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Original Article

Impact of Smoking and Alcohol Consumption on Early-Onset Gastric Cancer Development in Young Koreans: A Population-Based Study

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ABSTRACT

Purpose: Although smoking and alcohol consumption are known risk factors for gastric cancer (GC), studies assessing their effects on early-onset GC are limited. In this nationwide, population-based, prospective cohort study, we assessed the effects of smoking and alcohol consumption on early-onset GC in patients aged <50 years.
Materials and Methods: We analyzed data of patients aged 20–39 years who underwent cancer and general health screening in the Korean National Health Screening Program between 2009 and 2012. We calculated the adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for GC incidence until December 2020.
Results: We enrolled 6,793,699 individuals (men:women=4,077,292:2,716,407) in this cohort. The mean duration of follow-up was 9.4 years. During follow-up, 9,893 cases of GC (men:women=6,304:3,589) were reported. Compared with the aHRs (95% CI) of never-smokers, those of former and current-smokers were 1.121 (1.044–1.205) and 1.282 (1.212–1.355), respectively. Compared with the aHRs (95% CI) of non-consumers, those of low-moderate- and high-risk alcohol consumers were 1.095 (1.046–1.146) and 1.212 (1.113–1.321), respectively. GC risk was the highest in current-smokers and high-risk alcohol consumers (1.447 [1.297–1.615]). Interestingly, alcohol consumption and smoking additively increased the GC risk in men but not in women ($P_{interaction}$=0.002).
Conclusion: Smoking and alcohol consumption are significant risk factors for early-onset GC in young Koreans. Further studies are needed to investigate sex-based impact of alcohol consumption and smoking on GC incidence in young individuals.

Keywords: Early-onset gastric cancer; Smoking; Alcohol

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
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INTRODUCTION

Gastric cancer (GC) is one of the most common cancers in South Korea. *Helicobacter pylori* infection is one of the most common causes of GC. In 1998, a Korean nationwide study reported that the prevalence of *H. pylori* was as high as 67% [1]. However, its prevalence has decreased significantly to 41.5% in 2016 due to improved hygiene and widespread eradication therapy [2]. The prevalence of *H. pylori* showed a declining trend over 14 years (from 2005 to 2019). Particularly, for individuals in the 20-year age group, the prevalence decreased from 29.3% to 14.7%, and for individuals in the 30-year age group, the prevalence decreased from 49.1% to 30.4%.

However, the incidence of GC in young individuals did not decrease significantly despite the decline in the prevalence of *H. pylori* in this population. According to the Korean Cancer Registry, the total number of GC cases in 2017 was 29,685, with 3,510 cases occurring in individuals aged <50 years, accounting for 11.82% of all cases of GC [3]. In 2004, there were 4,674 GC patients aged <50 years. Therefore, other factors might contribute to GC in young Koreans. Apart from *H. pylori*, smoking and alcohol consumption are significant risk factors for GC [4]. However, genetic, hormonal, and other environmental factors can modify the effect of smoking and alcohol consumption on GC development [5]. A recent meta-analysis indicated that an individuals' sex can affect the association between alcohol consumption and GC risk [6].

We conducted a nationwide population-based cohort study to investigate the association between smoking, alcohol consumption, and GC development in patients aged <50 years. In particular, we analyzed the effect of patients' sex on the interaction between smoking and alcohol consumption.

MATERIALS AND METHODS

Data source and study cohort

We analyzed data from a prospective population-based cohort of individuals who underwent cancer screening and general health check-ups collected by the Korean National Health Insurance Corporation [7]. Initially, 6,891,614 individuals aged 20–39 years who underwent screening between 2009 and 2012 were enrolled. Those with missing data (n=71,610) or a history of cancer at the time of screening (n=23,036) were excluded. Additionally, patients who had a diagnosis of GC within 1 year (n=3,269) of enrollment were excluded to account for the possibility of missed cases of GC at the time of screening. The remaining 6,793,699 individuals were included in this study (**Supplementary Fig. 1**). The follow-up duration was calculated from the date of general health screening until the new diagnosis of GC, death, or the end of the study period on December 31, 2020, whichever came first.

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Hospital (IRB No. X-2210-785-901). As this study used a nationwide database and excluded collection of patient identifying information, the IRB waived the requirement for informed consent.

Definitions and clinical parameters

GC diagnoses were identified from claims data using the International Classification of Diseases, 10th revision (ICD-10) code C16. The C16 code refers to malignant neoplasms of the stomach and

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does not include benign neoplasms, such as gastric adenoma. Diabetes was defined as a fasting plasma glucose level ≥126 mg/dL, taking oral hypoglycemic agents or insulin, or ICD-10 codes E11–14. Hypertension was defined as systolic/diastolic blood pressure ≥140/90 mmHg, taking antihypertensive medication, or ICD-10 codes I10–13. Dyslipidemia was defined as fasting total cholesterol ≥240 mg/dL, taking lipid-lowering medications, or ICD-10 code E78. The history of medications prescribed within 1 year prior to registration was collected from the claims data.

The following data were extracted from the questionnaire: previous cancer diagnosis, smoking (never/former/current), alcohol consumption (non-consumer; low-moderate-risk alcohol consumer: men <40 g/day, women <20 g/day; high-risk alcohol consumer: men ≥40 g/day, women ≥20 g/day), and regular exercise (high-intensity: >20 minutes ≥3 times/week; moderate-intensity: >30 minutes ≥5 times/week over the last week, yes/no). On the screening day, anthropometric data, such as height, weight, and waist circumference, were collected, and systolic/diastolic blood pressure was measured.

Blood samples were drawn after an 8-hours fast. Laboratory data, including fasting plasma glucose and cholesterol (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), were analyzed.

Statistical analysis

To analyze continuous and categorical variables, we used Student's t-test and χ^2-test, respectively. GC incidence rates were calculated as the number of cases per 1,000 person-years at risk. The log-rank test was employed for the time-to-event analyses. To investigate the independent risk of smoking and alcohol consumption on GC development, we used a Cox proportional hazards model after adjusting for clinically important factors.

All analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA) and R (version 3.2.3; The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). A two-tailed test method was applied, and statistical significance was defined as a P-value <0.05.

RESULTS

Baseline characteristics of cohort

Baseline characteristics of the study population according to smoking and alcohol consumption status are shown in **Table 1**. Participants who were smokers were primarily men, obese, and demonstrated higher blood pressure, total cholesterol, and fasting serum glucose levels compared with never-smokers (all P<0.001). Diabetes, hypertension, or dyslipidemia was more prevalent in former- and current-smokers than in never-smokers (all P<0.001). Conversely, former-smokers (18.4%) were more likely to exercise regularly compared with never- (11.6%) or current-smokers (14.4%).

Alcohol consumption was more prevalent in men (P<0.001) than in women. Moreover, alcohol consumption was significantly associated with increased blood pressure, body mass index, waist circumference, cholesterol, and fasting serum glucose levels (all P<0.001). Participants with heavy alcohol consumption exhibited a higher prevalence of hypertension compared with non-consumers or mild-to-moderate-risk alcohol consumers. Additionally, alcohol consumers showed a tendency to engage in regular exercise than non-consumers.

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Table 1. Baseline characteristics of the participants according to smoking and alcohol consumption status

Characteristics	Smoking status				Alcohol consumption status			
	Never-smoker (n=3,719,097)	Former-smoker (n=701,098)	Current-smoker (n=2,373,504)	P-value	Non-consumer (n=2,563,789)	Low-moderate-risk consumer* (n=3,814,970)	High-risk consumer† (n=414,940)	P-value
Male	1,255,457 (33.76)	605,447 (86.36)	2,216,388 (93.38)	<0.0001	1,072,908 (41.85)	2,722,292 (71.36)	282,092 (67.98)	<0.001
Age	30.17±5.10	32.44±4.68	31.28±4.82	<0.0001	30.9±5.07	30.77±4.97	30.28±5.18	<0.001
Smoking status				-				<0.001
Never-smoker	-	-	-		1,948,936 (76.02)	1,657,809 (43.46)	112,352 (27.08)	
Former-smoker	-	-	-		157,814 (6.15)	486,058 (12.74)	57,226 (13.79)	
Current-smoker	-	-	-		457,039 (17.83)	1,671,103 (43.80)	245,362 (59.13)	
Alcohol consumption status				<0.0001				-
Non-consumer	1,948,936 (52.40)	157,814 (22.51)	457,039 (19.26)		-	-	-	
Low-moderate-risk consumer*	1,657,809 (44.58)	486,058 (69.33)	1,671,103 (70.41)		-	-	-	
High-risk consumer†	112,352 (3.02)	57,226 (8.16)	245,362 (10.33)		-	-	-	
Regular exercise‡	431,470 (11.60)	128,870 (18.38)	341,378 (14.38)	<0.0001	298,398 (11.64)	540,183 (14.16)	63,137 (15.22)	<0.001
Low income	1,057,828 (28.44)	121,494 (17.33)	510,103 (21.49)	<0.0001	743,813 (29.01)	844,031 (22.12)	101,581 (24.48)	<0.001
Obesity§	697,897 (18.77)	250,492 (35.73)	855,019 (36.02)	<0.0001	544,107 (21.22)	1,113,432 (29.19)	145,869 (35.15)	<0.001
Diabetes	46,186 (1.24)	16,497 (2.35)	66,367 (2.80)	<0.0001	43,080 (1.68)	74,570 (1.95)	11,400 (2.75)	<0.001
Hypertension	177,491 (4.77)	77,208 (11.01)	247,925 (10.45)	<0.0001	131,281 (5.12)	320,385 (8.40)	50,958 (12.28)	<0.001
Dyslipidemia	185,903 (5.00)	67,285 (9.60)	206,902 (8.72)	<0.0001	152,395 (5.94)	273,214 (7.16)	34,481 (8.31)	<0.001
BMI (kg/m^2)	22.20±3.45	24.03±3.34	24.00±3.57	<0.0001	22.44±3.60	23.32±3.52	23.84±3.77	<0.001
WC (cm)	74.23±9.55	81.41±8.86	81.58±8.97	<0.0001	75.26±9.89	78.80±9.69	80.09±10.28	<0.001
Fasting serum glucose	89.31±14.27	92.56±17.08	92.61±19.13	<0.0001	89.68±15.88	91.30±16.53	93.09±19.23	<0.001
Systolic blood pressure (mmHg)	114.58±12.64	121.00±12.87	121.67±12.67	<0.0001	114.96±12.69	119.16±13.03	121.5±13.73	<0.001
Diastolic blood pressure (mmHg)	71.82±9.08	75.83±9.41	76.23±9.25	<0.0001	71.96±9.09	74.70±9.39	76.47±9.90	<0.001
Total cholesterol (mg/dL)	180.94±32.24	190.62±34.55	188.24±35.16	<0.0001	182.05±33.42	185.79±33.78	187.66±34.71	<0.001
Gastric cancer during follow-up	4,699 (0.13)	1,213 (0.17)	3,981 (0.17)	<0.0001	3,520 (0.14)	5,700 (0.15)	673 (0.16)	<0.001
Follow-up duration								
Mean±SD	9.30±1.14	9.49±1.12	9.39±1.19	<0.0001	9.33±1.14	9.37±1.16	9.31±1.21	<0.001
Median (Q1–Q3)	9.51 (8.49–10.21)	10.01 (9.01–10.31)	10.00 (8.59–10.27)	<0.0001	9.55 (8.54–10.22)	9.67 (8.56–10.26)	9.62 (8.46–10.22)	<0.001

Data are shown as mean±standard deviation or number (%).
BMI = body mass index; WC = waist circumference; SD = standard deviation.
*Alcohol consumption <40 g/day for men and <20 g/day for women; †Alcohol consumption ≥40 g/day for men and ≥20 g/day for women; ‡Regular exercise was defined as high-intensity activity for more than 20 minutes ≥3 times/week or moderate-intensity activity for more than 30 minutes ≥5 times/week over the last week; §Obesity indicates a BMI ≥25 kg/m^2.

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Detailed information on the smoking and alcohol consumption status of the participants, including alcohol consumption frequency, the amount of alcohol consumed per drink, smoking duration, number of cigarettes smoked per day, and pack-years, is provided in **Supplementary Table 1**. Baseline characteristics according to sex are summarized in **Supplementary Table 2**.

Smoking, alcohol consumption, and GC risk

GC developed in 9,893 individuals during a median follow-up period of 9.35 years (0.17%, men:women=6,304:3,589). Patients with GC were mostly men, older, smokers, and alcohol consumers, and presented with comorbidities, such as diabetes, hypertension, and dyslipidemia compared with those without GC (P<0.001) (**Supplementary Table 3**). Conversely, engaging in regular exercise was not associated with GC risk.

To investigate the relation between smoking and GC incidence, adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) for GC were calculated (**Table 2**). Before adjustment (model 1), former and current-smokers exhibited a higher GC risk than never-smokers (**Fig. 1A**). After adjusting for sex, age, physical activity, and income, as well as diabetes, hypertension, dyslipidemia, and alcohol consumption status, both former and current-smokers were determined to have independent risk factors for GC (aHR [95% CI], 1.121 [1.044–1.205] and 1.282 [1.212–1.355], respectively). Further, GC risk significantly increased with the number of cigarettes smoked per day, duration of smoking, and pack-years (P-values for trend <0.001).

Subsequently, we investigated the association between alcohol consumption and GC risk (**Table 3**). The Kaplan–Meier curve illustrated an increase in GC risk with alcohol consumption (**Fig. 1B**). After adjusting for age, sex, physical activity, income, diabetes, hypertension, dyslipidemia, and smoking status, low-to-moderate-risk alcohol consumption increased the GC risk by 9.5%, whereas high-risk alcohol consumption increased the risk by 21.2% (**Table 3**). Additionally, GC risk significantly increased with the frequency of alcohol consumption, the amount of alcohol consumed per drink, and the average daily alcohol consumption (P-values for trend <0.001, **Table 3**).

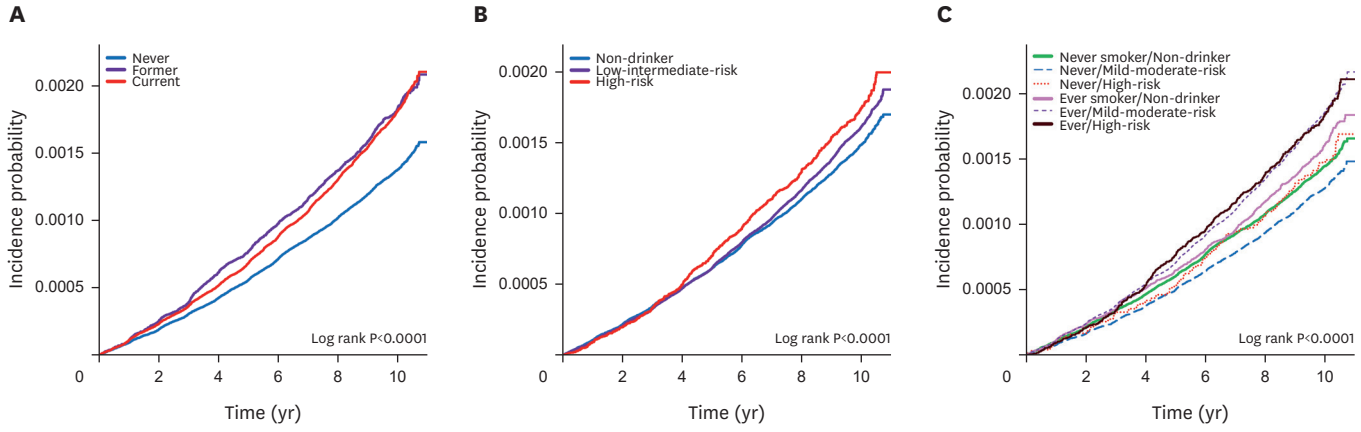

Fig. 1. Kaplan–Meier analysis results according to smoking and alcohol consumption status. (A) Gastric cancer risk by smoking status (never-/former-/current-smoker). (B) Gastric cancer risk by alcohol consumption status (non-/low-moderate-risk/high-risk consumer). (C) Combined effect of smoking (never-/ever-smoker) and alcohol consumption (non-/low-moderate-risk/high-risk consumer) on gastric cancer risk.

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Table 2. Risk of gastric cancer according to smoking status

Characteristics	No.	Gastric cancer	Duration	Rate*	Crude HR†	aHR1‡	aHR2§	aHR3‖
Never-smoker	3,719,097	4,699	34,584,392.6	0.136	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former-smoker	701,098	1,213	6,652,995.2	0.182	**1.330 (1.248–1.416)**	**1.156 (1.077–1.241)**	**1.154 (1.076–1.239)**	**1.121 (1.044–1.205)**
Current-smoker	2,373,504	3,981	22,295,636.8	0.179	**1.307 (1.253–1.364)**	**1.329 (1.258–1.403)**	**1.325 (1.255–1.399)**	**1.282 (1.212–1.355)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Never-smoker	3,719,097	4,699	34,584,392.6	0.136	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former-smoker (smoking duration <10 yr)	385,234	510	3,629,475.3	0.141	1.028 (0.938–1.126)	**1.117 (1.015–1.228)**	**1.117 (1.015–1.228)**	1.089 (0.989–1.199)
Current-smoker (smoking duration <10 yr)	739,459	569	6,843,310.0	0.083	**0.612 (0.561–0.668)**	1.040 (0.947–1.141)	1.039 (0.946–1.140)	1.011 (0.921–1.11)
Former-smoker (smoking duration ≥10 yr)	315,864	703	3,023,519.9	0.233	**1.690 (1.562–1.830)**	**1.219 (1.117–1.330)**	**1.215 (1.113–1.327)**	**1.179 (1.079–1.288)**
Current-smoker (smoking duration ≥10 yr)	1,634,045	3,412	15,452,326.8	0.221	**1.613 (1.543–1.685)**	**1.414 (1.336–1.498)**	**1.411 (1.332–1.494)**	**1.364 (1.286–1.447**)
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Never-smoker	3,719,097	4,699	34,584,392.6	0.136	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former-smoker (<20 cigarettes per day)	510,148	777	4,826,154.5	0.161	**1.176 (1.090–1.268)**	**1.101 (1.014–1.194)**	**1.100 (1.014–1.193)**	1.071 (0.987–1.163)
Current-smoker (<20 cigarettes per day)	1,560,657	2,231	14,613,134.9	0.153	**1.119 (1.064–1.177)**	**1.228 (1.156–1.304)**	**1.227 (1.155–1.303)**	**1.190 (1.120–1.266)**
Former-smoker (≥20 cigarettes per day)	190,950	436	1,826,840.7	0.239	**1.735 (1.573–1.914)**	**1.316 (1.185–1.462)**	**1.311 (1.180–1.456)**	**1.271 (1.143–1.413)**
Current-smoker (≥20 cigarettes per day)	812,847	1,750	7,682,501.9	0.228	**1.663 (1.575–1.757)**	**1.525 (1.427–1.630)**	**1.519 (1.421–1.623)**	**1.467 (1.371–1.571)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Never-smoker	3,719,097	4,699	34,584,392.6	0.136	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Former-smoker (<10 PY)	537,265	786	5,078,874.3	0.155	**1.130 (1.048–1.219)**	**1.099 (1.013–1.192)**	**1.098 (1.012–1.191)**	1.071 (0.986–1.162)
Current-smoker (<10 PY)	1,495,240	1,767	13,963,425.7	0.127	0.929 (0.879–0.981)	**1.170 (1.098–1.247)**	**1.169 (1.097–1.246)**	**1.137 (1.066–1.213)**
Former-smoker (≥10 PY)	163,833	427	1,574,120.9	0.271	**1.969 (1.783–2.174)**	**1.358 (1.221–1.511)**	**1.353 (1.216–1.505)**	**1.311 (1.178–1.460)**
Current-smoker (≥10 PY)	878,264	2,214	8,332,211.1	0.266	**1.938 (1.842–2.038)**	**1.538 (1.444–1.639)**	**1.533 (1.439–1.633)**	**1.482 (1.388–1.581)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

Bold font indicates statistical significance.
aHR = adjusted hazard ratio; PY = pack-years.
*Number of events per 1,000 person-years; †Not adjusted; ‡Adjusted for age, sex, exercise, and income; §Adjusted for age, sex, exercise, income, diabetes, hypertension, and dyslipidemia; ‖Adjusted for age, sex, exercise, income, diabetes, hypertension, dyslipidemia, and alcohol consumption.

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Table 3. Risk of gastric cancer according to alcohol consumption status

Characteristics	No.	Gastric cancer	Duration	Rate*	Crude HR†	aHR1‡	aHR2§	aHR3‖
Non-consumer	2,563,789	3,520	23,917,444.5	0.147	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Low-moderate-risk consumer	3,814,970	5,700	35,751,434.3	0.159	**1.080 (1.036–1.127)**	**1.137 (1.088–1.189)**	**1.137 (1.087–1.188)**	**1.095 (1.046–1.146)**
High-risk consumer	414,940	673	3,864,145.9	0.174	**1.183 (1.090–1.285)**	**1.312 (1.207–1.427)**	**1.307 (1.202–1.422)**	**1.212 (1.113–1.321)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Non-consumer	2,563,789	3,520	23,917,444.5	0.147	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Once per week	2,296,607	3,048	21,534,358.7	0.142	0.959 (0.914–1.007)	**1.060 (1.008–1.114)**	**1.060 (1.009–1.115)**	1.035 (0.984–1.088)
Twice per week	1,145,383	1,836	10,741,392.3	0.171	1.158 (1.094–1.225)	**1.211 (1.142–1.285)**	**1.210 (1.141–1.284)**	**1.155 (1.087–1.227)**
Three times per week	528,617	957	4,934,029.2	0.194	**1.317 (1.226–1.414)**	**1.320 (1.226–1.421)**	**1.317 (1.224–1.419)**	**1.242 (1.152–1.339)**
≥4 times per week	259,303	532	2,405,800.0	0.221	**1.505 (1.373–1.648)**	**1.431 (1.304–1.571)**	**1.428 (1.300–1.567)**	**1.334 (1.213–1.467)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Non-consumer	2,563,789	3,520	23,917,444.5	0.147	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
1–4 units per drink	1,409,559	1,904	13,036,844.3	0.146	0.995 (0.941–1.052)	1.054 (0.996–1.114)	1.055 (0.997–1.115)	1.037 (0.980–1.097)
5–9 units per drink	1,632,004	2,547	15,377,910.3	0.166	**1.120 (1.064–1.178)**	**1.191 (1.128–1.257)**	**1.190 (1.127–1.256)**	**1.135 (1.074–1.200)**
10–14 units per drink	851,436	1,432	8,014,409.9	0.179	**1.209 (1.137–1.285)**	**1.303 (1.220–1.392)**	**1.300 (1.217–1.389)**	**1.223 (1.143–1.309)**
≥15 units per drink	336,911	490	3,186,415.6	0.154	1.038 (0.944–1.140)	**1.193 (1.082–1.315)**	**1.189 (1.078–1.311)**	**1.110 (1.005–1.226)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Non-consumer	2,563,789	3,520	23,917,444.5	0.147	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Alcohol consumption (M: <20 g/day, F: <10 g/day)	2,950,960	4,213	27,638,654.9	0.152	1.033 (0.988–1.080)	**1.096 (1.046–1.148)**	**1.096 (1.046–1.149)**	**1.065 (1.016–1.117)**
Alcohol consumption (M: 20–39.9 g/day, F: 10-19.9 g/day)	864,010	1,487	8,112,779.4	0.183	**1.241 (1.168–1.319)**	**1.286 (1.207–1.370)**	**1.284 (1.205–1.368)**	**1.211 (1.135–1.292)**
Alcohol consumption (M: 40–59.9 g/day, F: 20–29.9 g/day)	252,498	411	2,358,260.4	0.174	**1.183 (1.068–1.310)**	**1.267 (1.142–1.405)**	**1.263 (1.139–1.401)**	**1.181 (1.063–1.312)**
Alcohol consumption (M: ≥60 g/day, F: ≥30 g/day)	162,442	262	1,505,885.5	0.174	**1.184 (1.044–1.342)**	**1.400 (1.234–1.588)**	**1.394 (1.228–1.582)**	**1.289 (1.134–1.465)**
P for trend					**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**

Bold font indicates statistical significance.

aHR = adjusted hazard ratio; PY = pack-years; M = male; F = female.

*Number of events per 1,000 person-years; †Not adjusted; ‡Adjusted for age, sex, exercise, and income; §Adjusted for age, sex, exercise, income, diabetes, hypertension, and dyslipidemia; ‖Adjusted for age, sex, exercise, income, diabetes, hypertension, dyslipidemia, and smoking.

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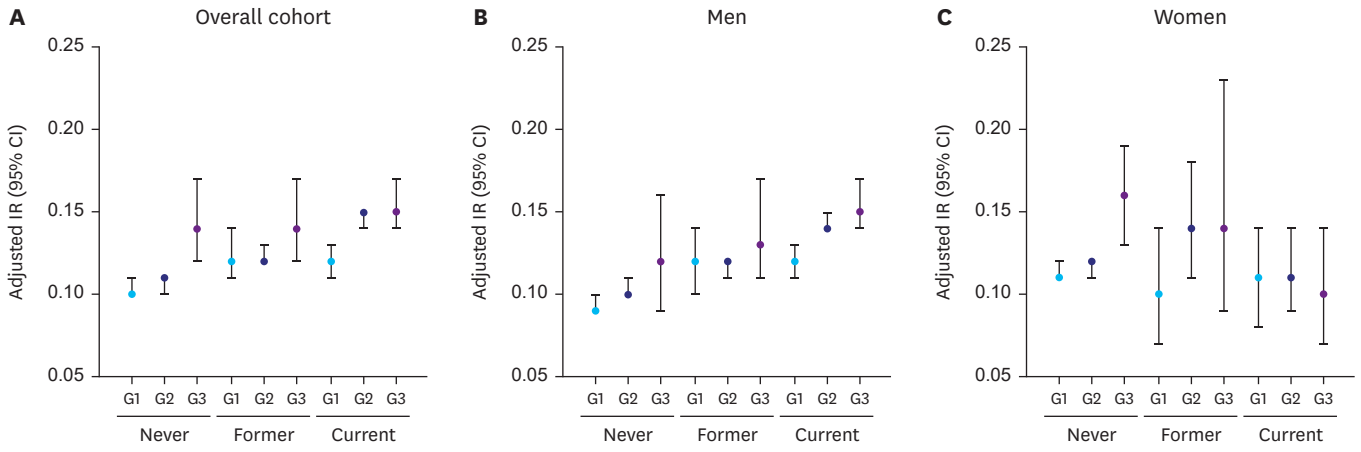

Fig. 2. Gastric cancer incidence rate according to smoking and alcohol consumption status. (A) Overall population; (B) Among men; (C) Among women. Smoking status was categorized into never/former/current-smokers. Alcohol consumption was categorized as non-consumer (G1), low-moderate-risk consumer (G2; men <40 g/day, women <20 g/day), and high-risk consumer (G3; men ≥40 g/day, women ≥20 g/day).
IR = incidence rate per 1,000 person-years; CI = confidence interval.

GC risk by smoking and alcohol consumption according to sex

Stratified analysis was conducted to determine whether alcohol consumption or smoking had a synergistic effect on the incidence of GC (**Table 4**, **Fig. 1C**). Among never-smokers, compared with non-consumers of alcohol, the GC risk increased after adjusting for clinical variables with high-risk alcohol consumers (1.367 [1.161–1.611]) but not with low-moderate-risk consumers (1.042 [0.982–1.106], **Table 4**). Among current-smokers, both low-moderate- and high-risk alcohol consumption increased GC risk (1.414 [1.324–1.510] and 1.447 [1.297–1.615], respectively). Among former-smokers, both low-moderate- and high-risk alcohol consumption significantly increased GC risk (1.180 [1.083–1.287] and 1.361 [1.118–1.658], respectively).

Interestingly, the effects of smoking and alcohol consumption differed according to sex ($P_{interaction}$ by sex = 0.002; **Table 4**, **Fig. 2**). Both smoking and alcohol consumption significantly increased GC risk in men. However, in women, high-risk alcohol consumption significantly increased GC risk only in never-smokers (1.412 [1.164–1.712]) but not in former- and current-smokers (1.289 [0.800–2.079] and 0.929 [0.658–1.311], respectively).

DISCUSSION

Smoking was consistently associated with an increase in GC incidence [8]. The Stomach cancer Pooling (StoP) project, which comprehensively collected data from 23 epidemiological studies, showed that GC was associated with current smoking (odds ratio [OR]: 1.25, 95% CI: 1.11–1.40), and that the risk of GC increased with the amount and duration of smoking [9]. Smoking was associated with an increased GC risk regardless of *H. pylori* infection in relatives of GC patients [10]. A meta-analysis including 42 observational studies showed that current smoking was associated with GC in both men (risk ratio [RR], 1.62; 95% CI, 1.50–1.75) and women (RR, 1.20; 95% CI, 1.01–1.43) [11]. The mechanisms contributing to the onset and progression of GC associated with smoking may involve the activation of nicotinic acetylcholine receptors, formation of DNA adducts, stimulation of angiogenesis, and modulation of immune responses in the gastric mucosa [12]. Smoking could also increase the susceptibility to *H. pylori* infection [12,13]. Nicotine, an active compound in cigarette smoke, promotes gastric tumor growth and neovascularization [14].

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Table 4. Risk of gastric cancer according to smoking and alcohol consumption status stratified by sex

Sex	Smoking status	Alcohol consumption status	No.	Gastric cancer	Duration	Rate*	Crude HR†	Adjusted HR1‡	Adjusted HR2§
Overall	Never-smoker	Non-consumer	1,948,936	2,597	18,139,351.0	0.143	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Low-moderate-risk consumer‖	1,657,809	1,950	15,405,947.2	0.127	0.884 (0.834–0.937)	1.042 (0.981–1.106)	1.042 (0.982–1.106)
		High-risk consumer¶	112,352	152	1,039,094.4	0.146	1.024 (0.869–1.206)	**1.371 (1.164–1.615)**	**1.367 (1.161–1.611)**
	Former-smoker	Non-consumer	157,814	271	1,493,420.0	0.181	**1.257 (1.109–1.425)**	**1.162 (1.021–1.323)**	**1.161 (1.020–1.321)**
		Low-moderate-risk consumer‖	486,058	836	4,621,550.6	0.181	**1.251 (1.157–1.352)**	**1.182 (1.084–1.288)**	**1.180 (1.083–1.287)**
		High-risk consumer¶	57,226	106	538,024.7	0.197	**1.369 (1.127–1.662)**	**1.368 (1.124–1.666)**	**1.361 (1.118–1.658)**
	Current-smoker	Non-consumer	457,039	652	4,284,673.5	0.152	1.058 (0.971–1.153)	**1.156 (1.053–1.269)**	**1.153 (1.051–1.267)**
		Low-moderate-risk consumer‖	1,671,103	2,914	15,723,936.5	0.185	**1.287 (1.220–1.357)**	**1.417 (1.326–1.513)**	**1.414 (1.324–1.510)**
		High-risk consumer¶	245,362	415	2,287,026.9	0.181	**1.265 (1.140–1.403)**	**1.454 (1.304–1.622)**	**1.447 (1.297–1.615)**
Male	Never-smoker	Non-consumer	529,082	584	4,957,618.4	0.118	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Low-moderate-risk consumer‖	695,418	770	6,510,634.3	0.118	1.004 (0.902–1.118)	1.091 (0.980–1.215)	1.091 (0.979–1.214)
		High-risk consumer¶	30,957	43	289,918.4	0.148	1.259 (0.924–1.716)	1.298 (0.952–1.769)	1.291 (0.947–1.760)
	Former-smoker	Non-consumer	127,327	236	1,213,174.6	0.195	**1.640 (1.410–1.907)**	**1.289 (1.108–1.499)**	**1.287 (1.106–1.497)**
		Low-moderate-risk consumer‖	435,027	764	4,154,956.8	0.184	**1.549 (1.391–1.725)**	**1.255 (1.127–1.398)**	**1.253 (1.125–1.396)**
		High-risk consumer¶	43,093	89	409,419.8	0.217	**1.837 (1.470–2.296)**	**1.474 (1.179–1.842)**	**1.465 (1.172–1.831)**
	Current-smoker	Non-consumer	416,499	607	3,916,666.7	0.155	**1.313 (1.172–1.471)**	**1.252 (1.118–1.403)**	**1.249 (1.115–1.400)**
		Low-moderate-risk consumer‖	1,591,847	2,829	15,005,060.5	0.189	**1.596 (1.460–1.745)**	**1.532 (1.402–1.675)**	**1.529 (1.398–1.671)**
		High-risk consumer¶	208,042	382	1,950,040.4	0.196	**1.662 (1.461–1.891)**	**1.629 (1.432–1.853)**	**1.620 (1.424–1.844)**
Female	Never-smoker	Non-consumer	1,419,854	2,013	13,181,732.7	0.153	1 (Ref.)	1 (Ref.)	1 (Ref.)
		Low-moderate-risk consumer‖	962,391	1,180	8,895,313.0	0.133	0.870 (0.809–0.934)	1.034 (0.962–1.112)	1.035 (0.963–1.112)
		High-risk consumer¶	81,395	109	749,176.0	0.145	0.955 (0.788–1.158)	**1.414 (1.165–1.715)**	**1.412 (1.164–1.712)**
	Former-smoker	Non-consumer	30,487	35	280,245.4	0.125	0.820 (0.587–1.146)	0.920 (0.659–1.286)	0.919 (0.658–1.283)
		Low-moderate-risk consumer‖	51,031	72	466,593.8	0.154	1.016 (0.803–1.285)	1.251 (0.989–1.583)	1.250 (0.988–1.582)
		High-risk consumer¶	14,133	17	128,604.8	0.132	0.871 (0.541–1.404)	1.292 (0.801–2.083)	1.289 (0.800–2.079)
	Current-smoker	Non-consumer	40,540	45	368,006.8	0.122	0.807 (0.601–1.085)	0.960 (0.714–1.290)	0.958 (0.713–1.287)
		Low-moderate-risk consumer‖	79,256	85	718,876.0	0.118	**0.781 (0.629–0.970)**	1.003 (0.807–1.246)	1.001 (0.806–1.244)
		High-risk consumer¶	37,320	33	336,986.5	0.098	**0.649 (0.460–0.915)**	0.931 (0.660–1.313)	0.929 (0.658–1.311)
P for interaction (sex)							**<0.0001**	**0.0018**	**0.0018**

Bold font indicates statistical significance.

HR = hazard ratio.

*Number of events per 1,000 person-years; †Not adjusted; ‡Adjusted for age, sex (overall), exercise, and income; §Adjusted for age, sex (overall), exercise, income, diabetes, hypertension, and dyslipidemia; ‖Alcohol consumption <40 g/day for male and <20 g/day for female; ¶Alcohol consumption ≥40 g/day for male and ≥20 g/day for female.

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Heavy alcohol consumption is also associated with GC risk [15,16]. Data from the National Health and Nutrition Examination Survey (1999–2010) showed that heavy alcohol use (≥5 alcoholic drinks daily) in adults was associated with a more than three-fold increase in the odds of developing GC [15]. A meta-analysis of 44 case-control and 15 cohort studies showed that, compared with non-consumers, the pooled RR was 1.07 for alcohol consumers and 1.20 for heavy alcohol consumers (consuming ≥4 alcoholic drinks daily) [16]. The findings presented in our study are similar to that of the meta-analysis (**Table 3**).

Few studies have investigated whether smoking and alcohol consumption simultaneously increase the risk of developing GC. In a population-based cohort study conducted in Norway, the combination of use of cigarettes (>20/day) and alcohol consumption (>5 occasions in 2 weeks) increased the risk of non-cardia GC by five times in individuals compared with non-users [17]. Similarly, we found that current-smokers/high-risk alcohol consumers were associated with an increased risk of GC compared with never-smokers/non-consumers of alcohol (**Table 4**).

In the present study, the effect of alcohol on early-onset GC differed according to sex. In young men, alcohol consumption increased the risk of GC, regardless of smoking status. However, in young women, high-risk alcohol consumption was associated with GC in never-smokers but not in former/current-smokers (**Table 4**). In a meta-analysis of 27 cohort studies, alcohol consumption was associated with GC incidence in men but not in women [6]. Even when subgroup analysis was performed according to smoking status or region, alcohol consumption in women did not show a significant association with GC [6]. Another cohort study from Japan also reported similar findings [18].

Some studies have reported that female sex hormones might protect against GC, which may partially explain these observations [19]. Alcohol consumption can increase the plasma levels of female sex hormones from ovaries, which explains why women experience an increased protective effect against alcohol compared with men [20]. He et al. [21] reported that low alcohol consumption (<12 g/day) was associated with a reduced GC risk in women (RR, 0.74), suggesting that women can experience a protective effect against GC development. These studies indicate that sex can be an effect modifier in the interaction between alcohol consumption and GC risk [6].

Men and women differ in their ability to metabolize alcohol. Compared with women, men have highly active forms of alcohol dehydrogenase in their stomach and liver [22], which can reduce alcohol absorption by 30% [23]. These sex differences in alcohol metabolism result in higher blood alcohol concentrations in women than in men, even if they both consume the same amount of alcohol. Moreover, the sensitivity to alcohol is higher in women than in men [24]. Despite the consumption of the same amount of alcohol, the effect of alcohol is greater in women than in men due to higher fat and lower water composition [25]. Therefore, high-risk alcohol consumption is defined as consumption of ≥40 g/day alcohol for men or ≥20 g/day alcohol for women. Nevertheless, the proportion of high-risk alcohol consumers was higher among men (6.92%, 282,092/4,077,292) than among women (4.89%, 132,848/2,716,407). Among smokers, this proportion was much lower among women than among men. Since the proportion of both high-risk alcohol consumers and current-smokers was significantly lower among women (1.37%, 37,320/2,716,407) than among men (5.10%, 208,042/4,077,292), there could be selection bias for women.

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The effect of alcohol consumption on the development of early-onset GC appears to be complex and depends on the histological type of GC and sex of the individual. The increased risk of developing GC due to alcohol consumption appears to be more pronounced in patients with intestinal-type GC. A pooled analysis within the StoP project consortium data showed a stronger association of heavy alcohol consumption with intestinal-type GC (OR, 1.54; 95% CI, 1.20–1.97) than with diffuse-type GC (OR, 1.29; 95% CI, 1.05–1.58) [26]. Intestinal-type GC can develop in the background of mucosal atrophy or intestinal metaplasia [27]. Environmental risk factors, including smoking, alcohol consumption, and dietary carcinogens can explain the higher incidence of intestinal-type GC in men [28]. In contrast, diffuse-type GC can occur in *H. pylori*-infected patients without atrophy and intestinal metaplasia and is more prevalent in young women [29]. A recent study has reported that estrogen promotes diffuse-type GC progression in *H. pylori*-infected young women [30]. We postulate that alcohol might have two conflicting effects in premenopausal women, i.e., protection against intestinal-type GC and induction of diffuse-type GC due to increased female sex hormones. Further studies are required to better understand the effect of female sex hormones on the development of the different types of GC.

Unfortunately, in the present study, *H. pylori* test results were not included in the cancer screening cohort data. Risk factors for *H. pylori* infection include male sex, older age, low socioeconomic status and education level, and living in crowded and unsanitary conditions [1]. There is conflicting evidence on the association between smoking and *H. pylori* infection [31]. A study using data from StoP project showed that smoking had no significant association with *H. pylori* infection and that alcohol consumption was also not associated with a high *H. pylori* prevalence [32]. One meta-analysis of observational studies indicated that alcohol consumption was associated with a lower prevalence of *H. pylori* infection [33]. This inverse relation between alcohol consumption and the prevalence of *H. pylori* infection was consistent, regardless of sex, age, area of residence, *H. pylori* detection methods or beverage types. Another recent meta-analysis revealed that among people aged <40 years, alcohol consumption was not associated with *H. pylori* infection risk [34]. Collectively, *H. pylori* infection status did not appear to be associated with alcohol consumption habits in the younger age group. Therefore, although *H. pylori* status could not be adjusted for in this study, the findings of our study may not be affected substantially.

Further, we analyzed data from the Healthcare System Gangnam Center cohort, which contained information on *H. pylori* status of the participants (**Supplementary Tables 4** and **5**). Among young participants (<40 years), alcohol consumption and smoking were not associated with *H. pylori* status in men. However, in women, the proportion of *H. pylori* seropositivity was higher in alcohol consumers (30.6%) than in non-consumers (25.5%, P<0.01, **Supplementary Table 5**). As female alcohol consumers are more likely to be *H. pylori* positive, the effect of alcohol consumption on GC risk should be more pronounced in women. However, in the present study, a significant association of alcohol consumption and smoking with GC risk was observed only in men. Therefore, alcohol consumption did not appear to increase the risk of developing GC in young women.

The limitations of this study must be acknowledged. First, we could not evaluate differences according to the histological types and sites of GC because the Korean National Health Insurance Corporation dataset lacked this information. A recent study analyzing 2,983 patients with gastric adenocarcinoma showed that gastric body cancer and diffuse-type histology were more common in women than in men [35]. Hence, the results might vary

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depending on GC histology and location. Second, we could not adjust for *H. pylori* infection status. Although *H. pylori* infection might not have substantially affected the outcomes of this study, further research is required to investigate its effect. Third, in the sample population, the proportion of men (n=4,077,292) was higher than that of women (n=2,716,407). This is partly explained by the fact that the target population were individuals aged <40 years and most of them were employee-insured subscribers. However, because the analyses were stratified by sex, it is unlikely that this could have impacted the results. Fourth, we used the ICD-10 code C16 to identify GC. Therefore, it is possible that cases of gastric adenocarcinoma, gastrointestinal stromal tumor (ICD-10 code: C16.9), and neuroendocrine carcinoma (C16.99) could be included in the study. However, because at least more than 90% of all GC cases are gastric adenocarcinomas and cases of gastrointestinal stromal tumor or neuroendocrine carcinoma are rare, this is unlikely to have affected the results of this study.

In conclusion, smoking and alcohol consumption are significant risk factors of early-onset GC in young Koreans. The effects of smoking and alcohol consumption may differ according to the sex of the individuals. In Korea, a decline in the prevalence of *H. pylori* infection did not lead to a similar reduction in the incidence rate of early-onset GC. Our findings might help screen high-risk groups for early-onset GC based on their smoking and alcohol consumption habits.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Smoking and drinking status of the study subjects in detail

Supplementary Table 2
Baseline characteristics according to sex, smoking and drinking status

Supplementary Table 3
Baseline characteristics according to gastric cancer incidence during the follow-up period

Supplementary Table 4
Baseline characteristics of the subjects (≤ 40 years old) who visited Seoul National University Healthcare System Gangnam Center in 2011

Supplementary Table 5
Association of *H. pylori* positivity with smoking, and alcohol according to sex in the young individuals (≤ 40 years old) who visited Seoul National University Healthcare System Gangnam Center in 2011

Supplementary Fig. 1
Study flow chart depicting patient enrollment.

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