

## Original Article

# The relationship of helicobacter pylori infection and the risk of colon neoplasia based on meta-analysis

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Received September 15, 2015; Accepted December 19, 2015; Epub February 15, 2016; Published February 29, 2016

**Abstract:** In this work, we explored the correlation between *H. pylori* infection and colon neoplasia with a meta-analysis approach. We searched the PubMed database covering all published articles up to Jan 2015. Both fixed and random effects model were employed to estimate the summarized odds ratios and 95% confidence interval. Total of thirty-three studies containing 8524 cases of colon cancer and 17373 control subjects were identified. The I-square was 80%, thus, the random effects model of meta analysis was chosen. The odds ratio for the association between *H. pylori* infection and colon neoplasia was 1.63 (95% CI 1.39-1.90). In this meta-analysis work, we successfully demonstrated that *H. pylori* infection indeed increase the risk of colon cancer.

**Keywords:** *Helicobacter pylori*, colon cancer, colon neoplasia, colon polyps, meta-analysis

## Introduction

*Helicobacter pylori* is a spiral-shaped, flagellated, and micro-aerophilic Gram-negative bacillus which was first described in 1982 by Marshall and Warren [1]. *H. pylori* is thought to colonize the gastric mucosa of more than 50% of the world's population, with the higher prevalence in the developing countries [2, 3]. Although most patients are asymptomatic, persistent infection may cause chronic gastritis and gastric cancer [4, 5].

In addition to gastric cancer, many studies have also focused on the potential correlation between *H. pylori* infection and colon cancer [6-8]. As a major cause of cancer-related morbidity and mortality, colon cancer is the third most common cancer and the fourth leading cause of cancer-related death around the world. However, the existing epidemiological studies have reported widely divided opinions regarding the correlation between *H. pylori* infection and colon cancer risk. Some research reported that *H. pylori* is pathogenically linked to colon cancer, but others showed no such correlation [9, 10]. Therefore, we carried out an exhaustive meta-analysis of published studies to obtain summarized risk estimates for the strength of association of *H. pylori* infection with colon cancer risk.

## Materials and methods

We carried out a literature search in PubMed, Medline, EBSCO, OVID and High Wire Press, including all papers published by January 2015. A combination of the following keywords has been used in the search filed: *Helicobacter pylori*, colorectal carcinoma, colorectal cancer, colon cancer, colorectal polypus, and colonic neoplasm. In addition, the reference lists of the relevant articles were also searched for appropriate studies.

### Study selection

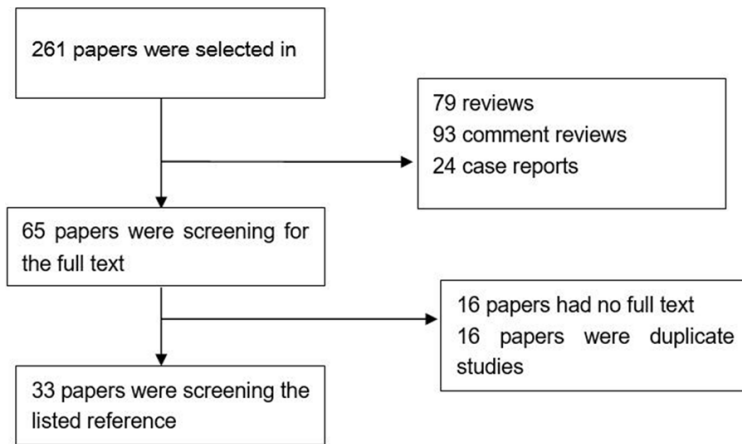
Searching criteria was pre-defined prior to the literature search; thus, eligible studies would be selected in this meta-analysis when they meet all the following criteria: 1) Studies examining the prevalence of colorectal neoplasm in *H. pylori*-infected patients and controls; 2) Published as a full article; 3) Used a case-control, nested case-control or cross-sectional with retrievable data; 4) Reported OR estimates with corresponding 95% confidence intervals (CIs) for the relationship between *H. pylori* and colorectal neoplasia or provided sufficient raw data to calculate crude OR and 95% CI; 5) Colorectal neoplasm should be confirmed by pathology; 6) With at least one kind of diagnostic methods for the judgment of *H. pylori* infec-

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**Table 1.** Study characteristics

No.	First author	Year	Country	Design	HP detection	Study disease	Number (case/control)	Neoplasm HP+	Control HP+	OR (95% CI)	Quality score
1	Talley	1991	USA	Case-control	IgG	Cancer	80/252	41	96	1.71 (1.03-2.84)	8
2	Penman	1994	UK	Case-control	UBT, IgG	Cancer	42/34	25	18	1.31 (0.52-3.26)	7
3	Moss	1995	USA	Case-control	IgG	Cancer	41/41	23	26	0.74 (0.3-1.79)	8
4	Meucci	1997	Italy	Case-control	IgG	Cancer and polyps	94/100	61	49	1.92 (1.08-3.43)	7
5	Thorburn	1998	USA	Nested Case-control	IgG	Cancer	233/233	159	158	1.02 (0.69-1.51)	9
6	Breuer	1999	Germany	Case-control	IgG	Cancer	98/98	76	61	2.1 (1.12-3.92)	7
7	Fireman	2000	Israel	Case-control	IgG	Cancer	51/51	41	32	2.43 (1.00-5.95)	9
8	Shmuely	2001	Israel	Case-control	IgG, CagA	cancer	67/92	50	63	1.35 (0.67-2.74)	7
9	Hartwich	2001	Poland	Case-control	UBT, IgG	Cancer	80/160	68	96	3.78 (1.89-7.53)	8
10	Siddheshwar	2001	UK	Case-control	IgG	Cancer and polyps	189/179	110	110	0.87 (0.58-1.33)	7
11	Limburg	2002	USA	Nested Case-control	whole cell, CagA	cancer	118/236	89	184	0.87 (0.52-1.46)	8
12	Konturek	2002	Poland	Case-control	IgG	cancer	50/100	43	58	4.45 (1.90-10.42)	9
13	Fujimori	2005	Japan	Cross-sectional	UBT, histology	Cancer and polyps	481/188	391	136	1.66 (1.12-2.46)	9
14	Mizuno	2005	Japan	Cross-sectional	IgG	cancer	142/163	117	93	3.52 (2.09-5.92)	6
15	Liou	2006	Taiwan	Cross-sectional	UBT, histology	Cancer and polyps	110/352	67	43	11.2 (7.11-17.6)	5
16	Georgopoulos	2006	Greece	Case-control	IgG	Cancer and polyps	78/78	62	53	1.83 (0.89-3.77)	9
17	Bulajic	2007	Serbia	Case-control	Histology	Cancer	83/40	6	13	0.16 (0.06-0.43)	8
18	D'Onghia	2007	Italy	Case-control	IgG	Cancer	29/50	13	19	1.33 (0.52-3.35)	7
19	Machida	2007	Japan	Case-control	IgG	Cancer	113/226	74	145	1.06 (0.66-1.70)	8
20	Jones	2007	UK	Case-control	Histology	Cancer and polyps	59/58	10	1	11.63 (2.10-64.45)	7
21	Zumkeller	2007	Germany	Case-control	IgG	Cancer and polyps	384/467	195	204	1.33 (1.01-1.74)	8
22	Bae	2009	Korea	Cross-sectional	UBT	Cancer and polyps	148/198	88	116	1.04 (0.67-1.60)	6
23	Buso	2009	Brazil	Case-control	IgG	Cancer and polyps	94/94	66	51	1.99 (1.09-3.61)	9
24	Engin	2010	Turkey	Case-control	IgG	Cancer	110/116	77	71	1.48 (0.85-2.57)	8
25	Lin	2010	China	Cross-sectional	IgG	Cancer	1923/7388	869	2785	1.37 (1.23-1.52)	5
26	Strofilas	2012	Greece	Case-control	IgG	Cancer	93/20	66	13	1.32 (0.47-3.67)	7
27	Hong	2012	Korea	Cross-sectional	UBT, IgG	Cancer and polyps	506/1689	318	935	1.36 (1.10-1.68)	6
28	Zhang	2012	Germany	Case-control	IgG	Cancer	1712/1669	790	669	1.28 (1.12-1.47)	8
29	Epplein	2013	USA	Case-control	IgG, IgA	Cancer	188/370	164	322	1.02 (0.60-1.72)	9
30	Nam	2013	Korea	Case-control	IgG	Cancer	127/470	87	248	1.95 (1.28-2.95)	9
31	Shmuely	2014	Israel	Cross-sectional	IgG	Cancer and polyps	112/161	84	77	3.27 (1.93-5.55)	6
32	Hassan	2014	USA	Case-control	IgG	Cancer and polyps	756/1756	266	466	1.50 (1.25-1.80)	8
33	Selgrad	2014	Germany	Case-control	IgG	Cancer and polyps	133/244	69	69	2.73 (1.76-4.24)	8

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**Figure 1.** Study flow diagram.

tion. On the other hand, any studies would be excluded if they didn't meet searching criteria or reported duplicated results that had been published in other articles. And when two papers reported the same results, the more informative publication would be selected. The methodological quality of each included study was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS). Three major parameters (selection, comparability, and exposure) of the NOS were evaluated. The NOS assigns a maximum of 2, 3 and 4 points for selection, comparability, and exposure/outcome, respectively. Therefore, scores range from 0 to 9 points. Articles with scores higher than 7 were considered of high quality (**Table 1**).

## Data extraction

To cross check the reliability of data, two investigators independently performed and verified data extraction according to a well-established protocol, namely, the first author's last name, the year of publication, the country of origin, the study design, the number of cases controls, study disease, the *H. pylori* detection method and etc. In case of conflicting evaluation results, an agreement was reached through discussion. When data were not available in the main text, relevant information would be confirmed by contacting the corresponding authors.

## Statistical analysis and research experience

The OR of colorectal cancer risk associated with the presence of *H. pylori* was estimated for each study. The  $\chi^2$ -based, Q-test and the  $I^2$  sta-

tistic were used to evaluate heterogeneity. Specifically, a significant Q statistic of  $P < 0.05$  indicated heterogeneity among studies. If the results of the heterogeneity test provided a  $P > 0.05$ , the OR were pooled according to the fixed-effect model. Otherwise, the random-effect model was used. The  $I^2$  statistic represented the percentage of the observed between-study variability that was due to heterogeneity rather than chance, and a value of  $> 50\%$  was considered to be indicative of a high level of heterogeneity.

The significance of the pooled OR was determined by a Z-test. A funnel plot was used to detect publication bias. Statistical analysis was undertaken using the program. Review Manager Version 5.2 (<http://community.cochrane.org/editorial-and-publishing-policy-resource/review-manager-revman>).

## Results

### Descriptive assessment and study characteristics

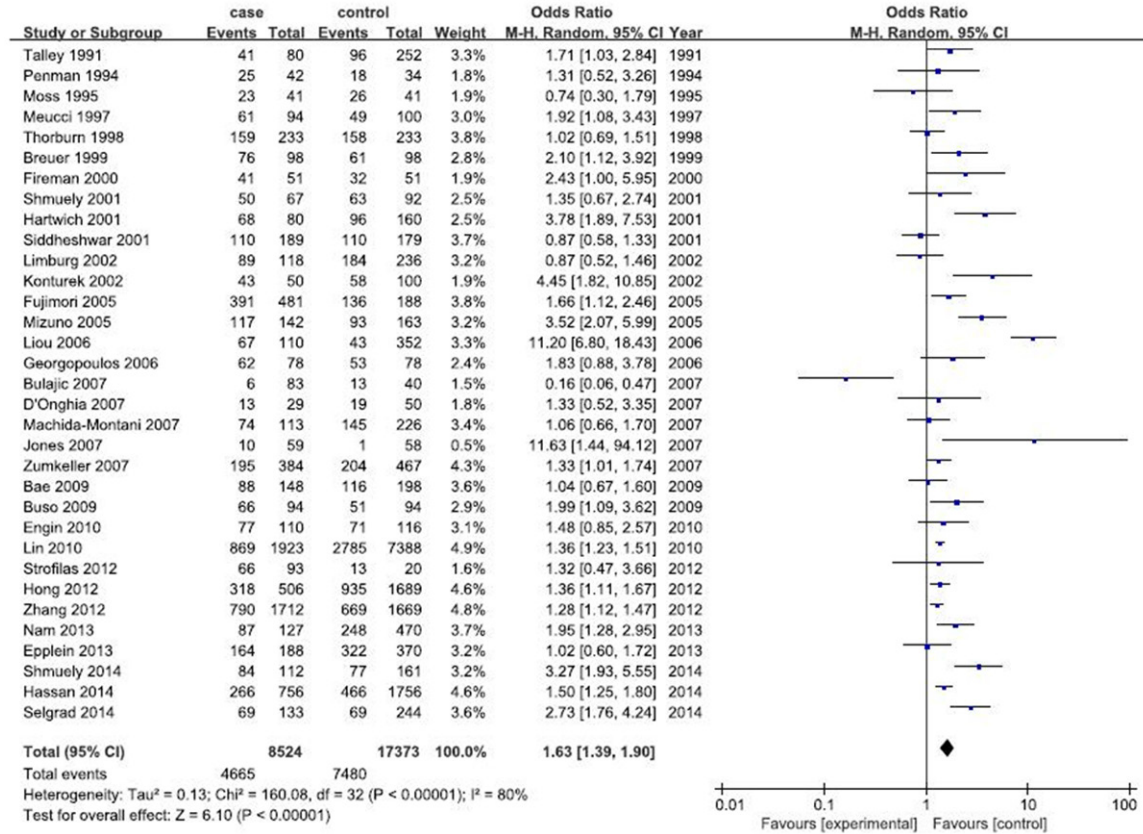
Among the 261 studies identified by using the search parameters described above, 65 studies proved to be eligible. We removed 16 duplicated studies. Another 16 studies with incomplete content were excluded as well. In addition, there were some other studies being eliminated because they were reviews/comment reviews/case reports without any original data. Eventually, we searched out 33 valid studies including 8524 cases and 17373 controls. The procedure of study selection is described in **Figure 1** and the characteristics of the studies are presented in **Table 1**.

We established a database based on the extracted information from each article (**Table 1**). The information such as first author, publication year, country of origin, type of design, numbers of cases and controls, prevalence of *H. pylori* in each group, OR, 95% CI and other relevant data has been presented.

### Meta-analysis results

**Figure 2** shows the meta-analysis results from all included studies. To minimize the effects of

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**Figure 2.** Forest plot of random effects meta-analysis of studies evaluating *H. pylori* infection and colon cancer risk. [95% confidence intervals (CI)].

**Table 2.** Sensitivity analysis and Meta-analysis results

Sensitivity Analysis	Studies Number	Z	P	OR (95% CI)
Fixed-effect Model	33	12.95	<0.00001	1.45 (1.37, 1.54)
Radom-effect Model	33	6.10	<0.00001	1.63 (1.39, 1.90)

heterogeneity (Q-value = 160.08, I<sup>2</sup> = 80%, P<0.05), the random-effect model was chosen, which showed pooled OR equal to 1.63 (95% CI 1.39-1.90, Z = 6.10, P<0.05), indicating that positive *H. pylori* status was linked to a significantly higher risk of colorectal adenoma and adenocarcinoma in patients than in controls.

### Sensitivity analysis

To compare the difference 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 1.45 (95% CI 1.37-1.54), similar to the results obtained from the random-effect model (Table 2), it also suggests that the meta-analy-

sis was reliable to a certain degree. Several subgroup analyses were conducted (Table 3). The 95% CI values were wider because fewer subjects were included. Other subgroup analyses suggested that Hp infection

might play an important role in the occurrence of colon tumor.

### Publication bias

Graphical exploration with funnel plots (Figure 3) showed that two studies [25, 27] might have significant publication bias. With publication bias being excluded, the funnel plot was shown in Figure 4, and the random-effect model OR was 1.54 (95% CI 1.37-1.74, Z = 7.06, P<0.05). It suggested little influence of publication bias on the results of the meta-analysis.

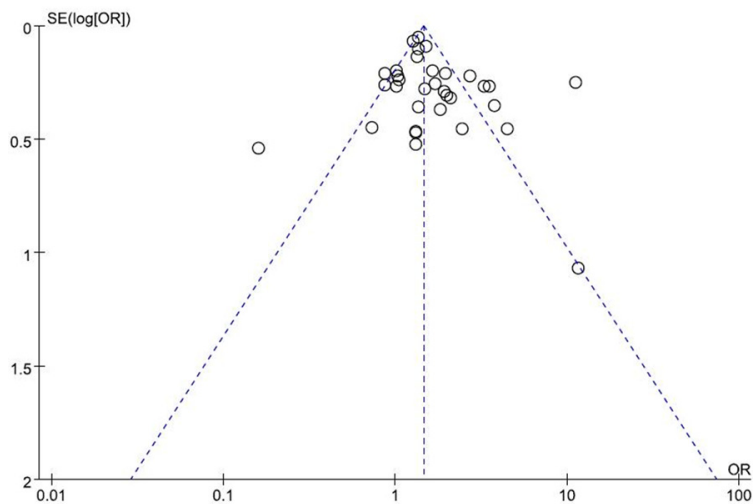
The fail-safe number (Nfs<sub>0.05</sub>) of this meta-analysis is 2446. There are at least 2446 negative studies needed to reverse the meta-analysis

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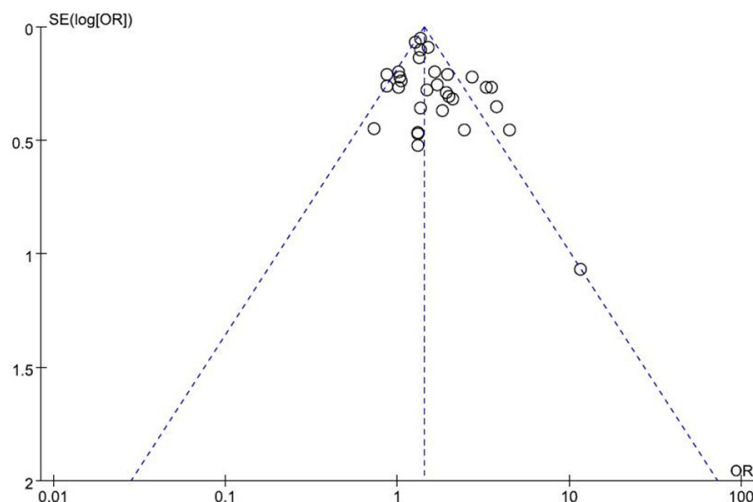
**Table 3.** Results of subgroup meta-analysis

Subgroup	NO. of studies	OR (95% CI)	$I^2$	$P^*$	Z	P
<b>Area of Source</b>						
East	6	1.34 (1.06, 1.83)	66	0.01	2.47	<0.05
West	27	1.35 (1.27, 1.74)	63	<0.05	4.96	<0.05
<b>Design</b>						
Case-control	24	1.37 (1.45, 1.68)	56	<0.05	5.45	<0.05
Cross-sectional	9	1.21 (1.02, 1.67)	58	<0.05	3.15	<0.05
<b>Category</b>						
Polyp	15	1.46 (1.68, 2.08)	48	0.02	7.88	<0.05
Cancer	19	1.57 (1.29, 1.83)	62	<0.05	4.14	<0.05
Total	33	1.63 (1.39-1.90)	61	<0.05	5.77	<0.05

\* $P > 0.05$  the fixed effects model is reported, otherwise the random effects model is reported. Several subgroup analyses were conducted.



**Figure 3.** Funnel plot of all studies included examining the relation between *H. pylori* infection and colon cancer.



**Figure 4.** The funnel plot with publication bias being excluded.

conclusion, indicating little influence of publication bias on the results of the meta-analysis.

### Discussion

*H. pylori* is a gram-negative bacterium and a well-known pathogen in the human stomach. Although the relationship between *H. pylori* and gastric pathologies has been extensively studied, its association with colorectal cancer, however, is not well understood [44] yet. Hypergastrinemia associated with *H. pylori* colonization has been hypothesized as a possible mechanism for tumorigenesis, due to its trophic effect on the intestinal mucosa. Several studies have evaluated this hypothesis and have found increased level of circulating gastrin in patients that have been diagnosed with colorectal cancer [45] and colonized with *H. pylori*. The results of these studies are difficult to interpret because there is no agreement whether the hypergastrinemia is a result of *H. pylori* colonization or it's independent of the colorectal neoplasia. Epidemiologic study suggested that there was some correlation between the prevalence of *H. pylori* and colorectal adenoma and adenocarcinoma. *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. CagA binds and activates human protein-tyrosine phosphatase-2 (SHP2), which then acts as an oncoprotein promoting cell growth [46-48].

In this study, we evaluated the possible link between *H. pylori* infection and the risk of colorectal neoplasia by carrying out a

quantitative meta-analysis. There are 33 studies (including 26 case-control studies and 7 cross-sectional studies) included in the meta-analysis, among which there are 19 positive studies and 14 negative studies.

To minimize the effects of heterogeneity that presented in the study the random-effect model was selected, which showed pooled OR equals to 1.63 (95% CI 1.39-1.90,  $Z = 6.10$ ,  $P < 0.05$ ), indicating *H. pylori* infection risk of colorectal cancer was 1.36 times of those infected.

To ensure reliability of the conclusion, we also carried out a sensitivity analysis. There was no difference in the results of the meta-analysis of fixed-effect model and random-effect model, showing that the meta-analysis result would not have been altered by either study approach. Both the funnel plot and the fail-safe number suggested that there were little influence of publication bias on the result of the meta-analysis. All of the above showed the conclusion is stable and reliable.

It's notable that our study has several limitations. First of all, several potential confounding factors such as age, gender, race and location may have not been taken into consideration. Since most studies were carried out within a specific country or area, it's uncertain whether the present findings could be applied to various geographic locations or ethnic groups. Not all of the studies have been adjusted based upon age, gender, 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. Therefore, further in-depth studies are needed to make more detailed comparisons. Furthermore, different testing methods were used for *H. pylori* infection (the 33 studies used with different measures such as IgG, UBT, CagA, whole cell, histology or combinations), and the difference may have led to the detection of different indicator of *H. pylori*.

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 out-

comes 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.

### Disclosure of conflict of interest

None.

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