REVIEW ARTICLE

Risk of Proximal Colon Neoplasia With Distal Hyperplastic Polyps

A Meta-analysis

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Background: Most guidelines for colorectal cancer screening do not consider distal hyperplastic polyps (HPs) to be markers for proximal colon neoplasia. However, many studies have shown an increased risk of proximal neoplasia (PN) in patients with distal HPs. We performed a systematic review to assess the association between distal HPs and PN.

Methods: We identified studies that compared the prevalence of PN and proximal advanced neoplasia in patients with distal HPs vs controls. Two masked investigators extracted data on individuals with distal HPs, distal adenomas, or no distal polyps. Using the DerSimonian and Laird method, we calculated summary risk ratios. Extensive subgroup analysis was performed.

Results: The prevalence of PN and proximal advanced neoplasia in persons with distal HPs was 26.0% and 4.4%, respectively. In studies comparing the risk of PN in patients with distal HPs vs those with no distal polyps, the summary risk ratio was 1.81 (95% confidence interval, 1.20-2.73). However, this increased risk disappeared if only high-quality studies on screening patients were considered. The risk ratio was 0.69 (95% confidence interval, 0.60-0.80) when comparing the risk of PN in those with distal HPs vs those with distal adenomas.

Conclusions: Overall, patients with distal HPs have an intermediate risk of PN compared with those with distal adenomas or no distal polyps; however, in asymptomatic screening individuals, there is no increased risk of PN or proximal advanced neoplasia. The discovery of HPs on screening flexible sigmoidoscopy should not automatically prompt follow-up colonoscopy.

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GUIDELINES FROM MEDICAL societies recommend screening for colorectal cancer (CRC) in average-risk individuals by using flexible sigmoidoscopy (FS) or other methods.[1-4] Most of these guidelines do not consider a distal hyperplastic polyp (HP) to be a marker for proximal colon neoplasia[2-4]; in other words, the discovery of a distal HP on screening FS would not be an indication for colonoscopy. However, HPs may have neoplastic potential because they may contain genetic changes seen in CRC, such as K-*ras* mutations and microsatellite instability,[5-7] and are associated with epidemiologic risk factors linked to CRC, including tobacco use, high dietary fat intake, and lack of dietary fiber.[8,9] During the past 15 years, studies comparing the prevalence of proximal neoplasia (PN) in patients with distal HPs, distal tubular adenomas (TAs), and no distal polyps have reported conflicting results. The purpose of this systematic review is to analyze the available data on the risk of PN in individuals with distal HPs, a clinically important issue regarding whether patients with HPs found on FS should be referred for colonoscopy.

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METHODS

STUDY IDENTIFICATION

We searched the MEDLINE (PubMed) and EMBASE databases (December 1966 to March 2004) using a combination of the title and abstract terms *hyperplastic* and *hyperplasia* with any of the following title and abstract terms: *polyp, adenoma, adenomatous, neoplasm, neoplasia, neoplastic, sigmoidoscopy, proctoscopy, endoscopy, colonoscopy, cancer*, and *screening*. Using the same terms, we searched the indexes of

abstracts from meetings of the American Gastroenterological Association, the American College of Gastroenterology, and the American Society of Gastrointestinal Endoscopy (January 1992 to December 2003). Abstracts for these conferences are published in the journals *Gastroenterology*, *American Journal of Gastroenterology,* and *Gastrointestinal Endoscopy,* respectively. In addition, we manually reviewed citations in all included articles, editorials, and review articles on CRC screening published between January 1992 and December 2003 in major gastroenterology, internal medicine, and oncology journals (*American Journal of Gastroenterology, Annals of Internal Medicine, British Medical Journal, Cancer, Gastroenterology, Gastrointestinal Endoscopy, Gut, Journal of the American Medical Association, The Lancet,* and *the New England Journal of Medicine*). Last, we also manually reviewed citations in the pertinent chapters of important gastroenterology textbooks.[10-12]

This search strategy was designed to be highly sensitive (but with low specificity). We manually reviewed the titles of all retrieved studies, and clearly irrelevant ones were excluded. We then reviewed the abstracts of the remaining, potentially relevant studies. After excluding inappropriate studies based on predefined exclusion criteria (see the following subsection), the full texts of the remaining studies were reviewed to confirm eligibility. Studies that were ultimately excluded after a full text review are individually described (see the "Results" section), along with reasons for exclusion.

INCLUSION AND EXCLUSION CRITERIA

We required eligible studies to be prospective, retrospective, or cross-sectional analyses designed to examine the prevalence of PN in patients with distal HPs compared with that in patients with distal TAs and patients with no distal polyps. Eligible studies were required to have been published as full articles in a peer-reviewed journal, as abstracts from a national or international conference, or as part of a major gastroenterology textbook. Studies published in non-English languages were eligible.

Studies that included patients with the following exclusion criteria were excluded: a history of CRC, inflammatory bowel disease, or a family history of polyposis or hereditary nonpolyposis CRC syndromes. Case reports or series and autopsy studies were excluded. Studies involving symptomatic patients were eligible but were subjected to subgroup analysis.

DATA ABSTRACTION AND ANALYSIS

Two masked investigators (O.S.L. and L.B.G.) independently abstracted data on the prevalence of PN and proximal advanced neoplasia (PAN) of the colon in 3 groups of patients: those with distal colonic HPs but no distal TAs, those with distal TAs with or without distal HPs, and those with no distal polyps. An advanced lesion was defined as any neoplastic polyp measuring 1 cm or greater or with villous, dysplastic, or malignant features. Proximal neoplasia included small proximal adenomas and PAN. The distal TA group excluded patients with distal advanced neoplasia or cancers (because such patients will always be referred for colonoscopy). The no distal polyp group included individuals with nonneoplastic, nonhyperplastic lesions, such as inflammatory polyps, lymphoid hyperplasia, and polyps with "normal histologic features." The same customized data abstraction form was used by both investigators. Disagreements were resolved by a second review and consensus. We attempted to contact study authors by telephone, mail, or e-mail to clarify ambiguous data or to fill in missing data.

Two outcomes were considered: PN (including advanced lesions) and PAN. For each outcome, we calculated the summary prevalence and the summary risk ratio (RR), with 95% confidence intervals (CIs), using the DerSimonian and Laird method based on a random-effects model. We tested for heterogeneity by calculating a Q statistic in the standard manner. Data analysis was performed using statistical analysis software (Comprehensive Meta-Analysis 1.023; Biostat Inc, Englewood, NJ, and SPSS version 11.0; SPSS Inc, Chicago, Ill).

SUBGROUP AND SENSITIVITY ANALYSIS

To assess the impact of the meta-analysis methods, we also calculated summary RRs using fixed-effects model techniques, that is, the inverse variance and Mantel-Haenszel methods. Because the data were expected to be heterogeneous, extensive subgroup analysis was performed using the following moderator variables: (1) patient symptoms (some studies included only asymptomatic screening individuals, whereas others included symptomatic patients [eg, diarrhea and hematochezia] undergoing diagnostic colonoscopy); (2) study design (in some studies, colonoscopy was performed on all patients regardless of distal findings ["universal colonoscopy" design], whereas in others, patients first underwent FS, with colonoscopy performed only in those found to have distal polyps of any type ["nonuniversal colonoscopy" design]; in the latter group, biopsy of the distal polyp was often not performed until the time of colonoscopy); (3) publication date (studies were stratified according to whether they were published after 1992 [this date was chosen because a preliminary review showed that approximately half the studies were published after 1992]); (4) sample size (studies were stratified according to whether they enrolled >300 total patients); (5) demarcation definition (some studies defined the demarcation between the proximal and distal colon as the splenic flexure or the descending sigmoid junction, whereas others defined it as the extent of FS); (6) distal polyp size (some studies restricted themselves to subjects with distal polyps <5 mm, whereas others had no size restrictions); (7) age (some studies restricted participants to those ≥50 years); (8) family history (some studies included individuals with a family history of CRC, some excluded such patients, and others did not comment on family history); and (9) study quality. Unlike randomized controlled trials, observational studies do not have commonly used and well-validated quality scoring systems.[13] Therefore, we created a simple scoring system for this meta-analysis. We assigned each study a score based on the type of publication (full article vs abstract), patient symptoms, study design, comparison groups, and sample size. Studies that were published in full, that included only asymptomatic screening patients, that featured a universal colonoscopy design, that included all 3 comparison groups, and that had 300 or more participants received 1 point for each category (for a maximum score of 5). Studies that were published as abstracts, that included symptomatic patients, that featured a nonuniversal colonoscopy design, that included only 2 of the 3 comparison groups, and that had fewer than 300 participants received 0 points for each category (for a minimum score of 0). Studies with low scores (0, 1, 2, or 3) were compared with studies with high scores (4 or 5). Because this meta-analysis included only published studies, we explored the possibility of publication bias by performing an inverted funnel plot analysis.

RESULTS

STUDY SELECTION

On preliminary review of the titles and abstracts of citations found by

Table 1. Characteristics of Included Studies in Chronological Order

Source	Study Type	Study Design	Sample Size, No.	Patient Type	Demarcation	Distal Polyp Size Restriction	Age Restriction, y	Family History Restriction	Study Quality Score*
Achkar and Carey,[46] 1988	Retrospective	Nonuniversal	172	Screening	Reach of 35 cm FS	<10 mm	≥50	Not specified	3
Provenzale et al,[55] 1988†	Retrospective	Universal	514	Both	DS	None	None	Not specified	3
Stoltenberg and Kirtley,[60] 1988‡	Prospective	Nonuniversal	100	Both	Reach of 35 cm FS	≤5 mm	Not specified	Excluded CRC FH	0
Ansher et al,[47] 1989	Retrospective	Universal	768	Diagnostic	SF	None	None	No restrictions	3
Provenzale et al,[56] 1990	Prospective	Universal	909	Both	DS	None	None	Not specified	3
Blue et al,[45] 1991	Prospective	Nonuniversal	168	Screening	Reach of 35 cm FS	None	Not specified	Excluded CRC FH	2
Foutch et al,[50] 1991	Prospective	Universal§	129	Screening	Reach of 60 cm FS	None	≥50	No restrictions	4
Lieberman and Smith,[51] 1991	Prospective	Universal	105	Screening	Distal 60 cm	None	≥50	No restrictions	4
Deal et al,[61] 1991‡	Retrospective	Nonuniversal	190	Screening	Reach of 60 cm FS	None	None	Not specified	1
Opelka et al,[54] 1992	Prospective	Nonuniversal	76	Screening	Reach of 60 cm FS	≤5 mm	None	Excluded CRC FH	2
Rex et al,[57] 1992	Prospective	Universal	480	Screening	DS	None	≥50	Excluded CRC FH	5
Brady et al,[48] 1993	Prospective	Universal	162	Screening	Reach of 60 cm FS	≤5 mm	≥50	Excluded CRC FH	4
Ellis et al,[49] 1993	Retrospective	Universal	430	Diagnostic	DS	≤5 mm	Not specified	No restrictions	3
Rokkas et al,[58] 1993	Prospective	Nonuniversal	75	Both	Reach of 60 cm FS	≤10 mm	None	Excluded CRC FH	1
Pennazio et al,[63] 1993	Prospective	Universal	216	Diagnostic	DS	None	None	Not specified	3
Nusko et al,[53] 1996	Prospective	Nonuniversal	304	Screening	DS	None	None	Not specified	3
Lieberman et al,[52] 2000	Prospective	Universal	2827 or 2880	Screening	SF or DS	None	50-75	Oversampled CRC FH	5
Pinsky et al,[62] 2003	Prospective	Nonuniversal	7250	Screening	SF or distal 50 cm	≤10 mm	55-74	Not specified	4
Imperiale et al,[64] 2003	Prospective	Universal	3025	Screening	SF	None	≥40	No restrictions	5
Lin et al,[59] 2003‡	Prospective	Universal	2043	Screening	SF	None	≥40	No restrictions	4
Ullah et al,[65] 2004	Retrospective	Nonuniversal	459	Screening	SF	None	None	Not specified	3

Abbreviations: CRC, colorectal cancer; DS, descending sigmoid junction; FH, family history; FS, flexible sigmoidoscopy; SF, splenic flexure.
*The study quality scoring system is described in the "Methods" section.
†Histologic confirmation was not obtained in all small polyps assumed to be hyperplastic.
‡Published in abstract form only.
§All individuals underwent FS and colonoscopy.

our search algorithm, 52 potentially pertinent studies were identified. Subsequently, the full text of each study was reviewed, and 31 were excluded: 13 because they reported the prevalence of PN in patients with distal TAs but not distal HPs,[14-26] 4 because they presented distal findings in patients stratified by proximal findings instead of vice versa,[27-30] 6 because subsequent follow-up findings were reported instead of concurrent proximal findings,[31-36] 1 because it reported the risk of neoplasia anywhere in the colon in patients with distal HPs,[37] 1 because it compared patients with distal HPs with patients with "any" distal polyp,[38] 1 because it provided data on patients with distal HPs with or without distal TAs,[39] 4 because they did not present polyp findings stratified by location or histologic features,[40-43] and, last, 1 because it did not report actual numbers of patients, although it concluded that distal HPs were not markers for PN because of a nonsignificant RR of 1.2.[44]

Twenty-one studies[45-65] met the inclusion criteria, representing a total of 20 402 participants. Characteristics of the included studies are described in **Table 1**. Of these studies, 3 compared the prevalence of PN in patients with distal HPs vs those with no distal polyps,[47,55,56] 8 compared the prevalence of PN in patients with distal HPs vs those with distal TAs,[45,49,53,54,58,60,61,65] and the remaining 10 included both comparisons.[46,48,50-52,57,59,62-64] Nine studies imposed age restrictions on eligible participants (either ≥50 or ≥40 years). Six studies excluded individuals with a family history of CRC. Four studies restricted participants to those with only diminutive distal polyps (≤5 mm). Two studies reported results for PAN only,[49,61] and 2 reported results for PAN and PN.[59,62] Three studies[59-61] were published in abstract form only.

DATA ANALYSIS

Of 20 402 individuals included in this analysis, 11 367 had no distal polyps, 4216 had distal HPs only, and 4819 had at least 1 distal TA. In

Table 2. Data From the Included Studies in Chronological Order*

Source	No Distal Polyps (PN/No PN), No.	Prevalence, %	Distal HPs (PN/No PN), No.	AR, %	Distal TAs (PN/No PN), No.	AR, %	Conclusion†
Achkar and Carey,[46] 1988	4/27	12.9	21/51	29.2	23/46	33.3	Positive
Provenzale et al,[55] 1988	141/339	29.4	22/12	64.7	NA	NA	Positive
Stoltenberg and Kirtley,[60] 1988	NA	NA	14/42	25.0	11/30	26.8	Positive
Ansher et al,[47] 1989	25/714	3.4	9/20	31.0	NA	NA	Positive
Provenzale et al,[56] 1990	198/664	23.0	15/32	31.9	NA	NA	Negative
Blue et al,[45] 1991	NA	NA	19/50	27.5	29/70	29.3	Positive
Foutch et al,[50] 1991	11/62	15.0	8/17	32.0	13/18	41.9	Positive
Lieberman and Smith,[51] 1991‡	18/47	27.7	6/15	28.6	8/11	42.1	Negative
Deal et al,[61] 1981	NA	NA	26/49	34.7	42/73	36.5	Positive
Opelka et al,[54] 1992	NA	NA	10/26	27.8	15/25	37.5	Positive
Rex et al,[57] 1992‡	59/318	15.7	8/37	17.8	22/36	37.9	Negative
Brady et al,[48] 1993‡	5/37	11.9	6/36	14.3	31/47	39.7	Negative
Ellis et al,[49] 1993	NA	NA	70/141	33.2	87/132	39.7	Positive
Rokkas et al,[58] 1993	NA	NA	16/29	35.6	9/21	30.0	Positive
Pennazio et al,[63] 1993	10/84	10.6	9/18	33.3	47/48	49.5	Positive
Nusko et al,[53] 1996	NA	NA	10/55	15.4	86/153	36.0	Negative
Pinsky et al,[62] 2003§	547/2270	19.4	368/1714	17.7	645/1706	27.4	Negative
Lin et al,[59] 2003	140/1498	8.6	25/173	12.6	56/141	28.4	Negative
Ullah et al,[65] 2004	NA	NA	25/86	22.5	135/213	38.8	Negative
Source	**No Distal Polyps (PAN/No PAN), No.**	**AR, %**	**Distal HPs (PAN/No PAN), No.**	**AR, %**	**Distal TAs (PAN/No PAN), No.**	**AR, %**	**Conclusion†**
Lieberman et al,[52] 2000§	71/1841	3.7	25/464	5.1	37/389	8.7	Negative
(Lieberman et al,[52] 2000)||	48/1717	2.7	13/451	2.8	38/523	6.8	Negative
Pinsky et al,[62] 2003§	131/2686	4.7	73/2009	3.5	100/2251	4.3	Negative
Imperiale et al,[64] 2003§	42/2342	1.8	9/291	3.0	18/211	7.9	Positive
Ullah et al,[65] 2004	NA	NA	11/100	9.9	80/268	23.0	Negative

Abbreviations: AR, absolute risk; HP, hyperplastic polyp; NA, not available; PAN, proximal advanced neoplasia; PN, proximal neoplasia; TA, tubular adenoma.
*Proximal adenomatous lesions include advanced neoplasia and cancer, but the distal TA group does not include distal advanced neoplasia and cancer.
†"Positive" indicates that the study concluded that distal HPs are markers for PN.
‡All patients had negative fecal occult blood test results.
§Patients with large (≥1 cm) or advanced distal colonic neoplastic lesions were excluded.
||The demarcation between the proximal and distal colon was defined as the descending sigmoid junction.

12 of the included studies,* the investigators concluded that distal HPs were markers for PN because the prevalence of PN in those with distal HPs was either similar to that in patients with distal TAs or significantly higher than that in patients with no distal polyps; the remaining 9 studies[48,51-53,56,57,59,62,65] concluded that distal HPs were not markers (**Table 2**).

Figure 1A describes the 11 studies that compared the prevalence of PN in patients with distal HPs vs those with no distal polyps. Using the DerSimonian and Laird method based on a random-effects model, the summary RR was 1.81 (95% CI, 1.20-2.73), indicating an elevated risk of PN in patients with distal HPs vs those with no distal polyps. There was significant heterogeneity (Q=84.7; $P<.001$). The summary prevalence of PN was 25.97% (95% CI, 23.95%-27.98%) in the distal HP group. Figure 1B describes the 16 studies that compared the prevalence of PN in patients with distal TAs vs those with distal HPs. The summary RR was 0.69 (95% CI, 0.60-0.80), showing a reduced risk of PN in patients with distal HPs vs those with distal TAs. There was borderline heterogeneity (Q=22.9; $P=.08$).

Four studies reported data on PAN (**Figure 2**). For patients with distal HP vs those with no distal polyps, the summary RR was 1.02 (95% CI, 0.62-1.68), with borderline heterogeneity (Q=4.74; $P=.09$). For patients with distal HPs vs those with distal TAs, the summary RR was 0.52 (95% CI, 0.32-0.84), again with borderline heterogeneity (Q=8.1; $P=.04$). The summary prevalence of PAN was 4.41% (95% CI, 3.87%-4.96%) in individuals with distal HPs. One study[52] reported results using 2 different definitions of the demarcation between the proximal and distal colon; this did not statistically significantly affect the results.

SUBGROUP AND SENSITIVITY ANALYSIS

Comparing the risk of PN in patients with distal HP vs those with no distal polyps, the inverse variance and Mantel-Haenszel methods (both based on a fixed-effects model) gave summary RRs of 1.17 (95% CI, 1.06-1.29) and 1.08 (95% CI, 0.98-1.19), respectively. For patients with distal HPs vs those with distal TAs, the inverse variance and Mantel-Haenszel methods gave summary RRs of 0.68 (95% CI, 0.62-0.74) and 0.66 (95% CI, 0.61-0.72), respectively.

Stratification by study design, publication date, demarcation definition, and restrictions on age, family history of CRC, and distal polyp size resulted in no clinically signifi-

*References 45-47, 49, 50, 54, 55, 58, 60, 61, 63, 66.

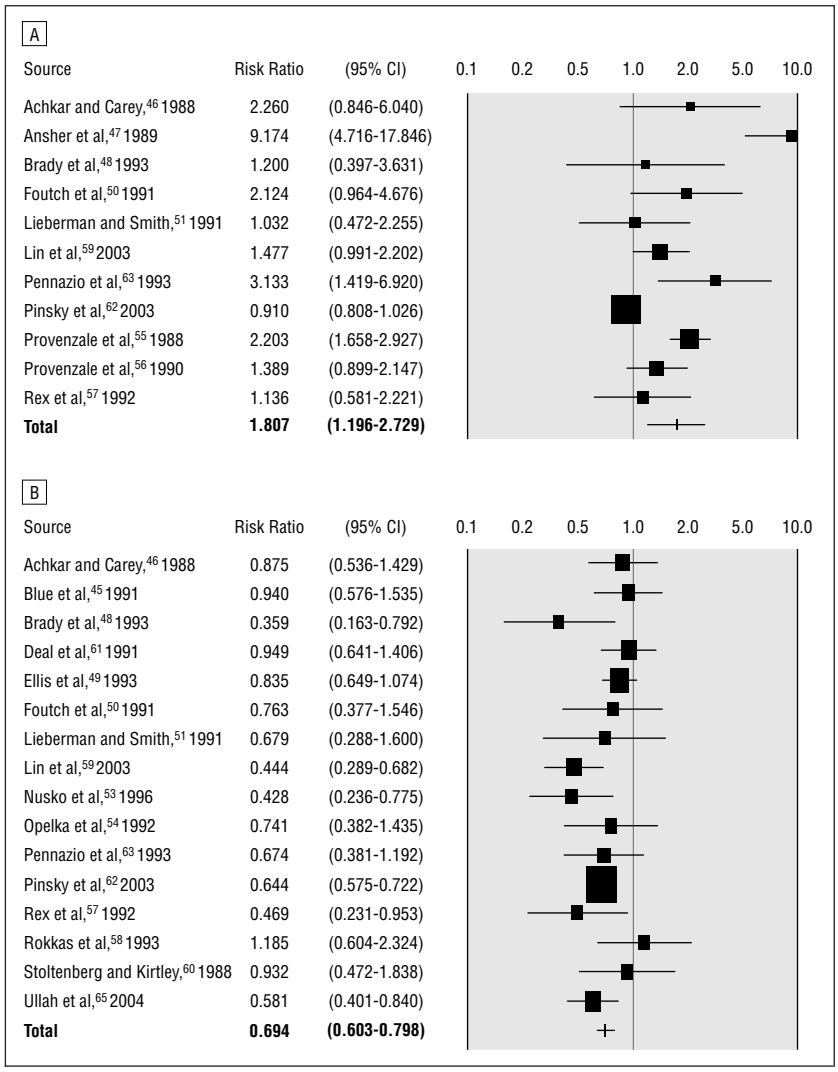

Figure 1. Forrest plots of studies comparing the prevalence of proximal neoplasia in patients with distal hyperplastic polyps vs those with no distal polyps (A) or those with distal tubular adenomas (B). The no distal polyp group and the distal tubular adenoma group are assumed to have a risk of 1.0. A high risk ratio implies that distal hyperplastic polyps are associated with more risk of proximal neoplasia. CI indicates confidence interval.

cant changes in the results (data not shown). Stratification by sample size showed a trend toward a higher risk of PN in smaller studies. The RR for PN was 1.03 in large studies vs 1.88 in small studies when the distal HP group was compared with the no distal polyp group, but the 95% CIs overlapped.

Because the test for heterogeneity is known to have low sensitivity and all our Q statistic values are either high or borderline, in the rest of this article we report only the results based on the DerSimonian and Laird method (random-effects model). Not only is this approach more conservative (ie, usually associated with wider CIs), but it is also more appropriate considering the heterogeneity present and will tend to lessen the impact of the 4 studies with extremely large sample sizes.

Figure 3 shows the summary RRs stratified by patient symptoms. For screening studies, the risk of PN in the distal HP group was statistically similar to that of the no distal polyp group (RR=1.25; 95% CI, 0.92-1.70) but lower than that of the distal TA group (RR=0.65; 95% CI, 0.55-0.76), whereas the opposite was true for diagnostic studies (RR=2.95; 95% CI, 1.40-6.21 and RR=0.85; 95% CI, 0.69-1.04, respectively). When studies were stratified by quality scores, in those with high scores, the risk of PN in the distal HP group was similar to that in the no distal polyp group (RR=1.18; 95% CI, 0.88-1.59) but lower than that in the distal TA group (RR=0.60; 95% CI, 0.50-0.70); again, the opposite was true for studies with low quality scores.

To test whether any study had a dominant effect, we excluded each study in turn and recalculated the summary RR.[64] We did not find a dominant study. To assess the impact of possible publication bias, we constructed an inverted funnel plot (data not shown). This figure exhibited asymmetry, suggesting publication bias, but the effect did not seem to be severe because the plot could be made symmetrical by eliminating 2 to 3 studies at the edge of the funnel.

COMMENT

In current practice, there are various approaches to dealing with small polyps found by FS.[67] Two previous meta-analyses[68,69] of the clinical significance of distal HPs have been published. One meta-analysis[68] summarized the results of 18 studies, including 3 reported only in abstract form. Using a random-effects model, the researchers concluded that distal HPs were associated with a prevalence of 21% to 25% for PN and 4% to 5% for PAN and "may justify examination of the proximal colon." The summary RR was nonsignificant at 1.3 (95% CI, 0.9-1.8) for PN but significant at 2.6 (95% CI, 1.1-5.9) for PAN (based on only 2 studies). Like our study, it showed a difference in results when the data were stratified according to patient symptoms. However, this meta-analysis did not include results from 3 studies that were included in our review[55,59,62] and included 1 study that we excluded owing to lack of a control group.[38] The other meta-analysis[69] included only 6 studies and concluded that distal HPs were not associated with PN, with a summary RR of 1.44 (95% CI, 0.79-2.62).

In our meta-analysis, for individuals with distal HPs, the overall prevalence was approximately 26% for PN and 4.4% for PAN. The overall RR for PN in the distal HP group was intermediate between the no distal polyp group and the distal TA

group. However, the observational studies included in our meta-analysis are heterogeneous; therefore, subgroup analysis is important and is discussed in the following subsection.

STRATIFICATION ACCORDING TO PATIENT SYMPTOMS

Compared with screening procedures, diagnostic colonoscopies on symptomatic patients are probably more likely to uncover neoplasia in the proximal and distal colon. Because the significance of distal HPs is relevant mainly to asymptomatic individuals, screening studies are more likely to give a valid answer to our study question. If we stratify the data according to whether diagnostic or screening procedures were performed, we find that only 6 of 14 screening studies* concluded that HPs were markers for PN, in contrast to 6 of 7 studies on symptomatic patients.[47,49,55,56,58,60,63] When we stratified the studies by patient symptoms, heterogeneity was eliminated for screening studies (Q=12.3) but not for diagnostic studies (Q=22.3). As expected, the mean prevalence of PN in patients with distal HPs is higher in diagnostic studies than in screening studies (approximately 32% vs 23%), but it is unclear why the relative risk in the distal HP group (compared with the other 2 groups) should also be higher in diagnostic studies.

STRATIFICATION ACCORDING TO STUDY QUALITY

Studies with higher quality scores tended to show that distal HPs were not markers for PN. This can be understood if we consider how study quality was defined in our review. Aside from being restricted to screening individuals and using a universal colonoscopy design, high-quality studies were more likely to include large numbers of individuals in each of the 3 comparison groups. In contrast, low-quality studies tended to be small studies that compared the prevalence of PN in patients with distal HPs with either those with distal TAs or those with no distal polyps. Studies that report only the former comparison may have inadequate statistical power, leading to a type II error. On the other hand, studies that report only the latter may demonstrate that the risk in the distal HP group is significantly higher than that in the no distal polyp group but may not show whether that risk is comparable with that in the distal TA group. The largest study[62] in our meta-analysis (with 7250 patients) did not have a true control group. Instead, the "no distal polyp" group consisted of patients with no distal polyps found on follow-up colonoscopy or distal "polyps" found to consist of normal tissue when biopsied during colonoscopy; this can potentially bias the results.

*References 45, 46, 48, 50-54, 57, 59, 61, 62, 65, 66.

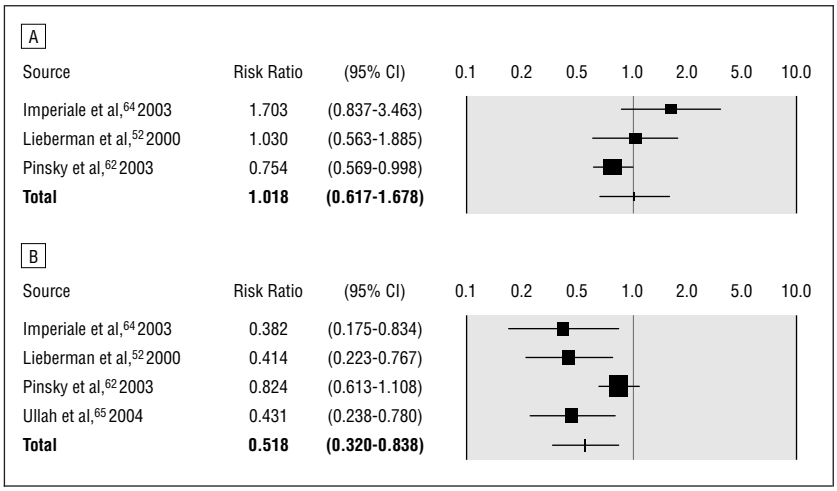

Figure 2. Forrest plots of studies comparing the prevalence of proximal advanced neoplasia in patients with distal hyperplastic polyps vs those with no distal polyps (A) or those with distal tubular adenomas (B). The no distal polyp group and the distal tubular adenoma group are assumed to have a risk of 1.0. A high risk ratio implies that distal hyperplastic polyps are associated with more risk of proximal advanced neoplasia. CI indicates confidence interval.

SENSITIVITY ANALYSIS ACCORDING TO META-ANALYTIC TECHNIQUE

The RR for PN in the distal HP group vs the no distal polyp group is higher when random-effects methods are used as opposed to fixed-effects methods (1.81 vs 1.17). The DerSimonian and Laird method, a random-effects method, is usually more conservative than fixed-effects methods. This usually means that the 95% CI of the summary effect size is wider, especially in the presence of large between-study heterogeneity because the random-effects model incorporates a between-study component of variance. However, the DerSimonian and Laird method can sometimes result in a larger summary effect size estimate because it gives more weight to small studies than fixed-effects methods. As the between-study variance becomes large (ie, when there is heterogeneity), the between-study variance comes to dominate the weights assigned to each study, and large and small studies will tend to be weighted almost equally.[70,71] In our meta-analysis, the summary effect size is larger using random-effects models because the smaller studies tend to report larger effect sizes than the larger ones (although the difference was not statistically significant), possibly owing to subtle publication bias. Specifically, when we compared the distal HP group with the no distal polyp group, the summary RRs were different with the 3 different techniques, which is consistent with the high degree of heterogeneity (Q=84.7). In contrast, when we compared the distal HP group with the distal TA group, the summary RRs were similar using the 3 techniques because the degree of heterogeneity was low (Q=22.9).

Despite our efforts, there are several limitations to this study. Publication bias is a concern in all meta-analyses because it is well known

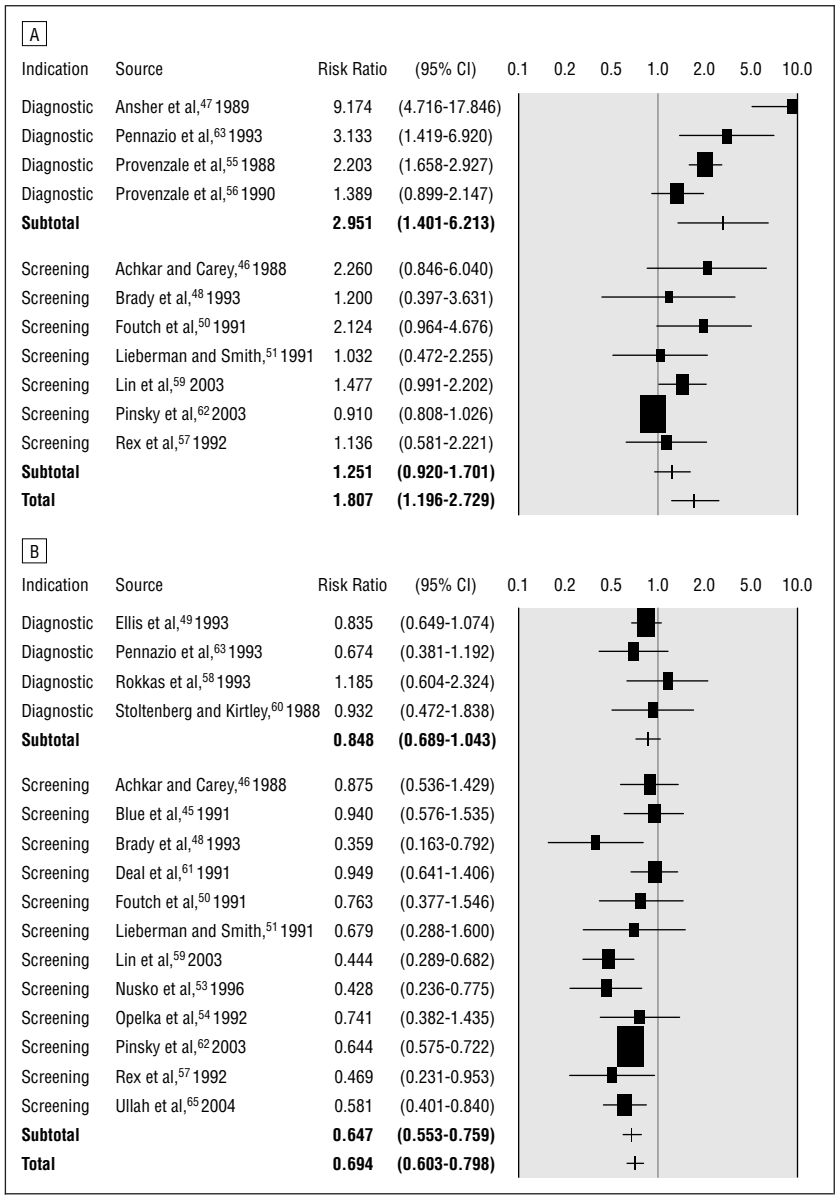

Figure 3. Subgroup analyses of studies comparing the prevalence of proximal neoplasia in patients with distal hyperplastic polyps vs those with no distal polyps (A) or those with distal tubular adenomas (B), stratified by patient symptoms. The no distal polyp group and the distal adenoma group are assumed to have a risk of 1.0. A high risk ratio implies that distal hyperplastic polyps are associated with more risk of proximal neoplasia. CI indicates confidence interval.

that studies with null results are less likely to be published. This may explain the large number of "positive" studies that reported an increased risk of PN in patients with distal HPs. In particular, 5 of these "positive" studies[45,54,58,60,61] were small and compared only the distal HP group with the distal TA group, making them highly susceptible to a type II error owing to lack of statistical power; it is probably no coincidence that 2 of these studies were reported in abstract form only. Our inverted funnel plot analysis indicates that publication bias may be present but is unlikely to be highly significant.

Most studies in this review look at the relationship between distal findings and PN (ie, adenomas). Many of these proximal adenomas were small (<5 mm); therefore, their clinical significance is uncertain. Small adenomas are still neoplastic and may be precancerous, but some studies[32,72] suggest that they are not associated with any increased risk of CRC.

Despite the large number of patients in this meta-analysis, the number of those with PAN is relatively small. This is the most likely reason for the lack of statistical significance when we compared the prevalence of PAN among the 3 groups, although there seems to be a trend toward a higher risk of PAN in patients with distal TA vs the other 2 groups.

The results of this study are important in determining whether individuals initially screened by FS should be referred for colonoscopy. Although some guidelines[4] consider colonoscopic screening of all individuals 50 years and older to be a "preferred" strategy, others[1,3] regard screening by FS every 5 years (with annual fecal occult blood testing) to be as acceptable as colonoscopy every 10 years. At present, only approximately 30% of age-eligible persons undergo any type of endoscopic screening in the United States.[73] Attempts to implement universal colonoscopic screening are affected by a variety of factors, including cost-effectiveness, patient acceptance, insurance coverage, and availability of adequately trained colonoscopists. Thus, it is likely that FS will continue to play an important role in CRC screening.

Although the overall summary RR of PN is elevated in patients with distal HPs vs those with no distal polyps, subgroup analysis demonstrates that studies that are more likely to provide valid answers to our study question show that distal HPs are not associated with an increased risk of PN. Specifically, studies that involve only asymptomatic screening individuals and are judged to have higher quality based on our scoring system show that the prevalence of PN in the distal HP group is similar to that in the no distal polyp group and lower than that in the distal TA group. The absence of an association between distal HPs and PN support current screening guidelines that recommend against the use of colonoscopic follow-up for patients with only HPs identified by screening FS. Currently, biopsies are often not performed during screening FS, with many practitioners automatically referring for colonoscopy all patients found to have distal polyps. This study illustrates that it is important for practitioners to biopsy distal polyps because some pa-

tients will be found to have distal HPs and may not require colonoscopy.

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