

ORIGINAL ARTICLE

Helicobacter pylori 혈청 반응 양성과 대장 신생물과의 상관관계

남관우, 백명기, 권정현, 조성훈, 나수진, 최명규

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Helicobacter pylori Seropositivity Is Positively Associated with Colorectal Neoplasms

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Background/Aims: *Helicobacter pylori* is a well known precursor to gastric cancer and gastric mucosa-associated lymphoid tissue lymphoma. This study was to determine whether *H. pylori* was associated with colorectal neoplasms in Korean subjects undergoing routine checkup.

Methods: A total of 10,082 subjects underwent routine checkups from January 2004 to April 2005. A *H. pylori* IgG test and stool occult blood test were included in the routine checkup program. Colonoscopy was performed if the stool occult blood test was positive or under subject request. Patients who underwent colonoscopy and had histologically confirmed cases of colorectal neoplasms were designated as the subject group and those without as the control group.

Results: Of the 10,082 subjects, 597 had full colonoscopy. The results identified 9 colorectal carcinomas and 118 adenomas. *H. pylori* seropositivity was identified in 6 (66%) subjects with colorectal carcinoma, 81 (68.6%) with colorectal adenoma and 248 (52.8%) controls. Subjects having colorectal neoplasms had a significantly higher *H. pylori* seropositivity rate compared with the controls (OR 1.94, 95% CI 1.28-2.95). This remained significant after adjusting for age, sex, body mass index, HbA1c and total cholesterol (OR 1.90, 95% CI 1.23-2.93). Patients with distal neoplasms also had a significantly higher *H. pylori* seropositivity rate (OR 1.88, 95% CI 1.17-3.01) which persisted after multivariate adjustment (OR 1.79, 95% CI 1.10-2.94).

Conclusions: Subjects with colorectal neoplasms present an increased *H. pylori* seroprevalence compared with controls. (Korean J Gastroenterol 2013;61:259-264)

Key Words: *Helicobacter pylori*; Colorectal neoplasms; Colonoscopy

INTRODUCTION

Helicobacter pylori infection is a well-known etiologic factor in the development of stomach cancer and gastric mucosal-associated lymphoid tissue lymphoma.¹ *H. pylori* infection has been epidemiologically linked to cardiovascular and cerebrovascular disease, and even to extragastric malignancies such as liver or colon cancer.²⁻⁴ The causal relationship between *H. pylori* and colorectal neoplasms have not

been clarified. Chronic *H. pylori* infection leads to gastric atrophy and hypochlorhydria, resulting in an increase in plasma gastrin levels. The resulting hypergastrinemia may play a role in the development of colon cancer in *in vitro* and *in vivo* models but currently published reports are conflicting.⁵⁻¹⁰ Recent publications have reported a positive association between *H. pylori* infection and colon cancer,¹¹⁻¹⁵ but these findings are controversial as other researchers did not identify any association between colorectal neoplasms and *H. pylori* infec-

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tion.¹⁶⁻¹⁸

The prevalence of colorectal cancer has rapidly increased in Korea, and it is now the third most common malignancy after gastric and lung cancers. As the prevalence of *H. pylori* infection in Korea is reported to be about 60%,¹⁹ it is important to determine whether this is a risk factor for colorectal cancer. If there is a significant association between *H. pylori* infection and colon cancer, it will help identify high-risk groups for colorectal cancer screening.

The objective of this study was to determine whether *H. pylori* IgG seropositivity was associated with pathologically confirmed colorectal neoplasms in Korean subjects undergoing a routine checkup.

SUBJECTS AND METHODS

1. Patients

This study was carried out by retrospectively analyzing the data of 10,082 subjects who had had a routine checkup at The Catholic University of Korea, Kangnam St. Mary's Hospital (Seoul, Korea) between January 2004 and April 2005. Participants were measured for their height and weight and their smoking, alcohol, medication, previous medical history and family history were taken. All participants underwent *H. pylori* IgG testing (Enzygnost[®]; Dade Behring, Marburg, Germany) and upper gastrointestinal endoscopy or barium study. Every participant also underwent blood tests including complete blood count, blood chemistry, HbA1c, lipid profile, thyroid function, alpha feto-protein and carcinoembryonic protein and a routine urinalysis. They were also instructed to submit stool for occult blood and parasite examinations. If they wanted to have a colon examination for screening purposes, they took a double contrast barium enema (DCBE). If the stool occult blood test or DCBE was positive or if the subject requested a screening colonoscopy, they were referred to our gastroenterology department, where colonoscopy was performed. If the DCBE reported colon cancer or polyps, confirmation was achieved by colonoscopic biopsy. We analyzed only colonoscopies performed within 6 months of the routine checkup date. Colorectal neoplasms with *H. pylori* seropositivity were designated as the case group and those without as the control group.

2. Ethics

This study was carried out with the approval of the hospital's institutional review board (KC10RISI0392).

3. Statistical analysis

The *H. pylori* IgG seropositivity was defined as ≥ 10.0 U/mL. We excluded one subject who failed to have a complete colonoscopy. *H. pylori* seropositivity was determined in subjects with colon cancer and advanced adenomas which was defined as adenomas at least 10 mm in diameter, having high grade dysplasia, villous or tubulovillous pathology or any combination of the above. The remaining subjects were designated as our control group. The frequency of *H. pylori* seropositivity was compared between subjects with colorectal neoplasms and controls by independent t-test and χ^2 tests. Logistic regression analysis was used to obtain the OR and 95% CI of colorectal neoplasms according to *H. pylori* IgG seropositivity. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

A total of 10,082 subjects elected to have a routine checkup during the study period. Of these, colonoscopy was done in 150 participants due to positive stool occult blood test and 65 due to positive DCBE. The remaining 383 participants decided on elective colonoscopy regardless of stool occult blood test or DCBE results. Total of 598 underwent colonoscopy and only one subject failed to complete the study. There were 335 *H. pylori*-positive subjects and 262 who were *H. pylori*-negative. There were no significant differences in age, sex, BMI, HbA1c or total cholesterol levels between the two groups. Though the data for smoking, alcohol, medication, previous medical history and family history were recorded, not all data was available and thus were not evaluated. Colonoscopic diagnosis of 9 cases of carcinoma and 172 cases of colorectal polyps were made, and histological confirmation revealed 9 cases of adenocarcinoma and 118 cases of colorectal adenoma (Table 1). Twenty one cases of DCBE were done in the case group and 19 turned out to be positive, while only 8 cases of stool occult blood tests were positive.

Table 2 summarizes the association between colorectal neoplasm and *H. pylori* infection. The rate of *H. pylori* seropo-

Table 1. Demographics of *Helicobacter pylori*-positive and -negative Groups

Variable	<i>H. pylori</i> -positive (n=335)	<i>H. pylori</i> -negative (n=262)	p-value
Age (yr)	56.9±9.5	55.6±11.3	0.116
Sex (male)	226 (67.4)	165 (63)	0.261
BMI (kg/m ²)	24.2±2.8	24.0±2.8	0.349
HbA1c (%)	5.4±0.9	5.4±0.8	0.497
Fasting glucose (mg/dL)	105.1±24.2	101.9±24.2	0.179
Total cholesterol (mg/dL)	196.6±41.4	192.7±33.8	0.263
LDL (mg/dL)	121.0±34.6	117.2±29.4	0.206
Colonoscopic finding			
Normal	234 (69.9)	212 (80.9)	0.002
Hyperplastic	14 (4.2)	10 (3.8)	0.823
Neoplastic	87 (26)	40 (15.3)	0.001
Cancer	6 (1.8)	3 (1.1)	0.738
Adenomas	81 (24.2)	37 (14.1)	0.020
Tubular	78 (23.3)	37 (14.1)	0.005
Tubulovillous	1 (0.3)	0 (0)	1.000
Villous	2 (0.6)	0 (0)	0.507

Values are presented as mean±SD or n (%).

Table 2. Prevalence of Colorectal Neoplasms

Colonoscopic finding	Prevalence (%)		p-value
	<i>H. pylori</i> IgG (–)	<i>H. pylori</i> IgG (+)	
Normal (n=470)	222 (47.2)	248 (52.8)	
Adenoma (n=118)	37 (31.4)	81 (68.6)	0.002
Adenoma ≥ 1 cm in size (n=20)	7 (35.0)	13 (65.0)	0.238
Tubulovillous/villous adenoma (n=3)	0 (0)	3 (100.0)	0.251
High grade adenoma (n=1)	0 (0)	1 (100.0)	1.000
Multiple (≥ 3) adenoma (n=31)	9 (29.0)	22 (71.0)	0.049
Advanced adenoma ^a (n=21)	7 (33.3)	14 (66.7)	0.212
Advanced adenoma or carcinoma (n=30)	10 (33.3)	20 (66.7)	0.139

Values are presented as n (%).

^aAdvanced adenomas defined as adenomas at least 10 mm in diameter, having high grade dysplasia, villous or tubulovillous pathology or any combination of the above.

Table 3. Univariate and Multivariate Analyses for the Risk of Colorectal Neoplasm

	<i>H. pylori</i> IgG antibody positive, n (%)	OR (95% CI)	Modified (95% CI)	p-value
Controls	248/470 (52.8)	1.00	1.00	
Neoplasms (adenoma + cancer)	87/127 (68.5)	1.94 (1.28-2.95)	1.90 (1.23-2.93)	0.004
Adenomas	81/118 (68.6)	1.96 (1.27-3.01)	1.93 (1.24-3.01)	0.004
Cancer	6/9 (66.7)	1.57 (0.39-6.35)	1.54 (0.36-6.51)	0.560
Advanced adenoma + cancer	20/30 (66.7)	2.40 (0.64-8.97)	2.39 (0.62-9.21)	0.206
Proximal neoplasms	47/71 (66.2)	1.63 (0.97-2.50)	1.52 (0.89-2.59)	0.120
Distal neoplasms	63/92 (68.4)	1.88 (1.17-3.01)	1.79 (1.10-2.94)	0.020

sitivity was higher in subjects with colorectal neoplasms than in the controls, particularly for patients with colorectal adenoma and multiple adenomas (≥ 3). Table 3 shows the univariate and multivariate analysis for the risk of colorectal neoplasms. Logistic regression analysis after adjusting for age, sex, BMI, HbA1c and total cholesterol revealed that subjects with colorectal neoplasms had a higher rate of seropositivity than controls (OR 1.90, 95% CI 1.23-2.93, p=0.004), and subjects with adenomas also had a higher rate of seropositivity (OR 1.93, 95% CI 1.24-3.01, p=0.004). Patients with neoplasms in the distal colon (descending and rectosigmoid colon) had a higher rate of *H. pylori* seropositivity (OR 1.79, 95% CI 1.10-2.94, p=0.020) whereas those in the proximal colon (ascending and transverse colon) did not.

DISCUSSION

In this study, we found a positive association between colorectal neoplasms and *H. pylori* infection in subjects undergoing routine checkups. The prevalence of seropositivity was significantly higher in subjects with adenomas than in subjects with normal colonoscopic findings. Positive association was not found in cancer patients because of the limited numbers. The risk increase was found to be greater in neoplasms located in the distal colon.

The strength of this study was that participants were selected from a relatively large number of subjects undergoing routine checkup who were asymptomatic. The overall prevalence of *H. pylori* and the incidence of colorectal neoplasms in our study population were similar to those reported recently in Korea.^{20,21} We selected the control subjects from the

same study population that produced the cases to eliminate socioeconomic and other potential background differences and to maximize the representativeness of the controls.

Two pertinent meta-analyses combining the results of 11 studies and 13 studies yielded summary ORs of 1.4 (95% CI 1.1-1.8) and 1.5 (95% CI 1.2-1.9),^{22,23} respectively, suggesting a moderate yet relevant increase in colorectal cancer risk in those infected. However, most of the case-control studies included in these meta-analyses had fewer than 100 patients and the ORs were matched for multiple variables in only a few studies, possibly resulting in bias and influencing the results. A recent large population-based case-control study in Germany, which was published after the meta-analyses, indicated a positive association between *H. pylori* seroprevalence and colorectal adenocarcinoma risk that persisted after adjustment for known potential confounders.²⁴ Also, a recent very large study done using a national histopathological database in the United States indicated that *H. pylori* gastritis was associated with colorectal neoplasms.¹¹ However, most of the studies reported have been based on Western populations, with only two reports in the meta-analyses coming from Japan.

Recently, several studies have been carried out in East Asia. A Korean cross-sectional study with relevant meta-analysis showed that *H. pylori* infection slightly increased the risk of colorectal neoplasms (OR 1.36 and 1.58).²⁵ A Chinese study indicated that *H. pylori* infection was a risk factor for colorectal polyps in children.²⁶ In a Japanese study of 332 routine checkup subjects, a significant increase in the incidence of adenomatous polyps and decrease in normal colonoscopic findings were observed in seropositive patients compared with seronegative individuals.¹⁵ Another Japanese study of 669 hospital patients also demonstrated a positive association of colorectal neoplasms with *H. pylori* (OR 1.66), specially higher risk in female patients.²⁷ In addition, a population-based case-control study of 239 asymptomatic Japanese male adenoma patients with 239 adenoma-free controls showed that *H. pylori* infection was a risk factor for adenoma (OR 2.26) as a whole and that this risk was enhanced by the presence of chronic atrophic gastritis, especially in the proximal colon.²⁸ To summarize, these East Asian studies support the association of *H. pylori* infection with the formation of colorectal neoplasms.

The causal relationship between *H. pylori* and colorectal

neoplasms have not been clarified. Chronic *H. pylori* infection leads to gastric atrophy and hypochlorhydria, resulting in an increase in plasma gastrin levels. Gastrin is known to induce higher mucosal cell proliferation in the colon.⁷ It is expressed by colorectal cell lines and by primary colon cancer and its receptors are increased.^{8,9} Also, gastrin has been reported as a potent mitogen capable of inducing cyclooxygenase-210, which leads to prostaglandin E2 production,²⁹ which may contribute to colon carcinogenesis.

Our study found that the risk increase was greater for neoplasms located in the distal colon. This is supported by a recent large case-control study which found that the risk for colorectal cancer was increased in the distal colon.²⁴ Animal studies have suggested that the mitogenic effect of gastrin are limited to the distal colon.^{7,30} Also, a case-control study on hypergastrinemia and colorectal adenoma found an increased risk for only distal colon adenoma³¹ while a prospective study found that elevated gastrin levels were more associated with rectal cancer than colon cancer.¹² These findings are consistent with our study and may explain why neoplasms in the distal colon were showed higher risk increase due *H. pylori* IgG seropositivity.

Our study supports a positive association of *H. pylori* with colorectal neoplasms; however, it may have included a selection bias, as patients who elected to undergo colonoscopy likely included those who were at high risk for colorectal neoplasm formation, and did not investigate other confounding factors for colorectal neoplasm formation such as aspirin intake, diet and family history. Patients with *H. pylori* infection in East Asia are more likely to have strains that are positive for the Cag A gene,^{32,33} which has been associated with an increased risk of colorectal adenocarcinoma.³⁴

However, one Korean study demonstrated that patients with gastric dysplasia had a significantly higher risk of having advanced colorectal adenoma (OR 3.382) regardless of *H. pylori* infection.¹⁷ In addition, a Japanese study comprising 121 newly diagnosed colorectal cancer cases and 226 matched controls suggested that gastric conditions such as chronic *H. pylori* infection and atrophic gastritis are unlikely to increase the risk for colorectal cancer.³⁵ Therefore, further large-scale population-based studies must be performed to further evaluate the association between *H. pylori* infection and colorectal neoplasm formation.

Limitations of our study included the relatively small num-

ber of colon adenocarcinoma cases, unknown medical history such as aspirin or COX-2 inhibitor uptake and failure to adjust for other colon carcinoma risk factors such as family history or smoking. We also did not control the subjects for previous colonoscopy, the strongest preventive known factor.^{36,37} The fact that we based *H. pylori* seropositivity on IgG ELISA which had its own limitation as the IgG is not an indication of current infection. The subjects may already have been treated for their *H. pylori* infection and not tested positive if urea breath testing or gastric biopsy had been used. Also, IgG ELISA might be misleading in elderly patients with mucosal atrophy who may develop seroconversion. Finally, as the routine check-ups were done 10 years before this analysis, it may not accurately depict the current rates of *H. pylori* infection and colorectal neoplasm prevalence.

In conclusion, our study supports the finding that *H. pylori* infection is associated with an increased risk of colorectal adenoma, and is consistent with several East Asian studies. There is also a small but relevant risk increase for colorectal neoplasm formation, especially in the distal colon. Further study is needed whether colorectal surveillance is effective in *H. pylori*-infected gastric cancer patients before gastrectomy. Further investigation into the role of *H. pylori* infection in carcinogenesis of the colon is necessary, and studies on whether *H. pylori* eradication reduces the incidence of colorectal neoplasm need to be performed.

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