

Helicobacter Pylori Infection Increases the Risk of Colorectal Adenomas: Cross-Sectional Study and Meta-Analysis

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Abstract

Background The studies concerning the association between *Helicobacter pylori* status and colorectal adenoma, premalignant lesions of colorectal cancers, are not consistent.

Methods This cross-sectional study investigated the association of colorectal adenoma with *H. pylori* infection in a consecutive series of 2,195 asymptomatic average-risk subjects who underwent screening colonoscopy and *H. pylori* testing. Multivariate analyses were adjusted for potential relevant confounders, including age, sex, smoking, alcohol consumption, family history of colorectal cancer, and regular use of aspirin. Furthermore, we performed a systematic literature review and meta-analysis of available studies, including the current study, to clarify whether *H. pylori* infection is associated with an increased risk of colorectal adenoma.

Results Among 2,195 eligible subjects, 1,253 subjects were *H. pylori* seropositive and 942 subjects were seronegative. In the *H. pylori* (+) group, the prevalence of colorectal adenoma

and advanced adenoma was significantly higher than in the *H. pylori* (–) group (25.3 vs. 20.1 %, $p = 0.004$ and 6.1 vs. 2.9 %, $p < 0.001$, respectively). In our multivariate analysis, *H. pylori* seropositivity was an independent risk factor for overall colorectal adenoma (OR = 1.36, 95 % CI = 1.10–1.68) and advanced adenoma (OR = 2.21, 95 % CI = 1.41–3.48). The positive association was confined in cases with any proximal adenoma. In the meta-analysis, which included ten studies and 15,863 patients, the pooled OR for colorectal adenoma related to *H. pylori* infection was 1.58 (95 % CI = 1.32–1.88).

Conclusion Our results from this cross-sectional study and current studies included in our meta-analysis indicated that *H. pylori* infection was associated with a modest increase in the risk for colorectal adenoma.

Keywords Colorectal neoplasms · *Helicobacter pylori* · Cross-sectional analysis · Meta-analysis

Abbreviations

| | |
|----------------------------|---------------------|
| CRC | Colorectal cancer |
| OR | Odds ratio |
| CI | Confidence interval |
| <i>Helicobacter pylori</i> | <i>H. pylori</i> |

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy in males and the second in females, with over 1.2 million new cancer cases and 608,700 deaths estimated to have occurred in 2008 [1]. Because the majority of CRCs originates from adenomatous polyps, colonoscopy helps prevent CRC by detecting precancerous adenomas so that they can be removed before they evolve

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into cancer [2, 3]. Therefore, the etiologies and risk factors for colorectal adenomas have attracted attention with regard to establishing a personalized strategy for the prevention and screening of CRC.

The heterogenetic and sporadic nature of colorectal adenomas has led to the discovery of many epidemiological associations with causes of this disease. As understanding of the underlying molecular mechanisms involved in colorectal carcinogenesis increases, the concept of microbial-epithelial interactions as an oncogenic trigger may provide a plausible hypothesis for the colorectal carcinogenesis [4]. In contrast with the other cancers of the gastrointestinal tract (gastric carcinoma, mucosa-associated lymphoid tissue lymphoma), a direct causal link between intestinal microbes and colorectal neoplasms has not been established. *Helicobacter pylori*, considered to be a class 1 carcinogenic pathogen, is a causal factor in the development of gastric carcinoma and, therefore, may be relevant in the carcinogenesis of other gastrointestinal tumors. Several hypotheses for the colorectal carcinogenic potential of *H. pylori* have been proposed, such as the induction of inflammation [5, 6], the production of mutagenic toxins [7] and hypergastrinemia [8–10]. Among them, the gastrin theory has attracted the attention based on in vivo and in vitro studies, which revealed that the gastrin have a trophic effect on colonic epithelial cell growth and proliferation [11], and systemic hypergastrinemia promoted the proliferation of normal and neoplastic colonic epithelium. Moreover, although large studies are scarce and there is great heterogeneity in study designs, the results of several studies and recent meta-analyses have suggested a possible small increase in risk of CRC secondary to *H. pylori* infection [12, 13].

Alternatively, results concerning the association between *H. pylori* status and colorectal adenoma, premalignant lesions of CRC, are not consistent, and different studies report varying estimates of association [14–23]. The inconsistent findings of these studies may be explained by varying study methodologies, such as different study population, small sample size or inadequate consideration of potential confounding variables. Therefore, we investigated the association of colorectal adenoma with *H. pylori* infection in average-risk health check-up participants and adjusted for potential relevant confounders. Furthermore, we performed a meta-analysis of available studies, including the current study, to clarify whether *H. pylori* infection is associated with an increased risk of colorectal adenoma.

Methods

Study Design and Participants

We conducted a cross-sectional study using a consecutive series of subjects who underwent screening colonoscopy

and *H. pylori* serology testing as part of a health check-up program between January 2010 and December 2010 at the Healthcare Center of Konkuk University Medical Center in Seoul, Korea. This study was approved by the Institutional Review Board of Konkuk University Medical Center.

Various packages of screening examinations, including colonoscopy and *H. pylori* serology, are available in our center. Most of the study subjects underwent examinations as part of an employee-based health check-up supported by their company. Some paid voluntarily for their health screening examinations. Subjects to be screened received a standard questionnaire, including questions regarding their personal medical history (including history of colorectal neoplasms and *H. pylori* eradication therapy), present medications (including regular use of aspirin), family history (including CRC in their first-degree relatives) and lifestyle habits (including smoking and alcohol consumption). The examinees received written information about the screening program, including a toll-free telephone number to call to obtain more information about the program or to schedule an appointment for screening. Telephone interviews were conducted to establish that the examinees who called to make an appointment for screening were asymptomatic (i.e., no abdominal pain, recent changes in bowel habits or visible rectal bleeding). Information about baseline characteristics, including age, sex, personal medical history, family history, smoking, and alcohol consumption, were obtained from the self-administrated questionnaire.

A consecutive series of 2,590 subjects who underwent screening colonoscopy and *H. pylori* serology testing were eligible during the study period. We excluded a total of 395 subjects who had invasive colorectal cancer ($n = 4$), refused to answer the questionnaire ($n = 96$), underwent incomplete colonoscopy ($n = 10$), had a history of colorectal neoplasms ($n = 77$), had prior *H. pylori* eradication therapy ($n = 100$), had prior gastric surgery ($n = 6$) or colorectal resection ($n = 2$). Among 2,195 eligible subjects, 1,253 subjects were *H. pylori* seropositive [*H. pylori* (+) group], and 942 subjects were *H. pylori* seronegative [*H. pylori* (–) group]. Figure 1 shows the flow diagram.

Anthropometry and Laboratory Assay

Anthropometry and laboratory assays were performed on the same day as the colonoscopy in most cases or within 6 months in others. Anthropometry data (including height, weight, and waist circumference) were measured by trained nurses, and laboratory assays (including serum glucose, triglycerides, and high-density lipoprotein cholesterol) were performed after a fasting period of at least 12 h.

Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters.

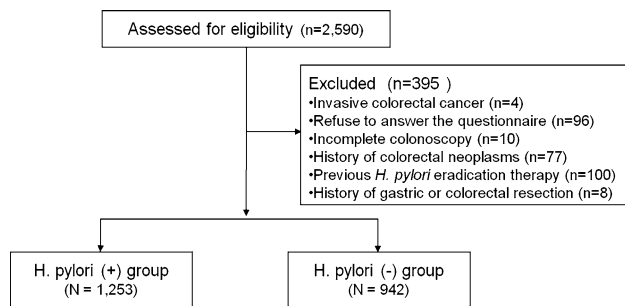


Fig. 1 Flow diagram of cross-sectional study

Metabolic syndrome was diagnosed based on the National Cholesterol Education Program/Adult Treatment Panel III criteria updated by the American Heart Association/National Heart, Lung, and Blood Institute [24].

H. pylori Serology

Helicobacter pylori serology testing was performed on the same day as the colonoscopy in most cases or within 6 months in others. Anti-*H. pylori* IgG was measured using an enzyme-linked immunosorbent assay (Platelia™ *H. pylori*, IgG Qualitative; Bio-Rad Laboratories, Hercules, CA). A subject was considered *H. pylori*-infected when the *H. pylori*-IgG was positive [25]. Among the study participants, 85 patients were tested for *H. pylori* infection status using both *H. pylori* serology and ¹³C-urea breath test (UBT). These patients were subjected to the *H. pylori* serology and ¹³C-UBT after an at least 8-h fast. For ¹³C-UBT, a baseline breath sample (normal exhalation for 4 s) was collected into a collection tube. A capsule containing 38 mg ¹³C-urea in 50 mL of water (HeliFinder cap.; BTO Pharm Co., Icheon, Korea) was then administered orally. A second breath sample was collected 20 min later. Breath samples were then analyzed via mass spectrometry (HeliView; MediChems, Seoul, Korea) to determine the ¹³C to ¹²C ratio, which was expressed per milliliter (‰). The change in ¹³C relative to the baseline value was expressed as $\Delta^{13}\text{C}$. A positive result was defined as a positive $\Delta^{13}\text{C} > 2\text{‰}$. Among the 47 patients with positive ¹³C-UBT, only one patient showed negative *H. pylori* serology, and three patients were negative results in *H. pylori* serology among the 38 patients with negative ¹³C-UBT. The diagnostic accuracy of *H. pylori* serology was investigated in these 85 patients by using the ¹³C-UBT as gold standard. The sensitivity, specificity, positive predictive value, and negative predictive value of *H. pylori* serology were 0.979 (95 % confidence interval [CI], 0.873–0.999), 0.921 (95 % CI, 0.775–0.979), 0.939 (95 % CI, 0.821–0.984), and 0.972 (95 % CI, 0.838–0.999), respectively. These results suggest that *H. pylori* serology appeared to be satisfactory for examining *H. pylori* infection.

Colonoscopy and Classification of Colorectal Adenoma

Bowel cleansing was achieved using PEG (Colyte4L®; Taejun Pharm. Co. Ltd., Seoul, Korea), and all the colonoscopies were performed for screening purposes with high-definition adult video CF-H260AI (Olympus, Tokyo, Japan) or EC-3490Fi (Pentax, Tokyo, Japan) colonoscopies by experienced staff endoscopists. The boundary between the proximal colon and the distal colon was defined as the junction of the splenic flexure and the descending colon, as assessed by the endoscopists. The size was estimated using open-biopsy forceps by the endoscopist. All colorectal neoplasms were histologically evaluated and classified according to the World Health Organization classification [26]. An advanced adenoma was defined as an adenoma 10 mm or greater in diameter, or with high-grade dysplasia, or with significant villous features (>25 %), or any combination thereof. The defining feature of CRC is invasion through the muscularis mucosa into the submucosa. Therefore, carcinoma in situ and intramucosal adenocarcinoma was classified as high-grade dysplasia.

Literature Search

The literature search was conducted using MEDLINE, PREMEDLINE and the Cochrane Library for potentially relevant articles published before September 2011. The following terms were used for the primary search: “*Helicobacter pylori*” AND (“colorectal” OR “colonic” OR “colon” OR “large intestine”) AND (“neoplasms” OR “polyp” OR “adenoma” OR “cancer”). A total of 350 articles were identified using this search strategy. Abstracts of articles from the literature search were individually evaluated independently for possible inclusion by the two authors (H.S.N. and L.S.M.). Studies meeting the following criteria were included: (1) English-language, (2) full-manuscript publication, (3) study design: clinical trials including cohort studies, cross-sectional studies and case-control studies, and (4) results: the prevalence of patients with colorectal adenoma according to *H. pylori* infection or the risk of colorectal adenoma in *H. pylori* (+) patients compared to *H. pylori* (–) patients (described using odds ratio [OR] and 95 % confidence interval [CI]). The studies conducted on only patients with CRC were excluded. Complete texts were obtained for articles that were potentially relevant. In addition, a recursive search of the reference sections of selected studies was performed manually to identify other potentially relevant articles. The results were combined and cross-checked, and any differences were resolved by reviewing the article and settled by consensus. In total, 330 articles were excluded from the initial literature pool, and the full manuscripts of the remaining 20 articles were reviewed in detail. Data were

extracted for (1) patient demographics, (2) prevalence of colorectal adenoma in *H. pylori* (+) and *H. pylori* (–) patients, (3) reported OR with 95 % CI and degree of adjustment to control for confounders. Data were extracted independently by the two authors (H.S.N. and L.S.M.) independently, and disagreement on data extraction was resolved by consensus. Finally, data from ten articles were selected for meta-analysis (Table 1).

Statistical Analysis

Continuous variables are expressed as the means \pm standard deviation, while categorical variables are presented as absolute values and percentages. The differences between the continuous variables were analyzed using the unpaired Student's *t* test, and differences between the categorical variables were analyzed using χ^2 tests and Fisher's exact tests as appropriate. Logistic regression analysis was used to obtain the ORs and 95 % CI of colorectal adenoma according to *H. pylori* infection. To examine the potential confounders for colorectal adenoma, the multivariate models were adjusted for age (≥ 50 years old), sex, smoking (≥ 20 pack-years), alcohol consumption (≥ 30 g/day of alcohol during the previous 12 months), family history of CRC (affected first-degree relatives), and regular use of aspirin. A *p* value less than 0.05 was considered to indicate statistical significance. The analyses were performed with SPSS (version 12.0 K; SPSS Inc., Chicago, IL).

For the meta-analysis, ORs were retrieved from the published manuscripts or calculated from crude data in some studies if not in the manuscript body. Because clinical heterogeneity of the study participants, study designs, and definitions were present among the studies selected for the meta-analysis, a random-effects model was applied. The pooled estimates were calculated using the inverse variance weighted estimation method. A test for heterogeneity across studies was also performed. A *p* value < 0.10 indicated statistically significant heterogeneity across studies, implying that combining the different studies to obtain a summary measure may be inappropriate. The meta-analysis was conducted using Review Manager (version 5.1; The Cochrane Collaboration, Oxford, UK).

Results

The baseline characteristics of the *H. pylori* (+) group and the *H. pylori* (–) group are presented in Table 2. There were no significant differences with regard to age, gender, family history of CRC, regular use of aspirin, BMI, and metabolic syndrome. Although the diastolic blood pressure in the *H. pylori* (+) group was statistically higher than in

the *H. pylori* (–) group, the mean diastolic blood pressure in both groups was within the reference range, and the difference was unlikely to be of clinical significance.

Table 3 shows the prevalence of colorectal adenoma in the *H. pylori* (+) and *H. pylori* (–) groups. Colorectal adenomas were detected in 506 of the 2,195 subjects (23.1 %). In the *H. pylori* (+) group, the prevalence of colorectal adenoma was 25.3 % (317/1,253), which was significantly higher than in the *H. pylori* (–) group at 20.1 % (189/942, *p* = 0.004). The advanced adenomas were detected in 103 of the 2,195 subjects (4.7 %). In the *H. pylori* (+) group, the prevalence of advanced adenoma was 6.1 % (76/1,253), which was significantly higher than in the *H. pylori* (–) group at 2.9 % (27/942, *p* < 0.001). Furthermore, the proportion of patients with any proximal adenoma (15.6 %, 196/936) in the *H. pylori* (+) group was significantly higher than that in the *H. pylori* (–) group (11.1 %, 105/753; *p* = 0.003).

In our multivariate analysis, controlling for age, gender, family history of CRC, smoking, alcohol consumption, BMI, and metabolic syndrome (Table 4), we found that *H. pylori* seropositivity was an independent risk factor for overall colorectal adenoma (adjusted OR = 1.36, 95 % CI = 1.10–1.68) and advanced adenoma (adjusted OR = 2.21, 95 % CI = 1.41–3.48). In addition, the effect of *H. pylori* infection for the risk of colorectal adenoma was different according to the location of colorectal adenoma (Table 5). The positive association with *H. pylori* seropositivity and overall colorectal adenoma was confined in patients with any proximal adenoma (adjusted OR = 1.50, 95 % CI = 1.16–1.95), not in patients with only distal adenoma (adjusted OR = 1.07, 95 % CI = 0.80–1.44).

For the meta-analysis, extracted data from ten studies with a total of 15,863 patients were included, and the pooled OR for colorectal adenoma related to *H. pylori* infection was 1.58 (95 % CI 1.32–1.88). The heterogeneity across studies was marginal (*p* = 0.01). Because of geographic differences in prevalence and strains of *H. pylori* infection [22, 25], subgroup analysis by the studies performed in Western and Eastern countries were performed (Fig. 2). In subgroup analysis using Western studies, five studies with a total of 1,571 patients were included. Meta-analysis of these studies revealed that the *H. pylori*-infected patients have an increased risk of having colorectal adenoma with a pooled OR of 1.58 (95 % CI 1.13–2.20). There was no significant heterogeneity (*p* = 0.28). In subgroup analysis using Eastern studies, six studies with a total of 14,292 patients were included. Meta-analysis of these studies revealed that *H. pylori*-infected patients have an increased risk of colorectal adenoma with a pooled OR of 1.59 (95 % CI 1.27–1.98), although there was significant heterogeneity (*p* = 0.004). The results of pooled ORs between the Western studies and Eastern studies appeared

Table 1 Demographics and outcome characteristics of included studies

| First author | Year | Country | Design | Setting | Mean age (years) | Gender (% Male) | Test for HP infection | Sample size, <i>n</i> | HP (-) group | | HP (+) group | | Odds ratio | 95 % confidence Interval | Adjusted variables |
|--------------------|------|---------|-----------------------|---|---|---|--|-----------------------|-----------------|---------------------------------|-----------------|---------------------------------|------------|--------------------------|--|
| | | | | | | | | | Total, <i>N</i> | Patients with adenoma, <i>n</i> | Total, <i>N</i> | Patients with adenoma, <i>n</i> | | | |
| Moss | 1995 | USA | Case-control study | Single center | Adenoma case: 67 ± 13 Control: 65 ± 11 | Adenoma case: 51 Control: 49 | Serology | 82 | 95 | 18 | 210 | 93 | 1.00 | 0.37–2.70 | |
| Aydin | 1999 | Turkey | Case-control study | Single center | Adenoma group: 48.5 ± 32.5 Control group: 49.4 ± 16.8 | Adenoma group: 55 Control group: 55 | Serology | 267 | 61 | 10 | 206 | 70 | 2.63 | 1.26–5.48 | |
| Breuer-Katschinski | 1999 | Germany | Case-control study | Multi-center cases versus hospital controls | Adenoma case: 61.9 ± 9.7 Hospital controls: 61.8 ± 9.7 | Adenoma case: 52 Hospital controls: 49 | Serology | 178 | 61 | 27 | 117 | 62 | 1.6 | 0.8–3.4 | Energy, fat, fiber, red meat, Ca ²⁺ , vitamin A, β-carotene, folic acid, body mass index, non-steroidal anti-rheumatic drug |
| Siddheshwar | 2001 | UK | Case-control study | Multi-center cases versus population controls | Adenoma case: 62.2 ± 9.1 Population controls: 62.6 ± 9.7 | Adenoma case: 62 Population controls: 62 | Serology | 196 | 59 | 22 | 137 | 76 | 2.6 | 1.3–5.4 | |
| Fujimori | 2005 | Japan | Cross-sectional study | Single center | Adenoma case: median 66 (20–94) Control: median 61 (27–89) | Adenoma case: 65 Control: 38.5 | Histopathology, rapid urease test, or urea breath test | 669 | 142 | 63 | 527 | 264 | 1.60 | 1.18–2.02 | Age |
| Mizuno | 2005 | Japan | Cross-sectional | Single center | HP (-) group: 62.7 ± 1.07 HP (+) group: 58.5 ± 1.18 | HP (-) group: 51 HP (+) group: 61 | Serology | 305 | 107 | 50 | 10 | 9 | 3.40 | 1.90–6.08 | |

Table 1 continued

| First author | Year | Country | Design | Setting | Mean age (years) | Gender (% Male) | Test for HP infection | Sample size, <i>n</i> | HP (-) group | | HP (+) group | | Odds ratio | 95 % confidence Interval | Adjusted variables |
|--------------|------|---------|-----------------------|------------------|--|---|--|-----------------------|-----------------|---------------------------------|-----------------|---------------------------------|------------|--------------------------|---|
| | | | | | | | | | Total, <i>N</i> | Patients with adenoma, <i>n</i> | Total, <i>N</i> | Patients with adenoma, <i>n</i> | | | |
| Bae | 2009 | Korea | Case-control study | Single center | Advanced adenoma group: 60.9 ± 8.6 Control group: 53.1 ± 10.4 | Advanced adenoma group: 86 Control group: 73 | Histopathology, rapid urease test, or urea breath test | 346 | 142 | 21 | 204 | 23 | 1.037 | 0.672–1.599 | Age, sex, gastric dysplasia |
| Lin | 2010 | Taiwan | Cross-sectional study | Single center | Male: median 54 (48–61) Female: median 52 (47–59) | 42 | Rapid urease test | 9,311 | 5,657 | Not mentioned | 3,654 | Not mentioned | 1.366 | 1.230–1.517 | Not mentioned |
| Abbass | 2011 | USA | Cross-sectional study | Single center | HP (-) group: 58.7 ± 11.2 HP (+) group: 59.5 ± 14.3 | HP (-) group: 42 HP (+) group: 34 | Rapid urease test or histopathology | 192 | 96 | 25 | 96 | 30 | 1.29 | 0.69–2.42 | |
| Inoue | 2011 | Japan | Case-control study | Population-based | Adenoma group: 49.4 ± 4.3 Control group: 49.9 ± 3.9 | HP (-) group: 26 HP (+) group: 45 | Serology | 478 | 110 | 38 | 368 | 201 | 2.52 | 1.57–2.05 | Current smoking status, total cholesterol |

HP *Helicobacter pylori*

Table 2 Baseline characteristics in study participants

| Characteristics | <i>H. pylori</i> (–) group (<i>n</i> = 942) | <i>H. pylori</i> (+) group (<i>n</i> = 1,253) | <i>p</i> |
|---|---|---|----------|
| Age (years), mean ± SD | 49.0 ± 10.4 | 49.4 ± 10.3 | 0.349 |
| Male gender, <i>n</i> (%) | 575 (61.0) | 786 (62.7) | 0.424 |
| Family history of CRC, <i>n</i> (%) | 47 (5.0) | 44 (3.5) | 0.104 |
| Regular use of aspirin, <i>n</i> (%) | 90 (9.6) | 118 (9.4) | 0.941 |
| Smoking ≥20 pack-years, <i>n</i> (%) | 146 (15.5) | 215 (17.2) | 0.323 |
| Alcohol consumption ≥30 g/day, <i>n</i> (%) | 237 (25.2) | 322 (25.7) | 0.805 |
| Body mass index (kg/m ²), mean ± SD | 24.0 ± 3.0 | 24.0 ± 3.0 | 0.914 |
| Metabolic syndrome, <i>n</i> (%) | 247 (26.2) | 347 (27.7) | 0.467 |
| Waist circumference (cm), mean ± SD | 85.5 ± 8.7 | 85.3 ± 8.9 | 0.480 |
| Systolic blood pressure (mmHg), mean ± SD | 117.7 ± 13.9 | 118.9 ± 15.6 | 0.054 |
| Diastolic blood pressure (mmHg), mean ± SD | 73.1 ± 10.9 | 74.3 ± 11.5 | 0.015 |
| Glucose (mg/dl), mean ± SD | 93.9 ± 18.6 | 94.3 ± 23.2 | 0.598 |
| Triglyceride (mg/dl), mean ± SD | 121.3 ± 95.4 | 121.4 ± 90.3 | 0.978 |
| HDL cholesterol (mg/dl), mean ± SD | 53.7 ± 13.9 | 53.6 ± 13.9 | 0.855 |

CRC colorectal cancer, SD standard deviation

to be identical. Figure 3 shows the funnel plot of publication bias with OR value as the horizontal axis and standard error of OR as the vertical axis. This graphical funnel plot of the ten studies appears symmetric.

Discussions

It is estimated that approximately 50 % of the world's population carries *H. pylori* in their stomachs despite the geographic differences in prevalence between Western and Eastern countries [27–29]. Recent evidence suggests an

epidemiological association between *H. pylori* infection and several extra-gastric disorders, including cardiovascular, skin, rheumatic, and some neoplastic diseases [30]. With regard to colorectal adenomas, four cross-sectional studies [14, 18–20], six case–control studies [15–17, 21–23], and one prospective cohort study [31] have addressed their association with *H. pylori* infection, reporting inconsistent associations for adenoma prevalence [14–23] and recurrence [31]. Five studies reported a statistically significant association [15, 18–20, 23], while the other four studies could not find any significant association [14, 16, 21, 22]. In one study by Breuer-Katschinski et al. [17], a statistically significant association was observed only in comparison to population-based controls. In a prospective cohort study of subjects who participated in chemoprevention trials, *H. pylori* seropositivity was not associated with an increased risk for recurrent adenoma development [31]. The reason for the inconsistent findings of these studies may be due to differing study participants, small sample sizes, and an inadequate consideration of potential confounding variables. Most case–control studies were performed on a small number of participants [15, 17, 21, 22]. Most cross-sectional studies failed to show a statistically significant association or performed multivariate analysis adjusted with only limited confounding variables [14, 18, 20]. A large-scale cross-sectional study by Lin et al. [19] showed significant association, but was performed in a single center with a single ethnic group of participants. In addition, it was unclear how many participants were average-risk for CRC. Robertson et al. [31] performed a prospective cohort study analyzing the data from subjects enrolled in the Antioxidant Polyp Prevention Study and the Calcium Polyp Prevention Study and concluded that serologic evidence of *H. pylori* infection was associated with an increased risk for recurrent adenoma development. However, the participants of this study were limited to a high-risk group that already had one or more adenomas, and the results may not be applicable to the average-risk population. In addition, the follow-up interval

Table 3 Prevalence of colorectal adenoma

| Colonoscopic finding | <i>H. pylori</i> (–) group (<i>n</i> = 942) | | <i>H. pylori</i> (+) group (<i>n</i> = 1,253) | | <i>p</i> |
|-----------------------------------|---|----------------|---|----------------|----------|
| | <i>N</i> | Prevalence (%) | <i>N</i> | Prevalence (%) | |
| Normal | 753 | – | 936 | – | |
| Colorectal adenoma | 189 | 20.1 | 317 | 25.3 | 0.004 |
| Adenoma ≥1 cm in size | 27 | 2.9 | 76 | 6.1 | <0.001 |
| Tubulovillous/villous adenoma | 4 | 0.4 | 4 | 0.3 | 0.731 |
| Adenoma with high-grade dysplasia | 3 | 1.6 | 2 | 0.6 | 0.367 |
| Multiple (≥3) adenoma | 31 | 3.3 | 53 | 4.2 | 0.264 |
| Any proximal adenoma | 105 | 11.1 | 196 | 15.6 | 0.003 |
| Advanced adenoma ^a | 27 | 2.9 | 76 | 6.1 | <0.001 |

^a Defined as an adenoma 1 cm or greater in diameter, or with high-grade dysplasia, or with significant villous features (>25 %), or any combination thereof

Table 4 Univariate and multivariate analyses for the risk of overall and advanced colorectal adenoma

| Variable | Overall colorectal adenoma | | | | Advanced colorectal adenoma ^a | | | |
|-------------------------------|----------------------------|----------|------------------------------------|----------|--|----------|------------------------------------|----------|
| | Univariate analysis | | Multivariate analysis ^b | | Univariate analysis | | Multivariate analysis ^b | |
| | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> |
| <i>H. pylori</i> (+) | 1.35 (1.10–1.66) | 0.004 | 1.36 (1.10–1.68) | 0.005 | 2.19 (1.40–3.42) | 0.001 | 2.21 (1.41–3.48) | 0.001 |
| Age (≥50 years old) | 2.64 (2.15–3.25) | <0.001 | 3.10 (2.48–3.87) | <0.001 | 3.21 (2.05–5.02) | <0.001 | 3.39 (2.13–5.42) | <0.001 |
| Male | 2.18 (1.74–2.72) | <0.001 | 2.18 (1.69–2.83) | <0.001 | 1.60 (1.03–2.47) | 0.037 | 1.39 (0.84–2.32) | 0.199 |
| Family history of CRC | 0.94 (0.57–1.56) | 0.804 | 1.05 (0.62–1.78) | 0.848 | 1.19 (0.47–3.00) | 0.712 | 1.42 (0.55–3.64) | 0.468 |
| Regular use of aspirin | 1.22 (0.88–1.70) | 0.223 | 0.82 (0.58–1.16) | 0.270 | 1.82 (1.05–3.17) | 0.034 | 1.24 (0.69–2.21) | 0.475 |
| Alcohol consumption ≥30 g/day | 1.51 (1.22–1.88) | <0.001 | 1.24 (0.96–1.60) | 0.104 | 1.54 (1.01–2.34) | 0.044 | 1.45 (0.89–2.37) | 0.138 |
| Smoking ≥20 pack-years | 1.81 (1.41–2.32) | <0.001 | 1.17 (0.89–1.54) | 0.273 | 1.97 (1.26–3.09) | 0.003 | 1.35 (0.82–2.25) | 0.241 |
| BMI ≥25 kg/m ² | 1.34 (1.09–1.64) | 0.005 | 1.08 (0.86–1.36) | 0.503 | 0.99 (0.66–1.51) | 0.978 | 0.81 (0.52–1.27) | 0.359 |
| Metabolic syndrome | 1.68 (1.36–2.08) | <0.001 | 1.27 (1.00–1.62) | 0.048 | 1.69 (1.12–2.54) | 0.012 | 1.39 (0.88–2.18) | 0.156 |

OR odds ratio, CI confidence intervals, CRC colorectal cancer, BMI body mass index

^a Defined as an adenoma 1 cm or greater in diameter, or with high-grade dysplasia, or with significant villous features (>25 %), or any combination thereof

^b Adjustment with *H. pylori* sero-positivity, age (≥50 years old), gender, family history of colorectal cancer, regular use of aspirin, alcohol consumption (≥30 g/day), Smoking (≥20 pack-years), BMI (≥25 kg/m²), and Metabolic syndrome

was 3 years after clearing colonoscopy, which seems to be an insufficient duration to evaluate the recurrence of colorectal neoplasms.

To compensate for those limitations, we first evaluated the association of *H. pylori* infection and the characteristics of colorectal adenoma using a large scale prospective health check-up registry. The average-risk patients for CRC were enrolled, and multivariate analysis was adjusted with relevant potential confounders, including age, gender, family history of CRC, regular use of aspirin, alcohol consumption, smoking, BMI, and metabolic syndrome. The results showed that *H. pylori* seropositivity was significantly associated with an increased risk of colorectal adenoma. Specifically, the association was stronger in large, proximal and advanced adenomas.

We then performed a meta-analysis investigating this association using all available studies and the OR for the association of evidence of *H. pylori* infection and the risk for colorectal adenoma was estimated to be 1.58 with a 95 % CI from 1.32 to 1.88, which is similar to the results of meta-analysis for the association of *H. pylori* infection and CRC (pooled OR 1.49 [95 % CI, 1.17–1.91]). It is well known that there was geographic differences in prevalence and strains of *H. pylori* [29]. *H. pylori* strains from East Asia are considered as having an “East Asian” type of

CagA that is more active and predominantly comprises a single type [32]. Populations expressing a high incidence of gastric carcinoma are mostly identical with regions where East Asian type CagA is predominant [29, 32]. Therefore, subgroup analysis divided into studies performed in Eastern and Western countries should be needed. The pooled ORs of Western and Eastern studies were very similar, which could mean that there were no geographic differences in the relationship between *H. pylori* and adenoma risk.

H. pylori is a causal factor in the development of gastric carcinoma and, therefore, might be relevant in the pathogenesis of other gastrointestinal cancers [4]. First possible mechanisms of oncogenesis include direct toxin-mediated cell-cycle dysregulation and chronic inflammation. The presence of *H. pylori* infection in CRC has been investigated in two studies which identified *H. pylori* DNA in specimens of CRC and adenoma [5, 6]. However, because *H. pylori* has a specific affinity for the gastric mucosa, its direct association with CRC development seems less plausible and participating cases of these studies were too small for meaningful conclusions to be made. In addition, Shmueli et al. [7] reported that, among patients infected with *H. pylori*, CagA+ seropositivity was associated with increased risk for both gastric carcinoma and CRC. They

Table 5 Univariate and multivariate analyses for the risk of proximal and distal colorectal adenoma

| Variable | Any proximal colonic adenoma | | | | Only distal colorectal adenoma ^a | | | |
|-------------------------------|------------------------------|----------|------------------------------------|----------|---|----------|------------------------------------|----------|
| | Univariate analysis | | Multivariate analysis ^b | | Univariate analysis | | Multivariate analysis ^b | |
| | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> | OR (95 % CI) | <i>p</i> |
| <i>H. pylori</i> (+) | 1.48 (1.15–1.91) | 0.003 | 1.50 (1.16–1.95) | 0.002 | 1.09 (0.82–1.46) | 0.556 | 1.07 (0.80–1.44) | 0.642 |
| Age (≥50 years old) | 2.92 (2.25–3.80) | <0.001 | 3.25 (2.46–4.28) | <0.001 | 1.75 (1.30–2.34) | <0.001 | 2.00 (1.47–2.72) | <0.001 |
| Male | 1.90 (1.44–2.50) | <0.001 | 2.04 (1.50–2.79) | <0.001 | 2.14 (1.53–2.99) | <0.001 | 1.87 (1.28–2.73) | 0.001 |
| Family history of CRC | 1.26 (0.71–2.21) | 0.434 | 1.47 (0.82–2.64) | 0.201 | 0.55 (0.22–1.38) | 0.204 | 0.58 (0.23–1.45) | 0.201 |
| Regular use of aspirin | 1.36 (0.93–1.99) | 0.114 | 0.93 (0.62–1.38) | 0.713 | 0.97 (0.59–1.60) | 0.915 | 0.74 (0.44–1.23) | 0.713 |
| Alcohol consumption ≥30 g/day | 1.23 (0.94–1.61) | 0.141 | 1.05 (0.77–1.43) | 0.783 | 1.75 (1.30–2.37) | <0.001 | 1.42 (1.00–2.00) | 0.050 |
| Smoking ≥20 pack-years | 1.52 (1.13–2.06) | 0.006 | 1.03 (0.74–1.44) | 0.846 | 1.85 (1.32–2.59) | <0.001 | 1.27 (0.88–1.83) | 0.209 |
| BMI ≥25 kg/m ² | 1.31 (1.02–1.68) | 0.033 | 1.10 (0.83–1.44) | 0.516 | 1.26 (0.94–1.69) | 0.122 | 1.04 (0.76–1.43) | 0.801 |
| Metabolic syndrome | 1.65 (1.28–2.13) | <0.001 | 1.31 (0.99–1.75) | 0.060 | 1.45 (1.07–1.97) | 0.017 | 1.12 (0.80–1.56) | 0.525 |

OR odds ratio, CI confidence intervals, CRC colorectal cancer, BMI body mass index

^a The boundary between the proximal colon and the distal colon was defined as the junction of the splenic flexure and the descending colon, as assessed by the endoscopists

^b Adjustment with *H. pylori* sero-positivity, age (≥50 years old), gender, family history of colorectal cancer, regular use of aspirin, alcohol consumption (≥30 g/day), smoking (≥20 pack-years), BMI (≥25 kg/m²), and metabolic syndrome

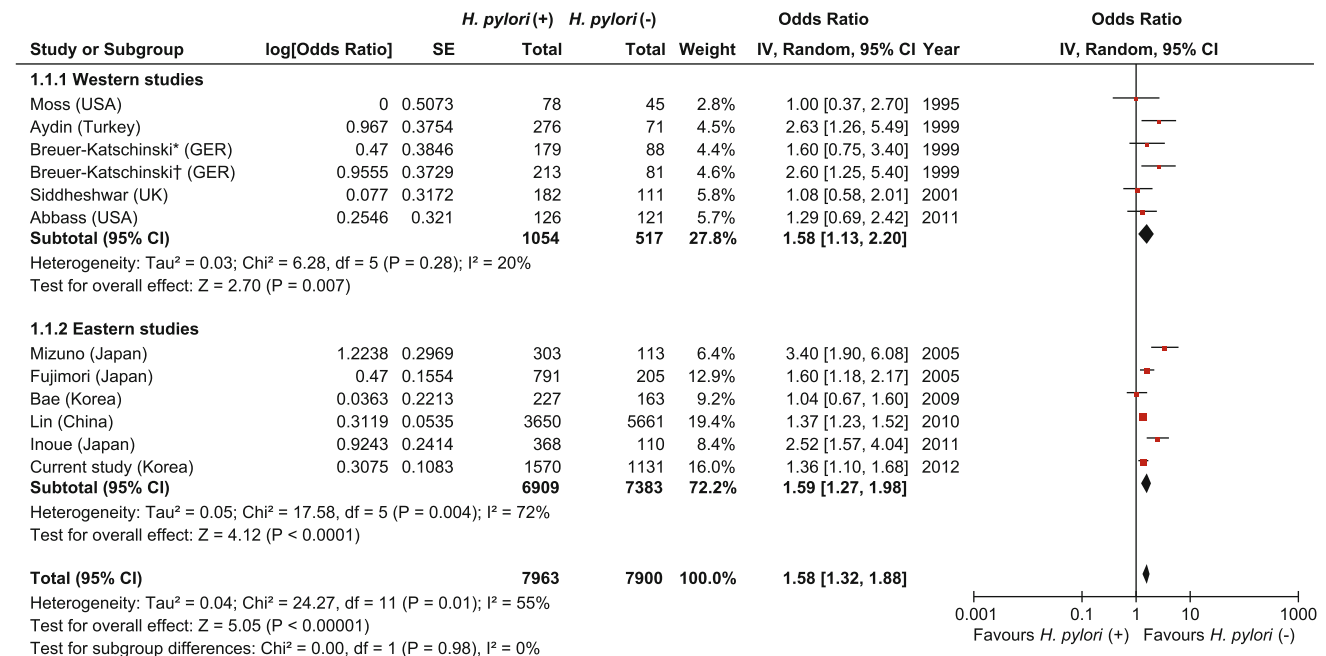


Fig. 2 Forest plot for the *H. pylori* infection as a risk factor for colorectal adenoma. *Multi-center cases versus hospital controls. †Multi-center cases versus population controls

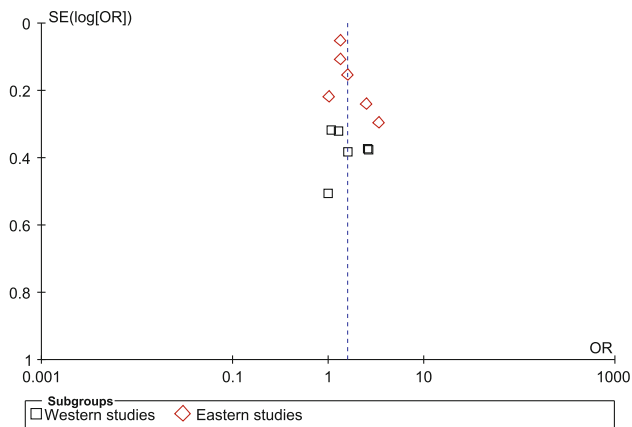


Fig. 3 Funnel plot of the ten studies which were included

suggested that the inconsistent relationship between *H. pylori* infection and colorectal neoplasms found in previous studies may be due to the varying frequency of CagA strains in the populations studied. The Cag pathogenicity island, vacuolating cytotoxin, and the outer-membrane blood group antigen-binding adhesion proteins were reported to be associated with the induction of malignant disease [4]. Second, other possible pathogenic mechanisms by which *H. pylori* exerts its malignant potential are hypergastrinemia accompanying *H. pylori* infection, which has been suggested to have a role in the development of colorectal carcinogenesis [11]. Persistent exposure to *H. pylori* for several years may result in gastric atrophy and transformation of gastric mucosal cells into gastrin-producing cells, which increase plasma level of gastrin and luminal release of gastrin [8–10, 12, 33]. Gastrin has a trophic effect on epithelial cell growth and proliferation not only in the stomach, but also in colon and rectum [11]. Thorburn et al. [34] showed that serum hypergastrinemia was associated with a 3.3-fold increase in the relative risk of developing CRC, with 8.9 % of CRCs attributable to increased serum gastrin levels. Therefore, gastrin may have a role in the development of colonic adenomas and the adenoma-carcinoma sequence. Gastrin effects are thought to be mediated by CCKB (CCK-2) receptors, which have been detected in CRC tissues [35]. Colucci et al. [36] demonstrated increased transcriptional activity of the COX-2 gene followed by prostaglandin E2 production in a human CRC cell line after CCKB receptor activation by gastrin-17. Another possible mechanism is that *H. pylori* carriage can also affect the normal gastrointestinal flora as a consequence of progressive chronic gastritis with glandular atrophy and decreased acid production, which might further influence colorectal carcinogenesis [30].

Our study has several limitations. Although we enrolled the average-risk health check-up patients and adjusted for potential confounders, the extent to which the results of this analysis can be applied to populations with different

sociodemographic characteristics is unclear because this study was performed at a single center with a cohort composed of ethnic Korean individuals. Therefore, we performed a meta-analysis, but there still existed the heterogeneity in study designs, and data collection as major confounding factors. Second, it was a cross-sectional study and therefore, precluded any assessment of causality of the reported association. Third, in the analysis of risk factors, we were unable to adjust for dietary variables. These variables may also play an important role in risk for *H. pylori* infection and colorectal adenoma. Fourth, the serology for *H. pylori* infection has reportedly provided highly reliable results [37]. However, the diagnostic accuracy of serology test for detection of *H. pylori* antibodies has been reported to be lower compared to a direct test, such as ^{13}C -UBT or stool antigen tests, especially with respect to excluding *H. pylori* infection. In addition, the diagnostic accuracy of serological kits for *H. pylori* infection that were made in Western countries has been reported to be lower when used among Asian populations [38]. Although our validation test of *H. pylori* serology compared with ^{13}C -UBT revealed to be satisfactory for examining *H. pylori* infection, we could not obtain the complete concordance between *H. pylori* serology and ^{13}C -UBT, which may also affect the results of our results.

The relation between *H. pylori* infection and colorectal carcinogenesis is far less convincing than for gastric carcinoma. Inconsistency of epidemiological evidence in the association between colorectal adenoma and *H. pylori* infection renders the effects of *H. pylori* on colorectal carcinogenesis hypothetical. This study indicates that *H. pylori* infection increased the risk of overall and advanced colorectal adenoma, especially located on the proximal colon. Since *H. pylori* infection can increase the risk of colorectal adenoma, especially advanced adenomas, the medical community should take into account that a preventive strategy is needed, for example, screening colonoscopy should be more aggressively applied to these patients. Furthermore, elucidating the pathophysiological role of *H. pylori* in the development of CRC is highly warranted.

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Conflict of interest No conflicts of interest exist.

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