

Alcohol Drinking, Cigarette Smoking and Risk of Colorectal Cancer in the Korean Multi-center Cancer Cohort

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Background: The present study aimed to examine the association between cigarette smoking, alcohol consumption and colorectal cancer risk among Korean adults.

Methods: Data from the Korean Multi-center Cancer Cohort between 1993 and 2005 were analyzed. The study population comprised 18,707 subjects aged older than 20 years old. The subjects were followed until December 31, 2011 (median follow-up of 11.2 years). The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence intervals of cigarette smoking and alcohol consumption for colorectal cancer risk.

Results: In men, longer duration and higher average amount of alcohol consumption were associated with elevated risk of colorectal cancer (HR 1.93 [1.17-3.18] for ≥ 30 years of consumption compared to non-drinkers; HR 2.24 [1.31-3.84] for ≥ 30 g/d). Former smokers showed a non-significantly elevated risk of colorectal cancer in men. There was no apparent association between alcohol consumption or cigarette smoking and colorectal cancer risk among women.

Conclusions: Alcohol consumption was associated with increased colorectal cancer risk among Korean men, and both a longer duration and a higher amount of consumption were associated with elevated risk.

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Key Words: Colorectal neoplasms, Smoking, Alcohol drinking, Prospective studies

INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide.¹ In Korea, colorectal cancer incidence has increased during the last decade, with an annual percentage change of 5.6% (6.1% in males and 4.5% in females) from 1999 to 2011 in age-adjusted rates.²

Alcohol consumption and cigarette smoking are regarded as major risk factors for gastrointestinal cancer, including colorectal cancer.³ Alcohol is a group 1 carcinogen with sufficient evidence for colorectal cancer,⁴ and the World Cancer Research Fund/American Institute of Cancer Research suggests that elevated risk

of colorectal cancer caused by excessive alcohol consumption (more than approximately 30 g per day of ethanol) is 'convincing' for men but probable for women.⁵ As a result of cumulative evidence from epidemiological studies, colorectal cancer has been listed as a cancer site with 'sufficient evidence' for human linked to group 1 carcinogen cigarette smoking.^{4,6-10}

However, epidemiological studies conducted in Korea have not shown a significant relationship between those risk factors, smoking¹¹ and alcohol¹²⁻¹⁵ and colorectal cancer risk. To elucidate these discrepancies, we examined the association between cigarette smoking, alcohol consumption and colorectal cancer risk in a Korean cohort study.

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MATERIALS AND METHODS

1. Study population

The Korean Multi-center Cancer Cohort is a population-based prospective cohort designed to investigate the relationship between exposures to environmental factors, lifestyle factors, host factors and the risk of cancer in Korea.¹⁶ From 1993 to 2005, a total of 19,252 participants (7,727 men and 11,525 women) were recruited. We excluded those who were younger than 20 years old (164 men and 341 women), who had no information about both cigarette smoking and alcohol consumption (65 men and 130 women), with a prior diagnosis of colorectal cancer (9 men and 19 women), or who were censored within one month from the baseline survey (2 men and 3 women). Finally, 18,522 participants (7,488 men and 11,034 women) were included in the final analysis. This study approved by the Institutional Review Board (IRB) at Seoul National University Hospital (IRB number 1407-097-597).

2. Exposure, covariate, and outcome assessment

Data on smoking habits, alcohol consumption, and other lifestyle factors were collected by direct interview at baseline.¹⁶ Participants were asked to answer questions of whether they drank alcoholic beverages ("Yes", "Yes, but not now", or "No" were the answer options to the question, "Have you ever drunk alcohol?"), and for "ever drinkers", consumption frequency and average quantity of one serving over the past year by beverage type was recorded. For cigarette smoking, cigarette-smoking habits ("Have you smoked more than 400 cigarettes during your entire life?"), smoking duration, average number of cigarettes smoked per day were asked. Cohort subjects were followed for cancer occurrence by using the Korea Central Cancer Registry database and for death by linking death certificated database of the Statistics Korea until December 31, 2011.

3. Statistical analysis

We used Cox proportional hazards model with age as the time scale to estimate multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).^{17,18} Due to substantial differences in smoking and alcohol use habits between men and women, all analyses were stratified by sex. All statistical analyses were performed by using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Table 1. General characteristics of the study subjects

Variable	Men	Women	Total
Total case	7,488	11,034	18,522
Colorectal cancer case	112 (1.5)	108 (1.0)	220 (1.2)
Age at baseline (yr)			
20-29	349 (4.7)	322 (2.9)	671 (3.6)
30-39	830 (11.1)	1,096 (9.9)	1,926 (10.4)
40-49	1,356 (18.1)	2,080 (18.9)	3,436 (18.6)
50-59	1,834 (24.5)	3,016 (27.3)	4,850 (26.2)
60-69	2,173 (29.0)	3,242 (29.4)	5,415 (29.2)
70-79	851 (11.4)	1,142 (10.3)	1,993 (10.8)
80-89	91 (1.2)	133 (1.2)	224 (1.2)
≥ 90	4 (0.1)	3 (0.0)	7 (0.0)
Education level (yr)			
Uneducated	880 (11.8)	3,203 (29.0)	4,083 (22.0)
1-12	6,133 (81.9)	7,603 (68.9)	13,736 (74.2)
≥ 13	422 (5.6)	186 (1.7)	608 (3.3)
Missing	53 (0.7)	42 (0.4)	95 (0.5)
Total time of moderate physical activity (h/wk)			
Never	1,536 (20.5)	1,357 (12.3)	2,893 (15.6)
0.5-7	2,010 (26.8)	3,149 (28.5)	5,159 (27.9)
≥ 7	1,736 (23.2)	3,009 (27.3)	4,745 (25.6)
Missing	2,206 (29.5)	3,519 (31.9)	5,725 (30.9)
Body mass index (kg/m ³)			
< 18.5	336 (4.5)	381 (3.5)	717 (3.9)
18.5-22	3,215 (42.9)	3,773 (34.2)	6,988 (37.7)
23-24	1,692 (22.6)	2,459 (22.3)	4,151 (22.4)
≥ 25	1,796 (24.0)	3,703 (33.6)	5,499 (29.7)
Missing	449 (6.0)	718 (6.5)	1,167 (6.3)

Values are presented as number only or number (%).

RESULTS

The general characteristics of study participants are shown in Table 1. More than half of participants were 50 to 69 years old at baseline (26.2% ages 50 to 59 years and 29.2% ages 60 to 69 years). The majority of men were current drinkers (64.5%), and most women were non-drinkers (78.5%). Moderate (10 to 29 g of alcohol per day) and heavy drinkers (more than 30 g of alcohol per day) was 17.1% and 23.0% in men, compared to 2.4% and 1.4% in women, respectively.

During a median 11.2 years of follow-up and 21.0 million person-years of observation, there were 220 colorectal cancer cases (112 men and 108 women). The age-specific incident rates of the study participants were comparable to those of Korean population (average annual incidence from 2003 to 2007) published in Cancer Incidence in Five Continents Volume X (data are not shown).¹⁹ The HRs and 95% CIs for colorectal cancer according to alcohol consumption are shown by sex in Table 2. The 31.5% of men had drunk alcohol for more than 30 years, whereas only 2.5% of women did. The Table 2 shows that current

male drinkers had a 70% increased risk of developing colorectal cancer (HR 1.70, 95% CI 1.05-2.76) compared to non-drinkers). Both longer duration and higher average amount of alcohol consumption were associated with elevated risk for colorectal

cancer (HR 1.93, 95% CI 1.17-3.18 for ≥ 30 years of consumption compared to non-drinkers; HR 2.24, 95% CI 1.31-3.84 for ≥ 30 g/d). In contrast, there was no association between alcohol consumption and colorectal cancer incidence in women nor was

Table 2. HRs and 95% CIs for colorectal cancer according to alcohol consumption in the Korean Multi-center Cancer Cohort, 1993-2005

	Men				Women			
	Number (%)	Person-year	Colorectal cancer case (n)	HR (95% CI) ^a	Number (%)	Person-year	Colorectal cancer case (n)	HR (95% CI) ^a
Alcohol consumption history								
Never drinker	1,845 (24.6)	20,102.6	22	ref.	8,660 (78.5)	103,189.0	90	Ref.
Former drinker	783 (10.5)	7,880.6	10	0.92 (0.43-1.96)	234 (2.1)	2,452.1	3	1.29 (0.40-4.16)
Current drinker	4,827 (64.5)	51,650.7	79	1.70 (1.05-2.76)	2,072 (18.8)	23,413.3	15	0.85 (0.49-1.47)
Missing	33 (0.4)	345.8	1	2.08 (0.28-15.71)	68 (0.6)	737.1	0	
Duration of alcohol consumption (yr)								
Never drinker	1,845 (24.6)	20,102.6	22	ref.	8,660 (78.5)	103,189.0	90	Ref.
< 15	704 (9.4)	8,016.2	1	0.31 (0.04-2.27)	975 (8.8)	11,339.2	8	1.09 (0.53-2.26)
15-29	2,111 (28.2)	23,552.6	23	1.32 (0.72-2.44)	793 (7.2)	8,683.7	7	0.96 (0.44-2.08)
≥ 30	2,377 (31.7)	23,129.3	60	1.93 (1.17-3.18)	284 (2.6)	2,909.1	1	0.33 (0.05-2.34)
Missing	451 (6.0)	5,179.1	6	0.99 (0.40-2.46)	322 (2.9)	3,670.5	2	0.67 (0.16-2.74)
Alcohol consumption amount (g/d)								
Never drinker	1,845 (24.6)	20,102.6	22	ref.	8,660 (78.5)	103,189.0	90	Ref.
< 10	1,823 (24.3)	19,271.4	24	1.28 (0.71-2.31)	1,408 (12.8)	14,953.8	9	0.82 (0.41-1.63)
10-29	1,282 (17.1)	13,115.5	20	1.77 (0.96-3.26)	264 (2.4)	2,792.1	2	0.95 (0.23-3.87)
≥ 30	1,723 (23.0)	17,270.9	38	2.24 (1.31-3.84)	151 (1.4)	1,666.3	1	0.76 (0.11-5.44)
Missing	815 (10.9)	10,219.4	8	0.77 (0.34-1.75)	551 (5.0)	7,190.3	6	0.97 (0.42-2.24)

HR, Hazard ratio; CI, confidence interval; Ref., reference. ^aAdjusted for body mass index (kg/m²; < 18.5, 18.5-22, 23-24, ≥ 25), moderate physical activity (h/wk; never, 0.5-6, ≥ 7), and cigarette smoking history (never smoker, former smoker, current smoker).

Table 3. HRs and 95% CIs for colorectal cancer according to cigarette smoking in the Korean Multi-center Cancer Cohort, 1993-2005

	Men				Women			
	Number (%)	Person-year	Colorectal cancer case (n)	HR (95% CI) ^a	Number (%)	Person-year	Colorectal cancer case (n)	HR (95% CI) ^a
Cigarette smoking history								
Never smoker	1,486 (19.8)	16,624.2	21	ref.	10,018 (90.8)	118,501.0	102	Ref.
Former smoker	1,714 (22.9)	16,538.6	34	1.33 (0.76-2.32)	208 (1.9)	2,138.7	3	1.14 (0.35-3.67)
Current smoker	4,280 (57.2)	46,733.7	57	0.97 (0.58-1.62)	761 (6.9)	8,618.5	3	0.30 (0.10-0.97)
Missing	8 (0.1)	83.3	0		47 (0.4)	533.0	0	
Smoking duration (yr)								
Never smoker	1,486 (19.8)	16,624.2	21	ref.	10,018 (90.8)	118,501.0	102	Ref.
< 20	1,200 (16.0)	12,908.6	7	1.04 (0.43-2.48)	295 (2.7)	3,399.0	1	0.33 (0.05-2.35)
20-39	2,259 (30.2)	24,596.6	34	1.05 (0.60-1.85)	340 (3.1)	3,661.6	1	0.22 (0.03-1.62)
≥ 40	1,606 (21.4)	14,479.2	31	1.00 (0.56-1.78)	162 (1.5)	1,607.9	1	0.46 (0.06-3.35)
Missing	937 (12.5)	11,371.2	19	1.37 (0.68-2.74)	219 (2.0)	2,621.8	3	0.93 (0.29-2.97)
Lifetime cigarette smoking (pack-year)								
Never smoker	1,486 (19.8)	16,624.2	21	ref.	10,018 (90.8)	118,501.0	102	Ref.
< 10	841 (11.2)	8,659.0	13	2.04 (1.01-4.14)	360 (3.3)	3,970.7	1	0.25 (0.04-1.83)
10-19	1,022 (13.6)	10,542.0	8	0.76 (0.33-1.74)	207 (1.9)	2,223.7	1	0.38 (0.05-2.77)
≥ 20	3,095 (41.3)	31,567.6	49	0.95 (0.56-1.60)	200 (1.8)	2,179.0	1	0.38 (0.05-2.76)
Missing	1,044 (13.9)	12,586.9	21	1.34 (0.68-2.63)	249 (2.3)	2,916.8	3	0.80 (0.25-2.57)

HR, Hazard ratio; CI, confidence interval; Ref., reference. ^aAdjusted for body mass index (kg/m²; < 18.5, 18.5-22, 23-24, ≥ 25), moderate physical activity (h/wk; never, 0.5-6, ≥ 7), and alcohol consumption history (never drinker, former drinker, current drinker).

there statistical significance.

The HRs and 95% CIs for colorectal cancer according to cigarette smoking are shown by sex in Table 3. Former smokers comprised 22.7% and current smokers comprised 56.7% in men, whereas 89.7% of women were non-smokers. Most male smokers (including former and current smokers) had smoked more than 20 pack-years in their lifetime, whereas most female smokers smoked 10 to 19 pack-years in their lifetime. Male former smokers showed a non-significantly elevated risk for colorectal cancer. Men who smoked less than 10 pack-years had a significantly higher risk for colorectal cancer. Smoking status and amount of lifetime cigarette smoking did not show a significant relationship with colorectal cancer in women. Smoking duration was not significantly related to colorectal cancer regardless of sex.

DISCUSSION

In this study, we analyzed the association between cigarette smoking, alcohol consumption and colorectal cancer risk among Korean adults. Both longer duration and high alcohol consumption amount were related to an increased risk of colorectal cancer in men. Male former smokers also showed an elevated colorectal cancer risk. In contrast, no apparent relationship between these risk factors and colorectal cancer were observed among women.

A hospital-based case-control study conducted in Korea showed an elevated risk of colorectal cancer only among heavy drinkers whose alcohol consumption was 30 g/d or more.¹² A health insurance-based cohort study also reported an elevated risk of distal colon and rectal cancer among men with frequent alcohol consumption (3-4 times/wk) or high average consumption amount or more than one bottle of Korean distilled spirits.²⁰ These results are consistent with our results. However, other Korean studies report no significant association¹⁴ or difference in risk by sub-sites.^{12,21}

A meta-analysis with 57 articles published between 1986 and 2010 showed a higher risk of colorectal cancer among heavy drinkers,²² and these elevated risks were more prominent in men than women and Asians rather than Europeans or North Americans.²² A meta-analysis of 16 prospective cohort studies showed a stronger association with rectal cancer than colon cancer risk, and the association was significant only among men (for rectal cancer, HR 1.64, 95% CI 1.39-1.93; for colon cancer, HR 1.79, 95% CI 1.38-2.33).²³ A pooled analysis of 8 cohort studies from North America and Europe reported a significant risk only among the highest consumption group and the elevated risk was more significant for distal colon and rectal cancer.²⁴ A pooled

analysis of five cohort studies conducted in Japan showed a significant association between alcohol consumption level and colorectal cancer risk in both sexes and all sub-sites of the colorectum.²⁵ Our results, in addition to those of another report^{22,24} that did not find significantly elevated risk of colorectal cancer among light drinkers, are consistent with a recent meta-analysis.²⁶

In regard to cigarette smoking and colorectal cancer risk, previous epidemiological studies conducted in Korea did not find clear associations.^{15,20,27} In a case-control study of men, none of the smoking variables, such as cigarette smoking history, duration of smoking, number of cigarettes per day, and age at start of smoking, were associated with colorectal cancer risk.¹⁵ A health insurance-based cohort study did not find any association between smoking and colorectal cancer in both men and women.²⁷ However, the most recent health insurance-based cohort study suggested marginal elevated risk for distal colon and rectal cancer among male former smokers.²⁰ In a Korean cohort study with an elderly population, former smokers showed a higher risk of colorectal cancer.¹¹ However, longer duration of smoking of 45 years and more was significantly associated with elevated risk, whereas higher pack-year was not associated with the risk.¹¹

In a meta-analysis, a stronger association with colorectal cancer risk was observed in former smokers than current smokers.^{28,30} The pooled relative risk in former smokers was 1.17 (95% CI 1.11-1.22), whereas that for current smokers was 1.07 (95% CI 0.99-1.16).²⁸ In another meta-analysis by sub-sites, the association was stronger for rectal cancer than colon cancer.²⁹ Similar to our results, the European Prospective Investigation into Cancer and Nutrition study showed significantly elevated risk of colorectal cancer only among former smokers but not among current smokers. However, the association was most prominent for proximal colon cancer.

We did not find an association between cigarette smoking and colorectal cancer risk among women. Less than 10% of women were 'ever smokers' in our study; therefore, statistical power was not adequate. A Norwegian cohort study suggested higher susceptibility for colorectal cancer among women; however, that study included more female smokers than our study.³¹

The strengths of our study include prospective study design, which clarifies the temporal association between exposures to risk factors and colorectal cancer occurrence. Outcome ascertainment via linkage to cancer registries and a death certificate database minimized follow-up loss.

A limitation of the study includes lack of replicate information on alcohol consumption and cigarette smoking habits, which may

change after the baseline survey. Although the median follow-up time was longer than 10 years, we do not have enough statistical power to analyze the data according to the sub-sites of colorectal cancer or former/current smoking/drinking status. Additionally, information on the duration of quitting smoking and exposure to secondhand smoke was not available.

Alcohol consumption was associated with increased colorectal cancer risk among Korean men, and both longer duration and higher amount of consumption were associated with elevated risk.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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