

Review Article

Relationship between *Helicobacter pylori* infection and colorectal cancer: a meta-analysis of observational studies

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Abstract: *Helicobacter pylori* infection has been proposed to be associated with bowel cancers. The purpose of this meta-analysis was to evaluate the association between *H. pylori* infection and CRC. In this study, all case-control studies up to January, 2017 were identified by searching PubMed and Cochrane library. In absence of significant heterogeneity fixed-effects model (Mantel-Haenszel method) was used otherwise random effects (Der Simonian-Laird method) model was used. Subgroup analysis was performed to assess the sources of heterogeneity (CRC subtype, geographic area, and study design type). 6 case-control studies, and 4 cross-sectional studies with a total of 16,857 participants and more than 3300 incident cases of CRC were included in our meta-analysis. In overall meta-analysis, pooled analysis of 10 observational studies imply that there is an increased risk of CRC in patients with history of *H. pylori* infection. But, pooling high quality studies showed that there was no significant association between *H. pylori* infection and risk of CRC. In subgroup analysis, association between *H. pylori* infection and CRC was observed only in cross-sectional studies but not in case-control studies. Both colon and rectal cancer did not show any significant association with *H. pylori* infection. Studies conducted in Asia showed a significant positive association of risk of CRC and *H. pylori* infection. Our meta-analysis suggests that there is no conclusive evidence to show the association between risk of CRC and *H. pylori* infection, and the heterogeneity present in the existing evidence which was neglected in many of the previous meta-analysis while deriving conclusions.

Keywords: *Helicobacter pylori*, colorectal cancer, meta-analysis

Introduction

Bowel cancers are the one of the common cancer across the globe [1]. Colorectal cancer (CRC) is the fourth most common cancer in UK and USA [2, 3]. Incidence of CRC has been decreasing by 3.2% per year since 1975 [3]. This decrease in the incidence is attributed to screening and treatment of colorectal polyps. Despite of decreasing trend, CRC is still one of the top leading cancers across the world [1]. In addition, 5-year survival rate is 17% for advanced CRC posing huge burden to patients and the society [3].

Several risk factors for CRC were being studied in past two decades including smoking, ethnicity, use of NSAIDs, gender, gastric cancer, *Helicobacter pylori* infection and others [4-7].

H. pylori infection was found to be a significant risk factor for several types of cancers including lung, gastric, pancreatic, oral, colorectal and other cancers [8-11]. *H. pylori* infections are one of the leading cause of infections worldwide. Many studies assessed the relationship between *H. pylori* infection and CRC [12-21]. But the existing evidence is not conclusive because studies showed increased risk or no significant association of risk of CRC due to *H. pylori* infection. In past, there were several attempts were made to pool the existing evidence by performing meta-analysis [22-28]. However, existing meta-analysis results were prone to bias due to inclusion of small sample size studies. Moreover, few studies were also published [16, 19]. In this updated pooled analysis, we assessed the relationship between *H. pylori* infection and CRC.

Table 1. Case-control studies assessing relationship between risk of CRC and H. pylori infection

Author, year	Country	Cases	Controls	Diagnostic method for H. pylori infection	Cases with H. pylori +ve	Controls with H. pylori +ve	Study quality
Zhang 2012 [12]	Germany	1712	1669	Serology	790	582	8
Thorburn 1998 [13]	USA	250	250	Serology	159	158	7
Machida-Montani 2007 [14]	Japan	113	226	Serology	82	162	7
Limburg 2002 [15]	Finland	118	236	Serology	89	184	7
Blasé 2016 [16]	Germany	392	774	Serology	213	121	7
Epplein 2013 [17]	Germany	188	370	Serology	NR	NR	7

Table 2. Cross-sectional studies assessing relationship between risk of CRC and H. pylori infection

Author, year	Country	Participants with H. pylori +ve	Participants with H. pylori -ve	Diagnostic method for H. pylori infection	Subjects with CRC in H. pylori +ve	Subjects with CRC in H. pylori -ve	Study quality
Selgrad 2014 [18]	Germany	138	239	Serology	69	64	7
Kim 2017 [19]	South Korea	5399	3517	Serology	162	62	8
Nam 2013 [20]	South Korea	335	262	Serology	NR	NR	7
Fujimori 2005 [21]	Japan	527	142	Histopathology, rapid urease test, or urea breath test	127	27	7

Methods

Literature search

A systematic literature search was conducted in biomedical literature databases including Pub Med and Cochrane library to retrieve published literature until January 2017 on association of risk of CRC with H. pylori infection. Different search strategies were built to search the databases using keywords related to colon cancer, rectal cancer, CRC, colorectal adenocarcinoma, Helicobacter pylori, H. pylori and Campylobacter pylori without any limits. A hand search of bibliographic sections of the included studies was done to check if any relevant studies were missed in initial search.

Study selection criteria

Studies were included if it is an observation study including cross-sectional, cohort or case-control study and studied risk of CRC in patients with H. pylori infection. Studies were excluded if sufficient information to calculate effect estimate was not provided or if studies were without original data (including reviews, case reports, case series and editorials) or study sample size less than 300 participants. Study selection process involves determining the initial eligibility by screening the title and abstract and if it seems eligible, full text of the article were retrieved and reviewed independently by

two reviewers. In the event of discrepancies between the two authors, a third reviewer then independently performed a full-text review to evaluate inclusion criteria.

Data collection and management

Two reviewers independently extracted data from the included studies to minimize inter-personal bias. The following data were extracted from each included study using a pre-designed data collection form: first author's name, publication year, country, source of participants, controls matching criteria, percentage of male subjects, sample size, number of CRC and H. pylori infected patients, diagnostic methods used to assess CRC and H. pylori infection and effect estimate along with its 95% confidence interval (CI). Study quality was assessed using New Castle Ottawa scale.

Data analysis

Prior to pooling, heterogeneity was assessed. Odds ratio was considered as the effect estimate for pooling. Heterogeneity was assessed using various ways including visual examination of forest plot, Cochrane Q test and I^2 statistic. In absence of significant heterogeneity fixed-effects model (Mantel-Haenszel method) was used otherwise random effects (Der Simonian-Laird method) model was used. Subgroup analysis was performed to assess the sources of

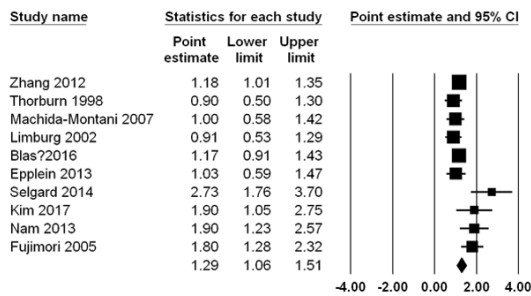


Figure 1. Forest plot depicting individual and pooled odds ratio and 95% CI.

heterogeneity. Subgroup analyses were performed according to CRC subtype (colon and rectal cancer), geographic area (Asian studies vs. rest of the world studies) and study design type (case-control vs. cross-sectional study). Sensitivity analysis was performed to assess the influence of single study on the pooled effect estimate. The publication bias was assessed using visual inspection of the funnel plot and Begg and Mazumdar adjusted rank correlation test. Dual and Tweedie's trim and fill method was used to adjust the pooled effect estimate for adjusting publication bias. Comprehensive Meta-Analysis software was used to perform statistical analyses.

Results

Study characteristics

The studies that met our inclusion criteria included 6 case-control studies [12-17] and 4 cross-sectional studies [18-21] with a total of 16,857 participants and more than 3300 incident cases of CRC published between 1998 and 2017, were used for the meta-analysis. Details of each of these studies are summarized in **Tables 1** and **2**. The studies were generally from Asia (n = 4) [12, 19-21] and Europe (n = 5) [14-18] and USA (n = 1) [13].

Main analysis

Significant heterogeneity was observed from the visual inspection of forest plot, Cochran $P < 0.01$ and I^2 of 67%. The random effect pooled OR from the 10 studies indicated that the risk of CRC is higher in patients with H. pylori infection by 29% (pooled OR H. pylori infection positive vs. negative = 1.29, 95% CI: 1.06-1.51). Effect estimates for the individual studies

and the pooled effect estimate are depicted in **Figure 1**.

Publication bias

On examining funnel plot, minimal asymmetry was evident (**Figure 2**). Similarly, Beggs test showed significant publication bias (Beggs P value -0.06). Dual and Tweedie's trim and fill method revealed that there were two missing studies. Upon using trim and fill method, effect estimate was adjusted after inclusion of missing study estimates. Adjusted pooled OR was found to be 1.15 (95% CI, 0.93-1.43) (**Figure 3**).

Sensitivity analysis

Sensitivity analysis by excluding each study at a time revealed none of the included study has a strong influence on the pooled OR as it ranges between 1.20 and 1.34 (**Figure 4**).

Subgroup analysis

Subgroup analyses were conducted to find out the source of heterogeneity (**Table 3**). Subgroup analyses were performed by the study design, region of the study conducted and site of cancer. After stratification by the subgroups, the high degree of heterogeneity was found across the study design, geographic region of the study conducted and site of cancer. When case-control studies were analyzed alone, the pooled OR was found to be 1.10 (95% CI 0.98-1.22). Whereas subgroup analysis of cross-sectional studies revealed pooled OR of 1.96 (1.61-2.30). Association between H. pylori infection and CRC was observed only in cross-sectional studies but not in case-control studies. When individual tumors according to site of organ was pooled, both colon and rectal cancer did not show any significant association with H. pylori infection. Studies conducted in Asia showed a significant positive association of risk of CRC and H. pylori infection whereas this is not the same in case of studies conducted in the rest of the world apart from Asia.

Discussion

Association between CRC and H. pylori infection is of interest in past three decades. Three possible mechanisms that supports the hypothesis of increased risk of CRC due to H. pylori

Helicobacter pylori infection and colorectal cancer

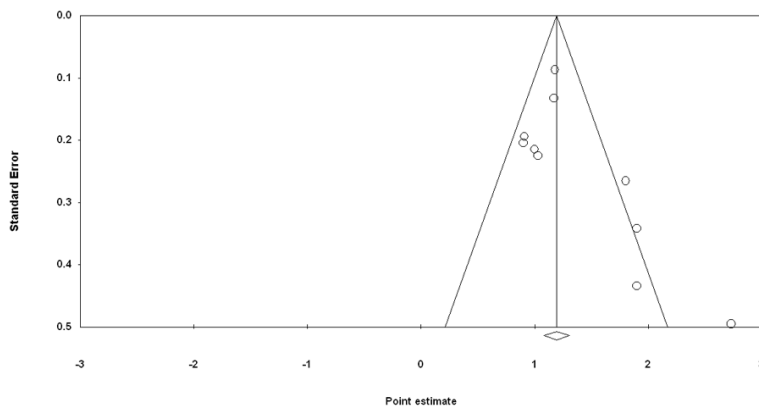


Figure 2. Funnel plot depicting the publication bias in the included studies (Bubbles indicate individual studies).

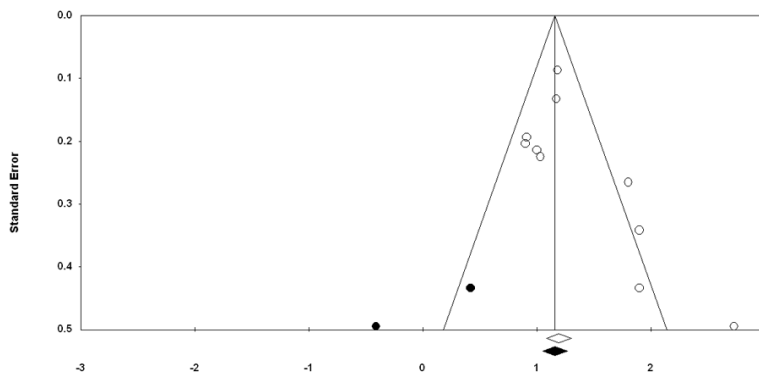


Figure 3. Dual and Tweedie's trim and fill method adjusted funnel plot.

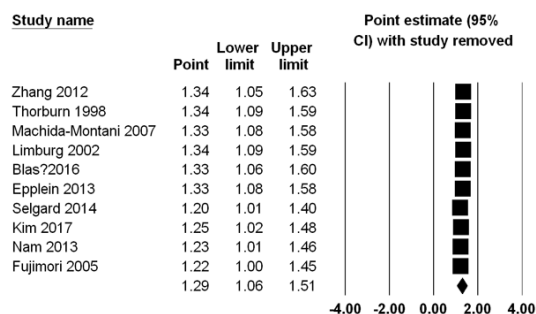


Figure 4. Forest plot depicting results of sensitivity analysis.

infection are as follows: 1. *H. pylori* infection leads to a state of hypergastrinemia due to the stimulation of gastric G cells and other mechanisms to stimulate the excess production of gastrin. Well established evidence shows that gastrin is a significant risk factor for gastric polyps and neuroendocrine tumors [29, 30]. 2. *H. pylori* infection causes inflammation of gastric epithelium leading to increased production and

activity of cyclooxygenase 2 leading to the development of colorectal polyps [31]. 3. Recent studies showed that some components of cell wall of *H. pylori* itself is carcinogenic to the colorectal epithelial cell lining [32, 33].

Present pooled analysis generated evidence by pooling data from observational studies which assessed the risk of CRC in patients with *H. pylori* infection. Overall pooled analysis of 10 observational studies imply that there is an increased risk of CRC in patients with history of *H. pylori* infection. But, pooling high quality studies including large sample size case-control studies showed that there was no significant association between *H. pylori* infection and risk of CRC. Moreover, pooled results of individual site cancers also indicate that there is no significant association between risk of colon or rectal cancer and *H. pylori* infection.

Present analysis included studies with sample size greater than 300 patients only which reduced the overall bias caused due to inclusion of small studies which are prone to small sample bias and prone to misleading results. After adjusting for publication bias using Dual and Tweedie's method, the positive significant association became non-significant association indicating missing studies or publication bias due to publishing positive results only. Major drawback with previous meta-analysis which suggested positive association between *H. pylori* infection and CRC were prone to bias caused by including small sample size studies [22-28]. This drawback was overcome in the present meta-analysis by excluding studies with sample size less than 300 [32, 34-37].

However, the evidence is inconclusive because of heterogeneity due to difference in the study characteristics including age, gender and various diagnostic methods used to assess CRC

Table 3. Results of main and sub-group analysis

Study	No. of studies	Pooled OR (95% CI)	Cochrane Q test <i>P</i> value	I ² value
All	10	1.29 (1.06-1.51)	<0.01	67%
Study design				
<i>Cross-sectional</i>	4	1.96 (1.61-2.30)	0.418	0%
<i>Case-control</i>	6	1.10 (0.98-1.22)	0.640	0%
Site of cancer				
<i>Colon cancer</i>	5	1.12 (0.97-1.26)	0.615	0%
<i>Rectal cancer</i>	5	1.11 (0.88-1.35)	0.221	30%
Geographical region				
<i>Asia</i>	4	1.45 (1.10-1.81)	0.016	67%
<i>Rest of the world</i>	6	1.16 (0.82-1.50)	0.011	69%

and *H. pylori* infection. Major limitation of the present study is that we did not searched grey literature and our search was restricted to articles published in English only.

In summary, the results of our meta-analysis based on the observational studies suggest that there is no conclusive evidence to show the association between risk of CRC and *H. pylori* infection. Present study highlighted the heterogeneity present in the existing evidence which was neglected in many of the previous meta-analysis while deriving conclusions. More studies including large sample size using standardized diagnostic methods are necessary to establish the relationship between *H. pylori* infection and risk of CRC.

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Disclosure of conflict of interest

None.

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