher than that in the no-distal-polyp group but fail to show whether that risk is comparable to that in the distal adenoma group.

The 3 largest studies have shown contradictory results. One study from Indiana on 3025 asymptomatic patients showed an elevated risk of proximal advanced neoplasia in those with distal hyperplastic polyps.[22] In contrast, a study involving 3121 US veterans showed no increased risk of proximal neoplasia in such patients.[11] Finally, data from 8802 patients in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer trial suggested that patients with distal hyperplastic polyps were at similar risk compared to those with small distal adenomas.[21] These studies arrived at different conclusions probably because of differences in study design and subjects. Unlike the other 2 studies, the PLCO trial had a "nonuniversal colonoscopy" design and did not have a true control group with no distal polyps.[21] The Veterans Administration study was confined to veterans, the vast majority of whom were male,[11] whereas the study from Indiana had a cohort with 42% women.[22]

Two meta-analyses have attempted to summarize the available data. One meta-analysis summarized the results of 18 studies, including 3 reported only as abstracts.[24] Using a random effects model, the authors showed that distal hyperplastic polyps were associated with an absolute risk of 21-25% for proximal neoplasia and "may justify examination of the proximal colon"; however, the risk ratio was nonsignificant. This meta-analysis did not include results from the recently published PLCO trial.[21] The other meta-analysis included only 6 studies and concluded that distal hyperplastic polyps were not associated with proximal neoplasia.[25]

Our study is designed to avoid some of the limitations of previous studies. All enrolled patients were asymptomatic, and colonoscopy was performed on everyone regardless of distal findings, ie, the "universal colonoscopy" design. We also included all 3 groups of interest in our comparisons:

patients with distal adenomas, distal hyperplastic polyps, and no distal polyps.

Despite our efforts, there are some limitations to this study. First, localization of the splenic flexure or sigmoid-descending junction by the colonoscopist can be inaccurate. This may affect the results, although the direction of bias cannot be easily determined because it is unclear whether the endoscopist tends to mistake the flexure as being more distal or more proximal than its actual location. The arbitrary demarcation of the colon into proximal and distal portions may not reflect the true extent evaluated by sigmoidoscopy; we have tried to address this problem by performing analyses using two different definitions of the demarcation. Second, many proximal neoplasms are small adenomas (<5 mm), therefore their clinical implication is uncertain. Small adenomas are still neoplastic and may be precancerous, but some studies have suggested that they are not associated with any increased risk of subsequent colon cancer.[26,27] Finally, despite the large sample size, the number of proximal advanced neoplasia is still relatively small. This is the most likely reason for the lack of statistical significance when we compared the prevalence of proximal advanced neoplasia among the 3 groups, even though there appears to be a trend toward higher risk in patients with distal adenomas.

Multivariate analysis showed that in addition to the presence of a distal adenoma, other independent predictors of proximal neoplasia include advanced age and male sex. Age and male sex are well-established risk factors for colonic neoplasia.[28-30] In our study, family history of colon cancer was not a statistically significant predictor, but this may be due to the effects of collinearity as well as the grouping together of family history in first- and second-degree relatives with colon cancer.

The results of this study are helpful in determining whether or not patients screened by sigmoidoscopy should be referred for colonoscopy. Although some guidelines advocate colonoscopic screening of all patients above the age of 50,[5,31] others consider screening with sigmoidoscopy every 5 years to be as acceptable as colonoscopy every 10 years.[4,32] Attempts to implement universal colonoscopic screening are affected by several factors, including cost-effectiveness, patient acceptance, insurance coverage, and availability of adequately trained colonoscopists. At present, only about 30% of age-eligible persons undergo any type of endoscopic screening for colorectal cancer.[33] Thus, it is likely that sigmoidoscopy will continue to be important for colorectal cancer screening.

Our study shows that distal hyperplastic polyps are not markers for proximal neoplasia or advanced neoplasia. The absolute risk for proximal neoplasia in patients with distal hyperplastic polyps was 12%, whereas the relative risk was similar to that in persons without distal polyps and much lower than in those with distal adenomas. Thus, this study supports current screening recommendations. It will be important for practitioners who perform screening sigmoidoscopy to biopsy distal polyps (as opposed to automatically referring all patients with distal polyps for colonoscopy).

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