Low Levels of Alcohol Consumption and Risk of Intestinal Metaplasia: A Cohort Study

Kyungeun Kim[1], Yoosoo Chang[2,3,4], Jiin Ahn[3], Hyo-Joon Yang[5], and Seungho Ryu[2,3,4]

ABSTRACT

Background: The impact of alcohol drinking on gastric precancerous lesions remains unclear. We investigated the relationship of alcohol intake with risk of atrophic gastritis (AG) and intestinal metaplasia (IM).

Methods: This study included 202,675 Korean adults free from AG and IM on their initial endoscopy who were followed with repeated endoscopic examinations. A parametric proportional hazards model was used to estimate the adjusted HR (aHR) with 95% confidence interval (CI) for incident AG and IM based on endoscopic diagnosis.

Results: During a mean follow-up of 4.7 years, 64,853 incident AG cases and 4,536 IM cases were identified. Alcohol consumption including drinking frequency, quantity, and binge drinking were consistently associated with increased risk of both AG and IM in a dose–response manner. After adjustment for confounders, the multivariable aHRs (95% CIs) for incident IM comparing average alcohol intake of <10, 10–<20, 20–<40, and ≥40 g/day with lifetime abstainers were 1.27 (1.02–1.56), 1.34 (1.07–1.66), 1.50 (1.20–1.86), and 1.54 (1.23–1.93), respectively. Former drinkers were also at a higher risk for AG and IM compared with lifetime abstainers. These associations were consistently observed in never smokers and in time-dependent analyses.

Conclusions: In a large cohort of Korean individuals, alcohol intake even at low levels was independently associated with increased risk of developing endoscopic AG and IM, supporting a role of alcohol consumption in the pathogenesis of AG and IM, the precursor lesions of stomach cancer.

Impact: Alcohol consumption from low-level drinking may contribute to gastric carcinogenesis.

Introduction

Gastric cancer remains the fifth most common cancer and the third leading cause of cancer-related death worldwide despite the decline in incidence during the past decades (1, 2). Gastric cancer is a multifactorial disease and its well-established risk factors include nonmodifiable risk factors (age and sex) and potentially modifiable risk factors such as *Helicobacter pylori* (*H. pylori*) infection, smoking, and low physical activity (2).

Alcohol drinking is an established risk factor in various cancers including cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum, and breast (3). However, the role of alcohol drinking in the risk of gastric cancer and its dose–response relationship is still controversial (4–11). Most previous studies did not incorporate changes in alcohol drinking status over time, even though drinking habits and other confounders can change over time during follow-up and alcohol drinking can be affected as a result of stomach conditions. Gastric cancer follows a sequential carcinogenesis pathway in the order of chronic gastritis, atrophic gastritis (AG), intestinal metaplasia (IM), dysplasia, and adenocarcinoma (12). A few studies have evaluated the effects of alcohol drinking on gastric precancerous lesions but with inconsistent results (13–21). However, those studies were limited by small sample size (16), cross-sectional design (14, 15, 17–20), different definitions of AG based on pepsinogen (15, 21), lack of detailed information on alcohol drinking, and inclusion of former drinkers in the reference group without consideration of sick quitter effect (13, 18–20).

Therefore, we investigated the dose–response association between alcohol drinking and the development of AG and IM in a large cohort of participants who underwent repeated endoscopic examination as a part of a health screening program. We differentiated between former drinkers and lifetime nondrinkers because the former drinkers may have quit alcohol drinking due to previous health problems including stomach conditions. We also accounted for changes in alcohol drinking status and other confounders during follow-up.

Materials and Methods

Study population

The current cohort study was performed in a subsample of the Kangbuk Samsung Health Study, a cohort study of Korean adults who underwent a comprehensive annual or biennial health examination at the clinics of Kangbuk Samsung Hospital Total Healthcare Screening Center in Seoul and Suwon, South Korea as described previously (22). Upper endoscopy, a screening test for stomach cancer, is widely performed every 1 to 2 years as a routine part of the health check-up program in Korea (23). The present cohort study included 302,021 participants who underwent baseline endoscopy from March 1, 2011 (when lifetime alcohol abstinence history was added as part of the

[1]Department of Pathology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. [2]Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. [3]Center for Cohort Studies, Total Healthcare Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. [4]Department of Clinical Research Design & Evaluation, SAIHST, Sungkyunkwan University, Seoul, Korea. [5]Division of Gastroenterology, Department of Internal Medicine and Gastrointestinal Cancer Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea.

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Corresponding Authors: Seungho Ryu, Department of Occupational and Environmental Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Samsung Main Building B2, 250 Taepyung-ro 2ga, Jung-gu, Seoul 04514, Korea. Phone: 82-2-2001-5137; Fax: 82-2-757-0436; E-mail: sh703.yoo@gmail.com; and Yoosoo Chang. Phone: 82-2-2001-5139; E-mail: yoosoo.chang@gmail.com

Cancer Epidemiol Biomarkers Prev 2020;29:2633–41

doi: 10.1158/1055-9965.EPI-20-0858

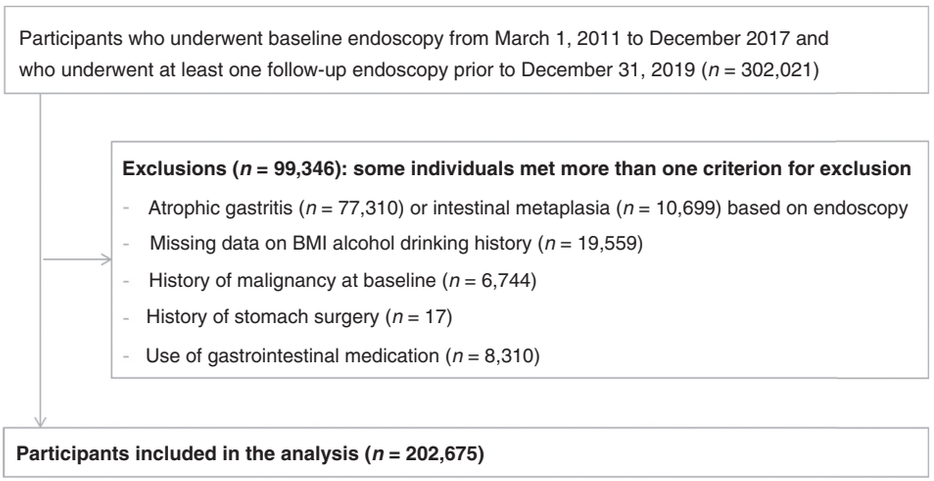

Figure 1.
Flow diagram for the selection of the study subjects. The flow chart summarizes the inclusion and exclusion criteria for selecting the study subjects. BMI, body mass index.

health questionnaire) to December 2017 and who underwent at least one follow-up endoscopy prior to December 31, 2019 (**Fig. 1**). A total of 99,346 participants were excluded for meeting one or more of the exclusion criteria; the final sample included 202,675 participants in the final analysis.

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBSMC 2020–03–034), which waived the requirement for informed consent due to the use of deidentified data obtained as part of routine health screening exams.

Data collection

As part of the health exam, information on demographic characteristics, health behaviors, diet, education level, and medical history were collected by standardized, self-administered questionnaires, as described previously (22, 23). Medical conditions diagnosed by a physician, including *H. pylori* infection, were assessed via the same questionnaire. Smoking status was categorized into never, former, or current smoker. Physical activity levels were assessed via the validated Korean version of the International Physical Activity Questionnaire Short Form and were categorized as inactive, minimally active, and health-enhancing physically active, as described previously (23, 24).

Lifetime abstainers were defined as those who never drank in their lives besides drinking a ritual sip during certain ceremonies. Current alcohol use was assessed as the frequency of alcohol consumption and the amount of alcohol consumed per drinking day. Average alcohol consumption per day was calculated using the frequency and amount of alcohol consumed per drinking day. First, alcohol drinking status based on current alcohol consumption was classified as nondrinking, light drinking, moderate drinking, heavy drinking, or heavier drinking, which correspond to 0, 0.1–<10, 10–<20, 20–<40, or ≥40 g/day, respectively (25). Then, with consideration of lifetime abstinence history, participants were classified as lifetime abstainer, current abstainer, light drinking, moderate drinking, heavy drinking, or heavier drinking. Current abstainers but former drinkers were defined as those with a previous history of drinking alcohol who were nondrinkers at the time of examination. Binge drinking was assessed using the specific question AUDIT-3 for defining binge drinking ("how often do you have six or more drinks on one occasion?" with five responses as never, less than monthly, monthly, weekly, and daily or almost daily), a part of the Alcohol Use Disorders Identification Test (AUDIT), which was developed by World Health Organization (WHO) as a simple method for screening individuals with harmful alcohol consumption (26). In addition, participants were asked about alcohol flushing, a proxy for aldehyde dehydrogenase 2 (*ALDH2*) deficiency and were categorized into flushers versus nonflushers (27–29).

Anthropometric parameters and sitting blood pressure (BP) were measured by trained nurses. Fasting blood tests included glucose, insulin, lipid profiles, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and high-sensitivity C-reactive protein (hsCRP) as described previously (22, 23). Insulin resistance was assessed with the homeostatic model assessment of insulin resistance (HOMA-IR) equation: fasting blood insulin (uU/mL) × fasting blood glucose (mmol/L)/22.5.

Endoscopic examinations were performed by experienced endoscopists using a conventional white light endoscope (GIF H260, Olympus Medical Systems; ref. 23). During endoscopy, any lesions suggestive of gastric pathology were imaged and described according to location, size, and shape. Endoscopists reported the presence of endoscopically suspected atrophy or IM of background gastric mucosa. Endoscopic AG was defined as thinning, whitish mucosal change or visible submucosal vascular patterns, and endoscopic IM as white plaque-like elevations in antrum and corpus (14). *H. pylori* infection status was evaluated histologically by Giemsa stain only when deemed necessary, such as in peptic ulcer disease, at the discretion of the endoscopist based on the Korean guidelines (30). The history of *H. pylori* infection was also identified through self-reporting of physician-diagnosed *H. pylori* infection on the standardized, self-administered questionnaires.

Statistical analysis

The baseline characteristics of the study participants are presented according to alcohol intake category (lifetime abstainer, current abstainer, 0.1–<10, 10–<20, 20–<40, ≥40 g/day; ref. 25). The primary endpoint was development of separately endoscopic AG and IM. Each participant was followed from his or her baseline exam until either development of the endpoint or to his or her last health exam conducted prior to December 31, 2019, whichever came first. For analysis of the association between alcohol consumption and incident AG, if AG was identified during follow-up, subsequent observations were not incorporated in the analysis. For analysis of the association between alcohol consumption and incident IM, if IM was identified during follow-up, the case was assumed to have developed IM, and

subsequent measurements were not incorporated in the primary analysis. In the case that AG developed before IM occurrence, participants were followed until IM development. The incidence rate was calculated as number of incident cases divided by number of person-years of follow-up. Because the development of endpoint would have occurred at an unknown time point between the two visits, the visit at which the endpoint was diagnosed and the prior visit, a parametric proportional hazards model was used to account for this type of interval censoring (31).

The adjusted HR (aHR) and 95% confidence interval (CI) were calculated for incident AG and incident IM according to alcohol intake category. Models were initially adjusted for age and sex and then were further adjusted for center, year of screening exam, smoking status, physical activity, body mass index (BMI), education level, total calorie intake, history of *H. pylori* infection, history of diabetes, history of hypertension, and history of cardiovascular disease (CVD; model 1). To explore whether inflammation or insulin resistance mediated the association of alcohol consumption with AG and IM, model 2 was further adjusted for hsCRP and HOMA-IR. Furthermore, we conducted time-dependent analyses in which changes in alcohol drinking status and confounders during follow-up were updated as time-varying covariates in the models. The proportional hazards assumption was assessed by examining graphs of estimated log (-log) survival, and no violations of the assumption were found. To determine linear trends of incidence, the number of categories was used as a continuous variable and tested on each model. To further explore the shape of the dose–response relationship of alcohol consumption with the development of IM, restricted cubic splines with knots were used at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of alcohol consumption. In a sensitivity analysis, participants in the top 25th percentile for serum GGT level, which is often used as a biomarker for alcohol drinking, were excluded to minimize the potential bias by misreporting or bias by disease-related secondary abstinence (15, 32).

Subgroup analyses were conducted by sex (men vs. women) and smoking status (never smokers vs. ever smokers). Among Koreans and other East Asian populations, the *ALDH2* variant is a common genotype and might modify the association between alcohol consumption and risk of AG/IM (27, 28, 33–35); thus, subgroup analysis was also performed by alcohol flushing (no vs. yes). Likelihood ratio tests were used to test interactions between alcohol intake and subgroup characteristics.

Statistical analyses were carried out using STATA version 16.0 (StataCorp LP). A *P* value less than 0.05 was considered statistically significant.

Results

Table 1 shows the baseline characteristics of the 202,675 participants. Lifetime abstainers were more likely to be older and female and to have a medication history of dyslipidemia and history of CVD, but were less likely to have a high education level. Among participants who were current alcohol drinkers, increasing alcohol consumption was positively associated with BP, glucose, liver enzymes, HOMA-IR, salt intake, total energy intake, and unfavorable lipid profiles, while increasing alcohol consumption was inversely associated with high education level. The baseline characteristics are also presented by sex (Supplementary Tables S1 and S2).

During a median follow-up of 4.5 years (interquartile range, 2.7–6.4 years; maximum, 8.8 years), 4,536 participants developed endoscopic IM (incidence rate, 4.8 per 1,000 person-years) and 64,853 participants developed endoscopic AG (incidence rate, 80.5 per 1,000 person-years). For participants who developed AG, the mean follow-up time since enrollment to development of AG was 3.3 years (median, 3.0 years; interquartile range, 1.9–4.6 years); for those who developed IM, the median follow-up time from enrollment to development of IM was 4.2 years (median, 4.0 years; interquartile range, 2.1–6.0 years). Increased alcohol intake categories were positively associated with increased risk of both AG and IM in a dose–response manner (**Table 2**). After adjustment for confounders (model 1), the multivariable aHRs (95% CIs) for incident IM comparing alcohol intake of <10, 10–19.9, 20–39.9, and ≥40 with lifetime abstainers as a reference were 1.27 (1.03–1.57), 1.35 (1.08–1.68), 1.50 (1.20–1.87), and 1.54 (1.23–1.93), respectively, and the corresponding aHRs (95% CIs) for incident AG were 1.08 (1.03–1.13), 1.15 (1.09–1.20), 1.20 (1.14–1.26), and 1.24 (1.18–1.31), respectively. Current abstainers (or former drinkers) were also at a higher risk for incident AG and IM compared with lifetime abstainers. Adjustment for hsCRP and HOMA-IR qualitatively did not change the results and the association of alcohol intake with AG and IM remained significant (**Table 2**, model 2). A total of 3,507 (1.7%) participants had information on alcohol consumption only at baseline; the remaining of the participants (98.3%) had at least two data on alcohol consumption at baseline and during follow-up. The participants with alcohol data at only baseline were more likely to be female, former drinker (current abstainer), have diabetes and history of CVD, and were less likely to be highly educated and heavy drinkers (Supplementary Table S3). The average alcohol consumption changed over time (Supplementary Table S4). Most lifetime abstainers (98.6%) maintained a constant state, but a small proportion (1.4%) started drinking. Among former drinkers, about half remained the same state, while the other started drinking again. A majority of light drinkers (82.2% of alcohol category 0.1 to 10 g/day) remained in a constant state, whereas heavy drinkers tended to reduce alcohol drinking over time. When changes in alcohol drinking status and confounders during follow-up were updated as time-varying covariates (**Table 2**, time-dependent model), the positive associations of alcohol category with incident AG and IM were slightly attenuated but remained significant even in the low-level drinking category defined as 10 to <20 g/day.

In spline regression analyses, there was a dose–response relationship between alcohol consumption levels and the development of AG and IM (**Figs. 2** and **3**). All drinking patterns including higher frequency of drinking, higher quantity of alcohol consumption per drinking day, and higher frequency of binge drinking were significantly associated with a higher risk of incident AG and IM in a dose-dependent manner ($P_{trend} < 0.05$; Supplementary Table S5). The significantly increased risk of incident AG and IM was observed from 1 to 2 times drinking per week and 1 to 2 drinks per day.

We performed analyses among never smokers to address the residual confounding by smoking and found similar results (**Table 3**); the association between alcohol category and incident AG/IM did not significantly differ by smoking status. The association between alcohol category and risk of IM was similar in men and women without significant interaction ($P_{interaction}$ by sex = 0.66), whereas the association with risk of AG tended to be stronger in men than in women ($P_{interaction}$ by sex = 0.03; Supplementary Table S6). Development of IM and AG by alcohol drinking did not statistically differ by the presence or absence of flushing, but the association tended to be stronger among participants with flushing (Supplementary Table S7).

In an additional sensitivity analysis, excluding participants with serum GGT of above its upper quartile (33 IU/L in this study

Table 1. Baseline characteristics according to lifetime drinking status ($n = 202,675$).

Characteristics	Overall	Lifetime drinking status					
		Lifetime abstainer	Current abstainer	0–<10 g/day	10–<20 g/day	20–<40 g/day	≥40 g/day
Number	202,675	5,595	17,292	99,090	36,834	24,911	18,953
Age (years)[a]	36.1 (6.4)	40.6 (8.3)	36.4 (6.7)	35.7 (6.0)	35.8 (6.3)	36.4 (6.7)	36.8 (6.8)
Male (%)	55.4	18.0	26.9	41.9	74.5	83.1	89.6
Current smoker (%)	20.8	3.5	6.6	11.9	27.2	39.0	47.2
HEPA (%)	15.0	14.0	12.8	13.7	15.9	17.5	19.0
High education level (%)[b]	86.1	79.5	81.8	88.0	87.2	85.1	81.3
Hypertension (%)[c]	7.8	7.2	4.5	5.2	8.8	12.7	16.2
Diabetes (%)[d]	2.2	2.5	1.7	1.6	2.3	3.3	4.3
History of CVD (%)	0.6	0.9	0.6	0.5	0.7	0.7	0.9
Medication for dyslipidemia (%)	1.3	2.8	1.1	1.0	1.4	1.8	2.1
Obesity (%)[e]	26.9	17.7	18.4	20.4	32.5	38.5	44.6
History of *H. pylori* infection[f]	5.0	5.0	4.5	4.6	5.2	5.5	6.5
Histological *H. pylori* infection[g]	67.0	58.4	65.3	63.3	69.9	71.4	70.7
Body mass index (kg/m^2)[a]	23.2 (3.4)	22.2 (3.3)	22.2 (3.4)	22.5 (3.3)	23.8 (3.3)	24.3 (3.2)	24.8 (3.2)
Systolic BP (mm Hg)[a]	108.5 (12.6)	105.2 (12.4)	103.1 (11.8)	105.9 (12.0)	111.2 (12.0)	113.6 (11.9)	115.9 (11.9)
Diastolic BP (mm Hg)[a]	69.3 (9.5)	66.9 (9.0)	66.1 (8.9)	67.4 (8.9)	71.1 (9.3)	73.0 (9.5)	74.8 (9.6)
Glucose (mg/dL)[a]	93.7 (12.6)	92.6 (11.9)	91.4 (11.8)	92.3 (11.1)	94.6 (12.4)	96.4 (14.7)	98.2 (16.2)
Total cholesterol (mg/dL)[a]	191.7 (33.4)	190.5 (33.4)	187.7 (32.3)	188.4 (32.4)	194.3 (33.5)	197.5 (34.0)	200.1 (35.0)
LDL-C (mg/dL)[a]	118.7 (31.5)	117.5 (30.8)	112.7 (29.9)	116.0 (30.6)	122.2 (32.0)	124.0 (32.2)	125.0 (33.0)
HDL-C (mg/dL)[a]	59.5 (15.4)	61.8 (15.1)	61.1 (14.9)	60.8 (15.3)	57.6 (15.3)	57.3 (15.4)	57.4 (15.2)
Triglycerides (mg/dL)[h]	86 (62–128)	76 (58–106)	75 (56–105)	78 (58–112)	95 (67–141)	107 (74–158)	118 (82–176)
AST (U/L)[h]	19 (16–24)	18 (15–22)	18 (15–22)	18 (16–22)	20 (17–25)	21 (18–27)	23 (19–29)
ALT (U/L)[h]	18 (12–27)	15 (11–21)	14 (11–21)	16 (12–24)	20 (14–31)	22 (15–33)	24 (17–36)
GGT (U/L)[h]	19 (13–33)	14 (11–20)	14 (11–21)	16 (12–24)	24 (16–38)	30 (20–51)	40 (24–67)
hsCRP (mg/L)[h]	0.4 (0.2–0.9)	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.4 (0.2–0.9)	0.5 (0.3–1.0)	0.5 (0.3–1.0)
HOMA-IR[h]	1.20 (0.79–1.77)	1.14 (0.75–1.68)	1.13 (0.76–1.66)	1.16 (0.77–1.71)	1.23 (0.82–1.83)	1.27 (0.84–1.90)	1.33 (0.87–2.00)
Total calorie intake (kcal/day)[h,i]	1,493 (1,123–1,907)	1,433 (1,063–1,825)	1,403 (1,031–1,809)	1,446 (1,086–1,847)	1,535 (1,171–1,947)	1,580 (1,209–2,011)	1,656 (1,260–2,109)
Sodium intake (mg/d)[h,i]	1,630.6 (1,052.6–2,455.9)	1,527.2 (968.8–2,358.5)	1,478.6 (937.4–2,283.0)	1,522.9 (992.0–2,302.9)	1,696.5 (1,108.9–2,513.4)	1,835.6 (1,192.2–2,689.7)	2,033.4 (1,327.7–2,974.7)

Note: SI conversion factors: to convert glucose to millimoles per liter, multiply by 0.0555; total cholesterol, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; AST, ALT, and GGT to microkatals per liter, multiply by 0.0167; and hsCRP to nanomoles per liter, multiply by 9.524.

Abbreviations: HDL-C, high-density lipoprotein cholesterol; HEPA, health-enhancing physically active; LDL-C, low-density lipoprotein cholesterol.

[a]Data are expressed as mean (SD).

[b]≥College graduate.

[c]Defined as systolic BP ≥140 mm Hg, diastolic BP ≥90 mm Hg, a history of hypertension, or current use of antihypertensive medications.

[d]Defined as a fasting serum glucose ≥126 mg/dL, HbA1c ≥6.5% a history of diabetes, or current use of antidiabetic medications.

[e]Body mass index ≥25 kg/m^2.

[f]History of *H. pylori* infection was identified through self-reporting of physician-diagnosed *H. pylori* infection via self-administered questionnaire.

[g]Among 6,203 (3.1%) participants whose biopsy was histologically tested for *H. pylori* infection by Giemsa stain.

[h]Median (interquartile range).

[i]Among 146,828 participants with plausible estimated energy intake levels (within three SDs of the log-transformed mean energy intake).

Table 2. HRs (95% CI) for intestinal metaplasia and atrophic gastritis by alcohol consumption category based on both lifetime drinking history and current drinking status (n = 202,675).

Alcohol consumption category	PY	Incident cases	Incidence density (10^3 PY)	Age and sex-adjusted HRs (95% CI)	Multivariable-adjusted HR (95% CI)[a]		HR (95% CI)[b] in model using time-dependent variable
					Model 1	Model 2	
Intestinal metaplasia	943,404.4	4536	4.8				
Lifetime abstainer	24,043.1	95	4.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<10 g/day	454,421.9	1,708	3.8	1.28 (1.03–1.58)	1.27 (1.02–1.56)	1.27 (1.02–1.56)	1.22 (0.99–1.51)
10–<20 g/day	174,157.6	927	5.3	1.42 (1.14–1.76)	1.34 (1.07–1.66)	1.34 (1.07–1.66)	1.25 (1.01–1.56)
20–<40 g/day	117,172.0	816	7.0	1.64 (1.32–2.05)	1.50 (1.20–1.86)	1.49 (1.19–1.86)	1.33 (1.07–1.67)
≥40 g/day	86,849.0	666	7.7	1.74 (1.39–2.17)	1.54 (1.23–1.93)	1.53 (1.22–1.91)	1.56 (1.24–1.95)
P for trend				<0.001	<0.001	<0.001	<0.001
Current abstainer	86,760.8	324	3.7	1.29 (1.02–1.62)	1.30 (1.03–1.64)	1.29 (1.02–1.63)	1.15 (0.91–1.46)
Atrophic gastritis	806,108.5	64,853	80.5				
Lifetime abstainer	20,271.7	2,069	102.1	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.1–<10 g/day	395,433.1	28,877	73.0	1.08 (1.03–1.13)	1.08 (1.03–1.13)	1.08 (1.03–1.13)	1.03 (0.92–1.14)
10–<20 g/day	147,121.4	12,159	82.6	1.16 (1.10–1.22)	1.15 (1.09–1.20)	1.14 (1.09–1.20)	1.13 (1.02–1.26)
20–<40 g/day	97,059.5	9,016	92.9	1.22 (1.16–1.28)	1.20 (1.14–1.26)	1.19 (1.13–1.25)	1.17 (1.05–1.31)
≥40 g/day	71,415.5	7,075	99.1	1.28 (1.22–1.35)	1.24 (1.18–1.31)	1.23 (1.17–1.30)	1.23 (1.11–1.38)
P_{trend}				<0.001	<0.001	<0.001	<0.001
Current abstainer	74,807.3	5,657	75.6	1.07 (1.02–1.12)	1.10 (1.05–1.16)	1.10 (1.04–1.15)	1.12 (0.99–1.26)

Abbreviation: PY, person-years.

[a]Estimated from parametric proportional hazard models to estimate HRs and 95% CIs. Multivariable model was adjusted for age, sex (men or women), center (Seoul or Suwon), year of screening exam (1-year category), smoking status (never, past, current, or unknown), total energy intake (in quintile or missing), physical activity (inactive, minimally active, health-enhancing physically active, or unknown), BMI (continuous), education level (high school graduate or less, community college or university graduate, graduate school or higher, or unknown), history of diabetes, history of hypertension, history of cardiovascular disease, and history of *H. pylori*; model 2: model 1 plus adjustment for HOMA-IR and hsCRP.

[b]Estimated from parametric proportional hazard models with alcohol consumption, smoking status, physical activity, total energy intake, and BMI as time-dependent variables and baseline age, education level, history of *H. pylori*, history of cardiovascular disease, history of diabetes, and history of hypertension as time-fixed variables.

population) did not substantially change the results (Supplementary Table S8).

Discussion

In this large cohort study with repeated measurements of upper endoscopy, the risk of incident IM and AG increased in a dose–response manner as alcohol consumption increased and this association was consistently observed in time-dependent analyses in which changes in alcohol drinking and other confounders were updated as time-varying covariates. All aspects of alcohol drinking including the drinking quantity, frequency and binge drinking were significantly associated with increased risk of incident IM and AG in a dose–response manner, and this association started from low-level alcohol drinking.

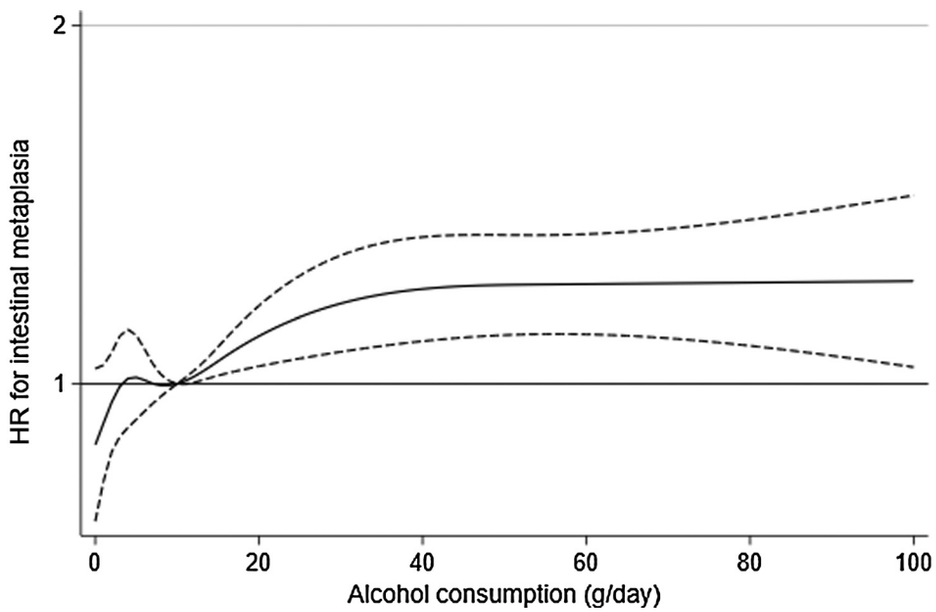

Figure 2.
Multivariable-adjusted HRs for intestinal metaplasia. Curves represent adjusted HRs for intestinal metaplasia based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of alcohol consumption distribution. Models were adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, physical activity, BMI, education level, total calorie intake, history of *H. pylori*, history of diabetes, history of hypertension, and history of cardiovascular disease.

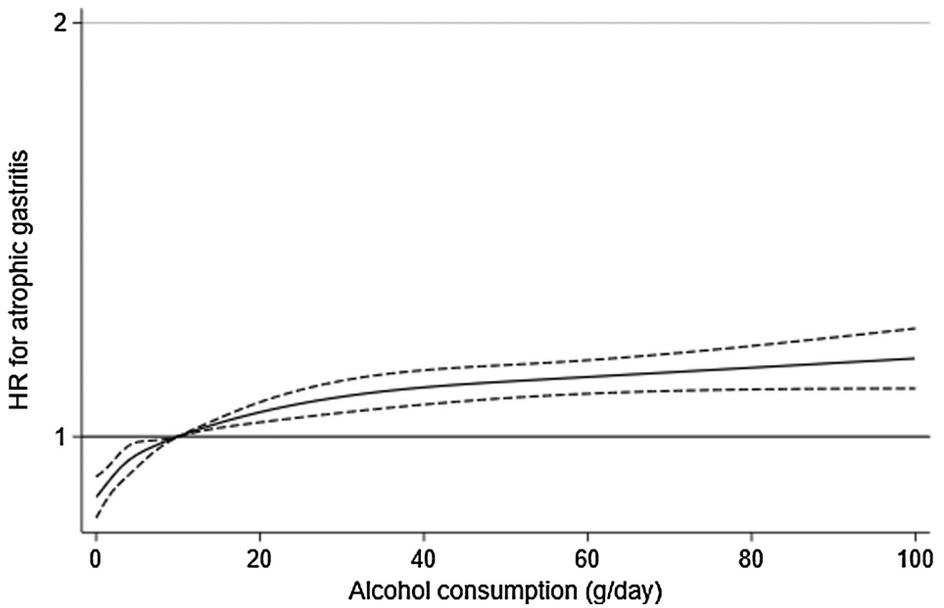

Figure 3.
Multivariable-adjusted HRs for atrophic gastritis. Curves represent adjusted HRs for atrophic gastritis based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of alcohol consumption distribution. Models were adjusted for age, sex, center, year of screening exam, smoking status, alcohol intake, physical activity, BMI, education level, total calorie intake, history of *H. pylori*, history of diabetes, history of hypertension, and history of cardiovascular disease.

The impact of alcohol drinking on gastric cancer risk remains controversial. Studies addressing this subject have reported inconsistent results, varying from a positive association (4, 8–10) to no evidence of association (11, 36). In 2016, the World Cancer Research Fund suggested that consumption of ≥3 alcoholic drinks (equivalent to ≥45 g/day) is a probable cause of gastric cancer (37). However, the relationship of nonheavy drinking with gastric cancer risk remains still unclear. Studies have reported a positive association of gastric cancer with heavy alcohol drinking (7, 9, 10, 38) and found a lack of association with moderate drinking (4) and even protective effect of light drinking on gastric cancer in women (7). These discrepant findings across the studies may be partly explained by different study populations with different ethanol metabolism capacities and differences in definitions of reference, alcohol measures, and subtypes of gastric cancers (7, 9, 10, 38). Furthermore, during the long duration between alcohol exposure at baseline and gastric cancer diagnosis, individuals with stomach lesions including precancerous lesions may be more likely to abstain from alcohol as a result of their gastric diseases; however, most studies have used a single measure of alcohol consumption at one time point (39). Precancerous lesions can help

Table 3. HRs (95% CI) for intestinal metaplasia and atrophic gastritis according to lifetime drinking status by smoking status.

	Multivariable-adjusted HR (95% CI)[a]	
Alcohol consumption category	**Intestinal metaplasia**	**Atrophic gastritis**
Never smoker (n = 107,846)		
Lifetime abstainer	1.00 (reference)	1.00 (reference)
0–<10 g/day	1.35 (1.03–1.77)	1.07 (1.02–1.13)
10–<20 g/day	1.33 (0.99–1.80)	1.15 (1.08–1.22)
20–<40 g/day	1.33 (0.96–1.86)	1.19 (1.11–1.28)
≥40 g/day	1.50 (1.04–2.17)	1.17 (1.08–1.27)
P_{trend}	<0.001	<0.001
Current abstainer	1.23 (0.91–1.67)	1.08 (1.01–1.14)
Ever smoker (n = 83,511)		
Lifetime abstainer	1.00 (reference)	1.00 (reference)
0–<10 g/day	1.03 (0.66–1.61)	1.08 (0.95–1.23)
10–<20 g/day	1.19 (0.76–1.86)	1.15 (1.01–1.30)
20–<40 g/day	1.38 (0.88–2.15)	1.21 (1.07–1.37)
≥40 g/day	1.38 (0.88–2.15)	1.26 (1.11–1.43)
P_{trend}	<0.001	<0.001
Current abstainer	1.21 (0.75–1.93)	1.15 (1.01–1.32)
$P_{interaction}$	0.084	0.187

[a]Estimated from parametric proportional hazard models to estimate HRs and 95% CIs. Multivariable model was adjusted for age, sex (men or women), center (Seoul or Suwon), year of screening exam (1-year category), total energy intake (in quintile or missing), physical activity (inactive, minimally active, health-enhancing physically active, or unknown), BMI (continuous), education level (high school graduate or less, community college or university graduate, graduate school or higher, or unknown), history of diabetes, history of hypertension, history of cardiovascular disease, and history of *H. pylori*.

understanding of the dynamic pathogenesis process and identifying risk factors for precancerous lesions can also help improve our understanding of etiologic risk factors of corresponding cancers (40). Until now, the impact of alcohol drinking on gastric precancerous lesions and its dose–response relationship has remained unclear (13–21). Recently, the American Gastroenterological Association Technical Review demonstrated that the random-effects pooled unadjusted relative risk of having gastric IM in current versus former or never alcohol users was 1.29 (95% CI, 1.12–1.50; ref. 41). However, all studies were limited by uncertain temporal relationships due to cross-sectional study designs; inconsistent differentiation among current, former, and never alcohol users; and lack of adjustments for confounding factors (13, 14, 18, 19, 41). In our detailed dose–response analysis with differentiation from lifetime abstainers versus current abstainers (former drinkers), alcohol drinking at even a light drinking level (<10 g/day) was consistently associated with increased risks of developing both AG and IM. These associations were consistently observed when updated status of alcohol drinking and other confounders over time were treated as time-varying covariates. Smoking is a well-known risk factor for gastric cancer and has been reported as an independent risk factor for gastric IM (23). Even when we performed analyses among never smokers to address the residual confounding by smoking, the association between alcohol drinking and incident precancerous lesions was consistently observed. Furthermore, all measured aspects of drinking patterns including frequency, quantity, and binge drinking were associated with increased risks of incident IM and AG in an independent dose–response manner, and these associations also started from light to moderate drinking.

Although the mechanism for alcohol-induced gastric carcinogenesis has not been fully understood, some suggested mechanisms are as follows: (i) genotoxic effects of ethanol itself or acetaldehyde, the first metabolite of ethanol and an evident carcinogen; (ii) cytochrome p450 2E1 (CYP2E1)-mediated production of reactive oxygen species (ROS) can activate signaling molecules involved in inflammation, angiogenesis, and cell migration as well as cause DNA damage; (iii) folate deficiency can provoke aberrant DNA methylation; (iv) the action of alcohol as a solvent for tobacco carcinogens; and (v) immunosuppression induced by long-term alcohol abuse (42–45). Alcohol consumption could contribute to both the occurrence of alcohol-induced gastritis and the promotion of gastric neoplasm development in the presence of underlying AG (13). Further research is needed to determine how alcohol drinking affects the entire gastric carcinogenesis.

Despite the many strengths of our study, there also are several limitations. First, alcohol drinking was assessed using self-administered structured questionnaires without an objective marker of alcohol consumption, such as phosphatidylethanol or carbohydrate-deficient transferrin, which was similar to most epidemiologic studies (46). Self-reported alcohol intake might be underestimated; however, after excluding participants with serum GGT above the 75th percentile, a commonly used marker of alcohol use, to minimize the potential bias by self-misreporting in drinking (15, 32, 47), the relationship between alcohol drinking and incident AG and IM supports an association of nonheavy drinking with gastric precancerous lesions. Previous studies have addressed the differential effect of types of alcoholic beverages on gastric cancer and reported that wine intake might lower the risk of gastric cancer, unlike that of beer or spirits (38, 48). However, in Korea, a culture of mixing two or more alcohol drinks called "drinking of bomb cocktails" is common, which makes it difficult to investigate the effect of each type of alcohol (49). Although our study focused on average alcohol consumption and drinking patterns relating to quantity, frequency, and binge pattern consumption, beverage type can also differently affect gastric precancerous and cancerous lesions, and we suggest that the effects of these different types of alcoholic beverage require further study. Second, AG and IM were diagnosed based on endoscopic findings but not on histologic findings. However, endoscopically diagnosed AG and IM have been reported to be in acceptable agreement with histologically diagnosed AG and IM and to be associated with gastric cancer development in previous reports (13, 50–54). Even so, varying degrees of sensitivity and specificity of endoscopic AG/IM have been reported: specifically, the sensitivity and specificity of endoscopic AG compared with histologic AG were 65.9% and 58.0% for antrum, 71.3% and 53.7% for corpus, respectively, whereas the sensitivity and specificity of endoscopic IM diagnosis based on histology were 24.0% to 24.2% and 88.0% to 91.9%, respectively (54–56). Third, the intra- and interobserver reliability tests among endoscopists were not performed in this study. Endoscopists involved in a routine health check-up program were unaware of the study purpose and individual's alcohol drinking status while performing procedures; thus, the possibility of misclassification on AG/IM might not have differed by alcohol drinking status. Fourth, *H. pylori* infection status was defined as self-report of physician-diagnosed *H. pylori* infection. In only a small proportion (<5%) of participants, *H. pylori* infection status was evaluated histologically at the discretion of the endoscopists, because a consensus treatment guideline in Korea covered only the treatment of peptic ulcer disease (including scar lesions), early gastric cancer, and marginal zone B-cell lymphoma (MALT type) during the study period (30), thus limiting our ability to account for histologically confirmed or more accurate measures of *H. pylori* infection in the analysis. Fifth, data on the intragastric location of AG and IM were not included in this study, although most studies in gastric carcinogenesis divided intragastric location into cardiac/noncardiac or proximal/distal. There is still controversy over the frequent location and histologic type of gastric cancer associated with alcohol intake according to race and study design, and thus further study is needed to clarify the alcohol effect on the entire gastric carcinogenesis (9, 57). Thus, we cannot exclude the possibility of some unmeasured or residual confounding factors in the observed findings. Finally, the subjects included in this study were young and middle-aged Koreans in areas where *H. pylori* is endemic and the *ALDH2* variant is common; furthermore, drinking patterns and the prevalence of gene variants encoding the alcohol-metabolizing enzymes differ among racial/ethnic groups (58). Thus, the applicability of our findings to other age groups, populations with a higher prevalence of comorbidities, and other race/ethnicity groups might be limited. Further research using *ALDH2* genotyping is needed to examine definitively whether the association between alcohol consumption and precursor lesions of gastric cancer differs by *ALDH2* polymorphism.

In conclusion, in this large-scale cohort study of young and middle-aged Korean adults, alcohol consumption from low-level drinking was consistently and independently associated with increased risks of developing AG and IM in a dose–response manner. Our findings indicate that no level of alcohol drinking appears to be safe in relation to premalignant lesions of gastric cancer in this population. However, our findings should be confirmed in other populations and further research is required to determine whether avoiding alcohol drinking can help reduce the development of precancerous lesions of gastric cancer and subsequently reduce gastric cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

K. Kim: Conceptualization, writing–original draft. **Y. Chang:** Conceptualization, resources, investigation, methodology, project administration, writing–review and editing. **J. Ahn:** Resources, data curation, investigation. **H.-J. Yang:** Resources, investigation. **S. Ryu:** Conceptualization, resources, formal analysis, supervision, investigation, visualization, methodology, writing–review and editing.

Acknowledgments

This research was supported by grants from Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (2018R1D1A1B07049620) to S. Ryu. The authors thank our staff members of Kangbuk Samsung Health Study for their hard work, dedication, and continuing support.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received June 3, 2020; revised July 29, 2020; accepted September 9, 2020; published first September 14, 2020.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
2. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev 2014;23:700–13.
3. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens–Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033–4.
4. Tramacere I, Negri E, Pelucchi C, Bagnardi V, Rota M, Scotti L, et al. A meta-analysis on alcohol drinking and gastric cancer risk. Ann Oncol 2012;23:28–36.
5. Tramacere I, Pelucchi C, Bagnardi V, Rota M, Scotti L, Islami F, et al. A meta-analysis on alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. Ann Oncol 2012;23:287–97.
6. Han X, Xiao L, Yu Y, Chen Y, Shu HH. Alcohol consumption and gastric cancer risk: a meta-analysis of prospective cohort studies. Oncotarget 2017;8:83237–45.
7. He Z, Zhao TT, Xu HM, Wang ZN, Xu YY, Song YX, et al. Association between alcohol consumption and the risk of gastric cancer: a meta-analysis of prospective cohort studies. Oncotarget 2017;8:84459–72.
8. Ma K, Baloch Z, He TT, Xia X. Alcohol consumption and gastric cancer risk: a meta-analysis. Med Sci Monit 2017;23:238–46.
9. Rota M, Pelucchi C, Bertuccio P, Matsuo K, Zhang ZF, Ito H, et al. Alcohol consumption and gastric cancer risk-a pooled analysis within the StoP project consortium. Int J Cancer 2017;141:1950–62.
10. Wang PL, Xiao FT, Gong BC, Liu FN. Alcohol drinking and gastric cancer risk: a meta-analysis of observational studies. Oncotarget 2017;8:99013–23.
11. Wang S, Freedman ND, Loftfield E, Hua X, Abnet CC. Alcohol consumption and risk of gastric cardia adenocarcinoma and gastric noncardia adenocarcinoma: a 16-year prospective analysis from the NIH-AARP diet and health cohort. Int J Cancer 2018;143:2749–57.
12. Correa P. The biological model of gastric carcinogenesis. IARC Sci Publ 2004: 301–10.
13. Song JH, Kim SG, Jin EH, Lim JH, Yang SY. Risk factors for gastric tumorigenesis in underlying gastric mucosal atrophy. Gut Liver 2017;11:612–9.
14. Joo YE, Park HK, Myung DS, Baik GH, Shin JE, Seo GS, et al. Prevalence and risk factors of atrophic gastritis and intestinal metaplasia: a nationwide multicenter prospective study in Korea. Gut Liver 2013;7:303–10.
15. Gao L, Weck MN, Stegmaier C, Rothenbacher D, Brenner H. Alcohol consumption and chronic atrophic gastritis: population-based study among 9,444 older adults from Germany. Int J Cancer 2009;125:2918–22.
16. Segawa K, Nakazawa S, Tsukamoto Y, Goto H, Yamao K, Hase S, et al. Chronic alcohol abuse leads to gastric atrophy and decreased gastric secretory capacity: a histological and physiological study. Am J Gastroenterol 1988;83:373–9.
17. Choi S, Lim YJ, Park SK. Risk factor analysis for metaplastic gastritis in Koreans. World J Gastroenterol 2006;12:2584–7.
18. Gomez JM, Frye JW, Patrie JT, Sauer BG, Shami VM, Stelow EB, et al. The presence of gastric intestinal metaplasia in patients undergoing EGD with biopsy is associated with a family history of gastric cancer in the United States. J Gastroenterol Hepatol Res 2013;2:726–9.
19. Leung WK, Ng EK, Chan WY, Auyeung AC, Chan KF, Lam CC, et al. Risk factors associated with the development of intestinal metaplasia in first-degree relatives of gastric cancer patients. Cancer Epidemiol Biomarkers Prev 2005;14:2982–6.
20. Lin S, Gao T, Sun C, Jia M, Liu C, Ma X, et al. Association of dietary patterns and endoscopic gastric mucosal atrophy in an adult Chinese population. Sci Rep 2019;9:16567.
21. Adamu MA, Weck MN, Rothenbacher D, Brenner H. Incidence and risk factors for the development of chronic atrophic gastritis: five year follow-up of a population-based cohort study. Int J Cancer 2011;128:1652–8.
22. Chang Y, Kim BK, Yun KE, Cho J, Zhang Y, Rampal S, et al. Metabolically-healthy obesity and coronary artery calcification. J Am Coll Cardiol 2014;63: 2679–86.
23. Kim K, Chang Y, Ahn J, Yang HJ, Jung JY, Kim S, et al. Smoking and urinary cotinine levels are predictors of increased risk for gastric intestinal metaplasia. Cancer Res 2019;79:676–84.
24. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–95.
25. Ezzati M, Lopez AD, Rodgers AA, Murray CJL. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. Geneva (Switzerland): World Health Organization; 2004.
26. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. Addiction 1993;88:791–804.
27. Brooks PJ, Enoch MA, Goldman D, Li TK, Yokoyama A. The alcohol flushing response: an unrecognized risk factor for esophageal cancer from alcohol consumption. PLoS Med 2009;6:e50.
28. Kim JS, Kim YJ, Kim TY, Song JY, Cho YH, Park YC, et al. Association of ALDH2 polymorphism with sensitivity to acetaldehyde-induced micronuclei and facial flushing after alcohol intake. Toxicology 2005;210:169–74.
29. Chang Y, Ryu S, Kim Y, Cho YK, Sung E, Kim HN, et al. Low levels of alcohol consumption, obesity, and development of fatty liver with and without evidence of advanced fibrosis. Hepatology 2020;71:861–73.
30. Kim SG, Jung HK, Lee HL, Jang JY, Lee H, Kim CG, et al. Guidelines for the diagnosis and treatment of Helicobacter pylori infection in Korea, 2013 revised edition. J Gastroenterol Hepatol 2014;29:1371–86.
31. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21: 2175–97.
32. Peterson K. Biomarkers for alcohol use and abuse–a summary. Alcohol Res Health 2004;28:30–7.
33. Chang JS, Hsiao JR, Chen CH. ALDH2 polymorphism and alcohol-related cancers in Asians: a public health perspective. J Biomed Sci 2017;24:19.
34. Shin MJ, Cho Y, Davey Smith G. Alcohol consumption, aldehyde dehydrogenase 2 gene polymorphisms, and cardiovascular health in Korea. Yonsei Med J 2017; 58:689–96.
35. Kwon HJ, Won YS, Park O, Chang B, Duryee MJ, Thiele GE, et al. Aldehyde dehydrogenase 2 deficiency ameliorates alcoholic fatty liver but worsens liver inflammation and fibrosis in mice. Hepatology 2014;60:146–57.
36. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut 2010;59:39–48.
37. World Cancer Research Fund International/American Institute for Cancer Research. Continuous Update Project Report: diet, nutrition, physical activity and stomach cancer. London; Washington (DC): WCRF International; AICR; 2016. Available from: https://www.wcrf.org/sites/default/files/Stomach-Cancer-2016-Report.pdf.
38. Duell EJ, Travier N, Lujan-Barroso L, Clavel-Chapelon F, Boutron-Ruault MC, Morois S, et al. Alcohol consumption and gastric cancer risk in the European

Prospective Investigation into Cancer and Nutrition (EPIC) cohort. Am J Clin Nutr 2011;94:1266–75.
39. Devaux M, Sassi F. Alcohol consumption and harmful drinking: trends and social disparities across OECD countries. Paris: OECD Publishing; 2015. OECD Health Working Papers No.: 79. Available from: https://www.oecd-ilibrary.org/content/paper/5js1qwkz2p9s-en.
40. Wacholder S. Precursors in cancer epidemiology: aligning definition and function. Cancer Epidemiol Biomarkers Prev 2013;22:521–7.
41. Altayar O, Davitkov P, Shah SC, Gawron AJ, Morgan DR, Turner K, et al. AGA technical review on gastric intestinal metaplasia-epidemiology and risk factors. Gastroenterology 2020;158:732–44.
42. Na HK, Lee JY. Molecular basis of alcohol-related gastric and colon cancer. Int J Mol Sci 2017;18:1116.
43. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer 2007;7:599–612.
44. Shin CM, Kim N, Cho SI, Kim JS, Jung HC, Song IS. Association between alcohol intake and risk for gastric cancer with regard to ALDH2 genotype in the Korean population. Int J Epidemiol 2011;40:1047–55.
45. Mufti SI, Darban HR, Watson RR. Alcohol, cancer, and immunomodulation. Crit Rev Oncol Hematol 1989;9:243–61.
46. Viel G, Boscolo-Berto R, Cecchetto G, Fais P, Nalesso A, Ferrara SD. Phosphatidylethanol in blood as a marker of chronic alcohol use: a systematic review and meta-analysis. Int J Mol Sci 2012;13:14788–812.
47. Whitfield JB. Serum gamma-glutamyltransferase and risk of disease. Clin Chem 2007;53:1–2.
48. Barstad B, Sorensen TI, Tjonneland A, Johansen D, Becker U, Andersen IB, et al. Intake of wine, beer and spirits and risk of gastric cancer. Eur J Cancer Prev 2005;14:239–43.
49. Ko S, Sohn A. Behaviors and culture of drinking among Korean people. Iran J Public Health 2018;47:47–56.
50. Fukuta N, Ida K, Kato T, Uedo N, Ando T, Watanabe H, et al. Endoscopic diagnosis of gastric intestinal metaplasia: a prospective multicenter study. Dig Endosc 2013;25:526–34.
51. Liu Y, Uemura N, Xiao SD, Tytgat GN, Kate FJ. Agreement between endoscopic and histological gastric atrophy scores. J Gastroenterol 2005;40:123–7.
52. Toyoshima O, Yamaji Y, Yoshida S, Matsumoto S, Yamashita H, Kanazawa T, et al. Endoscopic gastric atrophy is strongly associated with gastric cancer development after Helicobacter pylori eradication. Surg Endosc 2017;31:2140–8.
53. Ahn SY, Lee SY, Hong SN, Kim JH, Sung IK, Park HS, et al. Endoscopic diagnosis of open-type atrophic gastritis is related to the histological diagnosis of intestinal metaplasia and Cdx2 expression. Dig Dis Sci 2011;56:1119–26.
54. Park YH, Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. J Cancer Prev 2015;20:25–40.
55. Lee JY, Kim N, Lee HS, Oh JC, Kwon YH, Choi YJ, et al. Correlations among endoscopic, histologic and serologic diagnoses for the assessment of atrophic gastritis. J Cancer Prev 2014;19:47–55.
56. Lim JH, Kim N, Lee HS, Choe G, Jo SY, Chon I, et al. Correlation between endoscopic and histological diagnoses of gastric intestinal metaplasia. Gut Liver 2013;7:41–50.
57. Sasazuki S, Sasaki S, Tsugane S, Japan Public Health Center Study G. Cigarette smoking, alcohol consumption and subsequent gastric cancer risk by subsite and histologic type. Int J Cancer 2002;101:560–6.
58. Wall TL, Luczak SE, Hiller-Sturmhofel S. Biology, genetics, and environment: underlying factors influencing alcohol metabolism. Alcohol Res 2016;38:59–68.