

***Helicobacter pylori* Seropositivity Is Associated with Gastric Cancer Regardless of Tumor Subtype in Korea**

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Background/Aims: To evaluate the association between *Helicobacter pylori* (*H. pylori*) infection and gastric cancer (GC) according to tumor subtype in Korea. **Methods:** *H. pylori* status was determined serologically using the enzyme-linked immunosorbent assay. In total, 2,819 patients with GC and 562 healthy controls were studied. A logistic regression method was used after adjusting for possible confounders. **Results:** The prevalence of *H. pylori* infection was significantly higher in the GC patients (84.7%) than in the controls (66.7%) (odds ratio [OR], 3.13; 95% confidence interval [CI], 2.46-3.97). The adjusted OR was significantly higher in *H. pylori*-infected patients aged <60 years (OR, 4.69; 95% CI, 3.44-6.38) than in those aged ≥60 years (OR, 1.48; 95% CI, 0.88-2.46; $p < 0.001$). Subgroup analyses revealed no differences in seroprevalence between early gastric cancer (84.8%; OR, 3.01; 95% CI, 2.27-4.01) and advanced gastric cancer (84.6%; OR, 2.94; 95% CI, 2.24-3.85), cardia cancer (83.8%; OR, 2.98; 95% CI, 2.16-4.02) and noncardia cancer (84.8%; OR, 3.17; 95% CI, 2.48-4.04), and differentiated carcinoma (82.7%; OR, 2.99; 95% CI, 2.21-4.04) and undifferentiated carcinoma (86.8%; OR, 3.05; 95% CI, 2.32-4.00). **Conclusions:** The seroprevalence of *H. pylori* was higher in GC patients than in healthy controls, especially in younger patients. *H. pylori* infection is associated with GC, regardless of the tumor location, stage, or differentiation. (**Gut Liver 2010;4:466-474**)

Key Words: *Helicobacter pylori*; Gastric cancer; Prevalence; Odds ratio; Subgroup analysis

INTRODUCTION

Although several prospective studies have supported that *Helicobacter pylori* (*H. pylori*) infection is a risk factor for the development of gastric cancer,^{1,2} not all epidemiological studies have shown that positive relationship between *H. pylori* infection and gastric cancer.^{3,4} These discrepancies may be due to marked differences in gastric cancer incidence and *H. pylori* prevalence in different geographic regions. Some population-based studies have shown that high levels of *H. pylori* infection were not accompanied by high gastric cancer mortality, the so-called African⁵ and Asian enigmas.⁶ Another possible explanations for the discrepancies in the study are confounding factors affecting both *H. pylori* infection and gastric cancer development, and differing proportions of gastric cancer subtypes related to tumor location, histological type, and tumor stage.

Gastric cancer remains the second most common cause of cancer deaths worldwide, as well as being the most common malignancy in South Korea.^{7,8} Recently, the seroprevalence of *H. pylori* in South Korea was reported as 59.6-66.9%,^{9,10} showing that Korea is still a *H. pylori*-prevalent area. Epidemiological studies on the association between *H. pylori* and gastric cancer in South Korea,^{4,11-13} however, have shown inconsistent results, but each of these studies included no more than 200 patients with gastric cancer.

Substantial studies on gastric cancer subtypes have also yielded conflicting results. There are discrepancies in gastric cardia cancer between Western and most Asian pop-

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ulation studies.¹⁴⁻¹⁶ Studies on the association between *H. pylori* infection and gastric cancer according to histological type have yielded inconsistent results.¹⁷⁻¹⁹ Confounding factors such as age could affect both *H. pylori* infection and gastric cancer development.²⁰ Furthermore, the association between *H. pylori* infection and gastric cancer may be modified by the level of exposure to other factors such as smoking or alcohol.²¹

The aim of the current large-scale study was to evaluate the association between *H. pylori* infection and gastric cancer in a region of high prevalence of both *H. pylori* infection and gastric cancer after adjusting for possible confounding factors. We also evaluated whether the association is confined to specific subtypes of gastric cancer.

MATERIALS AND METHODS

1. Subjects

Fig. 1 shows the flow of participants. Between June 2003 and April 2007, 3,623 consecutive patients were diagnosed as having gastric cancer at the National Cancer Center Hospital. They underwent esophagogastroduodenoscopy (EGD) and biopsy. All biopsies were evaluated by a single experienced histopathologist (M-C Kook), and each case of gastric cancer was confirmed as adenocarcinoma. We excluded patients who did not provide written informed consent (n=202); those with a previous history of gastric cancer treatment, such as gastric resection, chemotherapy, or radiotherapy (n=107); those who did not have results of *H. pylori* infection (n=433); and patients

with a history of *H. pylori* eradication (n=62). Thus, a total of 2,819 patients was studied (Fig. 1A).

Gastric cancer cases were classified as cardia cancer if their centers were within 2 cm distal to the gastro-esophageal junction and as noncardia cancer otherwise.²² Tumor overlapped two or more sites that included the cardia, or were present at more than two separate sites simultaneously, were excluded from site-specific analysis. Gastric cancer was also divided into early and advanced cancer, after pathological examination following endoscopic or surgical resection. Early gastric cancer (EGC) was defined as a tumor that was confined to the mucosa or submucosa regardless of lymph node involvement,²³ and advanced gastric cancer (AGC) was defined as a tumor that invaded beyond the submucosa. In patients who did not undergo resection due to metastatic gastric cancer, tumor stage was determined by endoscopic and computer tomographic findings. Gastric cancers were classified histopathologically according to Lauren’s system (intestinal, diffuse, and mixed type)²⁴ and on the Japanese classification system (differentiated and undifferentiated carcinoma)²⁵ by a single pathologist. If a tumor was present at more than two separate sites synchronously, we included the dominant one in tumor depth.

Controls were enrolled from healthy adults who visited the health-care center at the National Cancer Center Hospital for the nationwide National Cancer Screening Program in Korea. From July 2007 through December 2007, 891 individuals were invited to participate as controls. Of those, 192 subjects declined to participate in

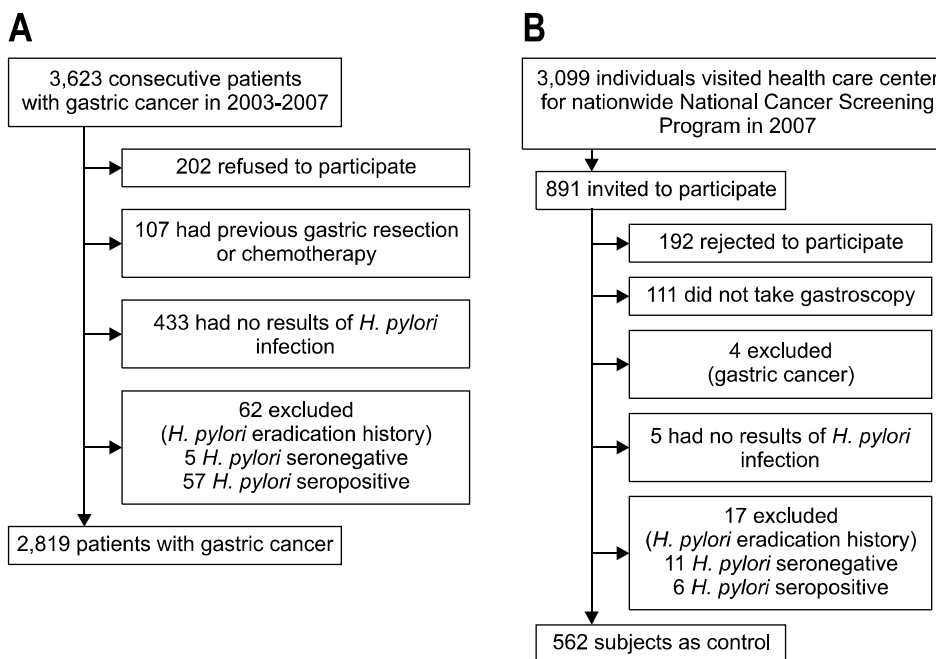


Fig. 1. Flow of the participants, gastric cancer patients (A) and control subjects (B), in the study.

the study and 111 individuals did not undergo EGD examination. Four individuals were excluded since they were diagnosed as having gastric adenocarcinoma, 5 were excluded due to unavailability of results of *H. pylori* infection, and 17 were excluded due to a history of *H. pylori* eradication. Thus, remaining 562 controls were studied (Fig. 1B).

Each subject was asked to answer a questionnaire under the supervision of a well-trained interviewer. The questionnaire included questions regarding demographic data (age, sex, and familial history of gastric cancer), environmental information (smoking, alcohol consumption, type of drinking water during childhood, number of sibling, type of residence), and socioeconomic data (familial income, education level). Smoking status was classified as ever- or nonsmokers. First-degree family history of gastric cancer was regarded positive if at least one of their parents or siblings had been diagnosed as having gastric cancer.

The study protocol was approved by the Institutional Review Board of the National Cancer Center, Korea (NCCNCS-09-264), and written informed consent was obtained from each of the patients before being enrolled into the study.

2. Serological examination

A blood sample was obtained from each participant. Anti-*H. pylori* IgG was measured using *H. pylori*-EIA-Well kit (Radim, Rome, Italy) according to the manufacturer's protocol, with a sensitivity of 88.0% and a specificity of 93.8% in the Korean population.²⁶ Patients were categorized as seropositive and seronegative for *H. pylori* according to a selective cutoff value of IgG (15 UR/mL).

3. Statistical analysis

All p-values were two-sided, and p-values less than 0.05 were considered statistically significant. We used the Student's t-test for continuous variables, and the χ^2 test and Fisher's exact test for categorical variables. Logistic regression models were used to estimate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs).

Data were adjusted for demographic characteristics and potential confounders. We also estimated the adjusted ORs by stage (EGC vs AGC), anatomical location (cardia versus noncardia), Japanese classification of cancer differentiation (differentiated versus undifferentiated), Lauren's classification (intestinal vs diffuse vs mixed), and age at diagnosis (<0 years vs ≥ 60 years). Cutoff point for age was chosen so that there would be an appropriate ratio of cancer patients and controls on each side of the cutoff

point. Statistical analysis was performed using Stata 9.2 (STATA Co., College Station, TX, USA).

RESULTS

1. Demographic characteristics and potential confounders

Table 1 shows the distribution of the case and control subjects by demographic characteristics. Compared with control subjects, case subjects were significantly older. The proportion of males, smoking history, alcohol consumption, and familial history of gastric cancer were significantly higher in case than in control subjects. Case subjects were more likely to have been exposed to non-purified water and a rural environment in their childhoods than were control subjects. Familial income and education level were lower in case than in control subjects. Using a model of best fit by multivariate logistic regression analysis, however, none of these variables was significantly related to the risk of *H. pylori* infection (Table 2).

2. Overall analysis

H. pylori seropositivity was 84.7% for patients with gastric cancer and 66.7% for controls, yielding a summary crude OR of 2.76 (95% CI, 2.26-3.39) and an adjusted OR

Table 1. Demographic Characteristics and Potential Confounders in Gastric Cancer Patients and Control Subjects

	Gastric cancer (n=2,819) (%)	Control (n=562) (%)	p-value
Age	58.1 \pm 12.0	53.0 \pm 7.2	<0.001
Sex (male)	1,939/2,819 (68.8)	281/562 (50.0)	<0.001
Ever smoker	1,348/2,201 (61.2)	235/560 (42.0)	<0.001
Ever drinker	1,486/2,199 (67.6)	343/562 (61.0)	0.003
Familial history of gastric cancer	664/2,819 (23.6)	54/562 (9.6)	<0.001
Drinking water during childhood			
Purified water	432 (19.7)	219 (39.0)	<0.001
Non-purified water	1,760 (80.3)	343 (61.0)	
Residence during childhood			
Urban	706 (32.1)	279 (49.7)	<0.001
Rural	1,492 (67.9)	282 (50.3)	
Familial income during childhood			
High to middle	1,269 (57.8)	405 (72.3)	<0.001
Low	926 (42.2)	155 (27.7)	
Education level			
≥ 12 yr	1,027 (46.7)	418 (77.4)	<0.001
<12 yr	1,173 (53.3)	122 (22.6)	
Sibling number	5.2 \pm 2.0	5.2 \pm 1.8	0.449

Student's t-test for continuous variables, and χ^2 test for categorical variables.

Differences in denominators were caused by non-responders.

of 3.13 (95% CI, 2.46-3.97). Female patients tended to have a higher OR for *H. pylori* seroprevalence compared to male patients, however it was not statistically significant ($p=0.126$) (Table 3). The seroprevalence of the control group was slightly higher than that (59.6%) of previous study performed in 2005, in which the subjects were asymptomatic Korean adults attending health check-ups.⁹

3. Subgroup analysis

1) EGC vs AGC

H. pylori seropositivity was found in 84.8% (1,055 of 1,244) of patients with EGC and 66.7% (375 of 562) of

control individuals, yielding an adjusted OR estimate of 3.01 (95% CI, 2.27-4.01). *H. pylori* seropositivity was detected in 84.6% (1,333 of 1,575) of patients with AGC, giving an adjusted OR compared with controls of 2.94 (95% CI, 2.24-3.85) (Fig. 2). There was no significant difference in *H. pylori* seropositivity between these two groups of patients (χ^2 test; $p=0.900$).

2) Cardia vs noncardia cancer

We found that 83.8% (181 of 216) of patients with cardia gastric cancer was *H. pylori* seropositive, giving an adjusted OR compared with controls of 2.98 (95% CI, 2.16-4.02). In comparison, 84.8% (2,207 of 2,603) of patients with noncardia cancer was *H. pylori* seropositive, yielding an adjusted OR of 3.17 (95% CI, 2.48-4.04) (Fig.

Table 2. Multivariate Logistic Regression Analysis of Risk for *H. pylori* Infection

	Crude OR	95% CI	Adjusted OR	95% CI
Age	0.99	0.98-1.00		
Sex (male)	1.11	0.92-1.33		
Ever smoker	1.17	0.96-1.41		
Ever drinker	1.08	0.89-1.31		
Sibling number	1.03	0.99-1.09		
Residence during childhood				
Urban				
Rural	1.26	1.03-1.53	1.25*	0.99-1.59
Familial income				
High to middle				
Low	0.95	0.78-1.15		
Drinking water				
Purified water				
Non-purified water	1.17	0.94-1.45		
Education level				
≥ 12 yr				
< 12 yr	1.03	0.85-1.25		
Familial history of gastric cancer	1.13	0.91-1.41		

OR, odds ratio; CI: confidence interval.
*Adjusted for sex, smoking, drinking water, education level, and socioeconomic status during childhood.

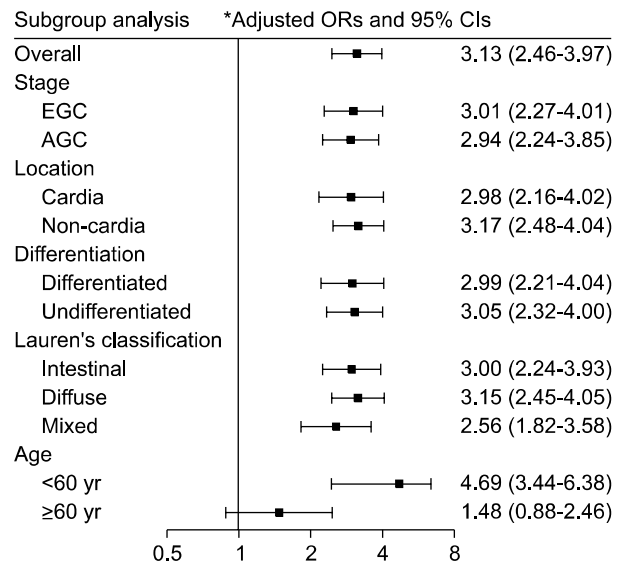


Fig. 2. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between *H. pylori* infection and gastric cancer, overall and by subgroup. *Adjusted for age, sex, familial history of gastric cancer, smoking, alcohol consumption, residence during childhood, source of drinking water, education level, and socioeconomic status during childhood.

Table 3. Prevalence of *H. pylori* Infection in Gastric Cancer Patients and Control Subjects

	Gastric cancer (n=2,819)	Control (n=562)	Crude OR OR (95% CI)	Adjusted OR* OR (95% CI)
Overall	84.7% (2,388/2,819)	66.7% (375/562)	2.76 (2.26-3.39)	3.13 (2.46-3.97)
Male	84.0% (1,629/1,939)	70.1% (197/281)	2.24 (1.69-2.97)	2.67 (1.96-3.63)
Female	86.3% (759/880)	63.3% (178/281)	3.63 (2.67-4.95)	3.56 (2.45-5.17)
≤ 45 yr	87.7% (164/187)	61.7% (29/47)	4.43 (2.13-9.21)	3.92 (1.56-9.84)
> 45 yr	85.9% (595/693)	63.7% (149/234)	3.46 (2.46-4.87)	3.88 (2.43-6.21)

OR, odds ratio; CI, confidence interval.
*Adjusted for age, sex, familial history of gastric cancer, smoking, alcohol consumption, residence during childhood, drinking water, education level, and socioeconomic status during childhood.

2). There was no significant difference in *H. pylori* seropositivity between these two groups of patients (χ^2 test; $p=0.698$).

3) Differentiated versus undifferentiated gastric cancer

We found that 82.7% (1,208 of 1,460) of patients with differentiated type gastric cancer was *H. pylori* seropositive, giving an adjusted OR compared with controls of 2.99 (95% CI, 2.21-4.04). In comparison, 86.8% (1,162 of 1,339) of patients with undifferentiated type gastric cancer was *H. pylori* seropositive, yielding an adjusted OR compared with controls of 3.05 (95% CI, 2.32-4.00) (Fig. 2). The prevalence of *H. pylori* seropositivity was significantly higher in gastric cancer patients with undifferentiated type than with differentiated type (χ^2 test; $p=0.003$; OR, 1.36 [95% CI, 1.11-1.67]). However, the significance disappeared after adjustment for age and sex (OR, 1.14 [95% CI, 0.91-1.42]).

4) Histological types according to Lauren's classification

Of the 1,349 patients with intestinal type gastric cancer, 1,125 (83.4%) were seropositive for *H. pylori*, yielding an adjusted OR compared with controls of 3.00 (95% CI, 2.24-3.93). In comparison, 87.1% (848 of 974) of patients with diffuse type gastric cancer, and 84.3% (86 of 102) of patients with mixed type gastric cancer were seropositive, yielding adjusted ORs compared with controls of 3.15 (95% CI, 2.45-4.05) and 2.56 (95% CI, 1.82-3.58), respectively (Fig. 2). The prevalence of *H. pylori* seropositivity in patients with diffuse type gastric cancer was significantly higher than in those with intestinal type gastric cancer (χ^2 test; $p=0.04$; OR, 1.35 [95% CI, 1.07-1.70]), but this difference was not observed after adjustment for age and sex (OR, 1.02 [95% CI, 0.79-1.32]).

5) Age at diagnosis

The *H. pylori* seropositivity rate in control subjects <60 years (64.4%, 288 of 447) was lower than that in control subjects ≥ 60 years (75.7%, 87 of 115). In contrast, the seropositivity rate was higher in case subjects <60 years (88.5%, 1,231 of 1,391) than that in case subjects ≥ 60 years (81.0%, 1,157 of 1,428). The adjusted OR of gastric cancer patients aged <60 years for the prevalence of *H. pylori* infection (4.69 [95% CI, 3.44-6.38]) was higher than that of those aged ≥ 60 years (1.48 [95% CI, 0.88-2.46]) (Fig. 2). This difference was significant, giving an OR of 1.80 (95% CI, 1.46-2.23).

DISCUSSION

This large-scale study was designed to investigate the association between *H. pylori* infection and gastric cancer in Korean patients. The large number of gastric cancer patients enrolled allowed subgroup analyses.

We found that the prevalence of *H. pylori* infection in gastric cancer patients was higher than in healthy control subjects, giving an overall adjusted OR of 3.24 (95% CI, 2.56-4.10). This result quantitatively supports the conclusion by the IARC that infection with *H. pylori* is a risk factor for gastric cancer in humans,²⁷ although this may have underestimated the real attributable risk of *H. pylori* infection for gastric cancer caused by short time interval between serum collection and cancer diagnosis.^{15,28} A combined analysis of prospective studies showed a summary OR of 3.0 for gastric noncardia cancer.²⁸ Because *H. pylori* does not colonize premalignant lesions of the stomach,²⁹ serum antibodies to *H. pylori* may decline by the time gastric cancer develops. Therefore, the best estimate of the OR of *H. pylori* for gastric noncardia cancer was suggested to be 5.9, after more than 10 years of follow-up.²⁸

We found that the strength of the association between *H. pylori* seropositivity and the risk of gastric cancer did not vary significantly by cancer stage. In previous analyses, however, the prevalence of *H. pylori* infection was significantly higher in patients with EGC than in those with AGC.^{19,20,30} Most untreated EGCs are reported to progress to AGC within 4-5 years.³¹ The lower frequency of *H. pylori* IgG antibodies in AGC may result from a decrease in antibody titer, due to the development of advanced *H. pylori*-associated atrophic gastritis concomitant with age. Intra-gastric environment of AGC patients is more inhospitable to *H. pylori*, resulting in disappearance of infection.^{29,32} Therefore, the histological characteristics of advanced cancer in the elderly typically show advanced atrophic changes caused by the presence of long-standing *H. pylori* infection yet the absence of infection. The mean age of patients with AGC was greater than that of patients with EGC in most studies included in meta-analysis.³⁰ The difference in OR between EGC and AGC likely reflects the decrease in prevalence of *H. pylori* infection by increasing age.¹⁹ Thus, our finding of no difference in *H. pylori* seropositivity between EGC and AGC patients may originate from the similar mean ages (58.6 and 57.3 years, respectively). This suggests that *H. pylori* may be associated with gastric carcinogenesis, but not cancer progression.

We found that *H. pylori* seropositivity was associated

with both gastric cardia and noncardia cancer. Although a strong positive association has been reported between *H. pylori* seropositivity in gastric noncardia adenocarcinoma,^{15,20,28} studies have found a null^{20,28} or inversely associated relationship¹⁵ between anti-*H. pylori* seropositivity and gastric cardia cancer. This association shows substantial geographic variation. Most studies in Asian populations have found a positive association between *H. pylori* seropositivity and cardia cancer,^{16,19} whereas most studies in Western populations have found nonassociation or an inverse association.^{15,33,34} This discrepancy may have been due, at least in part, to the classification in Western studies of some patients with esophageal adenocarcinoma as having gastric cardia cancer, particularly because it is not always possible to distinguish between adenocarcinomas that arise in the gastric cardia and in the lower esophagus.¹⁵ However, in some parts of Asia where Barrett's esophagus and adenocarcinomas of the lower esophagus are rare,¹⁶ tumors classified as cardia gastric cancers do not include any esophageal adenocarcinomas, making all cardia cancers of gastric origin, rather than a mixture of gastric and esophageal malignancies. Another hypothesis is that *H. pylori* colonization induces gastric atrophy, which results in reduced gastric acidity, less acid reflux into the esophagus, and a reduced risk of Barrett's esophagus and junctional cancers.^{35,36} Since the 1970s, there has been a substantial reduction in *H. pylori* prevalence, but a substantial increase in the incidence of gastric cardia adenocarcinoma in Western populations.^{37,38} Cardia cancer was recently reported to be positively associated with both gastric atrophy (OR, 3.92; 95% CI, 1.77-8.67) and gastroesophageal reflux disease (GERD) symptoms (OR, 10.08; 95% CI, 2.29-44.36), with the latter apparent only in the nonatrophic subgroup. These findings indicated that there are two etiologies of cardia cancer, one arising from severe atrophic gastritis and being of intestinal or diffuse subtype, similar to noncardia cancer, and the other related to GERD and the intestinal subtype, similar to esophageal adenocarcinoma.²² Thus, atrophic gastritis related to *H. pylori* infection would contribute to a positive association between *H. pylori* infection and cardia cancer in Asian countries, whereas GERD may contribute to a negative or null association in Western countries, where Barrett's esophagus is more common than Asian countries.

H. pylori has been reported to be a causal factor in the atrophic gastritis-intestinal metaplasia-intestinal type of gastric cancer sequence, hypothesized by Correa.³⁹ The prevalence of *H. pylori* infection seems to be greater in intestinal type than in diffuse type gastric cancers.^{18,40} However, most comprehensive studies have shown that

there is no difference in *H. pylori* seroprevalence between these two types,^{15,20,28} a finding consistent with the present study.

Gastric cancer can be classified as differentiated or undifferentiated carcinoma according to Japanese classification.²⁵ We found that both histological types have a similar association with *H. pylori* infection. Although previous studies showed that *H. pylori* infection may be associated with the differentiated, but not the undifferentiated type of gastric cancer,^{41,42} the number patients with undifferentiated type cancer was small (n=17 and 15, respectively, in two previous studies). Moreover, a recent study in Japan indicated that the ORs were similar (5.8 for differentiated and 5.1 for undifferentiated type).⁴³

Younger *H. pylori*-infected patients have been found to be at higher relative risk for gastric cancer than older patients,²⁰ a finding consistent with the present study. This can be explained by the lower infection rate in the younger controls, whereas the age-related prevalence of *H. pylori* infection increased significantly with the cohort effect in controls but not in cases.²⁰ In addition, *H. pylori* prevalence was higher in younger than in older gastric cancer patients, which may be due to the spontaneous disappearance of infection caused by increased mucosal atrophy and intestinal metaplasia with advanced age, inhospitable place for *H. pylori* colonization.^{29,32} Generally, patients with gastric cancer have more severe mucosal atrophy and intestinal metaplasia in the stomach than normal subjects.⁴⁴ Another hypothesis is that humoral immune response tends to decrease with age,⁴⁵ resulting in the underdetection of serum antibodies against *H. pylori*.

Meanwhile, earlier reports showed that the prognosis of patients with early onset of gastric cancer was poor, with a short survival potential, especially in patients who presented with advanced gastric carcinoma.^{46,47} In a few reports, however, the prognosis of patients with early-onset gastric cancer who underwent gastrectomy was better than that of older patients.^{48,49} Recent reports have showed no difference in surgical outcomes between older and younger patients with gastric cancer.⁵⁰⁻⁵³ Therefore, age does not appear to be an independent risk factor for gastric cancer. Regarding to sex, hormonal difference might be an important factor for prognosis in patients with gastric cancer. Several studies⁵⁴ found that female sex hormones and their analogues appear to be associated with gastric carcinogenesis and progression, and that pregnancy and delivery may accelerate growth of stomach cancer cells.⁵⁵⁻⁵⁷ Further studies are needed to evaluate different outcomes between both sexes in young gastric cancer patients.

The strengths of this study include the prospectively

collected large sample size, highly-qualified data obtained in a cancer center hospital of large volume, the assessment of tumor characteristics allowing subtype analyses, and the adjustment for potential confounders. However, this study had several limitations. First, because its design was cross-sectional, *H. pylori* status was assessed close to cancer diagnosis, making it likely that the magnitude of the association was underestimated. Second, this study did not include CagA serology which would have increased the sensitivity for the detection of *H. pylori* colonization.⁵⁸ In Korea, most *H. pylori* strains are CagA-positive.⁵⁹ Increasing mucosal atrophy and intestinal metaplasia with age can lead to the clearance of *H. pylori*.^{29,32} Because antibodies to CagA appear to persist longer than antibodies to *H. pylori* whole-cell,⁶⁰ CagA seropositivity may be a better marker of *H. pylori* exposure among patients with severe mucosal disruption,¹⁶ which would be helpful in assessing the actual seroprevalence of *H. pylori* in older patients and controls. Third, factors that may confound the association between *H. pylori* infection and gastric cancer, including diet and salt intake, were not investigated in this study. Fourth, although we adjusted for possible confounding factors, there may have been a selection bias in our recruitment of healthy control subjects from nationwide National Cancer Screening Program. Fifth, We did not evaluate gastric atrophy and GERD objectively, therefore we could not make a subgroup analysis about the effect of *H. pylori* infection on cardia gastric cancer. Differences in basal characteristics and sample size between case and control groups were also a weak point.

In summary, this cross-sectional study showed that the prevalence of *H. pylori* is significantly higher than in gastric cancer patients than in healthy control subjects in Korea. Moreover, its prevalence was higher in younger than older gastric cancer patients, and the association between *H. pylori* infection and gastric cancer exists regardless of tumor location, stage, and histological differentiation in a region in which both *H. pylori* and gastric cancer were highly prevalent.

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