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Original Contribution

Associations of Cigarette Smoking and Alcohol Consumption With Advanced or Multiple Colorectal Adenoma Risks: A Colonoscopy-based Case-Control Study in Korea

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The associations between alcohol consumption and cigarette smoking habits and the risk for colorectal adenomatous polyps according to the detailed clinical information about polyps were assessed in a large colonoscopy-based study. The study enrolled participants who visited the National Cancer Center of the Republic of Korea for cancer screening between April 2007 and April 2009. In 1,242 newly diagnosed colorectal adenoma patients and 3,019 polyp-free controls, past smokers (odds ratio (OR) = 1.31, 95% confidence interval (CI): 1.04, 1.65) and current smokers (OR = 1.70, 95% CI: 1.37, 2.11) had increased risks for adenomas compared with nonsmokers. Cigarette smoking conferred an even higher risk for advanced adenomas and 3 or more adenomas than for low-risk adenomas or a single adenoma. Dose-response relations were observed among the daily number of cigarettes smoked, the duration of smoking, the pack-years of smoking, and the risk for adenomas. A longer duration of alcohol consumption was associated with a higher risk for advanced adenomas (for >28 years of consumption: OR = 2.0, 95% CI: 1.10, 3.64) and 3 or more adenomas (OR = 2.19, 95% CI: 1.27, 3.76). In conclusion, cigarette smoking and alcohol consumption play roles in colorectal carcinogenesis, and the association differs by the clinical features of the adenomas.

adenoma; alcohol drinking; colorectal neoplasms; risk factors; smoking

Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer; OR, odds ratio.

Cigarette smoking has not been classified as a risk factor for colorectal cancer by the International Agency for Research on Cancer (IARC) (1). Recently, however, the IARC has recognized the colorectum as a tumor site for which there is sufficient evidence that tobacco smoking causes cancer (2). Two recent meta-analyses on cigarette smoking and colorectal cancer risk confirmed the increased colorectal cancer risk among smokers (3, 4). The following hypotheses have been proposed to explain the inconsistency of the association between tobacco smoking and colorectal cancer risk: 1) Case-control and cohort studies with relatively short follow-up periods have not properly considered the induction period between exposure and colorectal cancer development (3); 2) cigarette smoking may preferentially increase the risk of developing low-risk adenomas, which have a low probability of progressing toward advanced adenomas and adenocarcinomas (5); 3) the attenuation of the association between tobacco-smoking and colorectal cancer risk may be due to the lack of full colonoscopies in controls in most epidemiologic studies and the subsequent selection of controls with adenomas (6); and 4) cigarette smoking may be more strongly associated with an increased risk for certain types of colorectal cancers, such as microsatellite-instability tumors (7). For clarification of the second hypothesis, it would be helpful to investigate the associations between cigarette smoking habits and colorectal polyp risks by using detailed information concerning the histologic grades and multiplicities of the adenomas. Furthermore, the

classification of the colorectal polyp cases and controls based on full colonoscopies would resolve any uncertainty raised by the third hypothesis.

According to a systematic review performed by the World Cancer Research Fund/American Institute for Cancer Research (8), the consumption of more than 30 g/day of ethanol from alcoholic drinks is a ''convincing'' risk factor for colorectal cancer in males and is a ''probable'' risk factor for females. In addition, the IARC has added colorectal cancer to the list of cancers that are causally related to alcohol consumption, which is classified as ''carcinogenic to humans'' (group 1) (9). However, the association between alcohol consumption and colorectal polyp risk has been inconsistent (10–32).

Several previous studies on lifestyle risk factors used clinical classifications of colorectal polyps, such as the multiplicity of the adenomas (19, 22, 33–35), the anatomic location of the adenomas (19, 22, 26, 32–38), and high-risk versus low-risk adenomas (33, 39–41). However, most of these studies are still limited by relatively small numbers of study subjects and the use of limited clinical information about the polyps. In particular, the classification of multiple adenomas based on a classification of their locations has not been clearly described. Some studies excluded patients with multiple adenomas in the subgroup analyses of their anatomic locations (19, 35, 42), and other studies have classified adenomas in multiple anatomic sites as either rectal or distal adenomas (26, 38). However, patients with adenomas in multiple anatomic locations may possess different risk factor profiles than patients with adenomas in a single anatomic location.

The objective of the current study was to assess the associations between alcohol consumption and cigarette smoking habits and the risks for colorectal adenoma in a large colonoscopy-based study. The associations were tested according to the histologic grades, multiplicities, and anatomic locations of the colorectal adenomas.

MATERIALS AND METHODS

Study participants

The study participants were recruited at the National Cancer Center in Korea. Participants who had undergone colonoscopies were asked to enroll in the Colorectal Polyp Registry. A total of 12,405 participants were enrolled in the Colorectal Polyp Registry between April 9, 2007, and April 3, 2009. Of these participants, 10,206 were subjects in the cancer screening program. Participants between 30 and 70 years of age were asked to participate in a screenee cohort study. Of the 7,673 who were contacted by interviewers, 6,489 gave informed consent to provide comprehensive information regarding their lifestyles and 20 mL of blood (participation rate: 84.6%). The questionnaire items included sociodemographic characteristics (e.g., age, education, occupation, household income, and marital status), medical and disease history, cigarette smoking, alcohol consumption, regular exercise, and dietary intake habits. The detailed endoscopic findings and relevant pathologic findings were collected and entered into a database by research nurses. A self-administered questionnaire and the instructions for bowel preparation were sent to the participants 2 weeks prior to the scheduled visit. The study protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center.

After the exclusion of participants with a self-reported history of cancer or colorectal polyps, those who were younger than 30 or older than 70 years of age, and those with missing information regarding their cigarette smoking or alcohol consumption habits, 4,970 participants were available for the analysis. In this group, any participants with hyperplastic polyps ($n = 252$), serrated adenomas ($n = 24$), or other types of lesions ($n = 433$) were also excluded. Finally, 1,242 colorectal adenomatous polyp patients and 3,019 polyp-free controls were included in the final analysis. In the adenoma patients, at least 1 advanced adenoma was found in 120 patients, and 3 or more adenomas were found in 180 patients. Of the participants with adenomas, 554 had only adenomas in the proximal colon, 344 had only adenomas in the distal colon, 106 had only adenomas in the rectum, and 238 patients had adenomas at multiple anatomic sites.

Diagnosis and classification of colorectal polyps

All of the patients were primed for colonoscopy via mechanical bowel preparation. The patients received either two 45-mL doses of sodium phosphate (Fleet; C. B. Fleet Co., Inc., Lynchburg, Virginia) or 4-L doses of a polyethylene glycol solution (Colyte-F; Taejoon Pharm, Seoul, Korea) and underwent colonoscopy under conscious sedation with an intravenous administration of midazolam. The colonoscopy was performed to the cecum or to the terminal ileum by using white-light colonoscopic examination. The polyp sizes and morphologic characteristics were estimated and recorded by the endoscopists. The polypectomy procedures were performed by using standard video colonoscopes (model CF Q260L; Olympus Optical Co., Ltd., Tokyo, Japan). Each polyp that was removed was sent to a pathologist for histopathologic examination.

Advanced polyps were defined as either an adenoma with a diameter of at least 10 mm, a tubulovillous or villous adenoma, an adenoma with high-grade dysplasia, or a carcinoma in situ (43). The proximal colon was defined as the ascending colon, hepatic flexure, and transverse colon. The distal colon was defined as the splenic flexure, descending, sigmoid, and rectosigmoid colon. Rectal polyps were evaluated separately from polyps in the proximal and distal colon.

Assessment of cigarette smoking and alcohol consumption

Questions regarding cigarette smoking habits included the age at which smoking began, the age at which the subject quit regular smoking, the average numbers of cigarettes smoked per day during regular smoking, and the total duration of regular cigarette smoking. Using the age at which the subject quit regular smoking, we calculated the years since quitting smoking.

Table 1. Distributions of Demographic and Risk Factors and Their Associations With the Risk for Colorectal Adenoma, National Cancer Center, Republic of Korea, 2007–2009

	Polyp-free Controls (n = 3,019)		Any Adenoma (n = 1,242)		Type of Adenoma				No. of Adenomas				Location of Adenoma							
					Advanced Adenoma (n = 120)		Low-Risk Adenoma Only (n = 1,122)		1–2 (n = 1,062)		≥3 (n = 180)		Right Colon (n = 554)		Left Colon (n = 344)		Rectum (n = 106)		Multiple Locations (n = 238)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex																				
Male	1,503	49.8	890	71.7	86	71.7	804	71.7	734	69.1	156	86.7	381	68.8	233	67.7	75	70.8	201	84.5
Female	1,516	50.2	352	28.3	34	28.3	318	28.3	328	30.9	24	13.3	173	31.2	111	32.3	31	29.3	37	15.6
Age group, years																				
30–39	611	20.2	110	8.9	10	8.3	100	8.9	99	9.3	11	6.1	41	7.4	37	10.8	19	17.9	13	5.5
40–49	1,350	44.7	465	37.4	39	32.5	426	38.0	416	39.2	49	27.2	211	38.1	133	38.7	48	45.3	73	30.7
50–59	840	27.8	453	36.5	45	37.5	408	36.4	376	35.4	77	42.8	206	37.2	123	35.8	30	28.3	94	39.5
≥60	218	7.2	214	17.2	26	21.7	188	16.8	171	16.1	43	23.9	96	17.3	51	14.8	9	8.5	58	24.4
Waist circumference, cm																				
Male																				
<90	1,015	65.5	578	64.9	57	66.3	521	64.8	484	65.9	94	60.3	243	63.8	165	70.8	50	66.7	120	59.7
≥90	467	31.1	308	34.6	28	32.6	280	34.8	247	33.7	61	39.1	137	36.0	67	28.8	24	32.0	80	39.8
Unknown	21	1.4	4	0.4	1	1.2	3	0.4	3	0.4	1	0.6	1	0.3	1	0.4	1	1.3	1	0.5
Female																				
<80	780	51.5	134	38.1	12	35.3	122	38.4	126	38.4	8	33.3	70	40.5	37	33.3	14	45.2	13	35.1
≥80	726	47.9	215	61.1	22	64.7	193	60.7	199	60.7	16	66.7	103	59.5	71	64.0	17	54.8	24	64.9
Unknown	10	0.7	3	0.9	0	0.0	3	0.9	3	0.9	0	0.0	0	0.0	3	2.7	0	0.0	0	0.0
Marital status																				
Married	2,603	86.2	1,057	85.1	102	85.0	955	85.1	902	84.9	155	86.1	474	85.6	296	86.1	87	82.1	200	84.0
Single	264	8.7	116	9.3	13	10.8	103	9.2	102	9.6	14	7.8	55	9.9	29	8.4	12	11.3	20	8.4
Unknown	152	5.0	69	5.6	5	4.2	64	5.7	58	5.5	11	6.1	25	4.5	19	5.5	7	6.6	18	7.6
Educational level																				
Below middle school	309	10.2	177	14.3	22	18.3	155	13.8	145	13.7	32	17.9	79	14.3	40	11.6	16	15.1	42	17.7
High school	976	32.4	399	32.2	46	38.3	353	31.5	336	31.6	63	35.2	161	29.1	126	36.6	32	30.2	80	33.8
College or more	1,588	52.6	594	47.9	50	41.7	544	48.5	517	48.7	77	43.0	290	52.4	154	44.8	48	45.3	102	43.0
Unknown	144	4.8	71	5.7	2	1.7	69	6.2	64	6.0	7	3.9	24	4.3	24	7.0	10	9.4	13	5.5
Household income, 1,000 won/month[a]																				
<4,000	884	29.3	398	32.1	52	43.3	346	30.8	339	31.9	59	32.8	174	31.4	116	33.7	34	32.1	74	31.1
4,000–7,000	869	28.8	342	27.5	26	21.7	316	28.2	294	27.7	48	26.7	167	30.1	90	26.2	32	30.2	53	22.3
>7,000	827	27.4	317	25.5	29	24.2	288	25.7	272	25.6	45	25.0	140	25.3	91	26.5	21	19.8	65	27.3
Unknown	439	14.5	185	14.9	13	10.8	172	15.3	157	14.8	28	15.6	73	13.2	47	13.7	19	17.9	46	19.4
Smoking status																				
Nonsmoker	1,672	55.4	439	35.4	38	31.7	401	35.7	399	37.6	40	22.2	218	39.4	125	36.3	36	34.0	60	25.2
Former smoker	582	19.3	344	27.7	37	30.8	307	27.4	284	26.7	60	33.3	142	25.6	100	29.1	28	26.4	74	31.1
Current smoker	765	25.3	459	37.0	45	37.5	414	36.9	379	35.7	80	44.4	194	35.0	119	34.6	42	39.6	104	43.7

Alcohol consumption																							
Nondrinker	919	30.4	304	24.5	26	21.7	278	24.8	280	26.4	24	13.3	145	26.2	93	27.0	28	26.4	38	16.0			
Former drinker	136	4.5	65	5.2	8	6.7	57	5.1	50	4.7	15	8.3	29	5.2	14	4.1	7	6.6	15	6.3			
Current drinker	1,964	65.1	873	70.3	86	71.7	787	70.1	732	68.9	141	78.3	380	68.6	237	68.9	71	67.0	185	77.7			
Physical activity																							
HEPA active 1	805	26.7	298	24.0	23	19.2	275	24.5	256	24.1	42	23.3	132	23.8	86	25.0	21	19.8	59	24.8			
HEPA active 2	786	26.0	313	25.2	36	30.0	277	24.7	267	25.1	46	25.6	147	26.5	85	24.7	28	26.4	53	22.3			
HEPA active 3	580	19.2	247	19.9	24	20.8	223	19.9	214	20.2	33	18.3	113	20.4	66	19.2	23	21.7	45	18.9			
Unknown	848	28.1	384	30.9	37	30.8	347	30.9	325	30.6	59	32.8	162	29.2	107	31.1	34	32.1	81	34.0			
Family history of cancer																							
No	2,198	72.8	884	71.2	86	71.7	798	71.1	756	71.2	128	71.1	400	72.2	243	70.6	76	71.7	165	69.3			
Yes	683	22.6	299	24.1	29	24.2	270	24.1	256	24.1	43	23.9	134	24.2	79	23.0	26	24.5	60	25.2			
Unknown	138	4.6	59	4.8	5	4.2	54	4.8	50	4.7	9	5.0	20	3.6	22	6.4	4	3.8	13	5.5			
Family history of colorectal cancer																							
No	2,824	93.5	1,092	87.4	108	90.0	1,032	92.0	977	92.0	163	90.6	511	92.2	312	90.1	99	93.4	218	91.6			
Yes	57	1.9	43	3.5	7	5.8	36	3.2	35	3.3	8	4.4	23	4.2	10	2.9	3	2.8	7	2.9			
Unknown	138	4.6	59	4.8	5	4.2	54	4.8	50	4.7	9	5.0	20	3.6	22	6.4	4	3.8	13	5.5			

Abbreviation: HEPA, health-enhancing physical activity.
[a] One US dollar is worth approximately 1,100 Korean won.

Three categories were established for alcohol consumption: never drinkers, current drinkers, and former drinkers. The questions included the total duration of regular alcohol consumption and the amount and frequency of consumption of different types of alcoholic beverages (beer, soju, whisky, Korean rice wine, and fruit wine). The total alcohol intake was calculated by summing the products of the average amount of alcohol consumed and the consumption frequency of each alcoholic beverage.

Statistical analysis

The distributions of demographic and other risk factors for colorectal adenomas between the control and case groups were compared by using the chi-square test. The associations between the risk factors and the risk for colorectal adenomas were evaluated by using logistic regression models. Polytomous logistic models were used for the associations between the risk factors and multiple outcomes, for example, advanced/other adenomas, the number of adenomas (1–2/≥3), and the location of the adenomas (right colon/left colon/rectum/multiple sites). All of the models were adjusted for age as a continuous variable, sex, a family history of colorectal cancer in first-degree relatives, and waist circumference (≥90 cm/<90 cm for men and ≥80 cm/<80 cm for women, according to the obesity criteria proposed for the Asian population (44)). An additional adjustment for smoking status was made for the alcohol consumption analysis, and an adjustment for the duration of alcohol consumption was made for the cigarette smoking analysis. *P* values for the trends of the odds ratios were calculated by using the order of each risk factor category as a categorical variable. To test for statistical differences in the odds ratios between the case groups, we used one case group as a reference group and calculated the *P* value of the comparison case group. All analyses were conducted by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Compared with the control group, the adenoma patients were more likely to be older ($P < 0.001$) and male ($P < 0.001$) and to have a low educational level. Although there was no statistically significant difference in the proportion of participants with a family history of cancer in their first-degree relatives, the adenoma patients were more likely to have first-degree relatives who had been diagnosed with colorectal cancer (3.5% and 1.9% in patients and controls, respectively) (Table 1). Of the controls, 25% were current smokers. The proportions were 45.4% in male controls and 5.5% in female controls, which are comparable to the proportions of current smokers in the Korean adult population (47.7% for males and 7.4% for females in 2008) (45).

Compared with nonsmokers, current and former smokers had higher risks for colorectal adenoma (for current smokers: odds ratio (OR) = 1.70, 95% confidence interval (CI): 1.37, 2.12; for former smokers: OR = 1.31, 95% CI: 1.04, 1.65). The number of cigarettes smoked per day, the total

duration of cigarette smoking, and the pack-years of cigarette smoking were all associated with an increased risk of adenoma in a dose-dependent manner (Table 2). The associations were stronger for the risks of having advanced or multiple adenomas (Table 2). In the polytomous models, the odds ratios for total duration of cigarette smoking and pack-years of cigarette smoking were statistically different between the patients with advanced adenomas and those with low-risk adenomas ($P = 0.045$ for the ordered categories of total cigarette smoking duration and $P = 0.042$ for the ordered categories of cigarette pack-years). Cigarette smoking increased the risk of colorectal adenoma regardless of the anatomic site (Table 3). Although the risk estimates for the smoking variables and the colorectal adenomas were highest for patients with adenomas in multiple anatomic locations, the risk estimates for the various smoking variables were not statistically different across the anatomic sites (Table 3).

Former and current alcohol consumers did not demonstrate a significantly higher risk for colorectal adenoma (Table 4). However, a long duration of alcohol consumption was associated with a higher risk for advanced adenoma (OR = 2.0, 95% CI: 1.10, 3.64 for >28 years of consumption vs. never drank). Associations between alcohol consumption and adenoma risk were observed in patients with 3 or more adenomas (OR = 2.19, 95% CI: 1.27, 3.76 for >28 years of consumption vs. never drank; $P_{trend} = 0.002$) (Table 4) and those with adenomas in multiple anatomic locations (OR = 1.77, 95% CI: 1.12, 2.79 for >28 years of consumption vs. never drank; $P_{trend} = 0.014$) (Table 5). To exclude the possibility that the associations between exposures and adenomas in multiple anatomic locations were affected by the association between exposures and the number of adenomas, an additional analysis that restricted the cases to those with 2 or more adenomas was conducted. A long duration of alcohol consumption was associated with an elevated risk of adenomas in the proximal and distal colon and adenomas in multiple anatomic locations, but it was not associated with rectal adenoma risk (data not shown).

DISCUSSION

A recent meta-analysis investigating cigarette smoking and adenomatous polyp risk provided pooled risk estimates of 2.14 for current smokers and 1.82 for those who had ever smoked compared with those who had never smoked (46). Stronger associations were observed for high-risk adenomas. Two meta-analyses of cigarette smoking and colorectal cancer risk confirmed the increased colorectal cancer risk in smokers (3, 4). The pooled risk estimates for current/ever smokers and colorectal cancer risk ranged between 1.07 and 1.25 (3, 4). If cigarette smoking is involved in the early carcinogenic process of colorectal neoplasia, the associations between cigarette smoking and colorectal adenoma risk should be stronger for low-risk adenomas than for advanced or high-risk adenomas. In the meta-analysis, however, high-risk adenomas had a stronger association with cigarette smoking (pooled relative risk for high-risk adenomas vs. low-risk adenomas = 2.04 vs. 1.52, respectively; current vs. never smokers; $P_{heterogeneity} = 0.024$) in 6 studies that reported stratified results for high- and low-risk adenomas (46). Our results provide further support for a stronger association between advanced adenomas and cigarette smoking, and they also support a role for cigarette smoking in colorectal carcinogenesis.

Alcohol may induce folate deficiency in the colon and rectum, possibly by causing folate malabsorption or inhibiting critical enzymes (47). Intestinal bacteria, which have high alcohol dehydrogenase activity, can oxidize ethanol in the colon and produce substantial levels of acetaldehyde (47). In addition, alcohol may suppress tumor immune surveillance, affect DNA repair, alter the composition of bile acids, or induce the expression of liver cytochrome P-450 enzymes that may consequently activate other carcinogens (48). Our results are consistent with those reported by Kato et al. (19), who showed that alcohol intake was associated only with the risk for multiple adenomas, and Boutron et al. (12), who demonstrated that alcohol intake is strongly associated with an increased risk of large adenomas. However, 2 other studies did not find a differential effect of alcohol intake on the basis of the sizes of the adenomas (14, 18).

Several studies have classified the locations of the adenomas according to their anatomic sites. However, assessment of the anatomic location in cases with multiple polyps has not been clearly described (16, 19, 22, 32, 36, 37). A large number of colorectal adenoma patients had adenomas in multiple anatomic locations (238 of 1,242; 20%) in our study, and most of the patients with adenomas in multiple locations had at least 1 proximal colon adenoma (215 of 238; 91%). In general, cigarette smoking variables had a stronger association with rectal adenomas than with colon adenomas, and cigarette smoking had a similar or stronger association with adenomas in multiple locations than with only rectal adenomas. For alcohol consumption, one study reported a positive association between daily ethanol intake and rectal adenoma risk (36), whereas another study suggested that alcohol consumption is associated only with an increased risk for proximal colon adenoma (19). Additional analysis with restriction to cases with 2 or more adenomas was conducted, to test whether the associations are different between those individuals who have multiple adenomas at a single anatomic location and those who have multiple adenomas at different locations (data not shown). More years of drinking increased the risk for adenomas in multiple anatomic locations and adenomas only in the proximal or distal colon. In contrast, the alcohol consumption frequency and the average alcohol intake were associated with a decreased risk for rectal adenoma. The effects of cigarette smoking variables are strongest for the risk for adenomas in the rectum only, followed by the risk for adenomas in the distal colon only. The risk estimates for adenomas in multiple anatomic locations were similar to those for adenomas in the proximal or distal colon only. Although the results are limited by a relatively small number of cases with 2 or more adenomas in the rectum only ($n = 10$), these results are generally consistent with analysis of single adenoma by anatomic locations, which showed an association between rectal adenoma risk and cigarette smoking. In addition, the association between multiple adenomas and alcohol

Table 2. Cigarette Smoking and Its Association With the Risks for Colorectal Adenoma, According to the Type and Number of Adenomas, National Cancer Center, Republic of Korea, 2007–2009

	No. of Controls (n = 3,019)	Any Adenoma (n = 1,242)			Advanced Adenoma (n = 120)			Low-Risk Adenoma Only (n = 1,122)			1–2 Adenomas (n = 1,062)			≥3 Adenomas (n = 180)		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Cigarette smoking																
Never smoked	1,672	439	1.00	Referent	86	1.00	Referent	804	1.00	Referent	399	1.00	Referent	40	1.00	Referent
Former smoker	582	344	1.31	1.04, 1.65	37	1.80	0.95, 3.42	307	1.27	1.00, 1.61	284	1.29	1.02, 1.65	60	1.40	0.83, 2.34
Current smoker	765	459	1.70	1.37, 2.12	45	2.26	1.23, 4.16	414	1.65	1.32, 2.07	379	1.64	1.31, 2.07	80	2.16	1.31, 3.55
No. of cigarettes/day																
Never smoked	1,672	439			38	1.00	Referent	401	1.00	Referent	399	1.00	Referent	40	1.00	Referent
<12	421	200	1.33	1.04, 1.70	18	1.56	0.77, 3.16	182	1.31	1.02, 1.69	172	1.34	1.04, 1.74	28	1.27	0.71, 2.28
12–20	177	113	1.71	1.25, 2.34	11	2.22	0.96, 5.15	102	1.67	1.21, 2.30	95	1.70	1.23, 2.36	18	1.82	0.93, 3.57
>20	567	404	1.86	1.47, 2.35	46	3.00	1.56, 5.76	358	1.77	1.39, 2.25	326	1.77	1.39, 2.27	78	2.41	1.44, 4.03
P_{trend}[b]				0.002			0.013			0.009			0.015			0.005
Years of cigarette smoking																
Never smoked	1,672	439			38	1.00	Referent	401	1.00	Referent	399	1.00	Referent	40	1.00	Referent
<19	460	169	1.22	0.95, 1.58	16	1.59	0.77, 3.29	153	1.19	0.91, 1.55	146	1.22	0.93, 1.59	23	1.27	0.69, 2.34
19–26	421	235	1.59	1.23, 2.04	17	1.57	0.74, 3.32	218	1.58	1.22, 2.05	195	1.54	1.18, 2.01	40	1.95	1.11, 3.43
>26	313	331	2.09	1.62, 2.68	43	3.52	1.82, 6.80	288	1.97	1.52, 2.55	267	2.04	1.57, 2.66	64	2.34	1.38, 3.97
P_{trend}[b]				<0.001			0.007			<0.001			<0.001			0.022
Pack-years of cigarette smoking																
Never smoked	1,672	439	1.00	Referent	38	1.00	Referent	401	1.00	Referent	399	1.00	Referent	40	1.00	Referent
<13	444	186	1.32	1.03, 1.69	18	1.74	0.86, 3.53	168	1.28	0.99, 1.66	159	1.31	1.01, 1.70	20	1.40	0.78, 2.53
13–25	363	222	1.66	1.28, 2.15	17	1.73	0.82, 3.66	205	1.65	1.27, 2.15	192	1.69	1.29, 2.22	30	1.50	0.83, 2.70
>25	333	295	2.01	1.56, 2.59	38	3.52	1.79, 6.94	257	1.89	1.45, 2.45	231	1.89	1.45, 2.47	64	2.72	1.60, 4.63
P_{trend}[b]				<0.001			0.007			0.002			0.003			0.003
Age at the start of smoking, years																
Never smoked	1,672	439	1.00	Referent	38	1.00	Referent	401	1.00	Referent	399	1.00	Referent	40	1.00	Referent
>22	345	235	1.65	1.29, 2.10	25	2.19	1.14, 4.19	210	1.60	1.25, 2.06	194	1.62	1.26, 2.09	41	1.85	1.08, 3.18
20–22	453	262	1.51	1.18, 1.93	29	2.21	1.12, 4.33	233	1.45	1.12, 1.87	219	1.49	1.15, 1.93	43	1.66	0.96, 2.89
<20	391	236	1.70	1.31, 2.20	21	2.06	0.99, 4.27	215	1.67	1.28, 2.18	195	1.65	1.26, 2.17	41	2.10	2.00, 3.71
P_{trend}[b]				0.876			0.963			0.872			0.990			0.626
Years since smoking cessation																
Never smoked	1,672	439	1.00	Referent	38	1.00	Referent	401	1.00	Referent	399	1.00	Referent	40	1.00	Referent
>11	194	128	1.29	0.96, 1.74	12	1.49	0.66, 3.33	116	1.28	0.94, 1.73	107	1.31	0.96, 1.79	21	1.21	0.64, 2.30
5–11	168	114	1.57	1.15, 2.14	17	3.11	1.47, 6.57	97	1.45	1.05, 2.00	90	1.48	1.07, 2.06	24	2.12	1.14, 3.97
<5	104	43	1.05	0.69, 1.58	4	1.27	0.41, 3.98	39	1.03	0.67, 1.57	37	1.06	0.69, 1.64	6	0.96	0.37, 2.48
Current smoker	765	459	1.70	1.40, 2.12	45	2.28	1.24, 4.20	414	1.66	1.32, 2.07	379	1.65	1.31, 2.07	80	2.17	1.32, 3.58

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, age, waist circumference, family history of colorectal cancer, and duration of alcohol consumption.

[b] Using the order of categories with exclusion of the never smoked category.

Table 3. Cigarette Smoking and Its Association With the Risks for Colorectal Adenoma, According to the Location of the Adenoma, National Cancer Center, Republic of Korea, 2007–2009

	No. of Controls (n = 3,019)	Right Colon (n = 554)			Left Colon (n = 344)			Rectum (n = 106)			Multiple Location (n = 238)		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Cigarette smoking													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
Former smoker	582	142	1.11	0.81, 1.51	100	1.66	1.13, 2.45	28	1.63	0.84, 3.16	74	1.23	0.79, 1.94
Current smoker	765	194	1.49	1.11, 1.99	119	1.85	1.28, 2.67	42	1.93	1.04, 3.59	104	1.97	1.29, 3.03
No. of cigarettes/day													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
<12	421	93	1.25	0.90, 1.74	56	1.55	1.03, 2.34	15	1.42	0.68, 2.95	36	1.18	0.71, 1.96
12–20	177	47	1.45	0.95, 2.19	28	1.79	1.06, 3.02	14	3.02	1.36, 6.73	24	1.75	0.98, 3.16
>20	567	159	1.49	1.09, 2.03	112	2.24	1.51, 3.32	36	2.29	1.17, 4.49	97	2.12	1.36, 3.31
P_{trend}[b]				0.208			0.044			0.120			0.004
Years of cigarette smoking													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
<19	460	66	1.00	0.70, 1.43	51	1.49	0.98, 2.28	22	1.74	0.88, 3.46	30	1.16	0.68, 1.97
19–26	421	107	1.49	1.07, 2.09	58	1.61	1.05, 2.49	19	1.61	0.77, 3.36	51	1.79	1.10, 2.92
>26	313	137	1.76	1.27, 2.46	85	2.34	1.55, 3.54	26	2.92	1.44, 5.93	83	2.19	1.38, 3.47
P_{trend}[b]				0.002			0.016			0.194			0.006
Pack-years of cigarette smoking													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
<13	444	83	1.21	0.86, 1.69	51	1.48	0.97, 2.26	17	1.51	0.74, 3.09	35	1.30	0.78, 2.17
13–25	363	98	1.49	1.06, 2.10	64	2.02	1.32, 3.10	23	2.36	1.15, 4.81	37	1.34	0.80, 2.24
>25	333	115	1.60	1.14, 2.24	74	2.21	1.45, 3.38	24	2.55	1.24, 5.23	82	2.49	1.57, 3.94
P_{trend}[b]				0.065			0.045			0.094			0.001
Age at the start of smoking, years													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
>22	345	101	1.44	1.04, 1.99	56	1.71	1.13, 2.58	23	2.36	1.23, 4.53	55	1.76	1.10, 2.80
20–22	453	104	1.23	0.88, 1.72	81	2.02	1.34, 3.03	22	1.66	0.83, 3.35	55	1.51	0.94, 2.44
<20	391	102	1.53	1.08, 2.16	63	1.94	1.25, 3.00	22	1.90	0.93, 3.89	49	1.79	1.09, 2.93
P_{trend}[b]				0.855			0.710			0.709			0.991
Years since quitting smoking													
Never smoked	1,672	218	1.00	Referent	125	1.00	Referent	36	1.00	Referent	60	1.00	Referent
>11	194	52	1.07	0.72, 1.60	37	1.67	1.03, 2.69	9	1.54	0.65, 3.66	30	1.27	0.73, 2.19
5–11	168	35	0.98	0.63, 1.54	38	2.27	1.41, 3.68	9	1.82	0.77, 4.34	32	2.05	1.19, 3.54
<5	104	22	1.09	0.64, 1.85	13	1.36	0.70, 2.63	4	1.33	0.43, 4.12	4	0.45	0.15, 1.33
Current smoker	765	194	1.48	1.11, 1.99	119	1.85	1.28, 2.68	42	1.93	1.04, 3.59	104	1.99	1.29, 3.06

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, age, waist circumference, family history of colorectal cancer, and duration of alcohol consumption.

[b] Using the order of the categories with the exception of the "never smoked" category.

consumption was observed only among cases with multiple adenomas in the colon or multiple locations. Moreover, we cannot completely rule out the possibility that patients with colorectal adenomas in multiple anatomic locations may present a different risk factor profile from those with an adenoma in a single anatomic location.

Table 4. Alcohol Intake and Its Association With the Risks for Colorectal Adenoma, According to the Type and the Number of Adenomas, National Cancer Center, Republic of Korea, 2007–2009

	No. of Controls (n = 3,019)	Any Adenoma (n = 1,242)			Advanced Adenoma (n = 120)			Low-Risk Adenoma Only (n = 1,122)			1–2 Adenomas (n = 1,062)			≥3 Adenomas (n = 180)		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Alcohol use																
Never drinker	919	304	1.00	Referent	86	1.00	Referent	804	1.00	Referent	280	1.00	Referent	24	1.00	Referent
Former drinker	136	65	0.92	0.65, 1.31	8	1.30	0.55, 3.07	57	0.88	0.61, 1.27	50	0.82	0.56, 1.19	15	1.88	0.92, 3.88
Current drinker	1,964	873	0.98	0.82, 1.18	86	1.21	0.72, 2.02	787	0.96	0.80, 1.16	732	0.93	0.77, 1.12	141	1.60	0.98, 2.63
No. of drinks/week																
Never drinker	919	304	1.00	Referent	26	1.00	Referent	278	1.00	Referent	280	1.00	Referent	24	1.00	Referent
<1	586	207	0.95	0.76, 1.19	25	1.37	0.75, 2.47	182	0.91	0.72, 1.15	175	0.89	0.71, 1.13	32	1.54	0.87, 2.74
1–4	665	305	1.03	0.83, 1.28	35	1.44	0.80, 2.59	270	0.99	0.79, 1.25	248	0.95	0.75, 1.19	57	1.92	1.11, 3.31
>4	641	347	1.01	0.81, 1.27	28	0.99	0.53, 1.87	319	1.01	0.80, 1.28	295	0.98	0.77, 1.24	52	1.42	0.81, 2.49
P_{trend}				0.915			0.990			0.913			0.805			0.295
Years of drinking																
Never drinker	919	304	1.00	Referent	26	1.00	Referent	278	1.00	Referent	280	1.00	Referent	24	1.00	Referent
<20	594	147	0.89	0.69, 1.14	12	0.93	0.44, 1.96	135	0.89	0.69, 1.14	132	0.86	0.67, 1.11	15	1.24	0.61, 2.52
20–28	615	241	0.99	0.78, 1.25	23	1.37	0.70, 2.68	218	0.96	0.75, 1.22	205	0.91	0.71, 1.16	36	1.93	1.05, 3.56
>28	483	407	1.26	1.00, 1.58	50	2.00	1.10, 3.64	357	1.20	0.95, 1.51	322	1.15	0.91, 1.46	85	2.19	1.27, 3.76
P_{trend}				0.038			0.006			0.141			0.260			0.002
Alcohol intake/day, g																
Never drinker	919	304	1.00	Referent	26	1.00	Referent	278	1.00	Referent	280	1.00	Referent	24	1.00	Referent
<3	487	136	0.85	0.67, 1.09	15	1.15	0.59, 2.24	121	0.83	0.64, 1.07	116	0.80	0.62, 1.04	20	1.43	0.76, 2.68
3–10	439	203	1.16	0.92, 1.48	21	1.50	0.79, 2.86	182	1.13	0.89, 1.45	174	1.11	0.87, 1.43	29	1.71	0.94, 3.13
11–30	452	249	1.09	0.86, 1.40	32	1.76	0.94, 3.29	217	1.04	0.81, 1.33	204	1.02	0.79, 1.31	45	1.92	1.08, 3.41
>30	420	240	1.06	0.83, 1.37	18	1.01	0.49, 2.07	222	1.07	0.82, 1.38	199	1.00	0.77, 1.30	41	1.72	0.95, 3.13
P_{trend}				0.476			0.434			0.579			0.901			0.047

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, age, waist circumference, a family history of colorectal cancer, and smoking status.

Table 5. Alcohol Intake and Its Associations With the Risks for Colorectal Adenoma, According to the Location of the Adenoma, National Cancer Center, Republic of Korea, 2007–2009

	No. of Controls (*n* = 3,019)	Right Colon (*n* = 554)			Left Colon (*n* = 344)			Rectum (*n* = 106)			Multiple Locations (*n* = 238)		
		No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI	No.	OR[a]	95% CI
Alcohol use													
Never drinker	919	145	1.00	Referent	93	1.00	Referent	28	1.00	Referent	38	1.00	Referent
Former drinker	136	29	0.95	0.60, 1.52	14	0.66	0.36, 1.23	7	1.07	0.44, 2.57	15	1.24	0.63, 2.43
Current drinker	1,964	380	0.99	0.77, 1.26	237	0.89	0.67, 1.20	71	0.71	0.42, 1.18	185	1.40	0.93, 2.12
No. of drinks/week													
Never drinker	919	145	1.00	Referent	93	1.00	Referent	28	1.00	Referent	38	1.00	Referent
<1	586	93	0.96	0.71, 1.29	55	0.84	0.58, 1.21	21	0.86	0.47, 1.58	38	1.23	0.75, 2.01
1–4	665	141	1.10	0.82, 1.47	77	0.88	0.61, 1.62	23	0.64	0.35, 1.18	64	1.48	0.92, 2.36
>4	641	145	1.00	0.74, 1.36	98	0.98	0.68, 1.41	24	0.56	0.30, 1.05	80	1.51	0.95, 2.42
P_{trend}				0.896			0.928			0.023			0.083
Years of drinking													
Never drinker	919	145	1.00	Referent	93	1.00	Referent	28	1.00	Referent	38	1.00	Referent
<20	594	67	0.95	0.68, 1.33	37	0.68	0.44, 1.04	19	0.82	0.43, 1.58	24	1.30	0.72, 2.26
20–28	615	110	1.05	0.76, 1.44	68	0.92	0.63, 1.35	22	0.65	0.34, 1.23	41	1.28	0.76, 2.17
>28	482	170	1.20	0.89, 1.62	112	1.30	0.90, 1.86	22	0.69	0.36, 1.33	103	1.77	1.12, 2.79
P_{trend}				0.227			0.104			0.129			0.014
Alcohol intake/day, g													
Never drinker	919	145	1.00	Referent	93	1.00	Referent	28	1.00	Referent	38	1.00	Referent
<3	487	58	0.81	0.58, 1.13	38	0.77	0.52, 1.16	16	0.93	0.49, 1.75	24	1.12	0.65, 1.94
3–10	439	88	1.17	0.85, 1.61	58	1.10	0.75, 1.61	17	0.80	0.41, 1.52	40	1.60	0.97, 2.66
11–30	452	117	1.25	0.91, 1.73	57	0.84	0.56, 1.25	18	0.62	0.31, 1.20	57	1.64	1.00, 2.69
>30	420	103	1.12	0.80, 1.57	68	1.02	0.68, 1.52	15	0.49	0.24, 0.99	54	1.55	0.93, 2.57
P_{trend}				0.252			0.954			0.011			0.055

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for sex, age, waist circumference, a family history of colorectal cancer, and smoking status.

In addition to the severity and anatomic location of the adenomas, cigarette smoking and alcohol consumption were more strongly associated with the presence of 3 or more multiple adenomas than with 1 or 2 adenomas. Our results are consistent with those obtained in 3 studies conducted in Korea and Japan, which reported a stronger association between cigarette smoking and the risk for multiple adenomas than for a single adenoma (19, 22, 35).

The advantages of the current study include the colonoscopy-based outcome assessment, which minimized the contamination of the polyp-free control group with cases of adenoma or other types of polyps. Studies in which all of the controls underwent a full colonoscopy demonstrated higher risk estimates for cigarette smoking compared with studies in which some or all of the controls underwent a partial colon examination. The results from these studies suggest a possible misclassification of polyp patients who might have had proximal colon adenomas but were categorized as controls (46). Because all of our study participants underwent a full colonoscopy, the possibility of misclassification was minimized. Although the study had a cross-sectional design, the risk factor assessment was performed prior to the colonoscopy procedure. Therefore, potential information bias due to any prior knowledge of the participants' disease status should have been minimized. Furthermore, the use of detailed clinical information about the adenomas (such as multiplicity, severity, and the anatomic locations of adenomas) in a large number of patients enabled subgroup analyses with sufficient statistical power.

Participants who were provided questionnaire information were more likely to be a male or younger than the nonparticipants. The prevalence of adenoma was 25.9% in participants and 32.2% in nonparticipants, which was reasonable when considering the younger age distribution of the participants compared with the nonparticipants. The study participants were recruited in a single cancer screening center and, therefore, the results may not be generalized to the entire Korean population. However, the prevalence of colorectal adenoma in our study population was comparable with those of previous Korean studies (49, 50), and the prevalence of cigarette smoking and alcohol

consumption was comparable to that of the general population (45). Because colorectal adenomatous polyps are not rare, the rare disease assumption is not fulfilled, and therefore, the odds ratios overestimate the expected relative risk (51).

In conclusion, the current study provides additional support that cigarette smoking is associated with an increased risk of adenomas, regardless of anatomic location, severity, and number, whereas alcohol consumption is associated with an increased risk of advanced and multiple adenomas. The strong association with advanced adenoma or multiple adenomas suggests that alcohol consumption and cigarette smoking facilitate colorectal carcinogenesis.

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