American Journal of Epidemiology
Vol. 167, No. 9
DOI: 10.1093/aje/kwm400
Advance Access publication February 27, 2008

Original Contribution

Alcohol Drinking, Cigarette Smoking, and Risk of Colorectal Adenomatous and Hyperplastic Polyps

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Received for publication June 28, 2007; accepted for publication December 21, 2007.

The authors evaluated alcohol drinking and cigarette smoking in relation to risk of colorectal polyps in a Nashville, Tennessee, colonoscopy-based case-control study. In 2003–2005, cases with adenomatous polyps only ($n = 639$), hyperplastic polyps only ($n = 294$), and both types of polyps ($n = 235$) were compared with 1,773 polyp-free controls. Unordered polytomous logistic regression was used to calculate adjusted odds ratios and 95% confidence intervals. Consumption of at least five alcoholic drinks per week was not strongly associated with development of polyps. Odds ratios for all polyp types were increased for dose, duration, and pack-years of cigarette smoking and were stronger for hyperplastic polyps than for adenoma. Compared with never smoking, dose-response relations were particularly strong for current smoking and duration; for ≥35 years of smoking, odds ratios were 1.9 (95% confidence interval (CI): 1.4, 2.5) for adenomatous polyps only, 5.0 (95% CI: 3.3, 7.3) for hyperplastic polyps only, and 6.9 (95% CI: 4.4, 11.1) for both types of polyps. Compared with current smoking, time since cessation was associated with substantially reduced odds; for ≥20 years since quitting, odds ratios were 0.4 (95% CI: 0.3, 0.6) for adenoma only, 0.2 (95% CI: 0.1, 0.3) for hyperplastic polyps only, and 0.2 (95% CI: 0.2, 0.4) for both polyp types. These findings support the adverse role of cigarette smoking in colorectal tumorigenesis and suggest that quitting smoking may substantially reduce the risk of colorectal polyps.

adenomatous polyps; alcohol drinking; colonic polyps; colorectal neoplasms; intestinal polyps; smoking

Abbreviations: CI, confidence interval; PLCO, Prostate, Lung, Colorectal, and Ovarian.

Colorectal adenomatous polyps, also called adenomas, are known and well-defined precursors to colorectal cancer (1). Less well understood is the role of hyperplastic polyps in colorectal carcinogenesis. Until recently, hyperplastic polyps were mostly assumed to have no malignant potential; thus, few studies have evaluated risk factors for these polyps (2–10). However, it appears that some hyperplastic polyps may develop into microsatellite-unstable colorectal cancers through a hyperplastic polyp-serrated adenoma pathway (11–14). Thus, studies which evaluate both hyperplastic and adenomatous polyps are needed to elucidate possible differing risk profiles for these polyps.

Regular alcohol drinking and tobacco smoking have been associated with both adenomas and cancers in some

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(7, 15–44) but not other (2, 17, 20, 23–26, 27, 32, 37, 45–47) previous studies. Only a handful of investigators have evaluated these exposures in relation to risk of hyperplastic polyps (2–9), and many of these studies were either small with limited power (5, 6) or were sigmoidoscopy-based (3–5) and thus did not evaluate risk throughout the entire colon. Nevertheless, based upon two of these studies, it appears that some of the previously reported association of adenoma with smoking may be due to mixture of participants with both hyperplastic and adenomatous polyps in the case group (2, 3). Thus, colonoscopy-based studies are needed which separately evaluate risk associated with each polyp type. In this study, we evaluated whether regular alcohol drinking and cigarette smoking were related to hyperplastic polyps, adenomatous polyps, or both types of polyps, using data from a large, ongoing colonoscopy-based study of colorectal polyps.

MATERIALS AND METHODS

The Tennessee Colorectal Polyp Study

Participants were part of the Tennessee Colorectal Polyp Study, an ongoing colonoscopy-based case-control study being conducted in Nashville, Tennessee. Study methods have been published elsewhere (48). Briefly, eligible participants aged 40–75 years were identified from patients scheduled for colonoscopy at the Vanderbilt Gastroenterology Clinic and the Veterans Affairs Tennessee Valley Health System Nashville campus between February 1, 2003, and December 31, 2005. Excluded from our study were participants who had genetic colorectal cancer syndromes (e.g., hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis) or a prior history of inflammatory bowel disease, adenomatous polyps, or any cancer other than nonmelanoma skin cancer. Participants were recruited at colonoscopy. Potential participants missed at colonoscopy were recruited after colonoscopy ($n = 331$). The study was approved by relevant committees for the use of human subjects in research.

Among 4,623 eligible persons, 3,094 (67 percent) provided written informed consent and participated in at least one component of the study. Participants and nonparticipants were similar with respect to age, sex, and study location. Participants were slightly more likely to have a family history of colorectal neoplasia as an indication for colonoscopy. Among participants, 2,676 (58 percent of eligible persons and 87 percent of participants) completed a telephone interview following colonoscopy and were included in this analysis. Participants also completed a self-administered food frequency questionnaire developed to capture information on diet in the southeastern United States (49).

On the basis of the colonoscopy and pathology findings, participants were assigned as polyp-free controls, persons with other diagnoses, or cases with hyperplastic polyps only, adenomatous polyps only, or both adenomatous and hyperplastic polyps. In order to be diagnosed as a control, the participant must have had a complete colonoscopy reaching the cecum and have been polyp-free at colonoscopy. The current analyses included 299 cases with hyperplastic polyps only, 639 cases with adenomatous polyps only, 234 cases with both adenomatous and hyperplastic polyps, and 1,773 polyp-free controls, including 299 participants from a pilot feasibility study. (The pilot study was conducted in 2001–2002 and followed the same protocols as the full-scale study.) Both studies were approved by the Vanderbilt University institutional review board.

Assessment of alcohol drinking and smoking

Following colonoscopy, a standardized telephone interview was conducted by trained interviewers to obtain information on medication use, demographic factors, medical history, anthropometric factors, and lifestyle, including questions on smoking and alcohol drinking. The alcohol drinking questions defined regular drinking as consumption of five or more drinks per week for 12 months in a row. The questions elicited information on the age at which regular drinking began, whether the participant was still drinking regularly, the age at which regular drinking stopped, the total number of years of regular drinking, and the average number of drinks consumed per week. Information on type of alcohol consumed was not collected in the telephone interview. Regular cigarette smoking was defined as smoking of at least one cigarette per day for at least 3 months in a row. The questions on cigarette smoking elicited information on age at initiation of smoking, whether the participant was still smoking regularly, the age at which regular smoking stopped, the average number of cigarettes smoked per day (either currently or before quitting), and the largest number of cigarettes smoked per day during the participant's lifetime. Participants were also asked about whether they had ever smoked pipes or cigars and whether they had ever used chewing tobacco or other forms of tobacco.

Data analysis

Participants with incomplete information on alcohol drinking ($n = 32$) or smoking ($n = 2$) were excluded from those analyses. Chi-squared statistics and t tests were used to evaluate case-control differences in the distribution of potentially confounding factors. Odds ratios were used to measure the association of polyp risk with cigarette smoking or alcohol use. Multinomial logistic regression models were used to estimate odds ratios and 95 percent confidence intervals, after adjustment for potential confounders (50). Risk factors identified previously as having an independent association with polyps in this population were controlled in all models. These included age, sex, study location, educational attainment, body mass index, height, physical activity, and menopausal status. Models also controlled for race/ethnicity; year of recruitment; type of recruitment (pre- or post-colonoscopy); indication for colonoscopy; family history of colorectal neoplasia; use of nonsteroidal antiinflammatory drugs; daily intakes of fruits, vegetables, dairy products, and meat; and alcohol drinking or duration of smoking. Age was included as a continuous variable throughout the analyses, and categorical variables were treated as indicator variables in the model. Dose-response trends were estimated on the

basis of incremental odds ratios over the categories and were analyzed by entering categorical variables as continuous parameters in the models (51). All statistical tests were based on two-sided probabilities using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 presents the characteristics of all cases and controls. Adenoma cases, in comparison with polyp-free controls, were generally older, more likely to be male, had lower educational attainment, had lower income, had higher body mass index, were taller, and were less likely to be physically active. Most of these characteristics were also more common among hyperplastic cases and cases with both types of polyps than among controls. Ages were similar between hyperplastic cases and controls. The results were similar for both study sites (results not shown in table).

Alcohol drinking was not associated with risk of colorectal polyps (table 2). In comparison with never drinkers, persons who drank for 30 or more years had a weak and nonsignificantly increased risk of hyperplastic polyps (odds ratio = 1.3, 95 percent confidence interval (CI): 0.9, 1.8; p-trend = 0.21). Amount, age of initiation, and recency of cessation were also not associated with risk of colorectal polyps. Results for polyp risk were similar when data were restricted to screening colonoscopies, diagnostic colonoscopies, precolonoscopy recruitment, postcolonoscopy recruitment, or pilot study participants or were stratified by median time to interview (results not shown in table). To evaluate whether risk associated with alcohol use varied by sex, we performed stratified analyses (results not shown in table). Too few women were regular alcohol drinkers for us to obtain informative estimates in stratified analyses. Among men, the estimates were similar for adenoma risk and somewhat stronger for hyperplastic polyp risk, as compared with findings in the entire population. There were no clear dose-response relations between amount, duration, or recency of alcohol use and risk of developing colorectal polyps. We evaluated a possible interaction between smoking status and alcohol use and did not find one ($p = 0.40$). In results stratified by study site, we also observed similar patterns of association as in the entire population and among men.

Use of any type of tobacco was significantly associated with increased risk of colorectal polyps (table 3); however, neither pipe or cigar smoking nor other forms of tobacco use, including chewing tobacco, were independently associated with risk of polyps. Current regular cigarette smoking, in comparison with never smoking, was significantly associated with increased risk for all three groups of polyp cases and was particularly strong for hyperplastic polyps (odds ratio = 4.7, 95 percent CI: 3.2, 6.8) and both types of polyps (odds ratio = 7.5, 95 percent CI: 4.8, 11.9). For the cases with hyperplastic polyps and both types of polyps, significant trends were observed with increasing number of cigarettes smoked per day, years of smoking, pack-years of smoking, and age at smoking initiation (all p's for trend $<$ 0.0001). Among cases with adenomas only, significant trends were observed only with years of smoking (p-trend $<$ 0.0001) and pack-years of smoking (p-trend = 0.003). Regardless of polyp type, the association between dose and risk was strongest for years of smoking. In comparison with never smokers, odds ratios for a smoking duration of 35 or more years were 5.0 (95 percent CI: 3.3, 7.3) for hyperplastic polyp cases, 1.9 (95 percent CI: 1.4, 2.5) for adenoma cases, and 6.9 (95 percent CI: 4.4, 11.1) for cases with both types of polyps. However, the thresholds for duration differed among the three groups. Significantly increased risks were observed with 25 or more years of smoking for adenoma cases, 15 or more years of smoking for hyperplastic polyp cases, and fewer than 15 years of smoking for cases with both polyp types.

To evaluate whether significant differences were present between the case groups, we performed case-case comparisons. For all smoking measures, in comparison with adenoma-only cases, both cases with hyperplastic polyps and cases with both types of polyps were at increased risk (p-trend $<$ 0.0001). For all categories of smoking duration, in comparison with hyperplastic polyp-only cases, cases with both types of polyps were at elevated risk, although results were not statistically significant except for a duration of 15 years or less. Most other measures of smoking were also more strongly related to having both types of polyps than to having only hyperplastic polyps, although risk was not always significantly increased. The relations between smoking duration and polyp risk were similar when subgroup analyses were conducted for men, full-scale study participants, individual study sites, right-sided polyps, left-sided polyps, screening colonoscopies, diagnostic colonoscopies, precolonoscopy recruitment, and postcolonoscopy recruitment (results not shown in table). In comparison with current smokers, former smokers who had quit 10 or more years previously had a significantly reduced risk of polyps (p-trend $<$ 0.0001 for all polyp cases).

DISCUSSION

In this large case-control study, we found that cigarette smoking was associated with increased risk of adenomatous and hyperplastic colorectal polyps. The associations between cigarette smoking and increased polyp risk were particularly strong for current smoking and years of smoking and for cases with hyperplastic polyps or both types of polyps. Regular consumption of at least five alcoholic drinks per week was, at most, weakly associated with increased risk of hyperplastic polyps. There were no clear dose-response relations between measures of alcohol drinking and risk of hyperplastic polyps.

Regular alcohol intake has been reported as a risk factor for both colorectal adenoma and cancer in some (2, 7, 15–22, 38, 41–44, 52–550) but not all (6, 20, 23–27, 37, 45–47, 53, 56, 57) previous studies. In most adenoma studies with a positive finding, the association has been weak to moderate (16, 18–21, 36, 38, 43, 44, 55) and occasionally, though not always, limited to a subgroup such as men (17, 20, 43, 53), women (16, 21, 43), distal or rectal cases (26, 42, 44), proximal cases (55), large or advanced adenomas (7, 42, 43, 53), consumers of a specific type of alcohol (15, 17, 20, 26, 42,

TABLE 1. Characteristics of participants in the Tennessee Colorectal Polyp Study, 2003–2005

Characteristic	Controls		Cases with colorectal polyps								
			Hyperplastic only			Adenomatous only			Both adenomatous and hyperplastic		
	No.	%	No.	%	*p* value*	No.	%	*p* value*	No.	%	*p* value*
Mean age (years)	57.2 (7.9)†		56.9 (7.2)		0.53	59.6 (7.4)		<0.0001	59.5 (6.7)		<0.0001
Female sex	771	43.5	90	30.1	<0.0001	165	25.8	<0.0001	38	16.2	<0.0001
Race/ethnicity					0.05			0.21			0.63
White, Hispanic or non-Hispanic	1,532	86.4	275	92.0		532	83.3		208	88.5	
Black, Hispanic or non-Hispanic	185	10.4	20	6.7		80	12.5		23	9.8	
Other	33	1.9	2	0.7		18	2.8		2	0.9	
Unknown	23	1.3	2	0.7		9	1.4		2	0.9	
Study location					<0.0001			<0.0001			<0.0001
Academic medical center	1,155	65.1	153	51.2		329	51.5		97	41.3	
Veterans Affairs medical center	618	34.9	146	48.8		310	48.5		138	58.7	
Indication					0.47			0.13			0.07
Screening	930	52.5	146	48.8		352	55.1		106	45.1	
Family history	226	12.8	35	11.7		62	9.7		34	14.5	
Diagnostic/follow-up/bleeding	563	31.8	105	35.1		211	33.0		91	38.7	
Other	54	3.1	13	4.4		14	2.2		4	1.7	
Educational attainment					<0.0001			0.0002			<0.0001
High school or less	463	26.3	109	36.6		212	33.5		90	38.6	
Some college	518	29.5	97	32.6		189	29.9		83	35.6	
College graduate	324	18.4	46	15.4		116	18.3		33	14.2	
Graduate or professional education	453	25.8	46	15.4		116	18.3		27	11.6	
Annual household income					0.02			<0.0001			<0.0001
≤$15,000	152	9.1	40	13.9		90	15.0		32	14.5	
$15,001–$30,000	278	16.7	56	19.5		141	23.5		54	24.4	
$30,001–$50,000	364	21.8	65	22.7		122	20.3		64	29.0	
>$50,000	874	52.4	126	43.9		248	41.3		71	32.1	
Family history					0.92			0.63			0.41
None	1,438	83.5	247	84.6		511	82.0		181	80.1	
Polyps only	50	2.9	8	2.8		22	3.5		9	4.0	
Colorectal cancer	235	13.6	37	12.7		90	14.5		36	15.9	
Mean body mass index‡	28.1 (5.6)		28.6 (5.0)		0.09	28.6 (5.8)		0.04	28.6 (4.8)		0.13
Mean height (m)	172.3 (9.8)		175.2 (9.6)		<0.0001	175.2 (10.0)		<0.0001	177.2 (8.7)		<0.0001
Physically active in past 10 years	1,021	57.7	158	52.8	0.12	329	51.5	0.007	104	44.4	0.0001
Mean dietary intake (servings/day)											
Fruits and vegetables	5.3 (3.0)		5.3 (2.9)		0.85	5.5 (3.2)		0.22	6.4 (3.2)		<0.0001
Meat	5.6 (3.6)		6.2 (4.6)		0.09	5.8 (4.3)		0.34	6.2 (3.4)		0.05
Dairy products	1.1 (0.8)		1.1 (0.8)		0.46	1.1 (0.9)		0.30	1.2 (0.6)		0.09
Any use of nonsteroidal antiinflammatory drugs					0.30			0.60			0.57
Never use	657	37.1	100	33.4		248	38.8		92	39.2	
Former use	85	4.8	18	6.0		28	4.4		7	3.0	
Current use	744	42.0	103	34.5		251	39.3		101	43.0	
Unknown	287	16.2	78	26.1		112	17.5		35	14.9	
Ever use of oral contraceptives§	593	80.4	76	86.4	0.17	127	77.0	0.33	29	78.4	0.77
Postmenopausal§	552	74.8	65	73.9	0.85	138	83.6	0.02	33	89.2	0.05
Ever use of hormone replacement therapy§	473	64.0	60	68.2	0.44	116	70.7	0.10	27	73.0	0.27

* *p* value for comparison with polyp-free controls from *t* tests (continuous variables) or χ^2 tests (categorical variables).
† Numbers in parentheses, standard deviation.
‡ Weight (kg)/height $(m)^2$.
§ Among women only.

TABLE 2. Odds of developing colorectal polyps according to alcohol drinking, Tennessee Colorectal Polyp Study, 2003–2005*

		Comparison of polyp cases with controls									Comparison by polyp type					
	No. of controls	Hyperplastic polyps only			Adenomatous polyps only			Both hyperplastic and adenomatous polyps			Hyperplastic only vs. adenomatous only		Both types vs. hyperplastic only		Both types vs. adenomatous only	
		No.	OR†	95% CI†	No.	OR	95% CI	No.	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Alcohol use																
Never a regular drinker	1,043	130	1.0	Referent	328	1.0	Referent	107	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Former drinker	433	105	1.2	0.9, 1.6	175	0.9	0.7, 1.1	78	0.8	0.5, 1.1	1.4	1.0, 2.0	0.6	0.4, 1.0	0.9	0.6, 1.3
Current drinker	297	64	1.3	0.9, 1.9	132	1.2	0.9, 1.5	49	0.9	0.6, 1.4	1.1	0.7, 1.7	0.7	0.4, 1.1	0.8	0.5, 1.2
p-trend				0.13			0.44			0.46		0.42		0.09		0.24
No. of drinks/week‡																
5–9	253	42	1.1	0.7, 1.6	77	0.8	0.6, 1.1	19	0.5	0.3, 0.8	1.3	0.8, 2.1	0.4	0.2, 0.8	0.6	0.3, 1.0
10–19	192	48	1.5	1.0, 2.2	71	0.9	0.7, 1.3	37	1.1	0.7, 1.6	1.6	1.0, 2.5	0.7	0.4, 1.2	1.2	0.7, 1.9
≥20	284	79	1.2	0.9, 1.8	159	1.2	0.9, 1.5	71	0.9	0.6, 1.3	1.1	0.7, 1.6	0.7	0.5, 1.2	0.8	0.5, 1.2
p-trend				0.16			0.43			0.85		0.47		0.22		0.48
Years of drinking‡																
1–14	241	51	1.2	0.8, 1.8	69	0.7	0.5, 1.0	32	0.8	0.5, 1.2	1.9	1.1, 3.0	0.6	0.4, 1.1	1.1	0.7, 2.0
15–29	274	63	1.2	0.8, 1.7	112	1.1	0.8, 1.4	44	0.8	0.6, 1.3	1.1	0.7, 1.7	0.7	0.4, 1.2	0.8	0.5, 1.2
≥30	212	54	1.3	0.9, 1.8	125	1.1	0.8, 1.5	50	0.9	0.6, 1.3	1.1	0.8, 1.7	0.7	0.4, 1.1	0.8	0.5, 1.1
p-trend				0.21			0.34			0.36		0.62		0.09		0.14
Age (years) at starting to drink‡																
1–17	123	26	1.0	0.5, 2.1	43	0.4	0.2, 0.8	18	0.5	0.3, 1.0	2.3	1.0, 5.4	0.5	0.2, 1.5	1.2	0.5, 3.1
18–19	183	54	1.6	0.8, 2.9	102	0.8	0.5, 1.4	33	0.7	0.5, 1.2	1.9	0.9, 3.9	0.5	0.2, 1.3	1.0	0.4, 2.2
≥20	424	88	1.3	0.8, 2.3	162	0.6	0.4, 1.0	76	1.0	0.7, 1.4	2.0	1.1, 3.9	0.8	0.4, 1.8	1.6	0.8, 3.3
p-trend				0.13			0.96			0.77		0.19		0.18		0.76
Years since quitting drinking																
Current drinker	297	64	1.0	Referent	132	1.0	Referent	49	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
1–10	121	36	1.0	0.6, 1.7	52	0.8	0.5, 1.2	25	0.9	0.5, 1.5	1.3	0.7, 2.2	0.9	0.4, 1.7	1.1	0.6, 2.0
10–19	144	30	0.8	0.5, 1.3	63	0.8	0.6, 1.3	27	0.9	0.5, 1.6	0.9	0.5, 1.7	1.2	0.6, 2.3	1.1	0.6, 2.0
≥20	168	39	0.9	0.6, 1.5	60	0.6	0.4, 0.9	26	0.7	0.4, 1.2	1.6	0.9, 2.7	0.8	0.4, 1.5	1.2	0.7, 2.1
Never a regular drinker	1,043	130	0.8	0.5, 1.1	328	0.9	0.7, 1.1	107	1.1	0.7, 1.6	0.9	0.6, 1.3	1.4	0.9, 2.3	1.3	0.8, 2.0
p-trend				0.13			0.25			0.65		0.58		0.14		0.25

* Odds ratios were adjusted for age; sex; study site; year; recruitment type (pre- or postcolonoscopy); body mass index; height; indication for colonoscopy; educational attainment; race/ethnicity; family history of cancer and polyps; use of nonsteroidal antiinflammatory drugs; physical activity; menopausal status; daily intakes of fruits and vegetables, dairy foods, and meat; and cigarette smoking.

† OR, odds ratio; CI, confidence interval.

‡ Compared with persons who never drank alcohol regularly.

53), persons with the highest levels of intake (17, 21, 42, 52, 53), or a genetically defined subgroup (21, 27, 36, 58, 59). We observed a weak association in men with any current regular alcohol drinking but no dose-dependent risk. Very few studies (2, 4–7)—mostly small (5, 6) or sigmoidoscopy-based (4, 5) studies—have evaluated the association of hyperplastic polyp risk with alcohol intake, and only one of these studies also considered the combination of hyperplastic and adenomatous polyps (2). Four of the five previous studies (4–7) found alcohol intake to be associated with a weakly to moderately increased risk of hyperplastic polyps, although findings have not always been statistically significant (6, 7). The mechanism by which alcohol may affect polyp risk is not known. Some of the proposed mechanisms are nutritional deficiency, including folate deficiency; effects of acetaldehyde, such as hyperregeneration of the colonic mucosa, activation of procarcinogens, and generation of reactive oxygen species through the induction of cytochrome P-450 2E1; abnormal DNA methylation; and immune system suppression (60, 61).

TABLE 3. Odds of developing colorectal polyps according to tobacco use and cigarette smoking, Tennessee Colorectal Polyp Study, 2003–2005*

	No. of controls	Comparison of polyp cases with controls									Comparison by polyp type					
		Hyperplastic polyps only			Adenomatous polyps only			Both hyperplastic and adenomatous polyps			Hyperplastic only vs. adenomatous only		Both types vs. hyperplastic only		Both types vs. adenomatous only	
		No.	OR†	95% CI†	No.	OR	95% CI	No.	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Type of tobacco use																
Never a regular user	824	70	1.0	Referent	218	1.0	Referent	33	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Pipe/other tobacco user only	53	7	1.2	0.5, 2.9	25	1.2	0.7, 2.1	4	1.1	0.4, 3.4	1.0	0.4, 2.6	0.9	0.2, 3.5	1.0	0.3, 3.0
Former cigarette smoker	629	98	1.5	1.1, 2.2	238	1.1	0.9, 1.4	96	2.8	1.8, 4.3	1.4	0.9, 2.1	1.8	1.1, 3.1	2.5	1.6, 4.0
Current cigarette smoker	252	116	4.8	3.3, 7.1	150	1.8	1.3, 2.5	98	7.7	4.7, 2.4	2.6	1.7, 4.1	1.6	0.9, 2.8	4.2	2.5, 7.0
p-trend				<0.0001			0.003			<0.0001		<0.0001		0.06		<0.0001
Cigarette smoking																
Never smoker	877	77	1.0	Referent	243	1.0	Referent	37	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Former smoker	629	98	1.5	1.1, 2.1	238	1.1	0.9, 1.4	96	2.7	1.8, 4.2	1.4	0.9, 2.0	1.8	1.1, 3.1	2.5	1.6, 3.9
Current smoker	252	116	4.7	3.2, 6.8	150	1.8	1.3, 2.4	98	7.5	4.8, 11.9	2.6	1.7, 4.0	1.6	0.9, 2.8	4.2	2.6, 6.9
p-trend				<0.0001			0.0005			<0.0001		<0.0001		0.15		<0.0001
No. of cigarettes/day‡																
<20	341	67	2.1	1.5, 3.1	135	1.3	1.0, 1.7	51	3.2	2.0, 5.0	1.6	1.1, 2.5	1.5	0.8, 2.6	2.4	1.5, 4.0
20–29	293	72	2.2	1.5, 3.2	126	1.2	0.8, 1.6	72	4.1	2.6, 6.5	1.8	1.2, 2.9	1.9	1.1, 3.3	3.5	2.2, 5.7
≥30	247	75	2.5	1.7, 3.8	127	1.3	1.0, 1.7	71	4.5	2.8, 7.2	2.0	1.3, 3.1	1.8	1.0, 3.1	3.5	2.1, 5.7
p-trend				<0.0001			0.09			<0.0001		0.003		0.07		<0.0001
Years of cigarette smoking‡																
<15	266	19	0.7	0.4, 1.3	65	0.8	0.6, 1.2	25	2.0	1.2, 3.5	0.9	0.5, 1.6	2.7	1.3, 5.6	2.4	1.3, 4.3
15–<25	179	37	2.1	1.3, 3.3	64	1.1	0.8, 1.5	25	2.7	1.5, 4.7	2.0	1.2, 3.3	1.3	0.6, 2.5	2.5	1.4, 4.5
25–<35	193	51	2.8	1.8, 4.2	86	1.4	1.0, 2.0	47	5.0	3.0, 8.2	1.9	1.2, 3.1	1.8	1.0, 3.3	3.5	2.0, 5.9
≥35	243	107	5.0	3.3, 7.3	173	1.9	1.4, 2.5	97	6.9	4.4, 11.1	2.6	1.7, 4.1	1.4	0.8, 2.5	3.7	2.3, 6.1
p-trend				<0.0001			<0.0001			<0.0001		<0.0001		0.46		<0.0001
Pack-years of cigarette smoking‡																
<10	266	28	1.2	0.7, 1.8	78	1.0	0.8, 1.4	22	1.9	1.1, 3.2	1.1	0.7, 1.9	1.6	0.8, 3.3	1.8	1.0, 3.2
10–<30	265	69	2.6	1.8, 3.8	111	1.2	0.9, 1.7	48	3.5	2.2, 5.7	2.1	1.4, 3.3	1.3	0.8, 2.4	2.8	1.7, 4.7
≥30	350	117	3.1	2.1, 4.5	199	1.5	1.1, 2.0	124	6.2	4.0, 9.7	2.1	1.4, 3.2	2.0	1.2, 3.4	4.2	2.6, 6.7
p-trend				<0.0001			0.003			<0.0001		<0.0001		0.02		<0.0001
Age (years) at starting to smoke‡																
<18	438	104	2.1	1.5, 3.0	199	1.2	0.9, 1.5	97	3.3	2.2, 5.1	1.8	1.2, 2.6	1.6	0.9, 2.6	2.8	1.8, 4.4
18–20	289	77	2.7	1.9, 3.9	127	1.3	1.0, 1.7	74	4.5	2.9, 7.0	2.1	1.4, 3.1	1.7	1.0, 2.8	3.4	2.2, 5.5
≥21	154	33	2.3	1.5, 3.7	62	1.3	0.9, 1.8	23	2.7	1.5, 4.8	1.9	1.1, 3.1	1.2	0.6, 2.3	2.2	1.2, 4.0
p-trend				<0.0001			0.09			<0.0001		0.004		0.35		0.0002
Years since quitting smoking																
Current smoker	252	116	1.0	Referent	150	1.0	Referent	98	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
<10	114	35	0.6	0.4, 1.0	62	1.0	0.7, 1.5	27	0.7	0.4, 1.1	0.6	0.4, 1.1	1.0	0.6, 1.9	0.7	0.4, 1.1
10–19	146	31	0.4	0.3, 0.6	66	0.7	0.5, 1.1	27	0.4	0.3, 0.7	0.6	0.3, 0.9	1.0	0.6, 1.9	0.6	0.3, 1.0
≥20	369	32	0.2	0.1, 0.3	110	0.4	0.3, 0.6	42	0.2	0.2, 0.4	0.4	0.2, 0.7	1.4	0.8, 2.5	0.6	0.3, 0.9
Never smoker	877	77	0.2	0.1, 0.3	243	0.5	0.4, 0.7	37	0.1	0.1, 0.2	0.4	0.2, 0.6	0.6	0.4, 1.1	0.2	0.1, 0.4
p-trend				<0.0001			<0.0001			<0.0001		<0.0001		0.31		<0.0001

* Odds ratios were adjusted for age; sex; study site; year; recruitment type (pre- or postcolonoscopy); body mass index; height; indication for colonoscopy; educational attainment; race/ethnicity; family history of cancer and polyps; use of nonsteroidal antiinflammatory drugs; physical activity; menopausal status; daily intakes of fruits and vegetables, dairy foods, and meat; and alcohol drinking.

† OR, odds ratio; CI, confidence interval.

‡ Compared with persons who never smoked cigarettes regularly.

In previous studies, cigarette smoking has consistently been a risk factor for colorectal adenoma (15, 19, 20, 23–26, 28, 29, 32, 33, 37, 39, 43, 53), and often it has been a strong risk factor (23, 25, 39, 44, 53, 62). Although only a handful of investigators have evaluated smoking as a risk factor for hyperplastic colorectal polyps, they, too, have mostly found an increased risk (2–9). In only two previous studies have researchers separately and jointly evaluated both hyperplastic and adenomatous polyps (2, 3). A Minnesota colonoscopy-based study found that smoking was strongly associated with increased risk of hyperplastic polyps or both hyperplastic and adenomatous polyps but was not a risk factor for adenomatous polyps alone (2). The second study, a sigmoidoscopy-based study of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, also observed that smoking was most strongly associated with having both types of polyps (3). These findings parallel our results. In our study and the previous two studies, over 20 percent of all cases with adenoma also had one or more hyperplastic polyps. It is possible, given the strength of our associations with smoking, that some of the previously reported observations for adenomas and smoking may be partially due to the inclusion of adenoma cases with hyperplastic polyps in the case group. However, in contrast to the Minnesota study, both our study and the PLCO study found that smoking was moderately associated with risk of adenomatous polyps.

Previous studies have found that former smokers are at reduced risk for colorectal adenomatous and hyperplastic polyps in comparison with current smokers, but to our knowledge only one previous study has evaluated whether the reduced risk varies by time since smoking cessation (3). In the PLCO evaluation of left-sided polyps, recency was the most important determinant of polyp risk (3). In comparison with current smokers, regardless of polyp type, we found that smoking cessation of as little as 10 years' duration was associated with a moderately reduced risk of polyps and that smoking cessation of 20 or more years was strongly associated with reduced risk in comparison with current smoking. This finding has potentially important public health implications for smoking cessation and should be evaluated in future studies.

Several known or probable human carcinogens are present in cigarette smoke, including polycyclic aromatic hydrocarbons, nitrosamines, heterocyclic amines, aromatic amines, and benzene (63). More recently, smoking or nicotine has been associated with hypermethylation of CpG islands and increased DNA methyltransferase activity in cancer cells, suggesting that mechanisms such as chromosomal instability or inhibition of tumor suppressor genes may also play a role in the carcinogenic process, particularly in the microsatellite instability pathway (64, 65). This may explain why smoking was more strongly associated with hyperplastic polyps in our study; CpG island methylation occurs frequently in hyperplastic polyps (66, 67). Very recently, smoking has been reported to be most strongly related to microsatellite-instability-high colorectal cancers, most of which may progress through the proposed hyperplastic-serrated adenoma pathway (68).

As with any case-control study, the possibility of selection and recall biases may be a concern in this study. Virtually all participants were recruited prior to colonoscopy and thus prior to diagnosis. As a result, selection bias was minimized. Similarly to other case-control studies, recall bias could be a concern. However, all of these polyps were considered benign lesions; thus, the diagnosis of polyps is unlikely to have had a major impact on lifestyle changes or recall of lifestyle behaviors prior to interview. Additionally, most participants were interviewed within 13 days after the colonoscopy. The prevalence of colorectal polyps is relatively common in the general population; thus, the odds ratios estimated in our study may not have been good approximations of relative risk. Nevertheless, the odds ratio is a valid statistic for measuring the strength of an association, even for common diseases. We also used Poisson regression and found no substantial difference in the point estimates of the relative risk and odds ratio (69). Thus, properties of the odds ratio are not likely to explain the stronger association of smoking for hyperplastic polyps than for adenomas.

Unlike sigmoidoscopy-based studies, our study, based on colonoscopy, evaluated the presence of polyps in the entire colorectum. This minimized contamination of the control group with polyp cases. Another strength of our study was its large sample size. To our knowledge, it is also the largest study of both right- and left-sided polyps to have evaluated smoking and drinking in relation to the combination of adenomatous and hyperplastic polyps. We were able to evaluate many potential confounders. However, residual confounding due to dietary components may still exist, although we adjusted for intake of certain food groups. In our study, regular drinking was defined as consumption of five or more alcoholic drinks per week. If the threshold for increased or decreased risk is lower than this limit, this may explain why we did not observe an association with alcohol. As we noted above, some previous studies have found differing effects of specific alcoholic beverages (15, 17, 20, 26, 42, 53). However, we were not able to evaluate risks associated with intake of specific alcoholic beverages.

In summary, we found that risk of hyperplastic colorectal polyps was suggestively but weakly associated with duration of alcohol drinking and strongly associated with cigarette smoking. Adenoma risk, on the other hand, was only moderately associated with cigarette smoking. Having both hyperplastic and adenomatous polyps was very strongly associated with cigarette smoking. We further found that recency of smoking cessation was related to risk in a dose-dependent manner. These results are important for understanding the etiology of colorectal polyps and in designing public health strategies. Future studies are needed to confirm these findings and to elucidate the mechanisms by which cigarette smoking increases risk for colorectal polyps.

ACKNOWLEDGMENTS

This study was supported by grants P50CA950103 and R01CA97386 from the National Cancer Institute.

The authors thank the patient advocates, staff, and faculty of the Tennessee Colorectal Polyp Study for their assistance.

Conflict of interest: none declared.

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