Published in final edited form as:
Cancer Epidemiol Biomarkers Prev. 2009 August ; 18(8): 2310–2317. doi: 10.1158/1055-9965.EPI-09-0211.

The association of lifestyle and dietary factors with the risk of serrated polyps of the colorectum

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Abstract

Some serrated polyps of the colorectum are likely pre-invasive 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 multi-center chemoprevention trials. A serrated polyp (SP) 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 about three to four years. Using generalized linear regression, we computed risk ratios and 95% confidence intervals (CI's) as measures of the association between risk of serrated polyps and demographic, lifestyle, and dietary variables. Of the 2830 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 of 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 of serrated polyps. Our results suggest that several common lifestyle and dietary variables are associated with risk of serrated polyps, and some of these may differ for the right and left colorectum.

Keywords

serrated polyps; proximal colon; distal colon; lifestyle factors; diet

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Introduction

Serrated polyps of the colorectum are a diverse group of colorectal lesions that share a common feature of glandular serration, i.e., 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, non-neoplastic hyperproliferative lesions (2, 3). Thus, they were considered distinct from adenomas (traditionally defined as polyps with cytological 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 CIMP-H and 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 demonstrated 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 non-diagnostic 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.

In the present investigation, we pooled data from three large multi-center large bowel adenoma chemoprevention trials to explore the association of demographic, environmental, and dietary factors on the risk of 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 one and four years after the qualifying examination in the Antioxidant and Calcium studies (20, 22) and at three years in the Aspirin/Folate trial (19, 21). Treatment ended at the year four examination in the Antioxidant and Calcium studies, and at the year three examination for aspirin 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 histological review by a single study pathologist (DS) (5, 23). For the present analysis, we used the diagnosis which occurred at the time of central review in each original study. We did not re-review 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 one and four exams in the Antioxidant and Calcium studies (20, 22) and at year three 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 (HP)," "mixed polyps (hyperplastic-SSA-or SA- adenomatous)," "sessile serrated adenoma (SSA)," "traditional serrated adenoma (TSA)," or "serrated adenoma (SA)." As an additional endpoint we examined "advanced serrated polyps" which we defined as any serrated lesion (including HPs) > 1 cm, serrated adenomas (including TSA or SSA), or mixed polyps (hyperplastic-SSA-or SA- 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. Prior to 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: non-drinker, > 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 World Health Organization: normal (< 25 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (BMI ≥ 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 semi-quantitative food frequency questionnaire, initially developed by the National Cancer Institute and now maintained by Nutrition Quest (Berkeley, California) (25). This instrument previously has been validated by others (26–28). The surveys requested information regarding usual diet

over the prior year and included approximately 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, i.e., participants with following responses: eating less than 3 foods/day, skipping greater than 50 foods on the grid or calculated total energy intake greater than 5,000 kcal or less than 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) 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 for age, sex, clinical center, time since randomization, treatment assignment, and polyp study. All tests of statistical significance were two-sided.

Given the likely biologic 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 (i.e. a right and left-sided serrated polyp) and thus we used GEE modeling to account for possible within subject correlations. To compare the RR between right and left polyps, we created an indicator variable to specify the colorectal side (i.e., right, left). For any given risk factor (e.g. smoking), we used generalized estimating equation (GEE) methodology (30) with log link, Poisson family and exchangeable correlation to account for the fact that both 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 2915 subjects, 2830 (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 HP ≥ 1 cm, 15 with at least one mixed adenoma, and 120 with at least one SA. 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 to 15 lesions) than on the right (1.9%, n=53; range 1 to 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 (2 or more) serrated polyps, the average size was higher on the right 0.50 (± 0.31 cm) compared to the left 0.32 (± 0.13 cm).

Age, sex, race, and family history

Increasing age and sex were not materially associated with risk of serrated polyps (Table 2). However, race/ethnicity was strongly associated with risk of developing at least one serrated polyp: the RR 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 to Caucasians. These findings were similar for both the left and right colorectum (Table 2). Family history of polyps was more strongly associated with right-sided lesions, especially advanced lesions (RR 1.42 (95% CI 0.82–2.43); p for difference from left = 0.07).

Body Mass Index, smoking and alcohol intake

Higher BMI levels were associated with an increased risk of most types of serrated lesions (Table 2). Among obese persons the risk of one or more left-sided serrated lesions was 1.27 (95% CI 1.06–1.53) compared to 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 of left-sided (but not right sided) serrated polyps (Table 2). The RR for current smokers was 2.18 (95% CI 1.80–2.65) for any left-sided SP and 3.42 (95% CI 1.91–6.11) for advanced left-sided lesions. Alcohol consumption was not significantly associated with a risk of lesions on either side (Table 2).

Treatment effects

In the Antioxidant Polyp Prevention Study, randomization to beta-carotene and vitamins C and E were associated with non-significantly reduced risks of right-sided serrated polyps compared to placebo but clearly had no effect on left sided lesions (Table 3). Calcium supplementation was not consistently associated with risk of either left or right-sided serrated polyps. Aspirin treatment was associated with a reduced risk of serrated polyps, particularly on the right-side (81 mg of aspirin RR 0.56 (95% CI 0.34–0.91); 325 mg of aspirin RR 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 lesion. Subjects randomized to folate had an increased risk of right-sided serrated polyps, particularly if advanced (RR 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 of both 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 RR 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 of serrated polyps.

Discussion

In this large, pooled analysis, we observed that several demographic, lifestyle and dietary factors were associated with the risk of serrated polyps. In the left colorectum, obesity, cigarette smoking, dietary fat, total energy intake, and red meat intake were related to an increased risk of any and/or advanced serrated polyps. In the right colorectum, family history of polyps and folate treatment were associated with risk of serrated lesions whereas aspirin treatment was associated with a reduced risk of serrated polyps. African American and Hispanic race were both associated with a decreased risk of right and left serrated polyps compared to 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 of 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 of left-sided lesions in our study and one other (18) but not in others (15, 17). The association between higher BMI and increased risk of 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 of serrated polyp. Our finding of a strong positive relationship for former and current smoking and left-sided serrated polyps is similar to 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 of proximal hyperplastic polyps among current smokers (16). For advanced proximal lesions, we did observe a non-significant 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 of both right and left-sided serrated lesions. Similar to our results, one other study (15) reported a lower risk of hyperplastic polyps for both African Americans and Hispanics compared to 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 to 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) may differ from traditional adenomas. For example, increasing age is consistently associated with risk of traditional adenomas (38) yet we and others (15, 18, 39) did not find an relationship between age and risk of serrated (or hyperplastic) polyps. Typically, traditional adenomas are more strongly associated with male gender (38) where

as 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) where as 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 to adenomas (15, 18, 31, 32, 39). Other variables, such as aspirin intake or calcium supplementation, appear 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 of 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 biologic 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, MSI positivity, methylation or loss of hMLH1 or MGMT, exaggerated crypt serration, excess mucin expression and evidence architectural ‘dysplasia’ rather than classic cytological 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 adenomas. The left-sided lesions tend to exhibit KRAS mutations, p53, p16, and 18qLOH chromosomal instability, and classic cytological dysplasia (5, 12, 13, 41). In future investigations it will be important to explore the relationship between the epidemiologic variables and risk of 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 perform 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 histological 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 pathological 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 may only be applicable to subjects with previous adenomas. Finally, the changing definition of the serrated polyp over time, the lack of a diagnostic re-review of the slides, as well as 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 physiological, morphological, 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 vs. 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 (47) discusses there is still considerable crosstalk 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.

Acknowledgments

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under grants CA037287, CA046927 and CA059005.

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Table 1

Baseline Characteristics of subjects participating in the polyp prevention studies:

Characteristic	Antioxidant Polyp Prevention Study[1] (n = 864)	Calcium Polyp Prevention Study[2] (n = 930)	Aspirin/Folate Polyp Prevention Study[3] (n = 1121)
Age—yrs. (sd)	61.2 ± 8.3	61.0 ± 9.1	57.5 ± 9.6
Male—no. (%).	684 (79.2)	672 (72.3)	409 (63.5)
Smoker—no. (%)	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
Beta-Carotene	208		
Vitamin C/E	217		
B, C/E	225		
Calcium 1200 mg		464	
Aspirin 80mg only			169
Aspirin 325 mg only			167
Aspirin 80mg/ 1 mg folate			175
Aspirin 325 mg/ 1 mg folate			171
Folate only 1 mg			170
Race—no. (%)			
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-calories/day (sd)	1955.0 (757.7)	2024 (758.6)	1634 (667.0)
Carbohydrates—g/day (sd)	201.7 (80.1)	219.5 (82.0)	185.9 (77.4)
Fat—total—g/day (sd)	86.2 (43.0)	87.7 (7)	65.1 (34.3)
Fiber—g/day (sd)	14.2 (7.2)	16.4 (7.9)	13.3 (6.0)
Folate—mg/day (sd)	314.3 (165.3)	331.3 (168.1)	319.9 (156.6)
Red meat intake—servings/day (sd)	0.54 (0.42)	0.48 (0.38)	0.36 (0.31)

[1] Study one was the Antioxidant Polyp Prevention Study (22);

[2] Study two was the Calcium Polyp Prevention Study (20);

[3] Study three the Aspirin Folate Polyp Prevention Study (21)

Table 2

Lifestyle and demographic factors and the risk of serrated polyps

Variables		Serrated Polyps					Advanced Serrated Polyps				
		Left		Right		P difference	Left		Right		P difference
	N Total	n cases	RR (95% CI)	n cases	RR (95% CI)		n cases	RR (95% CI)	n cases	(95% CI)	
Family history of polyps											
No	1997	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 CRC											
No	1831	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	2009	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	2412	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 (yrs.)											
< 61 years	1409	352	1.0	140	1.0		53	1.0	37	1.0	
≥ 61 years	1421	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
Body Mass Index (kg/m^2)											
<25	903	191	1.0	81	1.0		25	1.0	25	1.0	
25 to 29.9	1355	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	1027	163	1.0	95	1.0		22	1.0	23	1.0	
Former	1272	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

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Variables		Serrated Polyps				P difference	Advanced Serrated Polyps				P difference
		Left		Right			Left		Right		
	N Total	n cases	RR (95% CI)	n cases	RR (95% CI)		n cases	RR (95% CI)	n cases	(95% CI)	
Alcohol											
Non-drinker	856	192	1.0	85	1.0		24	1.0	19	1.0	
Drinker	1849	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

*RR adjusted for age, sex, center, treatment, time since randomization, study number, and smoking status (when not the stratifying variable)

+Results could not be calculated because model did not converge.

Table 3

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

Polyp Prevention Study (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		
Beta-carotene	208	47	0.90 (0.63–1.28)	17	0.64 (0.35–1.15)		1	--	0	--	
Vitamins C & E	220	58	1.06 (0.76–1.48)	18	0.62 (0.35–1.10)		0	--	2	--	
Beta-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

RR adjusted for age, sex, center, time since randomization, and smoking status

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Table 4

Dietary factors and the risk of serrated polyps

Dietary variables	N Total	Serrated Polyps					Advanced Serrated Polyps				
		Left		Right		P for right-left difference	Left		Right		P for right-left difference
		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	

Dietary variables	N Total	Serrated Polyps					Advanced Serrated Polyps				
		Left		Right		P for right-left difference	Left		Right		P for right-left difference
		n cases	RR* (95% CI)	n cases	RR* (95% CI)		n cases	RR* (95% CI)	n cases	RR* (95% CI)	
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	

*RR adjusted for age, sex, center, treatment, time since randomization, study number, smoking status, and log calories

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