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META-ANALYSIS

Helicobacter pylori infection and inflammatory bowel disease in Asians: A meta-analysis

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Abstract

AIM: To investigate the relationship between *Helicobacter pylori* infection and inflammatory bowel disease (IBD) in an Asian population.

METHODS: The PubMed, EMBASE, and Cochrane Library databases were searched for observational studies published up until June 2014, without language restrictions. Additional references were obtained from reviewed articles.

RESULTS: Ten studies involving 1299 IBD patients and 1817 controls were included in the meta-analysis (24.9% of IBD patients had *H. pylori* infection *vs* 48.3% of the controls). The pooled risk ratio for *H. pylori* infection in IBD patients compared with controls was 0.48 (95%CI: 0.43-0.54; $P < 0.001$). There was no significant heterogeneity in the included studies ($I^2 = 21\%$). Egger's linear regression indicated that there was no significant publication bias ($P = 0.203$).

CONCLUSION: The *H. pylori* infection rate in Asian IBD patients is significantly lower than in non-IBD patients, indicating that infection protects against the development of IBD.

Key words: Asian population; Crohn's disease; *Helicobacter pylori*; Inflammatory bowel disease; Meta-analysis; Ulcerative colitis

Core tip: A meta-analysis was carried out to investigate the relationship between *Helicobacter pylori* (*H. pylori*) infection and inflammatory bowel disease (IBD) in an Asian population. A search of PubMed, EMBASE, and Cochrane Library databases identified ten studies involving 1299 IBD patients and 1817 controls that were included in the meta-analysis (24.9% of IBD patients had *H. pylori* infection *vs* 48.3% of the controls). This meta-analysis showed that in an Asian population, the *H. pylori* infection rate was significantly lower in IBD patients than in non-IBD patients, indicating a protective effect of *H. pylori* infection against IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD) is described as chronic inflammation of the gastrointestinal tract in genetically susceptible individuals exposed to environmental risk factors, and involves alternating active and quiescent phases leading to an increased health burden worldwide[1,2]. Crohn's disease (CD) and ulcerative colitis (UC) are the two primary subtypes of IBD. These diseases may result in intestinal damage, complications, and surgical interventions[3,4]. Commensal enteric bacteria are considered to have a critical role in the development of IBD. Continuous microbial antigenic stimulation can activate pathogenic immune responses and result in damage to intestinal mucosal barrier function and immunoregulation[5]. Genetic polymorphisms in the host most likely interact with intestinal bacteria to stimulate aggressive immunoreactions that cause chronic tissue injury. It is necessary to identify these host and microbial changes in individual patients in order to treat IBD[6,7].

Helicobacter species are characterized by microaerophilic metabolism, spiral shape, and peculiar motility, which contribute to their colonization of the gastrointestinal mucosal surface[8]. *Helicobacter pylori* (*H. pylori*) is a gram-negative pathogenic bacterium that is associated with chronic gastritis and is usually located on the surface of the stomach epithelium. Interestingly, *H. pylori* has also been identified in the normal colonic mucosa, colorectal neoplasms[9-11], and the intestinal mucosa of IBD patients[12,13]. Furthermore, *H. pylori* has been confirmed as a risk factor for colonic neoplasms[14,15], however, there is insufficient evidence to conclude that *H. pylori* has an important role in the pathogenesis of IBD.

Many observational studies have investigated the association between *H. pylori* infection and IBD. A meta-analysis involving 23 studies suggested that the *H. pylori* infection rate was lower in IBD patients than in non-IBD patients, and *H. pylori* was beneficial in preventing the development of IBD[16]. However, this meta-analysis only included one study that investigated the prevalence of *H. pylori* in an Asian population, and the conclusion may not be suitable for Asian populations. Therefore, we carried out an updated meta-analysis including only studies that determined the prevalence of *H. pylori* in IBD patients from Asian countries.

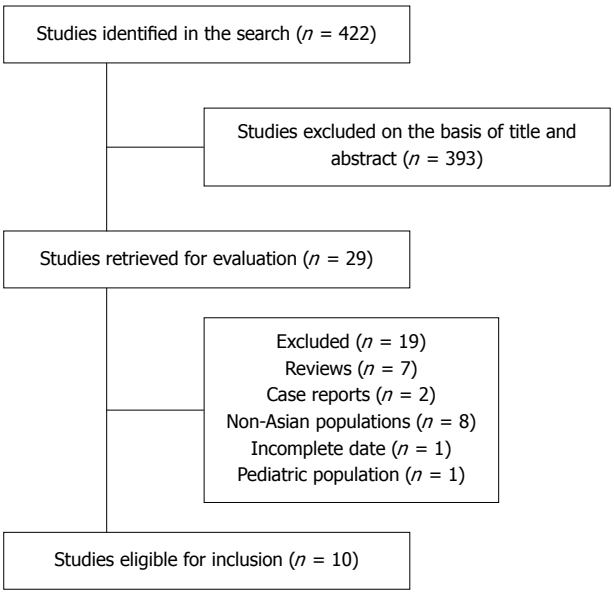

Figure 1 Flow diagram of the study selection process.

MATERIALS AND METHODS

Inclusion/exclusion criteria

Studies in line with the following criteria were included: (1) investigated the relationship between *H. pylori* infection and IBD; (2) used a case-control, cross-sectional, or cohort design; and (3) specifically included an Asian population. Studies were excluded if: (1) data from a previously published study were used; and (2) included a pediatric population.

Search strategy

We performed a search of PubMed, EMBASE, and the Cochrane Library for studies published up until June 2014. A search strategy was constructed using a combination of the following words: (*Helicobacter pylori* or *H. pylori*) and (IBD or CD or UC). Articles published in any language were included. A manual search of the references listed by studies retrieved from the online databases and from previously published systematic reviews was also performed to identify additional relevant studies.

Data extraction

Two investigators (Wu XW and Ji HZ) extracted data. Any differences regarding study inclusion, data extraction, and interpretation were resolved by consensus before the final analysis. Study variables were collected in the following categories: year of publication, country of origin, study center, characteristics of the patients, and *H. pylori* detection method. To avoid inclusion of duplicated data in the final analysis, retrieved studies were carefully evaluated and checked by comparing author names,

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

Ref.	Country	Study center	CD/UC, *n*	Control, *n*	Mean age, yr (CD/UC)	Male, % (CD/UC)	*Helicobacter pylori* detection
Matsumura *et al*[19] 2001	Japan	Multiple	90/NR	525	31.7/NR	70.0/NR	IgG
Furusu *et al*[20] 2002	Japan	Single	25/25	25	NR	NR	IgG/Histology
Moriyama *et al*[21] 2005	Japan	Single	29/NR	7	31.6/NR	59.0/NR	UBT
Ando *et al*[22] 2008	Japan	Single	38/NR	12	28.9/NR	74.0/NR	UBT
Hong *et al*[23] 2009	South Korea	Single	37/43	41	38.2/44.2	73.0/67.4	Histology
Pang *et al*[24] 2009	China	Single	52/54	106	36.7/42.3	57.7/55.6	IgG
Song *et al*[25] 2009	South Korea	Multiple	147/169	316	33.5/44.7	67.3/63.3	UBT
Zhang *et al*[13] 2011	China	Single	104/104	416	31.0/40.9	66.3/57.7	UBT
Jin *et al*[26] 2013	China	Single	NR/153	121	NR/44.6	NR/51.6	UBT/Culture
Xiang *et al*[27] 2013	China	Single	229/NR	248	46.2/NR	58.1/NR	UBT/Culture

CD: Crohn's disease; IgG: Immunoglobulin G; NR: Not reported; UBT: Urea breath test; UC: Ulcerative colitis.

geographic locations, and period of study.

Statistical analysis

Meta-analysis was carried out by combining the risk ratio (RR) in the IBD and control groups of the individual studies in a global RR. Statistical heterogeneity testing was performed using the χ^2 statistic and I^2, and an I^2 > 50% was considered to represent substantial heterogeneity[17]. A fixed effects model was selected when the heterogeneity test showed an I^2 < 50%, otherwise a random effects model was used. A funnel plot was used to determine publication bias[18]. Analyses were conducted using Review Manager software (RevMan version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The statistical methods of this study were reviewed by Liu from Department of Medical Statistics, School of Medicine, Nanjing University.

RESULTS

Search results

Our search identified 422 potentially relevant studies, of which 393 were excluded after title and abstract screening. Twenty-nine articles were retained for full-text review. Seven review articles, two case reports, eight studies including non-Asian populations, one study with incomplete data, and one study which included a pediatric population were subsequently excluded. We identified ten studies which fulfilled the inclusion criteria[13,19-27]. These studies included a total of 1299 cases of IBD and 1817 controls. Figure 1 shows the study flow diagram.

Characteristics of the included studies

The characteristics of the included studies and patients are presented in Table 1. Four studies were from Japan, four studies were from China, and two studies were from South Korea. All were case-control studies. Two of them were multicenter studies, and eight were single-center studies. The mean age of IBD patients ranged from 28.9 to 44.7 years. Two studies used serologic tests (immunoglobulin G) and eight studies used non-serologic tests (C-urea breath test, biopsy specimen histology, or biopsy sample culture) to detect *H. pylori*.

H. pylori and IBD

Of these studies, which included 1299 IBD patients and 1817 controls (Figure 2), 24.9% of patients in the IBD groups were found to have *H. pylori* infection, while 48.3% of patients in the control groups had *H. pylori* infection. The pooled RR of *H. pylori* infection rate in IBD patients compared to controls was 0.48 (95%CI: 0.43-0.54; P < 0.001). A fixed effects model was used for the meta-analysis as no significant heterogeneity in the included studies was observed (I^2 = 21%).

Nine studies included 751 CD patients and 1696 controls (Figure 3). The rate of *H. pylori* infection in CD patients was 21.3% compared with 47.7% in the control groups (RR = 0.43, 95%CI: 0.37-0.50; P < 0.001). A fixed effects model was selected for the meta-analysis as significant heterogeneity in the included studies was not observed (I^2 = 43%).

Six studies included 548 UC patients and 1025 controls (Figure 4). The rate of *H. pylori* infection was 29.9% in UC patients *vs* 52.5% in the control groups (RR = 0.55, 95%CI: 0.48-0.64; P < 0.001). We performed the meta-analysis with a fixed effects model as no significant heterogeneity was found in the included studies (I^2 = 0%).

Publication bias

The funnel plot revealed a reasonably symmetrical distribution of the included studies examining the association between *H. pylori* infection and IBD (Figure 5). Egger's linear regression indicated that there was no statistically significant evidence of publication bias (P = 0.203).

DISCUSSION

The prevalence of *H. pylori* infection varies markedly in different countries and regions. Higher prevalence rates are seen in some developing Asian countries[28,29], while lower rates have been found in many developed countries in Europe and North America[30,31]. Moreover,

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	RR M-H, fixed, 95%CI
Matsumura *et al* 2001	15	90	211	525	9.1%	0.41 [0.26, 0.67]
Furusu *et al* 2002	15	50	13	25	2.5%	0.58 [0.33, 1.02]
Moriyama *et al* 2005	3	29	5	7	1.2%	0.14 [0.04, 0.47]
Ando *et al* 2008	3	38	5	12	1.1%	0.19 [0.05, 0.68]
Song *et al* 2009	80	316	166	316	24.4%	0.48 [0.39, 0.60]
Pang *et al* 2009	33	106	65	106	9.5%	0.51 [0.37, 0.70]
Hong *et al* 2009	26	80	22	41	4.3%	0.61 [0.40, 0.93]
Zhang *et al* 2011	41	208	203	416	19.9%	0.40 [0.30, 0.54]
Xiang *et al* 2013	46	153	69	121	11.3%	0.53 [0.40, 0.70]
Jin *et al* 2013	62	229	119	248	16.8%	0.56 [0.44, 0.72]
Total (95%CI)		1299		1817	100.0%	0.48 [0.43, 0.54]
Total events	324		878			

Heterogeneity: χ^2 = 11.42, *df* = 9 (*P* = 0.25); I^2 = 21%
Test for overall effect: *Z* = 12.97 (*P* < 0.00001)

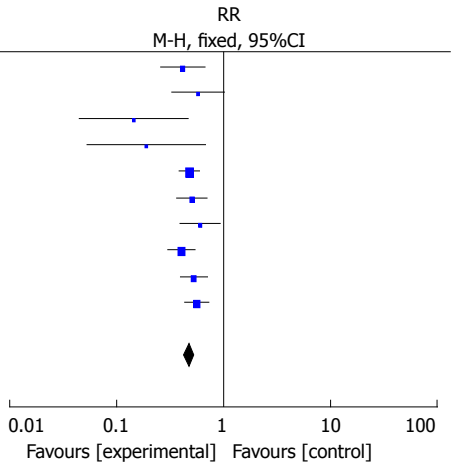

Figure 2 Forest plot of *Helicobacter pylori* infection rate in inflammatory bowel disease *vs* control groups.

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	RR M-H, fixed, 95%CI
Matsumura *et al* 2001	15	90	211	525	13.6%	0.41 [0.26, 0.67]
Furusu *et al* 2002	9	25	13	25	2.9%	0.69 [0.36, 1.32]
Moriyama *et al* 2005	3	29	5	7	1.8%	0.14 [0.04, 0.47]
Ando *et al* 2008	3	38	5	12	1.7%	0.19 [0.05, 0.68]
Pang *et al* 2009	13	52	65	106	9.4%	0.41 [0.25, 0.67]
Song *et al* 2009	26	147	166	316	23.2%	0.34 [0.23, 0.48]
Hong *et al* 2009	10	37	22	41	4.6%	0.50 [0.28, 0.92]
Zhang *et al* 2011	19	104	203	416	17.8%	0.37 [0.25, 0.57]
Xiang *et al* 2013	62	229	119	248	25.1%	0.56 [0.44, 0.72]
Total (95%CI)		751		1696	100.0%	0.43 [0.37, 0.50]
Total events	160		809			

Heterogeneity: χ^2 = 14.08, *df* = 8 (*P* = 0.08); I^2 = 43%
Test for overall effect: *Z* = 10.82 (*P* < 0.00001)

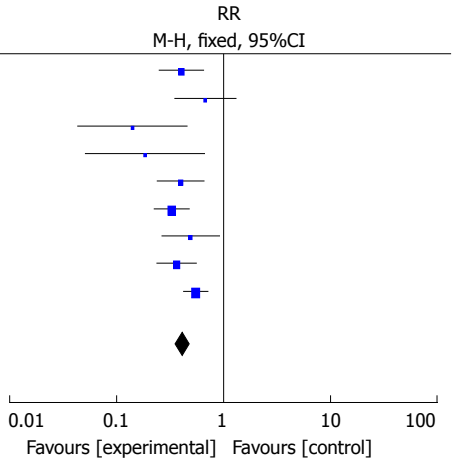

Figure 3 Forest plot of *Helicobacter pylori* infection rate in Crohn's disease *vs* control groups.

Study or subgroup	Experimental Events	Total	Control Events	Total	Weight	RR M-H, fixed, 95%CI
Furusu *et al* 2002	6	25	13	25	3.7%	0.46 [0.21, 1.02]
Song *et al* 2009	54	169	166	316	32.7%	0.61 [0.48, 0.78]
Pang *et al* 2009	20	54	65	106	12.4%	0.60 [0.41, 0.88]
Hong *et al* 2009	16	43	22	41	6.4%	0.69 [0.43, 1.12]
Zhang *et al* 2011	22	104	203	416	23.0%	0.43 [0.30, 0.64]
Jin *et al* 2013	46	153	69	121	21.8%	0.53 [0.40, 0.70]
Total (95%CI)		548		1025	100.0%	0.55 [0.48, 0.64]
Total events	164		538			

Heterogeneity: χ^2 = 3.53, *df* = 5 (*P* = 0.62); I^2 = 0%
Test for overall effect: *Z* = 8.04 (*P* < 0.00001)

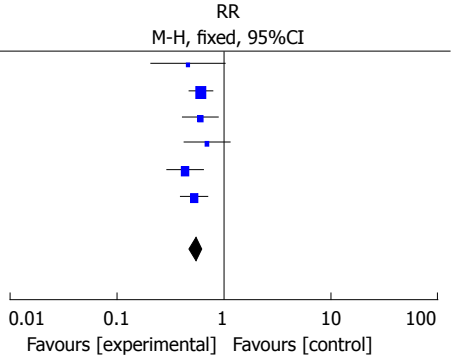

Figure 4 Forest plot of *Helicobacter pylori* infection rate in ulcerative colitis *vs* control groups.

the prevalence rates may vary significantly in different geographic regions or ethnic populations of the same country[32,33]. However, the variation in *H. pylori* infection rate in IBD patients of different race or region has not been completely clarified.

Our meta-analysis identified ten studies focused on the association between *H. pylori* infection and IBD in an Asian population. The included cases were from three east-Asian countries (China, Japan, and South Korea) that are considered to have similar ethnic origin, whereas the previous meta-analysis published in 2010 involved populations mostly from European and American countries[16]. By specifically including an Asian population, the heterogeneity and publication bias were both lower than those in the previous meta-analysis. The pooled rate of *H. pylori* infection in the

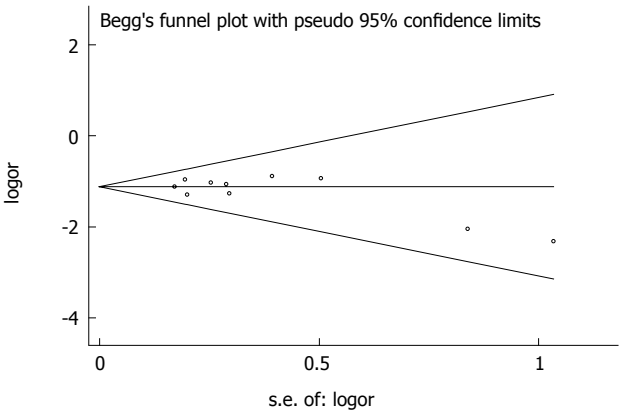

Figure 5 Funnel plot analysis.

IBD groups was a little lower than that reported in the previous meta-analysis (24.9% *vs* 27.1%), but the pooled rate of *H. pylori* infection in the control groups was higher than that previously reported (48.3% *vs* 40.9%). These discordant results suggest that ethnic origin may have a potential impact on the relationship between *H. pylori* infection and IBD.

The mechanism of *H. pylori* infection in preventing IBD is unclear. It has been hypothesized that *H. pylori* may downregulate proinflammatory immune responses in the host in order to promote its own survival, resulting in beneficial effects to the host. An animal experiment showed that long-term *H. pylori* infection can lead to distinct changes in microbiota composition in the large intestine, indicating that *H. pylori* may modulate the intestinal flora to affect the development of IBD[34]. Other research in animal colitis models suggested that *H. pylori* infection can regulate the immune responses, resulting in benefit to the host against other chronic inflammatory conditions such as IBD[35,36]. Papamichael *et al*[37] showed that *H. pylori* infection may play a protective role against IBD *via* the following mechanisms: increasing the levels of some cytokines, activating dendritic cells and T cells, downregulating the Th1/Th17 pathway, and inducing the generation of antibodies against *H. pylori*. In our meta-analysis, the lower pooled RR of *H. pylori* infection in IBD patients compared to controls suggests a protective effect of infection against the development of IBD. Subgroup analyses showed a tendency toward a more pronounced effect for CD when compared to UC. One of the included studies revealed a more evident association between *H. pylori* infection and IBD in patients < 60 years-old, which suggests that *H. pylori* infection may reduce the risk of IBD in younger adults[25]. Two studies found that the rate of *H. pylori* infection in IBD patients treated with antibiotics was lower than untreated patients. However, IBD patients without antibiotic treatment still showed a significantly lower rate of *H. pylori* infection than controls[24,25]. In a study with only 153 UC patients, the *H. pylori* infection rates in patients with diverse severity or extent of UC were significantly lower than those in the controls[26]. Another study showed that the *H. pylori* infection rates in patients with colonic, small intestine and ileocolonic CD were significantly lower than that in the control group[27]. We did not find any obvious correlation between the phenotypic characteristics of IBD patients and *H. pylori* infection rate in the included studies.

In conclusion, our meta-analysis shows that the rate of *H. pylori* infection in IBD patients from Asian countries is significantly lower than in non-IBD patients. However, there are some limitations in our meta-analysis, such as an insufficient number of included studies and potential heterogeneity. More prospective high-quality controlled studies are required to confirm the results of this meta-analysis.

COMMENTS

Background

Epidemiologic data show that *Helicobacter pylori* (*H. pylori*) infection has a protective effect against the development of autoimmune disease. Laboratory data suggest that *H. pylori* can induce immune tolerance and suppress the inflammatory response. Many observational studies have investigated the association between *H. pylori* infection and inflammatory bowel disease (IBD). Most of these studies found that the *H. pylori* infection rate in IBD patients was lower than that in non-IBD patients. However, conflicting outcomes have been observed and the exact mechanism of the protective effect of *H. pylori* in IBD development is still unclear.

Research frontiers

Numerous studies describing the *H. pylori* infection rates in IBD patients compared with healthy controls have been published in the past twenty years. A previous meta-analysis involving 23 studies suggested a lower *H. pylori* infection rate in IBD patients. *H. pylori* infection rate is related to ethnicity and region, however, the previous meta-analysis only included one study from an Asian country. This study investigated the relationship between *H. pylori* infection and IBD in an Asian population.

Innovations and breakthroughs

The authors demonstrated that the *H. pylori* infection rate in Asian IBD patients was significantly lower than in non-IBD Asian patients. The pooled *H. pylori* infection rate of IBD patients in this study was a little lower than the previous meta-analysis (24.9% *vs* 27.1%), but the pooled rate in the control group was higher than that previously reported (48.3% *vs* 40.9%). These results suggest that ethnic origin may have an impact on *H. pylori* infection rate, providing powerful evidence that *H. pylori* infection is a potential protective factor in the development of IBD.

Applications

The results of this meta-analysis show that IBD patients with a history of taking antibiotics had a lower *H. pylori* infection rate in two of the included studies, however, there were no available data for the controls. Antibiotic use may be partly responsible for the lower *H. pylori* infection rate in IBD patients. The exact mechanism of this interesting phenomenon should be investigated further. Large-sample and well-designed cohort studies with stringent disease and *H. pylori* infection definitions are required in order to delineate the protective effect of *H. pylori* infection in IBD development.

Terminology

H. pylori is a gram-negative, microaerophilic bacterium. It is present in patients with chronic gastritis and gastric ulcers. It is also linked to the development of duodenal ulcers and stomach cancer. *H. pylori* may be implicated in the pathogenesis of autoimmune diseases.

Peer-review

This is a well-designed and performed meta-analysis that confirms the results recently published for non-Asian cohorts. The results are interesting and are

worthy of publication.

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