

## Risk Factors for Gastric Tumorigenesis in Underlying Gastric Mucosal Atrophy

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See editorial on page 575.

**Background/Aims:** Atrophic gastritis is considered a pre-malignant lesion. We aimed to evaluate the risk factors for gastric tumorigenesis in underlying mucosal atrophy. **Methods:** A total of 10,185 subjects who underwent upper gastrointestinal endoscopy between 2003 and 2004 were enrolled in this retrospective cohort study. Follow-up endoscopy was performed between 2005 and 2014. Atrophic gastritis and intestinal metaplasia were assessed by endoscopy using the Kimura-Takemoto classification. *Helicobacter pylori* infection was evaluated based on serum immunoglobulin G antibody levels, the rapid urease test, or the urea breath test. **Results:** Atrophic gastritis was confirmed in 3,714 patients at baseline; 2,144 patients were followed up for 6.9 years, and 1,138 exhibited increased atrophy. A total of 69 subjects were diagnosed with gastric neoplasm during follow-up (35 adenoma and 34 carcinoma). Age  $\geq 55$  years (hazard ratio [HR], 1.234), alcohol consumption (HR, 1.001), and *H. pylori* infection (HR, 1.580) were associated with increased mucosal atrophy. The risk factors for gastric neoplasm in underlying mucosal atrophy were age  $\geq 55$  years (HR, 2.582), alcohol consumption (HR, 1.003), extent of mucosal atrophy (HR, 2.285 in C3-O1; HR, 4.187 in O2-O3), and intestinal metaplasia (HR, 2.655). **Conclusions:** Extent of atrophy, intestinal metaplasia, and alcohol consumption are significant risk factors for gastric neoplasm in underlying mucosal atrophy. (**Gut Liver 2017;11:612-619**)

**Key Words:** Atrophy; Stomach; Neoplasms; Epidemiology

### INTRODUCTION

Gastric carcinogenesis is believed to develop in a multistep process, progressing from chronic gastritis through atrophic gastritis (AG), intestinal metaplasia (IM), and dysplasia before ending in cancer.<sup>1</sup> AG is characterized by the loss of appropriate glands and a reduction in gastric secretory function which results from chronic inflammatory processes in the gastric mucosa.<sup>2</sup> IM is defined as the replacement of gastric columnar epithelial cells by cells with an intestinal morphology.<sup>3</sup> The initial stage of gastritis and atrophy is linked to chronic infection with *Helicobacter pylori*.<sup>1</sup> Two potential pathways have been proposed. The first one is *H. pylori*-induced chronic inflammation in epithelial cells that progresses into gastric atrophy (the "indirect action") and the other is gastric atrophy resulting from epithelial cells being infected by *H. pylori* bacterial agents such as cytotoxin-associated gene A (the "direct action").<sup>4</sup>

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer death in the world.<sup>5</sup> The highest incidence rates are observed in East Asia, South America and Eastern Europe.<sup>6</sup> A recent cohort study in the United States has reported an increasing trend of noncardiac gastric cancer in the young white population.<sup>7</sup> Another study in Sweden reported that the prevalence of AG among people aged 35 to 44 had increased over the past 20 years, which implies that the falling trend of gastric cancer might be reversed in the near future.<sup>8,9</sup> In Korea, the prevalence of endoscopic AG is relatively high: 59.4% in people older than 60 years.<sup>10</sup>

The Korean National Cancer Screening Program has recommended regular 2-year interval gastric cancer screening by upper endoscopy or upper gastrointestinal barium study for individuals over 40 years of age.<sup>11</sup> However, there have been no unified surveillance interval guidelines for high-risk patients

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such as those with AG or IM. A recent Korean study which conducted with an asymptomatic population reported that the rate of early gastric cancer (EGC) was higher in the annual screening group than in the biennial group (98.6% vs 80.7%,  $p < 0.01$ ) and endoscopic resection was performed more frequently in the annual group (56.9% vs 33.3%,  $p = 0.02$ ), thereby suggesting that intensive screening and surveillance might be useful for high-risk subpopulations with epidemiologic risk factors or premalignant lesions.<sup>12</sup> Another Korean study demonstrated that the proportion of EGC was higher in the vigilant screening group (patients who had undergone endoscopy within the past year) than in the non-vigilant screening group (66.7% vs 35.5%,  $p = 0.047$ ), and that endoscopic resection was performed more frequently in the vigilant group than in the non-vigilant group (26.7% vs 0%,  $p = 0.028$ ).<sup>13</sup> For these reasons, we have recommended regular surveillance endoscopy every one year for patients with severe AG and/or IM.

While AG is considered as a precancerous lesion, most patients with AG rarely experience gastric cancer. Therefore, stratifying the patients with AG by risk of gastric cancer may be important for the prevention and/or early detection of gastric cancer. Many studies have shown that the risk of gastric cancer was strongly associated with *H. pylori* infection, smoking, high intake of salty and smoked food, and low intake of fruits and vegetables.<sup>4</sup> However, few studies have been reported to investigate the risk factors for gastric neoplasm in patients with AG. In this study, we aimed to evaluate AG by endoscopy and analyze the risk factors for the aggravation of AG and gastric tumorigenesis in underlying gastric mucosal atrophy.

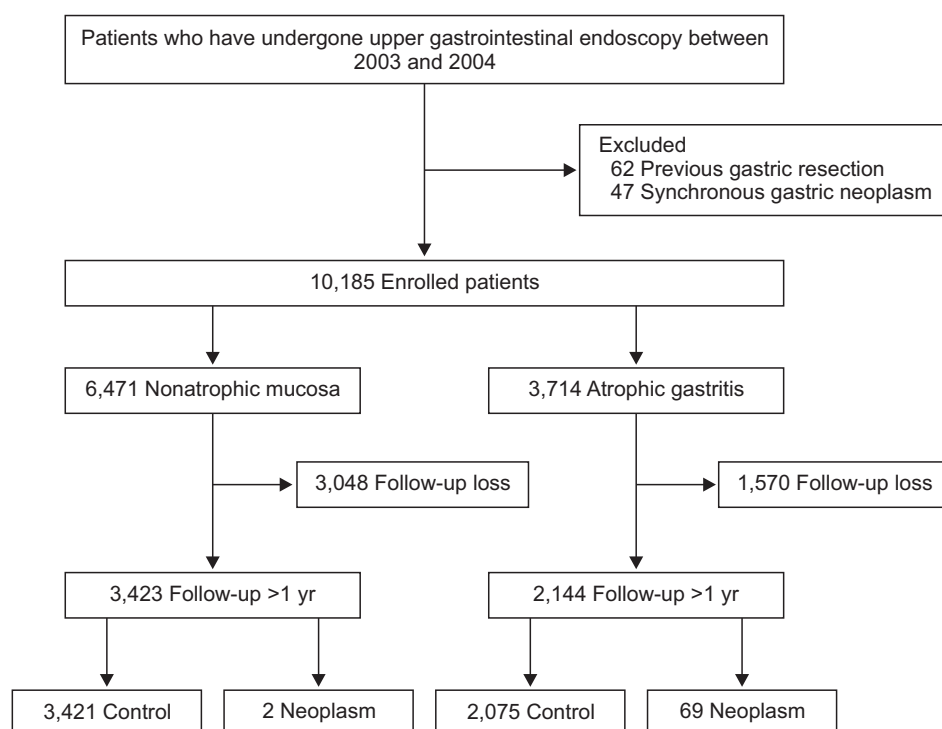
## MATERIALS AND METHODS

### 1. Patients

Between October 2003 and October 2004, 10,294 subjects underwent upper gastrointestinal endoscopy as part of their health check-up at Seoul National University Hospital Healthcare System Gangnam Center. A total of 109 subjects were excluded from the analysis because of previous gastric resection ( $n = 62$ ) or gastric neoplasm within the first year of surveillance ( $n = 47$ ; 18 adenoma, 29 carcinoma), resulting in a final cohort of 10,185 subjects whose medical records were reviewed retrospectively. AG was confirmed in 3,714 subjects (36.5%) by endoscopy, among whom 2,144 were followed up for more than 1 year until December 2014 (Fig. 1).

All subjects were requested to complete a self-administered, structured questionnaire on smoking history, alcohol intake, family history of gastric cancer, and history of *H. pylori* eradication therapy. Alcohol intake was measured by ascertaining the number of drinks per week, which was defined as beer (200 mL per glass), soju (50 mL per glass), wine (120 mL per glass), or liquor (30 mL per shot), each being equivalent to approximately 10 g of alcohol per drink. Heavy drinking was defined as more than 14 drinks per week for men and seven drinks per week for women.

The study protocol was approved by the ethics committee of Seoul National University Hospital (Institutional Review Board number: H-1503-123-658), and was conducted in accordance with the Declaration of Helsinki.



**Fig. 1.** Flow chart of the study population.

## 2. Endoscopic evaluation

Endoscopic gastric mucosal atrophy was evaluated according to the Kimura and Takemoto<sup>14</sup> classification system. Atrophy was classified as either closed type (C1–C3), in which the borders of atrophy did not exceed the cardia on the lesser curvature side of the gastric body, or open type (O1–O3), in which the borders of atrophy exceeded the cardia into the greater curvature side.<sup>14</sup> The characteristic features of each type of atrophy were as follows: limited to the antrum in C1, limited to the gastric angle or the lower body in C2, limited to the upper body in C3, limited to the surroundings of the gastric cardia with maintained folds of the greater curvature in O1, atrophy in the entire stomach with a lack of folds throughout the greater curvature in O3, and O2 as an intermediate type between O1 and O3.<sup>15</sup> Endoscopic gastric atrophy was divided into three grades: mild (C1, C2), moderate (C3, O1), and severe (O2, O3).

Endoscopic IM was diagnosed when whitish plaque-like elevations were seen in the antrum and/or body. When a diagnosis of IM was not clear or a suspicious neoplastic lesion was seen during endoscopy, an additional biopsy was conducted. Histologic IM was evaluated by the updated Sydney system.

All endoscopic findings were reviewed by four experienced endoscopists (J.H.S., E.H.J., J.H.L., and S.Y.Y.). Several meetings were held to improve the accuracy of diagnosis and minimize interobserver variation by extensively reviewing multiple cases with AG. Interobserver agreements on atrophy grades were assessed by Fleiss' kappa coefficient and were initially not good ( $\kappa=0.36$ ,  $p<0.001$ ) but improved substantially later ( $\kappa=0.62$ ,  $p<0.001$ ).

## 3. Follow-up and management

Asymptomatic individuals over 40 years of age were recommended to receive upper gastrointestinal endoscopy to screen for gastric cancer every 2 years. Individuals with AG and/or IM during initial screening endoscopy were recommended to receive annual endoscopic examination in our institute. Aggravated AG was defined as when the grade of mucosal atrophy was aggravated (from mild to moderate or severe, and from moderate to severe) or when IM developed by the time of follow-up endoscopy. When gastric neoplasms were diagnosed during follow-up endoscopy, adenoma with low- or high-grade dysplasia was recommended to be removed by endoscopic resection and was then followed up annually. Patients with adenocarcinoma were recommended to be treated by surgical or endoscopic resection according to the indication.

## 4. *H. pylori* status evaluation

Serum *H. pylori* immunoglobulin G (IgG) antibody test was routinely performed using a commercially available enzyme-linked immunosorbent assay (*H. pylori*-EIA-Well; Radim, Rome, Italy) on the same day of endoscopy. According to the manu-

facturer's instructions, an IgG value  $>30$  U/mL was considered to be reactive for *H. pylori*, 15 to 30 U/mL was considered to be weakly reactive, and  $<15$  U/mL was considered to be non-reactive. Reactive and weakly reactive were defined as a positive result.

In the presence of peptic ulcer disease, biopsy specimens from the lesser curvature of the antrum and/or body were obtained for rapid urease test (CLO test<sup>®</sup>; Delta West, Bentley, Australia). After *H. pylori* eradication therapy, the <sup>13</sup>C-urea breath test (Heliview<sup>®</sup>; Medichems, Seoul, Korea) was used to confirm the current *H. pylori* status.

The subject was considered as *H. pylori*-positive if any one of

**Table 1.** Baseline Characteristics of the Study Population (n=10,185)

Characteristic	Value
Age, yr	47.81±11.22
<55	7,339 (72.1)
≥55	2,846 (27.9)
Male sex	5,581 (54.8)
Smoking*	
Nonsmoker	1,242 (45.3)
Ex-smoker	1,072 (39.1)
Current smoker	425 (15.5)
Smoking, pack-year <sup>†</sup>	11.25±16.59
Heavy drinking <sup>‡</sup>	
No	2,249 (82.0)
Yes	494 (18.0)
Alcohol intake, drinks/wk <sup>‡</sup>	7.20±11.97
Family history of gastric cancer <sup>§</sup>	446 (14.7)
Mucosal atrophy at baseline	
Normal	6,471 (63.5)
C1	1,018 (10.0)
C2	1,313 (12.9)
C3	865 (8.5)
O1	338 (3.3)
O2	139 (1.4)
O3	41 (0.4)
Intestinal metaplasia	
Absent	8,759 (86.0)
Present	1,426 (14.0)
<i>Helicobacter pylori</i> infection status <sup>  </sup>	
Not infected	3,899 (40.5)
Eradicated	127 (1.3)
Infected	5,597 (58.2)
Follow-up period, yr <sup>¶</sup>	6.88±3.18

Data are presented as mean±SD or number (%).

\*Data available for 2,739 subjects; <sup>†</sup>Data available for 2,492 subjects;

<sup>‡</sup>Data available for 2,743 subjects; <sup>§</sup>Data available for 3,041 subjects;

<sup>||</sup>Data available for 9,623 subjects; <sup>¶</sup>Data available for 5,567 subjects.

these three tests (serology, rapid urease test, or <sup>13</sup>C-urea breath test) was positive or the bacteria were histologically detected by a Giemsa stain.

### 5. Statistical analysis

Descriptive statistical analyses included the calculation of rates and proportions for categorical data and of means and standard deviations for continuous data.

Associations of risk factors for AG were estimated in the 10,185 subjects by logistic regression analysis, in terms of the odds ratio (OR) and the corresponding 95% confidence intervals (CI). Relative risks for aggravation of AG and for gastric neoplasm were evaluated in the 2,144 subjects who had undergone follow-up endoscopy using the Cox proportional hazard regression model by computing the hazard ratio (HR) and 95% CI after multivariate adjustment.

Results were considered to be statistically significant if the two-sided p-value was less than 0.05 or if the 95% CI did not include unity. Data analysis was performed using the SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### 1. Baseline characteristics of the study population

Of the 10,185 subjects (mean age, 47.8 years; male, 54.8%), 3,714 (36.5%) were diagnosed with AG and 1,426 (14.0%) were diagnosed with IM. *H. pylori* was detected in 5,597 subjects (58.2%). Of the 4,026 subjects who were *H. pylori*-negative, 127 subjects (1.3%) had a history of *H. pylori* eradication therapy (Table 1).

### 2. Associations with risk factors for AG on endoscopic finding

Associations with risk factors for AG were estimated by logistic regression analysis. In multivariate analysis, old age ( $\geq 55$  years vs  $< 55$  years) (OR, 2.677; 95% CI, 2.214 to 3.238;  $p < 0.001$ ), male sex (OR, 2.151; 95% CI, 1.671 to 2.770;  $p < 0.001$ ), and *H. pylori* infection (OR, 3.224; 95% CI, 2.089 to 4.977; in eradicated vs no infection,  $p < 0.001$ ; OR, 3.405; 95% CI, 2.779 to 4.171; in infected vs no infection,  $p < 0.001$ ) were significant independent risk factors for AG (Table 2).

### 3. Risk factors for aggravation of AG on follow-up endoscopy

Of the 3,714 subjects with AG, 2,144 subjects (57.7%) had

**Table 2.** Associations with Risk Factors for Atrophic Gastritis Based on Endoscopic Findings

	AG (-) (n=6,471)	AG (+) (n=3,714)	OR*	95% CI	OR <sup>†</sup>	95% CI
Age, yr						
<55	5,250	2,089	Reference		Reference	
$\geq 55$	1,221	1,625	3.345	3.057–3.659	2.677	2.214–3.238
Sex						
Female	3,290	1,314	Reference		Reference	
Male	3,181	2,400	1.889	1.738–2.053	2.151	1.671–2.770
Smoking <sup>‡</sup>						
Nonsmoker	561	681	Reference		Reference	
Ex-smoker	384	688	1.476	1.248–1.745	0.854	0.662–1.102
Current smoker	185	240	1.069	0.856–1.334	0.781	0.573–1.066
Heavy drinking <sup>§</sup>						
No	923	1,326	Reference		Reference	
Yes	191	303	1.104	0.904–1.348	1.043	0.822–1.323
Family history of GC <sup>  </sup>						
No	1,118	1,477	Reference		Reference	
Yes	175	271	1.172	0.955–1.439	1.189	0.940–1.503
<i>H. pylori</i> infection status <sup>¶</sup>						
Not infected	3,124	775	Reference		Reference	
Eradicated	38	89	9.441	6.406–13.914	3.224	2.089–4.977
Infected	2,890	2,707	3.776	3.435–4.150	3.405	2.779–4.171

AG, atrophic gastritis; OR, odds ratio; CI, confidence interval; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*.

\*Univariate analyses of risk factors for AG; <sup>†</sup>Adjusted for age, sex, smoking, heavy drinking, family history of GC, and *H. pylori* infection; <sup>‡</sup>Data available for 2,739 subjects; <sup>§</sup>Data available for 2,743 subjects; <sup>||</sup>Data available for 3,041 subjects; <sup>¶</sup>Data available for 9,623 subjects.

**Table 3.** Risk Factors for Aggravation of Atrophic Gastritis at Follow-up Endoscopy (n=2,144)

	No change (n=1,006)	Aggravation (n=1,138)	HR*	95% CI	HR <sup>†</sup>	95% CI
Age, yr						
<55	617	636	Reference		Reference	
≥55	389	502	1.175	1.045–1.321	1.234	1.065–1.430
Sex						
Female	330	367	Reference		Reference	
Male	676	771	0.973	0.859–1.102	0.900	0.748–1.084
Smoking, pack-year <sup>‡</sup>	11.38±15.77	12.85±17.70	1.001	0.997–1.005	0.999	0.995–1.004
Alcohol intake, drinks/wk <sup>§</sup>	7.23±11.65	7.41±12.55	1.011	1.006–1.017	1.001	1.001–1.002
Family history of GC <sup>  </sup>						
No	644	789	Reference		Reference	
Yes	100	167	1.050	0.888–1.241	1.032	0.855–1.245
<i>H. pylori</i> infection <sup>¶</sup>						
No	159	96	Reference		Reference	
Newly infected	37	44	1.427	0.999–2.040	1.186	0.788–1.785
Eradicated	177	143	1.167	0.901–1.512	1.042	0.769–1.412
Persistent	437	685	1.865	1.506–2.310	1.580	1.220–2.046

HR, hazard ratio; CI, confidence interval; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*.

\*Univariate analyses of risk factors for atrophic gastritis; <sup>†</sup>Adjusted for age, sex, smoking, alcohol intake, family history of GC, and *H. pylori* infection status; <sup>‡</sup>Data available for 1,431 subjects; <sup>§</sup>Data available for 1,586 subjects; <sup>||</sup>Data available for 1,700 subjects; <sup>¶</sup>Data available for 1,778 subjects.

undergone follow-up endoscopy. During a mean follow-up of 6.9 years (range, 1.0 to 11.2 years), 1,138 subjects (53.1%) showed aggravation of AG and 1,006 subjects (46.9%) showed no change. Cox proportional hazards regression revealed that age ≥55 (HR, 1.234; 95% CI, 1.065 to 1.430; p=0.005), alcohol intake (HR, 1.001; 95% CI, 1.001 to 1.002; p<0.001), and sustained *H. pylori* infection (HR, 1.580; 95% CI, 1.220 to 2.046; p=0.001) were significantly associated with aggravation of AG (Table 3).

#### 4. Risk factors for gastric tumorigenesis in underlying gastric mucosal atrophy

A total of 69 subjects was diagnosed with gastric neoplasm (32 cases of adenoma with low grade dysplasia, two cases of adenoma with high grade dysplasia, 15 cases of well-differentiated adenocarcinoma, 10 cases of moderately differentiated adenocarcinoma, four cases of poorly differentiated adenocarcinoma, and eight cases of adenocarcinoma with signet ring cell) during follow-up in AG group. The incidences of gastric neoplasm during follow-up periods were significantly different among the AG groups (0.1% in normal, 1.6% in C1-C2, 5.2% in C3-O1, 12.0% in O2-O3, p<0.001), and increased with AG progression (r=0.184, p<0.001). The mean time interval to diagnosis was 6.6±2.7 years in mild AG (21/1,324, 1.6%), 5.8±3.4 years in moderate AG (37/670, 5.2%), and 4.9±2.4 years in severe AG (11/81, 12.0%) (r=-0.188, p=0.035). The independent risk fac-

tors for gastric neoplasm in underlying mucosal atrophy were age ≥55 (HR, 2.582; 95% CI, 1.375 to 4.849; p=0.003), alcohol intake (HR, 1.003; 95% CI, 1.001 to 1.004; p<0.001), baseline AG (HR, 2.285; 95% CI, 1.141 to 4.576; in moderate vs mild, p=0.020; HR, 4.187; 95% CI, 1.609 to 10.896; in severe vs mild, p=0.003), and presence of IM (HR, 2.655; 95% CI, 1.306 to 5.398; p=0.007). However, *H. pylori* infection was not significantly associated with the development of gastric neoplasm (Table 4).

## DISCUSSION

In this study, we analyzed the risk factors for the aggravation of AG and gastric tumorigenesis in underlying gastric mucosal atrophy. Moderate to severe AG and presence of IM were significant risk factors for gastric neoplasm. Although *H. pylori* infection was a risk factor for aggravating gastric mucosal atrophy, it was not significantly associated with the development of gastric neoplasm. It could be explained by the concepts of “point of no return” in the histological cascade from chronic gastritis to cancer.<sup>16</sup> *H. pylori* has been believed to influence on gastric carcinogenesis through the development of AG.<sup>17</sup> A nationwide cohort study which has reported from Taiwan found that a cohort of patients that underwent early *H. pylori* eradication exhibited a similar risk of gastric cancer compared with the general population, whereas the cohort of patients that underwent late eradication exhibited a higher risk of gastric cancer compared to the

**Table 4.** Risk Factors for Gastric Tumorigenesis in Underlying Gastric Mucosal Atrophy (n=2,144)

	Control (n=2,075)	Neoplasm (n=69)	HR*	95% CI	HR <sup>†</sup>	95% CI
Age, yr						
<55	1,225	28	Reference		Reference	
≥55	850	41	2.134	1.319–3.451	2.582	1.375–4.849
Sex						
Female	687	10	Reference		Reference	
Male	1,388	59	2.790	1.427–5.456	1.766	0.656–4.752
Smoking, pack-year <sup>‡</sup>	11.90±16.75	21.38±19.16	1.020	1.009–1.031	1.006	0.993–1.019
Alcohol intake, drinks/wk <sup>§</sup>	7.13±12.00	13.18±14.96	1.029	1.016–1.042	1.003	1.001–1.004
Family history of GC <sup>  </sup>						
No	1,389	44	Reference		Reference	
Yes	254	13	1.444	0.777–2.683	1.405	0.712–2.771
<i>H. pylori</i> infection <sup>¶</sup>						
No	245	10	Reference		Reference	
Newly infected	78	3	0.923	0.254–3.355	0.482	0.100–2.313
Eradicated	302	18	1.407	0.650–3.049	1.057	0.444–2.518
Persistent	1,094	28	0.706	0.343–1.454	0.492	0.211–1.147
Baseline AG						
Mild (C1, C2)	1,324	21	Reference		Reference	
Moderate (C3, O1)	670	37	3.471	2.032–5.930	2.285	1.141–4.576
Severe (O2, O3)	81	11	9.496	4.575–19.711	4.187	1.609–10.896
Intestinal metaplasia						
Absent	1,266	17	Reference		Reference	
Present	809	52	4.689	2.712–8.109	2.655	1.306–5.398

HR, hazard ratio; CI, confidence interval; GC, gastric cancer; *H. pylori*, *Helicobacter pylori*; AG, atrophic gastritis.

\*Univariate analyses of risk factors for gastric neoplasms; <sup>†</sup>Adjusted for age, sex, smoking, alcohol intake, family history of GC, *H. pylori* infection, baseline AG, and intestinal metaplasia; <sup>‡</sup>Data available for 1,431 subjects; <sup>§</sup>Data available for 1,586 subjects; <sup>||</sup>Data available for 1,700 subjects; <sup>¶</sup>Data available for 1,778 subjects.

general population.<sup>18</sup> In a Chinese randomized trial with 1,630 *H. pylori*-infected subjects who were followed up for 7.5 years, *H. pylori* eradication had failed to reduce the incidence of gastric cancer, but in subgroup analysis of patients without precancerous lesions such as AG, IM, or dysplasia, *H. pylori* eradication showed risk reduction of gastric cancer development.<sup>19</sup> A recent meta-analysis also demonstrated that *H. pylori* eradication was not beneficial in patients with IM or dysplasia regarding a reduction of risk of gastric cancer.<sup>16</sup>

Long-standing *H. pylori* infection would be an important risk factor for the aggravation of gastric mucosal atrophy. However, *H. pylori* might not increase the risk of gastric neoplasm after AG had been already developed, even though it had an important role in gastric carcinogenesis.

AG is usually diagnosed by histologic examination of gastric mucosa. However, multiple biopsies can be invasive and time-consuming procedures, and a few endoscopic biopsy samples may not reflect the entire extent of atrophy.<sup>20</sup> Although endoscopic diagnosis of AG is a basic method, it is flawed by a low

sensitivity, specificity and inter-observer variation.<sup>21</sup> A recent study identified significant correlations between endoscopic and histological diagnosis of AG.<sup>20</sup> Serum pepsinogen test is known to be another method for the diagnosis of AG. Measurement of the levels of serum pepsinogen may help detect AG or IM in a noninvasive manner, but its efficiency remains controversial.<sup>22</sup> The value of pepsinogen level as a biomarker of AG could vary among countries or populations, and may be affected by gastric acid inhibitors or some medical conditions.<sup>20</sup> Therefore, the serum pepsinogen test would be more suitable for mass screening of gastric cancer for the high-risk population.<sup>23</sup> Even though the endoscopic diagnosis of AG may have some limitations, we adopted this method to assess AG because most of the patients were followed up annually with endoscopy for cancer screening. In this study, AG and IM were evaluated by reviewing endoscopic images, and several meetings were held to improve the accuracy of diagnosis and minimize inter-observer variation by extensively reviewing multiple cases with AG. Inter-observer agreement of atrophy was low initially ( $\kappa=0.36$ ,  $p<0.001$ ) and



improved gradually but substantially ( $\kappa=0.62$ ,  $p<0.001$ ).

AG has been regarded as a precancerous lesion, but many patients with AG rarely experience gastric cancer during their lifetime. In this study, we focused on the process of developing gastric neoplasm (adenoma and cancer) from AG and the risk factors for gastric neoplasm in underlying gastric mucosal atrophy. In the results, old age, alcohol intake, extent of AG, and presence of IM were significantly associated with gastric neoplasm. In contrast, sex, smoking and a family history of gastric cancer was not associated with gastric neoplasm in AG. Male sex was a risk factor for AG but not for the aggravation of AG or the development of gastric neoplasm. These results are similar to the previous large-scaled observational study which reported that male sex was an independent risk factor for gastric precancerous conditions but not for gastric cancer.<sup>24</sup> These findings imply that male sex may be an increased risk of gastric cancer, especially in the early process of carcinogenesis such as AG. The mechanism of the sex-related differences in gastric carcinogenesis is still unknown, and further studies will be needed.

A possible relationship between alcohol consumption and risk for gastric cancer has long been hypothesized, but epidemiological evidence has been inconclusive.<sup>25</sup> The present study demonstrated that alcohol intake resulted in an increased risk for aggravation of AG and for gastric neoplasm.

The strength of this study includes a large number of subjects and long-term follow-up data. To the best of our knowledge, this study is the largest one that evaluates risk factors for gastric neoplasm in underlying mucosal atrophy. Moreover, the study population can be a representative of the general population because many of the subjects were asymptomatic and underwent endoscopy as part of a health check-up.

This study has some limitations. First, the rate of follow-up loss was approximately 40% of subjects who were diagnosed with AG during baseline endoscopy, which could represent a selection bias in this retrospective cohort study. Second, as the extent of AG was evaluated by spot endoscopic image, it might be underestimated by insufficient endoscopic images. To decrease this underestimation, we had reviewed both images and descriptions of each endoscopic examination.

In conclusion, extensive mucosal atrophy and presence of IM increase the risk for gastric neoplasm in underlying mucosal atrophy. Alcohol consumption is also a risk factor for gastric neoplasm. Therefore, annual endoscopic surveillance may be appropriate to screen gastric neoplasm in high-risk individuals who consume alcohol as well as exhibit moderate to severe mucosal atrophy and IM. Further prospective studies are needed to evaluate the role of endoscopic surveillance in high-risk individuals with AG.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was

reported.

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