The Association of Lifestyle and Dietary Factors with the Risk for Serrated Polyps of the Colorectum

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Abstract

Some serrated polyps of the colorectum are likely preinvasive lesions, evolving through a newly recognized serrated pathway to colorectal cancer. To assess possible risk and protective factors for serrated polyps and particularly to explore differences in risk factors between polyps in the right and left colorectum, we pooled data from three large multicenter chemoprevention trials. A serrated polyp was defined broadly as any serrated lesion (hyperplastic, sessile serrated adenoma, "traditional" serrated adenoma, mixed adenoma) diagnosed during each trial's main treatment period of ~3 to 4 years. Using generalized linear regression, we computed risk ratios and 95% confidence intervals as measures of the association between risk for serrated polyps and demographic, lifestyle, and dietary variables. Of the 2,830 subjects that completed at least one follow-up exam after randomization, 675 (23.9%) had at least one left-sided serrated polyp and 261 (9.2%) had at least one right-sided lesion. In the left colorectum, obesity, cigarette smoking, dietary fat, total energy intake, and red meat intake were associated with an increased risk for serrated polyps. In the right colon, aspirin treatment was associated with a reduced risk and family history of polyps and folate treatment were associated with an increased risk for serrated polyps. Our results suggest that several common lifestyle and dietary variables are associated with risk for serrated polyps, and some of these may differ for the right and left colorectum. (Cancer Epidemiol Biomarkers Prev 2009;18(8):2310–7)

Introduction

Serrated polyps of the colorectum are a diverse group of colorectal lesions that share a common feature of glandular serration, that is, a "saw-toothed" infolding of colonocytes in the lumen of the crypts (1). Historically, polyps with serrated architecture were thought to be a single entity, hyperplastic (or metaplastic) polyps, and considered indolent, nonneoplastic, hyperproliferative lesions (2, 3). Thus, they were considered distinct from adenomas (traditionally defined as polyps with cytologic dysplasia), the precursors to most colorectal cancers. Recently, there has been growing recognition that there are different types of serrated polyps (including hyperplastic, sessile serrated adenoma, "traditional" serrated adenoma, and mixed adenomas) and that a small subset of these may progress to adenocarcinoma through a novel pathway, the serrated polyp pathway (1, 4, 5), which has been linked to CpG island methylator phenotype-high (CIMP-H) and microsatellite instability–high (MSI–H) colorectal cancers (6).

Understanding of the biology, epidemiology, and natural history of serrated polyps is incomplete, and the appropriate categorization of the lesions is a matter of current investigation and discussion (1, 3, 5). A few recent studies showed that diagnostic agreement for the different types of serrated polyps is variable and that discrimination between the newly defined sessile serrated adenoma and the traditional hyperplastic polyp is challenging (7-9), although in a nondiagnostic research setting, the ability to reliably distinguish the different lesions was reported to be reasonable in some analyses (10, 11). Whatever the categorization that emerges, however, some distinctions are clear. For example, the serrated lesions on the right side of the large bowel tend to differ morphologically and perhaps biologically from those of the left (1, 12, 13).

Although no studies have formally explored the epidemiology of the various types of serrated polyps, several have examined risk factors for hyperplastic polyps (14-16). Because differences between different types of serrated polyps have only recently been recognized (and remain under debate), in reality the lesions studied were likely a heterogeneous mix of the currently recognized serrated polyp types. Nonetheless, the studies showed inverse associations between serrated polyps and high calcium and folate intake and positive associations with high intake of fat, alcohol, and cigarette smoking (14, 16-18). Most of these investigations have focused on the relatively common left-sided serrated polyps, and consequently, little is known about risk or protective factors associated with the right-sided lesions.

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In the present investigation, we pooled data from three large multicenter large bowel adenoma chemoprevention trials to explore the association of demographic, environmental, and dietary factors on the risk for serrated polyps, with specific attention to those occurring on the left and right side of the bowel.

Subjects and Methods

This analysis was based on pooled data from three placebo-controlled randomized colorectal adenoma chemoprevention trials: the Antioxidant Polyp Prevention Study (19), the Calcium Polyp Prevention Study (20), and the Aspirin/Folate Polyp Prevention Study (19, 21), the details of which are reported elsewhere. Written informed consent was obtained from each participant, and the institutional review board of every participating institution approved the studies.

Eligible subjects had at least one recently documented adenoma and underwent complete (to the cecum) colonoscopy at baseline with the endoscopist attesting all polyps and areas suspicious for neoplasia were removed. Subjects were then randomized to study agent or placebo (see Table 1, summarizing study name, date, size, intervention) with scheduled colonoscopic surveillance at 1 and 4 years after the qualifying examination in the antioxidant and calcium studies (20, 22) and at 3 years in the aspirin/folate trial (19, 21). Treatment ended at the year 4 examination in the antioxidant and calcium studies and at the year 3 examination for the aspirin/folate study (although folate treatment continued in most subjects). The location and estimated size of each colorectal lesion found during follow-up was recorded, and the polyps were removed and sent for central histologic review by a single study pathologist (D.C. Snover; refs. 5, 23). For the present analysis, we used the diagnosis that occurred at the time of central review in each original study. We did not rereview any slides for the present analysis.

For the pooled data, our primary endpoint was any serrated polyp that occurred during the treatment phase of each trial, including polyps removed at the year 1 and 4 exams in the antioxidant and calcium studies (20, 22) and at year 3 in the aspirin/folate trial (19, 21), as well as those found at interim examinations. Serrated polyps occurring in the folate continuation or observational follow-up are not included in these analyses.

Serrated polyps were defined as any polyp diagnosed by the study pathologist as hyperplastic, mixed polyps (hyperplastic–sessile serrated adenoma or serrated adenoma–adenomatous), sessile serrated adenoma, traditional serrated adenoma, or serrated adenoma. As an additional endpoint, we examined "advanced serrated polyps," which we defined as any serrated lesion (including hyperplastic polyps) of size >1 cm, serrated adenomas (including traditional serrated adenoma or sessile serrated adenoma), or mixed polyps (hyperplastic–sessile serrated adenoma or serrated adenoma–adenomatous). The following is a list of the other names serrated polyps are sometimes referred to in the literature: hyperplastic polyp, goblet type; type 1 hyperplastic polyp; hyperplastic polyp, microvesicular type; type 2 hyperplastic polyp; sessile serrated polyp; admixed polyp, and atypical hyperplastic polyp (24).

We grouped all serrated lesions into a single category because the diagnostic criteria for these lesions had changed over the course of the three polyp prevention studies and continues to evolve. The study pathologist's use of diagnostic categories such as serrated adenoma began toward the end of the second (calcium) study and occurred more frequently in the third (aspirin/folate) study as the concept of serrated polyp became more widely disseminated. Before this time, virtually all polyps with serrated architecture were classified as hyperplastic or mixed.

At enrollment, participants completed a questionnaire addressing basic demographic characteristics, lifestyle factors, medical history (including height and weight), and usual diet (using a validated food frequency questionnaire). Subjects were also asked about family history of polyps and/or colorectal cancer. We analyzed demographic factors, including age (quartiles), sex, and self-reported race and ethnicity (White, non-Hispanic origin; African American, non-Hispanic origin; Hispanic; other). Smoking status was categorized as never, former, and current users. Alcohol use was categorized into two categories: nondrinker, >0 drinks per day. Body mass index (BMI) was calculated from baseline information on height and weight and divided into three categories using the standard established by the WHO: normal (<25 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). In the first two studies, height and weight were assessed by study personnel (physician's initial assessment) and by self-report in the third study.

Dietary patterns were assessed at baseline with a self-administered semiquantitative food frequency questionnaire, initially developed by the National Cancer Institute and now maintained by Nutrition Quest (Berkeley, California; ref. 25). This instrument previously has been validated by others (26-28). The surveys requested information about usual diet over the previous year and included ~100 food items (plus open-ended questions for frequently eaten, unlisted foods). In the first two polyp prevention studies, we administered the same questionnaire (25), but in the third, we used the updated version (26). With this instrument, we assessed daily total energy intake, carbohydrates, protein, fiber (all, grain, bean, and fruit and vegetable), fat (all and saturated), and meat (red, chicken, processed). We excluded the food frequency questionnaire data for participants on whom the questionnaire data were not thought to be valid, that is, participants with following responses: eating less than three foods per day, skipping >50 foods on the grid, or calculated total energy intake >5,000 kcal or <500 kcal. Nutrient intakes were estimated using software developed in connection with the questionnaires (29).

Statistical Analysis. To assess the association between serrated polyps and demographic, lifestyle, and dietary factors, we estimated risk ratios [and 95% confidence intervals (95% CI)] for one or more adenomas after randomization, calculated with generalized linear regression analyses using a logarithmic linkage and a binomial distribution. We obtained relative risks and *P*'s for trend using orthogonal linear contrasts. We used Wald tests to assess main effects and statistical interactions. The estimated intakes of the dietary nutrients were adjusted for total energy intake using residuals computed from the linear regression of the log of the nutrient intake on the log of caloric intake (30). All effect estimates were adjusted

Table 1. Baseline characteristics of subjects participating in the polyp prevention studies

Characteristic	Antioxidant Polyp Prevention Study* (n = 864)	Calcium Polyp Prevention Study† (n = 930)	Aspirin/Folate Polyp Prevention Study‡ (n = 1,121)
Age ± SD, y	61.2 ± 8.3	61.0 ± 9.1	57.5 ± 9.6
Male, n (%)	684 (79.2)	672 (72.3)	409 (63.5)
Smoker, n (%)	577 (68.3)	621 (66.8)	638 (57.2)
Never	268 (31.7)	309 (33.2)	478 (42.8)
Former	389 (46.0)	442 (47.5)	471 (42.2)
Current	188 (22.3)	179 (19.3)	167 (15.0)
Treatment			
Placebo	214	466	169
β-Carotene	208		
Vitamin C/E	217		
B, C/E	225		
Calcium 1,200 mg		464	
Aspirin 81 mg only			169
Aspirin 325 mg only			167
Aspirin 81 mg/1 mg folate			175
Aspirin 325 mg/1 mg folate			171
Folate only 1 mg			170
Race, n (%)			
White	733 (85.2)	791 (85.1)	958 (85.5)
African American	58 (6.7)	75 (8.1)	68 (6.1)
Hispanic	19 (2.2)	27 (2.9)	61 (5.4)
Other	50 (5.8)	37 (4.0)	34 (3.0)
BMI, mean (SD)	26.9 (4.1)	27.4 (4.4)	27.4 (4.5)
Total energy intake (SD), calories/day	1,955.0 (757.7)	2,024 (758.6)	1,634 (667.0)
Carbohydrates (SD), g/day	201.7 (80.1)	219.5 (82.0)	185.9 (77.4)
Fat total (SD), g/day	86.2 (43.0)	87.7 (7)	65.1 (34.3)
Fiber (SD), g/day	14.2 (7.2)	16.4 (7.9)	13.3 (6.0)
Folate (SD), mg/day	314.3 (165.3)	331.3 (168.1)	319.9 (156.6)
Red meat intake (SD), servings per day	0.54 (0.42)	0.48 (0.38)	0.36 (0.31)

*Study 1 was the Antioxidant Polyp Prevention Study (22).
†Study 2 was the Calcium Polyp Prevention Study (20).
‡Study 3 the Aspirin Folate Polyp Prevention Study (21).

for age, sex, clinical center, time since randomization, treatment assignment, and polyp study. All tests of statistical significance were two sided.

Given the likely biological differences in serrated polyps of the right and left colorectum, we conducted separate analyses by colorectal location. The right colon included the cecum, ascending colon, hepatic flexure, and transverse colon; the left colorectum included the splenic flexure, descending colon, sigmoid colon, and rectum. In our analysis, subjects could have multiple endpoints (that is, a right- and left-sided serrated polyp), and thus, we used generalized estimating equation modeling to account for possible within subject correlations. To compare the relative risk between right and left polyps, we created an indicator variable to specify the colorectal side (that is, right, left). For any given risk factor (e.g., smoking), we used generalized estimating equation methodology (30) with log link, Poisson family, and exchangeable correlation to account for the fact that left- and right-sided polyps may be observed in the same patients. We used Wald tests to assess the significance of the interaction term between risk factor and the indicator variable of side while controlling for the same adjustment factors listed above. We also assessed the effect of each study's randomized treatment using intention-to-treat analyses.

Results

Of the 2,915 subjects, 2,830 (97.1%) completed at least one follow-up exam after randomization. Subjects from all three studies had similar characteristics at study entry (Table 1). The mean age of the study participants was 59.7 years (SD, ±9.3), and 70.1% were men. The mean length of follow-up from time of randomization to final study exam during the main treatment phase was 38.5 (SD, ±9.9) months.

Among the subjects with at least one follow-up exam, 812 (28.7%) had at least one serrated polyp detected; 675 (23.9%) had at least one left-sided serrated polyp, and 261 (9.2%) had at least one on the right side. There were 145 (5.1%) subjects with at least one advanced serrated lesion, which included 16 subjects with at least one hyperplastic polyp of ≥1 cm, 15 with at least one mixed adenoma, and 120 with at least one serrated adenoma. There were similar numbers of subjects with at least one advanced serrated polyp in the left (n = 87; 3.1%) and in the right (n = 68; 2.4%) colorectum. There was a higher percentage of persons with multiple serrated polyps (two or more) on the left side (11.1%; n = 313; range, 1-15 lesions) than on the right (1.9%; n = 53; range, 1-6). The average size of all serrated polyps was 0.35 cm (±0.19 cm), 0.33 cm for left-sided serrated polyps (±0.15 cm), and 0.45 cm (±0.31 cm) for those on the right. For advanced serrated polyps, average size was 0.49 (±0.31 cm) for all, 0.42 (±0.23 cm) for the left side, and 0.63 (±0.44 cm) for the right. Among subjects with multiple (two or more) serrated polyps, the average size was higher on the right 0.50 (±0.31 cm) compared with that on the left 0.32 (±0.13 cm).

Age, Sex, Race, and Family History. Increasing age and sex were not materially associated with risk for serrated polyps (Table 2). However, race/ethnicity was

strongly associated with risk for developing at least one serrated polyp: the relative risk among African Americans was 0.65 (95% CI, 0.50-0.85) and among Hispanics was 0.33 (95% CI, 0.20-0.55) compared with Caucasians. These findings were similar for the left and right colorectum (Table 2). Family history of polyps was more strongly associated with right-sided lesions, especially advanced lesions (relative risk, 1.42; 95% CI, 0.82-2.43; *P* for difference from left = 0.07).

BMI, Smoking, and Alcohol Intake. Higher BMI levels were associated with an increased risk for most types of serrated lesions (Table 2). Among obese persons, the risk for one or more left-sided serrated lesions was 1.27 (95% CI, 1.06-1.53) compared with those of normal weight (*P* for trend = 0.01; Table 2). A similar pattern was observed for left-sided advanced serrated lesions, but not for right sided serrated lesions.

We observed a strong association between cigarette smoking and risk for left-sided (but not right sided) serrated polyps (Table 2). The relative risk for current smokers was 2.18 (95% CI, 1.80-2.65) for any left-sided serrated polyp and 3.42 (95% CI, 1.91-6.11) for advanced left-sided lesions. Alcohol consumption was not significantly associated with a risk for lesions on either side (Table 2).

Treatment Effects. In the Antioxidant Polyp Prevention Study, randomization to β-carotene and vitamins C and E were associated with nonsignificantly reduced risks for right-sided serrated polyps compared with placebo but clearly had no effect on left-sided lesions (Table 3). Calcium supplementation was not consistently associated with risk for either left- or right-sided serrated polyps. Aspirin treatment was associated with a reduced risk for serrated polyps, particularly on the right-side [81 mg of aspirin relative risk, 0.56 (95% CI, 0.34-0.91); 325 mg of aspirin relative risk, 0.58 (95% CI, 0.36-0.95); Table 3]. However, the relative risks for advanced lesions differed between right and left (*P* for difference = 0.03) and aspirin 81 mg had no effect on advanced left-sided lesions. Subjects randomized to folate had an increased risk for right-sided serrated polyps, particularly if advanced (relative risk, 2.07; 95% CI, 1.14-3.77).

Dietary Variables. There were no remarkable associations with carbohydrate or total dietary fiber intake (Table 4). However, intake of dietary fat was modestly associated with an increased risk for left- and right-sided lesions (Table 4), and there were suggestions that higher total energy intake and higher red meat intake were associated with left-sided advanced lesions. Subjects in the highest quartile of total energy intake were 2.28 (95% CI, 1.23-4.24) times more likely to have an advanced left-sided lesion than those in the lowest quartile (*P* for trend = 0.03); in the same comparison for red meat intake, the relative risk was 1.93 (0.97-3.84; *P* for trend = 0.02). We did not observe relationships between any of the remaining dietary factors and risk for serrated polyps.

Table 2. Lifestyle and demographic factors and the risk for serrated polyps

Variables	*n* Total	Serrated polyps				*P* difference	Advanced serrated polyps				*P* difference
		Left		Right			Left		Right		
		n Cases	RR† (95% CI)	*n* Cases	RR† (95% CI)		*n* Cases	RR† (95% CI)	*n* Cases	RR† (95% CI)	
Family history of polyps											
No	1,997	461	1.0	172	1.0		56	1.00	36	1.00	
Yes	521	133	1.15 (0.96-1.40)	60	1.39 (1.04-1.86)	0.21	21	0.98 (0.60-1.60)	17	1.42 (0.82-2.43)	0.07
Family history of colorectal cancer											
No	1,831	435	1.0	161	1.0		48	1.0	33	1.0	
Yes	687	159	1.03 (0.88-1.22)	71	1.21 (0.92-1.60)	0.19	29	1.24 (0.80-1.93)	20	1.23 (0.74-2.06)	0.22
Sex											
Male	2,009	488	1.0	181	1.0		53	1.0	44	1.0	
Female	821	184	0.98 (0.84-1.14)	80	1.07 (0.82-1.39)	0.27	34	1.35 (0.87-2.08)	24	1.16 (0.72-1.87)	0.65
Race											
White	2,412	619	1.0	235	1.0		79	1.0	64	1.0	
Black	193	31	0.59 (0.42-0.81)	15	0.75 (0.44-1.27)		4	0.54 (0.20-1.50)	2	0.41 (0.11-1.55)	
Hispanic	105	7	0.31 (0.16-0.62)	4	0.41 (0.15-1.09)		3	0.57 (0.17-1.92)	1	0.31 (0.05-2.05)	
Other	116	15	0.62 (0.38-1.00)	7	0.64 (0.30-1.35)	0.62	1	0.39 (0.05-2.82)	1	0.38 (0.06-2.45)	*
Age, y											
<61	1,409	352	1.0	140	1.0		53	1.0	37	1.0	
≥61	1,421	320	0.94 (0.82-1.08)	121	0.86 (0.68-1.10)	0.71	34	0.98 (0.63-1.51)	31	1.06 (0.67-1.68)	0.59
BMI, kg/m^2											
<25	903	191	1.0	81	1.0		25	1.0	25	1.0	
25-29.9	1,355	308	1.09 (0.92-1.28)	113	0.96 (0.73-1.27)		38	1.11 (0.68-1.83	38	0.84 (0.49-1.45)	
≥30	648	172	1.27 (1.06-1.53)	65	1.13 (0.83-1.56)	0.59	21	1.64 (0.97-2.79)	21	1.33 (0.75-2.36)	0.52
P for trend			0.01		0.48			0.07		0.35	
Smoking†											
Never	1,027	163	1.0	95	1.0		22	1.0	23	1.0	
Former	1,272	333	1.67 (1.41-1.97)	113	0.98 (0.75-1.28)		39	1.74 (1.02-2.98)	32	1.21 (0.72-2.03)	
Current	511	173	2.18 (1.80-2.65)	52	1.11 (0.80-1.54)	0.0001	26	3.42 (1.91-6.11)	13	1.51 (0.80-2.86)	0.94
Alcohol											
Nondrinker	856	192	1.0	85	1.0		24	1.0	19	1.0	
Drinker	1,849	457	1.05 (0.90-1.22)	164	0.88 (0.68-1.14)	0.12	62	1.19 (0.73-1.92)	48	1.20 (0.73-1.98)	0.94

Abbreviation: RR, relative risk.
*Results could not be calculated because model did not converge.
†Relative risk adjusted for age, sex, center, treatment, time since randomization, study number, and smoking status (when not the stratifying variable).

Table 3. Effect of study treatment on the risk for any and advanced serrated polyps

PPS	*n* Total	Serrated polyps				*P* for the difference	Advanced serrated polyps				*P* for the difference
		Left		Right			Left		Right		
		n Cases	RR* (95% CI)	*n* cases	RR* (95% CI)		*n* Cases	RR* (95% CI)	*n* Cases	RR* (95% CI)	
Antioxidant PPS											
Placebo	207	52	1.0	28	1.0		2		2		
β-Carotene	208	47	0.90 (0.63-1.28)	17	0.64 (0.35-1.15)		1	—	0	—	
Vitamins C and E	220	58	1.06 (0.76-1.48)	18	0.62 (0.35-1.10)		0	—	2	—	
β-Carotene, C, E	198	36	0.73 (0.50-1.07)	15	0.60 (0.32-1.10)	0.32	0	—	3	—	—
Calcium PPS											
Placebo	459	135	1.0	49	1.0		4	1.0	8	1.0	
Calcium carbonate	454	107	0.81 (0.65-1.01)	44	0.93 (0.63-1.38)	0.53	7	1.83 (0.52-6.50)	5	0.63 (0.97-1.10)	0.16
Aspirin/folate PPS											
Placebo	363	85	1.0	41	1.0		23	1.0	22	1.0	
Aspirin 81 mg	366	67	0.77 (0.58-1.04)	24	0.56 (0.34-0.91)		15	1.32 (0.76-2.30)	11	0.60 (0.31-1.15)	
Aspirin 325 mg	355	85	0.94 (0.71-1.24)	25	0.58 (0.36-0.95)	0.14	35	0.78 (0.41-1.48)	15	0.50 (0.25-1.01)	0.03
Placebo	486	101	1.0	38	1.0		31	1.0	15	1.0	
Folate 1 mg	501	118	1.10 (0.87-1.39)	50	1.26 (0.84-1.89)	0.59	33	0.98 (0.61-1.57)	32	2.07 (1.14-3.77)	0.10

Abbreviation: PPS, polyp prevention study.
*Relative risk adjusted for age, sex, center, time since randomization, and smoking status.

Discussion

In this large pooled analysis, we observed that several demographic, lifestyle, and dietary factors were associated with the risk for serrated polyps. In the left colorectum, obesity, cigarette smoking, dietary fat, total energy intake, and red meat intake were related to an increased risk for any and/or advanced serrated polyps. In the right colorectum, family history of polyps and folate treatment were associated with risk for serrated lesions, whereas aspirin treatment was associated with a reduced risk. African American and Hispanic race were associated with a decreased risk for right and left serrated polyps compared with Caucasians.

No previous epidemiologic investigation has examined personal factors associated with the newly described lesions of the serrated pathway; however, several have reported associations with hyperplastic polyps (14-18, 31, 32). The inverse associations we observed for the dietary variables and risk for left-sided serrated polyps were similar to earlier findings for calcium (14, 18), carbohydrates (17), and fiber (14). Dietary fat was associated with an increased risk for left-sided lesions in our study and one other (18), but not in others (15, 17). The association between higher BMI and increased risk for left-sided serrated polyps has also been observed previously for hyperplastic polyps (18). In contrast to several previous studies (14, 15, 17), we did not find an association between higher alcohol intake and increased risk for serrated polyps. Our finding of a strong positive relationship for former and current smoking and left-sided serrated polyps is similar to that in most previous studies (14, 16-18, 31, 32).

Previously, only one study specifically examined risk factors for right-sided hyperplastic polyps (16). Similar to our results for any right-sided serrated polyp, they reported no significant association between smoking and the risk for proximal hyperplastic polyps among current smokers (16). For advanced proximal lesions, we did observe a nonsignificant increase in risk associated with current smoking status, a finding consistent with the literature linking smoking to MSI–H or CIMP-H neoplasia (33, 34), two molecular phenotypes frequently associated with the serrated pathway. Our finding of a protective effect of aspirin treatment in the right colon is similar to what others have reported for hyperplastic polyps (14, 15, 18); yet, our study is the first to specifically examine right-sided location. Future research will be needed to further explore these findings.

Race was the only variable significantly associated with a risk for right- and left-sided serrated lesions. Similar to our results, one other study (15) reported a lower risk for hyperplastic polyps for both African Americans and Hispanics compared with Caucasians. The clinicopathologic molecular evidence, however, points to a possible association between African American race and lesions of the serrated pathway, as evidenced by a higher proportion of MSI–H cancers and a greater proclivity for right-sided neoplasms compared with other races (35-37). In future studies, it will be important to compare the molecular and genetic characteristics of the precursor lesions in African Americans, Hispanics, and Caucasians.

The epidemiologic evidence suggests that some risk factors for serrated polyps (including hyperplastic polyps) may differ from traditional adenomas. For example, increasing age is consistently associated with risk for traditional adenomas (38), yet we and others (15, 18, 39) did not find a relationship between age and risk for serrated (or hyperplastic) polyps. Typically, traditional adenomas are more strongly associated with male gender (38), whereas in our study, serrated polyps were more closely related to female gender, especially for advanced serrated polyps. Furthermore, select lifestyle factors (such as BMI or smoking) show evidence of different associations in serrated polyps and traditional adenomas. For example, higher BMI is strongly associated with traditional adenomas located in the

right (or proximal) colon (40), whereas in our study, the association was strongest for serrated polyps of the left colorectum. There is also evidence to suggest a stronger relationship between cigarette smoking and serrated (hyperplastic) polyps compared with adenomas (15, 18, 31, 32, 39). Other variables, such as aspirin intake or calcium supplementation, seem broadly similar for serrated polyps and traditional adenomas (20, 21). Future investigations will be needed to understand the complex relationship(s) among personal factors, colonic location, and risk for different types of polyps.

Our findings of different risk factors for serrated polyps of the right and left colorectum may be the result of different biological pathways of carcinogenesis operating in the right and left colorectum. For example, a recent review describes two alternative pathways for the development of a serrated adenocarcinoma, one predominating in the right colon and another in the left colorectum (41). The more common pathway, "sessile serrated pathway," is hypothesized to begin with the sessile serrated adenoma largely in the right colon (41). The sessile serrated lesions are characterized by BRAF mutations, microsatellite instability positivity, methylation or loss of hMLH1 or MGMT, exaggerated crypt serration, excess mucin expression, and evidence of architectural dysplasia rather than classic cytologic dysplasia (5, 12, 13, 42). Alternatively, the "traditional serrated adenoma pathway" occurs mostly in the left colorectum and has the traditional serrated adenoma as the precursor lesion (41), which is estimated to be far less common than the sessile serrated adenoma. The left-sided lesions tend to exhibit K-*ras* mutations; p53, p16, and 18q loss of heterozygosity chromosomal instability; and classic cytologic dysplasia (5, 12, 13, 41). In future investigations, it will be important to explore the relationship between the epidemiologic variables and risk for serrated polyps of the sessile and traditional pathways.

At present, the diagnostic difficulty in discriminating the various types of serrated lesions has hampered our ability to conduct epidemiologic analysis using the different histologic types of serrated polyps as endpoints (5, 12, 13). Several recent studies by leading colorectal pathologists have assessed the problems in discriminating the different histologic subtypes of these lesions and have turned attention toward developing more accurate and reproducible nomenclature (7, 8, 43). Understanding the natural history of the serrated pathway(s) lesions and molecular phenotypes of sessile and traditional serrated adenomas will rely heavily on the ability of pathologists to reliably distinguish the various histologic types, which is a matter of current investigation (7, 8, 43).

Advantages of our study include a large well-characterized population that was thoroughly followed using a standardized protocol, including uniform pathologic review. However, this is a secondary analysis of our data, and the many associations that were assessed create a situation in which chance findings can easily emerge. For all three of our intervention studies, patients had to have at least one adenoma at study entry. Therefore, our results

Table 4. Dietary factors and the risk for serrated polyps

Dietary variables	*n* Total	Serrated polyps				*P* for right-left difference	Advanced serrated polyps				*P* for right-left difference
		Left		Right			Left		Right		
		n Cases	RR* (95% CI)	*n* Cases	RR* (95% CI)		*n* Cases	RR* (95% CI)	*n* Cases	RR* (95% CI)	
Total dietary fiber											
Q1	677	175	1.00	64	1.00		18	1.00	15	1.00	
Q2	676	185	1.08 (0.90-1.29)	58	0.92 (0.65-1.29)		31	1.47 (0.85-2.53)	20	1.32 (0.69-2.50)	
Q3	680	155	0.91 (0.75-1.11)	69	1.06 (0.76-1.48)		23	1.18 (0.66-2.10)	16	1.09 (0.55-2.14)	
Q4	678	137	0.88 (0.72-1.08)	59	0.95 (0.67-1.36)	0.17	14	0.81 (0.42-1.57)	16	1.16 (0.58-2.31)	0.48
P trend			0.10		0.99			0.41		0.83	
Carbohydrates											
Q1	676	175	1.00	53	1.00		14	1.00	13	1.00	
Q2	679	175	1.00 (0.83-1.20)	68	1.30 (0.92-1.84)		30	1.95 (1.04-3.63)	20	1.48 (0.76-2.87)	
Q3	680	173	1.00 (0.83-1.21)	74	1.38 (0.98-1.95)		25	1.57 (0.82-3.00)	18	1.28 (0.64-2.54)	
Q4	676	129	0.82 (0.67-1.01)	55	1.07 (0.74-1.56)		17	0.97 (0.48-1.97)	16	1.07 (0.52-2.18)	
P trend			0.09		0.63	0.20		0.58		0.98	0.73
Fat total											
Q1	679	124	1.00	46	1.00		16	1.00	12	1.00	
Q2	679	165	1.27 (1.03-1.56)	73	1.60 (1.12-2.28)		26	1.53 (0.84-2.77)	20	1.65 (0.85-3.21)	
Q3	676	191	1.45 (1.19-1.77)	63	1.36 (0.94-1.96)		25	1.86 (1.02-3.41)	23	2.38 (1.24-4.57)	
Q4	677	172	1.27 (1.03-1.56)	68	1.45 (1.01-2.10)		19	1.40 (0.74-2.65)	12	1.15 (0.54-2.42)	
P trend			0.01		0.13	0.37		0.22		0.43	0.40
Red meat											
Q1	697	138	1.00	59	1.00		18	1.0	20	1.00	
Q2	681	164	1.10 (0.90-1.35)	67	1.15 (0.82-1.63)		19	1.00 (0.54-1.85)	25	1.47 (0.82-2.63)	
Q3	663	167	1.12 (0.91-1.39)	66	1.15 (0.80-1.66)		24	1.79 (0.97-3.32)	13	0.95 (0.46-1.96)	
Q4	669	182	1.17 (0.93-1.48)	58	1.03 (0.68-1.57)	0.37	25	1.93 (0.97-3.84)	9	0.82 (0.34-1.96)	0.93
P trend			0.19		0.86			0.02		0.56	
Total energy intake											
Q1	677	146	1.00	62	1.00		20	1.00	21	1.00	
Q2	678	153	1.00 (0.82-1.22)	60	0.94 (0.67-1.33)		27	1.77 (1.04-3.03)	26	1.37 (0.79-2.37)	
Q3	680	170	1.07 (0.88-1.31)	61	0.93 (0.66-1.33)		18	1.41 (0.77-2.58)	10	0.59 (0.28-1.22)	
Q4	676	183	1.16 (0.94-1.42)	67	1.01 (0.71-1.44)	0.78	21	2.28 (1.23-4.24)	10	0.70 (0.33-1.51)	0.88
P trend			0.12		0.96			0.03		0.14	

Abbreviation: Q, quartile.
*Relative risk adjusted for age, sex, center, treatment, time since randomization, study number, smoking status, and log calories.

may only be applicable to subjects with previous adenomas. Finally, the changing definition of the serrated polyp over time, the lack of a diagnostic rereview of the slides, and the continued diagnostic uncertainty hampered our ability to define the serrated polyp type endpoint more precisely (such as hyperplastic, sessile serrated adenoma, or traditional serrated adenoma). In future studies, it will be important to replicate our findings and further refine the distinctions between the different types of serrated polyps.

Investigators have become increasingly aware that there are clear physiologic, morphologic, and biochemical differences between the right and left colon and that these differences may help shed light on how and why some polyps exhibit a proclivity for serration and hypermethylation (44-46). Our findings highlight for the first time the marked differences in the associations between risk factors and right- versus left-sided serrated polyps. These observations lend strong support to the concept that right- and left-sided serrated polyps may not arise through the same pathway, although as Imai and Yamamoto (47) discuss, there is still considerable cross-talk among the various pathways. An important question for future investigations is whether the differences in the environment of the right and left colorectum (such as differences in types of methylation in the distal and proximal locations) contributed to the differences in the risk and protective factors in the right and left.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Snover DC, Jass JR, Fenoglio-Preiser C, Batts KP. Serrated polyps of the large intestine: a morphologic and molecular review of an evolving concept. Am J Clin Pathol 2005;124:380–91.
2. Hawkins NJ, Bariol C, Ward RL. The serrated neoplasia pathway. Pathology 2002;34:548–55.
3. Cunningham KS, Riddell RH. Serrated mucosal lesions of the colorectum. Curr Opin Gastroenterol 2006;22:48–53.
4. Iino H, Jass JR, Simms LA, et al. DNA microsatellite instability in hyperplastic polyps, serrated adenomas, and mixed polyps: a mild mutator pathway for colorectal cancer? J Clin Pathol 1999;52:5–9.
5. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol 2003;27:65–81.
6. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. Histopathology 2007;50:113–30.
7. Odze R, Batts B, Goldstein N, et al. Interobserver variability in the diagnosis of hyperplastic and serrated colonic polyps. Mod Pathol 2007;1:247.
8. Farris AB, Misdraji J, Srivastava A, et al. Sessile serrated adenoma: challenging discrimination from other serrated colonic polyps. Am J Surg Pathol 2008;32:30–5.
9. Glatz K, Pritt B, Glatz D, et al. A multinational, internet-based assessment of observer variability in the diagnosis of serrated colorectal polyps. Am J Clin Pathol 2007;127:938–45.
10. Sandmeier D, Seelentag W, Bouzourene H. Serrated polyps of the colorectum: is sessile serrated adenoma distinguishable from hyperplastic polyp in a daily practice? Virchows Arch 2007;450:613–8.
11. O'Brien MJ, Yang S, Clebanoff JL, et al. Hyperplastic (serrated) polyps of the colorectum: relationship of CpG island methylator phenotype and K-ras mutation to location and histologic subtype. Am J Surg Pathol 2004;28:423–34.
12. O'Brien MJ, Yang S, Mack C, et al. Comparison of microsatellite instability, CpG island methylation phenotype, BRAF and KRAS status in serrated polyps and traditional adenomas indicates separate pathways to distinct colorectal carcinoma end points. Am J Surg Pathol 2006;30:1491–501.
13. Baker K, Zhang Y, Jin C, Jass JR. Proximal versus distal hyperplastic polyps of the colorectum: different lesions or a biological spectrum? J Clin Pathol 2004;57:1089–93.
14. Martinez ME, McPherson RS, Levin B, Glober GA. A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. Gastroenterology 1997;113:423–9.
15. Lieberman DA, Prindiville S, Weiss DG, Willett W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA 2003;290:2959–67.
16. Paskett ED, Reeves KW, Pineau B, et al. The association between cigarette smoking and colorectal polyp recurrence (United States). Cancer Causes Control 2005;16:1021–33.
17. Kearney J, Giovannucci E, Rimm EB, et al. Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States). Cancer Causes Control 1995;6:45–56.
18. Morimoto LM, Newcomb PA, Ulrich CM, et al. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? Cancer Epidemiol Biomarkers Prev 2002;11:1012–8.
19. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351–9.
20. 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;340:101–7.
21. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9.
22. Greenberg E, Baron J, Tosteson T, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. Polyp Prevention Study Group. N Engl J Med 1994;331:141–7.
23. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;110:748–55.
24. Young J, Jass JR. The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. Cancer Epidemiol Biomarkers Prev 2006;15:1778–84.
25. Block G, Hartman AM, Dresser CM, et al. A data-based approach to diet questionnaire design and testing. Am J Epidemiol 1986;124:453–69.
26. Block G, Woods M, Potosky A, Clifford C. Validation of a self-administered diet history questionnaire using multiple diet records. J Clin Epidemiol 1990;43:1327–35.
27. Sobell J, Block G, Koslowe P, Tobin J, Andres R. Validation of a retrospective questionnaire assessing diet 10-15 years ago. Am J Epidemiol 1989;130:173–87.
28. Subar AF, Thompson FE, Kipnis V, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. Am J Epidemiol 2001;154:1089–99.
29. Smucker R, Block G, Coyle L, Harvin A, Kessler L. A dietary and risk factor questionnaire and analysis system for personal computers. Am J Epidemiol 1989;129:445–9.
30. Willett WC. Nutritional epidemiology. New York: Oxford University Press; 1998.
31. Potter JD, Bigler J, Fosdick L, et al. Colorectal adenomatous and hyperplastic polyps: smoking and *N*-acetyltransferase 2 polymorphisms. Cancer Epidemiol Biomarkers Prev 1999;8:69–75.
32. Ji BT, Weissfeld JL, Chow WH, et al. Tobacco smoking and colorectal hyperplastic and adenomatous polyps. Cancer Epidemiol Biomarkers Prev 2006;15:897–901.
33. Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J Natl Cancer Inst 2000;92:1831–6.
34. Samowitz WS, Albertsen H, Sweeney C, et al. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. J Natl Cancer Inst 2006;98:1731–8.
35. Brim H, Mokarram P, Naghibalhossaini F, et al. Impact of BRAF, MLH1 on the incidence of microsatellite instability high colorectal cancer in populations based study. Mol Cancer 2008;7:68.
36. Ashktorab H, Smoot DT, Farzanmehr H, et al. Clinicopathological features and microsatellite instability (MSI) in colorectal cancers from African Americans. Int J Cancer 2005;116:914–9.
37. Shavers VL. Racial/ethnic variation in the anatomic subsite location of *in situ* and invasive cancers of the colon. J Natl Med Assoc 2007;99:733–48.

38. Peipins LA, Sandler RS. Epidemiology of colorectal adenomas. Epidemiol Rev 1994;16:273–97.
39. Shrubsole MJ, Wu H, Ness RM, et al. Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. Am J Epidemiol 2008;167:1050–8.
40. Jacobs ET, Ahnen DJ, Ashbeck EL, et al. Association between body mass index and colorectal neoplasia at follow-up colonoscopy: a pooling study. Am J Epidemiol 2009;169:657–66.
41. Makinen MJ. Colorectal serrated adenocarcinoma. Histopathology 2007;50:131–50.
42. Torlakovic E, Snover DC. Sessile serrated adenoma: a brief history and current status. Crit Rev Oncog 2006;12:27–39.
43. Torlakovic EE, Gomez JD, Driman DK, et al. Sessile serrated adenoma (SSA) vs. traditional serrated adenoma (TSA). Am J Surg Pathol 2008; 32:21–9.
44. Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002; 101:403–8.
45. Gervaz P, Bucher P, Morel P. Two colons-two cancers: paradigm shift and clinical implications. J Surg Oncol 2004;88:261–6.
46. Azzoni C, Bottarelli L, Campanini N, et al. Distinct molecular patterns based on proximal and distal sporadic colorectal cancer: arguments for different mechanisms in the tumorigenesis. Int J Colorectal Dis 2007;22:115–26.
47. Imai K, Yamamoto H. Carcinogenesis and microsatellite instability: the interrelationship between genetics and epigenetics. Carcinogenesis 2008;29:673–80.

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