REVIEW

Is the Distal Hyperplastic Polyp a Marker for Proximal Neoplasia?

A Systematic Review

Sachin Dave, MD, Siu Hui, PhD, Kurt Kroenke, MD, Thomas F. Imperiale, MD

CONTEXT: The current literature is unclear about the association between distal hyperplastic polyps and synchronous neoplasia (adenomatous polyps and cancer) in the proximal colon.

OBJECTIVE: To estimate the prevalence of proximal neoplasia associated with distal hyperplastic polyps.

DATA SOURCES: Database searches (MEDLINE and EMBASE from 1966 to 2001) and manual search of the bibliographies of included and excluded studies, case reports, editorials, review articles, and textbooks of Gastroenterology.

STUDY SELECTION: Studies describing the prevalence of proximal neoplasia in persons with distal hyperplastic polyps.

DATA EXTRACTION: Demographics, clinical variables, study design, and prevalence of proximal neoplasia associated with various distal colorectal findings.

DATA SYNTHESIS: Of 18 included studies, 12 involved asymptomatic individuals in which the pooled absolute risk of any proximal neoplasia associated with distal hyperplastic polyps was 25% (95% confidence interval [95% CI], 21% to 29%). In 4 studies where colonoscopy was performed irrespective of distal findings, the absolute risk was 21% (95% CI, 14% to 28%). The relative risk of finding any proximal neoplasia in persons with distal hyperplastic polyps was 1.3 (95% CI, 0.9 to 1.8) compared to those with no distal polyps. Among 6 studies of patients with symptoms or risk factors for neoplasia, the absolute risk of proximal neoplasia was 35% (95% CI, 32% to 39%) in persons with distal hyperplastic polyps. In 2 studies of screening colonoscopy, advanced proximal neoplasia (cancer, or a polyp with villous histology or severe dysplasia, or a tubular adenoma ≥ 1 cm) was present in 4% to 5% of persons with distal hyperplastic polyps, which was 1.5 to 2.6 times greater than in those with no distal polyps.

CONCLUSIONS: In asymptomatic persons, a distal hyperplastic polyp is associated with a 21% to 25% risk for any proximal neoplasia and a 4% to 5% risk of advanced proximal neoplasia,

and may justify examination of the proximal colon. Further study is needed to determine the risk of advanced proximal neoplasia associated with size and number of distal hyperplastic polyps.

KEY WORDS: colorectal cancer; cancer screening; sigmoidoscopy; colorectal neoplasms; systematic review.

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Colorectal polypoid lesions are classified into 3 groups: neoplastic polyps, which consist of adenomatous polyps and adenocarcinomas; non-neoplastic polyps, which include hyperplastic and inflammatory polyps as well as hamartomas; and submucosal lesions, such as lipomas and lymphoid aggregates.¹ Adenomatous polyps (or adenomas) are further categorized as tubular, tubulovillous, or villous based on histology. More than 80% to 90% of colorectal polyps detected on colonoscopy are adenomatous or hyperplastic polyps.^{2–7} Only adenomas are considered premalignant, yet only a small minority will progress to cancer.

Several studies indicate that there is an association between proximal and distal colorectal adenomas.^{8–14} Persons with distal adenomas are generally considered more likely to harbor proximal neoplasia, with the magnitude of risk proportional to the size, number, and histology of distal adenomas.^{8–14} The risk of neoplasia in the proximal colon associated with distal hyperplastic polyps is uncertain. Experts disagree on whether persons with distal hyperplastic polyps should undergo examination of the proximal colon with colonoscopy to look for synchronous neoplasia.^{15–17} Guidelines from the American College of Gastroenterology,^{18,19} and the American Society of Gastrointestinal Endoscopy²⁰ do not recommend colonoscopy for patients with distal hyperplastic polyps. Guidelines for colorectal cancer screening from the Agency for Health Care Policy and Research,²¹ American Cancer Society,²² and U.S. Preventive Services Task Force guidelines²³ do not make any explicit recommendations for a work-up when distal hyperplastic polyps are discovered by screening sigmoidoscopy. An association between distal hyperplastic polyps and proximal neoplasia could have a significant impact on both detection of

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Address correspondence and requests for reprints to Dr. Imperiale: Regenstrief Institute, Inc., 1050 Wishard Blvd., Indianapolis, IN 46202 (e-mail: imperial@hsrd.va.iupui.edu).

colorectal neoplasms and economic costs for screening strategies. To determine whether an association exists and its magnitude, we performed a systematic review of the literature to measure (1) the absolute risk of synchronous proximal neoplasia in persons with distal hyperplastic polyps and (2) the relative risk of proximal neoplasia associated with distal hyperplastic polyps as compared to no distal polyps and to distal adenomatous polyps.

METHODS

Data Sources

We performed a literature search of MEDLINE (1966–2001) and EMBASE (1990–2001) using the following search terms: intestinal polyps, hyperplasia, colonic, colorectal, sigmoid neoplasms, cancer, incidence, and prevalence for MEDLINE, and intestinal polyps, hyperplasia, large intestine, and cancer for EMBASE. The database search strategy was complemented by cross-referencing the bibliographies of included and excluded articles, case reports, review articles, editorials, and textbooks of Gastroenterology. We also manually searched 1999–2001 issues of *Gastroenterology*, *Gastrointestinal Endoscopy*, *The American Journal of Gastroenterology*, and *Diseases of the Colon and Rectum* for article titles and abstracts addressing the study question. Our search was limited to studies published in English and to those involving human subjects.

Study Selection

Our inclusion criteria were broad to ensure capturing all relevant literature. We included studies measuring the prevalence of proximal neoplasia (adenomas or cancer) associated with distal hyperplastic polyps. Case reports, autopsy studies, and review articles were excluded. Reasons for excluding candidate studies from our final analysis fell into the following categories:

1. The distal and proximal colon were either not explicitly defined or the definition was not clinically appropriate (e.g., distal colon defined as the rectum alone).^{24–28}
2. Study data did not allow estimation of the risk of proximal neoplasia associated with distal hyperplastic polyps.^{5,6,29–37}
3. The histology of some or all of the polyps was not specified.^{38,39}

Data Extraction

Two investigators independently determined whether studies would be included or excluded. Differences were resolved through discussion with a third investigator. Qualitative data were abstracted by a single investigator and included demographic variables, indications for colonoscopy, risk factors for colorectal neoplasms, definition of the distal colon, length of flexible sigmoidoscope, size of distal polyps, and whether colonoscopy was performed

irrespective of distal findings or only when a distal polyp was found. Clinical comparability of the studies was determined on the basis of description and comparison of study design, study population, intervention, and outcomes. Based on these factors, studies were categorized as screening studies or case-finding studies. *Screening* studies were those involving asymptomatic patients undergoing screening sigmoidoscopy and/or colonoscopy. *Case-finding* studies involved patients undergoing diagnostic colonoscopy either for gastrointestinal symptoms or for risk factors for colorectal neoplasia such as previous polyps, positive family history, or inflammatory bowel disease. Quantitative data were extracted by 2 investigators and included the proportion of proximal neoplasia associated with the distal findings of hyperplastic polyps, adenomatous polyps, and no distal polyps.

Analysis

The 2 outcome variables we considered, *any-sized* proximal neoplasia (adenomas and cancer) and *advanced* neoplasia, were treated as binary variables. Advanced neoplasia was defined as cancer, or a polyp with severe dysplasia or villous histology, and may or may not have included tubular adenomas ≥ 1 cm.^{13,14} Consistency among studies for the absolute risk of proximal neoplasia with each distal finding was measured with a test for homogeneity. When homogeneity was present, results were combined among studies to estimate the pooled absolute risk of proximal neoplasia for the 3 distal findings of no polyps, hyperplastic polyps, and adenomatous polyps. Ninety-five percent confidence intervals for each proportion were calculated based on weighted binomial proportions. When heterogeneity was present, pooled absolute risks were estimated using a random effects model, which results in wider confidence limits proportional to the degree of heterogeneity.⁴⁰ The Mantel-Haenszel test for homogeneity was used to assess similarity of risk ratios among studies for the relative risks of proximal neoplasia associated with distal hyperplastic polyps and distal adenomatous polyps as compared to no distal polyps.⁴¹ Pooled relative risks were calculated only when the absolute risks were found to be homogeneous among studies.

To investigate whether certain study characteristics explained the different proportions of proximal neoplasia associated with distal findings, logistic regression models were used to test individual study characteristics with the studies considered as random effects.⁴² The variables tested were study design (prospective, retrospective), definition of the distal colon, size of the distal polyps studied (diminutive or not), and whether colonoscopy was performed selectively (i.e., only those patients with distal findings) or in all patients.

RESULTS

The search of MEDLINE and EMBASE databases and the manual search of the bibliographies of retrieved articles,

textbooks of Gastroenterology, and 1997–2001 issues of the aforementioned Gastroenterology journals yielded a total of 34 studies that potentially addressed our study question. Of these, we included 18 studies and excluded 16 studies for the reasons described previously.

Of 12 screening studies, 10 reported only *any* proximal neoplasia while 2 studies reported only *advanced* proximal neoplasia.^{28,29} The remaining 6 studies were considered case-finding studies. Studies that provided insufficient data to determine whether patients had symptoms or risk factors or did not state that subjects were asymptomatic were classified as case-finding studies. Separation of studies into these 2 groups was supported by finding homogeneity of the risk of proximal neoplasia with distal hyperplastic polyps when the studies were stratified into screening (P value for homogeneity = .15) or case-finding groups (P value for homogeneity = .71). This homogeneity was lost (P = .02) upon combining the 2 groups. With both groups of studies, study design, interventions, and outcome definitions were comparable. All studies were cross-sectional in that all measured the risk of synchronous proximal neoplasia among subjects with various distal findings.

Any-sized Proximal Neoplasia

Screening Studies ($N = 10$). *Descriptive results.* Table 1 and Figure 1 summarize descriptive and quantitative data for the screening studies that measured prevalence of any-sized proximal neoplasia. The overall mean age of subjects among the studies was 61 years (range, 27 to 91 years). For 5 of 10 studies, the minimum age requirement was 50 years.^{43–46} In the 3 studies for which age was provided by type of distal polyp, mean age was 60.3 years for patients with distal hyperplastic polyps and 62.3 years for those with distal adenomatous polyps. Two studies that reported gender distribution showed a 2:1 and 3:1 male predominance.^{44,47} In 3 other studies from VA hospitals, gender distribution was not specified but presumably had a male predominance.^{4,43,48} The only study that reported race had a Caucasian (98%) predominance.⁴⁵ All studies were conducted in academic medical centers. Four of the studies were retrospective,^{47,48} while the rest were prospective.

Five studies excluded patients with a positive family history for colon cancer,^{37,44,45,49,50} while 3 studies did not comment on family history.^{47,48} In the 2 remaining studies, a positive family history was present in 20% and 12% of subjects.⁴³ The distal colon was defined as the segment of colon within reach of the 35-cm flexible sigmoidoscope in 3 studies^{46,49}; as the rectosigmoid region in 2 studies^{45–47}; and as the segment of the colon within reach of the 60-cm flexible sigmoidoscope in the remaining studies. Four studies included subjects with diminutive polyps only, of which 1 study defined a diminutive polyp as <10 mm, while the rest defined diminutive as ≤ 5 mm.^{44,46,50} In a regression model with the studies as random effects, none

of the study characteristics (prospective or retrospective study design [P = .3], distal polyp required for performance of colonoscopy [P = .36], distal polyp size [P = .85], and the length of flexible sigmoidoscope [P = .8]) had any effect on the risk of proximal neoplasia associated with distal hyperplastic polyps.

Quantitative results. When study groups were categorized according to distal findings, the absolute risks of proximal neoplasia were homogeneous for distal hyperplastic polyps (P = .15), distal adenomatous polyps (P = .66), and no distal polyps (P = .12). Absolute risks of proximal neoplasia for each distal finding are shown for each study in Figure 1. Proximal neoplasia was present in 16% (95% CI, 13% to 20%) of persons with no distal polyps, in 25% (95% CI, 21% to 29%) of those with distal hyperplastic polyps, and in 36% (95% CI, 32% to 39%) of those with distal adenomatous polyps (Table 2). The nonoverlapping confidence intervals indicate that the differences among the 3 proportions are statistically significant.

In 6 of the 10 screening studies, colonoscopy was performed only for subjects in whom a distal polyp was found by sigmoidoscopy. In the remaining studies, the proximal colon was examined irrespective of distal findings.^{43–45} Among these 4 studies in which a “no distal polyp” comparison group was available, the absolute risks of finding proximal neoplasia were 21% (95% CI, 14% to 28%) for distal hyperplastic polyps and 40% (95% CI, 33% to 47%) for distal adenomatous polyps. As compared to persons with no distal polyps, the relative risk of proximal neoplasia in this 4-study subgroup was 1.3 (95% CI, 0.9 to 1.8) for distal hyperplastic polyps and 2.5 (95% CI, 1.8 to 3.3) for distal adenomatous polyps. Among all 10 studies, the risk of proximal neoplasia in persons with distal adenomatous polyps was 1.5 (95% CI, 1.2 to 1.7) as compared to those with distal hyperplastic polyps.

Case-finding Studies ($N = 6$). *Descriptive results.* Table 3 and Figure 2 summarize the descriptive and quantitative data for the 6 case-finding studies.^{51–56} The studies were equally divided into retrospective and prospective studies. The mean age of subjects was 62 years among the 4 studies that reported age. Gender distribution was reported in all except 1 study, with the male:female ratio ranging from 1:1 to 1.5:1.⁵¹ The only study that reported racial distribution had a Caucasian to non-Caucasian ratio of 2.3:1.⁵² Some studies excluded certain types of patients, such as those with previous polyps or cancer, inflammatory bowel disease, bleeding or anemia, or a family history of colon cancer.^{52–54}

Colonoscopy results were reported irrespective of distal findings in 3 studies,^{52,54,55} while 3 studies reported colonoscopic findings only if a distal polyp were found. Three studies focused only on diminutive distal polyps, defined as 5 mm or less.^{34,54,56} The distal colon was defined as rectosigmoid in 3 studies^{52,54,56}; as the left colon in 1 study⁵⁵; within reach of the 60-cm sigmoidoscope in 1

Table 1. Descriptive and Quantitative Data for Screening Studies

First Author, Year of Study	Mean Age, Y (Range)	Study Design	Definition of Distal Colon	Size of Distal Polyp Studied	Distal Polyp Required for Colonoscopy	Total Number	Number of Patients with Proximal Neoplasia/Total Number for Each Group (%)			
							Distal Hyperplastic Polyps	Distal Adenomas	No Distal Polyps	Miscellaneous Polyps
Achkar, 1990 ¹⁵	56 (27 to 87)	Retrospective	Reach of 35-cm sigmoidoscope	9 mm or smaller	Yes	172	21/72 (29)	23/69 (33)		4/31 (13)
Blue, 1991 ⁴⁹	59 (31 to 91)	Retrospective	Reach of 35-cm sigmoidoscope	—	Yes	185	19/69 (26)	29/99 (29)		1/17 (6)
Brady, 1993 ³⁴	62 (50 to 81)	Prospective	Reach of 60-cm sigmoidoscope	≤5 mm	No	162	6/42 (14)	31/78 (40)	5/42 (12)	
Deal, 1991 ⁴⁸	— (43 to 80)	Retrospective	Distal 60 cm of colon	—	Yes	211	26/75 (35)	42/115 (37)		
Foutch, 1991 ⁴³	64 (≥50)	Prospective	Reach of 60-cm sigmoidoscope	—	No	129	8/25 (32)	13/31 (42)	11/73 (15)	
Lieberman, 1991 ⁴	64 (50 to 76)	Prospective	Reach of 60-cm sigmoidoscope	—	No	105	6/21 (29)	8/19 (42)	18/65 (28)	
Nusko, 1996 ⁴⁷	59 (42 to 83)	Retrospective	Rectosigmoid	—	Yes	304	10/65 (15)	86/239 (36)		
Opelka, 1992 ⁵⁰	62	Prospective	Reach of 60-cm sigmoidoscope	≤5 mm	Yes	76	9/30 (30)	16/40 (40)		1/6 (17)
Rex, 1992 ⁴⁵	—	Prospective	Rectosigmoid	—	No	480	8/45 (18)	22/58 (38)	58/377 (15)	
Stoltenberg, 1991 ⁴⁶	62 (52 to 72)	Prospective	Reach of 35-cm sigmoidoscope	≤5 mm	Yes	100	12/56 (21)	11/41 (27)

FIGURE 1. Screening studies. Proportions and 95% confidence intervals (95% CIs) of proximal neoplasia among persons with no distal polyps, distal hyperplastic polyps, and distal adenomatous polyps among the 10 screening studies.

study⁵³ and within the reach of the sigmoidoscope (with instrument length not specified) in 1 study.⁵¹

Quantitative results. The absolute risks of proximal neoplasia were homogenous across studies for persons with distal hyperplastic polyps, but not for those with distal adenomatous polyps ($P = .03$) or for those with no distal polyps ($P = .001$). The pooled absolute risk of proximal neoplasia in association with distal hyperplastic polyps was 35% (95% CI, 31% to 40%). The prevalence of proximal neoplasia in persons with distal adenomatous polyps ranged from 30% (95% CI, 14% to 46%) to 51% (95% CI, 45% to 57%), while the prevalence in those with no distal polyps varied from 3% (95% CI, 2% to 5%) to 23% (95% CI, 20% to 26%) (Fig. 2). The random effects pooled risk

estimates for proximal neoplasia were 44% (95% CI, 37% to 52%) for distal adenomatous polyps and 9% (95% CI, 3% to 26%) for no distal polyps. Because of a lack of homogeneity among case-finding studies, we did not calculate the relative risk of proximal neoplasia for distal hyperplastic or for distal adenomatous polyps as compared with no distal polyps.

Advanced Proximal Neoplasia

Screening Studies. Among the studies given in Table 1, only 3 describe histology and/or size of proximal neoplasia, and the numbers and proportions of advanced proximal neoplasms are not specified.⁴³

Table 2. Absolute and Relative Risks of Proximal Neoplasia in Screening Studies

Distal Findings	Number of Studies	Total Number of Patients	Absolute Risk of Proximal Neoplasia, % (95% CI)	Relative Risk of Proximal Neoplasia, % (95% CI)
No polyp	4	557	16 (13 to 20)	Reference group
Hyperplastic polyps	10	500	25 (21 to 29)	1.3 (0.9 to 1.8)
Adenomatous polyps	10	789	36 (32 to 39)	2.5 (1.8 to 3.3)

CI, confidence interval.

Table 3. Descriptive and Quantitative Data for Case Finding Studies

First Author, Year of Study	Mean Age, Y (Range)	Study Design	Definition of Distal Colon	Size of Distal Polyp Studied	Distal Polyp Required for Colonoscopy	Total Number	Number of Patients with Proximal Neoplasia/Total Number for Each Group (%)		
							Distal Hyperplastic Polyps	Distal Adenomas	No Distal Polyps
Ansher, 1989 ⁵⁵	59 (16 to 95)	Retrospective	Left colon	—	No	845	9/29 (31)	—	25/739 (3)
Ellis, 1993 ⁵⁶	65 (53 to 77)	Retrospective	Rectosigmoid	≤5 mm	Yes	430	70/211 (33)	87/219 (40)	—
Olsen, 1998 ⁵¹	—	Retrospective	Reach of sigmoidoscope	—	Only DHPs studied	139	57/139 (41)	—	—
Pennazio, 1993 ⁵⁴	64	Prospective	Rectosigmoid	≥5 mm for DHP	No	216	9/27 (33)	47/95 (50)	10/88 (11)
Provenzale, 1990 ⁵²	—	Prospective	Rectosigmoid as diagrammed in reports	—	No	970	15/47 (32)	139/274 (51)	198/862 (23)
Rokkas, 1993 ⁵³	61 (29 to 86)	Prospective	Reach of 60-cm sigmoidoscope	≤1 cm	Yes	75	16/45 (36)	9/30 (30)	—

DHP, distal hyperplastic polyp.

However, 2 recent cohort studies of screening colonoscopy provide information about the risk of advanced proximal neoplasia associated with distal hyperplastic polyps. In the VA cooperative study of screening colonoscopy, the association between distal hyperplastic polyps and advanced proximal neoplasia was dependent on how “distal” was defined. When “distal” included just the rectum and sigmoid colon, the risk of advanced proximal neoplasia was 2.7% in persons with no distal polyps and 2.8% in those with distal hyperplastic polyps.¹⁴ However, when the distal colon included the descending colon, the risk of advanced proximal neoplasia was 3.7% in persons with no distal polyps and 5.1% in those with distal hyperplastic polyps (odds ratio of 1.5; 95% CI, 0.9 to 2.4). In a similar study from an employer-based program of screening colonoscopy in which “distal” included the descending colon, the risk of advanced proximal neoplasia in persons with no distal polyps was 1.5% (95% CI, 0.9 to 2.1%), and 4.0% (95% CI, 1.3% to 6.7%) for persons with distal hyperplastic polyps.¹³ Because both age and gender were associated with advanced proximal neoplasia, the relative risk was adjusted for these factors and was 2.6 (95% CI, 1.1 to 5.9) among persons with distal hyperplastic polyps as compared to those with no distal polyps. Between these 2 cohort studies, the magnitude of the relative risk is consistent, suggesting increased risk for advanced proximal neoplasia among persons with distal hyperplastic polyps; however, the statistical significance of the results is discrepant.

Case-finding Studies. Only 1 study involving persons with symptoms or risk factors may have provided data regarding a possible association between advanced proximal neoplasia and distal hyperplastic polyps.¹⁴ In this study, 15% of 41 subjects who underwent colonoscopy for distal hyperplastic polyps as the sole indication were reported to have “large” polyps, but a definition of “large” was not provided. Of the 44 patients who underwent colonoscopy for a positive family history or for bleeding, proximal neoplasia was found in 48%, “large” polyps in 27%, advanced proximal neoplasia in 14%, and cancer in 7%.¹⁴

DISCUSSION

The quantitative findings from this analysis indicate that persons with distal hyperplastic polyps have a risk of proximal neoplasia that is intermediate between those persons with no distal polyps and those with distal adenomas. In the screening group of studies, the risk of proximal neoplasia was 25% with distal hyperplastic polyps, 16% with no distal polyps, and 36% with distal adenomas. Among a subgroup of 4 studies in which colonoscopy was performed irrespective of distal findings, the relative risk of proximal neoplasia in persons with distal hyperplastic polyps was 1.3 (95% CI, 0.9 to 1.8) as compared to those with no distal polyps. Not surprisingly, the risk of proximal neoplasia associated with distal hyperplastic polyps was lower in asymptomatic persons

FIGURE 2. Case-finding studies. Proportions and 95% confidence intervals (95% CIs) of proximal neoplasia among persons with no distal polyps, distal hyperplastic polyps, and distal adenomatous polyps among the case-finding studies.

who underwent colonoscopy after screening sigmoidoscopy as compared with those who underwent diagnostic colonoscopy for symptoms or for risk factors for colorectal neoplasia. Among the case-finding group of 6 studies involving patients with symptoms or risk factors for neoplasia, the risks of proximal neoplasia were statistically homogeneous only for the distal hyperplastic group, in which the risk was 35%. Risks of proximal neoplasia associated with distal hyperplastic polyps were consistent across studies, despite differences in length of the sigmoidoscope, size of the distal polyp, or definition of the distal colon. For example, when distal polyps were detected using a shorter sigmoidoscope (35 cm), the risk of finding proximal neoplasia was no different than when distal polyps were discovered with a longer (60 cm) sigmoidoscope.

The findings from the screening studies are the more important results of this analysis, because the risk estimates are more pertinent to colorectal cancer screening, and the absolute risks of proximal neoplasia for each distal finding were homogeneous. However, for completeness of this systematic review, we included studies in which colonoscopy was done because of symptoms or because of risk factors for colorectal cancer. In contrast to those of the screening studies, risk estimates for proximal neoplasia were heterogeneous and generally higher. None-

theless, the relative magnitude of risk for proximal neoplasia among the 3 subgroups of distal findings was similar to those of the screening studies. While this case-finding group of studies has less relevance to the screening setting, the consistency in relative prevalence between the screening and case-finding studies is reassuring to an extent and provides a type of clinical sensitivity analysis complementary to the main findings.

A strength of this analysis is the clinical and statistical comparability of the screening studies; patient populations were comparable, as reflected in the numerical consistency of the prevalence of proximal neoplasia within each distal subgroup. Statistical homogeneity within these subgroups allowed for precise and valid estimates of risk. Four of 10 studies contained a "control" group of subjects who underwent colonoscopy despite having no distal polyps, allowing calculation of a relative risk of finding proximal neoplasia for the other 2 distal subgroups.

The separation of absolute risk of proximal neoplasia is clear among the distal subgroups. However, the relative risk of proximal neoplasia between distal subgroups with no polyps and hyperplastic polyps did not achieve statistical significance. This discrepancy in quantitative findings is probably due to a loss of statistical power resulting from the inability to include 6 of 10 studies that did not include

proximal findings in subjects with no distal polyps. While these 6 studies may be considered less rigorous in study design, their estimates for prevalence of proximal neoplasia for the other 2 distal subgroups are no less valid than in the 4 studies that contained controls with no distal polyps. Because our estimates of absolute risk are based on a greater number of studies than those for the relative risk, we suggest that the former represent the more reliable measures of this analysis.

Our analysis has some important limitations, the most significant of which may be the clinical relevance of our primary outcome—proximal neoplasia—which included both cancer and any nonmalignant adenomatous polyp irrespective of size and histological features. Both because cancers were too few in number and because studies did not consistently separate cancer and large or histologically advanced adenomas from smaller adenomas, we could not assess the risk of these more-advanced lesions according to distal findings. Moreover, in clinical practice it is unclear whether the appropriate target lesion to detect should be any-sized proximal neoplasm or those with advanced features. This issue depends on at least 2 factors. One factor is the goal of screening: whether to detect and remove any adenoma or just the more advanced lesions. The second factor concerns the natural history of both types of polyps, for which very little data exist. Stryker and Wolffs⁵⁷ actuarial analysis revealed that the cumulative risk of cancer at the polyp site at 5, 10, and 20 years was 2.5%, 8%, and 24%, respectively for polyps greater than 10 mm in size; however, histology of the polyps was not known. Hofstad et al.⁵⁸ found that adenomas and hyperplastic polyps of 5–9 mm showed a tendency toward net regression in size at 3 years. Among 116 subjects with 1 or more polyps <10 mm, only 2 polyps showed intramucosal carcinoma at 3-year follow-up, and both were completely removed as determined by endoscopic and histological examination.

A second important limitation is the lack of information about the number, size, and location of distal lesions. It is possible that any or all 3 of these variables have an effect on the prevalence of proximal findings. Further, the aggregate nature of the data does not permit adjustment of risk estimates for variables such as age and family history that affect the risk colorectal neoplasia. While mean age was comparable overall, whether it was comparable across the 3 distal subgroups cannot be determined.

Given that the prevalence of proximal neoplasia in persons with distal hyperplastic polyps is intermediate between those with no distal polyps and those with distal adenomas, what are the clinical implications of our findings? The implications depend on what the goal of colorectal cancer screening is: to minimize the chances of missing any colorectal cancer, to reduce cancer mortality to a large extent but at lower risk and cost, or to detect and remove all neoplasms.⁵⁹ In our view, finding small, nonadvanced proximal neoplasms may not be important because they are unlikely to have an ominous natural

history. On the other hand, the 4% to 5% risk for advanced proximal neoplasia in persons with distal hyperplastic polyps suggests that examination of the proximal colon may be necessary. Current guidelines are to forgo examination of the proximal colon in asymptomatic persons with distal hyperplastic polyps. However, because polyps discovered on sigmoidoscopy are not routinely biopsied in the United States, the finding of “any polyp” is the threshold for triggering colonoscopy in most settings. Independent of whether distal polyps are biopsied during sigmoidoscopy, it would appear that the current strategy of deciding who should undergo colonoscopy solely according to the findings in the distal colon is unsatisfactory and inefficient. The inefficiency of this current strategy could be reduced by considering multiple factors that are associated with advanced proximal neoplasia, including age, gender, and family history.⁴⁹

Recent studies question the notion that hyperplastic polyps lack malignant potential. Hawkins and Ward showed that patients with colorectal cancer showing microsatellite instability had an increased number of hyperplastic polyps and serrated adenomas.⁶⁰ A recent analysis from the National Polyp Study showed that large hyperplastic polyps were associated with increased risk for an advanced adenoma anywhere in the colon as compared to persons with small (<1 cm) hyperplastic polyps (64% vs 46%; $P = .046$), suggesting that persons with large hyperplastic polyps may represent a high-risk subgroup.⁶¹

Epidemiologic data have shown that persons with hyperplastic polyps are similar to those with adenomas and cancer with respect to low exposure to dietary fiber, calcium, and nonsteroidal anti-inflammatory drugs, and increased exposure to dietary fat, cigarette smoking, and ethanol.⁶² Further, molecular studies have revealed several genetic alterations in hyperplastic polyps, including DNA microsatellite instability and mutation of K-ras and transforming growth factor- β RII.⁶³ It would appear that hyperplastic polyps are heterogeneous at the molecular level, and that this heterogeneity may correspond to variability at the clinical level.⁶⁴

In conclusion, distal hyperplastic polyps are associated with an absolute risk of proximal neoplasia of 25% in asymptomatic persons and a relative risk of 1.3 compared to those with no distal polyps. As suggested by some,⁶⁵ systematic reviews should not necessarily resolve a controversy, but should generate hypotheses and questions for further research. Given the uncertainty about the goals of screening and the proximal lesion that is clinically important to detect, we recommend more precise clinical and genetic study of hyperplastic polyps before suggesting changes to current clinical management. A more definitive study on this topic requires control groups of persons with no distal polyps and with small distal adenomas, and description of the size and histology of proximal neoplasia as well as the number, size, and location of all distal polyps. In the future, decisions about who requires colonoscopy after sigmoidoscopy might depend not just on the presence

of distal polyps, but on simultaneous consideration of associated clinical, epidemiological, and genetic factors.

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