REVIEW ARTICLE

Detection of Proximal Adenomatous Polyps With Screening Sigmoidoscopy

A Systematic Review and Meta-analysis of Screening Colonoscopy

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Background: The relative effectiveness of flexible sigmoidoscopy compared with colonoscopy to screen for colorectal cancer depends on the magnitude of the association between findings in the proximal and distal colon and the false-negative rate of screening sigmoidoscopy for proximal neoplasia. To address this, we performed a systematic review and meta-analysis of screening colonoscopy studies.

Methods: Published studies through July 31, 2000, of asymptomatic patients undergoing screening colonoscopy were identified from the MEDLINE database. We generated pooled estimates of the odds ratio for the association between findings in the distal and proximal colon and the prevalence of isolated proximal adenomatous neoplasia.

Results: Using the sigmoid–descending colon junction to identify the beginning of the distal colon, the pooled odds ratio for the association between distal adenomatous polyps and any proximal neoplasia was 2.40 (95% confidence interval [CI], 1.42-4.05). Diminutive distal adenomatous polyps were also associated with proximal neoplasia (odds ratio, 2.36; 95% CI, 1.30-4.29). Distal hyperplastic polyps were not associated with proximal neoplasia (odds ratio, 1.44; 95% CI, 0.79-2.62). The prevalence of isolated advanced proximal neoplasia in the 3 studies was 2%, 3%, and 5%. Using the sigmoid–descending colon junction to identify the beginning of the distal colon yields a pooled estimate of isolated proximal neoplasia of 16.3% (95% CI, 13.6%-19.1%).

Conclusions: Distal adenomatous polyps, including diminutive distal adenomatous polyps, are associated with an increased prevalence of synchronous proximal neoplasia. Two percent to 5% of patients undergoing screening colonoscopy may have isolated advanced proximal neoplasia. Even more patients may have isolated nonadvanced proximal neoplasia.

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COLORECTAL CANCER is the third most common cancer in men and women and the second most common cause of cancer-related mortality.[1] Colorectal cancers develop from precancerous adenomatous polyps over many years as a result of sequential somatic gene mutations. Precancerous adenomatous polyps are usually asymptomatic. Colonoscopic removal of adenomatous polyps effectively reduces the subsequent incidence of colorectal cancer.[2] Furthermore, early-stage colorectal cancer is often curable, whereas advanced cancers are much less likely to be cured.[3] As such, the disease is well suited for prevention with screening programs.

Fecal occult blood testing and flexible sigmoidoscopy have been used as screening tests to select patients for colonoscopy. Several randomized controlled trials[4-6] of fecal occult blood testing have demonstrated reduced colorectal cancer–related mortality rates. Similarly, observational studies[7-9] of sigmoidoscopy have also shown reduced cancer-related mortality rates. Based on the results of these studies, most professional organizations recommend screening for colorectal cancer with fecal occult blood testing, sigmoidoscopy, barium enema, or colonoscopy. Recently, there has been an emphasis on primary screening for colorectal cancer with colonoscopy.[10-14]

The effectiveness of screening sigmoidoscopy to detect proximal adenomatous polyps and cancers depends on the strength of association between distal and proximal colonic adenomas, and the proportion of patients without distal colonic adenomas who have adenomas in the proximal colon. To address this issue, we performed a systematic review and meta-analysis of studies of screening colonoscopy.

Table 1. Studies Included in the Meta-analysis

Source	Procedure	Definition of Distal	Patients, No.	Indication for Procedure
Lieberman et al,[10] 2000	Colonoscopy	Splenic flexure (secondary = rectosigmoid)	3121	Screening, FH
Imperiale et al,[11] 2000	Colonoscopy	Splenic flexure	1994	Screening
Nicholson et al,[19] 2000	Colonoscopy	Splenic flexure	1131	Screening, FH
Levin et al,[16] 1999	Sigmoidoscopy, then colonoscopy	Within reach of the flexible sigmoidoscope	2972	Screening, FH
Kadakia et al,[22] 1996	Sigmoidoscopy, then colonoscopy	Rectosigmoid or 60 cm	175	Screening
Brady et al,[20] 1993	Sigmoidoscopy, then colonoscopy	60 cm	162	Screening
Rex et al,[23] 1992	Colonoscopy	Rectosigmoid	482	Screening
Foutch et al,[24] 1991	Colonoscopy	Within reach of the flexible sigmoidoscope	129	Screening, FH
Lieberman and Smith,[21] 1991	Colonoscopy	60 cm	105	Screening, FH
Foutch et al,[25] 1991	Sigmoidoscopy, then colonoscopy	Within reach of the flexible sigmoidoscope	114	Screening
Rex et al,[26] 1991	Colonoscopy	Rectosigmoid	210	Screening
Johnson et al,[18] 1990	Colonoscopy	Splenic flexure	90	Screening
McConnell et al,[27] 1990	Colonoscopy	55 cm	125	FH

Abbreviation: FH, family history of colorectal cancer.

METHODS

A computerized search of the MEDLINE database was performed to identify studies of screening colonoscopy. To be included in this analysis, studies had to include only asymptomatic patients undergoing screening colonoscopy. Studies that included patients with polyps identified by sigmoidoscopy or barium enema were excluded. The key words used in the search were "adenoma or colonic neoplasms" combined with "colonoscopy." The resulting citations were then limited to those written in the English language between January 1, 1966, and July 31, 2000. After excluding all reviews, editorials, comments, and letters, 2036 studies were identified. The abstracts of these studies were then reviewed independently by 2 of us (K.N. and K.E.H.) to identify those potentially eligible for inclusion. These studies were then reviewed separately by a minimum of 2 of us (J.D.L., K.N., and K.E.H.). A standardized abstraction form was used to facilitate data abstraction. Thirteen studies met the final inclusion criteria. Several steps were undertaken to help ensure that we had not inadvertently excluded any relevant studies. First, the references from each article reviewed were manually searched for other articles. Next, the corresponding authors for each of the 13 studies and for 16 related studies were contacted by mail to request information regarding additional studies not identified by our search.[15] Seven of 29 authors who were contacted responded, and none had knowledge of any additional articles.

When more than 1 definition of a diminutive polyp was included in a single study, preference was given in the following order: (1) adenoma of 5 mm or less, (2) tubular adenoma of 10 mm or less, (3) adenoma of 10 mm or less, and (4) polyp of any histologic pattern of 5 mm or less. The primary definition of advanced adenomatous polyps was abstracted from each article. Only 3 articles[10,11,16] categorized adenomas as early or advanced stage. The primary criteria for advanced adenoma included cancer, high-grade dysplasia, and villous features in all 3 studies and size greater than 10 mm in 2 studies.[10,16]

STATISTICAL ANALYSES

For the primary analysis, pooled estimates of the odds ratio (OR) for the association between distal and proximal polyps were performed using random-effects models. Fixed-effects models of the association between distal and proximal polyps were also performed as a secondary analysis, and the results are provided for comparison. The Mantel-Haenszel test for heterogeneity was used to examine the studies for heterogeneity. Logistic regression was used to provide a pooled estimate of the proportion of patients with proximal adenomatous polyps in the absence of distal adenomas. For the logistic regression analyses, fixed-effects and random-effects models were generated. Because these 2 methods provided differing results in certain analyses, both results are reported. To examine our results for evidence of publication bias, we generated funnel plots. We also applied a formal test of publication bias, as described by Egger et al,[17] which examines the association between effect size and precision (ie, study size).

To explore for causes of heterogeneity between studies, separate analyses were performed according to the definition of the border between the proximal and distal colon used in each study. For studies in which results were reported for more than 1 definition of the distal colon, the primary definition from the study was used in the primary analyses; however, all available data were used in the stratified analyses. For example, if the study provided 2 definitions of the distal colon, it could be included in 2 of the strata for the stratified analyses. If no definition of the distal colon was provided but data on each patient were provided, the distal colon was arbitrarily defined to begin at the splenic flexure. All analyses were performed using statistical software (STATA 6.0; Stata Corp, College Station, Tex).

RESULTS

Thirteen articles met the inclusion criteria (**Table 1**).[10,11,16,18-27] Ten studies provided data on the prevalence of proximal adenomatous neoplasms regardless of the histologic features and size of the lesion (median, 22.6%; range, 4.7%-30.5%). Three studies reported data on the prevalence of advanced proximal neoplasms, with estimates of 2.5%, 4.1%, and 7.3%.

There was a significant association between distal adenomatous polyps and synchronous proximal adenomatous polyps (pooled OR, 2.68; 95% confidence interval [CI], 1.93-3.73) (**Figure 1** and **Table 2**). The pooled OR for the association between a distal adenoma and a synchronous advanced adenomatous polyp was 2.80 (95% CI, 1.45-5.42).

The estimated ORs for the association of distal adenomatous polyps with proximal adenomatous neoplasms and advanced proximal

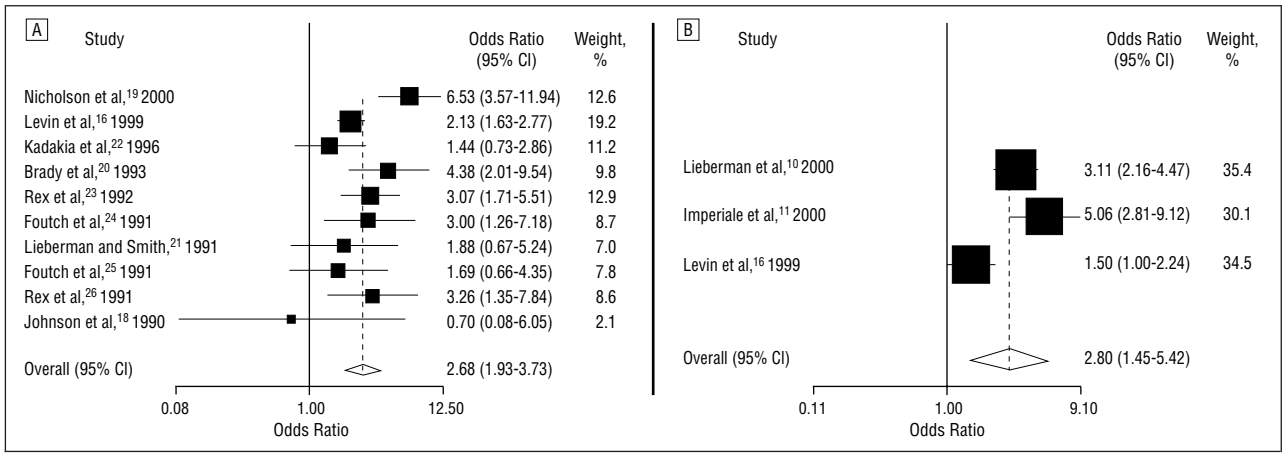

Figure 1. Summary plots of the association between distal and proximal adenomatous polyps. A, The association between any distal adenomatous polyp and any proximal adenomatous neoplasm. B, The association between any distal adenomatous polyp and an advanced proximal adenomatous neoplasm. Pooled estimates are derived from the random-effects model. CI indicates confidence interval.

lesions were greater than 1 in all but one small study.[18] Nevertheless, there was evidence of heterogeneity among studies regarding the magnitude of the association ($P=.02$ for any synchronous proximal adenoma and $P=.001$ for a synchronous proximal advanced adenoma). Despite the heterogeneity among studies, all studies examining the association of distal adenomas with advanced proximal lesions identified statistically significant associations. Among studies assessing the association between distal and proximal adenomas, all but 4 demonstrated statistically significant associations; these 4 studies also had the lowest estimate of the magnitude of the association between distal and proximal adenomatous polyps.

To explore this heterogeneity, we performed separate analyses based on the definition of the distal colon used in the study. The definition of distal colon had a modest effect on the strength of this association. When the distal colon was defined as the rectosigmoid junction, the splenic flexure, or other (eg, the area visualized by the sigmoidoscope or 55-60 cm from the anal verge), the pooled ORs for any synchronous proximal adenomatous polyp were 2.40 (95% CI, 1.42-4.05; test of heterogeneity, $P=.19$), 2.70 (95% CI, 0.29-24.7; test of heterogeneity, $P=.04$), and 2.27 (95% CI, 1.81-2.85; test of heterogeneity, $P=.43$), respectively. Although there remained heterogeneity in the separate analysis using splenic flexure as the definition of the distal colon, only 2 studies were included in this analysis. For studies examining the association between distal adenomas and synchronous advanced adenomatous neoplasia, the study finding the weakest association used findings from sigmoidoscopy to define the distal colon, whereas the other 2 studies used the splenic flexure.

Table 2. Pooled Odds Ratios for the Association Between Distal Polyps and Proximal Polyps

Most Advanced Distal Colon Neoplasm	Proximal Colon Neoplasm	Odds Ratio (95% CI)	
		Random Effects	Fixed Effects
Any adenoma	Any adenoma	2.68 (1.93-3.73)	2.40 (1.98-2.90)
	Advanced adenoma	2.80 (1.45-5.42)	2.38 (1.84-3.08)
Diminutive adenoma	Any adenoma	2.36 (1.30-4.29)	2.19 (1.68-2.85)
	Advanced adenoma	2.49 (0.96-6.44)	1.93 (1.43-2.60)
Hyperplastic polyp	Any adenoma	1.44 (0.79-2.62)	1.41 (0.78-2.55)
	Advanced adenoma	1.63 (0.61-4.33)	1.39 (0.85-2.28)

Abbreviation: CI, confidence interval.

We also examined whether inclusion of patients with a family history of colorectal cancer, the mean or median age of patients, and the proportion of male patients may explain the heterogeneity among studies assessing the association between any distal and any proximal adenoma. The mean or median age was similar among studies reporting these data, with all but one study[19] having a mean or median age of 61 to 65 years. One of 4 studies with the weakest estimated associations between distal and proximal adenomas included patients with a family history of colorectal cancer (20% of patients) compared with 3 of 6 studies with larger and statistically significant associations (5%, 12%, and 80% of patients). Of studies reporting the proportion of patients who were male, those that did not demonstrate significant positive associations (ie, those with the weakest estimated associations) included a median of 84% male patients vs 71% for studies with statistically significant positive associations.

Five studies[10,11,16,20,21] examined the association of diminutive adenomatous polyps with proximal adenomas or advanced proximal adenomas (one study examined both outcomes). Diminutive distal adenomatous polyps were significantly associated with synchronous proximal adenomatous polyps (**Figure 2** and Table 2). The pooled OR for the association of a diminutive distal adenomatous polyp with any synchronous proximal adenomatous polyp was 2.36 (95% CI, 1.30-4.29; test for heterogeneity, $P=.08$). Our pooled analysis of the association of diminutive distal polyps with proximal ad-

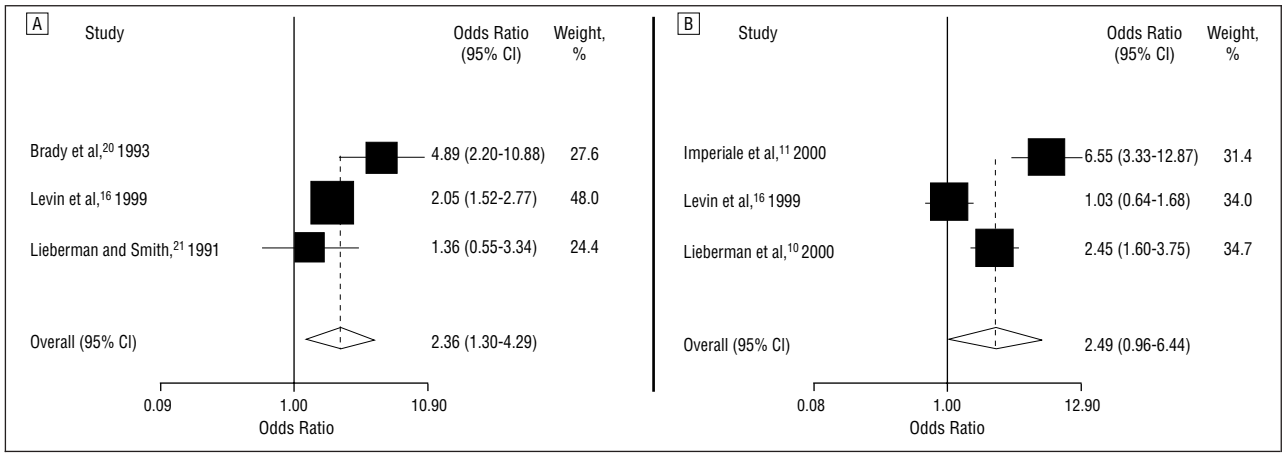

Figure 2. Summary plots of the association between diminutive distal adenomas and proximal adenomatous polyps. A, The association between diminutive distal adenomatous polyps and any proximal adenomatous neoplasm. B, The association between diminutive distal adenomatous polyps and an advanced proximal adenomatous neoplasm. Pooled estimates are derived from the random-effects model. CI indicates confidence interval.

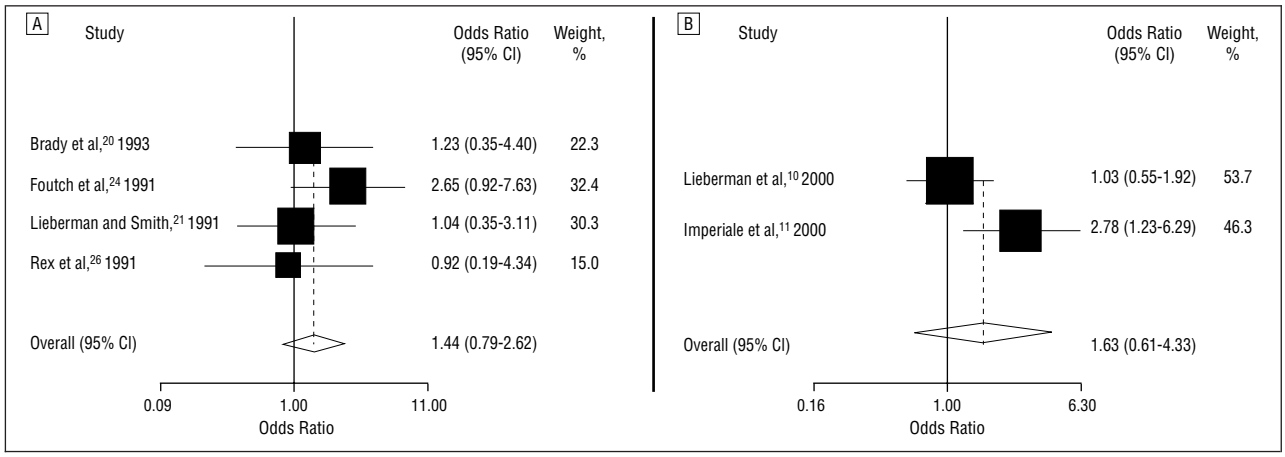

Figure 3. Summary plots of the association between distal hyperplastic polyps and proximal adenomatous polyps. A, The association between distal hyperplastic polyps and any proximal adenomatous neoplasm. B, The association between distal hyperplastic polyps and an advanced proximal adenomatous neoplasm. Pooled estimates are derived from the random-effects model. CI indicates confidence interval.

vanced adenomas yielded a nonsignificantly increased OR of 2.49 (95% CI, 0.96-6.44). In this case, there was substantial heterogeneity ($P<.001$), with 2 studies[10,11] demonstrating significant positive associations between diminutive distal adenomas and proximal advanced lesions, whereas the third study[16] found no association. Although there were too few studies to perform separate analyses according to the definition of the distal colon, there were substantial differences in the design of these studies. The 2 studies[10,11] demonstrating a significant association were prospective studies designed specifically to examine findings from screening colonoscopy. Each used the investigator-perceived location of the splenic flexure during colonoscopy to estimate the juncture of the proximal and distal colon. The study by Levin et al[16] that did not identify a significant association was a retrospective study. This study used findings from flexible sigmoidoscopy to define the junction of the proximal and distal colon. Furthermore, the control group in the latter study included only patients who had previously undergone screening flexible sigmoidoscopy and subsequently underwent colonoscopy despite having normal sigmoidoscopic findings and in whom there was no other apparent indication for the colonoscopy. These differences in design may have contributed to the observed heterogeneity.

In the primary analysis, distal hyperplastic polyps were not significantly associated with synchronous proximal adenomatous polyps (OR, 1.44; 95% CI, 0.79-2.62; test for heterogeneity, $P=.57$) (**Figure 3** and Table 2). Only 2 studies[10,11] examined the association of hyperplastic distal polyps with advanced proximal polyps. The pooled OR for this association was not statistically significant (OR, 1.63; 95% CI, 0.61-4.33; test for heterogeneity, $P=.06$).

The pooled estimate of the percentage of patients without a distal adenoma who had a proximal adenoma was 6.7% (95% CI, 5.8%-7.6%) using the fixed-effects model and 14.6% (95% CI, 9.7%-19.4%) using the random-effects model (**Figure 4**). Using the results of the fixed-effects models, this corresponds to a number needed to screen to detect any adenoma in a patient without a distal adenoma of 14.9, assuming 100% sensitivity of the screening test. The difference in results between the fixed-effects and random-effects models is explained by the greater effect of the

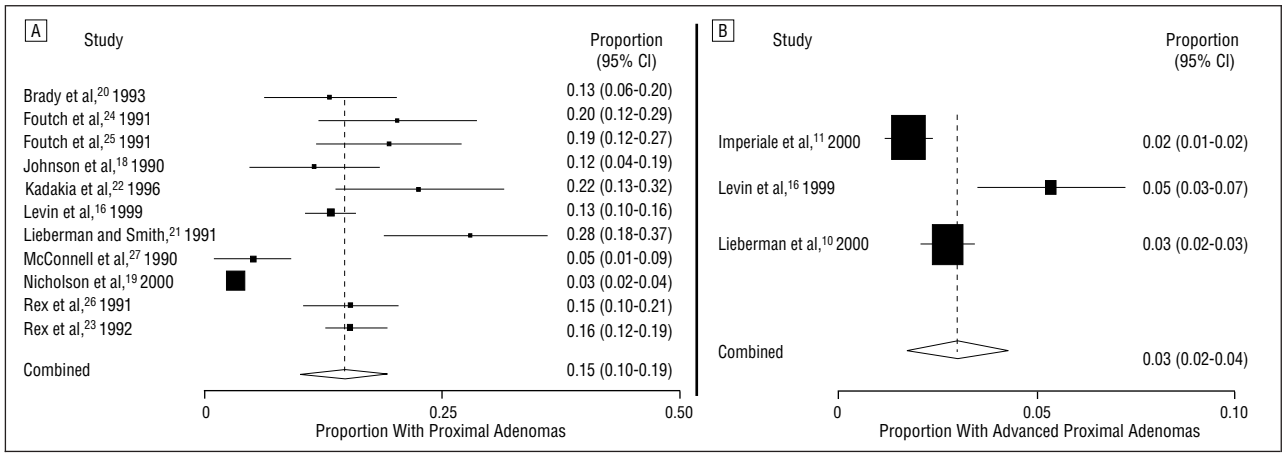

Figure 4. Summary plots of the proportion of patients without distal adenomatous polyps who have isolated proximal adenomas. A, The results for any isolated proximal adenoma. B, The results for isolated advanced proximal adenomas. Pooled estimates are derived from the random-effects model. CI indicates confidence interval.

Table 3. Pooled Estimate of the Prevalence of Isolated Proximal Neoplasms

	Any Adenoma, % (95% CI)		Advanced Adenoma, % (95% CI)	
Inclusion Criterion	**Random Effects**	**Fixed Effects**	**Random Effects**	**Fixed Effects**
Published articles before July 2000	14.6 (9.7-19.4)	6.7 (5.8-7.6)	3.0 (1.6-4.3)	2.4 (1.9-2.8)
Published articles before July 2000 plus abstracts	15.2 (10.6-19.8)	7.1 (6.2-8.0)	3.1 (2.2-4.1)	2.6 (2.2-3.0)
Published articles before July 2000 plus article after July 2000	14.0 (10.2-17.8)	8.4 (7.7-9.1)	2.4 (1.1-3.7)	1.3 (1.1-1.6)
Published articles before July 2000 plus abstracts and article after July 2000	14.6 (11.0-18.2)	8.6 (7.9-9.3)	2.8 (1.7-3.9)	1.5 (1.3-1.8)

Abbreviation: CI, confidence interval.

larger studies in the fixed-effects model. There was substantial heterogeneity among studies, with individual study estimates ranging from 3% to 28%. Stratified analyses demonstrated that for the 3 studies with a definition of the distal colon as the rectosigmoid colon, the fixed-effects and random-effects models both yielded a pooled probability estimate of 16.3% (95% CI, 13.6%-19.1%), with little heterogeneity ($P=.38$). This equates to a number needed to screen to detect an adenoma in a patient without a distal adenoma of 6.1. In the stratified analyses using the alternative definitions for the distal colon, the fixed-effects and random-effects models again produced much more consistent results, although there remained heterogeneity within these groups. Two studies (Nicholson et al[19] and McConnell et al[27]) seemed to be "outliers," reporting lower rates of isolated proximal neoplasms than the other studies. Eighty percent and 100% of patients included in these studies had a family history of colorectal cancer compared with a maximum of 20% of patients in the remaining studies.

Combining the 3 studies examining the risk of advanced proximal adenomas in the absence of distal adenomas yielded pooled estimates of 2.4% (95% CI, 1.9%-2.8%) using the fixed-effects model and 3.0% (95% CI, 1.6%-4.3%) using the random-effects model (Figure 4). The range of estimates from the individual studies was 2% to 5%. Using the results of the fixed-effects models, this corresponds to a number needed to screen to detect an advanced adenoma in a patient without a distal adenoma of 41.7, assuming 100% sensitivity of the screening test, although there was still evidence of heterogeneity ($P=.001$). Again, the 2 prospective studies[10,11] using a definition of the splenic flexure as the junction of the proximal and distal colon yielded similar results, with point estimates of 2% and 3%. In contrast, the retrospective study[16] using the area visualized by flexible sigmoidoscopy as the junction of the proximal and distal colon yielded a slightly higher point estimate of 5%.

Examination of funnel plots demonstrated possible publication bias, with larger studies having smaller estimates of proximal adenomas in the absence of distal adenomatous polyps (Egger test, $P=.001$). There was less evidence of publication bias in the studies of isolated advanced proximal neoplasms (Egger test, $P=.30$). Because of this evidence of possible publication bias, one of us (J.D.L.) manually searched the index of the published abstracts from the annual meetings of the American Gastroenterological Association, the American Society of Gastrointestinal Endoscopy, and the American College of Gastroenterology for 1999 to 2001. This search of published abstracts identified 3 studies[28-30] that met our inclusion criteria and provided enough data to include in an analysis. Inclusion of these studies in the analyses resulted in nearly identical results (**Table 3**). After our data collection for published articles was completed, at least 1 additional study[31] was published. In this large study (2620 subjects with-

out distal adenomas), 11.5% and 0.8% of patients without distal adenomas had proximal adenomas and an advanced proximal adenoma, respectively. Inclusion of this study in our analyses has a minimal effect on the estimated prevalence of isolated proximal neoplasms but results in lower estimates of the prevalence of isolated proximal advanced adenomas, particularly in the fixed-effects model (Table 3).

COMMENT

Colorectal cancer is an important cause of cancer-related mortality.[1] Strong evidence[2,4-9] supports recommendations for screening with flexible sigmoidoscopy, fecal occult blood testing, or both. To date, a randomized trial of screening colonoscopy vs screening with flexible sigmoidoscopy, fecal occult blood testing, or both has not been performed. Despite this, several researchers[12-14] have called for screening colonoscopy because colonoscopy is more sensitive at detecting proximal adenomas and offers a therapeutic intervention in a single procedure.

Screening sigmoidoscopy is used to identify patients with distal colonic neoplasms. These patients are then referred for total colonoscopy and polypectomy. For screening sigmoidoscopy to be most effective, proximal colonic adenomas must be strongly associated with distal colonic neoplasms. Nearly all studies included in our analyses suggested a positive association between distal and proximal colonic neoplasms, although there was substantial heterogeneity among estimates of the magnitude of this association. Among patients in whom the most advanced distal adenoma was a diminutive adenoma, there was a significantly increased risk of proximal adenomas (OR, 2.35). We did not observe a significantly increased association between distal hyperplastic polyps and proximal adenomas (OR, 1.44).

This study demonstrates that many patients without distal adenomas have proximal adenomas. Including all studies in the primary analysis (fixed-effects model), we estimated that 1 in 15 patients without a distal adenoma has a proximal adenoma and that 1 in 42 has an advanced proximal adenoma. Assuming that the distal colon includes only the rectum and sigmoid colon results in an estimated number needed to screen to detect an isolated proximal neoplasm of only 6.1. Thus, although patients with distal colonic neoplasms are more likely to have proximal colonic neoplasms, screening sigmoidoscopy programs that refer only those patients with distal colonic adenomas for colonoscopy will miss many proximal adenomas. These data support the argument for screening colonoscopy.

The ultimate decision as to the appropriate screening test for colorectal cancer is only partially informed by our results. Because of the low compliance rates for screening guidelines,[32] consideration of patient and physician factors is important. For example, screening sigmoidoscopy requires a less intense bowel preparation regimen that may be preferred by some patients. The ability of primary care physicians to perform sigmoidoscopy in their offices may also be important.[33] The total cost and cost-effectiveness of these procedures are also important.[12,14,34-36]

Because of the complicated nature of this decision, it is likely that there will be varied use of the available screening tests for many years. Our analysis did not demonstrate a significant association between hyperplastic polyps and proximal adenomas. This supports the current screening sigmoidoscopy guidelines recommending that small polyps undergo biopsy examination and that only adenomatous polyps are an indication for colonoscopy. Performing a biopsy may be expensive for primary care physicians, which may be a disincentive to perform screening sigmoidoscopy.[35]

There are mixed opinions[37-39] regarding whether colonoscopy should be performed if only diminutive adenomas are found by sigmoidoscopy. This uncertainty is reflected even in the most recent screening guidelines endorsed by the major gastroenterology professional societies.[3] Although we did not demonstrate a positive association between diminutive distal adenomas and advanced proximal adenomas in the primary analysis, there was some potential evidence in this direction (OR, 2.49; 95% CI, 0.96-6.44). In addition, we demonstrated a significant association between diminutive distal adenomas and any proximal adenoma (OR, 2.36; 95% CI, 1.30-4.29). These data support performing colonoscopy in all patients with distal colonic adenomas, even if they are diminutive.

The recommendation to proceed with colonoscopy in patients with only diminutive distal adenomas identified by flexible sigmoidoscopy can be further justified by considering the natural history of adenomatous polyps. Current guidelines recommend sigmoidoscopy every 5 years.[3] If all distal polyps are removed at the time of the first sigmoidoscopy, it is unlikely that new advanced polyps would develop in the distal colon during the recommended 5-year screening interval.[2,40] Thus, if only the identification of an advanced adenoma on sigmoidoscopy were to lead to colonoscopy, such a strategy would be unlikely to ever prompt performance of colonoscopy after the first screening sigmoidoscopy. This in turn would allow any proximal adenomatous polyp to remain undetected and to progress toward cancer.

There are several potential limitations of our analyses. There was relative heterogeneity among studies examining the association between any distal adenoma and proximal neoplasms. As such, the pooled estimates must be interpreted with caution. In examining the analyses of the association between distal and proximal colonic findings, it seems that patient age and sex and inclusion of patients with a family history of colorectal cancer were unlikely to explain the differing estimates of the magnitude of the association. In contrast, some of the heterogeneity was explained by differing definitions of the distal colon. It may be difficult to precisely determine the location of the sigmoid–descending colon junction or the splenic flexure during colonoscopy. Furthermore, previous stud-

ies[3] have demonstrated that depth of insertion of a flexible sigmoidoscope may vary substantially between examinations but that most examinations reach at least the junction of the sigmoid and the descending colon. Of the 3 studies examining the association between distal colonic findings and proximal advanced neoplasia, the one that used findings from sigmoidoscopy to define the distal colon consistently had different results from the 2 studies that used the endoscopically identified splenic flexure to define the distal colon. However, other factors may still contribute to this heterogeneity, as suggested by Lieberman et al[10] who analyzed data using 2 different definitions of the distal colon. In their analyses, there were relatively small differences in their estimates of the magnitude of the association between distal colonic adenomas and advanced proximal neoplasia using the different definitions.

Heterogeneity among studies included in the analysis of the prevalence of isolated proximal adenomas was also at least partly explained by varying definitions of the distal colon. Defining the distal colon as only the rectum and sigmoid colon (or the area observed by flexible sigmoidoscopy) leaves more proximal colon to harbor synchronous adenomas and should always yield higher estimates of the prevalence of isolated proximal neoplasms than using a definition of the distal colon beginning at the splenic flexure. For example, in the study by Lieberman et al,[10] the prevalence of isolated proximal advanced neoplasia increases from 2.7% to 3.7% using the more distal definition of the junction of the proximal and distal colon. Similarly, the study by Ikeda et al[31] had the lowest estimate of isolated advanced proximal neoplasia and used the splenic flexure as the definition of the beginning of the distal colon. However, an interesting observation from our analyses was that the 2 studies composed predominantly of patients with a family history of colorectal cancer had a lower prevalence of isolated proximal neoplasia than the other studies. In light of this finding, studies designed specifically to address the question of whether the prevalence of isolated proximal adenomatous polyps differs among patients with and without a family history of colorectal cancer are needed.

In performing a meta-analysis, it is always possible that certain studies will be missed. We arbitrarily selected only studies published through July 2000 and studies that included only asymptomatic patients undergoing screening colonoscopy. To minimize the chance of missing a published study, we queried the corresponding authors of the articles included in our meta-analysis and the authors of several related articles. No additional articles meeting our inclusion criteria were identified by those researchers who responded to our query.

Although we believe that we identified all relevant published studies, it remains possible that important unpublished data may have been missed. Such publication bias can result in misleading estimates from meta-analysis if the results of the unpublished studies differ from those of the published studies. To look for evidence of publication bias, we generated funnel plots and used a formal statistical test. In fact, it seemed that there may be an element of publication bias in our estimate of the risk of proximal adenomas in patients without distal adenomas. The larger studies tended to have lower estimates of proximal adenomas in the absence of distal adenomas than did the smaller studies. Therefore, it is possible that small studies demonstrating low rates of isolated proximal adenomas were less likely to be published.

To examine the potential impact of this publication bias, we performed a manual search of the abstracts from recent meetings of 3 large gastroenterology societies. This search yielded 3 additional studies with sufficient data for inclusion in the analyses. In addition, while we were performing our study, at least 1 additional article[31] was published on this topic. Inclusion of the abstracts or the later published study resulted in minimal change to our estimate of the prevalence of any isolated proximal neoplasm. However, inclusion of the published study resulted in lower estimates of the prevalence of isolated proximal advanced neoplasia.

In conclusion, our synthesis of the published English-language medical literature between January 1, 1966, and July 31, 2000, demonstrated relatively modest associations between distal colonic adenomas and the prevalence of adenomas in the proximal colon. There was substantial heterogeneity among these studies, which was at least partly explained by the investigator's definition of the distal colon. A significant association was also seen between diminutive distal adenomas and proximal adenomas, but not between hyperplastic polyps and proximal adenomas. Based on these findings, we suggest that patients with distal colonic adenomas found by sigmoidoscopy be referred for screening colonoscopy, even if the distal lesion is a diminutive adenoma. However, given the relatively modest strength of this association, the false-negative rate of screening sigmoidoscopy for proximal colonic adenomas is relatively high. Our meta-analysis demonstrates that sigmoidoscopy programs that refer only patients with distal colonic adenomas for total colonoscopy would miss isolated advanced proximal adenomas in approximately 1.3% to 2.4% of patients with "normal" findings on sigmoidoscopy. Even more patients will have isolated nonadvanced adenomas. These data can be used by physicians to counsel their patients about screening options and by policymakers when deciding what screening programs to recommend. Finally, our analyses suggest that the prevalence of isolated proximal colonic neoplasia may differ among those with and without a family history of colorectal cancer. This issue warrants further study.

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