Association of *Helicobacter pylori* Infection with Gastric Adenocarcinoma

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Gastric adenocarcinoma is the most prevalent cancer in South Korea, and *Helicobacter pylori* (*H. pylori*) infection is also common. This study was performed to examine the association between *H. pylori* infection and gastric cancer, taking into account various other factors. To investigate the association between gastric adenocarcinoma and *H. pylori* infection, determined by urease-positive reaction in the CLO test, a total of 175 paired specimens (175 tumor and 175 tissues adjacent to tumor) of stomach cancer patients and a total of 113 control specimens were obtained. The positive *H. pylori* infection rates were 78.9% (138/175) among the patients in specimens of tumor or tissues adjacent to the tumor and 41.6% (47/113) among controls in the CLO test. A positive correlation between *H. pylori* infection and gastric cancer was observed (age-adjusted odds ratio, 7.0; MH χ^2=34.5 with $P<0.0005$). These data suggest that stomach cancer patients in Korea have high infection rates of *H. pylori* regardless of site specificity, and this infection might be causally associated with stomach cancer.

Key words: Gastric adenocarcinoma — *Helicobacter pylori* — CLO test — Cancer causation

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped organism that was isolated from the gastric mucosa of patients with chronic gastritis in 1983.[1] *H. pylori* is now accepted as the major cause of type B gastritis, and *H. pylori* gastritis is strongly associated with duodenal ulcer and gastric ulcer.[2–4] Atropic gastritis has also been reported to be a precursor lesion for gastric cancer.[5] Recent studies on the prevalence of *H. pylori* in gastric cancer patients have stimulated interest in its potential role in the development of gastric adenocarcinoma.[6, 7] A report suggests that the acquisition of *H. pylori* early in life increases the risk of developing both gastric cancer and gastric ulcer.[8]

Many epidemiological data suggest that high rates of *H. pylori* infection might be related to high rates of gastric cancer.[9, 10] On the other hand, dietary factors such as consumption of smoked foods (sources of nitroso compounds), pickled foods and salted foods may be also related to stomach cancer.[11, 12] In Korea, gastric adenocarcinoma is the most frequently diagnosed malignant disease,[13] and among 50 countries selected around the world, Korea was ranked first for age-adjusted death rates from stomach cancer during the period from 1986 to 1988 in a report by the American Cancer Society.[14] Thus, it is worthwhile to investigate the relationship between *H. pylori* infection and stomach cancer in Korea. The techniques used to screen *H. pylori* infection are Giemsa staining Warthin-Starry technique, serologic techniques for *H. pylori* IgG antibodies,[15, 16] the [^{14}C]- or [^{13}C]urea breath test,[17] polymerase chain reaction assay for gastric juice aspirates,[18] and the CLO test to detect urease secreted by *H. pylori* in gastric mucosa.[19, 20] Among them, the CLO test is a simple, rapid and highly specific, and is commonly used for the diagnosis of *H. pylori*. Here, we compared the infection rates of *H. pylori* in stomach tissues within the tumor, normal tissues adjacent to the tumor of the same gastric cancer patient and stomach tissues of controls by means of the CLO test to examine the putative association between the infection and gastric adenocarcinoma.

MATERIALS AND METHODS

Sample collection Paired specimens (tumor, 175; non-cancer tissues adjacent to tumor, 175) were obtained from a total of 175 patients (118 men, 57 women) who had

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undergone gastrectomy for gastric adenocarcinoma between 1992 and 1995 at Korea Cancer Center Hospital, Seoul, South Korea. A total of 113 control gastrectomy specimens were obtained at autopsy of normal members of the population (81 men, 32 women) at the Korea National Institute of Scientific Investigation; each specimen was collected within 3 to 5 h after death due to traffic accidents during winter (at a temperature below 0°C). The site (antrum, body, cardia, etc.) of each specimen collected, and the age and sex of the study subjects were recorded. Slides and tissue blocks were obtained from gastrectomy specimens. All specimens were separately labelled and immediately stored at −80°C. Histological classification of gastric carcinoma into diffuse and intestinal types was based on Lauren's classification. Information on age and sex of the patients was obtained before the surgical operation. Since normal stomach tissue from living individuals is generally unavailable, we chose to use normal stomach tissues of autopsied donors who had died in traffic accidents.

CLO test *H. pylori* produces large amounts of urease, and the CLO test detects this urease in gastric mucosal biopsies. The CLO test kit (Delta West Pty. Ltd., Australia, provided by Korea Green Cross Corporation, Seoul, South Korea) was used to detect *H. pylori*, and it is known to have high sensitivity and specificity.[19, 20] Specimens (2 to 5 mg each) were prepared, and CLO test kits were kept in a warm place (30 to 40°C) for 30 min before the experiment. Each sample was placed on the gel of the kit at 37.5°C for 3 h and then brought to room temperature. When the color of the gel changed from orange to pink or magenta within 30 min to 24 h, the samples were regarded as positive for *H. pylori* infection.

Statistical analysis The rate of *H. pylori* infection in the gastric adenocarcinoma patients was calculated and compared with that in the control samples. The two-sided α

Table I. *H. pylori* Infection Rates (%) of Gastric Adenocarcinoma Patients and Controls by Sex, Site of Tumor, Degree of Differentiation, and Histological Type

Characteristic		Patients			Controls	
		Pairs[b]	Adjacent	Tumor		
	N[a]	(N=175)	(N=175)	(N=175)	(N=113)	
Age (yr.)						
Male	(N=118)	Mean and range; 55, 30–76			(N=81)	39, 17–71
Female	(N=57)	Mean and range; 53, 27–73			(N=32)	42, 12–84
Sex (%)						
Male	(N=118)	77.9[c]	70.3	42.3	(N=81)	44.4
Female	(N=57)	80.7	77.2	43.9	(N=32)	34.4
Sites (%)						
Antrum	(N=72)	80.6	75.0	47.3	(N=12)	41.7
Antrum+Body	(N=42)	73.8	71.4	38.1	(N=67)	43.3
Body	(N=42)	81.0	69.1	42.9	(N=34)	34.0
Cardia	(N=17)	76.5	70.6	41.2	—	
Uncertainty	(N=2)	—	—	—	—	
Degree of differentiation (%) (below: only for patients)						
Moderate	(N=47)	82.6	80.4	43.5		
Poor	(N=107)	79.4	69.1	45.8		
Mucinous	(N=16)	87.5	75.0	50.0	NA[d]	
Signet ring	(N=3)	100	100	33.3		
Not classified	(N=2)	100	100	50.0		
Histological type (%)						
Diffuse	(N=107)	77.6	72.0	43.0		
Intestinal	(N=43)	79.1	74.4	44.2	NA	
Mixed	(N=4)	51.0	51.0	25.5		
Not classified	(N=21)	90.5	76.2	47.6		

a) Number of cases.
b) Pairs of tumor and tumor-adjacent samples from gastric adenocarcinoma patients. Infection was regarded as positive when either one of them was positive.
c) *H. pylori* infection positive rate (%).
d) Not applicable.

level was conservatively set at 0.05 for the confidence interval of odds ratio (OR). All P values were calculated by use of the χ^2 test.[21] Age-adjusted OR was obtained by the Mantel-Haenszel (MH) method[22] and MH χ^2 values were also calculated.

RESULTS

Paired specimens of tumor ($n=175$) and adjacent tissue ($n=175$) from a total of 175 gastric adenocarcinoma patients and specimens from 113 non-cancer subjects (control) were collected. The mean age was 54.4 years (men, 55 years; women, 53 years) in cancer patients and 40.5 years (men, 39 years; women, 42 years) in controls, and the ranges of age were 27 to 76 years (men, 30–76 years; women, 27–73 years) and 12 to 71 years (men, 17–71 years; women, 12–84 years), respectively. The characteristics of the specimens of 175 gastric adenocarcinomas patients are shown in Table I.

Histological classification was based on the degree of differentiation (moderate, poor, mucinous, and signet ring cell type) or Lauren's classification (diffuse and intestinal type). One hundred and seven cases (61.1%) of the total gastric adenocarcinomas were classified as poorly differentiated, 47 cases (26.3%) as moderately differentiated, 16 cases (9.7%) as mucinous, 3 cases (1.7%) as signet ring cell type, and 2 cases (1.2%) as not classified.

H. pylori infection was found in 79% to 83% of poorly or moderately differentiated cases. The proportion of the diffuse-type gastric adenocarcinoma in males (58.5%) was lower than that in females (66.7%), whereas the intestinal type was more frequent in males (males: 27.0%, females: 15.8%). Approximately 78% to 79% of diffuse (107 cases) or intestinal type (43 cases), determined by Lauren's classification, was CLO test-positive. *H. pylori* infection rates in gastric cancer showed no significant difference according to either degree of differentiation or histological type.

H. pylori infection rates by age group and sites within the case or control group were not different, but the difference of infection rate between cancer patients and controls was statistically significant (Table II). A much higher rate of *H. pylori* infection was observed in specimens of gastric adenocarcinomas than in control specimens for all sites and all ages.

Among gastric adenocarcinoma patients, 78.9% (138/175) was shown to be positive for either the tumor or adjacent tissue specimen, whereas only 41.6% (47/113) of the control specimens was positive in the CLO test, revealing a strong statistical association with gastric adenocarcinoma. The age-adjusted OR was 7.03 (MH $\chi^2=34.5$; $P<0.0005$) for both sexes, 6.1 (MH $\chi^2=18.9$; $P<0.001$) for males and 8.6 (MH $\chi^2=13.7$; $P<0.001$) for females, and the site-adjusted OR was 5.2 (MH $\chi^2=6.1$;

Table II. *H. pylori* Infection in Specimens of Gastric Adenocarcinomas Cases and Control (Normal Population) by Age and Sex

Sex	Age (yr.)	Patients			Controls		
		No.	*H. pylori* (+)[a]	% Positive	No.	*H. pylori* (+)	% Positive
Male	–20	—	—	—	6	3	50.0
	20–29	—	—	—	15	8	3
	30–39	15	13	86.7	22	10	45.5
	40–49	18	15	83.3	26	10	38.5
	50–59	43	32	74.4	7	3	42.9
	60–69	34	25	73.5	4	2	50.0
	70–	8	7	87.5	1	—	—
		118	92	77.9	81	36	44.4
Female	–20	—	—	—	1	—	—
	20–29	1	1	100	5	1	20.0
	30–39	9	7	77.8	11	5	45.5
	40–49	11	10	77.9	8	3	37.5
	50–59	15	12	80.0	2	—	—
	60–69	19	14	73.7	2	1	50.0
	70–	2	2	100	3	1	33.3
		57	46	80.7	32	11	34.4
Total		175	138	78.9	113	47	41.6

a) Indicates positive in the CLO test for *H. pylori* infection.

Table III. OR, χ^2 and P Values: the Association between *H. pylori* Infection and Gastric Adenocarcinoma

H. pylori	No. of specimens	No. of control specimens	Crude		Age and site-adjusted		
			OR (95% CI)[a]	P value[b]	OR[c]	MH χ^2	P value[d]
Overall							
Negative	37	66	1.0		1.0		
Positive	138	47	5.2 (3.1–8.7)	$P<0.001$	7.0	34.5	$P<0.0005$
Males							
Negative	26	45	1.0		1.0		
Positive	92	36	4.4 (2.4–8.2)	$P<0.001$	6.1	18.9	$P<0.001$
Females							
Negative	11	21	1.0		1.0		
Positive	46	11	8.0 (3.0–21.4)	$P<0.001$	8.5	13.7	$P<0.001$
Sites							
Antrum (−/+)[e]	14/58	7/5	1.0/5.8 (1.7–19.3)	$P<0.025$			
Antrum & Body (−/+)	11/31	38/29	1.0/3.7 (1.6–8.5)	$P<0.005$			
Body (−/+)	8/34	21/13	1.0/6.9 (2.5–18.7)	$P<0.001$			
Total (−/+)	33/123	66/47	1.0/5.2 (3.1–8.8)	$P<0.001$	5.2	6.1	$P<0.025$

a) CI, confidence interval.
b) Determined by χ^2 test from the crude OR.
c) Calculated by the MH method.
d) Determined by χ^2 test.
e) (−/+) indicates (negativity/positivity) in the CLO test for *H. pylori* infection.

Table IV. *H. pylori* Infection in the Tumor and Tumor-adjacent Tissue Paired Specimens from Gastric Adenocarcinomas Patients by Tumor Sites, Degree of Differentiation and Lauren's Classification

Classification		No. of tumor and tumor-adjacent pairs	Responses to CLO test, N (%)			
			+ +[a]	+ −[b]	− +[c]	− −[d]
Tumor sites	Antrum	72	30 (41.7)	4 (5.6)	24 (33.3)	14 (19.4)
	Antrum and body	42	15 (35.7)	1 (2.4)	15 (35.7)	11 (26.2)
	Body	42	13 (31.0)	5 (11.9)	16 (38.1)	8 (19.0)
	Cardia	17	6 (35.3)	1 (5.9)	6 (35.3)	4 (23.5)
	All sites	2	—	—	—	2 (100)
	Total	175	64 (36.6)	11 (6.3)	63 (36.0)	37 (21.1)
Degree of differentiation	MD[e]	46	19 (41.3)	1 (2.2)	18 (39.1)	8 (17.4)
	PD[f]	107	38 (35.5)	11 (10.3)	36 (33.6)	27 (20.6)
	Mucinous	16	6 (37.5)	2 (12.5)	6 (37.5)	2 (12.5)
	Signet ring cell	3	1 (33.3)	—	2 (66.7)	—
	NC[g]	2	1 (50.0)	—	1 (50.0)	—
	Total	175	64 (36.6)	11 (6.3)	63 (36.0)	37 (21.1)
Lauren's classification	Diffuse	107	38 (35.5)	6 (5.6)	34 (31.8)	24 (22.4)
	Intestinal	42	17 (40.7)	2 (4.8)	15 (35.7)	8 (19.0)
	Mixed	4	1 (25.5)	—	1 (25.5)	2 (50.0)
	NC[g]	22	7 (31.8)	3 (13.6)	9 (40.9)	2 (9.1)
	Total	175	64 (36.6)	11 (6.3)	63 (36.0)	37 (21.1)

a) Indicates that both tumor and tumor-adjacent tissue are positive in the CLO test.
b) Indicates that tumor tissue is positive but tumor-adjacent tissue is negative in the CLO test.
c) Indicates that tumor tissue is negative but tumor-adjacent tissue is positive in the CLO test.
d) Indicates that both tumor and tumor-adjacent tissue are negative in the CLO test.
e) MD: moderately differentiated.
f) PD: poorly differentiated.
g) NC: not classified.

P<0.025) as shown in Table III. The greater OR in females than that of males seems to be attributable to the smaller sample size.

As regards the distribution of patients by tumor site of the stomach, the tumor was located at the antrum in 72 cases (44%), at the antrum and body in 42 cases (24%), at the body in 42 cases (24%), and at the cardia in 17 cases (10%). *H. pylori* infection was found in all tumor sites without significant difference by site (Table IV). When *H. pylori* infection was compared by histological classification, about 80% of poorly differentiated or moderately differentiated types was infected. About 80% of diffuse (107 cases) or intestinal type (42 cases) was also shown to be positive in the CLO test (Table IV). When stomach specimens were classified into four groups 79% (138/175) of the tumor and tissue adjacent to the tumor group, 43% (75/175) of the tumor group, 73% (127/175) of the tissue adjacent to the tumor group, and 42% (47/113) of the control group were positive in the CLO test.

DISCUSSION

Much research has been carried out to investigate the association between *H. pylori* infection and gastric cancer.[5, 6] Most epidemiologic studies have found that the prevalence of IgG antibodies against *H. pylori* in the sera, which might reflect the previous infection status, was significantly higher among gastric cancer patients than in the control group.[6, 9, 23]

The purpose of this study was to analyze site-specific infection rates of *H. pylori* in stomach tissues of cancer patients and to compare the infection rates of *H. pylori* in the stomach in tumor tissues, tissues adjacent to the tumor and normal control specimens. Here, we should mention that the autopsy tissues used in this study might not be entirely representative of the normal population, but they were the only tissues obtainable for this study. To ensure the freshness of tissues, specimens were selectively prepared soon (3–5 h) after fatal traffic accidents during the winter time when the temperature was below 0°C. The overall *H. pylori* infection rates were 78.9% in gastric cancer patients and 41.6% in normal control subjects (OR=7.03; *P*<0.0005). In contrast, a recent study in Korea reported that the infection rates showed only a slight difference between gastric cancer patients (60%) and control subjects (51.9%).[24] However, they did not examine the infection of tissues adjacent to the tumor, which showed a higher positive rate of infection (72.6%) than the tumor itself (42.9%) in our study. In addition, the lower infection rates for both case and control group raises the possibility that the socioeconomic status of their study group may have been different from that of our group, since socioeconomic status has been reported to be related to the *H. pylori* infection.

Several epidemiologic and immunological studies have shown that rates of *H. pylori* infection increase in an age-dependent manner,[23, 25] but in this study the rates of *H. pylori* infection by age group were not different. This may be due to the small sample size in this study. There were no significant differences in *H. pylori* infection by histological classification, in agreement with previous epidemiologic studies.[10, 26] A case-control study in Italy has also shown that *H. pylori* infection in gastric cancer patients was not age-related and *H. pylori* infection status was not specific to the gastric cancer sites.[27] Males revealed a stronger association between *H. pylori* infection and stomach cancer (higher risk of gastric adenocarcinoma) than females.[28]

In our study, even though crude and age-adjusted ORs of females were greater than those of males, the MH χ^2 value was greater in males, suggesting a stronger association between the two factors. The greater OR for females than males seems to have resulted from the smaller sample size of females. Histologically, intestinal type is known to be predominant, although the majority of gastric adenocarcinomas in our study was of diffuse type, perhaps due to the relatively small sample size. According to a previous report from Korea the proportion of diffuse type was greater (total sample size, *n*=556) than the proportion of intestinal type in gastric carcinoma when the duration of symptoms caused by gastric carcinoma was less than 6 months and the tumor size was over 10 cm.[29] In addition to *H. pylori* infection, dietary habits such as consumption of pickled and salted foods were reported to be in part involved in gastric carcinogenesis in Koreans.[11, 30] However, it has not been established whether dietary habits are related to *H. pylori* infection. The causal relationship of *H. pylori* infection with gastric adenocarcinoma may be confirmed when other risk factors for stomach cancer are fully elucidated.

The population attributable risk percent of *H. pylori* in Korea, i.e., the maximum proportion of gastric adenocarcinoma attributable to *H. pylori* infection assuming that the infection is the sole causal factor of gastric adenocarcinoma, could be estimated to be 78% for both sexes, 76% for males, and 82% for females, when the prevalence of *H. pylori* among the Korean general population is estimated to be 60%.[31] These attributable risk values would be different if the true prevalence rate of *H. pylori* among the general population and the relative or OR of representative gastric adenocarcinoma patients in Korea were different from the above values.

In this preliminary study, we found that among specimens of 175 stomach cancer patients 78.9% were infected with *H. pylori* in either the tumor or tissues adjacent to the tumor. Interestingly, however, only 42.9% (75/175) was CLO test-positive among tumor specimens, while 72.6% (127/175) was positive among tissues adjacent to

the tumor. The control group was 41.6% CLO test-positive. Our results indicate that 1) a high percentage of Koreans is infected with *H. pylori*, thought to be one of the risk factors for stomach cancer and 2) the tissues adjacent to the tumor may be more suitable for *H. pylori*

detection than the tumor itself, presumably reflecting the preferred habitat of *H. pylori*.

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