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The Association Between *Helicobacter pylori* Seropositivity and Colorectal Adenoma : A Case-Control Study

혈청 *Helicobacter pylori* 양성과 대장의 선종성 용종과의 연관성 : 환자 대조군 연구

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학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

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① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

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논문 제목: The Association Between *Helicobacter pylori* Seropositivity and Colorectal Adenoma : A Case-Control Study

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ABSTRACT

Introduction: Several studies on the association between *Helicobacter pylori (H. pylori)* infection and colorectal adenoma have been reported recently. But the results have been controversial. The aim of this study is to examine whether *H. pylori* seropositivity is associated with colorectal adenoma.

Methods: Individuals who underwent screening colonoscopy were recruited. After colonoscopy, the subjects were grouped into two groups: subjects with colorectal adenoma (cases) and subjects whose colonoscopic findings were normal (controls). Individuals with hyperplastic or malignant polyp were excluded. All subjects were questioned about smoking, alcohol, weekly exercise, diabetes mellitus, hypertension, medication history and a family history of colorectal cancer. Subjects underwent various anthropometric and laboratory tests including serum IgG antibody against *H. pylori*.

Results: Total 1,780 age and sex matched subjects were allocated in each group: 890 in case and 890 in control group. The mean age of subjects was 55.5±7.6 years and 1,358 (76.3%) were male. The *H. pylori* serology was positive for 1,035 (58.1%) and negative for 745 (41.9%) subjects. By univariate analysis, the prevalence of *H. pylori* was slightly higher in the adenoma group than in the control group, but this association was not statistically significant (OR, 1.19; 95% CI, 0.98-1.44; P=0.074). Hypertension, smoking, alcohol, abdominal obesity, obesity, triglyceride and a family history of colorectal cancer were significantly higher in the adenoma group than control group. Multivariate analysis to adjust for possible confounders

revealed that *H. pylori* infection was not a significant risk factor for colorectal adenoma (OR, 1.20; 95% CI, 0.98-1.46; P=0.075). *H. pylori* infection was not associated with the characteristics of colorectal adenoma such as number, size, location or advanced adenoma (size> 1cm, high grade dysplasia, villous component).

Conclusions: In this large-scale case-control study, the association of *H. pylori* seropositivity and colorectal adenoma was not statistically significant, so *H. pylori* infection might not be a risk factor for colorectal adenoma. Further studies are necessary for the identification of association with *H. pylori* infection and colorectal adenoma.

Keywords: Colorectal adenoma; *Helicobacter pylori*

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Introduction

Colorectal cancer is the second most common cause of cancer in women and the third most common in men in 2008 with it being the fourth most common cause of cancer death.(1) Colorectal cancer incidence rates have rapidly increased in Eastern Asia, an area historically at low risk. Colorectal adenoma is the premalignant lesion in colorectal cancer. It develops into colorectal carcinoma through the adenoma-to-carcinoma sequence.(2) Colorectal neoplasms may be caused by dietary factors, smoking, alcohol consumption and genetic factors, but the exact etiology is still unknown.(3) Identification of the etiology of colorectal neoplasms may be essential for its prevention and treatment.

Helicobacter pylori (H. pylori) is a Gram-negative, microaerophilic bacterium that infects the gastric mucosa and causes inflammation and several gastric diseases, such as peptic ulcer, gastric cancer and gastric lymphoma of mucosa-associated lymphoid tissue. In 1994, *H. pylori* was classified as a type I carcinogen for humans by the IARC/WHO due to the association between *H. pylori* and gastric cancer.(4)

The association of *H.pylori* infection and colorectal adenoma, the precancerous lesion of colorectal adenocarcinoma, has been examined in recent decades. Several studies have suggested that hypergastrinemia induced by *H. pylori* is associated with intestinal mucosal cell proliferation, which increases the growth of cancer cell line resulting in colorectal adenoma and

adenocarcinoma.(5, 6) But the pathogenic mechanisms regarding *H. pylori*`s contribution to colonic neoplasms have yet to be clarified. Some epidemiologic studies have observed an increased prevalence of colorectal adenomas in patients infected with *H.pylori*(7-12) while others report a negative association.(13-15) Moreover, few large-scale population-based epidemiological studies have demonstrated that the association with colorectal adenomas and *H. pylori* infection.

The purpose of this research was to examine the association between colorectal adenomas and *H. pylori* infection in healthy individuals whom we consider to reflect the general population.

Methods

This was a cross-sectional, age-sex matched case-control study. Initially, 4,276 subjects underwent colonoscopy for screening at Seoul National University Hospital Healthcare System Gangnam Center during a routine health check-up from January 2006 to December 2007. They also underwent various anthropometric and laboratory tests including serum IgG antibody against *H. pylori*. The sample frame included 3,585 subjects who were eligible for the following exclusion criteria: age>75 years or <40 years; incomplete colonoscopic examination; diagnosis of colorectal cancer in this check-up; a history of colonic disease, such as colorectal adenomatous polyps,

cancer, inflammatory bowel disease and bowel resection; a colonic examination including colonoscopy, sigmoidoscopy or barium enema in the previous 10 years; symptoms like rectal bleeding, severe lower abdominal pain or change in bowel habits. 1,159 (32.3%) subjects had colorectal adenomas in them. Subjects who had hyperplastic polyps in the control group were excluded. We formed the adenoma group and the control group on subjects who underwent *H. pylori* serology testing. We matched the two group for age and sex which are considered major confounders on colorectal adenoma. Finally, 1,780 age and sex matched subjects were allocated to each group: 890 in the case and 890 in the control group. The Institutional Review Board of Seoul National University Hospital approved the research protocol, and the study was conducted in accord with the Helsinki Declaration.

Subjects were questioned about weekly exercise, alcohol consumption, current smoking, medical history of diabetes mellitus or hypertension, medication history (aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS)) and a family history of colorectal cancer. Height, weight and waist circumference were measured. Venous samples to measure total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, fasting glucose level, high sensitivity C-reactive protein (hs-CRP) and IgG antibody against *H. pylori* were drawn after an overnight fasting. IgG antibodies to *H. pylori* were detected using a rapid enzyme linked immunosorbent assay (EIA WELL; REF K5HPG kit; RADIM, Roma, Italia). The sensitivity and specificity of the method were 95.8% and 96.2%, according to the manufacturer`s statement. (For more information see: http://www.radim.it)

Abdominal obesity was defined by the Regional Office for the Western Pacific Region of the World Health Organization WC criteria based on the ATP III-WPRO. Fasting glucose, triglyceride and HDL cholesterol were categorized by the criteria of metabolic syndrome of NCEP ATP III.

Colonoscopies were performed by experienced gastroenterologists (FICE 4400 series, Fujinon, Japan). The location, sizes, numbers and types of all adenomatous polyps were recorded. Locations were categorized as proximal colon (including the cecum, ascending colon or transverse colon) and distal colon (including the splenic flexure, descending colon, sigmoid colon or rectum). Colorectal adenoma was defined as an adenoma in the colorectum regardless of grading of villous component. Hyperplastic or malignant polyps were excluded. Advanced adenoma was defined as an adenoma of diameter ≥10mm, adenoma with high-grade dysplasia or containing >25% villous features.

Statistical analysis

We compared the case and control group. Continuous variables were analyzed using the Student`s *t* test and expressed as means±s.d.. Categorical variables were analyzed using the chi-square test or univariate analysis. We computed odds ratios (OR) and 95% confidence interval (95% CI) using conditional logistic regression. In the multivariate conditional logistic regression models, we included variables with $P<0.10$ in the univariate analysis to identify independent predictors of colorectal adenoma after adjusting for other variables. *P* values of <0.05 were considered statistically

significant. Statistical analysis was carried out using SPSS 12.0 (SPSS, Chicago, IL, USA) and STATA 12.0 (Stata Corp, College Station, TX, USA).

Results

1. Baseline characteristics of the study subjects

The study sample included 1,780 age and sex matched subjects allocated in each group: 890 in adenoma (case) and 890 in normal (control) group. The mean age of all 1,780 subjects was 55.5±7.6 years and each group contained 679(76.3%) men. The *H. pylori* serology was positive for 1,035 (58.1%) and negative for 745 (41.9%) subjects. The rates of current smoking, alcohol consumption, hypertension and family history of colorectal cancer were higher in the adenoma group than in the control group. In addition, waist circumference, body mass index and triglyceride levels were higher and HDL cholesterol levels were lower in the adenoma group. The two groups did not differ in the frequency of diabetes mellitus, exercise (≥3 per week), regular aspirin use, regular NSAID use and the levels of total cholesterol, fasting glucose, hs-CRP. There were 499 (56.1%) *H. pylori* seropositive subjects in the control group and 536 (60.2%) in the adenoma group. The difference was not statistically significant (P=0.074) (Table 1).

Table 1. Comparisons of the baseline characteristics of the adenoma and control groups

	Control group (*N*=890)	Adenoma group (*N*=890)	*P*
Age (years)	55.5±7.6	55.5±7.6	1.000
Male, *N* (%)	679 (76.3)	679 (76.3)	1.000
H. pylori seropositivity, *N* (%)	499 (56.1)	536 (60.2)	0.074
Current smoking, *N* (%)	182 (20.4)	239 (26.9)	0.001
Alcohol consumption, *N* (%)	138 (15.5)	172 (19.3)	0.032
Hypertension, *N* (%)	244 (27.4)	298 (33.5)	0.004
Diabetes mellitus, *N* (%)	99 (11.1)	99 (11.1)	1.000
Family history of colorectal cancer, *N* (%)	22 (2.5)	38 (4.3)	0.032
Regular aspirin use, *N* (%)	143 (16.1)	136 (15.3)	0.647
Regular NSAID use, *N* (%)	21 (2.4)	20 (2.2)	0.876
Exercise (≥3 per week), *N* (%)	129 (14.5)	110 (12.4)	0.187
Waist circumference (cm)	85.9±7.1	88.1±7.3	<0.0001
Body mass index (kg/m^2)	23.7±2.6	24.5±2.6	<0.0001
Total cholesterol (mg/dl)	196.6±34.1	195.3±35.4	0.446
Triglyceride (mg/dl)	112.3±68.1	125.3±74.2	<0.001
HDL cholesterol (mg/dl)	53.2±13.2	51.1±12.8	<0.001
Fasting glucose (mg/dl)	100.2±21.3	100.4±18.0	0.889

hs-CRP (mg/l)	0.1±0.4	0.1±0.3	0.398

H. pylori, *Helicobacter pylori*; HDL cholesterol, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein.

Results are expressed as mean±s.d. or *N* (%).

2. *H. pylori* seropositivity and colorectal adenoma

According to univariate analysis, the prevalence of *H. pylori* was slightly higher in the adenoma group than the control group, but this association was not statistically significant (OR, 1.19; 95% CI, 0.98-1.44; *P*=0.074). Hypertension, current smoking, alcohol consumption, abdominal obesity (waist circumference), obesity, triglyceride level and a family history of colorectal cancer were significant positive risks for adenoma. Multivariate analysis after adjusting for the variables with *P*<0.10 in the univariate analysis revealed that *H. pylori* infection was not a significant risk factor for colorectal adenoma (OR, 1.20; 95% CI, 0.98-1.46; *P*=0.075). Current smoking, obesity, triglyceride level and a family history of colorectal cancer were statistically significant risk factors of colorectal adenoma (Table 2).

Table 2. Risks for colorectal adenoma

	Univariate analysis		Multivariate analysis[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
H. pylori seropositivity	1.19 (0.98-1.44)	0.074	1.20 (0.98-1.46)	0.075
Hypertension	1.35 (1.10-1.66)	0.004	1.19 (0.96-1.48)	0.107

Diabetes mellitus	1.00 (0.73-1.36)	1.000		
Current smoking	1.52 (1.19-1.93)	0.001	1.45(1.13-1.87)	0.004
Alcohol consumption	1.31 (1.02-1.69)	0.032	1.18 (0.91-1.54)	0.211
Waist circumference (Male>90cm, Female>80cm)	1.60 (1.31-1.96)	0.000	1.24(0.96-1.58)	0.095
Obesity (Body mass index ≥25kg/m^2)	1.70 (1.39-2.08)	0.000	1.44 (1.12-1.86)	0.004
Triglyceride (≥ 150mg/dl)	1.72 (1.36-2.18)	0.000	1.47 (1.14-1.89)	0.003
HDL cholesterol (Male<40mg/dl, Female<50mg/dl)	1.24 (0.98-1.58)	0.072	1.03 (0.80-1.32)	0.847
Fasting glucose (≥110mg/dl)	1.10 (0.87-1.41)	0.394		
Family history of colorectal cancer	1.84 (1.05-3.22)	0.032	2.04 (1.13-3.68)	0.018
Regular aspirin use	0.94 (0.72-1.21)	0.647		
Regular NSAID use	0.95 (0.52-1.76)	0.876		
Exercise (≥3 per week)	0.83 (0.63-1.09)	0.187		

OR, odds ratio; CI, confidence interval; *H. pylori*, *Helicobacter pylori*; HDL cholesterol, high-density lipoprotein cholesterol.

[a]Adjusted for the variables with P<0.10 in the univariate analysis.

3. *H. pylori* seropositivity and characteristics of colorectal

adenoma in the adenoma group

We performed a sub-group analysis about *H. pylori* seropositivity and characteristics of colorectal adenoma in the adenoma group. The *H. pylori* serology was positive for 536 (60.2%) and negative for 354 (39.8%) subjects. *H. pylori* seropositivity was not associated with the characteristics of colorectal adenoma such as size (<1cm vs. ≥1cm), number (1 or 2 vs. ≥3), location (only distal vs. any proximal colon), pathology (tubular vs. tubulovillous or villous), dysplasia (low grade vs. high grade) or advanced adenoma (size≥1cm, villous component or high-grade dysplasia) (Table 3). Multivariate analysis also showed that *H. pylori* infection was unrelated with the characteristics of colorectal adenoma (Table 4).

Table 3. Colorectal adenoma characteristics in the adenoma group

	H. pylori (-) group *N*=354 (39.8%)	*H. pylori* (+) group *N*= 536 (60.2%)	*P*
Adenoma ≥ 1cm in size	37 (10.5)	50 (9.3)	0.581
Multiple (≥3) adenoma	56 (15.8)	103 (19.2)	0.195
Any proximal adenoma	230 (65.0)	356 (66.4)	0.656
Tubulovillous/villous adenoma	11 (3.1)	17 (3.2)	0.957
Adenoma with	4 (1.1)	5 (0.9)	0.747

high-grade dysplasia			
Advanced adenoma[a]	38 (8.9)	58 (10.4)	0.414

Results are expressed as *N* (%).

[a] Size≥1cm, villous component or high-grade dysplasia.

Table 4. Multivariate analysis for the association of *H. pylori* seropositivity and colorectal adenoma characteristics

	OR (95% CI)	*P*
Adenoma ≥ 1cm in size	0.83 (0.52-1.33)	0.449
Multiple (≥3) adenoma	1.28 (0.88-1.86)	0.193
Any proximal adenoma	1.02 (0.76-1.36)	0.901
Tubulovillous/villous adenoma	1.05 (0.47-2.34)	0.897

OR, odds ratio; CI, confidence interval

Discussion

In this study, *H. pylori* seropositivity was slightly higher in the adenoma group than control group, but this association was not statistically significant. So *H. pylori* infection might not be a risk factor for colorectal adenoma. *H. pylori* seropositivity was not associated with the characteristics of colorectal adenoma.

There are possible explanations for the putative relationship between *H. pylori* infection and colorectal neoplasm. A few studies have suggested that fecal shedding of *H. pylori* and its antigens means *H. pylori* moves through the intestine in direct contact with colonic mucosa.(16, 17) Others identified *H. pylori* DNA in colorectal adenoma and adenocarcinoma specimens.(18, 19) But its direct association with colorectal neoplasm development seems less plausible because *H. pylori* has a specific affinity for the gastric mucosa. Another mechanism is that persistent *H. pylori* exposure may result in transformation of gastric cells into gastrin-producing cells, which induce hypergastrinemia.(20, 21) Gastrin has a trophic effect on colorectal mucosa and is related to expression of inflammatory mediators like COX-2 and IL-8, whose inhibition can contribute to the prevention of colorectal cancer development.(22) *H. pylori* strains expressing the cytoxin-associated gene (CagA) results in enhanced inflammatory response and higher gastrin levels compared to CagA- strains.(23)

Several epidemiologic studies have examined the association between *H. pylori* and colorectal adenomas. Recently, a case-control study by Inoue *et al.* showed that *H. pylori* seropositivity increased the risk of colorectal adenomas (OR, 2.52; 95% CI, 1.57-4.05).(11) Hong *et al.* suggested that *H. pylori* seropositivity was a risk factor for any proximal adenoma (OR, 1.50; 95% CI 1.16-1.95), but not for only distal adenoma (OR, 1.07; 95% CI, 0.80-1.44)(12). On the other hand, a prospective study by Robertson *et al.* showed that *H. pylori* seropositivity was not associated with an increased risk for recurrent adenoma development (RR, 0.76; 95% CI, 0.60-0.96).(14) Abbass *et al.* found

that the higher prevalence of colon adenoma in *H. pylori* positive patients was not statistically significant (P=0.52).(15)

The discrepant results of previous studies about the relationship between *H. pylori* seropositivity and colorectal adenomas might have been due to small sample size, sample bias, insufficient adjusting of confounding factors and race differences with a varying frequency of CagA+ *H. pylori*.(24) This study has several advantages. It was a large sample size, case-control study and we used a healthy population that was considered to approximate the general population. Furthermore, age and sex matching was carried out because age and sex were well known risk factors for colorectal adenoma. We carried out a conditional logistic regression analysis adjusting with many possible confounding factors.

In our study, *H. pylori* seropositivity is slightly higher in colorectal adenoma subjects, but not statistically significant. Previous epidemiologic studies showed controversial results. It means that the other unknown mechanisms or factors cause the negative association between *H. pylori* and colorectal neoplasm could present. Besides, the regional distribution of colorectal cancer does not mirror that of gastric cancer and in Asia, there are converse trends over time for the two cancers.(25) In Western countries, the frequency of *H. pylori* infection is lower but colorectal adenomas are higher than Eastern countries. And in Asia, *H. pylori* infection is decreasing, but the occurrence of colorectal adenomas is increasing over time.

This study has some limitations. First, we measured *H. pylori* infection only by *H. pylori* antibodies in human serum, which may not represent actual *H.*

pylori infection and recent eradication of *H. pylori* by treatment. Past historical data of diagnosis and treatment of *H. pylori* infection were not included in this study. Second, our study lacks information on *H. pylori* CagA status and serum gastrin levels. Third, this study is a cross-sectional case-control design. So the temporal sequence of *H. pylori* infection and colorectal adenoma cannot be determined nor could the pathologic mechanisms underlying the association between colorectal adenoma and *H. pylori* infection be identified.

In conclusion, the association of *H. pylori* seropositivity and colorectal adenoma was not statistically significant, so *H. pylori* infection might not be a risk factor for colorectal adenoma in this large-scale, age-sex matched case-control study. A large-scale prosepective study including *H. pylori* CagA status and serum gastrin levels is necessary for the identification of association with *H. pylori* infection and colorectal neoplasm. Clarifying the pathophysiological role of *H. pylori* in the development of colorectal neoplasm is also needed.

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국문 초록

서론: *Helicobacter pylori (H. pylori)* 감염과 대장의 선종성 용종과의 연관성에 대해서 최근 여러 연구가 있어왔으나 연구결과들은 상반된 결과들이 보고되었다. 본 연구에서는 혈청 *H. pylori* 양성과 대장의 선종성 용종과의 연관성에 대해 알아보고자 하였다.

방법: 검진 목적의 대장내시경을 받은 수진자들을 대상으로 하였다. 대장내시경을 받은 후, 수진자들은 대장에 선종성 용종이 있는 군(환자군)과 정상인 군(대조군)으로 나뉘었다. 과증식성 용종이나 악성 용종이 있는 수진자들은 제외되었다. 수진자들을 대상으로 흡연 여부, 음주력, 운동력, 당뇨, 고혈압, 약제 복용력, 대장암의 가족력을 조사하였다. 이들에게 다양한 신체계측 및 혈액검사를 하였고 *H. pylori* 감염은 ELISA를 이용한 항헬리코박터 항체 IgG를 측정하여 진단하였다.

결과: 총 1,780명이 분석에 포함되었으며 성별과 연령을 매칭하여 각각 890명의 선종군과 대조군으로 구분하였다. 평균 연령은 55.5±7.6세였고, 1,358명(76.3%)이 남성이었다. *H. pylori* 양성인 수진자가 1,035명(58.1%), 음성인 수진자가 745명(41.9%)이었다. 단변량 분석에서 H. pylori 양성률은 대조군에 비해 선종군에서 약간 더 높았으나 이러한 연관성은 통계적으로 유의하지 않았다 (OR, 1.19; 95% CI, 0.98-1.44; P=0.074). 고혈압, 흡연, 음주, 복부 비만, 비만도, 중성

지방 수치, 대장암의 가족력은 대조군에 비해 선종군에서 유의미하게 더 높았다. 대장 선종의 위험인자를 보정한 다변량 분석에서 *H. pylori* 감염은 대장의 선종성 용종의 중요한 위험 인자가 아니었다 (OR, 1.20; 95% CI, 0.98-1.46; P=0.075). *H. pylori* 감염과 선종의 수, 크기, 위치, 진행성 선종의 발생은 통계적으로 유의한 연관성을 보이지 않았다.

결론: 본 대단위 환자-대조군 연구에서 *H. pylori* 양성률은 대조군에 비해 선종군에서 약간 더 높았으나 이러한 연관성은 통계적으로 유의하지 않았다. *H. pylori* 감염과 대장의 선종성 용종과의 연관성을 밝히기 위해 추가적인 연구가 필요하겠다.

주요어 : 헬리코박터 파일로리, 대장 선종

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