Prevalence and Risk Factors of Atrophic Gastritis and Intestinal Metaplasia: A Nationwide Multicenter Prospective Study in Korea

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Background/Aims: Atrophic gastritis (AG) and intestinal metaplasia (IM) are premalignant gastric lesions. The aims of this study were to evaluate the prevalence of endoscopic AG and IM and to document the risk factors for these lesions.

Methods: In total, 4,023 subjects were enrolled at eight hospitals in Korea. AG and IM were diagnosed by endoscopy. Helicobacter pylori immunoglobulin G antibodies were measured. Results: The prevalences of endoscopic AG and IM were 40.7% and 12.5%. In a multivariate analysis, the risk factors for AG were age groups of 40 to 59 years and >60 years, male sex, positive H. pylori serology, IM, and education below the college level (odds ratio [OR], 2.55, 5.00, 1.38, 1.41, 4.29, and 1.35, respectively). The risk factors for IM were age groups of 40 to 59 years and >60 years, male sex, positive H. pylori serology, AG, having relatives with gastric cancer, education below the college level and consumption of dairy products (OR, 3.16, 3.25, 1.88, 2.17, 3.68, 1.48, 1.47, and 1.40, respectively). The conclusions: A nationwide survey regarding the prevalence of endoscopic AG and IM and their risk factors in Korea supports the hypothesis that endoscopic diagnosis of these premalignant lesions could be helpful to describe a group at high risk for gastric cancer. (Gut Liver 2013;7:303-310)

Key Words: Atrophic gastritis; Intestinal metaplasia; Prevalence; Risk factors; Endoscopy

INTRODUCTION

Gastric cancer, the incidence of which became declining in many industrialized countries, is still one of the major causes of mortality from cancer death in the world.1 Whereas the postoperative 5-year survival rates are 90% to 95% for early gastric cancer (EGC), only 20% to 40% of patients with advanced gastric cancer are expected to survive for 5 years or more.2,3 Moreover, surgery is no more needed in a considerable fraction of patients who are diagnosed with EGC, owing to recent advances in endoscopic resection techniques and technologies. Therefore, early detection of EGC through the vigilant follow-up in the high risk groups is probably the effective strategy for improving survival and quality of life.

The pathogenesis of gastric cancer, particularly the intestinal type, can be explained by a cascade from chronic gastritis through atrophic gastritis (AG), intestinal metaplasia (IM), and dysplasia to cancer. AG is characterized by chronic inflammatory processes of gastric mucosa that leads to the loss of glandular structure and a reduction of gastric secretory function. The presence of AG is known to be a risk of gastric cancer, which increases with the degree and extension of atrophy.4 IM is defined as replacement of gastric columnar epithelial cells by cells of intestinal morphology with the presence of goblet cells, Paneth cells and absorptive cells.5 Both AG and IM represent an obligatory transitional step in gastric carcinogenesis and are undisputed indicators of an increased risk for gastric cancer as compared with chronic gastritis in the absence of these le-
sions. Therefore, the recognition of these lesions by endoscopy in a general population indicates the necessity of follow-up endoscopy, which helps the early detection of gastric cancer leading to a better prognosis and treatment by endoscopic resection.

The prevalence of AG and IM vary among countries. That is, they are relatively high in countries with a higher prevalence of *Helicobacter pylori* infection and gastric cancer.\(^9\) *H. pylori* infection is the major cause of chronic gastritis, which leads to AG and IM over a long period. However, despite a high rate of *H. pylori* infection, there are some regions with a low prevalence of precancerous lesions and gastric cancer.\(^9\) Therefore, other factors such as host and environmental factors might play a role in these differences.

In Western countries, AG and IM are generally observed in histological examination of random biopsies obtained during endoscopy, whereas in Asian countries including Korea, the presence and extension of AG and IM are frequently observed by endoscopy. A health check-up program designed to detect gastric cancer was implemented by the South Korean government in 2001 for biannual evaluation of Korean citizens over age 40. Thus, if we know the endoscopic prevalence of AG and IM in the general population and their role in the localization of high risk group of gastric cancer, it would be very useful for prevention of gastric cancer.

From this background, the aims of this study were to evaluate the prevalence of endoscopic AG and IM, and to document the risk factors for the development of these precancerous lesions with the special reference to *H. pylori* infection, host and environmental factors in a Korean general population.

**MATERIALS AND METHODS**

1. **Study population**

A total of 4,023 subjects who underwent screening endoscopy during a routine general check-up from January to December in 2011, were prospectively enrolled at eight nationwide healthcare centers in Korea. Subjects with a history of gastrointestinal surgery or with systemic disease requiring chronic medication except hypertension and diabetes mellitus were excluded. This study was reviewed and approved by the Institutional Review Board of the eight participating hospitals and written informed consent was obtained from all participating subjects.

2. **Questionnaire**

All subjects, who provided informed consents, underwent a clinical interview based on a structured questionnaire to assess personal and clinical data under the supervision of a well-trained interviewer before the endoscopy at the eight participating healthcare centers. The questionnaire included questions regarding demographic data, the presence of upper gastrointestinal symptoms, such as epigastric pain or discomfort, dyspepsia, epigastric soreness, and abdominal pain during the previous year, comorbid disease, history of *H. pylori* eradication, drug history including nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, alcohol consumption, smoking history, consumption of dairy products, and relatives of gastric cancer.

3. **Endoscopic examination**

All of the endoscopic examinations were carried out and assessed by endoscopy experts of the eight participating healthcare centers. The endoscopic findings were examined, in a standardized manner, for typical macroscopic changes including erythema (diffuse, spotty, or linear), erosions (small superficial defects in the mucosa with flat edge and white/yellow color or small bleeding spots [petechiae]), absence of rugae, and visible blood vessels. Investigators did agree with simplification of endoscopic definition about AG and IM. Endoscopic AG was defined as thinning, whitish mucosal change or visible submucosal vascular patterns and endoscopic IM as white plaque-like elevation in antrum and corpus. Any overlapping findings were described.

4. **Determination of *H. pylori* status**

Blood samples were obtained from each participant immediately after endoscopy. Isolated serum samples were neatly arranged in storage boxes and stored at -70°C. *H. pylori* infection was diagnosed by enzyme-linked immunosorbent assay (ELISA) for anti-*H. pylori* immunoglobulin G (IgG) using a Genedia kit (Genedia *H. pylori* ELISA; Green Cross Medical Science Corp., Eumseong, Korea), with duplicate determinations according to the manufacturer’s guidelines. The Genedia kit used *H. pylori* antigen obtained from Korean *H. pylori* strains, with a sensitivity and specificity in Korean adults of 97.8% and 92.0%, respectively. The cutoff optical density (OD, 450 nm) of *H. pylori* IgG was 0.406.

5. **Statistical analysis**

All statistical analyses were performed using the Stat View software package (SAS Institute, Cary, NC, USA). Continuous variables were analyzed by Student’s t-test. Categorical variables were analyzed using chi-squared test or Fisher’s exact test. Multivariate logistic regression was used for the analysis of risk factors, which were expressed as the odds ratio (OR) and 95% confidence intervals (CI). The p-values of less than 0.05 were considered statistically significant.

**RESULTS**

1. **Baseline characteristics of subjects**

A total of 4,023 subjects were included in the study. This study group comprised 2,358 males (58.6%) and 1,665 females (41.4%). The mean age was 48.7±11.3 (mean±standard deviation [SD]) years with a range from 15 to 98 years. *H. pylori* IgG positivity was demonstrated in 2,407 subjects (59.8%). Baseline
Table 1. Baseline Characteristics of the 4,023 Subjects

| Variable                                      | Value                      |
|-----------------------------------------------|----------------------------|
| Age, yr                                       | 48.7±11.3                  |
| Weight, kg                                    | 65.7±11.9                  |
| Height, cm                                    | 165.0±9.07                 |
| Body mass index, kg/m^2                       | 24.0±3.2                   |
| Cholesterol, mg/dL                            | 194.2±37.6                 |
| Triglyceride, mg/dL                           | 126.7±95.4                 |
| Fasting glucose, mg/dL                        | 94.7±38.3                  |
| Gender, male                                  | 2,358 (58.6)               |
| Age, yr ≤39                                   | 865 (21.5)                 |
| Age, yr 40-59                                 | 2,486 (61.8)               |
| Age, yr ≥60                                   | 672 (16.7)                 |
| Smoking Never                                 | 2,099 (53.3)               |
| Smoking Current                               | 864 (21.9)                 |
| Smoking Previous                              | 978 (24.8)                 |
| Alcohol Never                                 | 1,259 (31.8)               |
| Alcohol Current                               | 2,445 (61.8)               |
| Alcohol Previous                              | 251 (6.4)                  |
| Income level, $/mo ≤2,500                     | 1,273 (32.4)               |
| Income level, $/mo 2,500-8,500                 | 2,359 (60.0)               |
| Income level, $/mo ≥8,500                     | 300 (7.6)                  |
| Education above college graduate              | 1,849 (46.8)               |
| NSAIDs use above 1/wk                         | 438 (11.1)                 |
| H. pylori IgG positive                        | 2,407 (59.8)               |
| High salt diet                                | 882 (22.2)                 |
| H. pylori eradication history                 | 518 (13.0)                 |
| Gastrointestinal symptoms                     | 1,094 (27.4)               |
| Consumption of dairy product                  | 969 (24.4)                 |
| Relatives of gastric cancer                   | 451 (11.4)                 |

Data are presented as mean±SD or number (%).
NSAI,D nonsteroidal anti-inflammatory drug; H. pylori, Helicobacter pylori; IgG, immunoglobulin G.

characteristics of subjects including height, weight, body mass index (BMI), cholesterol, triglyceride, fasting glucose, smoking, alcohol, education, income level, NSAID use, high salt diet, history of H. pylori eradication, gastrointestinal symptoms, consumption of dairy product, and relatives of gastric cancer are described in Table 1.

2. Prevalence rates of AG and IM

The prevalence rates of AG and IM, diagnosed by endoscopic findings, were 40.7% (1,638 of 4,023) and 12.5% (502 of 4,023), respectively. The prevalence rates of AG and IM in males were significantly higher than those in females (43.3% vs 37.1% and 15.4% vs 8.3%, respectively; p<0.001) (Tables 2 and 3). The prevalence rate of AG increased with age (from 29.9% in those aged less than 40 years to 59.4% in those aged 60 years or older) (Fig. 1A). The prevalence rate of IM also increased with age (from 3.4% in those less than 40 years of age to 17.4% in those 60 years or older; p<0.001) (Fig. 1B).

3. The identification of risk factors for AG by univariate and multivariate analysis

In a univariate analysis of risk factors for AG, older age group of above 40 to 59, older age group of above 60 years, male gender, H. pylori IgG positivity, IM, and low education below college were found to be associated with a high risk of AG (Table 2). Multivariate analysis showed that the significant independent risk factors for AG were older age group of 40 to 59 (OR, 2.55; 95% CI, 2.05 to 3.18), above 60 years old (OR, 5.00; 95% CI, 3.71 to 6.74) compared with below 40, male gender (OR, 1.38; 95% CI, 1.17 to 1.64), H. pylori IgG positivity (OR, 1.41; 95% CI, 1.19 to 1.66), IM (OR, 4.29; 95% CI, 3.55 to 5.50), and low education below college (OR, 1.35; 95% CI, 1.01 to 1.79) (Table 4).

4. The identification of risk factors for IM by univariate and multivariate analysis

In a univariate analysis of risk factors for IM, older age group of above 40 to 59, older age group of above 60 years, male gender, H. pylori IgG positivity, AG, BMI, triglyceride level, H. pylori eradication, relatives of gastric cancer, smoking, alcohol, low education, and consumption of dairy product were found to be associated with a high risk of IM (Table 3). Multivariate analysis showed that the significant independent risk factors for IM were older age group of 40 to 59 (OR, 3.16; 95% CI, 2.11 to 4.72), above 60 years old (OR, 3.25; 95% CI, 2.05 to 5.15), male gender (OR, 1.88; 95% CI, 1.39 to 2.54), H. pylori IgG positivity (OR, 2.17; 95% CI, 1.72 to 2.74), AG (OR, 3.68; 95% CI, 2.95 to 4.60), relatives of gastric cancer (OR, 1.48; 95% CI, 1.12 to 1.96), low education below college (OR, 1.47; 95% CI, 1.06 to 2.00), and consumption of dairy product at least five times per week (OR, 1.40; 95% CI, 1.12 to 1.76) (Table 5).

DISCUSSION

The development of gastric cancer is generally accepted to be a multistep progression from H. pylori-related chronic inflammation of the gastric mucosa, to AG, IM, dysplasia, and, finally, intestinal-type gastric cancer. The risk of gastric cancer is closely related to the degree and extension of AG and IM. Therefore, evaluating the prevalence and risk factors for these precancerous lesions such as AG and IM may be helpful to prevent the development of gastric cancer.

However, it is nearly impossible to take biopsy from antrum and body in the general population without definite lesion,
especially in a huge population as our study. Thus, it is necessary to evaluate prevalence rates of endoscopic AG and IM, especially where the health check-up endoscopy is popular for gastric cancer screening. In the present study, the prevalence of AG and IM were found to be 40.7% and 12.5%, respectively. In Western Europe, the overall prevalence rates of AG and IM were approximately one-third and one-fourth of subjects, respectively. In our study, the prevalence of AG and IM were 55.5% and 28.5%, respectively, in Japan. Previously, we have shown that the prevalence rates of AG and IM, diagnosed by histology, were 42.5% and 28.6%, respectively in the antrum. Considering histological diagnosis of IM is more accurate and sensitive than endoscopic diagnosis, the prevalence rate of endoscopic IM in the present study, 12.5%, is not very low. Another reason of lower prevalence of IM in this study could be explained by the population of the participating subjects: 21.5% was below 40 years old, and only 16.7% was ≥ 60.

In our study, the prevalence of AG and IM increased significantly with age and this phenomenon could be explained by *H. pylori* infection. *H. pylori* infection usually occurs in the childhood, but AG and IM progress in the elderly population due to long infectious periods with *H. pylori*. In addition, the prevalence of AG and IM in males were significantly higher than those in females. It is generally understood that the prevalence of *H. pylori* infection and gastric disorders in males is more common than that in females. Furthermore, seropositivity of *H. pylori* was found to be the risk factor of AG and IM in the present study. As it is well known, *H. pylori* infection is the most common risk factor of glandular atrophy and subsequent IM. Our consistent results support that endoscopic diagnosis of AG and IM could be a useful tool for localization of high risk group of gastric cancer without histology.

Interestingly, AG and IM were found to be a risk factor for each other in our study. Usually, these two lesions have been associated with chronic inflammatory processes such as *H. pylori* infection. Thus, these results might be originated from that atrophy and IM ensue sequentially over time after *H. pylori* infection. In addition, the degree of IM has been correlated with the degree of atrophy. However, IM can also occur without atrophy. Furthermore, the risk factors for AG and IM were rather different. Bacterial factors were found to be important risk factor for AG but host and environmental factors were more important for IM, suggesting that sometimes it does not go together.

In our study, low education below college was a risk factor for the development of AG and IM. Previous reports showed that lower education was associated with *H. pylori* infection and the development of AG in *H. pylori* infected subjects.
lower education is usually associated with lower socioeconomic status and poorer hygiene, it is identified as risk factors for *H. pylori* infection.\textsuperscript{22,23} \textit{H. pylori} infection is likely to contribute to this association between low education and the high prevalence of AG and IM.

The proportion of family history of gastric cancer was found...
to be 11% in this study, rather higher than that in the general population. This could be originated from more concern of the relatives of gastric cancer about their health they might frequently receive health check-up, compared general population. Interestingly, family history of gastric cancer was a risk factor for the development of IM, but not of AG in our study. First-degree relatives of gastric cancer were found to have a higher risk of developing gastric cancer.

The possible causes of familial aggregation of gastric cancer are not only genetic factors but also environmental factors including Helicobacter pylori infection, excessive intake of salt and N-nitroso compound, and a deficiency of dietary antioxidants among gastric cancer patients and their family members. Relatives of gastric cancer have an increased prevalence of precancerous lesions including AG and IM, and Helicobacter pylori plays an instrumental role in determining the risk of precancerous lesions among relatives of gastric cancer.

Consequently, prophylactic Helicobacter pylori eradication is advised to the relatives of gastric cancer in Korea for prevention of gastric cancer. Similar to the family history of gastric cancer, consumption of dairy product at least five times per week was a risk factor for the development of IM but not AG. Previously, milk or yogurt prevents the development of AG and IM through its defense mechanism against the attachment of Helicobacter pylori to the gastric mucosa and also, consumption of fermented dairy products confers an enhanced therapeutic benefit on Helicobacter pylori eradication. As our study showed different result further studies are necessary in the future.

Our study has limitations. The diagnosis of AG and IM was made only by endoscopic findings and not confirmed by histology. Although histological examination is considered as the gold standard for diagnoses of AG and IM, interobserver variation...
tion for diagnoses of AG on biopsy specimens has been shown to be high,\textsuperscript{23,34} and sampling errors exist, especially when multifocal AG is present.\textsuperscript{25,36} Also, there are few reports concerning the high agreement between the endoscopic and histological atrophy scores.\textsuperscript{27,28} The image quality of conventional endoscopes has improved dramatically over the last decade and typical endoscopic findings are interpreted as signs of AG and IM. In addition, to prevent the interobserver variation in the diagnosis of AG and IM, only endoscopic experts participated in this study. Even though the significance of typical endoscopic findings in relation to histology is still uncertain,\textsuperscript{16,26} similar results regarding the prevalence and risk factor of endoscopic AG and IM to those from the histological AG and IM support clinical significance of our study. Also, the severity and location of endoscopic AG and IM were not classified mainly because there is no standardized grading system of atrophy and IM. In addition, as the endoscopy of this study was performed as one of health check-up it was very difficult to ask the participating doctors to fill up all of those things in detail.

In conclusion, the prevalence of endoscopic AG and IM in the general population were not so high in Korea, especially in case of IM. The risk factors of AG and IM were similar but relatives of gastric cancer and consumption of dairy product were the risk factors of IM, but not of AG. Therefore, it is worthwhile to describe the degree and extent of AG and IM in detail during endoscopy, according to diagnostic criteria.

CONFLICTS OF INTEREST

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

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