RESEARCH ARTICLE

Helicobacter pylori Infection and the Risk of Colorectal Adenoma and Adenocarcinoma: an Updated Meta-analysis of Different Testing Methods

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Abstract

  Background and Aims: *Helicobacter pylori* infection may be associated with an increased risk of colorectal carcinoma. However, as most studies on this subject were relatively small in size and differed at least partially in their designs, their results remain controversial. In this study, we aimed to carry out a meta-analysis to evaluate the potential association of *H. pylori* infection with colorectal adenoma and adenocarcinoma risk, covering all of the different testing methods. **Methods:** We conducted a search in PubMed, Medline, EBSCO, High Wire Press, OVID, and EMBASE covering all published papers up to March 2013. According to the established inclusion criteria, essential data were then extracted from the included studies and further analyzed by a systematic meta-analysis. Odds ratios were employed to evaluate the relationship between *H. pylori* infection and the risk of colorectal neoplasms. **Results:** Twenty-two studies were included, and the odds ratio for the association between *H. pylori* infection and colorectal cancer was 1.49 (95% confidence interval 1.30-1.72). No statistically significant heterogeneity was observed. Publication bias was ruled out. **Conclusion:** The pooled data suggest *H. pylori* infection indeed increases the risk of colorectal adenoma and adenocarcinoma.

  Keywords: *Helicobacter pylori* - colorectal adenoma - adenocarcinoma - risk - meta-analysis

Introduction

Colorectal cancer is a major cause of cancer-related morbidity and mortality; it is the 3rd most common malignancy and 4th most common cause of cancer mortality worldwide (Tenesa et al., 2009). Despite important advances in its detection, surgical treatment, and chemotherapy, the prognosis for colorectal cancer patients remains poor when accompanied by recurrence and metastasis (Jemal et al., 2009). Therefore, prevention of these cancers may be better than a cure, so identifying risk factors for colorectal cancer is necessary.

Specific genetic and molecular alterations in colonic epithelial cells result in the inactivation of tumor suppressor genes, such as APC, DCC, DPC4, and p53, along with the activation of oncogenes (Fearon et al., 1990). These genetic mutations lead to the transformation of normal epithelium into dysplastic epithelium with increased proliferation, resulting in the development of adenomatous polyps, which have the malignant potential to progress to adenocarcinoma. In addition, external or environmental factors presumably play a significant role, and inflammatory bowel diseases, obesity, alcohol consumption, and certain dietarypatterns, which have been termed the 'processed meat pattern', the 'prudent vegetable pattern', and the 'high-sugar pattern' (Zhu et al., 2013), have all been implicated as risk factors for the development of either colonic adenomas or carcinomas.

Helicobacter pylori is a gram-negative bacterium and a well-known pathogen in the human stomach (De Luca et al., 2004). Chronic infection and subsequent inflammation from *H. pylori* is a known cause of peptic ulcer disease, and its association with gastric cancer has led to its being classified as a class 1 carcinogen by the World Health Organization (Lochhead et al., 2007). Although the relationship between *H. pylori* and gastric pathologies has been extensively studied, its association with colorectal cancer is not well understood.

Several previous reports have studied the relationship between *H. pylori* and colorectal adenoma and adenocarcinoma. The majority of these studies used positive serology as a marker for *H. pylori* infection, while comparatively few studies also used the 13C-urea breath test, urease test, or histological diagnosis of biopsied gastric specimens. However, conflicting data have been obtained. Hence, whether *H. pylori* infection is a risk factor for colorectal adenoma and adenocarcinoma remains largely uncertain. Therefore, we carried out an updated systematic review and meta-analysis of published studies to evaluate the association between*H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma.

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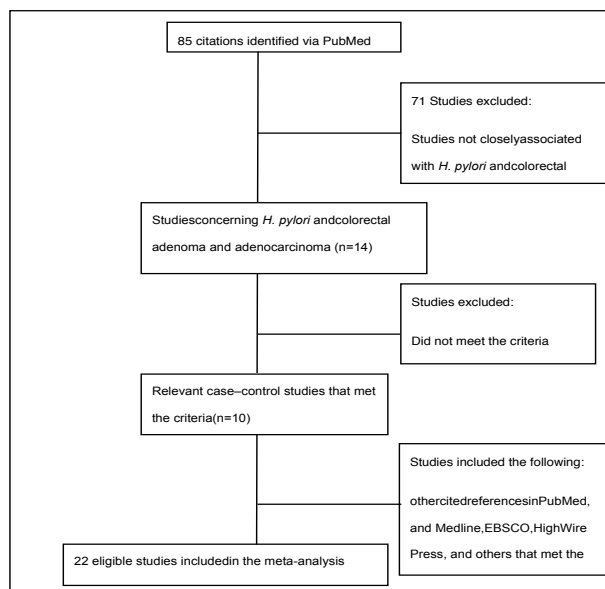
Figure 1. Study Selection Flowchart

Materials and Methods

We carried out a literature search without a language limitation in PubMed, Medline, EBSCO, High Wire Press, OVID, and EMBASE, including all published papers up to March 2013. We used a combination of the following keywords: *Helicobacter pylori*, colorectal carcinoma, colorectal cancer, colon cancer, and colonic neoplasms. The reference lists of the relevant articles were also searched for appropriate studies. A search for unpublished literature was not performed.

Study Selection

We included studies that met the following inclusion criteria: 1) studies examining the prevalence of colorectal neoplasms in *H. pylori*-infected patients and controls; 2) observational studies; 3) sample sizes, odds ratios (ORs), and their 95% confidence intervals (CIs) or information from which such data could be inferred; 4) statistically acceptable methods of data collection and analysis; and 5) the use of an internal comparison when calculating the risk estimates. We excluded studies that did not meet the inclusion criteria. Studies were included or excluded based on a consensus between two authors (D.Y.B and X.S.X).

Data Extraction

The data were extracted and entered into a database. The extraction was performed independently by two reviewers. For conflicting evaluations, an agreement was reached through discussion. For data not provided in the main text, the relevant information was obtained by contacting the corresponding authors when possible.

Statistical Analysis and Research Experience

The OR of colorectal cancer risk associated with the presence of *H. pylori* was estimated for each study. For the detection of any possible sample size bias, the OR and its 95% CI of each study was plotted against the number of participants in that study. A χ^2-based Q statistic test was performed to assess heterogeneity. If the results of the
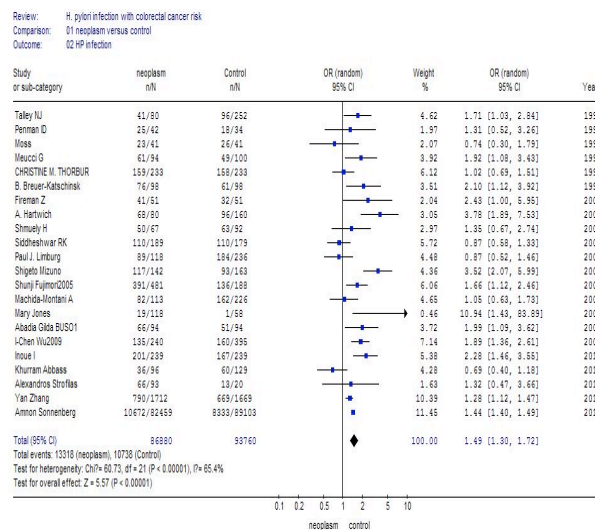

Figure 2. Study Estimates, Summary Estimate, and Their 95% CI for Association Between *H. pylori* Infection and Colorectal Adenoma and Adenocarcinoma in Published Studies. For each study, the study-specific odds ratio and the summary estimate obtained by a random-effects model are shown

heterogeneity test provided a *p*>0.05, the ORs were pooled according to the fixed-effect model (Mantel-Haenszel). Otherwise, the random-effect model (DerSimonian and Laird) was used. The significance of the pooled ORs was determined by a Z-test. A funnel plot was used to detect publication bias. Statistical analysis was undertaken using the program Review Manager 4.2. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Liu et al., 2012; Shu et al., 2012; Xu et al., 2012; Xu et al., 2012; Yu et al., 2012; Zhan et al., 2012; Zhan et al., 2012; Zhang et al., 2012; Chen et al., 2013; Dai et al., 2013; Deng et al., 2013; Gu et al., 2013; Huang et al., 2013; Liu et al., 2013; Liu et al., 2013; Liu et al., 2013; Lu et al., 2013; Sun et al., 2013; Wei et al., 2013; Wu et al., 2013; Yang et al., 2013; Yin et al., 2013; Yin et al., 2013).

Results

Literature Search and Meta-analysis Databases

From the primary electronic database (PubMed), a total of 85 potentially relevant papers concerning colorectal neoplasms were screened for the relevant data on *H. pylori* infection. After careful review, papers that were not closely associated with *H. pylori* and colorectal adenoma and adenocarcinoma were excluded. This resulted in the selection of ten relevant case-control studies. In addition, the reference lists of the relevant articles were also searched for appropriate studies. We conducted a manual search in PubMed, Medline, EBSCO, High Wire Press, OVID, EMBASE, and other databases, which resulted in 12 more studies that met the inclusion criteria. Thus, 22 case-control studies were included in this study (Figure 1).

H Pylori Infection Increases Risk of Colorectal Adenoma and Adenocarcinoma

Table 1. Characteristics of 22 Studies Investigating the Association Between *Helicobacter pylori* Infection and the Risk of Colorectal Adenoma and Adenocarcinoma

First author, Year	Country	Design	Method of HP detection	Sample size	Number of cases	Control number	Type of controls	Neoplasm HP(+)	Control HP(+)	OR	95 % CI	Matching variables	Mean age - cases	Mean age - control	Sex and HP	Location and HP
Talley et al., 1991	USA	Case-control study	IgG	332	80	252	76 healthy volunteers, 176 noncancer patients	41	96	1.17	1.03-2.84	Convenience sample	NA (60.5)	NA (61.0)		
Penman et al.,1994	UK	Case-control study	14C urea breath test and serology (IgG)	76	42	34	Hospital non-cancer patients awaiting surgery	25	18	1.31	0.52-3.26	Matched for age and gender	68.3 (44-93)	67.7 (36-88)		
Moss et al., 1995	USA	Case-control study	IgG	82	41	41	Colonoscopy participants	23	26	0.74	0.3-1.79	Matched for age, gender, and race	68.0 (30-90)	65.0 (31-85)		
Meucci et al., 1997	Italy	Case-control study	IgG	194	94	100	Hospital noncancer patients	61	49	1.92	1.08-3.43	Matched for age and gender	65.3 (35-81)	63.1 (37-81)		
Christine et al., 1998	USA	Case-control study	IgG	466	233	233	Participants of the health insurance program	159	158	1.02	0.69-1.51	Matched for age, gender, education, region, and date of serum collection	NA (52.7)	NA (52.6)		
B. Breuer-Katschinski et al, 1999	Germany	Case-control study	IgG	182	98	98	Population-based: registered inhabitants in the same city	76	61	2.1	1.12-3.92	Matched for age and gender	62.2 (9.1)	62.6 (9.1)		
Fireman et al., 2000	Israel	Case-control study	IgG	102	51	51	Endoscopy patients with iron deficiency or abdominal pain	41	32	2.43	1.00-5.95	Convenience sample	66.6 (36-87)	62.7 (20-93)		
A. Hartwich et al., 2001	Poland	Case-control study	UBT, IgG	240	80	160	Not specified	68	96	3.78	1.89-7.53	Matched for age and gender	64.0 (47-82)	63.0 (47-82)		
Shmuely et al., 2001	Israel	Case-control study	IgG, CagA	159	67	92	47 other cancer patients and 45 TEE controls	50	63	1.35	0.67-2.74	Convenience sample	69.0 (64-76)	NA (57-73)		
Siddheshwar et al., 2001	England	Case-control study	IgG	368	189	179	Patients with gastrointestinal symptoms but normal colonoscopies or barium enema results; patient with diverticular disease or angiodysplasia	110	110	0.87	0.58-1.33	Matched for age, gender, social class	72.0 (42-91)	61.0 (27-89)		
Paul et al., 2002	Finland	Case-control study	Whole cell assay, CagA assay	354	118	236	Noncancer male smokers	89	184	0.87	0.52-1.46	Matched for age, study center and date of serum collection	59.1 (5.3)	58.8 (4.9)		
Shigeto et al., 2005	Japan	Case-control study	IgG	305	142	163	Patients who underwent colonoscopy	117	93	3.52	2.07-5.99	Matched for age and gender	HP(+) 58.5	HP(-) 62.7		
Shunji et al., 2005	Japan	Cross-sectional study	13C-urea breath test, urease test, or histological diagnosis of biopsied gastric specimens, at least one method	669	481	188	Without tumors	391	136	1.66	1.12-2.46	Matched for age	NA (40-80)	NA (40-80)	More females, but not statistically significant	Not statistically significant
Mary et al., 2007	UK	Case-control study	Immunohistochemistry	176	118	58	Patients had biopsies for non-specific gastrointestinal symptoms, iron deficiency investigation or diarrhea, but with normal colorectal tissue	19	1	10.9	1.43-83.89	Not matched		51.60 (22-86)	More females in each group	
Ai et al., 2007	Japan	Case-control study	IgG, CagA	339	113	226	Health check-up program participants who were confirmed to be cancer-free	82	162	1.05	0.63-1.73	Matched for age, gender, and residence	59.6	59.5		
Buso et al., 2009	Japan	Case-control study	IgG	188	94	94	Normal colonoscopies	66	51	1.99	1.09-3.62	Matched for age and gender	59.79 ± 12.25	58.98 ± 11.55	A significant difference for women (P = 0.03)	HP(+) was significantly greater in the cases with distal adenomas than in the controls (P = 0.038).
I-Chen et al., 2009	Taiwan	Case-control study	CagA	635	240	395	Community based control: healthy subjects who voluntarily participated in one large multi-year study of childhood neoplasms at the same period of this study	135	160	1.89	1.36-2.61	Matched for age and gender	64.5 ± 12.7	40.2 ± 6.2		
Izumi et al., 2011	Japan	Case-control study	Serum antibodies	478	239	239	Population controls: n participants of the health check-up program, confirmed to be colorectal neoplasm-free	201	167	2.28	1.46-3.55	Matched for age	49.9 (3.9)	49.4 (4.3)		Distal adenoma risk was significantly increased by the presence of H. pylori infection
Khurram et al., 2011	USA	Cross-sectional study	Rapid urease test (CLO test) or histopathology	192	63	129	Without colorectal adenoma and adenocarcinoma	36	60	0.69	0.40-1.18	Matched for age	HP(+) 59.5 (14.3) HP(-) 58.7 (11.2)	NA	Not statistically significant	Not statistically significant
B. Breuer et al., 1999	Greece	Case-control study	IgG, CagA	113	93	20	Population who were scheduled for hernia	66	13	1.32	0.47-3.66	Demographically matched	69.1 ± 10.1	64.2 ± 14.8	Not statistically significant	Statistically significant
Yan et al., 2012	Germany	Case-control study	IgG	3381	1712	1669	Population-based: randomly selected from lists of residents supplied by population registries	790	669	1.28	1.12-1.47	Matched for age, sex, and county of residence	68 (33-94)	69 (34-98)	Not statistically significant	Not statistically significant
Sonnenberg et al., 2013	USA	Case-control study	histopathology	156000	82459*	89103	Population-based: patients who had undergone both a colonoscopy and an esophago-gastro-duodenoscopy, but with hyperplastic polyps or with no polyps	10672	8333	1.44	1.40-1.49	Demographically matched	NA	NA		

We established a database according to the extracted information from each article (Table 1). The first author, publication year, country of origin, type of design, numbers of cases and controls, matching conditions, prevalence of *H. pylori* in each group, OR, adjustment for confounders and mean age, and other relevant data are presented.

Several measures can detect the *H. pylori* infection status, such as enzyme-linked immunosorbent assay (ELISA), 13C-urea breath test, rapid urease test, and histological diagnosis of biopsy specimens (Korkmaz et al., 2013). One or more of these were used in all 22 studies, and other necessary information is listed in the forest plots of this meta-analysis. We also considered the confounding factors, but the 21 primary manuscripts contained insufficient data for subgroup analyses of the confounding factors.

Test of Heterogeneity

We analyzed the heterogeneity of the included studies. The test value of χ^2 was 60.73, with 21 degrees of freedom. The I-square value is another index to test for heterogeneity; in our study, I-square was 65.4% and $p<0.05$. Thus, a random-effect model was used.

Quantitative Data Synthesis
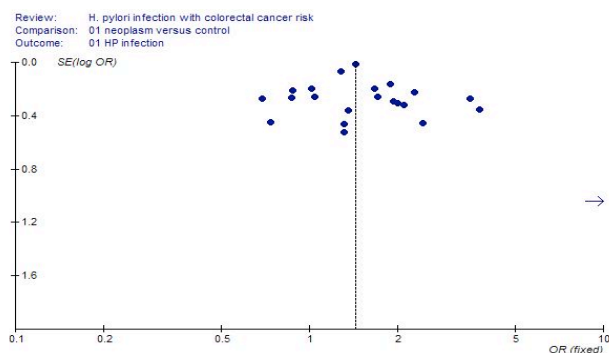
To evaluate the

Figure 3. Funnel Plot for 22 Published Studies

possible relationship between *H. pylori* infection and colorectal cancer risk, the data available for our meta-analysis were obtained from 22 studies of 86880 cases and 93760 controls, of which 13318 cases and 10738 controls were *H. pylori* positive. As shown in Figure 2, the overall OR was 1.49 (95% CI 1.30-1.72), and the test for the overall effect Z value was 5.57 ($p<0.05$).

Sensitivity Analysis

To compare the differences and to evaluate the sensitivity of the meta-analysis, we also report the results of a fixed-effect model for *H. pylori* and colorectal cancer risk: the combined OR was 1.44 (95% CI 1.40-1.48), similar to the results obtained from the random-effect model. Additionally, we conducted one-way sensitivity analysis by excluding any single included study. An I-square value was then estimated for the evaluation of the stability of the meta-analysis. As a consequence, the I-square value ranged from 59.8% to 67.0% when any single study was omitted from the meta-analysis, suggesting the meta-analysis was robust.

Bias Diagnostics

The funnel plot (Figure 3) was symmetrical, which suggests little influence of publication bias on the results of the meta-analysis.

Discussion

In this study, we evaluated the possible relationship between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma by carrying out a quantitative meta-analysis. The results suggest that *H. pylori* infection may be a risk factor forcolorectal adenoma and adenocarcinoma.

H. pylori is a noncarcinogenic bacterium in most mouse models, but it has significant effects on the transforming growth factor β1 (TGFβ1)/Rag-2-deficient mouse model (Engle et al., 2002; Erdman et al., 2003). These mice do not develop inflammation or cancers in germ-free or specific pathogen-free environments; however, they develop both colonic adenomas and carcinomas when colonized with *H. pylori* (Engle et al., 2002; Erdman et al., 2003).

The mechanism by which *H. pylori* infection increases the risk of colorectal cancer has not yet been elucidated. One proposed mechanism of carcinogenesis is inflammation and disruption of the cell cycle. *H. pylori* contains a pathogenicity island, cytotoxin-associated

gene A (CagA); the presence of CagA in *H. pylori* has been associated with a higher risk of gastric cancer (Beales et al., 1996; Maeda et al., 2007). CagA binds and activates human phosphatase (SHP2), which then acts as an oncoprotein promoting cell growth (Lochhead et al., 2007). In addition, hypergastrinemia, which is associated with *H. pylori* colonization, has been hypothesized as a possible mechanism for tumorigenesis because of its trophic effect on the intestinal mucosa (Mulholland et al., 1993; Sobhani et al., 1993; A. Hartwich et al., 2001). Several studies have evaluated this hypothesis and have found increased levels of circulating gastrin in patients colonized with *H. pylori* who are diagnosed with colorectal cancer (Thorburn et al., 1998; A. Hartwich et al., 2001; Georgopoulos et al., 2006). The results of these studies are difficult to interpret because it is unclear whether the hypergastrinemia is a result of *H. pylori* colonization and independent of the colorectal neoplasia.Another possible mechanism of carcinogenesis involves a reduction in the gastric acid provoked by the chronic gastritis caused by *H. pylori*, which could alter the normal gastrointestinal flora.

Our study has several limitations. First, the differences in the methods used to test for *H. pylori* infection (the 22 studies used such different measures as serum antibodies, 13C-urea breath test, rapid urease test, histological diagnosis of biopsied gastric specimens, and combinations), and these differences may have led to the detection of different indicators of *H. pylori*. Indeed, the different methods may have different shortcomings. Although the use of serum antibodies to study the association of *H. pylori* infection with colorectal cancer is the most common type of test, it is problematic because of the high prevalence of *H. pylori* among the general population, particularly in endemic regions, and because seropositivity does not necessarily indicate active colonization by this microbe. Polymerase chain reaction (PCR) methods have also been used to evaluate the presence of *H. pylori* in colorectal malignancies. Like serologic studies, studies using PCR methods have been equivocal. Two studies found that detection of *H. pylori* via PCR was significantly higher in colorectal adenocarcinoma tissues compared with normal colorectal tissues (Grahn et al., 2005; Jones et al., 2007), but a third study found that only 1.2% of malignant colorectal tissue samples were positive for *H. pylori*, compared with 6% of normal tissues (Bulajic et al., 2007). The 13C-urea breath test has 97% sensitivity and specificity in *H. pylori* detection (Chen et al., 2003); however, as in PCR-based studies, the evidence is not convincing. Fujimori et al. (2005) reported that even subjects infected with *H. pylori* occasionally test seronegative, especially the elderly; when *H. pylori* status is evaluated only by *H. pylori* IgG seropositivity, the risk of *H. pylori*-associated gastric cancer would appear to be lower than the de facto risk. Thus, such bias might have affected previous studies. Taking the 13C-urea breath test, rapid urease test, and histological examination together, the results suggest that *H. pylori* infection may increase the risk of colorectal adenoma and adenocarcinoma development in subjects aged 40-80 years. However, other studies have also shown that there is no significant association between *H.*

pylori positivity by 13C-urea breath tests and colorectal adenomas (Liou et al., 2006).

Second, excepting the studies of Mizuno et al. (2005) and Fujimori et al. (2005), who excluded patients with a history of *H. pylori* eradication therapy, none of the other studies included in this meta-analysis mentioned whether the patients had previously used antibiotic therapies. Compared with control subjects, colorectal cancer patients were more likely to use antibiotic therapies. If colorectal cancerpatients who have been treated with *H. pylori* eradication therapy were recruited into these case-control studies, a false-negative result of the relationship could be concluded.

Third, due to the inevitable heterogeneity among the selected studies, the pooled results of our meta-analysis could incorporate the biases of the individual studies and generate new sources of bias. The majority of the studies included in the present meta-analysis were conducted in Western countries, with only a few representing Asian nations (mainly Japan); thus, it is uncertain whether the present findings are generalizable to different geographic locations and populations, especially Asian and African populations. Further studies should provide information on the potential risk differences based upon geographic location or ethnic differences. Furthermore, not all of the studies adjusted for age, sex, country of birth, educational level, smoking status, average lifetime physical activity, average lifetime alcohol consumption, body mass index, diabetes, history of colorectal cancer in first-degree relatives, or the regular use of nonsteroidal anti-inflammatory drugs. More in-depth studies are warranted to make more detailed comparisons.

There were also strengths to our analysis. We were able to analyze the potential relationship between sex and the location of colorectal neoplasms with *H. pylori*. In all, six studies clarified sex-based differences. Buso et al. (2009) found that female subjects infected with *H. pylori* had a significantly stronger risk of colorectal tumor development. Fujimori et al. (2005) and Jones et al. (2007) found that the OR for colorectal adenocarcinoma in *H. pylori*-infected female subjects was higher than that in males, but this result was not statistically significant. The greatest risk for colonic adenomas in women is associated with hormonal factors. The mean age of female patients examined in these studies was over 50 years, so they most likely had reduced sex hormone levels. Estrogen and progesterone reduce the risk of adenomas and adenocarcinomas in the colon. A possible interaction between *H. pylori* and low levels of female sex hormones has been described in the development of colonic neoplasias in women. Five of the included studies clarified location-based differences. Zhang et al. (2012) showed the elevation of risk to be essentially confined to left-sided colorectal cancer, with an odds ratio of 1.22 (95% CI 1.02, 1.45); this suggests that *H. pylori* infection may be associated with a small yet relevant risk increase in the left colorectal region. Buso et al. (Buso et al., 2009) and Inoue et al. (2011) showed that distal adenoma risk was significantly increased in the presence of *H. pylori* infection. Meanwhile, Inoue et al. (2011) found that the proximal adenoma risk increased in a stepwise manner

with the presence and progression of *H. pylori*-related chronic gastritis, showing a maximal and significant increase in the presence of *H. pylori* CagA (crude OR 4.51, 95% CI 1.43-14.2). Fujimori et al. (2005) and Abbass et al. (2011) found no significant association between the location of colorectal neoplasms and *H. pylori* status.

In conclusion, our analysis suggests that *H. pylori* infection may be a risk factor for colorectal adenoma and adenocarcinoma. However, further studies, including prospective, long-term examinations of large groups of patients, are needed to evaluate the exact clinical outcomes in the colon of *H. pylori* and its eradication, as well as to examine the biological basis of *H. pylori*-associated neoplasia in the gastrointestinal tract.

Acknowledgements

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