Risk Factors for Hyperplastic and Adenomatous Polyps: Evidence for Malignant Potential?[1]

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Abstract

Recent studies have suggested that hyperplastic polyps may be benign precursor lesions for a distinct subset of colorectal tumors. We conducted a clinic-based case-control study to evaluate risk factors for hyperplastic polyps. Cases with hyperplastic polyps ($n = 219$), adenomas ($n = 437$), and both types of polyps ($n = 138$), along with colonoscopy-negative controls ($n = 708$), were identified at a gastroenterology practice in the Minneapolis area during 1991–1994. A self-administered questionnaire was used to collect risk factor information. Risk factors for hyperplastic and adenomatous polyps were generally similar to those for colorectal cancer. Male sex, smoking, and alcohol consumption were associated with increased risk of all polyp groups; nonsteroidal anti-inflammatory drug use, hormone replacement therapy use, and calcium intake were associated with reduced risk. There was no apparent association between increasing age and hyperplastic polyp risk ($P = 0.21$) in this analysis, although it was a strong risk factor for adenoma ($P < 0.001$). The odds ratio (OR) for hyperplastic polyps associated with >25 pack-years of smoking was 4.1 [95% confidence interval (CI), 2.2–7.6], whereas the OR for adenoma alone was 1.3 (95% CI, 0.8–2.3). The OR estimate for individuals diagnosed with both polyp types was 4.2 (95% CI, 1.9–9.3). These results suggest, as one possibility, that the consistent association of adenoma and smoking observed in previous studies may be partially attributable to the inclusion of individuals with both adenomas and hyperplastic polyps in the adenoma case group. To the contrary, individuals with both polyp types may be expressing a phenotype distinct from those who have only adenomas and should be considered separately. Further studies are necessary to establish which polyp phenotypes are related to smoking. Overall, the similarity of the risk profiles of colorectal hyperplastic polyps, adenoma, and cancer provides additional support for the growing body of evidence that some hyperplastic polyps may have neoplastic potential.

Introduction

Despite being the most common type of polyp detected in the human colon and rectum, relatively little is known about the etiology, natural history, or growth rate of hyperplastic polyps (1). The primary basis for the lack of interest and paucity of characterizing studies of these polyps is probably the long-accepted belief that hyperplastic polyps are benign lesions that have little or no potential for malignancy (2). Indeed, the American College of Gastroenterology has recommended that a hyperplastic polyp found at endoscopy is not an indication for subsequent colonoscopy (3).

Recent studies have suggested that hyperplastic polyps (and the histologically related serrated adenomas and mixed polyps) may either lie in the classic adenoma-carcinoma pathway for a subset of tumors or define a distinct mutator-phenotype pathway independent of adenomatous polyps (4). Such hypotheses should re-ignite interest in hyperplastic polyps, highlighting the dearth of epidemiological data. On a molecular level, hyperplastic polyps display features of neoplastic change that are intermediate between normal mucosa and adenomas or carcinomas, including proliferative activity, *p53* overexpression, and hypomethylation of the c-*myc* gene (5–12). It has also been found that hyperplastic polyps have a high frequency of *ras* mutations, generally considered to be an early event in carcinogenesis (11).

Three previous epidemiological studies have assessed lifestyle and dietary risk factors for hyperplastic polyps and found that they share common risk factors such as alcohol intake, cigarette smoking, BMI,[3] fiber intake, and NSAID use with colorectal adenomas and carcinomas (13–15). However, these studies were limited by small sample sizes and lack of data on several hypotheses, such as exogenous hormones and reproductive factors. We conducted a case-control study of hyperplastic and adenomatous polyps to further evaluate these established colorectal cancer risk factors, as well as to explore the relationships among other colon cancer risk factors such as reproductive factors and exogenous hormone use. Because we

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[3] The abbreviations used are: BMI, body mass index; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy; MET, metabolic equivalent; NSAID, nonsteroidal anti-inflammatory drug; WHR, waist:hip ratio; MSI, microsatellite instability.

ascertained the presence of both hyperplastic and adenomatous polyps in our study population, we were able to stratify polyp cases into three groups: cases with hyperplastic polyps only; cases with adenomatous polyps only; and cases with both types of polyps.

Subjects and Methods

Study Subjects. Subject recruitment for this case-control study has been described elsewhere (16). Briefly, cases and controls were recruited through a large multiclinic private gastroenterology practice, Digestive Healthcare, in the greater metropolitan Minneapolis-St. Paul area. Patients scheduled for colonoscopy at Digestive Healthcare clinics between April 1991 and April 1994 were screened for specific eligibility criteria and recruited for the study before colonoscopy. To be eligible, a subject must have: (*a*) resided in the Minneapolis-St. Paul metropolitan area; (*b*) been 30–74 years of age; (*c*) been able to speak English; (*d*) had no known genetic syndrome associated with a predisposition to colonic neoplasia; (*e*) reported no personal history of cancer (except nonmelanoma skin cancer); and (*f*) had no history of inflammatory bowel disease. Informed consent was obtained from all study subjects. Indications for colonoscopy included bleeding, follow-up to sigmoidoscopy or barium enema, family history, and screening; these were similar for hyperplastic polyps and controls, although adenoma patients were more likely to have had sigmoidoscopy follow-up or bleeding.

Eligible subjects were sent materials describing the study and self-administered questionnaires (including a food frequency questionnaire) before their clinic visit. At colonoscopy, the signed consent form and completed questionnaires were collected, and blood was drawn. Colonoscopy findings were recorded on standardized forms. Polyp size was measured *in vivo* by comparison of the polyp with a fully opened standard-sized flexible colonoscopy forceps. Upon removal, polyps were examined histologically by the study pathologist. Investigators were blind to the final diagnosis. Only participants with a complete colonoscopy reaching the cecum were eligible for the study.

Data Collection. Information on physical activity, smoking habits, anthropometry, medical history, reproductive history and exogenous hormone use (women), demographic information, and family history of polyps and cancer was collected in a structured, close-ended format using self-administered questionnaires before knowledge of the diagnosis by the subject. Dietary history was assessed using an adaptation of the Willett semiquantitative food frequency questionnaire, which has been evaluated for reliability and validity (17–19). Multivitamin and individual supplement use and dietary intake were recorded to quantify total daily nutrient intake. When data items were incomplete, study staff followed up the participants by phone.

Pathology. All removed polyps were examined histologically by the study pathologist using diagnostic criteria established for the National Polyp Study (20). Study participants were subsequently categorized into one of three groups: adenomatous polyp only ($n = 438$); hyperplastic polyp only ($n = 219$); and both adenomatous and hyperplastic polyps ($n = 138$). The control group ($n = 708$) comprised individuals whose colonoscopy detected no polyps or other pathology. Participants with polyps showing invasive carcinoma were excluded from the study. The participation rate for all eligible patients who had had a complete colonoscopy was 68%.

Statistical Analysis. ORs were used to evaluate the association between each exposure and each polyp histology (specifically, the hyperplastic polyp group, the adenomatous polyp group, and the group presenting with both types were each compared with the common control group). By use of Stata 6.0 for Windows (Stata Corp., College Station, TX) statistical software, polytomous logistic regression was performed to compute ORs and 95% CIs. The unadjusted association between each risk factor and polyps was evaluated, followed by the age-adjusted relationship between each risk factor and polyps. Potential confounders were evaluated by first fitting a full multivariate model with all potential confounders and then eliminating factors separately to evaluate the effect on the OR (of any group of polyp cases) of interest. Only covariates that altered the OR by 10% were included as confounders. Covariates evaluated as potential confounders were age, sex, race/ethnicity, HRT use (ever/never), BMI (kg/m^2), WHR, pack-years of smoking, regular aspirin use (at least one tablet/week for at least a year), regular NSAID use, MET-hours of recent physical activity (21), intake: of dietary fiber, percentage of kilocalories from fat, vitamin B_6, vitamin B_{12}, folate, methionine, and alcohol. Variables retained for multivariate adjustment were age, sex, BMI, percentage of kilocalories from fat, dietary fiber intake (g), HRT use, pack-years of smoking, dietary intake of folate, vitamin B_6, vitamin B_{12}, methionine, and alcohol. All adjustment variables were included in the model as continuous variables except for HRT use and sex. Tests for trend between each categorical variable and polyp were evaluated. Associations for anthropometric characteristics (BMI and WHR) and physical activity were stratified by sex. All significance tests were two-sided.

Results

Case and control groups were similar with respect to education (Table 1). Age was strongly associated with a diagnosis of adenomatous polyps and of presenting with both types of polyps, and there was only a slight suggestion of an association with hyperplastic polyps. Being female was associated with a reduced risk of all three classes of polyp diagnosis.

The relationship between anthropometric characteristics and physical activity with polyps was analyzed separately for men and women (Table 2). Among men, a higher BMI and WHR were associated with an increased risk of hyperplastic polyps, adenomas, and presentation with both types of polyps. The relationship between physical activity and polyp risk, however, appeared to differ by group of polyp; there was a suggestion of an inverse association between total and vigorous physical activity (data not shown for vigorous physical activity) and risk of hyperplastic polyps, but adenoma and presentation with both appeared unrelated. The relationship among women was even more inconsistent. There was a suggestion that high WHR may be associated with increased risk of hyperplastic polyps and presentation with both types of polyp cases, but not adenoma. High BMI was unrelated to polyp risk in any group of women. There was a trend toward increased risk for hyperplastic polyps and presentation with both types of polyps with increasing physical activity.

Although cases and controls were similar with respect to most dietary intakes of nutrients for all groups of polyp cases, those with adenomas and with presentation with both were less likely than controls to use multivitamins. All three groups of polyp cases were more likely to be current smokers and heavier alcohol consumers and less likely to be regular NSAIDS users than polyp-free controls. Table 3 shows the multivariate-adjusted ORs and 95% CIs for these diet and lifestyle factors. High calcium intake from both diet and supplements (>1275

Table 1 Demographic characteristics and polyp risk

	Controls *n* (%)	Cases with hyperplastic polyps (n = 219)					Cases with adenomatous polyps (n = 437)					Cases with both types of polyps (n = 138)				
		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted	
			OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]
Age[b]																
<40	91 (13)	23 (11)	1.0		1.0		23 (5)	1.0		1.0			1.0			
40–49	182 (26)	43 (20)	0.9	0.5–1.6	0.9	0.4–2.3	71 (16)	1.5	0.9–2.6	2.5	1.0–5.9	15 (11)	3.1	0.7–14.0	1.0	
50–59	220 (31)	84 (38)	1.5	0.9–2.5	1.6	0.7–3.7	134 (31)	2.3	1.4–3.9	4.0	1.7–9.3	47 (34)	9.3	2.2–39.3	5.3	1.7–16.9
60–69	170 (24)	57 (26)	1.3	0.8–2.3	1.4	0.6–3.2	162 (37)	3.8	2.3–6.3	6.0	2.6–13.7	55 (40)	14.8	3.5–62.2	4.9	1.5–15.8
70+	45 (6)	12 (6)	1.1	0.5–2.3	1.6	0.5–5.0	47 (11)	4.2	2.2–7.8	7.0	2.5–19.0	21 (15)	21.5	4.8–96.3	20.0	5.7–70.0
P			0.88		0.21			<0.001		<0.001			<0.001		<0.001	
Sex																
Male	270 (38)	122 (56)	1.0		1.0		264 (60)	1.0		1.0		92 (67)	1.0		1.0	
Female	438 (62)	97 (44)	0.5	0.4–0.7	0.6	0.5–0.9	173 (40)	0.4	0.3–0.5	0.4	0.3–0.6	46 (33)	0.3	0.2–0.4	0.4	0.3–0.6
P			<0.001		0.01			<0.001		<0.001			<0.001		<0.001	
Education																
≤12 yr	236 (33)	76 (35)	1.0		1.0		157 (36)	1.0		1.0		57 (41)	1.0		1.0	
12+ yr	472 (67)	143 (65)	0.9	0.7–1.3	0.7	0.5–1.2	280 (64)	1.0	0.7–1.2	0.9	0.6–1.3	81 (59)	0.8	0.5–1.2	1.0	0.5–1.9
P			0.59		0.23			0.71		0.54			0.22		0.99	

[a] Multivariate adjustment for age, sex, BMI, HRT (yes/no), smoking (pack-years), and alcohol, where appropriate.
[b] Because of the small cell size, the <40 and 40–49 groups were collapsed for those with both kinds of polyps in the multivariate-adjusted model.

mg/day) appeared to be associated with a decreased risk of both hyperplastic polyps and presentation with both types, but not adenomas. Intakes of other dietary nutrients (fat, folate, vitamin D, and multivitamins) were, for the most part, not associated with polyp risk of any type. Risk for all groups of polyp cases was associated with both current smoking and pack-years of smoking. Smoking was most strongly related to risk of hyperplastic polyps and of presentation with both. Alcohol consumption was associated with an increased risk of both adenomatous polyps and presentation with both and, more weakly, with hyperplastic polyps. Regular nonaspirin NSAID use was inversely associated with all groups of polyp cases, although only statistically significantly so with adenoma. The findings for regular aspirin use showed a similar but weaker pattern for adenoma and presentation with both.

Table 4 shows the multivariate-adjusted ORs and 95% CIs for hormonal and reproductive factors. HRT use (current or former) was associated with a statistically significantly reduced risk of adenomas, and there was also a suggestion that risk was reduced for hyperplastic polyps and for presentation with both. Oral contraceptive use, parity, and age at first live birth were not associated with polyp risk in any group.

Discussion

The results from this study suggest that colonoscopy patients who present with hyperplastic polyps, with adenomas, and with both types share many risk factors with each other and with colorectal cancer (22–24). Being male, smoking, and alcohol consumption are associated with an increased risk of polyps, whereas regular NSAID use, HRT use, and high calcium intake are associated with reduced risk. The strength of associations for hyperplastic polyps appeared to be somewhat attenuated for these risk factors, relative to adenomas. Such differences might be explained if the specific molecular steps in progression, and even the likelihood of progression, vary somewhat by polyp type and these, in turn, are modified by different host and environmental factors. To our knowledge, the current study is the first analysis comparing all three groups of subjects with polyps and their associations with a wide array of risk factors for colorectal cancer within one study population.

Age was a strong risk factor for adenomas and for presenting with both kinds of polyps but was not statistically associated with hyperplastic polyps alone. Previous studies have observed, as we did, that the average age of hyperplastic polyp cases is younger than that for adenomas (23). Although it appears from our data that risk of hyperplastic polyps, unlike most neoplastic events, is unrelated to age, this relationship may have been obscured because our clinic-based sampling did not represent a random sample of the population.

Previous research indicates that various measures of obesity, in addition to physical activity, may be important in colon cancer etiology (24). The relationship between BMI, WHR, and physical activity and polyp risk differed by sex. High BMI and WHR were associated with an increased risk of all case groups among men, but not women. These findings are similar to those found in a previous case-control study of hyperplastic polyps (15), although that study did not analyze men and women separately. Frequent physical activity was inversely related to hyperplastic polyp risk among men, although there was a suggestion of a positive association among women. In previous studies, physical inactivity was associated adenoma risk, especially large adenomas (>1 cm; Refs. 25, 26). In the current study, there was little suggestion that physical activity and adenomas were related, although this relationship was not analyzed by polyp size. Although Martinez *et al.* (15) found a strong inverse association between high physical activity and hyperplastic polyp risk, the small numbers of cases in that study may have precluded stratified analyses, obscuring any interaction by sex. The positive association of adenoma with BMI and WHR among men that we found in our study has also been observed in other studies (26, 27). The relationship of weight, physical activity, and polyps/colon cancer is a complex one and differs markedly by sex (28, 29).

In the current study, calcium intake appeared to be associated with a reduced risk of hyperplastic polyps and of presenting with both types of polyps. This inverse relationship was also seen in a previous case-control analysis of hyperplastic polyps, in which both dietary fiber and calcium significantly reduced risk (15). Contrary to results from a previous prospective study of dietary risk factors of hyperplastic polyps (14),

Table 2 Anthropometrics, physical activity, and polyp risks[a]

	Controls *n* (%)	Cases with hyperplastic polyps (*n* = 219)				Cases with adenomatous polyps (*n* = 437)				Cases with both types of polyps (*n* = 138)				
		Cases *n* (%)	Age-adjusted		Multivariate-adjusted		Cases *n* (%)	Age-adjusted		Multivariate-adjusted		Cases *n* (%)	Age-adjusted		Multivariate-adjusted	
			OR	95% CI	OR[b]	95% CI[b]		OR	95% CI	OR[b]	95% CI[b]		OR	95% CI	OR[b]	95% CI[b]
MEN																
BMI (kg/m^2)																
<24.2	67 (25)	18 (15)	1.0		1.0		43 (17)	1.0		1.0		12 (13)	1.0		1.0	
24.2–26.4	66 (25)	23 (20)	1.3	0.6–2.6	1.3	0.6–2.6	57 (22)	1.3	0.8–2.2	1.2	0.7–2.1	24 (27)	2.0	0.9–4.3	1.8	0.9–4.0
26.5–29.6	67 (25)	43 (37)	2.4	1.3–4.6	2.2	1.2–4.3	87 (34)	2.1	1.3–3.5	2.2	1.3–3.7	23 (26)	2.1	0.9–4.6	1.9	0.8–4.3
29.7+	65 (25)	33 (28)	1.9	1.0–3.7	1.7	0.9–3.4	71 (28)	1.8	1.1–3.0	1.6	1.0–2.8	30 (34)	2.8	1.3–6.1	2.6	1.2–5.6
P			0.02		0.04			0.01		0.02			0.01		0.02	
WHR																
<0.91	69 (26)	15 (13)	1.0		1.0		35 (13)	1.0		1.0		9 (10)	1.0		1.0	
0.91–0.95	52 (19)	28 (24)	2.5	1.2–5.1	2.3	1.1–4.9	60 (23)	2.0	1.2–3.6	1.9	1.1–3.4	16 (18)	2.0	0.8–5.1	2.1	0.8–5.4
0.96–1.0	83 (31)	41 (34)	2.3	1.1–4.4	1.9	0.9–3.9	84 (32)	1.7	1.0–2.8	1.5	0.9–2.6	25 (28)	1.8	0.8–4.2	1.7	0.7–4.2
1.1+	63 (24)	35 (29)	2.5	1.3–5.1	1.6	0.7–3.5	82 (31)	2.1	1.3–3.6	1.7	0.9–3.2	40 (44)	3.8	1.7–8.5	3.0	1.2–7.7
P			0.02		0.44			0.02		0.18			<0.01		0.02	
Physical activity (MET-hours of physical activity)																
<12.3	68 (25)	37 (30)	1.0		1.0		70 (27)	1.0		1.0		21 (23)	1.0		1.0	
12.3–24.7	68 (25)	32 (26)	0.9	0.5–1.5	0.9	0.5–1.6	65 (25)	0.9	0.5–1.4	0.9	0.5–1.4	24 (26)	1.1	0.5–2.1	1.1	0.6–2.3
24.8–46.9	67 (25)	26 (21)	0.7	0.4–1.3	0.7	0.4–1.4	50 (19)	0.7	0.4–1.2	0.8	0.5–1.3	20 (22)	1.0	0.5–2.0	1.0	0.5–2.2
47.0+	67 (25)	27 (22)	0.7	0.4–1.3	0.7	0.3–1.2	78 (30)	1.0	0.6–1.7	1.0	0.6–1.6	27 (29)	1.1	0.6–2.2	1.1	0.5–2.1
P			0.25		0.15			0.96		0.86			0.80		0.99	
WOMEN																
BMI (kg/m^2)																
<22.7	103	26	1.0		1.0		44	1.0		1.0		7	1.0		1.0	
22.7–25.8	107	19	0.8	0.4–1.6	0.8	0.4–1.7	41	0.6	0.4–1.1	0.7	0.4–1.2	11	1.0	0.4–2.7	1.2	0.4–3.3
25.9–29.8	109	24	1.0	0.5–1.7	0.9	0.5–1.7	44	0.9	0.5–1.4	0.8	0.5–1.4	17	1.5	0.7–3.4	1.8	0.8–4.1
29.9+	105	27	1.2	0.7–2.1	1.1	0.6–2.0	41	0.8	0.5–1.3	0.8	0.5–1.3	11	1.0	0.4–2.5	1.1	0.5–2.8
P			0.56		0.72			0.46		0.43			0.68		0.55	
WHR																
<0.76	96	15	1.0		1.0		40	1.0		1.0		4	1.0		1.0	
0.76–0.82	119	22	1.5	0.9–2.5	1.3	0.7–2.4	36	1.0	0.6–1.5	0.9	0.5–1.4	7	1.8	0.8–4.2	1.4	0.6–3.5
0.83–0.89	110	33	1.0	0.5–1.9	0.9	0.4–1.8	54	0.8	0.5–1.3	0.7	0.4–1.3	17	1.7	0.6–4.2	1.6	0.6–4.4
0.90+	103	24	1.7	0.8–3.9	1.2	0.5–3.2	40	0.5	0.2–1.1	0.4	0.2–1.1	17	1.8	0.6–5.8	1.4	0.4–5.1
P			0.43		0.99			0.08		0.06			0.28		0.50	
Physical activity (MET-hours of physical activity)																
<11	111	23	1.0		1.0		41	1.0		1.0		7	1.0		1.0	
11–23.4	109	18	0.8	0.4–1.6	1.0	0.5–2.1	42	0.8	0.5–1.3	0.7	0.4–1.3	11	1.4	0.5–3.6	1.3	0.5–3.8
23.5–41.1	109	21	1.2	0.6–2.2	1.5	0.8–2.9	49	1.1	0.7–1.7	1.0	0.6–1.6	10	1.7	0.7–4.1	1.8	0.7–4.8
41.2+	109	35	1.5	0.8–2.7	1.7	0.9–3.2	41	0.9	0.5–1.4	0.7	0.4–1.2	18	1.9	0.8–4.7	2.1	0.8–5.3
P			0.12		0.07			0.84		0.35			0.13		0.09	

[a] Quartiles of BMI, WHR, and physical activity were determined based on the distribution among controls of each sex.
[b] Multivariate adjustment for age, BMI, HRT (yes/no), smoking (pack-years), and alcohol, where appropriate.

folate intake was not significantly associated with reduced risk in this analysis.

To our knowledge, this is the first epidemiological study to analyze the relationship of exogenous hormone use, reproductive factors, and hyperplastic polyp risk. Although the majority of studies suggest a role for reproductive factors for adenoma and carcinoma (24), parity and age at first birth were not associated with risk of hyperplastic polyps or presentation with both. HRT use is consistently associated with an approximate halving of risk of both adenoma and colon cancer (16, 30, 31), and in the current study, HRT use was associated with a reduced risk of hyperplastic polyps as well, although to a lesser degree than adenoma.

Both current smoking and pack-years of cigarettes were associated with increased risk for hyperplastic polyps and presentation with both, but the association with adenomas was weak (current smoking) or null, even for long duration of smoking. Although the association between smoking and hyperplastic polyps has been observed in previous studies (14, 15), the observation that adenomas are only weakly, if at all, related to smoking contradicts a relatively strong and consistent relationship in colorectal adenoma etiology. Previous epidemiological studies [including an earlier analysis of these data (22)] have almost universally found that long-term, heavy cigarette smoking is associated with a 2–3-fold elevated risk of colorectal adenoma (32). In the present analysis, we differentiated individuals with only adenomatous polyps from those who presented with both adenomatous and hyperplastic polyps. The absence of a relationship between smoking and adenoma, along with the strongly positive association between smoking and hyperplastic polyps and presentation with both, suggests the possibility that the consistently observed association of adenoma and smoking in the literature may be attributable to the heterogeneity of the adenoma case group, as it is usually defined. Other studies, including our own previous reports (33, 34), considered the important aspect of the joint presentation to be adenomas. The marked difference in findings between those with and without hyperplastic polyps (irrespective of adenomas) in this study suggest that the association between adenoma and smoking may be partially attributable to the inclusion of

Table 3 Diet and lifestyle factors and polyp risk

	Controls *n* (%)	Cases with hyperplastic polyps (n = 219)				Cases with adenomatous polyps (n = 437)					Cases with both types of polyps (n = 138)				
		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted		Cases *n* (%)	Age- and sex-adjusted		Multivariate-adjusted	
			OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]
Percentage of calories from fat[b]																
<26	166 (24)	47 (22)	1.0		1.0		101 (23)	1.0		1.0		22 (16)	1.0		1.0	
26–30	168 (24)	46 (22)	0.9	0.6–1.5	0.8	0.4–1.6	93 (22)	0.9	0.6–1.3	1.0	0.6–1.7	20 (15)	0.9	0.4–1.6	0.7	0.3–2.0
31–35	181 (26)	56 (26)	1.0	0.6–1.5	1.3	0.7–2.4	132 (31)	1.0	0.7–1.5	1.1	0.7–1.8	54 (40)	1.9	1.1–3.3	2.2	1.0–5.2
36+	173 (25)	65 (30)	1.2	0.8–1.9	1.1	0.6–2.0	105 (24)	1.0	0.7–1.4	0.6	0.3–1.1	40 (29)	1.7	1.0–3.1	1.2	0.5–3.2
P			0.35		0.59			0.96		0.16			0.01		0.24	
Percentage of calories from fat[b]																
<235	172 (25)	52 (24)	1.0		1.0		99 (23)	1.0		1.0		36 (26)	1.0		1.0	
235–340	173 (25)	64 (30)	1.1	0.7–1.7	1.1	0.6–2.0	123 (28)	1.1	0.8–1.6	1.2	0.7–2.0	35 (26)	0.8	0.5–1.3	0.5	0.2–1.4
341–570	173 (25)	49 (23)	0.9	0.6–1.4	1.0	0.5–2.0	123 (28)	1.1	0.8–1.6	1.2	0.7–2.1	39 (29)	0.9	0.6–1.5	1.3	0.6–2.9
571+	170 (25)	49 (23)	0.9	0.6–1.4	1.3	0.7–2.5	86 (20)	0.8	0.5–1.1	1.0	0.6–1.7	26 (19)	0.6	0.4–1.1	0.7	0.3–1.9
P			0.44		0.44			0.25		0.91			0.18		0.95	
Vitamin D (IU/day)[b]																
<135	172 (25)	51 (24)	1.0		1.0		91 (21)	1.0		1.0		44 (32)	1.0		1.0	
135–270	173 (25)	54 (25)	0.9	0.6–1.5	1.1	0.5–2.0	133 (31)	1.2	0.8–1.7	1.5	0.9–2.6	36 (26)	0.6	0.4–1.0	0.6	0.2–1.3
271–460	172 (25)	46 (22)	0.8	0.5–1.3	1.0	0.5–2.0	98 (23)	0.9	0.6–1.3	1.3	0.7–2.2	27 (20)	0.5	0.3–0.8	0.5	0.2–1.3
461+	171 (25)	63 (29)	1.2	0.7–1.8	1.6	0.8–2.9	109 (25)	1.0	0.7–1.4	1.3	0.7–2.2	29 (21)	0.5	0.3–0.9	0.5	0.2–1.2
P			0.57		0.17			0.57		0.58			0.01		0.09	
Calcium (mg/day)[b]																
<600	173 (25)	58 (27)	1.0		1.0		117 (27)	1.0		1.0		43 (32)	1.0		1.0	
600–900	172 (12)	69 (14)	1.2	0.8–1.7	1.0	0.5–1.8	108 (25)	0.9	0.6–1.2	0.9	0.5–1.6	41 (30)	0.9	0.6–1.5	0.8	0.4–1.8
901–1275	171 (38)	45 (29)	0.8	0.5–1.2	0.8	0.4–1.4	94 (22)	0.8	0.5–1.1	0.8	0.5–1.4	26 (19)	0.5	0.3–1.0	0.2	0.1–0.7
1276+	172 (25)	42 (20)	0.7	0.5–1.1	0.6	0.3–1.1	112 (26)	0.9	0.6–1.3	1.2	0.7–2.0	26 (19)	0.6	0.3–1.0	0.5	0.2–1.3
P			0.05		0.08			0.47		0.66			0.01		0.04	
Multivitamin use (folate, B_6, B_{12})																
No	445 (68)	144 (69)	1.0		1.0		314 (76)	1.0		1.0		108 (81)	1.0		1.0	
Yes	207 (32)	65 (31)	1.1	0.8–1.5	1.3	0.8–2.2	102 (24)	0.7	0.6–1.0	0.8	0.5–1.2	25 (19)	0.5	0.3–0.9	0.9	0.4–1.8
P			0.78		0.23			0.04		0.28			0.01		0.72	
Smoking status																
Never	334 (45)	46 (21)	1.0		1.0		158 (36)	1.0		1.0		30 (22)	1.0		1.0	
Former	270 (38)	105 (48)	2.5	1.7–3.7	2.5	1.4–4.4	201 (46)	1.3	1.0–1.7	1.6	1.1–2.5	67 (48)	2.1	1.3–3.5	1.4	0.6–3.3
Current	104 (15)	68 (31)	4.7	3.0–7.4	4.1	2.2–7.6	78 (18)	1.7	1.2–2.5	1.3	0.8–2.3	41 (30)	5.5	3.2–9.6	6.1	2.8–13.5
P			<0.001		<0.001			<0.01		0.12			<0.001		<0.001	
No. of pack-years																
0	339 (48)	49 (23)	1.0		1.0		162 (38)	1.0		1.0		30 (22)	1.0		1.0	
>0–25	222 (32)	82 (38)	2.5	1.7–3.7	2.1	1.2–3.7	146 (34)	1.3	1.0–1.8	1.5	1.0–2.3	47 (35)	2.4	1.4–3.9	2.0	0.9–4.5
26+	142 (20)	86 (40)	3.7	2.5–5.6	4.8	2.6–8.6	124 (29)	1.5	1.1–2.0	1.3	0.8–2.3	59 (43)	3.7	2.2–6.0	4.2	1.9–9.3
P			<0.001		<0.001			0.01		0.14			<0.001		<0.001	
Alcohol (g/day)																
0	199 (28)	47 (22)	1.0		1.0		122 (28)	1.0		1.0		36 (26)	1.0		1.0	
>0–7	397 (56)	116 (53)	1.3	0.9–1.9	1.4	0.8–2.5	204 (47)	1.0	0.8–1.4	1.2	0.8–1.9	60 (44)	1.1	0.7–1.7	1.1	0.5–2.4
8+	110 (16)	56 (26)	1.8	1.2–2.9	1.6	0.7–3.9	111 (25)	1.5	1.0–2.1	2.2	1.1–4.3	42 (30)	1.9	1.1–3.3	3.3	1.2–8.8
P			0.01		0.20			0.06		0.04			0.02		0.05	
Regular nonaspirin NSAID use																
No	561 (80)	184 (84)	1.0		1.0		390 (90)	1.0		1.0		117 (85)	1.0		1.0	
Yes	143 (20)	34 (16)	0.8	0.5–1.2	0.6	0.3–1.1	45 (10)	0.5	0.4–0.8	0.4	0.2–0.7	21 (15)	0.9	0.6–1.5	0.7	0.3–1.6
P			0.29		0.10			<0.01		<0.01			0.74		0.38	
Regular aspirin use																
No	485 (69)	153 (70)	1.0		1.0		304	1.0		1.0		107 (78)	1.0		1.0	
Yes	222 (31)	66 (30)	0.9	0.6–1.2	1.0	0.6–1.6	132	0.8	0.6–1.0	0.7	0.5–1.1	31 (22)	0.5	0.3–0.7	0.6	0.3–1.3
P			0.45		0.93			0.07		0.13			<0.01		0.18	

[a] Multivariate adjustment for age, sex, BMI, HRT (yes/no), smoking (pack-years), and alcohol, where appropriate.
[b] Quartiles of nutrient intake were determined based on the distribution among controls.

individuals with both adenomas and hyperplastic polyps in the adenoma case group. To the contrary, individuals with both polyp types may be expressing a phenotype distinct from those who have only adenomas and should be considered separately. Additional studies, examining the relationship of individuals with their different patterns of presentations, as well as those with serrated adenomas (35) and smoking, may provide information to further clarify the smoking-polyp relationship.

Unlike the adenoma-carcinoma sequence attributable to alterations of the APC (adenomatous polyposis coli)/β-catenin pathway (36), precursor lesions of MSI tumors have not been well defined. Several authors have postulated that right-sided hyperplastic polyps may give rise to sporadic colorectal carcinomas, specifically those with MSI (37, 38). In this model, right-sided hyperplastic polyps progress to carcinoma through a series of genetic and pathologic changes, including *hMLH1*

Table 4 Hormonal and reproductive factors and polyp risks

	Controls *n* (%)	Cases with hyperplastic polyps ($n = 97$)				Cases with adenomatous polyps ($n = 173$)					Cases with both types of polyps ($n = 46$)				
		Cases *n* (%)	Age-adjusted		Multivariate-adjusted		Cases *n* (%)	Age-adjusted		Multivariate-adjusted		Cases *n* (%)	Age-adjusted		Multivariate-adjusted	
			OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]		OR	95% CI	OR[a]	95% CI[a]
Ever use HRT																
No	206 (49)	54 (57)	1.0		1.0		103 (61)	1.0		1.0		24 (54)	1.0		1.0	
Yes	218 (51)	40 (43)	0.6	0.4–1.0	0.7	0.4–1.1	65 (39)	0.5	0.3–0.7	0.5	0.3–0.7	20 (46)	0.6	0.3–1.1	0.7	0.3–1.2
P			0.04		0.09			<0.001		<0.001			0.11		0.19	
Ever use oral contraceptives																
No	170 (39)	44 (46)	1.0		1.0		84 (49)	1.0		1.0		22 (48)	1.0		1.0	
Yes	261 (61)	52 (54)	0.9	0.5–1.4	0.9	0.5–1.5	87 (51)	1.0	0.6–1.4	1.2	0.8–1.9	24 (52)	1.6	0.8–3.3	1.9	0.9–4.1
P			0.43		0.67			0.79		0.45			0.20		0.08	
Parity																
0	66 (15)	14 (14)	1.0		1.0		21 (12)	1.0		1.0		7 (15)	1.0		1.0	
1 or 2	152 (35)	35 (36)	1.1	0.5–2.1	1.1	0.5–2.3	66 (38)	1.4	0.8–2.5	1.4	0.8–2.6	11 (24)	0.7	0.3–1.9	0.7	0.3–2.0
3 or 4	157 (36)	36 (37)	1.0	0.5–1.9	1.0	0.5–2.1	56 (32)	0.7	0.5–1.7	0.9	0.5–1.6	19 (41)	0.9	0.3–2.2	0.8	0.3–2.0
5 or more	64 (14)	12 (12)	0.7	0.3–1.7	0.7	0.3–1.7	30 (17)	1.0	0.5–2.0	1.0	0.5–2.1	9 (20)	0.8	0.3–2.4	0.6	0.2–1.8
P			0.43		0.45			0.43		0.40			0.91		0.41	
Age at first live birth																
<20	87 (23)	22 (26)	1.0		1.0		26 (17)	1.0		1.0		8 (20)	1.0		1.0	
20–24	177 (48)	34 (41)	0.7	0.4–1.3	0.7	0.4–1.4	80 (53)	1.3	0.8–2.3	1.4	0.8–2.4	22 (56)	1.0	0.4–2.5	1.1	0.4–2.7
25–29	78 (21)	22 (26)	1.1	0.6–2.2	1.4	0.7–2.8	36 (24)	1.5	0.8–2.7	1.7	0.9–3.2	7 (18)	0.8	0.3–2.5	1.1	0.4–3.5
30 or older	31 (8)	5 (6)	0.7	0.2–1.9	0.6	0.2–1.8	10 (7)	1.0	0.4–2.3	1.1	0.5–2.8	2 (5)	0.6	0.1–2.9	0.7	0.1–3.8
P			0.91		0.97			0.59		0.36			0.49		0.86	

[a] Multivariate adjustment for age, BMI, HRT (yes/no), smoking (pack-years), and alcohol, where appropriate.

promoter methylation, *hMLH1* loss, and MSI (37, 39, 40). Such a model, describing an alternative pathway to colorectal cancer, provides a plausible explanation for the observed absence of sporadic adenomas with MSI. Our current study, in which a strong association between smoking and hyperplastic polyps was observed, along with our recent report (41), in which smoking was found to be associated with MSI positivity in colon tumors, may provide epidemiological evidence to support the hypothesis that hyperplastic polyps may be precursor lesions along such a pathway that leads to some MSI-positive tumors.

The strengths of this study include its specific focus on both hyperplastic polyps as well as adenoma, giving us the ability to compare different polyp types within the same population and the same analysis. The selection of a control group that was drawn from the same clinic and that had undergone complete colonoscopy as well decreases the possibility of misclassification of controls who may have a higher prevalence of asymptomatic polyps (42). Standardized pathology review provided complete ascertainment of polyp type, allowing us to separate those presenting with both kinds of polyps as a unique group; in the past, other studies may have generally included this presentation with adenomas.

Limitations of this study include the relatively small sample size of the hyperplastic group and those with both pathologies ($n = 219$ and 138, respectively), especially in our analyses that are stratified by sex. Although comparable with, or larger than, most previous studies, it is possible that some associations in our study were masked because of insufficient power. We were unable to evaluate other pathological and molecular characteristics, such as polyp size, location, and MSI. Many of the recent studies reporting evidence for the neoplastic potential of hyperplastic polyps have been limited to large, right-sided lesions, and our inability to distinguish between various types of hyperplastic polyps in this heterogeneous group precluded our evaluation of this type of lesion. The results of this study may be limited by its clinic-based setting; because only those who underwent colonoscopy were eligible for this study, the population may not be representative of the general population. In particular, controls who have a reason to seek colonoscopic examination, such as worry over family history, are overrepresented in our study population and may bias our estimates of the association between risk factors and polyp risk. Finally, the relatively low response rate in our study may have affected the validity of our estimates. However, pathology information (and therefore, case-control status) was unknown at the time of the subjects' enrollment, making differences in response rates between case groups and controls, and the possibility of selection bias, unlikely.

The results of this study suggest that hyperplastic polyps, adenomas, and the presence of both are associated with similar lifestyle-related risk factors, and these are generally concordant with those found for colorectal carcinoma (43); differences in risk factor patterns include age and smoking. Because some hyperplastic polyps may be precursor lesions for malignancy, knowledge of factors that may predict their occurrence will become important to increase understanding of their etiology and biology.

References

1. Joss, J. R. Nature and clinical significance of colorectal hyperplastic polyp. Semin Colon Rectal Surg., *2:* 246–252, 1991.

2. Winawer, S. J., Fletcher, R. H., Miller, L., Godlee, F., Stolar, M. H., Mulrow, C. D., Woolf, S. H., Glick, S. N., Ganiats, T. G., Bond, J. H., Rosen, L., Zapka, J. G., Olsen, S. J., Giardiello, F. M., Sisk, J. E., Van Antwerp, R., Brown-Davis, C., Marciniak, D. A., and Mayer, R. J. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology, *112:* 594–642, 1997.

3. Bond, J. H. Polyp guideline: diagnosis, treatment, and surveillance for patients with nonfamilial colorectal polyps. Ann. Intern. Med., *119:* 836–843, 1993.

4. Hamilton, S. R. Origin of colorectal cancers in hyperplastic polyps and serrated adenomas: another truism bites the dust. J. Natl. Cancer Inst., *93:* 1282–1283, 2001.

5. Polyak, K., Hamilton, S. R., and Vogelstein, B. Early alteration of cell-cycle-regulated gene expression in colorectal neoplasia. Am. J. Pathol., *149:* 381–387, 1996.

6. Kang, M., Mitomi, H., and Sada, M. Ki-67, p53, and Bcl-2 expression of serrated adenomas of the colon. Am. J. Surg. Pathol., *21:* 417–423, 1997.

7. Risio, M., Coverlizza, S., and Ferrari, A. Immunohistochemical study of epithelial cell proliferation in hyperplastic polyps, adenomas, and adenocarcinomas of the large bowel. Gastroenterology, *94:* 899–906, 1988.

8. Bosari, S., Moneghini, L., and Graziani, D. Bcl-2 oncoprotein in colorectal hyperplastic polyps, adenomas, and adenocarcinomas. Hum. Pathol., *26:* 534–540, 1995.

9. Sinicrope, F. A., Ruan, S. B., and Cleary, K. R. Bcl-2 and p53 oncoprotein expression during colorectal tumorigenesis. Cancer Res., *55:* 237–241, 1995.

10. Kaklamanis, L., Savage, A., and Mortenson, N. Early expression of bcl-2 protein in the adenoma-carcinoma sequence of colorectal neoplasia. J. Pathol., *179:* 10–14, 1996.

11. Otori, K., Oda, Y., and Sugiyama, K. High frequency of K-ras mutation in human colorectal hyperplastic polyps. Gut, *40:* 660–663, 1997.

12. Kikuchi, Y., Dinjens, W. N., and Bosman, F. T. Proliferation and apoptosis in proliferative lesions of the colon and rectum. Virchows Arch., *431:* 111–117, 1997.

13. Zahm, S. H., Cocco, P., and Blair, A. Tobacco smoking as a risk factor for colon polyps. Am. J. Public Health, *81:* 846–849, 1991.

14. Kearney, J., Giovannucci, E., Rimm, E. B., Stampfer, M., Colditz, G. A., Ascherio, A., Bleday, R., and Willet, W. C. Diet, alcohol, and smoking and the occurrence of hyperplastic polyps of the colon and rectum (United States). Cancer Causes Control, *6:* 45–56, 1995.

15. Martinez, M. E., McPherson, R. S., Levin, B., and Glober, G. A. A case-control study of dietary intake and other lifestyle risk factors for hyperplastic polyps. Gastroenterology, *113:* 423–429, 1997.

16. Potter, J. D., Bostick, R. M., Grandits, G. A., Fosdick, L., Elmer, P., Wood, J., Grambsch, P., and Louis, T. A. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. Cancer Epidemiol. Biomark. Prev., *5:* 779–784, 1996.

17. Willett, W. C., Sampson, L., Stampfer, M. J., Rosner, B., Bain, C., Witschi, J., Hennekens, C. H., and Speizer, F. E. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am. J. Epidemiol., *122:* 51–65, 1985.

18. Munger, R. G., Folsom, A. R., Kushi, L. H., Kaye, S. A., and Sellers, T. A. Dietary assessment of older Iowa women with a food frequency questionnaire: nutrient intake, reproducibility, and comparison with 24-hour dietary recall interviews. Am. J. Epidemiol., *136:* 192–200, 1992.

19. Rimm, E. B., Giovannucci, E. L., Stampfer, M. J., Colditz, G. A., Litin, L. B., and Willett, W. C. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am. J. Epidemiol., *135:* 1114–1126, 1992.

20. O'Brien, M. J., Winawer, S. J., Zauber, A. G., Gottlieb, L. S., Sternberg, S. S., Diaz, B., Dickersin, G. R., Ewing, S., Geller, S., and Kasimian, D. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology, *98:* 371–379, 1990.

21. Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., and Paffenbarger, R. S. Compendium of physical activities: classification of energy costs of human physical activities. Med. Sci. Sports Exercise, *25:* 71–80, 1993.

22. Potter, J. D., Bigler, J., Fosdick, L., Bostick, R. M., Kampman, E., Chen, C., Louis, T. A., and Grambsch, P. Colorectal adenomatous and hyperplastic polyps: smoking and *N*-acetyltransferase 2 polymorphisms. Cancer Epidemiol. Biomark. Prev., *8:* 69–75, 1999.

23. Isbister, W. H. Hyperplastic polyps. Aust. NZ J. Surg., *63:* 175–180, 1993.

24. Potter, J. D., Slattery, M. L., Bostick, R., and Gapstur, S. M. Colon cancer: a review of the epidemiology. Epidemiol. Rev., *15:* 499–545, 1993.

25. Giovannucci, E. Activity, obesity, and colorectal adenoma. Cancer Causes Control, *7:* 253–263, 1996.

26. Giovannucci, E., Ascherio, A., Rimm, E. B., Colditz, G. A., Stampfer, M. J., and Willett, W. C. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann. Intern. Med., *122:* 327–334, 1995.

27. Kono, S., Handa, K., Hayabuchi, H., Kiyohara, C., Inoue, H., Marugame, T., Shinomiya, S., Hamada, H., Onuma, K., and Koga, H. Obesity, weight gain and risk of colon adenomas in Japanese men. Jpn. J. Cancer Res., *90:* 805–811, 1999.

28. Slattery, M. L., Potter, J., Caan, B., Edwards, S., Coates, A., Ma, K. N., and Berry, T. D. Energy balance and colon cancer—beyond physical activity. Cancer Res., *57:* 75–80, 1997.

29. Slattery, M. L., Potter, J. D., Curtin, K., Edwards, S., Ma, K. N., Anderson, K., Schaffer, D., and Samowitz, W. S. Estrogens reduce and withdrawal of estrogens increases risk of microsatellite instability-positive colon cancer. Cancer Res., *61:* 126–130, 2001.

30. Potter, J. D. Hormones and colon cancer. J. Natl. Cancer Inst., *87:* 1039–1040, 1995.

31. Grodstein, F., Newcomb, P. A., and Stampfer, M. J. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am. J. Med., *106:* 574–582, 1999.

32. Giovannucci, E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol. Biomark. Prev., *10:* 725–731, 2001.

33. Ulrich, C. M., Kampman, E., Bigler, J., Schwartz, S. M., Chen, C., Bostick, R., Fosdick, L., Beresford, S. A., Yasui, Y., and Potter, J. D. Colorectal adenomas and the C677T MTHFR polymorphism: evidence for gene-environment interaction? Cancer Epidemiol. Biomark. Prev., *8:* 659–668, 1999.

34. Kim, H. S., Newcomb, P. A., Ulrich, C. M., Keener, C. L., Bigler, J., Farin, F. M., Bostick, R. M., and Potter, J. D. Vitamin D receptor polymorphism and the risk of colorectal adenomas: evidence of interaction with dietary vitamin D and calcium. Cancer Epidemiol. Biomark. Prev., *10:* 869–874, 2001.

35. Feldman, M., Scharschmidt, B. F., Sleisenger, M. H., and Klein, S. Sleisenger & Fordtran's Gastrointestinal and Liver Disease, Ed. 6. Philadelphia: W. B. Saunders Company, 1998.

36. Vogelstein, B., Fearon, E. R., Hamilton, S. R., Kern, S. E., Preisinger, A. C., Leppert, M., Nakamura, Y., White, R., Smits, A. M., and Bos, J. L. Genetic alterations during colorectal-tumor development. N. Engl. J. Med., *319:* 525–532, 1988.

37. Hawkins, N. J., and Ward, R. L. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. J. Natl. Cancer Inst., *93:* 1307–1313, 2001.

38. Jass, J. R., IIino, H., Ruszkiewicz, A., Painter, D., Solomon, M. J., and Koorey, D. J. Neoplastic progression occurs through mutator pathways in hyperplastic polyposis of the colorectum. Gut, *47:* 43–49, 2000.

39. Perucho, M. Microsatellite instability: the mutator that mutates the other mutator. Nat. Med., *2:* 630–631, 1996.

40. Ionov, Y., Peinado, M. A., Malkhosyan, S., Shibata, D., and Perucho, M. Ubiquitous somatic mutations in simple repeated sequences reveal a new mechanism for colonic carcinogenesis. Nature (Lond.), *363:* 558–561, 1993.

41. Slattery, M. L., Curtin, K., Anderson, K., Ma, K. N., Ballard, L., Edwards, S., Schaffer, D., Potter, J., Leppert, M., and Samowitz, W. S. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. J. Natl. Cancer Inst., *92:* 1831–1836, 2000.

42. Potter, J. D. Invited commentary: old problem, new wrinkles. Am. J. Epidemiol., *147:* 911–913, 1998.

43. Potter, J. D. Colorectal cancer: molecules and populations. J. Natl. Cancer Inst., *91:* 916–932, 1999.

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