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ORIGINAL PAPER

Helicobacter pylori infection is an independent risk factor for colonic adenomatous neoplasms

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Abstract Abstract Purpose *Helicobacter pylori* infection is considered to have a positive association with colorectal neoplasms. In this study, we evaluated the association between *H. pylori* infection and colorectal adenomas, based on the characteristics of these adenomas in Korea, where the prevalence of *H. pylori* infection is high and the incidence of colorectal cancer continues to increase.

Methods The study cohort consisted of 4,466 subjects who underwent colonoscopy and esophagogastroduodenoscopy during screening (1,245 colorectal adenomas vs. 3,221 polyp-free controls). We compared the rate of *H. pylori* infection between patients with adenoma and polyp-free control cases, using multivariable logistic regression analysis.

Results The overall rate of positive *H. pylori* infection was higher in adenoma cases than in polyp-free control cases (55.0 vs. 48.5%, $p < 0.001$). The odds ratio (OR) of positive *H. pylori* infection in patients with adenoma compared to polyp-free controls was 1.28 (95% CI 1.11–1.47). The positive association of *H. pylori* infection with colorectal adenomas was more prominent in advanced adenomas (OR 1.84, 95% CI 1.25–2.70) and multiple adenomas (OR 1.72, 95% CI 1.26–2.35). Based on the location of these adenomas, the OR was significant only in patients with colonic adenomas (OR 1.31, 95% CI 1.13–1.52) and not in those with rectal adenoma (OR 0.85, 95% CI 0.58–1.24).

Conclusion Helicobacter pylori infection is an independent risk factor for colonic adenomas, especially in cases of advanced or multiple adenomas, but not for rectal adenomas.

Keywords *H. Pylori* · Adenoma · Colonoscopy · Risk factor

Introduction

The incidence of colorectal cancer (CRC) has continued to increase in most of East Asia including Korea, while in Western countries, it shows a plateau or marginal decline after peaking [1, 2]. Recent cancer statistics in Korea indicate that CRC is the third most common cancer and the fourth leading cause of death among all cancers [3]. Since early detection of colorectal adenomas can prevent the development of CRC, identification of high-risk patients for colorectal adenomas and adequate surveillances for them are important. The previous research studies highlight smoking, alcohol intake, factors relating to metabolic syndrome, and other lifestyle-related contributors as risk factors for colorectal adenomas [4–7]. In addition, some meta-analyses have suggested that *Helicobacter pylori* infection confers 1.2–1.6 times greater risk of CRC [8–11]. The risk of colorectal adenomas was also increased in *H. pylori*-infected subjects in meta-analyses [odds ratio (OR) 1.8–1.9] [8, 12]. Recently, a large-scale Western study based on a national database showed that the association

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between *H. pylori*-positive gastritis and colonic neoplasm was strengthened with the increase in size and number of colonic adenomas. This was further corroborated based on the histopathological progression, from hyperplastic polyp to an adenomatous polyp, advanced adenoma, and/or adenocarcinoma [13]. In a Japanese case–control study, *H. pylori* infection was also a risk factor for colorectal adenomas. Moreover, the research indicated that *H. pylori*-related chronic gastritis cases were at higher risk of proximal adenomas, and not of distal adenomas [14]. In addition, several Korean studies have found that positive serology for *H. pylori* is associated with colorectal adenomas. However, they showed different outcomes based on the location of adenomas [15, 16]. In the interim, the seroprevalence of *H. pylori* infection has been as high as over 50% in Korea, despite the gradually decreasing trend [17]. Thus, it is important to determine whether *H. pylori* infection is an independent risk factor for colorectal adenomas in Korea, where the prevalence of *H. pylori* infection is still high and the incidence of CRC continues to increase over time. The aim of this study was to evaluate the association between *H. pylori* infection and colorectal adenomas in Korea and identify how the severity and the location of the adenomas influence the association.

Materials and methods

Study design and population

Consecutive patients who participated in the voluntary health screening program of the National Cancer Center, Korea, between April 2007 and December 2009 were considered. Participants who underwent colonoscopy during screening were enrolled in the "Colorectal Polyp Registry at the National Cancer Center of Korea." Among the 16,330 participants enrolled in the Colorectal Polyp Registry, 11,965 participants simultaneously underwent upper endoscopy, as well as rapid urease test and were eligible for our study. Among them, 6,601 subjects were provided informed consent forms including information on a survey for demographic and lifestyle factors. Participants with past medical history of CRC or polyps were excluded from the study ($n = 1{,}422$). In addition, participants who were diagnosed with other pathological types of colorectal polyps (i.e., hyperplastic polyp, nonspecific change, serrated polyp) were excluded ($n = 713$). Finally, around 4,466 participants who met the inclusion/exclusion criteria were included in the analysis (Fig. 1). Participants' clinicopathological data were obtained from review of medical records. Body mass index (BMI) was calculated as [weight (kg)/height (m^2)], which was measured using InBody 3.0 (Biospace, Seoul, Korea), which is a body composition analyzer. This study was approved by the Institutional

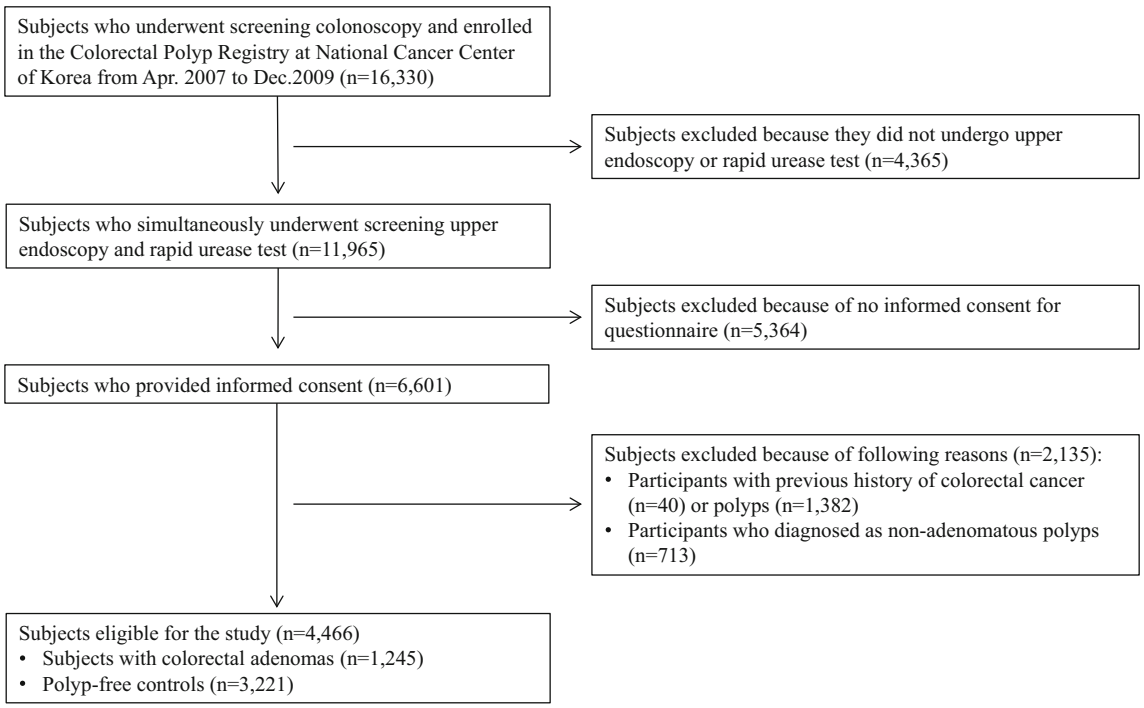

Fig. 1 Inclusion and exclusion criteria for the study

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Evaluation of colonic neoplasm

All selected subjects were examined using video colonoscopy (Olympus CF-H260 or CF-Q260, Olympus Optical Co., Ltd, Tokyo, Japan) by seven experienced colonoscopists. The participants received either 4 L doses of a polyethylene glycol solution (colyte f powder, Taejoon Pharm, Seoul, Korea) or two 45 mL doses of sodium phosphate (C. B. Fleet Co., Inc., Lynchburg, Virginia) before the examinations. Almost all participants who had colonic polyps were scheduled for the endoscopic polypectomy during the procedure. Biopsy specimens were examined by experienced pathologists who were unaware of patients' clinical findings. We reviewed histopathological data (tubular adenoma, tubulovillous or villous adenoma, and low-/high-grade dysplasia) of colonic adenomas from the pathology reports, and the information about polyp size (0–9 and 10+ mm), number (1–2 and 3+), and location (colon, rectum, and concurrent colon and rectum) from the endoscopy reports. Adenomatous polyps with villous architecture, of size 10 mm or more, and exhibiting high-grade dysplasia were considered as advanced adenomas [18].

Upper endoscopy and *H. pylori* evaluation

All subjects underwent upper endoscopy (GIF-Q260, Olympus Optical Co., Ltd, Tokyo, Japan), during which a gastric biopsy specimen was routinely obtained from the greater curvature of the corpus for a rapid urease test (Pronto Dry, Medical Instruments Corporation, Solothurn, Switzerland), in order to identify *H. pylori*. The presence of gastric lesions was recorded, and biopsy samples were obtained from the lesions for histological evaluation as appropriate.

Statistical analysis

We compared the baseline characteristics among subjects who were confirmed to have colorectal adenomas and polyp-free controls, using Pearson's Chi-square test for categorical variables. In addition, we compared the status of *H. pylori* infection between cases diagnosed with adenoma and those in the control group. The differences between the two groups were then investigated according to sex and age distribution. The prevalence of colorectal adenomas was also compared based on the presence of *H. pylori* using Pearson's Chi-square test. Next, the association between *H. pylori* infection and risk of colorectal adenomas was evaluated by logistic regression, using ORs and 95% confidence intervals (CIs). Adjustments were also made for confounding factors that were significant in the Chi-square test, among the baseline characteristics (e.g., sex, age, BMI, marital status, educational background, household income, smoking status, alcohol consumption, and family history of CRC). We then stratified the association between *H. pylori* infection status and risk of colorectal adenomas by severity (low risk vs. advanced adenoma) and number (1–2 and 3+) of adenomas, as well as anatomical location (colon, rectum, and concurrent colon and rectum). STATA software, version 12.0 (StataCorp, College Station, Texas, USA), was used for all of the analyses. All p values were two-sided, and p values <0.05 were considered significant.

Results

Population and baseline demographic data

Among 4,466 enrolled subjects, 1,245 subjects (27.9%) were confirmed to have colorectal adenomas and 3,221 subjects were classified as polyp-free controls. The baseline demographics of the cases with adenoma and polyp-free controls are shown in Table 1. The group of patients with adenomas was older and showed a higher proportion of males, higher BMI, lower education level, and higher consumption of alcohol and tobacco as compared to the polyp-free controls. A family history of CRC was more common in subjects with adenomas.

Helicobacter pylori infection rate

The overall rate of positive *H. pylori* infection was higher in adenoma cases than in polyp-free controls (55.0 vs. 48.5%, $p < 0.001$) (Table 2), which was more prominent in the female subjects ($p = 0.001$) than in the male subjects ($p = 0.06$). In the groups of subjects in their 40's and those are 60 years and older, the higher rates of *H. pylori* infection in subjects with adenoma compared with the polyp-free control group were more prominent.

Helicobacter pylori infection and risk of colorectal adenoma

The prevalence of colorectal adenomas, even in advanced cases or multiple adenomas, was increased in *H. pylori*-positive subjects (30.5 vs. 25.2%) (Table 3). *H. pylori* infection was associated with an increased risk of adenomas after adjusting for sex, age, BMI, education level,

Table 1 General characteristics of adenoma cases and poly-free controls

	n (%)		*p* value
	Control ($n = 3,221$)	Adenoma ($n = 1,245$)	
Sex			
Male	1,521 (47.2)	874 (70.2)	<0.001
Female	1,700 (52.8)	371 (29.8)	
Age (years)			
30–39	700 (21.7)	120 (9.6)	<0.001
40–49	1,496 (46.5)	505 (40.6)	
50–59	817 (25.4)	444 (35.7)	
60+	208 (6.5)	176 (14.1)	
Body mass index (kg/m^2)			
<25	2,337 (72.6)	779 (62.6)	<0.001
≥25	882 (27.4)	466 (37.4)	
Missing	2 (0.1)	0 (0.0)	
Marital status			
Married	2,728 (84.7)	1,078 (86.6)	0.127
Single	234 (7.3)	75 (6.0)	
Missing	259 (8.0)	92 (7.4)	
Educational background			
Middle school	319 (9.9)	164 (13.2)	0.006
High school	1,025 (31.9)	390 (31.6)	
College or more	1,660 (51.5)	607 (48.8)	
Missing	216 (6.7)	81 (6.5)	
Household income (10,000 won/month)			
<400	950 (29.5)	399 (32.1)	0.335
400–700	931 (28.9)	355 (28.5)	
>700	824 (25.6)	306 (24.6)	
Unknown	516 (16.0)	185 (14.9)	
Smoking status			
Non-smoker	1,791 (55.6)	430 (34.5)	<0.001
Ex-smoker	692 (21.5)	390 (31.3)	
Current-smoker	653 (20.3)	400 (32.1)	
Missing	85 (2.6)	25 (2.0)	
Alcohol consumption			
Nondrinker	996 (30.9)	302 (24.3)	<0.001
Ex-drinker	161 (5.0)	59 (4.7)	
Current drinker	2,004 (62.2)	871 (70.0)	
Missing	60 (1.9)	13 (1.0)	
Family history of colorectal cancer			
No	2,893 (89.8)	1,098 (88.2)	0.004
Yes	168 (5.2)	94 (7.6)	
Missing	160 (5.0)	53 (4.3)	

smoking status, alcohol consumption, and family history of CRC (OR 1.28, 95% CI 1.11–1.47) (Table 4). The number of participants having advanced adenomas was 118/1,245 (9.5%), and the OR of positive *H. pylori* infection was high in subjects with advanced adenomas (OR 1.84, 95% CI 1.25–2.70), whereas the OR was 1.23 in subjects with low-risk adenomas. Likewise, the OR of positive *H. pylori* infection was higher in subjects who had three or more adenomas (OR 1.72, 95% CI 1.26–2.35) as compared to an OR of 1.22 in subjects who had one or two adenomas (Table 5). Based on the analysis of the location of adenomas, the OR was significant only in subjects with colonic adenomas, not in those with rectal adenomas (OR 1.31 vs. OR 0.85).

Discussion

We confirmed a significant increase in the rate of *H. pylori* infection in subjects with colorectal adenomas as compared to the rate in the polyp-free control group. This relationship between *H. pylori* infection and colorectal adenomas was further corroborated in cases of advanced or multiple adenomas. However, the positive relationship was only significant for adenomas of the colon and not for rectal adenomas. We excluded the individuals with non-adenomatous polyps, because the association between *H. pylori* infection and non-adenomatous colorectal polyps was not much evaluated, and then, it is uncertain whether its association is comparable to that of *H. pylori* infection with polyp-free controls. A previous study showed that hyperplastic polyps were also associated with *H. pylori*-positive gastritis with weaker strength than adenomatous polyps (OR 1.24 vs. OR 1.52) [13]. For reference, the rate of *H. pylori* infection in the individuals with non-adenomatous polyps was 49.9% (356/713) in our study, which was close to those of the polyp-free control group. In the multivariate analysis, the OR of positive *H. pylori* infection in patients with non-adenomatous polyps compared to the polyp-free controls was 0.97 (95% CI 0.81–1.16). The analysis including these individuals with non-adenomatous polyps as controls ($n = 3{,}934$) showed that the OR of positive *H. pylori* infection in patients with adenomas compared to controls was 1.29 (95% CI 1.11–1.50). More studies about a role of *H. pylori* in the non-adenomatous colorectal polyps are warranted in the future.

Several studies have similar outcomes regarding *H. pylori* as a risk factor for overall colorectal adenomas; however, they indicated conflicting results for the location of these adenomas [15, 16, 19]. One study reported that *H. pylori* infection increased the risk of colorectal adenomas, with a predilection for the proximal colon [16], while another study stated that the distal colon was at the greater risk [15]. The latter study was supported by several previous studies suggesting that the effect of gastrin on colorectal neoplasm was limited to the distal colon [11, 20, 21]. These are not consistent with our results that showed greater association of *H. pylori* with colonic adenomas rather than with rectal adenomas. Stewart et al. [22] suggested that there is a different impact of *H. pylori* on the

Table 2 *H. pylori*-positive rate among colorectal adenoma cases and polyp-free controls

	%		*p* value
	Control ($n = 3{,}221$)	Adenoma ($n = 1{,}245$)	
Overall	48.5 (1,561/3,221)	55.0 (685/1,245)	<0.001
Sex			
Male	50.8 (773/1,521)	54.8 (479/874)	0.060
Female	46.4 (798/1,700)	55.5 (206/371)	0.001
Age group			
30–39	46.3 (324/700)	54.2 (65/120)	0.110
40–49	48.3 (723/1.496)	57.6 (291/505)	<0.001
50–59	52.3 (427/817)	52.3 (232/444)	0.997
60+	41.8 (87/208)	55.1 (97/176)	0.009

Table 3 Prevalence of colorectal adenomas according to *H. pylori* infection status

	n (%)			*p* value
	Overall ($n = 4{,}466$)	Rapid urease test		
		Negative ($n = 2{,}220$)	Positive ($n = 2{,}246$)	
Adenomas	1,245 (27.9)	560 (25.2)	685 (30.5)	<0.001
Advanced adenomas[a]	118 (2.6)	43 (1.9)	75 (3.3)	0.003
3+ adenomas[b]	191 (4.3)	73 (3.3)	118 (5.3)	0.001

[a] Adenoma with villous architecture, of size 10 mm or more, or high-grade dysplasia

[b] Adenomas more than two

Table 4 Association between *H. pylori* infection status and risk of colorectal adenomas by severity of adenomas

	Control ($n = 3{,}221$)	All adenomas ($n = 1{,}245$)		Advanced adenomas[b] ($n = 118$)		Low-risk adenomas ($n = 1{,}127$)	
	n (%)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)	*n* (%)	OR[a] (95% CI)
Rapid urease test							
Negative	1,660 (51.5)	560 (45.0)	1.00	43 (36.4)	1.00	517 (45.9)	1.00
Positive	1,561 (48.5)	685 (55.0)	1.28 (1.11–1.47)	75 (63.6)	1.84 (1.25–2.70)	610 (54.1)	1.23 (1.07–1.42)

[a] Adjusted for sex, age, body mass index, educational background, smoking status, alcohol consumption, and family history of colorectal cancer

[b] Adenoma with villous architecture, of size 10 mm or more, or high-grade dysplasia

Table 5 Association between *H. pylori* infection status and risk of colorectal adenomas according to the number and location of adenomas

	Control (n = 3,221)	1–2 adenomas (n = 1,054)		3+ adenomas[b] (n = 191)		Colon (n = 1,051)		Rectum (n = 113)		Concurrent colon and rectum (n = 80)	
	n (%)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)	n (%)	OR[a] (95% CI)
Rapid urease test											
Negative	1,660 (51.5)	487 (46.2)	1.00	73 (38.2)	1.00	467 (44.4)	1.00	62 (54.9)	1.00	31 (38.8)	1.00
Positive	1,561 (48.5)	567 (53.8)	1.22 (1.06–1.41)	118 (61.8)	1.72 (1.26–2.35)	584 (55.6)	1.31 (1.13–1.52)	51 (45.1)	0.85 (0.58–1.24)	49 (61.3)	1.70 (1.07–2.70)

[a] Adjusted for sex, age, body mass index, educational background, smoking status, alcohol consumption, and family history of colorectal cancer

[b] Adenomas more than two

colorectal area resulting from contrasting immune functions of the colon and the rectum. In line with this observation, several researchers have suggested that the rectum has a different anatomical origin and vascular drainage compared to the colon; then, there are clinical, biological, and epidemiological distinctions between colon and rectal cancers, which could be attributed to the differences in their respective immune mechanisms [23, 24]. Furthermore, the differences in the immune mechanisms might be responsible for increased risk of colonic adenomas associated with *H. pylori* infection, but not in case of rectal adenomas.

We routinely used the rapid urease test for all subjects, which is different from recent Korean studies that used serological tests. [15, 16] Thus, our study explains the association between existing *H. pylori* infection status and colorectal adenomas more accurately; however, it is not sufficient to identify the duration of infection. Meanwhile, there have been only a few studies that used the rapid urease test for *H. pylori* evaluation. Moreover, they rarely adjusted for possible confounding factors. Two studies have failed to prove the association between *H. pylori* and colorectal adenomas [25, 26]. However, a multivariable analysis using direct *H. pylori* test showed that current *H. pylori* infection increased the risk of colorectal adenoma (OR 1.37) [27]. Our study not only had figures similar to theirs, but also confirmed the plausible relationship between current *H. pylori* infection and colorectal adenomas by evaluating advanced or multiple adenomas. Another recent study that involved histopathological evaluation of gastric biopsy specimens also found positive correlation between *H. pylori*-related gastritis and colonic adenomas [13]. In particular, it was more significant in cases of advanced adenomas (OR 1.80), which is consistent with (OR 1.84) our study. These recent studies using direct *H. pylori* test strongly imply that current *H. pylori* infection is an independent risk factor for colonic adenomas. Most of the previous studies using serology for *H. pylori* have shown inconsistent and inconclusive results [12], and it is possible that different direct or indirect modalities for testing for *H. pylori* infection may affect the study outcomes.

With reference to a causal relationship between *H. pylori* infection and colorectal neoplasm, several mechanisms have been suggested. One of the most reliable mechanisms is that *H. pylori*-induced hypergastrinemia stimulates colonic carcinogenesis by cell proliferation, and some studies have supported this claim [20, 28]. However, other studies failed to determine the relationship between hypergastrinemia and colorectal neoplasms [29, 30]. Similarly, a limited number of studies have found a direct effect of *H. pylori* colonization on the colonic mucosa [31, 32]. Another suggestion is that specific *H. pylori* toxin-induced inflammatory response may

be responsible for activating colonic carcinogenesis [33]. It was postulated that *H. pylori cagA* seropositivity was especially associated with increased risk of colonic neoplasm in some studies [34, 35], whereas there was no significant association between *cagA* seropositivity and CRC, in other studies [36, 37]. In addition, *H. pylori*-related chronic atrophic gastritis (CAG) increased the risk of colorectal neoplasm, that is, CAG-induced hypochlorhydria might contribute to colorectal carcinogenesis [38]. Further studies with regard to pathogenic mechanisms should be continued that can help reveal critical points about *H. pylori* infection and its involvement in the development of colorectal adenomas.

Alcohol consumption, smoking, obesity, and family history of colorectal neoplasms are well-known risk factors for colorectal neoplasm [4, 5, 39–42]. These risk factors may possibly act as significant confounders in the analysis of the role played by *H. pylori* infection in developing colorectal neoplasms. These risk factors need to be considered and statistically evaluated. The present study, which was conducted on a relatively large-scale, evaluated the variable confounding factors, thereby supporting previous studies, indicating *H. pylori* infection as an independent risk factor for colorectal adenomas.

In this study, the overall prevalence of colorectal adenoma was 27.9%. The prevalence of adenoma was 36.4 and 17.9% in males and females, respectively, which was comparable with data from other Korean studies during the same period [19, 42]. In the meantime, it has been known that estrogen along with progestin reduced the risk of CRC [43]. Another study stated that metabolic syndrome posed as a risk factor for CRC, indicating conflicting results based on gender differences and tumor location, which implied that the proximal colon might be influenced to a greater extent by sex hormones [44]. We found that *H. pylori* infection is significantly associated with colorectal adenomas in female patients ($p = 0.001$), which supports observations in several previous studies that showed a strong association of *H. pylori* infection with colorectal adenomas in females [45, 46]. However, the effect of *H. pylori* infection on the relationship between colorectal neoplasm and sex hormone has been rarely studied, which warrants further investigation.

There were several limitations in this study. Firstly, the enrolled subjects voluntarily participated in colonoscopic examinations, and the overall rate of *H. pylori* infection was somewhat lower than 56–59% as stipulated by previous Korean studies during comparable years [47, 48]. It is likely that our subjects may have had higher health concerns, better lifestyles, or economic statuses as compared with the general population. Secondly, since the information relating to the previous history of CRC or polyps mainly relied on self-reported questionnaires, this may be vulnerable to recall bias and can affect the association that we found. However, colorectal neoplasms were objectively categorized by highly experienced colonoscopists, who were blinded to the results of the rapid urease test and patients' clinical information, in order to minimize errors from the information. Thirdly, we cannot exclude a possibility of reversal causality caused from the cross-sectional nature of the study, which makes it difficult to estimate the chronology of colorectal histological changes with the age and the period of *H. pylori* affected. Fourthly, we did not investigate *H. pylori*-specific Ab including CagA and VacA. Hence, there is no knowledge of heterogeneity of the *H. pylori* exposure that might affect the development of colorectal adenomatous polyp. Fifthly, the individuals who did not undergo a simultaneous upper endoscopy and excluded from the study may differ from study participants who did upper endoscopy. However, a simultaneous upper endoscopy was also performed for screening purpose, not for the clinical indications. Meanwhile, biennial gastric cancer screening via either an upper endoscopy or an upper gastrointestinal series has been conducted in Korea nationwide since 1999 [49]. Thus, some participants, who had undergone upper endoscopy by the national screening just before our study enrollment, did not want to undergo a simultaneous upper endoscopy. Sixthly, only 55% of the participants with both colonoscopy and upper endoscopy provided informed consent, which may lead the selection bias and affect generalizability of the study. Finally, some lifestyle factors that were missed in the present study cannot be ignored. Factors such as physical activity, use of NSAIDs or aspirin, and routine dietary habits may also have positive or negative association with the prevalence of colorectal adenomas [6, 7]. Thus, our findings need to be substantiated by considering these lifestyle factors and eliminating possible confounders in future studies.

This study has the following implications. Firstly, this is a large-scale study conducted in an area that has a high prevalence of *H. pylori* infection. We especially considered other demographic or clinical confounding factors that can influence the development of colorectal adenomas. Secondly, we obtained detailed information for the respective endoscopies based on the size, number, and location of the colorectal adenomas. Therefore, statistically, our results support previous studies, in that *H. pylori* infection increases the risk of colonic adenomas. Thirdly, the sensitivity and specificity of the rapid urease test performed at the greater curvature of the colonic corpus to detect the presence of *H. pylori* were as high as 96 and 100%, respectively, in our institute [50]. In addition, it has the advantage of minimizing selection bias, since we routinely performed the rapid urease test in all subjects who underwent screening with upper endoscopy. Finally, many of subjects who are screened at our

center usually undergo upper endoscopy and colonoscopy at a few years' intervals, and the patients who have been endoscopically diagnosed with gastric or duodenal ulcers (scar) are eligible for *H. pylori* treatment in Korea. Therefore, further evaluation of the effects of *H. pylori* treatment or persistent infection on the development or recurrence of colorectal adenomas seems possible.

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