Clinical risk assessment for gastric cancer in asymptomatic population after a health check-up
An individualized consideration of the risk factors

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Abstract
For the prevention of gastric cancer, the detection of risk factors associated with precancerous conditions may be more informative. The aim of this study was to identify the risk factors of gastric cancer, including precancerous conditions: atrophic gastritis (AG), intestinal metaplasia (IM), and dysplasia.

The clinical and endoscopic findings of 60,261 adults who underwent gastroduodenoscopy as part of a health check-up were reviewed retrospectively. Subgroup analysis was conducted according to age, sex, cancer stage, and histology based on Lauren classification. Gastric cancer was diagnosed in 75 patients (0.12%). Both IM and AG were independent risk factors for gastric cancer in all subgroups. Male, older age, obesity, diabetes mellitus (DM), a salty and spicy diet, and *Helicobacter pylori* (*H. pylori*) were significantly associated with precancerous conditions. However, risk factors related to precancerous conditions were different according to age and sex. In <40 years, *H. pylori* was the only risk factor related to precancerous conditions, whereas DM with a salty and spicy diet were additional risk factors in ≥40 years. In female individuals, obesity was significant risk factor for precancerous conditions as well as *H. pylori* infection.

AG and IM are independent risk factors for gastric cancer. To prevent gastric cancer, *H. pylori* eradication may be more useful in <40 years, whereas additional factors such as DM, obesity, salty and spicy diet may be important in female or ≥40 years.

Abbreviations: AG = atrophic gastritis, BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, *H. pylori* = *Helicobacter pylori*, IM = intestinal metaplasia, ORs = odds ratios, WH-O = World Health Organization.

Keywords: atrophic gastritis, dysplasia, gastric cancer, intestinal metaplasia, risk factor

1. Introduction
Gastric cancer is the fifth most common cancer worldwide<sup>[1,2]</sup> and the third leading cause of cancer mortality. Many people

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have been performed health check-up based on organized or individualized screening to detect of gastric cancer at an early stage. In Japan and Korea, screening using endoscopy or a barium study is routinely conducted in all individuals 40 years of age and older.<sup>[3,4]</sup> However, unlike the situation in these countries with a high incidence of gastric cancer, screening is less appropriate in those with a low incidence of gastric cancer and may not be cost-effective.<sup>[5,6]</sup> Therefore, other methods to recognize individuals at high risk for gastric cancer are needed, such as via a surveillance strategy based on risk factor analysis. In the prevention of gastric cancer, the detection of risk factors associated with precancerous conditions may be more informative than an assessment of risk factors associated with gastric cancer, even though the latter are the focus of most studies.

*Helicobacter pylori* infection is a well-established risk factor for gastric cancer of both the intestinal and the diffuse type.<sup>[7]</sup> Chronic *H. pylori* gastritis progresses through premalignant stages of atrophic gastritis (AG), intestinal metaplasia (IM), and dysplasia to eventually develop into gastric cancer.<sup>[7–10]</sup> Premalignant lesions are also an important risk factor for gastric cancer development. Recently, associations between cancer and body mass index (BMI) and diabetes mellitus (DM) were reported. In 2 meta-analyses,<sup>[11,12]</sup> an increased BMI was shown to be related to an increased incidence of colorectal cancer. In 2 other studies, an association between DM and cancer of the liver and colon was proposed.<sup>[13,14]</sup> However, few studies have examined the relationship between obesity and DM and the risk of gastric cancer.

Therefore, in this study, we identified the risk factors of gastric cancer including precancerous conditions, among
subjects who underwent a health check-up. We also investigated the association with gastric cancer and metabolic cause, such as DM and BMI, and analyzed whether the risk factors in this population differed according to age, sex, and histology.

2. Materials and methods

2.1. Study population

A cross-sectional study was conducted on 60,261 people who underwent an upper endoscopy at the Health Promotion Center of the Gangnam Severance Hospital in Seoul, South Korea, from January 2008 to December 2013. We excluded the following criteria: individuals who had a personal history of gastric cancer or any type of cancer, history of gastric surgery including resection and gastrectomy, any symptoms: weight loss, abdominal pain, or dyspepsia. For individuals screened more than twice, the screening results in each case per year were considered.

This study was approved by the Institutional Review Board of Gangnam Severance Hospital (Institutional Review Board number 3-2014-0068).

2.2. Data collection

The clinical data of the study participants were collected by a review of the electronic medical records. Age was categorized as younger (<40 years) or older (≥40 years). BMI was classified according to the Western Pacific regional office of the World Health Organization (WHO) as normal (<23 kg/m²), overweight (23–24.9 kg/m²), and obesity (≥25 kg/m²). Smoking history, alcohol consumption, dietary style (spicy and/or salty), and the presence of DM were determined in a questionnaire. H. pylori infection was detected by the following methods: immunoglobulin G specific for H. pylori in serum (ELFA, enzyme-linked fluorescence assay, Vidas (bioMerieux Vitek, Inc. Hazelwood, MO, USA)), rapid urease test (CLOtest; Delta West, Bentley, Australia), and pathology (Giemsa staining). If the result of at least 1 of 3 tests (serologic test, rapid urease test, histologic evaluation) was positive, the patient was determined as positive for H. pylori infection.

2.3. Endoscopic evaluation of gastric cancer and precancerous conditions

Endoscopic examinations were performed using an endoscope (GIF-H260; Olympus Medical Systems, Tokyo, Japan) equipped with an electronic endoscopy system (EVIS LUCERA; Olympus Medical Systems). Gastric cancer confirmed by endoscopic biopsy at screening was reported according to the WHO classification: well, moderately, or poorly differentiated tubular adenocarcinomas, or signet ring cell carcinoma. Histology was assessed according to Lauren classification as intestinal, diffuse, and mixed type. In the 55 patients with gastric cancer who were treated at our hospital, the cancer stage was divided into early versus advanced based on final pathologic reports. Precancerous conditions were defined as AG, IM, and dysplasia. Gastric dysplasia was confirmed by histologic examination of tissue obtained at endoscopic biopsy. Gastric atrophy and IM were diagnosed based on the gross endoscopic findings reported by the study’s endoscopic specialists.

2.4. Statistical analysis

Categorical variables were analyzed by a χ² test to investigate the relationships between groups and the various clinical and lifestyle features. Continuous variables were analyzed using Student t test. Data for age and BMI are expressed as the mean±SD. Risk factors of gastric cancer and precancerous conditions are represented as odds ratios (ORs) with the 95% confidence interval (CI), as determined by multiple logistic regression. P<0.05 was considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 20.0 for Windows (SPSS, Chicago, IL).

3. Results

3.1. Clinicopathological characteristics of the study population

Among the 60,261 adults (32,227 males; 28,034 females), 75 had gastric cancer and 11,045 had premalignant lesions. The baseline characteristics of the subjects who underwent an endoscopic examination are presented in Table 1. The features indicative of gastric cancer are listed in Table 2.

3.2. Risk factors for gastric cancer

Table 3 shows the risk factors for gastric cancer. According to a univariate analysis, male sex, obesity, H. pylori infection, and endoscopically confirmed AG and IM were significant. In a multivariate analysis, only AG (OR = 8.47, 95% CI: 4.65–15.40, P = 0.001) and IM (OR = 5.80, 95% CI: 3.24–10.35, P < 0.001) were statistically significant risk factors.

An analysis of the gastric cancers by histology type (Table 4) identified endoscopic AG and IM as significant risk factors. Additional significant risk factors for the diffuse type were obesity

### Table 1: The baseline characteristics of study population.

| Number (%) |
|------------|
| Sex        |
| Male       | 32,227 (53.5) |
| Female     | 21 (28.0)     |
| Age, y (mean±SD) |
| <40        | 14,239 (23.6) |
| ≥40        | 46,022 (76.4) |
| Endoscopic resection |
| 20 (26.7) |
| Unknown    | 20 (26.7)     |
| BMI, kg/m² (mean±SD) |
| <25        | 40,238 (66.8) |
| ≥26        | 20,003 (33.2) |
| Combined DM |
| 2425 (4.0) |
| Alcohol history |
| 29,975 (49.7) |
| Smoking    |
| Never      | 25,367 (42.1) |
| Ex-smoker  | 10,068 (16.7) |
| Current smoker | 10,977 (18.2) |
| Diet style (salty and spicy) |
| 22,177 (36.8) |
| Helicobacter pylori |
| 24 (32.0) |
| Negative   | 11,106 (50.9) |
| Positive   | 10,947 (49.6) |
| Atrophic gastritis |
| 8045 (13.4) |
| Intestinal metaplasia |
| 5697 (9.9) |

BMI = body mass index, DM = diabetes mellitus, SD = standard deviation.
(OR = 2.37, 95% CI: 1.10–6.81, P = 0.026) and *H. pylori* infection (OR = 2.41, 95% CI: 1.02–5.67, P = 0.044). Endoscopically confirmed AG and IM were also significant risk factors in early- and advanced-stage cancer (Table 5); DM (OR = 6.62, 95% CI: 1.32–33.02, P = 0.021) was an additional significant risk factor in advanced- but not in early-stage gastric cancer.

### 3.4. Age-related risk factors for gastric cancer and precancerous conditions

Table 7 shows the risk factors according to age group. In both age groups, AG and IM were significant risk factors for gastric cancer. In younger versus older individuals, AG (OR = 16.6 vs 8.85) and IM (OR = 17.2 vs 4.84) had a higher OR for the risk of gastric cancer. In the young age group, *H. pylori* was the most important risk factor related to precancerous conditions. However in the older age group, DM was an additional risk factor for precancerous conditions, as were male sex and *H. pylori* infection.

### 3.5. Sex-related risk factors for gastric cancer and precancerous conditions

Table 8 shows the risk factors according to sex. In both males and females, AG was significant risk factors for gastric cancer, whereas IM was statistically significant only for males. For precancerous conditions, obesity (OR = 2.61, 95% CI: 0.93–7.25, P < 0.001) was an additional risk factor in females, as were old age and *H. pylori* infection.

### Table 2

Clinicopathologic characteristics of gastric cancer.

| Gastric cancer (n = 75) | Number (%) |
|-------------------------|------------|
| Age, y (mean ± SD) | 52.4 ± 12.5 |
| Sex | |
| Male | 54 (72.0) |
| Female | 21 (28.0) |
| Treatment modality | |
| Operation | 35 (46.6) |
| Endoscopic resection | 20 (26.7) |
| Unknown | 20 (26.7) |
| Stage | |
| Early gastric cancer | 47 (63.5) |
| Advanced gastric cancer | 8 (10.7) |
| Location | |
| Cardia | 1 (1.3) |
| Noncardia | 74 (98.7) |
| WHO classification | |
| Well differentiated | 18 (24.0) |
| Moderately differentiated | 14 (18.7) |
| Poorly differentiated | 19 (25.3) |
| Signet ring cell | 24 (32.0) |
| Lauren classification | |
| Intestinal | 36 (48.0) |
| Diffuse | 35 (46.7) |
| Mixed | 4 (5.3) |

SD = standard deviation, WHO = World Health Organization.

### Table 3

The risk factors for gastric cancer.

|                                  | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|----------------------|
|                                  | Control (n, %) Cancer (n, %) | OR (95% CI) | P |
| Sex                              |                      |                      |    |
| Male                             | 32,173 (53.5) 54 (72.0) | 1.47 (0.80–2.66) | 0.210 |
| Female                           | 28,013 (46.5) 21 (28.0) |                      |    |
| Age, y                           |                      |                      |    |
| <40                             | 14,228 (23.6) 11 (14.7) | 1 | 0.068 |
| ≥40                             | 45,960 (76.4) 64 (85.3) |                      |    |
| BMI, kg/m²                       |                      |                      |    |
| <25                             | 40,203 (66.8) 39 (52.0) | 1 | 0.006 |
| ≥25                             | 19,968 (33.2) 36 (48.0) | 1.48 (0.88–2.45) | 0.132 |
| DM                              | 2422 (4.0) 3 (4.1) | 0.991 |
| Alcohol history                  | 9530 (28.5) 15 (37.5) | 0.209 |
| Smoking                          |                      | 0.302 |
| Never                            | 25,362 (54.7) 3 (83.3) | 1 | 0.001 |
| Ex-smoker                        | 10,679 (21.7) 1 (16.7) | 0.106 |
| Current smoker                   | 10,977 (23.7) 0 | 0.096 |
| Diet style (salty and spicy)     | 22,144 (36.8) 33 (44.0) | 0.002 |
| *Helicobacter pylori*            |                      | 0.052 |
| Negative                         | 11,086 (50.4) 20 (30.8) | 1 | 1.000 |
| Positive                         | 10,902 (49.6) 45 (69.2) | 0.001 |
| Atrophic gastritis               | 7990 (13.3) 55 (73.3) | 0.001 |
| Intestinal metaplasia            | 5646 (9.4) 51 (68.0) | 0.001 |

BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, OR = odds ratio.
4. Discussion

Although the incidence of gastric cancer and mortality from the disease are declining, it is still a frequent cause of cancer-related deaths worldwide.\(^{[7,8]}\) The mortality from gastric cancers is, in large part, due to the poor response to treatment of patients with advanced-stage disease. Thus, efforts at mortality reduction have been aimed at early intervention with respect to modifiable risk factors.\(^{[15-17]}\)

When detected at an early stage, gastric cancer is often curable. The most common form of gastric cancer is adenocarcinoma, which can be divided into intestinal and diffuse types.\(^{[18]}\) The intestinal type of gastric cancer is widely accepted to be preceded by a cascade of premalignant lesions. Because the progression to gastric cancer is generally a slow process, early detection is important, as earlier treatment improves both survival and prognosis and may ultimately alter the natural course of the disease.\(^{[19]}\) Thus, endoscopic surveillance of premalignant gastric lesions is a useful diagnostic tool. In East Asia, nationwide screening programs for gastric cancer have resulted in a higher detection rate of early gastric cancer than is the case in western countries.\(^{[1,4]}\) However, in the latter, nationwide screening programs may be less appropriate because of the low incidences of gastric cancer, especially considering that endoscopic screening is an invasive procedure with a high economic burden.\(^{[20,21]}\) In these countries with a low incidence of gastric cancer the control of risk factors may be a more appropriate strategy to reduce mortality from the disease.

Gastric cancer is a multifactorial disease in which \(H.\) pylori infection has been well-established as a primary cause. \(H.\) pylori causes chronic inflammation of the gastric mucosa, with the subsequent development of premalignant disease stages leading to gastric cancer.\(^{[7-10]}\) In our study, endoscopic AG and IM were significant risk factors for gastric cancer. Precancerous conditions such as AG and IM carry a high risk of progression to gastric cancer. Among the epidemiologically related risk factors for precancerous conditions, \(H.\) pylori infection, older age, and male sex were significant. Additional risk factors for precancerous conditions were obesity and DM.

\(H.\) pylori infection is strongly associated with both intestinal and diffuse types of gastric cancer.\(^{[7,8]}\) Some studies have reported cost-effective cancer prevention based on early intervention, such as \(H.\) pylori eradication,\(^{[22,23]}\) but this approach has yet to be confirmed. However, our results support early intervention to eradicate \(H.\) pylori as a strategy for cancer prevention, given that \(H.\) pylori infection and male sex were the only risk factors for precancerous conditions in individuals <40 years. This age group also had a higher OR of \(H.\) pylori infection. The risk factors for precancerous conditions associated with age ≥40 years were, in addition to \(H.\) pylori infection, DM and a salty or spicy diet. Previous studies reported that, in addition to older age, males are at higher risk of noncardia gastric cancer than females, in agreement with the findings of this study.\(^{[13,24]}\)

From our data, gross endoscopic AG and IM were identified as independent risk factors for gastric cancer regardless of the subgroup analysis. Both AG and IM had a higher OR for the risk of gastric cancer in individuals <40 years than in those ≥40 years. Current recommendations in South Korea and Japan are that all adults >40 years should undergo regular screening every 2 years, regardless of symptoms. Our results suggest the need for regular surveillance for asymptomatic individuals younger than 40 years of age in whom AG or IM is detected.

### Table 4

Multivariate analysis of risk factors according to histology of gastric cancer.

| Intestinal type (n = 36) | OR (95% CI) | P     | Diffuse type (n = 35) | OR (95% CI) | P     |
|-------------------------|------------|-------|-----------------------|------------|-------|
| Male                    | 3.35 (1.98–9.01) | 0.025 | Male                  | 0.82 (0.36–1.79) | 0.612 |
| \(H.\) pylori            | 1.41 (0.67–3.12) | 0.341 | BMI, kg/m\(^2\)       |              |       |
| Atrophic gastritis      | 6.39 (2.78–14.64) | <0.001 | <25                   | 1           |       |
| Intestinal metaplasia   | 8.93 (3.62–22.00) | <0.001 | ≥25                   | 2.37 (1.10–6.81) | 0.313 |

BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, OR = odds ratio.

### Table 5

Multivariate analysis of risk factors according to stage of gastric cancer.

| Early gastric cancer (n = 47) | OR (95% CI) | P   | Advanced gastric cancer (n = 8) | OR (95% CI) | P   |
|------------------------------|------------|-----|--------------------------------|------------|-----|
| Male                         | 1.35 (0.50–3.61) | 0.546 | DM                             | 6.62 (1.32–33.02) | 0.021 |
| BMI, kg/m\(^2\)              |              |       | Atrophic gastritis            | 18.08 (1.90–171.64) | 0.012 |
| <25                          | 1.78 (0.77–4.11) | 0.175 | Intestinal metaplasia         | 8.14 (1.45–45.44) | 0.017 |
| ≥25                          | 1           |       |                                |             |     |
| Alcohol history              | 1.80 (0.76–4.19) | 0.176 |                                |             |     |
| \(H.\) pylori                | 2.06 (0.80–5.28) | 0.130 |                                |             |     |
| Atrophic gastritis           | 7.50 (2.84–19.77) | <0.001 |                                |             |     |
| Intestinal metaplasia        | 4.22 (1.64–10.79) | 0.003 |                                |             |     |

BMI = body mass index, CI = confidence interval, DM = diabetes mellitus, OR = odds ratio.
A significant risk factor in diffuse-type gastric cancer is obesity. Based on our results, in gastric carcinogenesis, diffuse-type cancer differs from the intestinal type which follows a multistep cascade from premalignant lesions. Advanced-stage gastric cancer may be influenced by additional factors related to disease progression that are not determinants in early-stage cancer. For example, DM was a meaningful factor only for advanced-stage gastric cancer.

Obesity is one of the strongest emerging risk factors for many types of cancer.[11,12] DM affects populations throughout the world and its association with liver and colon cancers has been reported.[13,14] However, the few studies that have attempted to establish an association between BMI, DM, and the risk of gastric cancer have yielded conflicting results.[12,14] In our study, obesity (BMI ≥2.5 kg/m²) was associated with diffuse-type adenocarcinoma. Furthermore in females, obesity poses an increased risk of gastric cancer. A strength of our study was the subgroup analyses, given by the patients in the survey.

both obesity and DM are metabolic diseases that are becoming increasingly common. While known environmental factors, such as smoking and a salty diet are still important risk factors in gastric cancer, DM and obesity have been gaining in importance, reflecting changing life styles. In both conditions, the accumulation of adipose tissue together with hyperinsulinemia and insulin resistance can impair apoptosis and stimulate gastric mucosal proliferation.[29,30] Chronic injury of the gastric mucosa can then lead to the development of gastric cancer. Tobacco also could lead to mucosal damage through direct contact or indirectly through the blood flow. Tobacco contains several chemical carcinogens, and high levels of carcinogenic N-nitroso compounds, which are often associated with gastric cancer, have been found in the bloodstream of smoker.[31,32] Although smoking is a well-known risk factor for gastric cancer, it was not a significant risk factor in this study. This is because this research was a retrospective study and depended on the answers given by the patients in the survey.

This study suggests the need to reconsider the risk factors of gastric cancer. A strength of our study was the subgroup analyses,
with respect to histology and cancer stage in the case of gastric cancer, and age and sex in the case of gastric cancer and precancerous conditions. Because gastric cancer is one of the representative heterogeneous cancers, as it shows different biological behaviors according to age, sex, and histologic type. To our knowledge, although a premalignant stage, including both AG and IM, is known to be a high risk for the development of gastric cancer, few studies have focused on identifying the risk factors leading to these precancerous conditions, which would allow an earlier intervention. Moreover, the present study provides support for the importance of metabolic disease control in the prevention of gastric cancer.

There were several limitations to our study. First, AG and IM were not described according to their extent and severity but, rather, based on gross endoscopic findings, which were not biopsy proven. However, biopsy was not considered appropriate in the study population because there were no doubtfull lesions and the procedure is both invasive and costly. Since the endoscopists who contributed to this study each had >3 years of experience, their assessments were considered reliable and the detection of AG and IM was considered sufficient. Second, a family history of gastric cancer was not included in the analysis. Third, the salty and spicy diet was analyzed based on a questionnaire, not on an objective index. Our questionnaire does not include the amount or concentration of sodium in the questionnaire, not on an objective index. Our questionnaire does not include the amount or concentration of sodium in the ingested food. However, we consider that the dietary habits revealed by a questionnaire can reflect the diet style of the subject. These may have been due to the retrospective nature of this study, in which complete records were not available and some important data may have been missing.

In conclusion, endoscopically confirmed AG and IM are independent risk factors for AG, IM, dysplasia, and gastric cancer in all subgroups. To prevent gastric cancer, _H. pylori_ eradication may be the most important in individuals younger than 40 years, whereas additional factors such as DM, salty and spicy diet may be important in older than 40 years. Obesity is important risk factor in female to prevent gastric cancer, especially diffuse type.

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