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Original Article

Helicobacter pylori infection increases the risk of colorectal adenoma and adenocarcinoma: evidence from an updated meta-analysis

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Abstract: Many studies have reported the association of *Helicobacter pylori* infection with an increased risk of colorectal cancer, but the results remain inconsistent. In this study, we conducted a meta-analysis to explore the relationship between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma. We searched the PubMed database and the reference lists of included articles to identify studies relating to the association between *H. pylori* infection and risk of colorectal cancer. Odds ratios were employed to evaluate the relationship between *H. pylori* infection and the risk of colorectal cancer. 16 studies with 14176 cases and 33552 controls were finally included into the meta-analysis. Overall, *H. pylori* infection can increase the risk of colorectal adenoma and adenocarcinoma (OR = 1.793, 95% CI 1.298-2.477), although statistically significant heterogeneity was observed. Publication bias was ruled out. Subgroup analysis revealed that the positive correlation did not differ by geographic variation in terms of western country and eastern country, but might vary when divided further. Our meta-analysis was able to demonstrate a positive association in Asian and European countries, but was underpowered to determine the risk of colorectal neoplasia associated with *H. pylori* in the USA population. This meta-analysis demonstrates a possible indication of relationship between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma.

Keywords: Helicobacter pylori, colorectal cancer, colorectal adenoma, colorectal adenocarcinoma, meta-analysis

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in males and the second in females worldwide [1]. Developing countries such as China have underwent rapid increase in the incidence of CRC due to demographical changes and the implementation of western lifestyle during the past two decades. As a major public health burden in the world, the cause of CRC is still unclear. Epidemiological studies have revealed that some risk factors and interactions between genetic and environmental factors may play important roles in colorectal carcinogenesis [2]. It is estimated that up to 90% of CRCs originate from colorectal adenomas via the sequence from adenoma to adenocarcinoma as a consequence of several molecular events, which largely originates from a relatively benign adenoma that finally progressed to cancer [3]. The etiological factors and pathogenesis underlying CRC development appear to be complex and heterogeneous.

Helicobacter pylori, a well-known pathogen in the human stomach, was first discovered by *Marshall and Warren* in 1982 in patients with chronic gastritis and gastric ulcer [4]. Chronic infection of *H. pylori* combined with subsequent inflammation is a well-documented cause of peptic ulcer disease, and due to its association with gastric cancer, *H. pylori* has been defined as a class I carcinogen by the World Health Organization [5]. Evidence from both *in vivo* and *in vitro* studies show *H. pylori* colonization might also trigger tumor formation in extra-gastric target organs, such as the large bowel. This seems plausible for the following hypotheses: First, *H. pylori* induces inflammation in the colonic mucosa and alters the normal gastroin-

testinal flora, thus collectively produces a direct carcinogenic effect. Second, *H. pylori* increased the gastrin release, which has a trophic effect on colonic epithelial cell growth and proliferation. Third, *H. pylori* caused systemic hypergastrinaemia, which promotes the proliferation of normal and neoplastic colonic epithelium [6-11].

Recently, many studies have focused on the association between *H. pylori* and CRC. Some concluded that *H. pylori* infection is associated with an increased risk of CRC while others yielded a null association. Hence, there is still insufficient evidence to implicate *H. pylori* with CRC. Furthermore, several pertinent large observational studies have been published in recent years. Therefore, we carried out an updated meta-analysis of published studies to evaluate the association between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma.

Materials and methods

Data sources and searches

To collect all published reports describing the incidence and prevalence of CRC in *H. pylori* infected population and the controls, we performed a comprehensive literature search using the PubMed database up to October 2015 with the following search terms: Helicobacter pylori and (colorectal or colon or rectum or large bowel) and (cancer or carcinoma or neoplasm or neoplasia or adenoma or polyp). The search was augmented by manual search of the reference lists of included articles for potentially relevant studies that may have been missed with the computer-assisted strategy. We performed the final search on 20th October 2015, and the search was performed in duplicate. Two authors reviewed the search results to reduce the possibility of missing the published papers. For data missing, we contacted the authors for the relevant information.

Study selection

We included studies that met the following inclusion criteria: 1) studies examining the prevalence of colorectal neoplasms in *H. pylori* (+) patients and *H. pylori* (-) controls; 2) study design: clinical trials including cohort studies, cross-sectional studies and case-control studies; 3) statistically acceptable methods of data collection and analysis; 4) results: the prevalence of patients with colorectal adenoma and adenocarcinoma according to *H. pylori* infection or the risk of colorectal adenoma and adenocarcinoma in *H. pylori* (+) patients compared to *H. pylori* (-) patients; 5) sample sizes, odds ratios (ORs), and their 95% confidence intervals (CIs) as well as those with enough information for calculating these data; 6) full manuscript publication or abstract with enough information in English language. We excluded studies that did not meet the inclusion criteria. Full texts were obtained for studies that were potentially relevant. In addition, a recursive search of the reference articles of included studies was conducted manually to identify possibly relevant articles. Studies were included or excluded based on the consensus between two authors (Ye Fan and Yue Guan) and when necessary with the assistance of Zhaojun Xu. All selections were performed in duplicate.

Data extraction

Two trained investigators (Ye Fan and Yue Guan) independently extracted the data from the included studies via manual review using a predefined form including the following items: the first author's name, year of publication, country of origin, study design, the *H. pylori* detection method, the numbers of cases and controls, characteristics (age and sex) of the participants, and so on. Discrepancy between data extracted was resolved via consensus. The results were compared, and disagreements were discussed among all authors and resolved with consensus. All data were crosschecked.

Statistical analysis

OR with 95% CI were retrieved from the published manuscripts or calculated from crude data in some studies if not available in the manuscript. The pooled estimates were calculated using the inverse variance weighted estimation method. Heterogeneities of included studies were calculated based on *Q* statistics using the *Mantel-Haunszel* weight and I^2 statistics [12]. Heterogeneity between studies was confirmed when studies yield a p value of <0.10 and an I^2 value >50%. For studies with heterogeneity, a random effects model was applied based on the *Der Simonian-Laird* method [13].

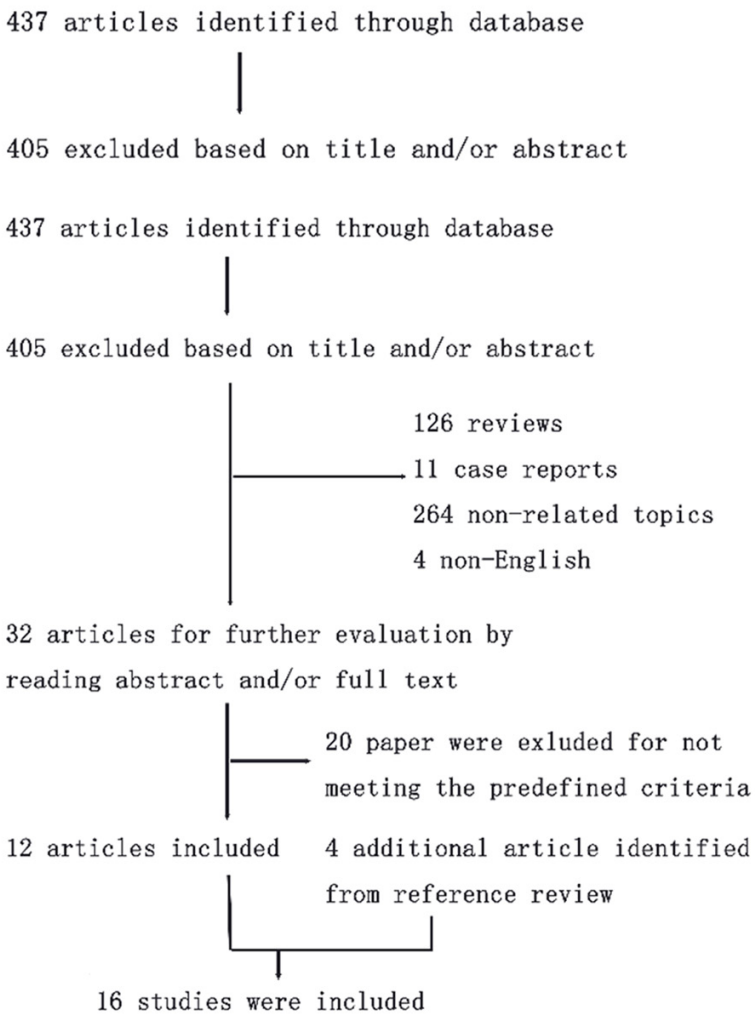


Figure 1. Study flow diagram.

The potential publication bias was assessed graphically using Begg's and Egger's test and funnel plots. All analyses were performed with Stata software (version 12.0). All *p* values were two-sided, and $P<0.05$ implicated statistical significance. To explore possible explanations for heterogeneity, we conducted stratified analyses by geographic variation. To evaluate the sensitivity of the meta-analysis, we utilized one-way sensitivity analysis to evaluate the stability of the meta-analysis by sequentially excluding one study each time to test the robustness of the main results.

Results

The initial search identified 437 citations, of which 32 were considered of potential value. The full text of these 32 articles was retrieved for detailed evaluation. After further evaluation, 20 of them were subsequently excluded from the meta-analysis. Four additional articles were included from the reference reviews. Finally, 16 articles published from December 1991 to June 2015 were used in the meta-analysis. These studies included a total of 14176 cases of *H. pylori* (+) patients and 33552 *H. pylori* (-) controls (**Figure 1** shows the study flow diagram). The study by *Shruti Patel et al* provided two groups of data involving Hispanic population and other races respectively. Both groups of data were included in our meta-analysis. The study performed by *Michael Selgrad et al* applied two methods detecting *H. pylori* infection and provide the corresponding OR separately. Both data were included in our meta-analysis. Among the sixteen studies, three in Germany [14, 21, 28], three in Japan [15, 17, 20], two in Taiwan China [16, 18], four studies were performed in the United States [22, 23, 25, 26], two in Korea [19, 24], one in Turkey [27] and one in UK [29] (**Table 1**). In summary, seven studies were performed in the Eastern countries and nine in the Western countries. There were seven case-control studies, seven cross-sectional studies and two cohort studies.

Quantitative data synthesis

Fourteen studies provided OR estimates for the association between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma, one study provided HR and one provided RR. A total of 14176 cases of *Hp* (+) cases and 33552 *Hp* (-) controls were included in the analysis. The OR ranged from 0.594 (95% CI 0.315-1.120) to 2.73 (95% CI 1.76-4.24). Most studies indicated an increase in the risk of CRC (OR>1). The summary OR was 1.793 (95% CI

Table 1. Characteristics of the included studies in the meta-analysis

First author	Year	Country	Design	Setting	Method of HP detection	Number of cases (HP+)	Number of controls (HP-)	Neoplasm cases	Neoplasm controls	OR	95% CI	Quality score
Selgrad M [14]	2014	Germany	Case-control	Single center	Serological (IgG)	138	239	69	64	2.73	1.76-4.24	7
Selgrad M [14]	2014	Germany	Case-control	Single center	Serological CagA	138	239	NA	NA	2.25	1.29-3.94	7
Mizuno S [15]	2014	Japan	Cross-sectional	Single center	Serological (IgG)	10	107	9	50	3.4	1.90-6.08	7
Lin YL [16]	2010	Taiwan China	Cross-sectional	Single center	Rapid urease test	3654	5657	NA	NA	1.366	1.230-1.517	7
Inoue I [17]	2011	Japan	Case-control	Single center	Serology	368	110	201	38	2.52	1.57-4.05	7
Hsu WY [18]	2014	Taiwan China	Retrospective cohort	Multi-center	Pathological or microscopic findings by endoscopy	6022	24088	35	85	1.73 (HR)	1.08-2.77	7
Hong SN [19]	2012	Korea	Cross-sectional	Single center	Serology (IgG) UBT	1253	942	317	189	1.35	1.10-1.66	6
Fujimori S [20]	2005	Japan	Cross-sectional	Single center	Histopathology rapid urease test or urea breath test 527	142	391	90	1.6	1.18-2.02	6	
Epplein M [21]	2013	Germany	Cohort study	Multi-center	Serological (IgG)	486	72	422	63	1.03	0.59-1.77	7
Brim H [22]	2014	USA	Case-control	Single center	Serological (IgG)	366	890	158	298	1.5	1.1-2.0	7
Shruti P [23]	2014	USA	Cross-sectional	Single center	Histologically	236	562	102	38	1.04	0.67-1.61	7
Shruti P [23]	2014	USA	Cross-sectional	Single center	Histologically	137	198	15	27	0.81	0.41-1.59	7
Bae RC [24]	2009	Korea	Case-control	Single center	Several (biopsy, CLO, test, UBT)	204	142	21	23	0.594	0.315-1.120	6
Abbass K [25]	2011	USA	Cross-sectional	Single center	Rapid urease test or histopa-thology	96	96	30	25	1.29	0.69-2.42	7
Moss SF [26]	1995	USA	Cross-sectiona	Single center	Serology	210	95	93	18	1.0	0.37-2.70	6
Aydin A [27]	1999	Turkey	Case-control	Single center	Serology	206	61	70	10	2.63	1.26-5.48	6
Breuer-Katschinski B [28]	1999	Germany	Case-control	Multi-center	Serology	117	61	62	27	1.6 (RR)	0.8-3.4	7
Siddheshwar RK [29]	2001	UK	Case-control	Multi-center	Serology	146	90	36	21	1.08	0.58-1.99	7

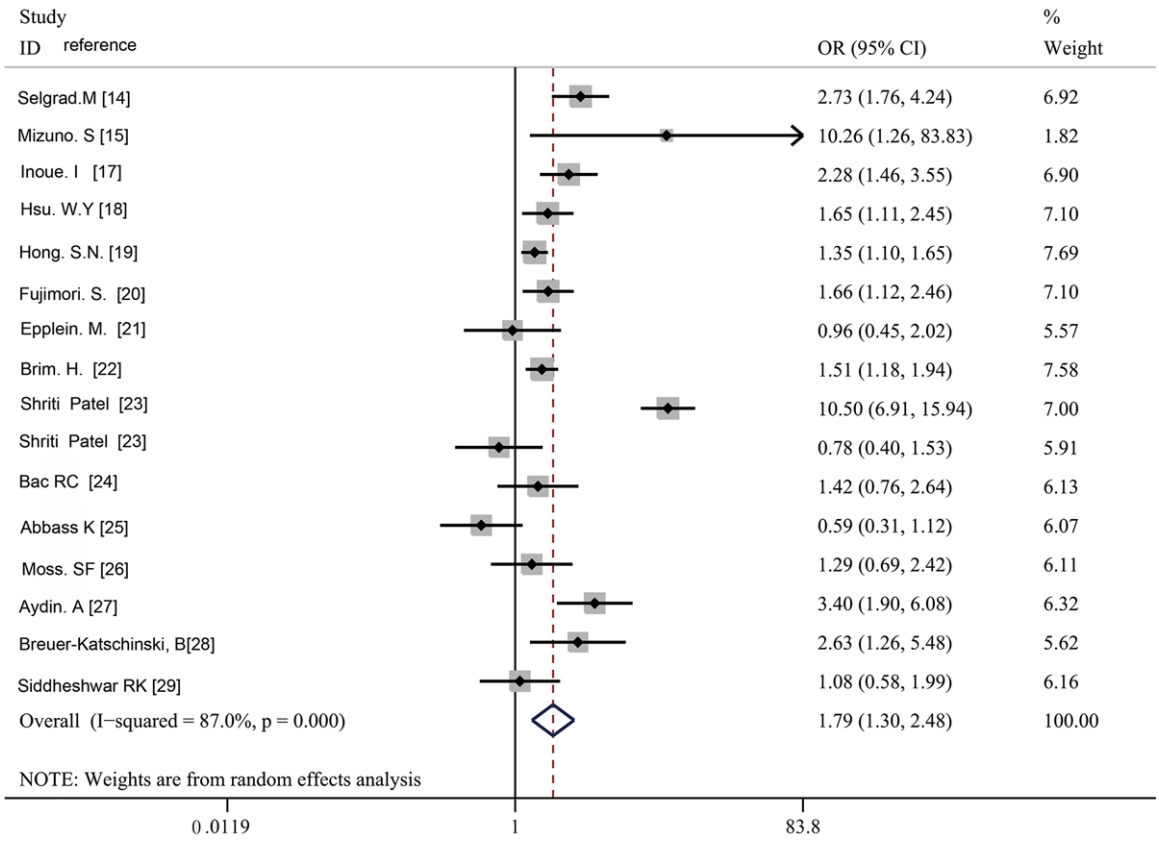
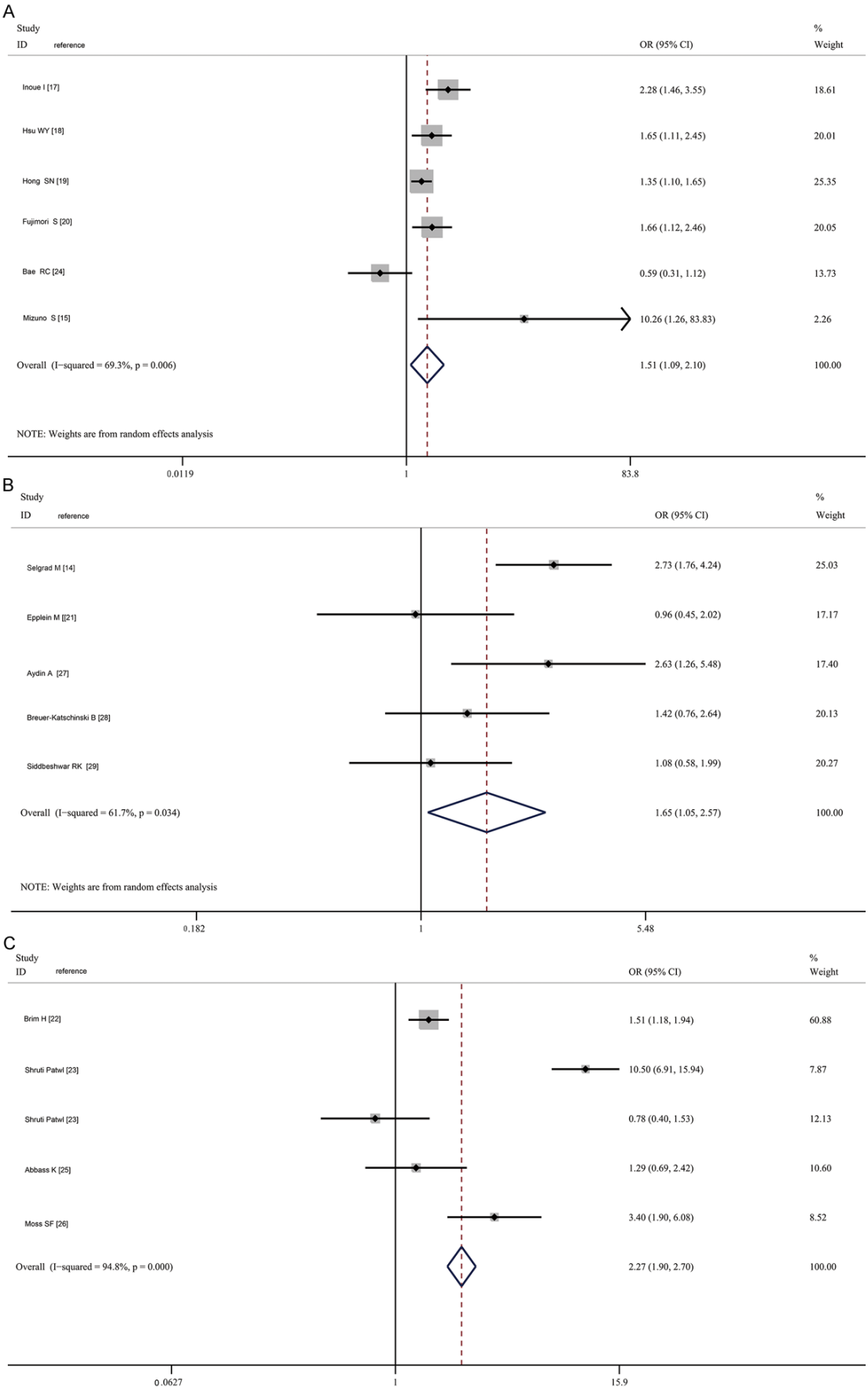


Figure 2. Random effects meta-analysis of studies evaluating Helicobacter pylori infection and colorectal carcinoma risk.

1.298-2.477; $P_{heterogeneity}$ = 0.008, I^2 = 87%, Q = 115.5) (**Figure 2**). The heterogeneity across studies was marginal (P = 0.01). Due to geographic differences in prevalence and strains of *H. pylori* infection, subgroup analysis according to studies conducted in Western and Eastern countries were performed.

In subgroup analysis using Western country studies, nine studies with a total of 2,138 cases and 2364 controls were included. Meta-analysis of these studies showed that the *H. pylori* infected patients have an increased risk of colorectal adenoma and adenocarcinoma with a pooled OR of 1.924 (95% CI 1.155-3.205). When omitting the data collected from the Hispanics population in the study performed by *Shruti Patel et al*, the pooled OR for Western country studies was 1.597 (95% CI 1.178-2.165; $P_{heterogeneity}$ = 0.004, I^2 = 64.4%, Q = 22.50). In subgroup analysis using Eastern country studies, six studies with a total of 8,384 cases and 250,531 controls were included. The study performed by *Ying-Lung Lin et al* was excluded from this analysis as it did not provided the exact number of patients developing neoplasm. Similar to the results of the overall positive association, the pooled ORs for Western and Eastern country studies were 1.924 (95% CI 1.155-3.205) and 1.510 (95% CI 1.087-2.099) respectively. The study by *Shruti Patel et al* provided two groups of data, and the data collected from the US Hispanic population bring great heterogeneity to this meta-analysis. With the absence of this data, pooled OR overall was 1.563 (95% CI 1.266-1.929; $P_{heterogeneity}$ = 0.000, I^2 = 64.6%, Q = 39.59), and the pooled OR for Western country studies was 1.597 (95% CI 1.178-2.165; $P_{heterogeneity}$ = 0.004, I^2 = 64.4%, Q = 22.50). Studies show that the *H. pylori* prevalence of the Hispanics population was 40.9%, which is higher than the non-Hispanics populations; while the adenoma detection rate was 14.5%, which is significantly lower than their non-Hispanic counterparts. And this may partly explain this result. Meta-analysis of these studies revealed that *H. pylori*-infected patients have


A
Study
ID reference
OR (95% CI)
% Weight
Inoue I [17] 2.28 (1.46, 3.55) 18.61
Hsu WY [18] 1.65 (1.11, 2.45) 20.01
Hong SN [19] 1.35 (1.10, 1.65) 25.35
Fujimori S [20] 1.66 (1.12, 2.46) 20.05
Bae RC [24] 0.59 (0.31, 1.12) 13.73
Mizuno S [15] 10.26 (1.26, 83.83) 2.26
Overall (I-squared = 69.3%, p = 0.006) 1.51 (1.09, 2.10) 100.00
NOTE: Weights are from random effects analysis
0.0119
1
83.8
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Study
ID reference
OR (95% CI)
% Weight
Selgrad M [14] 2.73 (1.76, 4.24) 25.03
Epplein M [[21] 0.96 (0.45, 2.02) 17.17
Aydin A [27] 2.63 (1.26, 5.48) 17.40
Breuer-Katschinski B [28] 1.42 (0.76, 2.64) 20.13
Siddbeshwar RK [29] 1.08 (0.58, 1.99) 20.27
Overall (I-squared = 61.7%, p = 0.034) 1.65 (1.05, 2.57) 100.00
NOTE: Weights are from random effects analysis
0.182
1
5.48
C
Study
ID reference
OR (95% CI)
% Weight
Brim H [22] 1.51 (1.18, 1.94) 60.88
Shruti Patwl [23] 10.50 (6.91, 15.94) 7.87
Shruti Patwl [23] 0.78 (0.40, 1.53) 12.13
Abbass K [25] 1.29 (0.69, 2.42) 10.60
Moss SF [26] 3.40 (1.90, 6.08) 8.52
Overall (I-squared = 94.8%, p = 0.000) 2.27 (1.90, 2.70) 100.00
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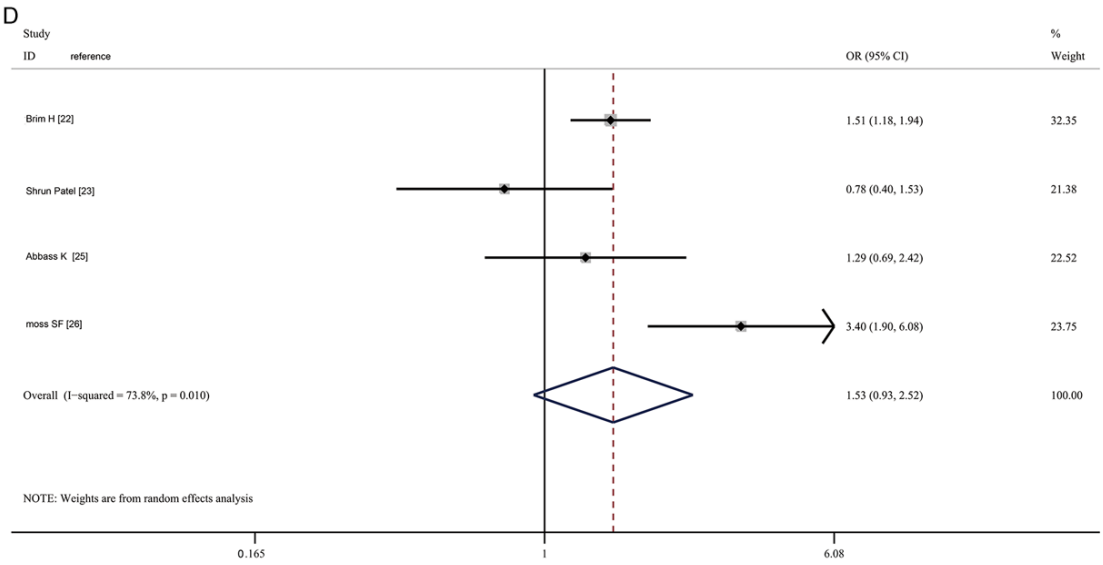

Figure 3. Stratified meta-analyses for Helicobacter pylori infection and risk of colorectal carcinoma and adenocarcinoma risk. A: Asian countries, B: European countries, C: America, D: American result without the data of US Hispanic population.

an increased risk of colorectal adenoma and adenocarcinoma with a pooled OR of 1.510 (95% CI 1.087-2.099), although there exist significant heterogeneity (P = 0.004).

In order to further explore the source of heterogeneity, we conducted subgroup analysis by the criteria of the European country, Asian country and America. Results show that, for the Asian part, the same result was yielded as their included studies was same (**Figure 3A**). For the European countries analysis, positive association with a pooled OR of 1.645 (95% CI 1.053-2.571) was seen, and the heterogeneity ($P_{heterogeneity}$ = 0.034, I^2 = 61.7%, Q = 10.44) still exsit (**Figure 3B**). In the American group of five studies, a pooled OR of 2.253 (95% CI 0.911-5.575) was achieved, indicating that the association between *H. pylori* infection and the risk of CRC was not significant, though there exist considerable heterogeneity ($P_{heterogeneity}$ = 0.000, I^2 = 94.8% Q = 11.43) (**Figure 3C**). When we exclude the data from the US Hispanic population in the study of *Shruti Patel et al*, the pooled OR was 1.534 (95% CI 0.934-2.519), indicating an association with no significance, however the heterogeneity was slightly reduced ($P_{heterogeneity}$ = 0.010, I^2 = 73.8%, Q = 11.43) (**Figure 3D**). Considering the limited number of studies included, we should take the conclusion critically and carefully.

Sensitivity analysis

To confirm the stability of the results, we evaluated the influence of one single study on the main results by systematically excluding each study and recalculated the overall summary estimates. Results show that no single study markedly influenced the significance of the summary ORs and the leave-one-out ORs ranged from 1.563 to 1.925, similar to the results obtained from the random-effect model. The statistical significance of the results was not altered when any single study was omitted, and thus confirmed the robustness of the results. *I*-square value was then estimated for the evaluation of the stability of the meta-analysis. Results yielded was that the *I*-square value ranged from 64.6% to 87.9% when one single study was omitted from the meta-analysis, suggesting heterogeneity was exist across studies in the meta-analysis.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias. The shape of the funnel plots for studies on the association between *H. pylori* infection and the risk of colorectal adenoma and adenocarcinoma did not reveal any evidence of obvious asymmetry (**Figure 4**). The *p*-value for Egger's linear regression method (*P* = 0.666) indicated

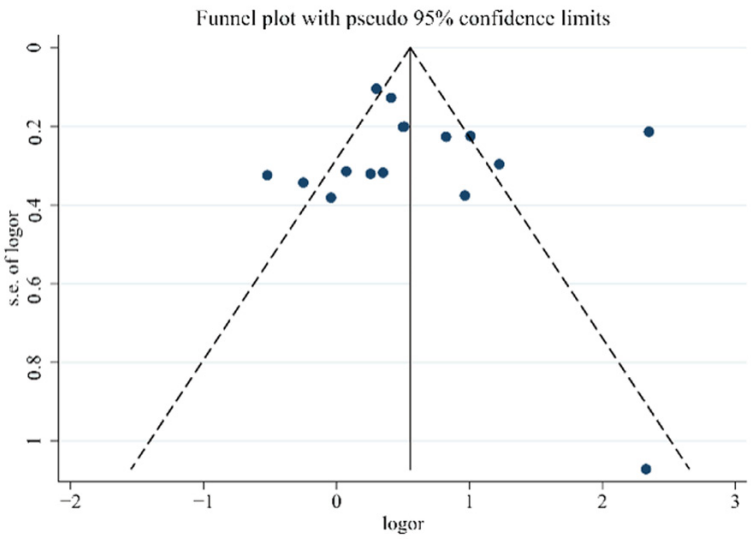

Figure 4. Funnel plot of included studies.

that there was no statistical evidence of publication bias.

Discussion

The previous meta-analysis performed by *Q. Wu et al* published in 2013 reported a positive association between *H. pylori* infection and the risk of colorectal neoplasia [30]. And further, another meta-analysis conducted by *F. Wang et al* suggested a promoting effect of *Helicobacter pylori* on the risk of CRC, as well as the possible trigger point during the sequence that *H. pylori* might exert its effect [31]. *Sung Noh Hong et al* carried out a cross-sectional study and meta-analysis concerning whether *H. pylori* infection increases the risk of colorectal adenomas [19]. Results from both the cross-sectional study and their meta-analysis showed that *H. pylori* infection was associated with a modest increase in the risk for colorectal adenoma. Since the number of studies focusing on the risk of colorectal neoplasia in *H. pylori* positive and negative population is limited, and the meta-analysis of *Sung Noh Hong et al* included inadequate number of studies, thus collectively making the hypothesis that increased risk of CRC exist in *H. pylori* infected population much open to debate. In our meta-analysis we aimed to explore whether an increased risk of colorectal adenoma and adenocarcinoma in *H. pylori* infected population compared with those negative exist from an updated evidence.

Hence, we included all eligible studies and chose OR to represent the association of *H. pylori* infection and the risk of CRC in the meta-analysis. The pooled ORs yielded was estimated to be 1.793 with a 95% CI from 1.298 to 2.477, which is similar to that from previous meta-analysis. Since significant heterogeneity was observed across studies, which might lower the reliability of the summary OR estimates. We then explored the source of heterogeneity by subgroup analysis and sensitivity analysis.

As is well known, the prevalence of *H. pylori* infection in the general populations was different in Western and Eastern countries. The pooled ORs for the Western and Eastern studies in the meta-analysis were very similar and the difference was not significant, indicating that there was no geographic disparity in the association between *H. pylori* infection and the risk of colorectal neoplasia. Considering the heterogeneity was still marginal in the Western countries group, we further divided studies of this group into European country group and American group. The pooled OR of 1.645 (95% CI 1.053-2.571) in European country indicated a positive association. However, a summary OR of 2.253 (95% CI 0.911-5.575) failed to demonstrate a positive association in American studies. When the data from the US Hispanic population was omitted, the pooled OR of 1.534 (95% CI 0.934-2.519) still demonstrated a null association. Subgroup analysis shows that this analysis was underpowered to detect a difference in risk of colorectal neoplasia in American population. Sensitivity analysis showed that the result of meta-analysis would not be altered by any single study, and thus confirming robustness of our study. Of note, the heterogeneity could be significantly lowered by excluding the data from the US Hispanic population in the study of *Shruti Patel et al*, and so were the situations in subgroup analysis that involved this data.

H. pylori prevalence was higher in the US Hispanic population but CRC detection rate was lower than their non-Hispanic subjects. There was no evidence in the Hispanics for an association between *H. pylori* infection and

adenoma detection. One possible explanation might be confounding factors such as genetic differences that leads to induced incidence of adenoma in Hispanics. High prevalence of *H. pylori* colonization among controls and relatively low detection rate of CRC in the cases might mutually conceal an association between *H. pylori* and CRC, especially when the association is not very strong. Additionally, discrepancies between studies may be due to the assay applied in the detection of *H. pylori* infection. The majority of studies reporting a positive association between *H. pylori* and colorectal adenomas and adenocarcinomas have utilized seroprevalence of *H. pylori* while in the study of *Shruti Patel et al* histologically proven H. pylori infection was applied. The reason for the inconsistent findings of studies in non-Hispanic subjects and Hispanic population may due to small sample sizes, difference in study participants, and an inadequate consideration of potential confounding variables. Since genetic and environmental factors that may play a role in CRC etiologies may vary among different races, further studies assessing the relationship between *H. pylori* infection and colonoscopy findings are warranted.

This meta-analysis has several limitations. First, the majority of studies included were retrospective observational studies, making them susceptible to recall and selection bias. Second, significant heterogeneity was observed across studies, which might lower the reliability of the pooled OR estimates. Third, although we have included all the available studies in this meta-analysis, the number of studies and participants is still limited.

In conclusion, we report a positive association between *H. pylori* infection and an increased risk of colorectal adenoma and adenocarcinoma from an updated evidence. This association is positive in Asian and European countries, but is inconclusive in American population.

Disclosure of conflict of interest

None.

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References

[1] Gao CM, Ding JH, Li SP, Liu YT, Cao HX, Wu JZ, Tang JH, Tajima K. Polymorphisms in XRCC1 gene, alcohol drinking, and risk of colorectal cancer: a case-control study in Jiangsu Province of China. Asian Pac J Cancer Prev 2014; 14: 6613-8.

[2] Mahmoudi T, Karimi K, Arkani M, Farahani H, Nobakht H, Dabiri R, Asadi A, Zali MR. Parathyroid hormone gene rs6256 and calcium sensing receptor gene rs1801725 variants are not associated with susceptibility to colorectal cancer in Iran. Asian Pac J Cancer Prev 2014; 15: 6035-9.

[3] Cotton S, Sharp L, Little J. The adenoma-carcinoma sequence and prospects for the prevention of colorectal neoplasia. Crit Rev Oncog 1996; 7: 293-342.

[4] Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984; 1: 1311-5.

[5] Lochhead P, El-Omar EM. Helicobacter pylori infection and gastric cancer. Best Pract Res Clin Gastroenterol 2007; 21: 281-97.

[6] Limburg PJ, Stolzenberg-Solomon RZ, Colbert LH, Perez-Perez GI, Blaser MJ, Taylor PR, Virtamo J, Albanes D. Helicobacter pylori seropositivity and colorectal cancer risk: a prospective study on male smokers. Cancer Epidemiol Biomarkers Prev 2002; 11: 1095-9.

[7] Buso AG, Rocha HL, Diogo DM, Diogo PM, Diogo-Filho A. Seroprevalence of Helicobacter pylori in patients with colon adenomas in a Brazilian university hospital. Arq Gastroenterol 2009; 46: 97-101.

[8] Konturek SJ, Konturek PC, Hartwich A, Hahn EG. Helicobacter pylori infection and gastrin and cyclooxygenase expression in gastric and colorectal malignancies. Regul Pept 2000; 93: 13-9.

[9] Grahn N, Hmani-Aifa M, Frans en K, Soderkvist P, Monstein HJ. Molecular identification of Helicobacter DNA present in human colorectal adenocarcinomas by 16S rDNA PCR amplification and pyrosequencing analysis. J Med Microbiol 2005; 54: 1031-5.

[10] Bulajic M, Stimec B, Jesenofsky R, Kecmanovic D, Ceranic M, Kostic N, Schneider-Brachert W, Lowenfels A, Maisonneuve P, Löhr JM. Helicobacter pylori in colorectal carcinoma tissue. Cancer Epidemiol Biomarkers Prev 2007; 16: 631-3.

[11] Jones M, Helliwell P, Pritchard C, Tharakan J, Mathew J. Helicobacter pylori in colorectal neoplasms: is there an aetiological relationship? World J Surg Oncol 2007; 5: 51.

[12] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[13] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[14] Selgrad M, Bornschein J, Kandulski A, Hille C, Weigt J, Roessner A, Wex T, Malfertheiner P. Helicobacter pylori but not gastrin is associated with the development of colonic neoplasms. Int J Cancer 2014; 135: 1127-31.
[15] Mizuno S, Morita Y, Inui T, Asakawa A, Ueno N, Ando T, Kato H, Uchida M, Yoshikawa T, Inui A. Helicobacter pylori infection is associated with colon adenomatous polyps detected by high-resolution colonoscopy. Int J Cancer 2005; 117: 1058-9.
[16] Lin YL, Chiang JK, Lin SM, Tseng CE. Helicobacter pyloriinfection concomitant with metabolic syndrome further increase risk of colorectal adenomas. World J Gastroenterol 2010; 16: 3841-6.
[17] Inoue I, Mukoubayashi C, Yoshimura N, Niwa T, Deguchi H, Watanabe M, Enomoto S, Maekita T, Ueda K, Iguchi M, Yanaoka K, Tamai H, Arii K, Oka M, Fujishiro M, Takeshita T, Iwane M, Mohara O, Ichinose M. Elevated risk of colorectal adenoma with Helicobacter pylori-related chronic gastritis: a population-based case-control study. Int J Cancer 2011; 129: 2704-11.
[18] Hsu WY, Lin CH, Lin CC, Sung FC, Hsu CP, Kao CH. The relationship between Helicobacter pylori and cancer risk. Eur J Intern Med 2014; 25: 235-40.
[19] Hong SN, Lee SM, Kim JH, Lee TY, Kim JH, Choe WH, Lee SY, Cheon YK, Sung IK, Park HS, Shim CS. Helicobacter pylori infection increases the risk of colorectal adenomas: cross-sectional study and meta-analysis. Dig Dis Sci 2012; 57: 2184-94.
[20] Fujimori S, Kishida T, Kobayashi T, Sekita Y, Seo T, Nagata K, Tatsuguchi A, Gudis K, Yokoi K, Tanaka N, Yamashita K, Tajiri T, Ohaki Y, Sakamoto C. Helicobacter pylori infection increases the risk of colorectal adenoma and adenocarcinoma, especially in women. J Gastroenterol 2005; 40: 887-93.
[21] Epplein M, Pawlita M, Michel A, Peek RM Jr, Cai Q, Blot WJ. Helicobacter pylori protein-specific antibodies and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2013; 22: 1964-74.
[22] Brim H, Zahaf M, Laiyemo AO, Nouraie M, Pérez-Pérez GI, Smoot DT, Lee E, Razjouyan H, Ashktorab H. Gastric Helicobacter pylori infection associates with an increased risk of colorectal polyps in African Americans. BMC Cancer 2014; 14: 296.
[23] Patel S, Lipka S, Shen H, Barnowsky A, Silpe J, Mosdale J, Pan Q, Fridlyand S, Bhavsar A, Abraham A, Viswanathan P, Mustacchia P, Krishnamachari B. The association of H. pylori and colorectal adenoma: does it exist in the US Hispanic population? J Gastrointest Oncol 2014; 5: 463-468.
[24] Bae RC, Jeon SW, Cho HJ, Jung MK, Kweon YO, Kim SK. Gastric dysplasia may be an independent risk factor of an advanced colorectal neoplasm. World J Gastroenterol 2009; 15: 5722-5726.
[25] Abbass K, Gul W, Beck G, Markert R, Akram S. Association of Helicobacter pylori infection with the development of colorectal polyps and colorectal carcinoma. South Med J 2011; 104: 473-476.
[26] Moss SF, Neugut AI, Garbowski GC, Wang S, Treat MR, Forde KA. Helicobacter pylori seroprevalence and colorectal neoplasia: evidence against an association. J Natl Cancer Inst 1995; 87: 762-763.
[27] Aydin A, Karasu Z, Zeytinoglu A, Kumanlioglu K, Ozacar T. Colorectal adenomateous polyps and Helicobacter pylori infection. Am J Gastroenterol 1999; 94: 1121-1122.
[28] Breuer-Katschinski B, Nemes K, Marr A, Rump B, Leiendecker B, Breuer N, Goebell H. Helicobacter pylori and the risk of colonic adenomas. Colorectal adenoma study group. Digestion 1999; 60: 210-215.
[29] Siddheshwar RK, Muhammad KB, Gray JC, Kelly SB. Seroprevalence of Helicobacter pylori in patients with colorectal polyps and colorectal carcinoma. Am J Gastroenterol 2001; 96: 84-88.
[30] Wu Q, Yang ZP, Xu P, Gao LC, Fan DM. Association between Helicobacter pylori infection and the risk of colorectal neoplasia: a systematic review and meta-analysis. Colorectal Dis 2013; 15: e352-64.
[31] Wang F, Sun MY, Shi SL, Lv ZS. Helicobacter pylori infection and normal colorectal mucosa-adenomatous polyp-adenocarcinoma sequence: a meta-analysis of 27 case-control studies. Colorectal Dis 2014; 16: 246-52.