Risk Factors for Advanced Colorectal Adenomas: A Pooled Analysis

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Abstract

Although most colorectal cancers arise from adenomatous polyps, most adenomas do not progress to invasive cancer. Understanding the epidemiology of advanced adenomas, specifically those with severe dysplasia, carcinoma *in situ*, or intramucosal carcinoma, is crucial to uncovering why some adenomas progress and some do not. Using data from four colonoscopy-based adenoma case-control studies, we compared two case groups: subjects with advanced adenomas (those with severe dysplasia, carcinoma *in situ*, or intramucosal carcinoma; $n = 119$) and subjects with nonadvanced adenomas (those with none, mild, or moderate dysplasia; $n = 441$) to a polyp-free control group ($n = 1866$) in regard to frequently studied risk factors for colorectal neoplasia. All of the cases were newly diagnosed and had no prior history of adenomas. We used an unordered polytomous logistic model to calculate multivariate odds ratios for advanced and nonadvanced adenoma cases relative to polyp-free controls. Among women, ever use of hormone replacement therapy was more strongly associated with reduced risk of advanced adenomas relative to polyp-free controls [odds ratio (OR), 0.4; 95% confidence interval (CI), 0.2–0.9] than with reduced risk of nonadvanced adenomas (OR, 0.7; 95% CI, 0.4–1.0). Among men, increased physical activity (≥2 h/week) was more strongly associated with reduced risk for advanced adenomas (OR , 0.4; 95% CI, 0.2–1.0) than with reduced risk for nonadvanced adenomas (OR, 0.8; 95% CI, 0.5–1.2). Apart from these differences, most other risk factors, including body size and cigarette smoking were similar in their association with advanced and nonadvanced adenomas, suggesting that many risk factors for colorectal neoplasia may be important to adenoma formation but not to dysplasia *per se*.

Introduction

Colorectal adenomatous polyps are recognized as the precursor lesions for most cases of colorectal cancer (1, 2). However, whereas most carcinomas are thought to arise from adenomas (3, 4), only 1–10% of people with resected adenomas will later develop invasive cancer (5, 6). Thus far, the important indicators for progression from adenomas have been pathologic characteristics of the adenoma, such as larger size, villous (as opposed to tubular) histology, and severe (as opposed to mild or moderate) dysplasia (7–13). Of these three, the most frequently studied characteristic in epidemiological studies has been size (5, 14–18). Size, proportion of villous histology, and degree of dysplasia are highly correlated with one another (8, 10, 13). However, invasive cancer and CIS[2] are sometimes found in small, tubular adenomas (10, 19, 20), and the distribution of highly dysplastic adenomas by subsite is more highly correlated with that of cancer than is that of large or villous adenomas (21, 22). These observations support the argument that degree of dysplasia is more important than size as a marker for progression along the adenoma-carcinoma sequence (21). Given the high prevalence of adenomas (as high as 20%–50%; Refs. 4–6, 23, 24) in contrast to the rarity of colorectal cancer, identifying risk factors for dysplastic lesions may facilitate the development of strategies to prevent colorectal cancer.

The study of dysplasia is complicated by inconsistent use of the terms severe dysplasia, CIS, and intramucosal carcinoma. Generally, pathologists call abnormal cellular growth that is confined to the intraepithelial layer and does not cross the muscularis mucosae either severe dysplasia or CIS; they call abnormal cellular growth that invades the lamina propria but does not invade the submucosa intramucosal carcinoma (7). Invasion beyond the muscularis mucosae is classified as clinically important invasive cancer. In this study, we classified adenomas as advanced if they were highly dysplastic but did not extend beyond the muscularis mucosa. Among endoscopically screened subjects, we identified those with severe dysplasia, CIS, or intramucosal carcinoma. We compared these subjects with a group who had nonadvanced adenomas (those with none, mild, or moderate dysplasia) and a polyp-free control group.

Materials and Methods

The study subjects were participants in five endoscopy-based studies of colorectal adenomas affiliated with the following

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[2] The abbreviations used are: CIS, carcinoma *in situ;* CU, Columbia University; UM, University of Minnesota; UNC, University of North Carolina; USC, University of Southern California; WF, Wake Forest University; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy.

universities and principal investigators: CU, A. I. N.; UM, J. D. P.; UNC, R. S. S.; USC, R. W. H.; and WF, R. M. B. The details of these studies have been described elsewhere (25–33); only background information important to this study will be highlighted.

Study Design. Four of these studies were colonoscopy-based studies of self-referred or selected populations (CU, UM, UNC, and WF); the USC study was a sigmoidoscopy-based screening study. The four colonoscopy-based case-control studies were selected for the primary analyses because they represented the U.S. colonoscopy-based studies that were completed when pooling began in 1996. The sigmoidoscopy-based study was added for secondary analyses of left-sided lesions. The studies also differed in the mode of interview: two primarily used telephone interviews after colonoscopy (CU and UNC); two used mailed questionnaires sent before the colonoscopies (UM and WF); and one used in-person interviews subsequent to the sigmoidoscopy (USC).

Eligibility Criteria. Eligibility requirements for the four colonoscopy-based studies were similar in regard to age (three included subjects 30 years of age and older, the other included only those 35 years and older), language (English-speaking), sex (male and female), and exclusions based on prior medical conditions (prior colorectal cancer, history of inflammatory bowel disease, and familial adenomatous polyposis). The sigmoidoscopy-based study restricted the study population to ages 50–75. Only some studies included subjects who had a history of adenomas, the others only included subjects with no previous diagnosed adenomas. Therefore, we restricted all of the analyses to subjects with newly diagnosed adenomas who did not have a previous history of adenomas. Because only some studies collected data on subjects with hyperplastic polyps, we restricted the control group to those without adenomatous and without hyperplastic polyps. We examined the impact such a restriction might have on our results through the use of secondary analyses that included in the groups with advanced and nonadvanced adenomas only those subjects without hyperplastic polyps.

Case Definition. All five of the centers were originally asked to contribute all of the cases of CIS from their respective studies. However, because of differences in terminology across studies as well as variations in the number of cases from each site, we requested all of the slides of severe dysplasia, CIS, and intramucosal carcinoma from each site for uniform pathologic review (C. M. F-P.). We also reviewed a random sample of nonadvanced adenomas. Our independent pathologist agreed with the diagnosis of the individual center pathologists 82% of the time; details of the reliability study are described elsewhere (34). The numbers of advanced adenoma cases from each study site were 76 (CU), 18 (UM), 17 (UNC), 15 (USC), and 8 (WF). As most pooled analyses rely on the case diagnosis of each center, the original case definition was used for the main analyses. However, we performed additional analyses using the results from the uniform slide review.

Comparison Groups. We used two comparison groups. The first was the standard comparison group for most case-control studies of adenomas: individuals found by colonoscopy or sigmoidoscopy to be polyp-free. The numbers of polyp-free controls supplied by each study site were 508 (CU), 707 (UM), 507 (UNC), 100 (USC), and 144 (WF). The second was a comparison group of subjects with adenomas that had no, mild, or moderate dysplasia. This second group was selected so that risk factors for progression could be examined. We selected the nonadvanced adenoma cases using a 1:4 matching scheme, matching them to the cases of advanced adenomas by sex and age within 5 years. The numbers of adenoma cases used for comparison from each study site were 269 (CU), 72 (UM), 68 (UNC), 60 (USC), and 32 (WF).

Exposure Variable Definition. We developed definitions for exposure variables using questionnaire data on smoking, alcohol use, body size, family history, physical activity, reproductive history, selected dietary variables, and demographic variables including age, sex, race, and educational status. These definitions were created after reviewing all five of the questionnaires but before conducting the analyses. Questionnaires across the five studies differed in focus, and some exposures were not available for all of the studies. For example, reproductive history data and aspirin use were not available for all of the studies. All five of the studies used a food frequency questionnaire to assess dietary intake; two used variations of the Block questionnaire (CU and UNC), and the other three used variations of the Willett questionnaire (UM, USC, and WF). Not all of the studies provided the same nutrient and food group data; here we restricted our analyses to dietary fat, dietary fiber, and caloric intake. Other differences limited the study of certain exposures. For example, some studies had collected detailed alcohol use histories, but others had collected only data on current or recent alcohol intake. Therefore, only current alcohol use could be assessed. For the dietary data, we defined as outliers any data points that were >3 SDs from the logarithm of the mean.

Statistical Analysis. For univariate analyses, we assessed differences across the three outcome groups (the cases with advanced adenomas, the cases with nonadvanced adenomas, and the polyp-free controls) using ANOVA for continuous variables, the χ^2 test for categorical variables, and Fisher's exact test for small cell counts (35). For multivariate analyses, we used unordered polytomous logistic regression to analyze all three of the outcome groups simultaneously (36).

The unordered polytomous logistic model produces two sets of coefficients, one for the comparison of advanced adenomas with polyp-free controls and a second for the comparison of nonadvanced adenoma cases with polyp-free controls; these coefficients are exponentiated to produce the ORs. The coefficients and SEs are used to estimate the 95% CI. We used the exponentiated difference in these coefficients (or equivalently, the ratio of the OR for advanced adenoma cases *versus* polyp-free controls to the OR for nonadvanced adenoma cases *versus* polyp-free controls) as an estimate of the capacity of a given risk factor to distinguish cases with advanced dysplasia from cases with nonadvanced adenomas.

We estimated these regression models with male and female cases combined using sex-specific indicator variables for sex-specific exposures (*e.g.*, HRT). Indicator variables for study site were used to control for site-specific differences. First, a saturated model containing all of the relevant exposure variables was estimated. Then variables were removed from this saturated model based on log likelihood tests (36). Parameter estimates for variables remaining in the model were also examined with the fuller model to assess confounding. The unordered polytomous model requires that the same set of covariates be used for all of the case groups. Thus, variables remaining in the final model indicate risk factors for at least one but not necessarily both case groups. The overall fit of the model was assessed using the Hosmer-Lemeshow goodness-of-fit test for separate pairs of logistic models (36). Binary logistic regression was also used to assess pathologic characteristics such as size, histology, and location of adenoma in

regard to risk for advanced adenomas relative to nonadvanced adenoma cases.

Results

Age, study site, and gender-adjusted ORs are presented in Table 1. These analyses revealed few differences between risk factors for advanced adenomas and nonadvanced adenomas. Family history of colorectal cancer was associated with nonadvanced adenomas (OR, 1.5; 95% CI, 1.1–2.1) but not advanced adenomas (OR, 1.0; 95% CI, 0.6–1.9). Large body size (highest quartile) was associated both with advanced adenomas (OR, 2.0; 95% CI, 1.2–3.6) and nonadvanced adenomas (OR, 1.6; 95% CI, 1.2–2.3). Among women, HRT was more strongly associated with advanced adenomas (OR, 0.4; 95% CI, 0.2–1.0) than with nonadvanced adenomas (OR, 0.8; 95% CI, 0.5–1.2).

The best-fitting multivariate-adjusted model is presented in Table 2. The associations for cigarette smoking and body size were similar between cases of advanced adenomas and cases of nonadvanced adenomas. Among men, >2 h of leisure physical activity per week was more strongly associated with a reduced risk of advanced adenomas (OR, 0.4; 95% CI, 0.2–1.0) than of nonadvanced adenomas (OR, 0.8; 95% CI, 0.5–1.2). There was no association between leisure physical activity and colorectal neoplasia in women. The multiplicative interaction term for physical activity and gender was statistically significant ($P < 0.05$). Among women, HRT was more strongly associated with advanced adenomas (OR, 0.4; 95% CI, 0.2–0.9) than with nonadvanced adenomas (OR, 0.7; 95% CI, 0.4–1.0).

Table 3 presents more detailed analyses of cigarette and alcohol consumption. Associations for most measures of cigarette smoking were extremely modest and similar between cases with advanced adenomas and those with nonadvanced adenomas. Consumption of four or more bottles/cans of beer per week was more strongly associated with advanced adenomas (OR, 1.7; 95% CI, 0.9–3.2) than with nonadvanced adenomas (OR, 1.1; 95% CI, 0.7–1.6).

We stratified our final models into two age groups: below 65 years and 65 years or older. In these analyses, the reduced risk of advanced adenomas associated with HRT in women was only found in women 65 and older (OR, 0.1; 95% CI, 0.01–0.8), and the increased risk associated with cigarette smoking in men was found to be much stronger among younger men. For example, long duration of cigarette smoking (≥35 years of smoking) was related to risk of both advanced and nonadvanced adenomas in men younger than 65 years (OR, 2.0; 95% CI, 0.6–6.5; OR, 2.3; 95% CI, 1.2–4.5, respectively) but not in men 65 years or older (OR, 0.9; 95% CI, 0.3–3.0; OR, 1.1; 95% CI, 0.5–2.5, respectively).

We performed several different secondary analyses on the best-fitting model presented in Table 2 (data not shown). First, we estimated this model using only cases confirmed through uniform pathologic review. In this analysis, HRT was no longer related to advanced adenomas (OR, 1.0; 95% CI, 0.4–2.8). Otherwise, overall interpretations did not change. Second, we examined only left-sided lesions from the four colonoscopy-based studies combined with the one sigmoidoscopy-based study; such analyses did not dramatically alter the results. Third, we restricted the model to subjects with lesions diagnosed in the colon (as opposed to rectum); there were no major differences in findings. Fourth, we restricted the case group to those subjects who did not also have a diagnosis of hyperplastic polyps, which also did not change the findings.

Table 4 summarizes the results from a multivariate logistic model examining pathologic characteristics (*i.e.*, size, histology, and location of lesion), comparing cases of advanced adenomas with nonadvanced adenoma cases. Larger size (OR, 6.1; 95% CI, 3.2–11.6), tubulovillous histology (OR, 1.9; 95% CI, 1.0–3.4), and rectal location (OR, 2.4; 95% CI, 1.1–5.2) were associated with risk of advanced adenomas. Because of the correlation between dysplasia, size, and histology, we reran our main models to see if the associations differed if we compared the following groups: (*a*) those with advanced adenomas (in terms of dysplasia), large size, and any villous component *versus* (*b*) those with nonadvanced adenoma, small size, and tubular histology *versus* polyp-free controls. Combining all three of the classifications meant the case groups were smaller (and CIs wider; group a had 73 subjects compared with 119 and group b had 178 compared with 441 in the analyses we present); however, the overall interpretations did not change. For example, physical activity was related to group a but not group b in men (OR, 0.5 *versus* 1.0) and HRT was more strongly related to group a than group b in women (OR, 0.5 *versus* 0.9). Smoking, body size, and fiber had similar interpretations in the two different analyses.

Discussion

Overall Results. Overall, there were few differences between risk factors for advanced adenomas and risk factors for nonadvanced adenoma, suggesting that many risk factors for colorectal neoplasia may be important to adenoma formation but do not have an additional effect on the degree of dysplasia *per se*. The two exceptions are physical activity among men and HRT use among women. We also confirmed findings from other studies that certain pathologic characteristics, such as large adenoma size, villous histology, and rectal location, strongly increase the likelihood of advanced adenomas (7–13, 22). When we compared (*a*) those with advanced adenomas (in terms of dysplasia), large size, and any villous component *versus* (*b*) those with nonadvanced adenoma, small size, and tubular histology *versus* polyp-free controls, we did not find any major differences in terms of risk factor associations from our main models, which classified case groups based solely on dysplasia.

Physical Activity. Physical activity has been consistently associated with both colorectal adenomas (37–41) and cancer (14, 42–48), despite the inconsistencies in the measurement instruments used across studies. Some studies (14, 16), but not all (49), have reported a stronger association with physical activity and larger adenomas. In the pooled data presented here, even after combining diverse measures, physical activity was more strongly associated with reduced risk of advanced adenomas than to reduced risk of nonadvanced adenomas and was seen only in men. Lack of an association in some studies of women may reflect the failure of measurement instruments to capture activities that are specific to women.

HRT. We found that HRT was associated with a 60% decrease (OR, 0.4) in risk of advanced adenomas and a 30% decrease (OR, 0.7) in risk of nonadvanced adenomas. The reduction in risk associated with HRT ranges from 0.6 to 0.9 in studies of colorectal cancer (50). HRT has also been inversely related to risk of colorectal adenomas (27, 51, 52), but few data exist on potential difference by adenoma size. HRT may protect against colorectal neoplasia by reducing the likelihood of hypermethylation of the *ER* gene (27).

Cigarette Smoking. The pooled data presented here add to the accumulating evidence that cigarette smoking is likely to be related to the early stages of adenoma initiation and formation,

Table 1 Age, study site, and gender-adjusted ORs for variables from four colonoscopy-based studies

	Advanced adenoma cases (n = 119)	Nonadvanced adenoma cases (n = 441)	Polyp-free controls (n = 1866)	Advanced cases relative to polyp-free controls OR (95% CI)	Nonadvanced cases relative to polyp-free controls OR (95% CI)	Advanced cases relative to nonadvanced cases OR (95% CI)
Education						
< High school	25	72	347	1.0	1.0	
High school	27	87	400	1.1 (0.6–2.0)	1.2 (0.8–1.8)	0.9 (0.5–1.7)
Some college	23	92	483	0.7 (0.4–1.4)	1.0 (0.7–1.5)	0.7 (0.4–1.4)
College graduate	44	189	628	0.7 (0.4–1.3)	1.1 (0.8–1.6)	0.7 (0.4–1.2)
Race						
White	102	390	1572	1.0	1.0	
Black	13	40	229	1.0 (0.5–1.9)	0.8 (0.5–1.2)	1.3 (0.6–2.6)
Other	4	9	64	0.8 (0.3–2.3)	0.5 (0.2–1.9)	1.8 (0.5–6.0)
Smoking status						
Never	43	168	844	1.0	1.0	
Former	55	198	728	1.2 (0.8–1.8)	1.1 (0.8–1.4)	1.1 (0.7–1.7)
Current	20	74	291	1.6 (0.9–2.8)	1.4 (1.0–2.0)	1.1 (0.6–2.0)
Family history[a]						
No first degree	98	331	1306	1.0	1.0	1.0
First degree	15	74	187	1.0 (0.6–1.9)	1.5 (1.1–2.1)	0.7 (0.4–1.3)
Body mass index						
First quartile (low)	28	94	461	1.0	1.0	
Second quartile	29	135	454	1.4 (0.8–2.4)	1.8 (1.3–2.5)	0.8 (0.4–1.4)
Third quartile	29	109	458	1.5 (0.8–2.5)	1.5 (1.1–2.1)	0.9 (0.5–1.7)
Fourth quartile (high)	31	92	451	2.0 (1.2–3.6)	1.6 (1.2–2.3)	1.2 (0.7–2.3)
Alcohol use						
Nondrinker	56	200	1075	1.0	1.0	
<4 drinks per week	13	52	249	0.9 (0.5–1.7)	1.0 (0.7–1.4)	0.9 (0.5–1.8)
4–< 9 drinks per week	15	74	245	0.9 (0.5–1.7)	1.2 (0.9–1.7)	0.7 (0.4–1.4)
≥9 drinks per week	35	115	297	1.3 (0.8–2.1)	1.2 (0.9–1.6)	1.1 (0.7–1.9)
Daily caloric intake						
First quartile (low)	37	146	452	1.0	1.0	
Second quartile	31	92	455	0.9 (0.6–1.6)	0.7 (0.5–1.0)	1.3 (0.8–2.3)
Third quartile	19	89	451	0.7 (0.4–1.2)	0.8 (0.6–1.1)	0.9 (0.5–1.6)
Fourth quartile (high)	24	94	454	0.9 (0.5–1.6)	0.9 (0.6–1.2)	1.1 (0.6–1.9)
Dietary fiber						
First quartile (low)	33	127	454	1.0	1.0	
Second quartile	28	112	447	0.9 (0.5–1.5)	0.9 (0.7–1.2)	1.0 (0.5–1.7)
Third quartile	28	112	458	0.9 (0.5–1.5)	0.9 (0.7–1.3)	1.0 (0.5–1.7)
Fourth quartile (high)	22	72	451	0.8 (0.4–1.5)	0.7 (0.5–1.0)	1.2 (0.6–2.3)
Dietary fat						
First quartile (low)	37	128	452	1.0	1.0	
Second quartile	19	91	454	0.5 (0.3–0.9)	0.7 (0.5–1.0)	0.7 (0.4–1.3)
Third quartile	30	82	449	0.9 (0.6–1.6)	0.7 (0.5–1.0)	1.3 (0.7–2.3)
Fourth quartile (high)	25	122	454	0.8 (0.5–1.4)	1.1 (0.8–1.5)	0.7 (0.4–1.3)
Aspirin						
No	16	80	560	1.0	1.0	
Yes	11	37	283	1.1 (0.5–2.4)	0.7 (0.4–1.0)	1.6 (0.7–4.0)
Other nonsteroidal anti-inflammatory drugs						
No	24	97	618	1.0	1.0	
Yes	3	12	139	0.6 (0.2–2.0)	0.6 (0.3–1.1)	1.0 (0.3–3.8)
Leisure Activity						
Less than 2 h/week	95	336	1405	1.0	1.0	
More than 2 h/week	16	73	316	0.7 (0.4–1.2)	0.8 (0.6–1.1)	0.8 (0.4–1.5)
Age at menarche[b]						
<12	7	25	178	1.0	1.0	
12 years	7	29	251	0.7 (0.2–1.9)	0.8 (0.4–1.4)	0.8 (0.3–2.8)
13 years	14	48	301	0.9 (0.4–2.4)	0.9 (0.5–1.6)	1.0 (0.4–2.8)
>13 years	18	58	253	1.4 (0.6–3.5)	1.3 (0.8–2.2)	1.0 (0.4–2.9)
Parity[b]						
Nulliparous	11	40	199	1.0	1.0	
1	9	14	128	1.5 (0.6–4.0)	0.6 (0.3–1.3)	2.4 (0.8–6.9)
2	11	45	280	0.8 (0.3–2.0)	0.9 (0.5–1.5)	0.9 (0.4–2.3)
3	5	32	190	0.8 (0.3–2.3)	1.3 (0.7–2.2)	0.6 (0.2–1.9)
4+	13	39	250	1.8 (0.7–4.3)	1.3 (0.8–2.3)	1.3 (0.5–3.5)
Use of oral contraceptives (OCs)[b]						
Never	37	127	543	1.0	1.0	
Ever	8	35	448	0.8 (0.3–1.9)	0.9 (0.6–1.5)	0.9 (0.3–2.3)
Use of hormone replacement therapy (HRT)[b]						
Never	37	112	575	1.0	1.0	
Ever	8	43	401	0.4 (0.2–1.0)	0.8 (0.5–1.2)	0.5 (0.2–1.3)

[a] Family history analyses restricted to subjects whose indication for colonoscopy was not because of previous family history.
[b] Women only.

Table 2 Multivariate-adjusted[a] ORs for the pooled analysis of risk factors for advanced and nonadvanced adenomas among female and male subjects combined

	Advanced adenoma cases relative to polyp-free controls OR (95% CI)	Nonadvanced adenoma cases relative to polyp-free controls OR (95% CI)	Advanced cases relative to nonadvanced adenoma cases OR (95% CI)
Smoking status			
Never	1.0	1.0	
Former	1.0 (0.6–1.5)	1.1 (0.9–1.5)	0.9 (0.5–2.0)
Current	1.4 (0.8–2.6)	1.4 (0.9–2.0)	1.0 (0.5–2.0)
Body mass index			
First quartile (lowest)	1.0	1.0	
Second quartile	1.3 (0.7–2.3)	2.0 (1.4–2.8)	0.7 (0.4–1.4)
Third quartile	1.4 (0.8–2.6)	1.7 (1.2–2.5)	0.8 (0.4–1.2)
Fourth quartile (highest)	2.1 (1.1–3.9)	2.0 (1.4–2.9)	1.1 (0.6–1.5)
Dietary fiber			
First quartile (lowest)	1.0	1.0	
Second quartile	0.9 (0.5–1.6)	0.9 (0.7–1.3)	0.9 (0.5–1.7)
Third quartile	1.0 (0.6–1.9)	1.0 (0.7–1.5)	1.0 (0.5–1.9)
Fourth quartile (highest)	1.0 (0.5–2.2)	0.6 (0.4–1.0)	1.6 (0.7–3.6)
Leisure Activity			
Among women			
Less than 2 h/week	1.0	1.0	
More than 2 h/week	1.6 (0.7–3.6)	1.1 (0.6–1.7)	1.5 (0.6–3.9)
Among men			
Less than 2 h/week	1.0	1.0	
More than 2 h/week	0.4 (0.2–1.0)	0.8 (0.5–1.2)	0.5 (0.2–1.3)
Use of HRT among women			
Never	1.0	1.0	
Ever	0.4 (0.2–0.9)	0.7 (0.4–1.0)	0.6 (0.2–1.4)

[a] All estimates reflect adjustment for age, study site, gender, race, total energy intake, and all other variables in table.

and not to growth or dysplasia. However, the existing data have been somewhat inconsistent on the role of cigarette smoking in colorectal neoplasia, perhaps because of methodologic differences. For example, one case-control study of colorectal CIS reported a 2–3-fold increase in risk associated with current heavy cigarette smoking (53), although the adenoma status of the comparison group was not known in this study. Two other studies have examined the association between cigarette smoking and dysplasia; one reported no differences by degree of dysplasia (54), whereas the other reported a stronger association for adenoma cases with severe dysplasia (55). It this latter study, the group with severe dysplasia did not include subjects with CIS or intramucosal carcinoma as defined here. Three studies supported a stronger association between cigarette smoking and larger adenomas (55–57), but all three compared cases with large adenomas to polyp-free controls. In the one study that explicitly compared large adenomas to small adenomas, no association was seen (18). One study reported that smoking in the distant past increases large adenomas (58), but this was not confirmed in another study (59).

Alcohol Consumption. Intake of beer was more strongly associated with advanced adenomas than with nonadvanced adenomas, but these differences were not statistically significant. The specific association with beer has also been reported in other studies of colorectal neoplasia (4, 60–62). The effect of alcohol on adenoma size has been mixed; one study supports an association with large size (63) and another reports similar increases in risk of both small and large adenomas (64).

Study Challenges. In all pooled studies (65), the analyses depend on the extent to which the individual survey instruments include the same risk factors and measure them in the same way. Defining exposures uniformly often meant sacrificing detail. Fortunately, several key variables, such as history of cigarette smoking, body size, and ever use of HRT, were measured in a very similar fashion by all of the questionnaires. Pooling data from different questionnaires may have led to bias in the estimates of risk factors for both nonadvanced adenomas and for advanced adenomas. Nevertheless, because the exposure variables were defined a priori and created without regard to outcome status, the bias was probably nondifferential, leading to underestimates of risk. Therefore, the estimates for risk factors presented here may be conservative. However, pooling questionnaires also may lead to residual confounding because summary variables are cruder; for positive confounding, this would lead to an overestimate of risk.

Whereas all of the sites had central review of all of their cases, we were concerned that there may be different pathologic criteria used at the five studies, especially because one site (CU) contributed substantially more cases of advanced adenomas than the other sites. Demographic considerations such as age and sex composition could not explain these differences. We collected pathologic slides of these cases, and a single pathologist rereviewed them using uniform review criteria. This review revealed that the majority of cases (82%) classified as advanced adenomas by other sites were also classified as advanced adenoma by our study pathologist (34).

We reviewed only a sample of slides for the nonadvanced adenoma cases (34), hence that group may have contained subjects with undetected advanced adenomas within this group. This type of nondifferential misclassification of outcome status would bias any comparisons between advanced adenomas and nonadvanced adenomas toward the null (and comparisons between the nonadvanced adenomas and polyp free controls away from the null), reducing the likelihood of detecting potential differences in risk factor associations (66). Because the uniform slide review confirmed the status of the cases of advanced

Table 3 Multivariate-adjusted[a] risk estimates for patterns of cigarette smoking and alcohol intake among female and male subjects in the pooled analysis

	Advanced adenoma cases relative to polyp-free controls OR (95% CI)	Nonadvanced adenoma cases relative to polyp-free controls OR (95% CI)	Advanced adenoma cases relative to nonadvanced adenoma cases OR (95% CI)
Smoking habits			
Years of smoking			
<15	1.1 (0.6–2.1)	1.2 (0.9–1.8)	0.9 (0.5–1.7)
15–<25	1.0 (0.5–2.0)	1.0 (0.7–1.5)	1.0 (0.5–2.0)
25–<35	0.9 (0.5–1.9)	1.0 (0.7–1.5)	0.9 (0.4–1.9)
≥35	1.2 (0.7–2.2)	1.4 (1.0–2.0)	0.9 (0.5–1.6)
Number of cigs/day			
<10	1.2 (0.7–2.2)	0.9 (0.7–1.4)	1.3 (0.7–2.4)
10–<20	0.7 (0.4–1.4)	1.3 (1.0–1.8)	0.6 (0.3–1.1)
21–<30	0.9 (0.4–2.3)	1.3 (0.8–2.2)	0.7 (0.3–1.8)
≥30	1.4 (0.7–2.6)	1.2 (0.8–1.8)	1.1 (0.6–2.2)
Smoking > 20 yrs ago			
<16 pack yrs	1.0 (0.6–1.9)	1.1 (0.8–1.5)	1.0 (0.5–1.8)
≥16 pack yrs	0.6 (0.3–1.2)	1.0 (0.7–1.6)	0.5 (0.2–1.8)
Smoking ≤20 yrs ago			
<10 pack yrs	1.1 (0.5–2.2)	0.9 (0.6–1.4)	1.1 (0.5–2.5)
10–< 20 pack yrs	2.1 (1.0–4.5)	1.2 (0.8–1.9)	1.7 (0.8–3.9)
≥20 pack yrs	1.4 (0.6–3.4)	1.2 (0.7–1.8)	1.3 (0.5–3.1)
Drinking habits			
Beer			
Nondrinker	1.0	1.0	
<4 bottles/cans/week	1.3 (0.7–2.6)	1.2 (0.8–1.8)	1.1 (0.6–2.3)
≥4 bottles/cans/week	1.7 (0.9–3.2)	1.1 (0.7–1.6)	1.6 (0.8–3.1)
Wine			
Nondrinker	1.0	1.0	
<2 glasses per week	1.1 (0.5–2.5)	1.1 (0.7–1.8)	1.0 (0.4–2.3)
≥2 glasses per week	0.8 (0.4–1.3)	1.0 (0.7–1.4)	0.8 (0.4–1.4)
Liquor			
Nondrinker	1.0	1.0	
<3 shots per week	1.8 (0.9–3.4)	1.1 (0.7–1.6)	1.6 (0.8–3.3)
≥3 shots per week	1.2 (0.7–2.0)	1.0 (0.8–1.4)	1.2 (0.7–2.0)

[a] All estimates reflect adjustment for age, study site, gender, race, body mass index, total energy intake, total fiber intake, leisure activity, and HRT use.

Table 4 Multivariate-adjusted[a] logistic model of pathologic predictors for advanced adenomas from four colonoscopy-based studies

	Advanced adenoma cases	Nonadvanced adenoma cases	OR 95% CI
Size			
<1 cm	19	238	1.0
≥1 cm	96	180	6.1 (3.2–11.6)
Histology			
Tubular	28	219	1.0
Tubulovillous	74	158	1.9 (1.0–3.4)
Villous	12	20	1.8 (0.7–4.5)
Site			
Proximal	27	147	1.0
Distal	64	219	1.2 (0.7–2.2)
Rectum	21	42	2.4 (1.1–5.2)

[a] Adjusted for age, study site, gender, and all variables in the table.

adenomas identified by other sites, the misclassification bias between the cases of advanced adenomas and polyp-free controls should not be substantial. Also, we found similar associations among pathologic characteristics, such as size and villous histology to those reported in a number of other studies, offering some evidence for the validity of our case definition.

Study Strengths. One advantage of this study over another study on risk factors for colorectal CIS (53) is that our control group was endoscopically neoplasia-free. Without a screened control group, it is impossible to determine whether risk factors are related to adenoma formation, growth, or dysplasia. We compared cases who had advanced adenomas with two comparison groups; we were therefore able to explore the impact of risk factors along different steps of the adenoma-carcinoma sequence. Also, by comparing risk factors in an unordered polytomous logistic model, we could formally evaluate statistical heterogeneity. Most studies examining risk factor differences by adenoma size compare a group who have large adenomas to polyp-free controls rather than to a group with small adenomas.

This study also benefits from some of the methodologic advantages of precursor studies. These include a reduced likelihood of recall bias and selection bias (4, 67). Recall bias is minimized in this study because all of the subjects underwent the same procedures, either colonoscopy or sigmoidoscopy, and many were unaware of their case classification at the time of interview. In addition, because subjects with adenomas do not differ from control in symptomatology, they are unlikely to have changed behavior as a result of their adenomas. Selection bias was also minimized because polyp-free controls were identified by the same selection procedures as the case groups. Indications for colonoscopy (*e.g.,* bleeding) were similar across case groups.

Summary. Overall, this study suggests that there are few differences between risk factors for advanced adenomas and risk

factors for nonadvanced adenomas. Given the difficulty in measurement and the probable misclassification across case groups, null findings can have alternative interpretations. One interpretation is that many risk factors for colorectal neoplasia may be important to adenoma formation but do not have an additional effect on dysplasia. However, there are at least two possible alternative explanations. The first is that the key risk factors for advanced adenomas have not been measured by these questionnaires or that the level of detail of these pooled data were not sufficient. The second is that the nondifferential misclassification between the advanced adenoma case group and the nonadvanced adenoma case group biased any potential differences toward the null. Whatever the final interpretation, risk factors for dysplasia itself remain to be identified.

Designing future epidemiological studies specifically to address the question of risk factors for intermediate steps along the adenoma-carcinoma sequence demands careful consideration of case definition and uniform pathologic review. It will also be helpful to incorporate information on molecular markers important to cancer progression, such as *p53*, known to be important in later stages of colorectal neoplasia because most adenomas do not progress to cancer. Understanding risk factors for advanced adenomas can help lead to the development of more targeted, less invasive, colorectal screening recommendations, as well as a clearer picture of pathways to neoplasia.

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