The Relationship Between Distal and Proximal Colonic Neoplasia: A Meta-Analysis

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OBJECTIVES: To investigate the association between proximal colonic neoplasia and distal lesions as a function of the lesion type. The extent to which health, demographic, and study characteristics moderate this association was also examined.

DATA SOURCES: Google Scholar, Web of Science, Scopus, and PubMed.

STUDY ELIGIBILITY CRITERIA: Studies allowing the calculation of OR of proximal neoplasia(PN) and proximal advanced neoplasia (PAN) for distal hyperplastic polyps (HP), nonadvanced adenomas (NAA), adenomas (AD), and advanced neoplasia (AN); also, studies for which the proportions of subjects with isolated (i.e., not accompanied by distal lesions) PN (IPN) and PAN (IPAN) over the total number of subjects with PN or PAN could be calculated.

STUDY APPRAISAL AND SYNTHESIS METHODS: Thirty-two studies were included for calculating OR between proximal neoplasia and distal lesions and 40 studies for proportions of IPN and IPAN. Subgroup analyses were conducted for presence of symptoms, prevalence of PN and PAN, age, proportion of males, geographic region, study design, and demarcation point.

RESULTS: The association between distal lesions and proximal neoplasia increased with the severity of the distal lesions. Odds of PN were higher in subjects with HP compared to subjects with a normal distal colon. Odds of PN and PAN were higher in subjects with NAA, AD, and AN than in subjects with a normal distal colon. PAN were more strongly associated with distal lesions in asymptomatic populations, in young populations, and in populations with a low prevalence of PAN. In approximately 60% of the subjects with PN and PAN, these neoplasia were isolated.

LIMITATIONS: The present results may be affected by publication bias and dichotomization in the subgroup analyses. Limitations related to the individual studies include self-selection, lesion misclassification and misses, and technological advances leading to changes in the detection of lesions during the time span of the included studies.

CONCLUSIONS AND IMPLICATIONS OF KEY FINDINGS: All types of distal lesions are predictive of PN. All types of distal neoplasia are predictive of PAN. The association between distal lesions and proximal neoplasia increases with the severity of the distal lesion. The association between distal lesions and proximal advanced neoplasia is stronger in low-risk groups as compared to high-risk groups.

KEY WORDS: cancer screening; colorectal cancer; systematic review.
J Gen Intern Med 27(3):361–70
DOI: 10.1007/s11606-011-1919-y

Received June 23, 2011
Revised September 29, 2011
Accepted October 3, 2011
Published online November 8, 2011

INTRODUCTION

The use of flexible sigmoidoscopy followed by colonoscopy in colorectal cancer screening programs relies on the assumption that distal lesions are reliable markers of proximal neoplasia. It is widely established that subjects with distal advanced neoplasia (AN) have increased odds of proximal neoplasia (PN) and proximal advanced neoplasia (PAN).[1–3]

Whether distal hyperplastic polyps (HP) are also markers of PN and PAN is debatable. Formal guidelines generally do not consider HP to be markers of PN or PAN.[3–5] Seven of nine colonoscopy studies published to date revealed no significant associations between HP and PN,[6–14] and only one of eight colonoscopy studies reported a significant association between HP and PAN.[6,10,15–20] Pathology studies, however, suggest that HP could develop into cancer through microsatellite instability and hypermethylation pathways.[21–25] The published pathological evidence has been suggested as one of the reasons why physicians tend not to adhere to formal guidelines and refer patients with HP alone for colonoscopy.[26] The association between distal nonadvanced adenomas (NAA) and PN and PAN is equivocal as well, and screening recommendations leave the follow-up program for subjects with NAA to the judgment of the clinician.[3,27,28]

The effectiveness of flexible sigmoidoscopy for screening not only depends on whether distal lesions are markers of PN or PAN, but also on the PN and PAN that are isolated, that is, not accompanied by distal lesions (IPN and IPAN, respectively). It has been suggested that in about half of the subjects, PN do not have distal markers and are thus not identifiable by the sigmoidoscopy outcome alone.[16,18,29] It has further been shown that the prevalence of IPN is higher in subjects older than 60 years, those with a family history of colorectal cancer, and those with 10 pack-years of smoking.[30]

Three previous meta-analyses[31–33] have summarized the empirical evidence regarding the association between distal lesions and proximal neoplasia. Subjects with HP had higher odds of PN compared to subjects having a normal distal colon,[33] and subjects with NAA were more likely to also have PN than subjects without distal neoplasia.[32] Neither HP[31,33] nor NAA[32] appeared to increase the odds of PAN. These past meta-analyses

need to be updated, however. A large number of relevant studies have been published since, offering the opportunity for a more powerful synthesis. Furthermore, the previous meta-analyses did not summarize the effects of demographic factors, such as age, gender, or geographic region, which show differential effects on the prevalence of colonic lesions.[34,35] It is possible that the association between distal lesions and proximal neoplasia is also sensitive to these factors. Lastly, the existing meta-analyses did not investigate the extent to which demographic factors moderate the proportions of subjects with IPN and IPAN.

The aim of this meta-analysis was to investigate the relationship between distal lesions and proximal neoplasia as a function of lesion type, to estimate the proportion of subjects with isolated proximal neoplasia in the population, and to examine the extent to which health, demographic, and study characteristics are moderators of the association between distal lesions and proximal neoplasia and of the proportions of subjects with isolated proximal neoplasia.

METHOD

A literature search was carried out between 11 and 26 November 2010 using Google Scholar, Web of Science, Scopus, and PubMed. Each of the terms "proximal neoplasia", "advanced proximal neoplasia", "proximal advanced neoplasia", "proximal neoplasms", and "proximal adenoma" was combined with each of the terms "distal", "hyperplastic", "adenoma", "nonadvanced", "advanced", "sigmoidoscopy", and "colonoscopy" in a full-text search.

Exclusion Criteria

The following types of studies were excluded:

- Studies in which subjects with a positive sigmoidoscopy outcome were referred to colonoscopy. These studies either lacked subjects with a normal distal colon to be used as a reference, or used as a reference subjects whose distal biopsies were found to consist of normal mucosa during histological examination conducted after colonoscopy.
- Studies focusing on patient groups with colorectal cancer, inflammatory bowel disease, hyperplastic polyposis syndrome, hereditary nonpolyposis syndrome, diverticulosis, or HIV.
- Studies including only subjects younger than 50 years, as these subjects have lower odds of colorectal lesions as compared to subjects that are 50 years and older, who are the typical target group of screening programs.[36,37]
- Studies in which nonneoplastic proximal lesions were aggregated together with neoplastic ones, and studies reporting only proximal cancer.
- Studies focusing on subjects who underwent polypectomy.
- Studies with internal inconsistencies inhibiting the calculation of odds ratios.
- Studies in languages other than English.

Data Extraction

The following data were collected from each study: sample size, presence or absence of symptoms (including a positive fecal occult blood test or barium enema) in more than 50% of the population, mean age, proportion of male subjects, Western (American or European) or Eastern (Asian) population, prospective or retrospective study design, and demarcation point of distal colon (splenic flexure, 60-cm sigmoidoscope length, or rectosigmoid). An e-mail was sent to the corresponding authors of the studies with missing demographic data.

Thirty-two studies met the criteria described in the previous section. Twenty-nine studies classified subjects with respect to their most advanced distal lesion. Of the remaining three studies, one provided the number of all distal lesions per subject and the other two included a group of subjects with mixed hyperplastic and adenomatous polyps. We classified the subjects in these three studies based on their most advanced distal lesion.

Twenty-eight studies reported the number of subjects per type of distal lesion without distinguishing between single and multiple lesions, whereas the remaining four reported subjects with single and multiple lesions separately. It has previously been shown that multiple distal lesions are associated with increased odds of proximal neoplasia compared to single lesions of the same type.[38,39] To conform with the methodology followed by the majority of the studies included, however, in these four studies we clustered the subjects with single and multiple lesions together and classified them according to the type of their lesions only.

OR of PN and PAN were calculated for the following distal lesions: hyperplastic polyps (HP), nonadvanced adenomas (NAA), adenomas (AD), and advanced neoplasia (AN). AN were defined as adenomas with a size of 10 mm or greater, adenomas with villous portions, high-grade dysplasias, and adenocarcinomas. Non-hyperplastic lesions were considered as normal findings. OR were calculated as the number of subjects with PN (or PAN) in the group of subjects with distal lesions compared to the number of subjects with PN (or PAN) in the reference group. OR of HP were calculated with the subjects having a normal distal colon as the reference group. OR of NAA, AD, and AN were calculated by using two reference groups: subjects with a normal distal colon, as in Lin et al.,[33] and subjects with no distal neoplasia, as in Lewis et al.[32] The results were not statistically different. The percentual differences in the summary OR (defined as the absolute difference of the two summary OR divided by the summary OR with the normal-distal-colon group as reference) were: NAA–PN= 5.9%, AD–PN=−1.4%, AN–PN=−3.6%, NAA–PAN=18.9%, AD–PAN=−0.2%, and AN–PAN=19.5%. The summary OR presented herein are based on a combination of the two reference groups: the subjects with a normal distal colon were used as the reference group; when this group was not available in a study, the reference group consisted of the subjects with no distal neoplasia instead. OR were not calculated when zero events were observed. OR were meta-analyzed using the random-effects Mantel-Haenszel method.

Absolute risks (AR) of PN and PAN were calculated for subjects with a normal distal colon, HP, NAA, AD, and AN. The absolute risk of PN (or PAN) for subjects with a certain distal-colon condition (i.e., normal, HP, NAA, AD, or AN) was defined as the percentage of subjects with PN (or PAN) and this distal-colon condition out of the total number of subjects with this condition. Proportions of IPN or IPAN were defined as the number of subjects with IPN or IPAN over the total number of subjects with PN or PAN. AR and proportions of IPN and IPAN were meta-analyzed using the DerSimonian-Laird random-effects method.

Subgroup analyses of OR and proportions of IPN and IPAN were conducted according to the presence or absence of symptoms, age younger than 60 years versus 60 years or older, proportion of males lower versus equal to or higher than 0.5, study conducted in Western or Eastern region, prospective or retrospective study design, and splenic flexure or rectosigmoid used as demarcation point. Subgroup analysis of OR was also conducted for PN and PAN prevalence lower versus equal to or higher than the median PN and PAN prevalence. A z-test was used to compare the summary odds ratios between subgroups.[40] To investigate the possibility of publication bias the asymmetry of the funnel plots was assessed by Egger's test.

RESULTS

The literature search yielded 2320 titles (Fig. 1). After excluding 748 duplicates within and among databases, 1572 abstracts were reviewed. Of these, 1324 were excluded based on the criteria described in the method section. The full texts of the remaining 248 publications were reviewed. Thirty-two publications fulfilled the criteria and were included in the meta-analysis (Table 1).

Figure 2 illustrates the sample size and the number of times each of the 32 studies was included in past meta-analyses as a function of the publication year. A significant positive correlation was found between publication year and sample size (r=0.49, p=0.005). A shift from prospective towards retrospective studies can also be observed, but without reaching significance (r=0.28, p=0.122). Of the eight studies published before 2005 but not included in the most recent meta-analysis,[33] six[38,41,42,46,49,51] were not taken into consideration probably because they did not provide data on HP, one[54] was excluded on the grounds that it did not provide suitable HP data, and one[55] was not mentioned. We used the first seven studies[38,41,42,46,49,51,54] to estimate the association between AD and PN/PAN.

Table 2 shows the summary estimates of AR and OR for the association between distal lesions and proximal neoplasia. The odds of PN were higher in subjects with HP compared to those having a normal distal colon. Subjects with HP did not show evidence of increased odds of PAN. Note that only 2 of the 9 included studies yielded a significantly positive association between HP and PN. Absolute risks and odds of both PN and PAN were higher in subjects with NAA, AD, and AN than in subjects having a normal distal colon. A positive trend between the association of distal and proximal lesions and the severity of the distal markers can be noticed.

In order to estimate the proportions of IPN and IPAN, a literature search was conducted using the terms "isolated proximal" and "sigmoidoscopy" in Google Scholar, Web of Science, Scopus, and PubMed. A manual review of the references in each newly retrieved and selected article was also performed. Eight additional studies were identified in this way.

Figure 3 shows the proportions of IPN and IPAN per study. The random-effects summary estimates were 0.61 (95% CI= 0.55–0.67) and 0.58 (95% CI=0.53–0.63) for IPN and IPAN, respectively. In the population, these proportions correspond

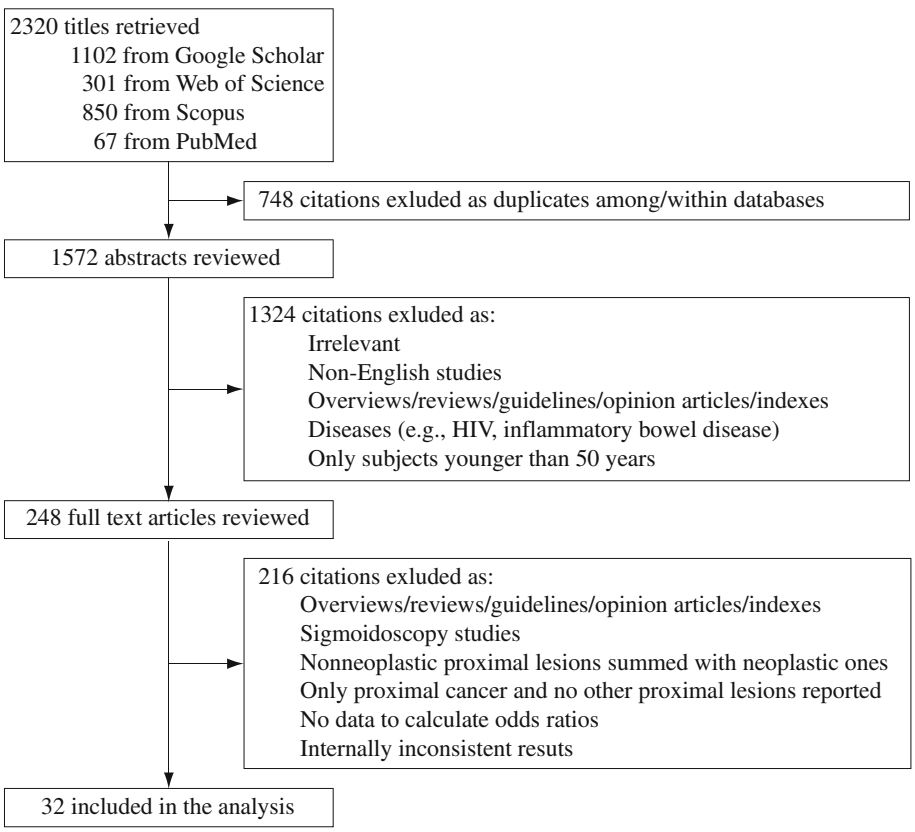

Figure 1. Flow diagram of study selection.

Table 1. Characteristics of the Studies Included in the Meta-Analysis

	Reference	Sample size	Symptoms	Mean age (years)	Proportion male	Geographic region	Demarcation point	Study design
1	Ang et al. 2002[41] *	450	Yes	71.0	0.45	0	0	1
2	Betés Ibáñez et al. 2004[42]	2210	No	57.9	0.75	0	0	1
3	Binda et al. 2007[6] *	830	Yes	65.0	0.41	0	0	1
4	Brady et al. 1993[7]	162	No	62.0	0.76	0	1	0
5	Byeon et al. 2007[15]	860	No	54.4	0.55	1	0	0
6	Choe et al. 2007[43] *	2435	No	57.7	0.67	1	0	1
7	Chung et al. 2006[44]	1541	Yes	55.1	0.52	1	2	1
8	Erarslan et al. 2009[45]	1064	No	66.0	0.38	0	0	1
9	Foutch et al. 1991[8]	129	No	64.0	0.98	0	1	0
10	Hammer et al. 2000[38]	3268	Yes	68.0**	0.49	0	0	0
11	Ikeda et al. 2000[46]	3131	No	51.9	1.00	1	0	1
12	Imperiale et al. 2003[16]	3025	No	59.8	0.58	0	0	1
13	Johnson et al. 1990[47]	88	No	65.0	0.68	0	0/2	0
14	Kadakia et al. 1996[48]	175	No	65.0	0.61	0	0	0
15	Khan et al. 2003[49]	1301	No	65.7	0.70	0	2	1
16	Leung et al. 2005[17]	4646	Yes	55.0	0.50	1	0	0
17	Lieberman & Smith 1991[9]	105	No	64.0	1.00	0	1	0
18	Lieberman et al. 2000[18]	3118	No	62.9	0.97	0	0/2	0
19	Lin et al. 2005[10] *	2188	No	60.7	0.49	0	0/2	0
20	Liou et al. 2007[19]	2106	No	59.4	0.57	1	0	1
21	Liu et al. 2005[20]	5973	No	56.6	0.63	1	0	0
22	Nicholson et al. 2000[50]	1131	No	54.0	0.63	0	0	1
23	Odelowo et al. 2002[51]	5514	No	65.1	—	0	0	1
24	Okamoto et al. 2005[52]	6196	Yes	60.1	0.65	1	2	0
25	Park et al. 2009[53]	3951	No	52.1	0.60	1	0	0
26	Pennazio et al. 1993[11]	216	Yes	64.0	0.67	0	2	1
27	Provenzale et al. 1988[12]	514	Yes	—	0.51	0	2	1
28	Provenzale et al. 1990[13]	970	Yes	—	0.47	0	2	0
29	Rex et al. 1992[14]	482	No	62.5	—	0	2	0
30	Sciallero et al. 1997[54]	3088	Yes	59.9	0.55	0	2	1
31	Strul et al. 2006[37] *	917	No	60.9	0.48	0	0/2	1
32	Thiis et al. 1999[55]	193	No	67.4	0.56	0	2	0
Additional studies included in the IPN and IPAN analysis								
33	Al-Enezi et al. 2010[56]	530	No	45.0	0.66	1	0	1
34	Castiglione et al. 1995[57]	2937	Yes	—	—	0	2	1
35	Chiu et al. 2005[58]	1846	No	52.5	0.60	1	0	0
36	Gryska et al. 1987[59]	49	No	54.5	—	0	2	1
37	Kim et al. 2007[60]	4491	No	48.4	0.53	1	0	1
38	Lieberman et al. 1988[61]	98	Yes	65.0	0.94	0	1	1
39	Schoenfeld et al. 2005[62]	1463	No	58.9	0.00	0	0	0
40	Soon et al. 2008[63]	1382	No	58.8	0.60	1	0	1

Only the subjects that were 50 years or older have been included in the analysis
***Median age*
Geographic region: Western (American or European)=0; Eastern (Asian)=1. Demarcation point: Splenic flexure=0; 60 cm (length of sigmoidoscope)=1; Rectosigmoid=2. Study design: Prospective=0; Retrospective=1
Abbreviations: IPAN, isolated proximal advanced neoplasia; IPN, isolated proximal neoplasia

to random-effects estimates of 0.09 (95% CI=0.07–0.11) for IPN and 0.02 (95% CI=0.01–0.03) for IPAN.

Table 3 shows the OR after splitting the studies according to the presence of symptoms, prevalence of PN and PAN, age, proportion of males, geographic region, study design, and demarcation point of the distal colon.

Symptoms and prevalence of proximal neoplasia. Symptomatic populations with NAA showed higher odds of PN compared to asymptomatic populations. For PAN, the opposite effect held, with NAA and AN being stronger predictors in asymptomatic populations. Moreover, the association between AN and PAN was stronger in populations with a PAN prevalence lower than the median PAN prevalence of all populations for which PAN prevalence could be calculated.

Age and gender. AN were more strongly associated with PAN in younger populations. No other subgroup differences based on age or gender were found. To gain a better understanding of the moderating role of age, an additional subgroup analysis was conducted for the studies for which OR could be calculated separately for subjects younger than 50 years versus 50 years or older, and found that the OR for AN–PN and NAA–PAN were significantly higher for the subgroups of younger subjects (Table 4).

Geographic region. The NAA–PAN association was stronger in Western regions than in Eastern ones.

Study design. No differences were found between the OR of prospective and retrospective studies.

Demarcation point. The definition of demarcation point did not affect the OR of PN. Note, however, that the number of studies was limited. Odds ratios between NAA/AN and PAN were significantly higher in studies using the splenic flexure as the

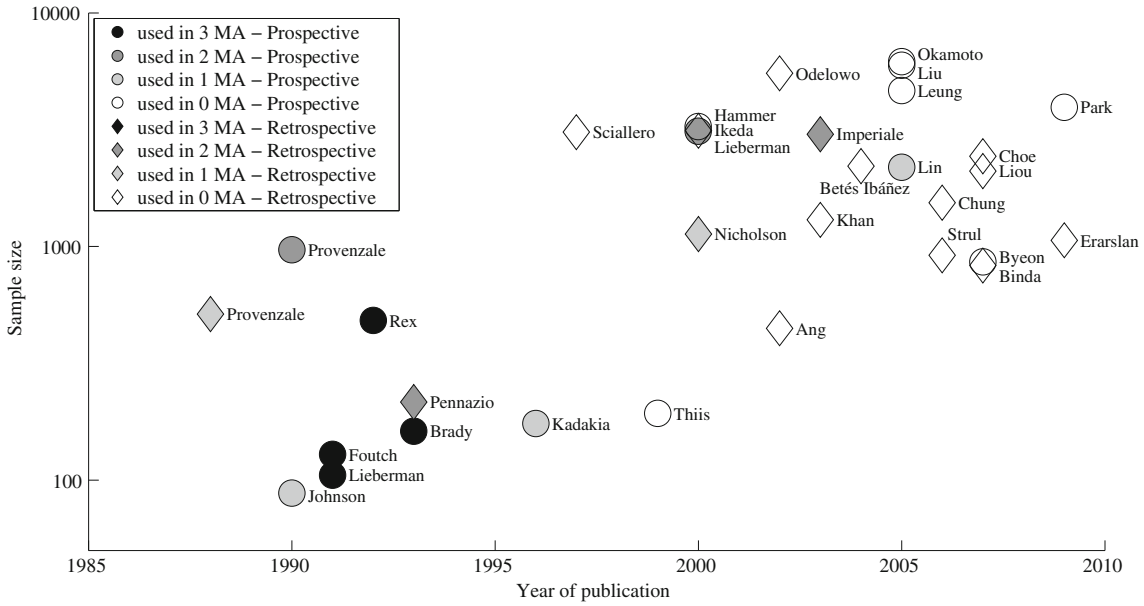

Figure 2. Scatter plot of studies per year of publication as a function of sample size and study design. Abbreviations: MA, meta-analysis.

demarcation point as compared to the odds ratios of the studies using the rectosigmoid as demarcation. Figure 4 illustrates this effect for the association between AN and PAN.

Subgroup analyses were also conducted for proportions of IPN and IPAN. None of the investigated factors (presence of symptoms, age, proportion of males, geographic region, study design, and demarcation point) was found to be a moderator of these proportions.

To investigate the possibility of publication bias the asymmetry of the funnel plots was assessed by Egger's test. A slight bias inflating the association between PN and AN was found (intercept (95% CI)=−2.92 (−5.67, −0.17), p=0.041). Because the PN–AN association is strong and generally accepted, however, we do not consider this finding to be of clinical significance. In all other lesion associations and proportions of IPN and IPAN the funnel plot asymmetry was not significant.

Table 2. Summary Estimates of Absolute Risks (%) and Odds Ratios of PN and PAN in Subjects with Distal HP, NAA, AD, and AN

		N*	AR (95% CI)	OR (95% CI)
PN	Normal distal	13	14.8 (10.1–20.3)	—
	HP	9 (2)	27.2 (17.6–38.0)	1.8 (1.3–2.5)
	NAA	11 (9)	28.1 (23.0–33.5)	2.6 (2.1–3.3)
	AD	16 (12)	29.7 (25.0–34.6)	3.8 (3.1–4.6)
	AN	8 (6)	32.8 (27.0–38.9)	3.4 (2.4–4.9)
PAN	Normal distal	12	1.9 (1.4–2.4)	—
	HP	8 (1)	2.3 (1.6–3.2)	1.2 (0.8–2.0)
	NAA	17 (10)	5.2 (3.2–7.6)	2.1 (1.7–2.5)
	AD	11 (8)	8.3 (4.8–12.7)	3.1 (2.2–4.3)
	AN	14 (12)	14.5 (11.6–17.6)	5.8 (4.0–8.6)

**Numbers in brackets indicate the studies for which the calculated association was significantly positive at the 0.05 level*

Odds ratios of HP were calculated with the subjects having a normal distal colon as reference. For the odds ratios of NAA, AD, and AN, the subjects with a normal distal colon were used as reference; when this group was not available, the reference consisted of the subjects with no distal neoplasia

Abbreviations: AD, adenomas; AN, advanced neoplasia; HP, hyperplastic polyps; N, number of studies; NAA, nonadvanced adenomas; PAN, proximal advanced neoplasia; PN, proximal neoplasia

COMMENT

The relationship between distal lesions and proximal neoplasia. This article provided a meta-analysis of the relationship between distal lesions and proximal neoplasia as a function of lesion type. Thirty-two studies were retrieved providing information suitable for calculating odds ratios for PN and PAN. Concerning PAN, 18 studies were included, which, compared to the two studies available in past meta-analyses, resulted in more precise estimates of the summary effects. Forty studies were included for analyzing proportions of IPN and IPAN. The extent to which health, demographic, and study characteristics moderate the association between distal lesions and proximal neoplasia as well as the proportions of IPN and IPAN was also examined.

Subjects with HP showed higher odds of PN compared to subjects having a normal distal colon, whereas they did not show evidence of increased odds of PAN, in line with Lin et al.[33] Subjects with NAA showed higher odds of both PN and PAN, supporting and extending Lewis et al.[32] who found a significant association between NAA and PN and "potential evidence" (p. 418) but not a significant association between NAA and PAN. Note that Lewis et al.[32] focused on "diminutive adenomas", but the term had multiple definitions and we believe that the term corresponds better to NAA.

Health characteristics. PAN were better predicted in asymptomatic populations, young populations, and populations with a low PAN prevalence; that is, in low-risk groups. This supports past evidence showing that subjects diagnosed at a young age are more likely to have advanced malignancies, possibly due to genetic predispositions.[64,65]

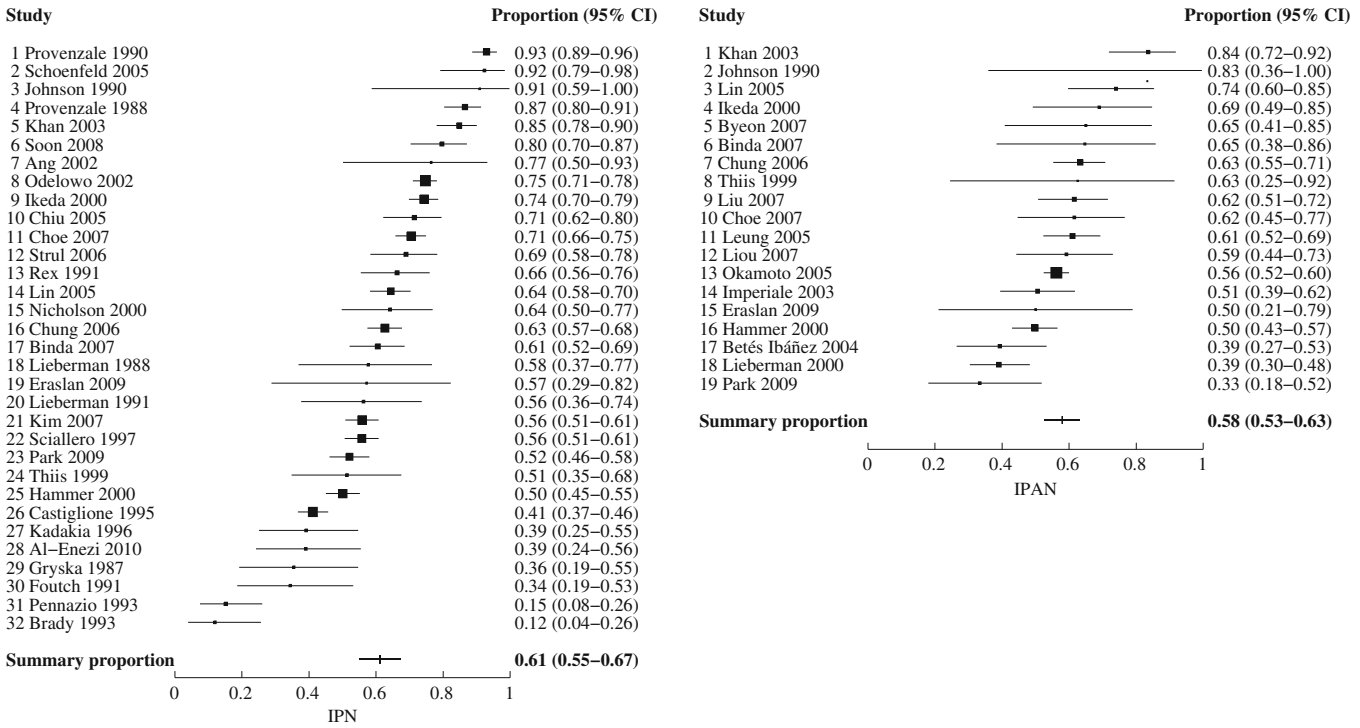

Figure 3. Forest plots with proportions of isolated proximal neoplasia (IPN, left) and isolated proximal advanced neoplasia (IPAN, right) defined as the number of subjects with IPN or IPAN over the total number of subjects with PN or PAN. The error bars are depicted at the 95% CI. The area of the squares corresponds to the weight of each study in the random-effects model. Note that some studies provided data that allowed the calculation of proportions of both IPN and IPAN. The variance of true effect sizes τ^2 was 0.118 and 0.035 for IPN and IPAN, respectively.

Demographic characteristics. It is widely established that men have a higher and earlier risk of colonic neoplasia than women.[6,10,11,20,35,42–44,52,53,58,66–71] Age and gender are interacting factors, with women younger than 50 years having a lower risk of proximal than distal neoplasia, while males in the same age group have a higher prevalence of distal than proximal neoplasia,[16,65,72] women between 50 and 70 years showing an increasing incidence of proximal neoplasia compared to women of younger age,[62,65,69] and gender differences diminishing after the age of 70.[62] With respect to geographic region, it has been suggested that although Eastern populations have fewer incidences of isolated proximal neoplasia, lesions that are more likely distal,[8,38,44,45,73–76] and a 10-year delay in the incidence of colonic neoplasia,[43] Western and Eastern populations are becoming increasingly comparable due to the Westernization of the Eastern lifestyle. Note that the existing information concerns prevalences. We found no differences between genders and geographic regions regarding the association between distal lesions and proximal neoplasia.

Study design characteristics. The study of Lin et al.,[33] the only meta-analysis investigating the moderating effect of the demarcation point of the distal colon, reported no clinically significant differences in lesion associations between studies using a different demarcation point. We found that studies using the splenic flexure as demarcation yielded significantly higher OR between NAA/AN and PAN compared to studies using the rectosigmoid as demarcation. Note that the majority of the colonoscopy studies used the splenic flexure as the demarcation point, but this does not reflect clinical practice, in which the sigmoidoscope may not reach the area beyond the rectosigmoid in more than 60% of procedures.[77,78] The association between NAA/AN and PAN is thus likely weaker in a screening setting than the estimates provided in studies using the splenic flexure as demarcation.

Proportions of IPN and IPAN. The summary estimates of percent proportions of subjects with IPN and IPAN were about 60%, which is higher than the estimates of about 50% provided in past meta-analyses. We found no subgroup differences of demographic factors for proportions of either IPN or IPAN. Note that our analysis concerned the proportion of subjects with IPN and IPAN, and not the population prevalence of IPN and IPAN which is affected by the general prevalence of PN and PAN (i.e., accompanied by distal lesions or not). That is, the increasing population prevalence of IPN with age reported in previous studies[30,79] is due, at least in part, to the increasing prevalence of proximal/colonic neoplasia with age, no matter whether the proximal neoplasia are isolated or not.

Study Limitations

Self-selection. A number of biases may have affected the results of the meta-analysis. First, the subjects in the studies were likely to be more health-conscious and aware of preventive medicine than the general population.[9,15,37,42,55,80,81] Moreover,

Table 3. Subgroup Analysis for Health, Demographics, and Study Characteristics of the Summary Odds Ratios of PN and PAN in subjects with Distal HP, NAA, and AN

			HP		NAA		AN	
			N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
Health characteristics								
Symptoms	No	PN	5	1.4 (1.0–1.9)	7	2.1 (1.7–2.6)	5	3.3 (2.3–4.6)
	Yes		4	2.4 (1.3–4.3)	4	3.2 (2.5–4.2)	3	3.8 (2.0–7.3)
	No	PAN	6	1.3 (0.8–2.1)	12	2.5 (2.0–3.1)	9	8.1 (5.3–12.2)
	Yes		2	0.8 (0.1–4.3)	5	1.7 (1.3–2.2)	5	3.9 (2.4–6.4)
Prevalence PN	Low (<0.147)	PN	1	—	5	2.6 (1.8–3.7)	4	3.5 (1.8–6.6)
	High (≥0.147)		8	1.9 (1.3–2.8)	6	2.6 (1.8–3.7)	4	3.3 (2.4–4.5)
Prevalence PAN	Low (<0.025)	PAN	5	1.3 (0.6–2.8)	7	2.0 (1.4–2.8)	5	9.9 (5.6–17.4)
	High (≥0.025)		3	1.1 (0.6–2.2)	10	2.1 (1.6–2.8)	9	4.9 (3.3–7.3)
Demographic characteristics								
Age	<60 years	PN	0	—	3	2.2 (1.6–3.1)	3	3.4 (2.4–4.9)
	≥60 years		8	1.5 (1.1–2.0)	8	3.0 (2.4–3.8)	5	3.3 (1.8–6.0)
	<60 years	PAN	5	1.3 (0.6–2.8)	10	2.3 (1.9–2.9)	8	8.1 (5.1–13.0)
	≥60 years		3	1.0 (0.6–1.7)	7	1.8 (1.3–2.4)	6	3.6 (2.1–6.2)
Gender	<50% males	PN	3	1.4 (1.1–2.0)	3	2.9(2.1–4.0)	3	3.9 (1.9–8.0)
	≥50% males		5	2.5 (1.4–4.5)	8	2.5 (1.9–3.4)	5	3.2 (2.4–4.2)
	<50% males	PAN	2	1.1 (0.4–2.5)	2	1.9 (1.2–3.1)	2	4.7 (1.7–13.3)
	≥50% males		6	1.2 (0.7–2.3)	15	2.1 (1.7–2.6)	12	6.0 (3.9–9.4)
Geographic region	Western	PN	9	1.8 (1.3–2.5)	8	3.0 (2.4–3.8)	5	3.3 (1.8–6.0)
	Eastern		0	—	3	2.2 (1.6–3.1)	3	3.4 (2.4–4.9)
	Western	PAN	4	1.2 (0.8–1.9)	8	2.5 (1.9–3.3)	7	6.0 (4.1–8.8)
	Eastern		4	1.0 (0.3–3.4)	9	1.7 (1.4–2.1)	7	6.2 (3.5–11.3)
Study characteristics								
Study design	Prospective	PN	6	1.4 (1.1–1.9)	4	3.1 (1.9–4.9)	2	4.9 (1.9–12.5)
	Retrospective		3	2.8 (1.3–6.3)	7	2.4 (1.9–3.1)	6	3.1 (2.5–3.9)
	Prospective	PAN	5	1.2 (0.6–2.4)	9	1.9 (1.5–2.5)	7	5.6 (3.2–9.6)
	Retrospective		3	1.2 (0.5–2.7)	8	2.2 (1.7–3.0)	7	6.1 (3.5–10.9)
Demarcation point	Splenic flexure	PN	2	1.4 (1.0–2.0)	6	2.3 (1.7–2.9)	5	3.8 (2.4–6.1)
	Rectosigmoid		4	2.3 (1.2–4.5)	4	3.2 (2.4–4.2)	3	2.9 (2.2–3.9)
	Splenic flexure	PAN	8	1.2 (0.8–2.0)	13	2.4 (2.0–2.9)	10	7.8 (5.8–10.5)
	Rectosigmoid		—	—	4	1.5 (1.1–1.9)	4	2.6 (2.2–3.1)

A z-test was used to compare the summary odds ratios between subgroups. p<0.05 are annotated in bold
Abbreviations: AN, advanced neoplasia; HP, hyperplastic polyps; NAA, nonadvanced adenomas; PAN, proximal advanced neoplasia; PN, proximal neoplasia

most studies were conducted in university hospitals and medical centers in urban areas,[19,53] or in private clinics requiring private health insurance[42,82] and compensations as high as $500,[19] possibly contributing to self-selection bias.

Misclassification and misses. Other sources of bias are lesion misses, false positives, and lesion misclassification. Miss rates of about 26% and 13% of adenomas smaller than 5 mm and between 5 and 10 mm, respectively, have been reported.[83,84] Small adenomas may be misclassified as HP,[85,86] and adenomatous changes in a portion of HP may not be noticed without histological examination. Moreover, endoscopists usually compare the size of polyps to the width of

Table 4. Subgroup Analysis for Age Younger than 50 years Versus 50 years or Older of the Summary Odds Ratios of PN and PAN in Subjects with Distal NAA and AN

			NAA		AN	
			N	OR (95% CI)	N	OR (95% CI)
Age	<50 years	PN	2*	3.2 (1.5–6.6)	2‡	6.8 (3.2–14.5)
	≥50 years		6†	2.0 (1.6–2.5)	4§	2.8 (2.0–3.9)
	<50 years	PAN	3‖	6.9 (2.6–18.3)	1#	—
	≥50 years		7¶	2.3 (1.6–3.4)	5**	5.9 (3.4–10.3)

* *References: 6, 43;* † *References: 6, 7, 37, 43, 47, 55;* ‡ *References: 6, 43;* § *References: 6, 37, 43, 55;* ‖ *References: 6, 36, 43;* ¶ *References: 6, 16, 18, 19, 43, 47, 55;* # *Reference: 36;* ** *References: 6, 16, 18, 43, 55*
A z-test was used to compare the summary odds ratios between subgroups. p<0.05 are annotated in bold
Abbreviations: AN, advanced neoplasia; NAA, nonadvanced adenomas; PAN, proximal advanced neoplasia; PN, proximal neoplasia

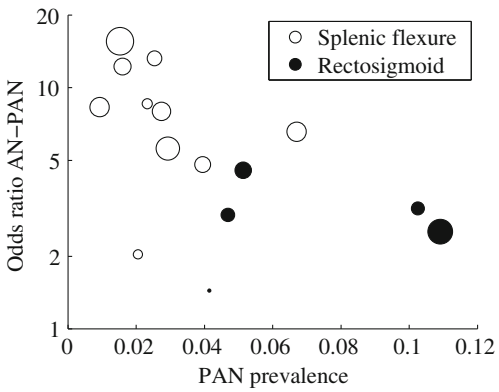

Figure 4. Scatter plot of the odds ratio for the association between distal advanced neoplasia (AN) and proximal advanced neoplasia (PAN) versus the PAN prevalence for studies using the splenic flexure or the rectosigmoid as the demarcation point of the distal colon. The area of the circles represents the sample size of each study. The size of the circles in the legend corresponds to a sample size of 1000.

biopsy forceps, which has been associated with underestimation of polyp size.[87,88]

Dichotomization. The subgroup analyses relied on dichotomized age, gender, and PN/PAN prevalence groups. This approach may have led to power loss and reduced measurement reliability.[89]

Technological advances. The included studies spanned more than two decades. Technical advances in colonoscopy, such as high-definition imaging[90,91] and optimization of withdrawal techniques[92–94] have improved the detection of lesions, particularly of those between 0 and 5 mm.[93] The analyses were repeated separately for the studies published before or after 2000 and before or after 2005 and no statistically significant differences in the reported odds ratios and proportions of IPN and IPAN were found.

CONCLUSION

The present results are important for identifying persons who may need to undergo a colonoscopy. We found that all types of distal lesions are predictive of proximal neoplasia and that PAN are better predicted by distal lesions in low-risk groups. The association between distal lesions and proximal neoplasia increased with the severity of the distal lesion. The fact that more than half of the proximal neoplasia are isolated urges the investigation of other risk factors, including genetic predisposition and environmental risks, which could contribute to predicting proximal neoplasia.

Although a number of screening programs employ colonoscopy, flexible sigmoidoscopy will probably gain territory in view of the results of four large-scale randomized clinical trials of screening flexible sigmoidoscopy performed in Norway (NORCCAP),[95] the UK (UKFSST),[96] Italy (SCORE),[97] and the US (PLCO).[98] NORCCAP reported a reduction of 76% for distal colorectal cancer, and in UKFSST the incidence of colorectal cancer was reduced by 33% and the corresponding mortality by 40% (see also[99] for a review and meta-analysis). UKFSST found no effect of screening on the incidence of proximal cancer. It remains to be observed whether a reduced incidence of colorectal cancer and corresponding mortality will occur in the other two trials, in which the criteria for colonoscopy referral are closer to those in the present meta-analysis.

ACKNOWLEDGMENTS: *The research of Dimitra Dodou and Joost de Winter is supported by the Dutch Technology Foundation (STW), applied science division of the Netherlands Organisation for Scientific Research (NWO) and the Technology Program of the Ministry of Economic Affairs. Preliminary results of this work were presented at a poster session during the 3rd Dutch Biomedical Engineering Conference,Egmond aan Zee, The Netherlands, January 20–21, 2011.*

Conflict of Interest: *None.*

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