American Journal of Epidemiology
Vol. 169, No. 6
DOI: 10.1093/aje/kwn401
Advance Access publication January 15, 2009

Meta- and Pooled Analysis

Association Between Body Mass Index and Colorectal Neoplasia at Follow-Up Colonoscopy: A Pooling Study

Elizabeth T. Jacobs, Dennis J. Ahnen, Erin L. Ashbeck, John A. Baron, E. Robert Greenberg, Peter Lance, David A. Lieberman, Gail McKeown-Eyssen, Arthur Schatzkin, Patricia A. Thompson, and María Elena Martínez

Initially submitted September 12, 2008; accepted for publication December 3, 2008.

A direct relation between body mass index (BMI) and risk of colorectal adenomas and cancer has been reported, but few studies have had adequate sample size for conducting stratified analyses by sex, family history, colorectal subsite, or features of metachronous lesions. Data from 8,213 participants in 7 prospective studies of metachronous colorectal adenomas were pooled to assess whether the association between BMI and metachronous neoplasia varied by these factors. A statistically significant direct association between BMI and the odds of nonadvanced adenomas ($P_{trend} < 0.001$) was observed, while the relation for advanced adenomas was of marginal significance ($P_{trend} < 0.07$). In sex-stratified analyses, obesity was statistically significantly associated with the odds of any metachronous lesion among men (odds ratio = 1.36, 95% confidence interval: 1.17, 1.58) but not among women (odds ratio = 1.10, 95% confidence interval: 0.89, 1.37). The associations with BMI appeared to be limited to proximal neoplasia, with statistically significant results for BMI and proximal ($P_{trend} < 0.001$), but not distal ($P_{trend} < 0.85$), neoplasia. Exploratory analyses indicated that BMI was significantly related to most histologic characteristics of metachronous adenomas among men but not among women. Our results provide further support for the association between BMI and metachronous colorectal adenomas, particularly among men, thereby indicating that body size may affect colorectal carcinogenesis at comparatively early stages.

adenoma; body mass index; colorectal neoplasms; meta-analysis as topic; neoplasms, second primary; recurrence

Abbreviations: BMI, body mass index; CI, confidence interval; HRT, hormone replacement therapy; OR, odds ratio.

Prior investigations have consistently reported an association between body size and colorectal adenomas (1–12) and cancers (13–16). However, among studies reporting sex-stratified analyses of this topic, many have shown stronger associations for men than for women (8, 11, 17–22), including 4 meta-analyses of the relation between body mass index (BMI) and cancer (13–16). Evidence is inconsistent as to whether the risk associated with BMI varies according to colorectal subsite, with stronger associations seen for neoplasia of the distal colorectum in some studies (4, 9, 23–26) and in the proximal colon for others (1, 27). Results from meta-analyses indicate that there is a greater association for body size and colon cancer than for body size and rectal cancer (13–16). Several studies have shown that body size may be a stronger risk factor for larger or more advanced lesions (1, 4, 5, 7, 11), although others have reported either a greater association for nonadvanced adenomas (10) or no differences (9).

Many of the studies that have investigated the link between body size and colorectal adenomas have had a limited sample size for conducting stratified analyses by sex, family history of colorectal cancer, colorectal subsite, and features of advanced adenomas. Within the context of a large pooled population of 8,213 subjects with anthropometric data from 7 studies of metachronous colorectal adenomas (28–34), we addressed whether BMI was associated with nonadvanced and advanced metachronous colorectal neoplasia and whether these relations varied by sex, family history of

Correspondence to Dr. Elizabeth T. Jacobs, Arizona Cancer Center, Mel and Enid Zuckerman College of Public Health, University of Arizona, P.O. Box 245024, Tucson, AZ 85724-5024 (e-mail: jacobse@u.arizona.edu).

colorectal cancer, or anatomic site of adenomas. We also explored whether BMI was associated with specific features of metachronous lesions, including size, multiplicity, tubulovillous or villous histology, and high-grade dysplasia.

MATERIALS AND METHODS

Study population

Data were available for the current analyses from participants in 7 studies of colorectal adenomas from a pooling project of 8 studies (28–35), as described elsewhere (36) and presented in Web Table 1. (This information is described in a supplementary table that is posted on the *Journal*'s website (http://aje.oxfordjournals.org/).) Briefly, studies included in the parent pooling population were prospective investigations that had reported results in the literature by June 2005 and that had met the following selection criteria: 1) The original study had at least 800 participants who had undergone a baseline colonoscopy with at least 1 adenoma detected and removed; 2) participants underwent at least 1 follow-up colonoscopy specified by a predetermined surveillance schedule; and 3) endpoint data were available for the characteristics of any adenomas or cancers detected during follow-up, including size, number, and histopathology. From the pooled studies, data were available for analysis from a total of 10,021 participants with study endpoints; however, information on BMI was not collected in the National Polyp Study ($n = 939$). Exclusion criteria for the current analysis were the presence of a colorectal cancer at baseline ($n = 27$), no follow-up colonoscopy performed after 6 months on study ($n = 827$), or lack of data for BMI ($n = 15$), resulting in a final sample size of 8,213 (5,842 male and 2,371 female) participants. Consent from participants and approval by their respective institutional review boards were obtained for all parent studies.

Each study included in our analyses had collected data for variables such as age, sex, race, smoking, family history of cancer, and history of polyps via self-administered questionnaires completed at baseline. Height and weight were measured by study staff for the Wheat Bran Fiber Trial, the Ursodeoxycholic Acid Trial, the Polyp Prevention Trial, and the Calcium Polyp Prevention Study, while self-reported values were collected for the Antioxidant Polyp Prevention Study and the Aspirin Folate Trial (Web Table 1). For the Veterans Affairs Cooperative Study, weights were measured and heights were self-reported. BMI was calculated as weight (kg)/height $(m)^2$. Participants were classified into categories of body size as follows: BMI of <25.0 was normal weight, BMI of 25.0–29.9 was overweight, and BMI of ≥ 30.0 was obese. We repeated our analyses with underweight (BMI, <18.5) participants excluded, and the results were unchanged; therefore, we included all participants with available BMI data in the current analyses.

Study endpoints

Metachronous colorectal neoplasia was defined as adenomas or cancers detected by colonoscopy after at least 6 months of follow-up (median, 47.2 months). Personnel at each study site reviewed endoscopy and pathology reports and extracted data regarding size, histology, number, and degree of dysplasia, followed by central pathology review at each site. The size of lesions was determined by endoscopy report or pathology reports if the data were not available from the former. Metachronous neoplasia was then classified as either nonadvanced (<10 mm in size, tubular histology, and no high-grade dysplasia) or advanced (≥ 10 mm in size and/or the presence of tubulovillous or villous histology and/or the presence of high-grade dysplasia and/or cancer). Lesions at or proximal to the splenic flexure were categorized as ''proximal,'' and those distal to the splenic flexure were classified as ''distal.''

Statistical analysis

Analyses were conducted with STATA, version 10.0, software (StataCorp LP, College Station, Texas) and SAS, version 9.0, software (SAS Institute, Inc., Cary, North Carolina). Before selecting a model for the analyses, we first assessed heterogeneity between study-specific risk estimates for each exposure variable by conducting a log-likelihood ratio test (37) and comparing the multivariate model presented in the tables with a multivariate model including additional interaction terms between each study indicator variable and the exposure variable of interest. Heterogeneity was deemed to be present when the likelihood ratio test yielded $P < 0.05$. We further examined heterogeneity visually by constructing forest plots that included the odds ratios and 95% confidence intervals for each parent study individually. These plots also contain *I*-squared values (38) and *Q* statistics (39) that were calculated for these associations; heterogeneity was detected for the relation between BMI and metachronous neoplasia among women but not among men. We also observed heterogeneity in the associations between overweight and proximal and distal neoplasia in the total population that, upon sex stratification, was confined to the results for women. Because of the observed heterogeneity for some associations, we conducted all analyses by using mixed-effects models as described below, whether or not they exhibited heterogeneity.

Mixed-effect models containing both fixed and random effects were used for analysis of the association between BMI and outcome by use of the xtmelogit command in STATA software and with the variable for study as the random effect. The outcome categories for the primary analyses were as follows: 1) any metachronous neoplasia versus no metachronous neoplasia, 2) nonadvanced metachronous adenoma versus no metachronous neoplasia, and 3) advanced metachronous neoplasia versus no metachronous neoplasia. The variables assessed for confounding included age at baseline, sex, race, study, family history of colorectal cancer, history of polyps prior to baseline, and baseline adenoma characteristics. Of these, age, sex, study, and smoking (never, former, current) changed the point estimate by 10% or greater (40) and were included in the final models. In analyses of BMI by colorectal subsite, participants were counted as having distal lesions if they had distal lesions only and no proximal lesions; for the analysis of proximal

lesions, participants had proximal lesions only and no distal lesions. For analyses of associations between BMI and characteristics of metachronous lesions (size, dysplasia, histology, and number), mixed-effect models were again used, with each characteristic compared with those that did not recur. All analyses were conducted with the waist/hip ratio as the exposure measure, and results were similar to those for BMI; therefore, only the findings for BMI are presented. All P values for this work are 2 sided.

RESULTS

Relative to participants who were classified as normal weight, a higher proportion of overweight and obese participants were male or black, and a lower proportion were smokers (Table 1). Participants who were overweight and obese had a greater percentage of proximal lesions at baseline than did those of normal weight.

For the overall study population, there were statistically significant trends of increasing odds of any metachronous neoplasia ($P_{trend} < 0.001$) and nonadvanced adenoma ($P_{trend} < 0.001$) with increasing BMI, but the trend for advanced neoplasia was of borderline statistical significance ($P_{trend} < 0.07$) (Table 2). The interaction between BMI and sex was statistically significant in polytomous regression models including both nonadvanced and advanced adenomas ($P < 0.05$); therefore, all analyses were stratified by sex. The results for any metachronous lesions among men were similar to those of the overall population (odds ratios (ORs) = 1.11 (95% confidence interval (CI): 0.97, 1.26) and 1.36 (95% CI: 1.17, 1.58) for overweight and obesity, respectively). The same was true for nonadvanced metachronous lesions (ORs = 1.10 (95% CI: 0.96, 1.27) and 1.34 (95% CI: 1.14, 1.58) for overweight and obesity, respectively), and the associations with advanced neoplasia were of comparable strength (ORs = 1.10 (95% CI: 0.89, 1.34) and 1.40 (95% CI: 1.11, 1.77)). In contrast, among women, there was a statistically significant association of overweight with the odds of any neoplasia (OR =1.22, 95% CI: 1.01, 1.47) and for nonadvanced lesions (OR = 1.32, 95% CI: 1.07, 1.63), but there were no significant associations for obesity; for advanced neoplasia, there was no association over BMI categories ($P_{trend} < 0.45$) (Table 2). Forest plots of the associations for BMI and metachronous lesions for each sex separately by study revealed little heterogeneity in the measures of association among men; however, heterogeneity was detected for nonadvanced endpoints among women (Web Figures 1 and 2) (refer to the *Journal*'s website (http://aje.oxfordjournals.org/)).

Previous reports have indicated that the relation between body size and colorectal cancer might be stronger for premenopausal than for postmenopausal women (9, 41). We therefore conducted exploratory analyses of the data stratified by age as a proxy for menopausal status and did not detect a stronger association for BMI in women younger than 55 years of age as compared with those 55 years of age or older ($P_{interaction} < 0.55$; data not shown). There were no clear patterns of variation in risk by family history for either men or women (Table 3), and tests for interaction between BMI and family history were not statistically significant for any recurrence ($P_{interaction} < 0.23$), nonadvanced adenomas ($P_{interaction} < 0.50$), or advanced neoplasia ($P_{interaction} = 0.71$).

The association between BMI and colorectal neoplasia was limited to proximal lesions. The odds ratios for proximal neoplasia were 1.16 (95% CI: 1.02, 1.33) for overweight and 1.34 (95% CI: 1.15, 1.57) for obesity ($P_{trend} < 0.001$), while for the distal colorectum, the odds ratios were 1.06 (95% CI: 0.88, 1.29) and 1.02 (95% CI: 0.81, 1.27), respectively ($P_{trend} < 0.85$) (Table 4). In sex-stratified analyses, the results for men and women were similar for both distal and proximal neoplasia, with no statistically significant interactions between BMI and sex for either endpoint. Results from analyses restricted to rectal neoplasia alone were similar to those for distal lesions (data not shown).

Sex-stratified exploratory analyses of the relation between BMI and specific features of metachronous adenomas (large size, tubulovillous or villous histology, high-grade dysplasia, multiplicity) indicated that BMI was statistically significantly associated with each of these features among men (Table 5). There were no clear relations between BMI and metachronous adenoma features among women.

DISCUSSION

In this pooled analysis of 7 prospective studies of metachronous colorectal neoplasia, we confirmed previous findings that BMI is associated with risk of metachronous colorectal lesions. This relation appeared to be confined to men and to lesions of the proximal colon. Among men, the association for BMI was seen for both nonadvanced and advanced neoplasia and was present for all features of metachronous lesions with the exception of tubular histology among overweight men. In contrast, for women, there were no clear relations with neoplasia of any type. Unlike the results from a previous report (11), a family history of colorectal cancer did not modify the association between BMI and metachronous lesions.

Many investigations have reported that the associations between body size and risk of colorectal adenoma or cancer vary by sex. Most indicated a stronger relation among men as compared with women (8, 11, 17–22, 42, 43), although some have reported the converse (1, 10, 44) or a similar effect in both sexes (5, 26, 41, 45, 46). With regard to colorectal cancer, results from 4 meta-analyses have shown a statistically significant association with BMI for both men and women, with a stronger relation for men (10, 13–16). More variable findings regarding differences in association by sex have come from studies of colorectal adenoma and BMI; 2 reported stronger associations for men (8, 11) and 2 for women (1, 10). The reasons for the differences between our findings and those of the latter 2 studies are unclear. Larsen et al. (10), in a cross-sectional study of prevalent adenomas, compared the mean and median BMI of those with and without colorectal neoplasia. Among women, a significant linear trend ($P < 0.03$) of increasing BMI was observed across groups defined by no neoplasia (mean BMI = 25.2), low-risk adenomas (mean BMI = 25.5),

Table 1. Baseline Characteristics of Study Participants ($n = 8,213$), by Category of Body Mass Index

Baseline Characteristics	Normal Weight (BMI, <25)[a]		Overweight (BMI, 25–<30)[a]		Obese (BMI, ≥30)[a]	
	No.	%	No.	%	No.	%
Mean age at baseline, years (SD)	62.4 (10.1)		62.3 (9.2)		61.2 (8.9)	
Male	1,373	58.9	2,922	77.5	1,547	73.3
Race						
White	2,093	89.8	3,357	89.0	1,852	87.8
Black	95	4.1	209	5.5	157	7.4
Other	144	6.2	205	5.4	101	4.8
Family history of colorectal cancer[b,c]	519	23.8	902	25.5	455	23.1
Current smoker	501	21.6	552	14.7	243	11.6
Previous polyps[d]	584	25.6	983	26.7	486	23.4
Baseline adenoma characteristics						
Mean no. (SD)	1.6 (1.1)		1.8 (1.3)		1.8 (1.3)	
Large size (≥10 mm)	764	34.1	1,217	33.7	665	32.6
Villous histology	503	24.6	775	22.9	447	24.1
Any proximal adenoma	1,033	46.3	1,857	51.2	1,140	56.1

Abbreviations: BMI, body mass index; SD, standard deviation.
[a] Normal weight ($n = 2,332$); overweight ($n = 3,771$); and obese ($n = 2,110$).
[b] History of colorectal cancer in 1 or more first-degree relatives.
[c] Data were missing for the following variables: 530 participants for family history, 42 for current smoking, 169 for previous polyps, 22 for number of adenomas, 317 for size, 923 for histology, and 326 for location.
[d] History of polyps prior to baseline.

Table 2. Adjusted Odds Ratios[a] and 95% Confidence Intervals for Any, Nonadvanced, and Advanced Metachronous Colorectal Neoplasia According to Body Mass Index Categories in the Pooled Population and by Sex[b]

Metachronous Neoplasia	Normal Weight (BMI, <25)			Overweight (BMI, 25–<30)				Obese (BMI, ≥30)				P_{trend}
	Odds Ratio	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	
Total population ($n = 8,213$)												
Any	1.00	1,038	2,332	1.13	1.01, 1.26	1,844	3,771	1.29	1.14, 1.45	1,065	2,110	<0.001
Nonadvanced	1.00	752	2,332	1.16	1.03, 1.30	1,379	3,771	1.32	1.16, 1.51	804	2,110	<0.001
Advanced	1.00	286	2,332	1.03	0.87, 1.22	465	3,771	1.20	0.99, 1.46	261	2,110	<0.07
Men ($n = 5,842$)												
Any	1.00	676	1,373	1.11	0.97, 1.26	1,481	2,922	1.36	1.17, 1.58	843	1,547	<0.001
Nonadvanced	1.00	500	1,373	1.10	0.96, 1.27	1,104	2,922	1.34	1.14, 1.58	634	1,547	<0.001
Advanced	1.00	176	1,373	1.10	0.89, 1.34	377	2,922	1.40	1.11, 1.77	209	1,547	<0.01
Women ($n = 2,371$)												
Any	1.00	362	959	1.22	1.01, 1.47	363	849	1.10	0.89, 1.37	222	563	<0.24
Nonadvanced	1.00	252	959	1.32	1.07, 1.63	275	849	1.21	0.95, 1.53	170	563	<0.07
Advanced	1.00	110	959	0.97	0.71, 1.32	88	849	0.86	0.60, 1.24	52	563	<0.45

Abbreviation: BMI, body mass index.
[a] Regression models adjusted for age, smoking, and study; total population analysis additionally adjusted for sex.
[b] $P_{interaction} < 0.05$ for sex and body mass index.

Table 3. Adjusted Odds Ratios[a] and 95% Confidence Intervals for Any, Nonadvanced, and Advanced Metachronous Colorectal Neoplasia According to Body Mass Index Categories in the Pooled Population, by Family History

BMI Category	No Family History of Colorectal Cancer[b] (n = 5,807)											
	Any				Nonadvanced				Advanced			
	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.
Total population												
Normal weight (BMI, <25)	1.00		747	1,658	1.00		548	1,658	1.00		199	1,658
Overweight (BMI, 25–<30)	1.08	0.95, 1.22	1,265	2,633	1.09	0.95, 1.25	946	2,633	1.02	0.83, 1.25	319	2,633
Obese (BMI, ≥30)	1.25	1.08, 1.45	758	1,516	1.26	1.08, 1.47	569	1,516	1.25	0.99, 1.57	189	1,516
P_{trend}		<0.01				<0.01				<0.06		
Men												
Normal weight (BMI, <25)	1.00		507	1,029	1.00		378	1,029	1.00		129	1,029
Overweight (BMI, 25–<30)	1.08	0.93, 1.26	1,045	2,082	1.06	0.90, 1.25	777	2,082	1.11	0.87, 1.41	268	2,082
Obese (BMI, ≥30)	1.31	1.10, 1.55	612	1,147	1.27	1.06, 1.53	457	1,147	1.43	1.09, 1.87	155	1,147
P_{trend}		<0.01				<0.01				<0.01		
Women												
Normal weight (BMI, <25)	1.00		240	629	1.00		170	629	1.00		70	629
Overweight (BMI, 25–<30)	1.09	0.86, 1.38	220	551	1.17	0.90, 1.52	169	551	0.87	0.59, 1.30	51	
Obese (BMI, ≥30)	1.11	0.85, 1.44	146	369	1.18	0.88, 1.59	112	369	0.91	0.58, 1.42	34	369
P_{trend}		<0.43				<0.22				<0.60		
	Family History of Colorectal Cancer[b] (n = 1,876)											
	Any				Nonadvanced				Advanced			
	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.
Total population												
Normal weight (BMI, <25)	1.00		225	519	1.00		155	519	1.00		70	519
Overweight (BMI, 25–<30)	1.28	1.02, 1.61	470	902	1.41	1.10, 1.80	358	902	0.99	0.70, 1.40	112	902
Obese (BMI, ≥30)	1.45	1.12, 1.88	245	455	1.62	1.22, 2.14	188	455	1.11	0.74, 1.66	57	455
P_{trend}		<0.01				<0.001				<0.62		
Men												
Normal weight (BMI, <25)	1.00		122	244	1.00		88	244	1.00		34	244
Overweight (BMI, 25–<30)	1.21	0.90, 1.63	349	653	1.25	0.90, 1.72	265	653	1.05	0.67, 1.66	84	653
Obese (BMI, ≥30)	1.71	1.20, 2.43	184	299	1.75	1.21, 2.54	141	299	1.47	0.87, 2.50	43	299
P_{trend}		<0.01				<0.01				<0.15		
Women												
Normal weight (BMI, <25)	1.00		103	275	1.00		67	275	1.00		36	275
Overweight (BMI, 25–<30)	1.15	1.06, 2.15	121	249	1.77	1.19, 2.62	93	249	1.01	0.58, 1.74	28	249
Obese (BMI, ≥30)	1.11	0.74, 1.67	61	156	1.31	0.83, 2.06	47	156	0.74	0.37, 1.44	14	156
P_{trend}		<0.38				<0.12				<0.43		

Abbreviation: BMI, body mass index.

[a] Models adjusted for age, sex, smoking, and study.

[b] Data for family history of colorectal cancer in 1 or more first-degree relatives were missing for 530 participants as follows: normal weight (n = 155), overweight (n = 236), and obese (n = 139); normal weight men (n = 100), overweight men (n = 187), and obese men (n = 101); and normal weight women (n = 55), overweight women (n = 49), and obese women (n = 38).

Table 4. Adjusted Odds Ratios[a] and 95% Confidence Intervals for Distal or Proximal Metachronous Colorectal Neoplasia According to Category of Body Mass Index

BMI Category	Distal[b]				Proximal[c]			
	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.
Total population[d]								
Normal weight (BMI, <25)	1.00		204	1,498	1.00		461	1,755
Overweight (BMI, 25–<30)	1.06	0.88, 1.29	335	2,262	1.16	1.02, 1.33	861	2,788
Obese (BMI, ≥30)	1.02	0.81, 1.27	164	1,209	1.34	1.15, 1.57	506	1,551
P_{trend}		<0.85				<0.001		
Men[e]								
Normal weight (BMI, <25)	1.00		131	828	1.00		293	990
Overweight (BMI, 25–<30)	0.95	0.75, 1.19	252	1,693	1.17	0.99, 1.38	696	2,137
Obese (BMI, ≥30)	1.03	0.80, 1.35	128	832	1.42	1.17, 1.71	393	1,097
P_{trend}		<0.40				<0.001		
Women[e]								
Normal weight (BMI, <25)	1.00		73	670	1.00		168	765
Overweight (BMI, 25–<30)	1.40	1.00, 1.96	83	569	1.17	0.91, 1.50	165	651
Obese (BMI, ≥30)	0.89	0.58, 1.35	36	377	1.19	0.90, 1.56	113	454
P_{trend}		<0.92				<0.19		

Abbreviation: BMI, body mass index.

[a] Models adjusted for age, sex, smoking, and study.

[b] Descending colon, sigmoid colon, or rectum.

[c] Ascending colon, hepatic flexure, transverse colon, or splenic flexure.

[d] Participants with only distal or only proximal neoplasia included and compared with those with no metachronous lesions; those with both types were excluded as follows: normal weight ($n = 373$), overweight ($n = 648$), and obese ($n = 395$); normal weight men ($n = 252$), overweight men ($n = 533$), and obese men ($n = 322$); and normal weight women ($n = 121$), overweight women ($n = 115$), and obese women ($n = 73$).

[e] $P_{interaction} = 0.72$ and 0.31 for body mass index by sex for distal neoplasia and for proximal neoplasia, respectively.

and advanced neoplasia (mean BMI = 26.7); however, similar differences in BMI were not detected for men. Although the reasons for this are unclear, flexible sigmoidoscopy was used as the screening modality (10), therefore favoring detection of distal lesions. This feature may explain some of the differences in results between our study and theirs, as in the current work no association for body size and distal lesions was demonstrated for men, but for women there was a marginally significant relation between overweight and distal neoplasia. In the other study in which a stronger effect was found for women than for men, Neugut et al. (1) used a case-control design, and BMI (kg/m^2) was calculated for men, but the Quetelet index (kg/m) was used to describe body size for women, and this approach may have contributed to the stronger results found for women in that work. Elucidation of the best measure of body size for women in epidemiologic studies continues to be an active area of research and requires further investigation.

In general, findings regarding the association between colorectal neoplasia and body size have been less evident in women than in men. Effect modification by menopausal status or hormone replacement therapy (HRT) has been proposed as an explanation for sex differences in the effect of BMI (41). In one study of this topic, women who were classified as ''estrogen positive'' (premenopausal or postmenopausal but taking HRT) had an increased risk for colon cancer with increasing BMI, but those who were ''estrogen negative'' (postmenopausal with no HRT use) showed no association between BMI and colon cancer (41). Although data for menopausal status and HRT use were unavailable, our own exploratory analyses of the data for women stratified by age (<55 years vs. ≥55 years) yielded no differences in the association between BMI and metachronous lesions. Nonetheless, possible differences in the disease process between pre- and postmenopausal women remain a plausible explanation for the less consistent findings observed for

Table 5. Sex-stratified Adjusted Odds Ratios[a] and 95% Confidence Intervals for Features of Metachronous Colorectal Neoplasia According to Category of Body Mass Index Compared With Those Who Had No Metachronous Lesions[b]

Characteristics[c]	Men									Women								
	Overweight (BMI, 25–<30)				Obese (BMI, ≥30)					Overweight (BMI, 25–<30)				Obese (BMI, ≥30)				
	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	P_{trend}	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	Odds Ratio	95% Confidence Interval	Recurrence, no.	Total, no.	P_{trend}
Size																		
<10 mm	1.07	0.93, 1.23	1,199	2,640	1.32	1.13, 1.55	688	1,392	<0.001	1.29	1.04, 1.58	299	785	1.17	0.93, 1.48	185	526	<0.10
≥10 mm	1.26	0.98, 1.62	252	1,693	1.56	1.18, 2.08	139	843	<0.01	0.90	0.62, 1.32	53	539	0.80	0.51, 1.26	31	372	<0.33
Histology																		
Tubular	1.09	0.95, 1.25	1,157	2,598	1.35	1.15, 1.58	675	1,379	<0.001	1.25	1.01, 1.54	278	764	1.17	0.92, 1.48	175	516	<0.13
Tubulovillous or villous	0.98	0.76, 1.27	201	1,642	1.37	1.02, 1.84	117	821	<0.05	1.06	0.72, 1.57	53	539	0.88	0.55, 1.40	29	370	<0.66
Dysplasia																		
No HGD	1.11	0.97, 1.26	1,451	2,892	1.34	1.15, 1.56	813	1,517	<0.001	1.21	1.00, 1.46	356	842	1.10	0.88, 1.36	219	560	<0.27
HGD	1.03	0.55, 1.94	30	1,471	2.38	1.25, 4.51	30	734	<0.01	2.70	0.69, 10.56	7	493	1.92	0.38, 9.66	3	344	<0.36
Multiplicity																		
1	1.10	0.96, 1.27	1,104	2,545	1.34	1.14, 1.58	634	1,338	<0.001	1.32	1.07, 1.63	275	761	1.21	0.95, 1.53	170	511	<0.07
>1	1.10	0.89, 1.34	377	1,818	1.40	1.11, 1.77	209	913	<0.01	0.97	0.71, 1.32	88	574	0.86	0.60, 1.24	52	393	<0.45

Abbreviations: BMI, body mass index; HGD, high-grade dysplasia.

[a] Models adjusted for age, sex, smoking, and study.

[b] Reference group for all comparisons is normal body mass index (<25 kg/m^2).

[c] Data were missing for size as follows: overweight men ($n = 30$), obese men ($n = 16$), overweight women ($n = 11$), and obese women ($n = 6$); and for histology as follows: overweight men ($n = 123$), obese men ($n = 51$), overweight women ($n = 32$), and obese women ($n = 18$).

body size in women than in men. Stronger associations for BMI in men than in women might also be explained in part by the tendency of men to exhibit central adiposity, while women tend to deposit fat in the thighs and buttocks (47). The known metabolic effects associated with abdominal fat (48) may therefore influence the risk of colorectal neoplasia in men differently than in women (49).

It has been hypothesized that proximal colon neoplasia and distal colorectum neoplasia arise from distinct molecular pathways (50, 51). Most of the studies that have conducted analyses by colorectal subsite have shown a significant association between body size and distal adenomas or cancer (4, 9, 23–26), but some have reported a stronger association for proximal adenoma (1, 27). The 2 studies that found an association for BMI and proximal lesions demonstrated this finding in women only, which is in contrast to our results that show an association for proximal adenomas that is largely confined to men. As with the distal colorectum, we found no association of BMI with rectal lesions. Although relatively few data have been reported on the association between BMI and risk of rectal adenomas, meta-analyses of colon and rectal cancers separately consistently demonstrate weaker associations for cancers of the rectum as compared with those of the colon (13–16). The possible explanations for the various results regarding adenoma found by different investigations may be related to differing endpoints (adenoma incidence, metachronous adenomas), sample sizes, and use of various reference groups for comparison.

The pooled study population for the current work provided a valuable opportunity to explore whether BMI influenced specific features of metachronous neoplasia. Our data show that BMI does not appear to have differential effects on larger as compared with smaller lesions. This finding contrasts with some previous reports (1, 3, 4, 7, 11), which demonstrated a stronger association of body size with larger adenomas, but our results mirror those of another study that reported no differences with regard to BMI between nonadvanced and advanced adenomas (9). In contrast, BMI was associated with all types of metachronous lesions in males. Among women, there were no relations observed between body size and individual features. There was a suggestion that obesity may have a greater influence on the development of neoplasia with high-grade dysplasia as compared with low-grade dysplasia in men, but this was a modest difference. Nonetheless, these results may offer some insights into how BMI may ultimately affect the development of colorectal cancer, as high-grade dysplasia in neoplasia has been found to be strongly associated with subsequent colorectal cancer in this study population (36).

Strengths of this study include its prospective design, the protocol-specified procedures for surveillance colonoscopy, and the availability of complete data for characteristics of incident metachronous neoplasia, including dysplasia and histology. Further, the large sample size allowed for the generation of precise estimates and for stratification of the analyses by sex, family history, and colorectal subsite, as well as for exploratory analyses of the association between BMI and neoplasia characteristics. This pooled study also has some advantages over a meta-analysis. Few of the studies included in the current work have published results for BMI and metachronous lesions, for example; thus, the pooling of the data allowed us to explore associations not included in the original publications with a consistent protocol that included thorough data checks. There were also potential limitations to this analysis. One is that some of the component studies in the current work used reported weights and heights rather than measured weights and heights, which may have introduced measurement error to the study. Nonetheless, the correlation between self-reported and measured BMI was shown to be high among the 4,808 participants in the European Prospective Investigation into Cancer and Nutrition (52). Further, our analyses were not done using a continuous variable for BMI; rather, participants were grouped into categories based on BMI, and only very extreme misreporting of BMI would be likely to have an effect on the results. Another limitation was that data regarding menopausal status and HRT use were not available for the current analyses, and issues surrounding effect modification by these factors could be explored only by using age as a proxy measure. In addition, baseline colonoscopies conceivably may have been less complete in our participants who were overweight or obese, as compared with normal weight individuals, because of technical difficulties with the procedure or its preparatory bowel cleansing. If so, one might expect that small adenomas would tend to be missed at baseline in these individuals, and that subsequent surveillance colonoscopy might thus detect more frequent, and more advanced, adenomas. We were unable to address this possibility directly in the current work; however, the protocols for all of the included studies called for a complete examination of the entire colorectum with no polyps remaining at the time of study enrollment.

In summary, our results confirm previous findings that BMI is associated with the odds of colorectal neoplasia, and they support the notion that the relation is substantially stronger among men than women and for proximal, as opposed to distal, adenomas. These findings support the concept that body size may affect colorectal carcinogenesis at comparatively early stages.

ACKNOWLEDGMENTS

Author affiliations: Arizona Cancer Center, University of Arizona, Tucson, Arizona (Elizabeth T. Jacobs, Erin L. Ashbeck, Peter Lance, Patricia A. Thompson, María Elena Martínez); Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona (Elizabeth T. Jacobs, María Elena Martínez); Denver Veterans Affairs Medical Center, Denver, Colorado (Dennis J. Ahnen); University of Colorado, Denver, Colorado (Dennis J. Ahnen); Section of Biostatistics and Epidemiology, Dartmouth Medical School, Lebanon, New Hampshire (John A. Baron, E. Robert Greenberg); Fred Hutchinson Cancer Research Center, Seattle, Washington (E. Robert Greenberg); College of Medicine, University of Arizona, Tucson, Arizona (Peter Lance); Division of Gastroenterology and Hepatology, Oregon Health and Science University, Portland, Oregon (David Lieberman); Portland Veterans Affairs Medical Center,

Portland, Oregon (David Lieberman); Dalla Lana School of Public Heath, University of Toronto, Toronto, Ontario, Canada (Gail McKeown-Eyssen); Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada (Gail McKeown-Eyssen); Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Arthur Schatzkin); and Department of Pathology, University of Arizona, Tucson, Arizona (Patricia A. Thompson).

This work was supported by the National Cancer Institute (grants CA-41108, CA-23074, CA95060, CA37287, CA37287, CA23108, CA 59005, and CA 26852). Dr. Jacobs is supported by a K07 Career Development Award (grant CA106269) from the National Cancer Institute. Funding for the Veterans Affairs Study was supported by the Cooperative Studies Program, Department of Veterans Affairs.

Conflict of interest: none declared.

REFERENCES

1. Neugut AI, Lee WC, Garbowski GC, et al. Obesity and colorectal adenomatous polyps. *J Natl Cancer Inst*. 1991; 83(5):359–361.
2. Bayerdörffer E, Mannes GA, Ochsenkuhn T, et al. Increased risk of 'high-risk' colorectal adenomas in overweight men. *Gastroenterology.* 1993;104(1):137–144.
3. Giovannucci E, Ascherio A, Rimm EB, et al. Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann Intern Med*. 1995;122(5):327–334.
4. Giovannucci E, Colditz GA, Stampfer MJ, et al. Physical activity, obesity, and risk of colorectal adenoma in women (United States). *Cancer Causes Control*. 1996;7(2):253–263.
5. Bird CL, Frankl HD, Lee ER, et al. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am J Epidemiol*. 1998;147(7):670–680.
6. Kono S, Handa K, Hayabuchi H, et al. Obesity, weight gain and risk of colon adenomas in Japanese men. *Jpn J Cancer Res.* 1999;90(8):805–811.
7. Boutron-Ruault MC, Senesse P, Meance S, et al. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. *Nutr Cancer.* 2001;39(1): 50–57.
8. Erhardt JG, Kreichgauer HP, Meisner C, et al. Alcohol, cigarette smoking, dietary factors and the risk of colorectal adenomas and hyperplastic polyps—a case control study. *Eur J Nutr.* 2002;41(1):35–43.
9. Terry MB, Neugut AI, Bostick RM, et al. Risk factors for advanced colorectal adenomas: a pooled analysis. *Cancer Epidemiol Biomarkers Prev.* 2002;11(7):622–629.
10. Larsen IK, Grotmol T, Almendingen K, et al. Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals [electronic article]. *BMC Gastroenterol*. 2006;6:5.
11. Jacobs ET, Martinez ME, Alberts DS, et al. Association between body size and colorectal adenoma recurrence. *Clin Gastroenterol Hepatol*. 2007;5(8):982–990.
12. Wolf LA, Terry PD, Potter JD, et al. Do factors related to endogenous and exogenous estrogens modify the relationship between obesity and risk of colorectal adenomas in women? *Cancer Epidemiol Biomarkers Prev.* 2007;16(4):676–683.
13. Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J Gastroenterol*. 2007; 13(31):4199–4206.
14. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev.* 2007;16(12): 2533–2547.
15. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am J Clin Nutr.* 2007; 86(3):556–565.
16. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612): 569–578.
17. Must A, Jacques PF, Dallal GE, et al. Long-term morbidity and mortality of overweight adolescents. A follow-up of the Harvard Growth Study of 1922 to 1935. *N Engl J Med.* 1992; 327(19):1350–1355.
18. Russo A, Franceschi S, La Vecchia C, et al. Body size and colorectal-cancer risk. *Int J Cancer.* 1998;78(2):161–165.
19. Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int J Obes Relat Metab Disord.* 2004;28(4):559–567.
20. Hou L, Ji BT, Blair A, et al. Body mass index and colon cancer risk in Chinese people: menopause as an effect modifier. *Eur J Cancer.* 2006;42(1):84–90.
21. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*. 2006;98(13):920–931.
22. Campbell PT, Cotterchio M, Dicks E, et al. Excess body weight and colorectal cancer risk in Canada: associations in subgroups of clinically defined familial risk of cancer. *Cancer Epidemiol Biomarkers Prev.* 2007;16(9):1735–1744.
23. MacInnis RJ, English DR, Hopper JL, et al. Body size and composition and colon cancer risk in men. *Cancer Epidemiol Biomarkers Prev.* 2004;13(4):553–559.
24. Martínez ME, Giovannucci E, Spiegelman D, et al. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. *J Natl Cancer Inst*. 1997;89(13):948–955.
25. Le Marchand L, Wilkins LR, Mi MP. Obesity in youth and middle age and risk of colorectal cancer in men. *Cancer Causes Control*. 1992;3(4):349–354.
26. Graham S, Marshall J, Haughey B, et al. Dietary epidemiology of cancer of the colon in western New York. *Am J Epidemiol*. 1988;128(3):490–503.
27. Lin J, Zhang SM, Cook NR, et al. Body mass index and risk of colorectal cancer in women (United States). *Cancer Causes Control*. 2004;15(6):581–589.
28. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med*. 2000; 342(16):1149–1155.
29. Baron JA, Cole B, Sander RS, et al. A randomized trial of aspirin as a chemopreventive agent against colorectal adenomas. *N Engl J Med.* 2003;348(10):891–899.
30. Alberts DS, Martinez ME, Roe DJ, et al. Lack of effect of a high-fiber cereal supplement on the recurrence of colorectal adenomas. Phoenix Colon Cancer Prevention Physicians' Network. *N Engl J Med*. 2000;342(16):1156–1162.
31. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med*. 1999;340(2):101–107.
32. Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. *N Engl J Med*. 1994;331(3):141–147.

33. Alberts DS, Martinez ME, Hess LM, et al. Phase III trial of ursodeoxycholic acid to prevent colorectal adenoma recurrence. *J Natl Cancer Inst*. 2005;97(11):846–853.
34. Lieberman DA, Weiss DG, Bond JH, et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med*. 2000; 343(3):162–168.
35. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993;329(27):1977–1981.
36. Martinez ME, Lieberman DA, Schatzkin A, et al. Advanced colorectal neoplasia diagnosed during surveillance following colonoscopic polypectomy: a pooled analysis. *Gastroenterology*. In press.
37. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons, Inc; 2000.
38. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
39. Cochran W. The combination of estimates from different experiments. *Biometrics*. 1954;10:101–129.
40. Mickey RM, Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol*. 1989;129(1): 125–137.
41. Slattery ML, Ballard-Barbash R, Edwards S, et al. Body mass index and colon cancer: an evaluation of the modifying effects of estrogen (United States). *Cancer Causes Control*. 2003; 14(1):75–84.
42. Engeland A, Tretli S, Austad G, et al. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. *Cancer Causes Control*. 2005;16(8):987–996.
43. Adams KF, Leitzmann MF, Albanes D, et al. Body mass and colorectal cancer risk in the NIH-AARP cohort. *Am J Epidemiol*. 2007;166(1):36–45.
44. Lukanova A, Björ O, Kaaks R, et al. Body mass index and cancer: results from the Northern Sweden Health and Disease Cohort. *Int J Cancer*. 2006;118(2):458–466.
45. Møller H, Mellemgaard A, Lindvig K, et al. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer*. 1994;30A(3):344–350.
46. Wang Y, Jacobs EJ, Patel AV, et al. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. *Cancer Causes Control*. 2008;19(7): 783–792.
47. Power ML, Schulkin J. Sex differences in fat storage, fat metabolism, and the health risks from obesity: possible evolutionary origins. *Br J Nutr*. 2008;99(5):931–940.
48. Hsu IR, Kim SP, Kabir M, et al. Metabolic syndrome, hyperinsulinemia, and cancer. *Am J Clin Nutr*. 2007;86(3): s867–s871.
49. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. *Am J Clin Nutr*. 2007;86(3): s836–s842.
50. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. *J Surg Oncol*. 2004; 88(4):261–266.
51. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med*. 1990;113(10):779–788.
52. Spencer EA, Appleby PN, Davey GK, et al. Validity of self-reported height and weight in 4808 EPIC-Oxford participants. *Public Health Nutr*. 2002;5(4):561–565.