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META-ANALYSIS

Helicobacter pylori infection and esophageal cancer risk: An updated meta-analysis

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Abstract

AIM: To clarify the association between *Helicobacter pylori* (*H. pylori*) infection and the risk of esophageal carcinoma through a meta-analysis of published data.

METHODS: Studies which reported the association between *H. pylori* infection and esophageal cancer published up to June 2013 were included. The odds ratios (ORs) and corresponding 95%CIs of *H. pylori* infection on esophageal cancer with respect to health control groups were evaluated. Data were extracted independently by two investigators and discrepancies were resolved by discussion with a third investigator. The statistical software, STATA (version 12.0), was applied to investigate heterogeneity among individual studies and to summarize the studies. A meta-analysis was performed using a fixed-effect or random-effect method, depending on the absence or presence of significant heterogeneity.

RESULTS: No significant association between *H. pylori* infection and esophageal squamous cell carcinoma (ESCC) risk was found in the pooled overall population (OR = 0.97, 95%CI: 0.76-1.24). However, significant associations between *H. pylori* infection and ESCC risk were found in Eastern subjects (OR = 0.66, 95%CI: 0.43-0.89). Similarly, cytotoxin-associated gene-A (CagA) positive strains of infection may decrease the risk of ESCC in Eastern subjects (OR = 0.77, 95%CI: 0.65-0.92), however, these associations were not statistically significant in Western subjects (OR = 1.26, 95%CI: 0.97-1.63). For esophageal adenocarcinoma (EAC) the summary OR for *H. pylori* infection and CagA positive strains of infection were 0.59 (95%CI: 0.51-0.68) and 0.56 (95%CI: 0.45-0.70), respectively.

CONCLUSION: *H. pylori* infection is associated with a decreased risk of ESCC in Eastern populations and a decreased risk of EAC in the overall population.

Key words: *Helicobacter pylori*; Esophageal carcinoma; Cancer risk; Meta-analysis

Core tip: Based on this meta-analysis, we found that *Helicobacter pylori* infection may have a protective effect against esophageal squamous cell carcinoma in

Eastern populations and against esophageal adenocarcinoma in the overall population.

Xie FJ, Zhang YP, Zheng QQ, Jin HC, Wang FL, Chen M, Shao L, Zou DH, Yu XM, Mao WM. *Helicobacter pylori* infection and esophageal cancer risk: An updated meta-analysis. *World J Gastroenterol* 2013; 19(36): 6098-6107 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i36/6098.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i36.6098

INTRODUCTION

Esophageal cancer (EC), which mainly consists of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), is the eighth most common cancer worldwide, with 481645 new cases in 2008, and is the sixth leading cause of cancer death, with 406533 deaths[1]. Despite advances in the molecular mechanism of carcinogenesis, the etiology of this malignancy remains unclear. A better understanding of the influencing factors and underlying mechanisms involved in EC development and progression will provide appropriate targets for the development of effective strategies for the prevention of this prevalent malignancy.

Helicobacter pylori (*H. pylori*) is a helical-shaped Gram-negative bacterium and has been identified as the major causative agent of various benign and malignant gastrointestinal tract diseases[2]. A study showed that cytotoxin-associated gene-A (CagA)-positive strains conferred a greater risk than CagA-negative strains[3]. Islami *et al*[4] carried out an excellent meta-analysis and reported an inverse association between CagA-positive *H. pylori* colonization and the risk of EAC, but not ESCC. However, recent studies reported inconclusive results, and some showed the reverse relationship between *H. pylori* and ESCC[5,6]. Therefore, an updated meta-analysis was performed which included all eligible studies to evaluate the association between *H. pylori* infection and EC risk.

MATERIALS AND METHODS

Search strategy

To identify all articles that examined the association between *H. pylori* infection and esophageal carcinoma, we conducted a literature search in the PubMed databases up to April 2013 using the following MeSH terms and keywords: "*Helicobacter pylori*" [MeSH] OR (*Campylobacter pylori*) OR (*H. pylori*) OR (*H. pylori*) AND ("Esophageal Neoplasms" [MeSH] OR (Cancer of Esophagus) OR (Cancer of the Esophagus) OR (Esophageal Cancer) OR (Esophagus Cancer) OR (Esophagus Neoplasm) OR (Neoplasms, Esophageal). Additional studies were identified by a hand search from references of original studies or review articles on this topic. Two authors reviewed the search results to reduce the possibility of missing relevant published papers. Where data were missing, we contacted the authors for the relevant information. Eligible studies included in this meta-analysis had to meet the following criteria: (1) Articles should clearly describe studies on the association between *H. pylori* infection and esophageal cancer risk; and (2) The esophageal cancer diagnoses and the sources of cases and controls should be stated. The literature excluded in this study was mainly due to the following reasons: lacking a normal control group, reviews, the research design being not scientific and reasonable, and including repeated data. A total of 27 publications met the eligibility criteria and were included in the present study[5-31].

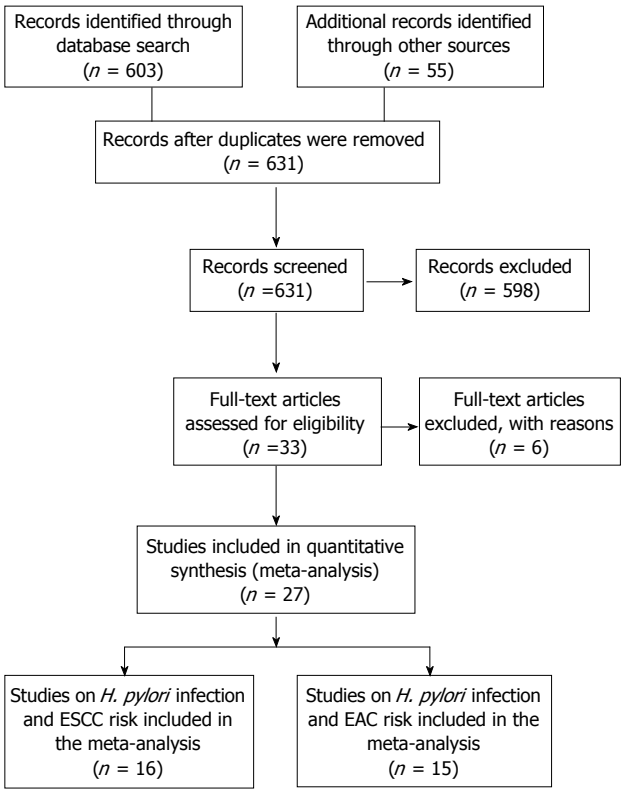

Figure 1 Flow diagram of study identification. ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; *H. pylori*: *Helicobacter pylori*.

Data extraction

The following data from each article were extracted: authors, year of publication, country of participants, study design, source of controls, number of controls and of cases, *H. pylori* detection method, and *H. pylori* infection status. The data were extracted and registered in two databases independently by two investigators (Zheng QQ and Wang FL) who were blind to journal names, institutions and funding grants. Any discrepancy between these two investigators was resolved by a third investigator (Xie FJ), who participated in the discussion and made the ultimate decision. Equivocal or missed data were excluded in order to unify the formation of the information[11,23]. One article was used as a partial adjusted value, due to crude data[10], and 2 articles that were included totally or partially in another article[32,33].

Table 1 Characteristics of literatures included in the meta-analysis

Ref.	Study area	Year	Study type	HP Dm	*Hp*$^+$ definition[1]	ESCC				EAC				Matched/ adjusted[3]	Control
						Case		Control		Case		Control			
						Hp$^+$	CagA$^+$	*Hp*$^+$	CagA$^+$	*Hp*$^+$	CagA$^+$	*Hp*$^+$	CagA$^+$		
Murphy *et al*[7]	Finnish	2012	Pop	S	HpSe$^+$	64/82	35/82	63/82	36/82	-	-	-	-	Yes/yes	Matched with age, smoking and Alcohol consumption, and date of blood draw to controls, all of cases and controls were male smokers
Khoshbaten *et al*[9]	Iran	2011	Pop	S	HpSe$^+$	58/100	28/100	83/100	36/100	-	-	-	-	Yes/no	Sex-matched and age-matched health individuals, any clinical evidence of gastrointestinal symptoms were excluded
Venerito *et al*[8]	Germany	2011	Clin	S, H, U	His$^+$, HpSe$^+$, CagA$^+$ or U$^+$	53/75	42/75	53/75	40/75	-	-	-	-	Yes/no	Sex and age-matched individuals with upper GI symptoms but no malignancy of the upper GI tract
Whiteman *et al*[11]	Australia	2010	Pop	S	HpSe$^+$	54/208	-	302/1316	-	35/260	-	302/1316	-	Yes/yes	Randomly selected from the same areas, matched to each stratum of age and state
Cook *et al*[10]	Finnish	2010	Pop	S	HpSe$^+$	64/78	35/78	71/91	42/91	-	-	-	-	Yes/yes	Matched to case for age, years of smoking, cigarettes per day, or body mass index
Wu *et al*[5]	Taiwan	2009	Pop	S	HpSe$^+$	112/317	91/317	563/1103	268/700	-	-	-	-	No/yes	One part of control is matched by gender and age, but another part wasn't matched
Hu *et al*[6]	Taiwan	2009	Pop	S	HpSe$^+$	66/180	-	102/194	-	-	-	-	-	Yes/yes	Healthy and cancer-free individuals, matched to age, sex and ethnicity
Früh *et al*[12]	Canada	2008	Clin	S	CagA$^+$ or VacA$^+$	-	-	-	-	36/100	29/100	43/101	30/101	Yes/yes	Healthy GRERD-free, non-blood-related family member and friends of other cancer/surgical patients
Derakhshan *et al*[24]	Iran	2008	Clin	S	HpSe$^+$	-	-	-	-	9/19	-	28/38	-	Yes/yes	Dyspeptic patients with no peptic ulcer or tumor in their endoscopy
Anderson *et al*[25]	Ireland	2008	Pop	S	HpSe$^+$	-	-	-	-	55/123	57/123	157/253	150/253	Yes/yes	Randomly selected population-based controls, frequency matched to EAC cases for age and sex
Löfdahl *et al*[23]	Sweden	2008	Pop	S	HpSe$^+$ or CagA$^+$	-	-	-	-	130/230	-	304/499	-	Yes/no	Random selected from the population register, frequency matched for age and sex
Anandasabapathy *et al*[26]	United States	2007	Clin	H	His$^+$	-	-	-	-	4/25	-	10/30	-	No/no	Barrett's patients with no dysplasia
Iijima *et al*[27]	Japan	2007	Clin	S, H, U	HpSe$^+$, His$^+$ or U$^+$	60/73	-	56/73	-	-	-	-	-	Yes/yes	Endoscoped patients with no localized lesion, matched to cases for age and sex
Kamangar *et al*[14]	China	2007	Pop	S	HpSe$^+$	231/335	178/335	662/992	552/992	-	-	-	-	No/yes	Randomly selected from the entire baseline participants in the stdy cohort
Simán *et al*[13]	Sweden	2007	Pop	S	HpSe$^+$	15/37	24/37	68/129	82/129	4/12	6/12	24/47	32/47	Yes/yes	Randomly selected from the study cohorted, matched with age, sex, and date enrollment
Wang *et al*[28]	China	2006	Pop	S	HpSe$^+$	?/107	-	?/107	-	-	-	-	-	Yes/yes	Neighborhood controls, randomly selected, and matched to cases for age and gender
Wu *et al*[15]	Taiwan	2005	Pop	S	HpSe$^+$	28/127	-	74/171	-	-	-	-	-	No/yes	Randomly selected from the same community
de Martel *et al*[29]	United States	2005	Pop	S	HpSe$^+$	-	-	-	-	19/51	9/18	74/150	44/71	Yes/yes	Randomly selected from the study cohorted, matched with age, sex, and date enrollment race, and study site
Ye *et al*[16]	Sweden	2004	Pop	S	HpSe$^+$	32/85	63/85	198/499	293/499	18/97	42/97	198/499	293/499	Yes/yes	Randomly selected population-based controls, frequency matched to EAC cases for age and sex

[2]Wang *et al*[30]	China	2003	Pop	S	$HpSe^+$	33/63	-	145/310	-	-	-	-	-	Yes/no	Healthy subjects with no difference in age and gender
Wu *et al*[22]	United States	2003	Pop	S	$HpSe^+$	-	-	-	-	49/80	18/80	230/356	106/356	Yes/yes	Matched to cases for age, sex, neighborhood of residence, and race
El Omar *et al*[21]	United States	2003	Pop	S	$HpSe^+$	31/53	7/26	84/210	46/224	35/108	5/68	84/210	46/224	Yes/no	Matched to cases for age, sex, and study center
Weston *et al*[20]	United States	2000	Clin	H	His^+	-	-	-	-	3/20	-	96/217	-	No/no	Patients with GERD symptoms but no Barrett's esophagus
Vieth *et al*[19]	Germany	2000	Clin	H	His^+	-	-	-	-	66/138	-	468/712	-	No/no	Patients with non-ulcer dyspepsia and no endoscopic signs of GERD
Peek *et al*[18]	United States	1999	Clin	S, H	$HpSe^+$ or His^+	-	-	-	-	11/30	3/30	20/48	25/48	No/no	Patients endoscoped for reasons other Than GERD or Barrett's
Oberg *et al*[31]	United States	1999	Clin	H	His^+	-	-	-	-	5/37	-	32/229	-	No/no	Patients with foregut symptoms and benign diseases
Talley *et al*[17]	United States	1991	Clin	S	$HpSe^+$	20/41	-	96/252	-	-	-	-	-	No/no	Asymptomatic volunteers and patients with benign esophageal, lung, or culoskeletal disorders

[1]*Helicobacter pylori* (*H. pylori*) positivity definition; [2]Because the article showed that there was no difference in age and gender between cases and health controls, this study was analyzed as a matched population study; [3]Individual-matching of controls to cases for age and gender/reporting adjusted ORs for the association between *H. pylori* and cancer. Clin: Clinical based; Pop: Population based; NR: Not reported; Hp Dm: Hpdetection method; S: Serology; H: Histology; U: Rapid urease test; His^+: Positive histological examination of tissue samples; $HpSe^+$: Sero-positivity for antibodies to whole-cell; $VacA^+$: Sero-positivity for antibodies to VacA; $CagA^+$: Sero-positivity for antibodies to cytotoxin-associated gene-A; U^+: Positive rapid urease test; GERD: Gastroesophageal reflux disease; ESCC: Esophageal squamous cell carcinoma; EAC: Esophageal adenocarcinoma; GI: Gastrointestinal.

Statistical analysis

The dichotomous data on *H. pylori* positive results in the EC group and control group were summarized. OR and 95%CI of OR were calculated to assess the association between *H. pylori* infection and EC risk. If the *H. pylori* data were not shown in the article, the OR and 95%CI: value were extracted. An analysis of the heterogeneity of the studies was performed using the χ^2-based Q test. A P value less than 0.05 was considered significant for heterogeneity. If the studies were shown to be homogeneous with $P > 0.05$ for the Q-statistics, the summary of OR was calculated by a fixed-effects model (the Mantel-Haenszel method), otherwise, the random-effects model (the DerSimonian and Laird method) was used. The potential publication bias was assessed graphically using Begg's test and funnel plots. All analyses were performed with STATA software (version 12.0; Stata Corp LP, College Station, TX, United States), using two-sided P values.

RESULTS

Eligible studies

Twenty-seven eligible studies on *H. pylori* infection and esophageal cancer were identified through the literature search and selection based on the inclusion and exclusion criteria (Figure 1). The year of publication for these studies ranged from 1991 to 2012. There were 18 studies on Western (Finland, Germany and Ireland) populations and 9 studies on Eastern (Iran and China) populations. With respect to study type, 17 studies were population-based, 10 studies were hospital-based and one study did not specify. Adjusted ORs with corresponding 95%CIs were reported in 17 studies. The selected study characteristics are summarized in Table 1.

Test of heterogeneity

We analyzed the heterogeneity of all 16 studies on ESCC and the fifteen studies on EAC, respectively. For *H. pylori* infection in the ESCC risk study, the Q statistic was significant ($P < 0.01$) and the I^2 statistic showed a high variation ($I^2 = 74.5\%$) among the study results, thus a random-effect model was used for further analysis (Figure 2A and Table 2). In the EAC study, no significant heterogeneity was observed in the overall comparison ($I^2 = 29.9\%$, $P_{heterogeneity} = 0.131$), and a fixed-effect model was used to calculate the overall ORs (Figure 2B and Table 2).

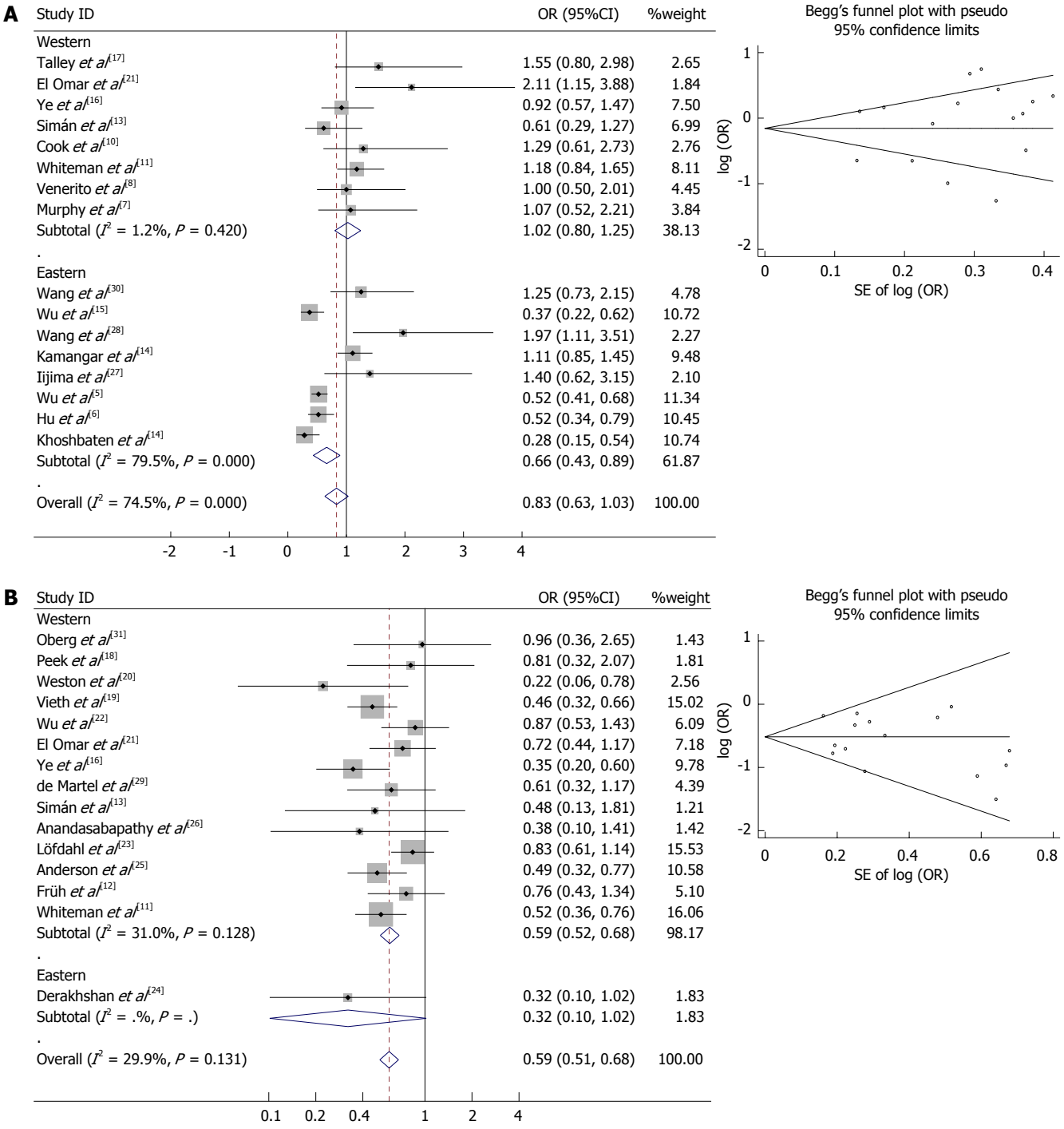

Figure 2 Forest plot and Begg's funnel plot of the association between *Helicobacter pylori* infection and esophageal carcinoma. Studies are sorted in order of publication year. A: Esophageal squamous cell carcinoma (random-effect model); B: Esophageal adenocarcinoma (fixed-effect model).

H. pylori infection and ESCC risk

The association between *H. pylori* infection and ESCC risk is shown in Figure 2A and Table 2. With the exception of the clinical-based Western studies, $CagA^+$ strains in the Eastern and Western studies did not show obvious heterogeneity calculated using the fixed-effect model. The remaining results were significantly heterogeneous ($P < 0.01$) calculated using the random-effect model.

In the random-effects model, no statistically significant factor influenced the risk of ESCC in the presence of *H. pylori* infection (OR = 0.83, 95%CI: 0.63-1.03). When population-based studies were analyzed alone, the combined OR for the association between *H. pylori* infection and ESCC risk was 2.86 (95%CI: 1.60-5.11). When clinical-based studies were analyzed alone, the combined OR for *H. pylori* infection was 1.49 (95%CI: 0.66-2.31). When stratified by study location, there was a statistically significant decrease in ESCC risk in the Eastern population (OR = 0.66, 95%CI: 0.43-0.89), however, we did not find a significant association in the Western popula-

Table 2 Meta-analysis of the *Helicobacter pylori* infection on the risk of esophageal squamous cell carcinoma and esophageal adenocarcinoma

	Studies	P^1	$I^{2,2}$	Overall OR (95%CI)
Esophageal squamous cell carcinoma				
Case/control (1961/5704)				
All studies	16	< 0.01	74.50%	0.83 (0.63, 1.03)
Population-based studies	14	< 0.01	76.00%	0.79 (0.59, 1.00)
Clinical-based studies	2	0.86	< 0.01	1.49 (0.66, 2.31)
Eastern studies	8	< 0.01	79.50%	0.66 (0.43, 0.89)
Western studies	8	0.42	1.20%	1.02 (0.80, 1.25)[3]
Studies with matched controls	11	< 0.01	71.80%	0.90 (0.61, 1.20)
Studies without matched controls	5	< 0.01	82.90%	0.79 (0.46, 1.12)
Hp^+ only definition as $HpSe^+$	14	< 0.01	76.80%	0.81 (0.60, 1.02)
Adjusted results	11	< 0.01	80.50%	0.84 (0.56, 1.12)
$CagA^+$ *vs* Hp^-	9	0.03	52.00%	0.97 (0.76, 1.24)
Eastern study	3	0.22	35.00%	0.77 (0.65, 0.92)[3]
Western studies	6	0.39	3.60%	1.26 (0.97, 1.63)[3]
Esophageal adenocarcinoma				
Case/control (1330/4705)				
All studies	15	0.131	29.9	0.59 (0.51, 0.68)
Population-based studies	8	0.106	40.9	0.62 (0.52, 0.73)
Clinical-based studies	7	0.319	14.5	0.53 (0.40, 0.68)
Eastern study	1	-	-	-
Western studies	14	0.128	31	0.60 (0.52, 0.68)
Studies with matched controls	10	0.139	33.6	0.62 (0.53, 0.72)
Studies without matched controls	5	0.333	12.7	0.49 (0.36, 0.66)
Hp^+ definition as $HpSe^+$	8	0.299	16.6	0.55 (0.45, 0.66)
Hp^+ definition as His^+	4	0.334	11.7	0.46 (0.33, 0.64)
Adjusted results	8	0.200	28.6	0.51 (0.40, 0.61)
$CagA^+$ *vs* Hp^-	8	0.11	39.9	0.56 (0.45, 0.70)
Eastern study	0	-	-	-
Western studies	8	0.11	39.9	0.56 (0.45, 0.70)

[1]*P* value for *Q* statistical in random effects model; [2]Higgins I^2 statistic for heterogeneity in random effects model; [3]The overall value synthesized by fixed effects model. $HpSe^+$: Sero-positivity for antibodies to whole-cell; $CagA^+$: Sero-positivity for antibodies to cytotoxin-associated gene-A.

tion (OR = 1.02, 95%CI: 0.80-1.24). In the sub-group analyses of "Hp^+ only definition as $HpSe^+$", "studies with matched controls", "studies without matched controls" no significant correlation between *H. pylori* infection and ESCC risk was found.

As studies have indicated that individuals infected with CagA-positive *H. pylori* strains have a higher risk of developing peptic ulcers and gastric cancer compared to those harboring CagA-negative *H. pylori* strains[34,35], the association between $CagA^+$ stains and ESCC was also evaluated (Figure 3A). The overall OR was 0.97 (95%CI: 0.76-1.24) and showed high heterogeneity among the studies (I^2 = 52.0%, $P_{heterogeneity}$ = 0.03). This high heterogeneity may be caused partly by regional or ethnic differences, as heterogeneity values may weaken during location subgroup analysis. Similarly, $CagA^+$ strains of infection may decrease the risk of ESCC in Eastern subjects (OR = 0.77, 95%CI: 0.65-0.92), but not in Western subjects (OR = 1.26, 95%CI: 0.97-1.63) or the overall population (OR = 0.90, 95%CI: 0.78-1.05).

H. pylori infection reduced the risk of EAC

Forest plot analyses are shown in Figure 2B. The overall positive rate of *H. pylori* infection in EAC was 35.96% (479/1332), which was significantly lower than that in normal controls 44.00% (2070/4705; OR = 0.71, 95%CI: 0.63-0.81). Quantitative meta-analyses showed that, compared with the control group, the combined OR of EAC in the presence of *H. pylori* infection was 0.59 (95%CI: 0.51-0.68). Table 2 also shows the results of subgroup analyses. The summary OR (95%CI) for clinical-based and population-based studies were 0.62 (95%CI: 0.52-0.73) and 0.53 (95%CI: 0.40-0.68), respectively. In the sub-group analyses of "Western studies", "studies with matched controls", "studies without matched controls", "Hp^+ definition as $HpSe^+$" and "adjusted results", *H. pylori* infection was also inversely associated with EAC risk. Furthermore, compared with the *Hp*-population, $CagA^+$ strains of *H. pylori* also played a protective role in EAC carcinogenesis (OR = 0.56, 95%CI: 0.45-0.70, Figure 3B). However, only one study focused on the Eastern population and the OR was 0.32 (95%CI: 0.10-1.02).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omitting a single study each time, and no substantial change in the corresponding pooled OR (data not shown) was observed. Begg's funnel plot and Egger's test were performed to assess publication bias. Begg's funnel plots were symmetrical (Figure 2), and the *P* values for ESCC

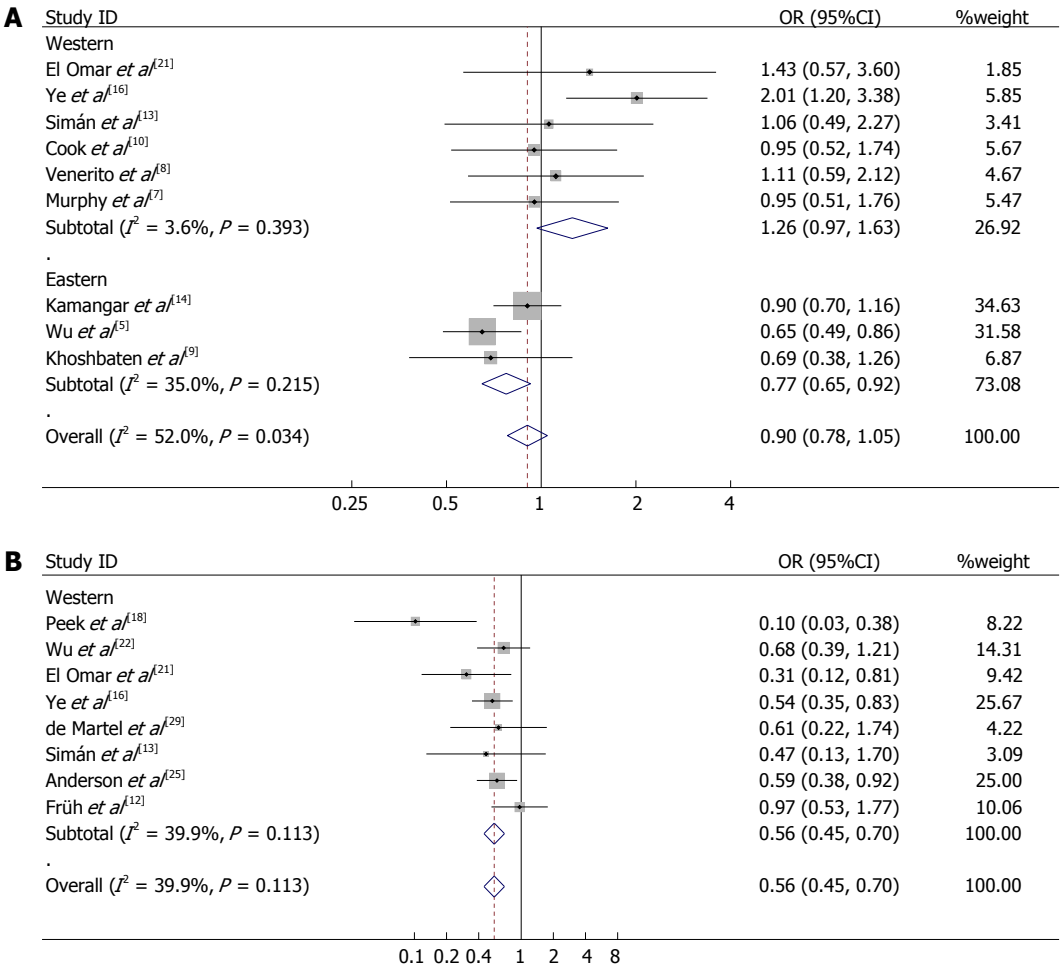

Figure 3 Meta-analysis with a fixed-effect model for the association between cytotoxin-associated gene-A-positive *Helicobacter pylori* infection and esophageal cancer. A: Esophageal squamous cell carcinoma (random-effect model); B: Esophageal adenocarcinoma (fixed-effect model).

and EAC were 0.753 and 0.621, respectively. The statistical results still did not show publication bias using Egger's test, and the *P* values for ESCC and EAC were 0.424 and 0.371, respectively. Therefore, there was no significant publication bias in the eligible studies.

DISCUSSION

In the present study, we collected all available, published studies and performed a meta-analysis to examine the association between *H. pylori* infection and the risk of esophageal cancer. Twenty-seven studies were critically reviewed to clarify the controversial results from previous reports. Our meta-analysis showed that *H. pylori* infection significantly decreased the risk of EAC in Western populations. In terms of ESCC risk, no significant association was found when the Eastern and Western populations were pooled. In the stratified analysis of study location, no significant association between *H. pylori* infection and ESCC risk in Western subjects was found. However, we observed a significant association between *H. pylori* infection and decreased risk of ESCC in East Asian populations.

There are several explanations for this phenomenon. There are fundamental differences in the carcinogenesis pathways between ESCC and EAC. Possible risk factors for ESCC include cigarette smoking, alcohol consumption, hot-temperature food, low intake of vegetables, salty food, pickled vegetables, nutrient deficiency, chronic mucosal irritation and a family history of cancer[36,37], while EAC is closely related to Barrett's esophagus[38,39]. Genetic differences between ethnic groups may also induce diverse effects. For example, Umar *et al*[40] conducted a meta-analysis which showed that the PLCE1 polymorphism conferred significant risk for gastric and esophageal tumors in Asians (Chinese), but not in Caucasians. In Eastern populations, the incidence rates of EAC are generally higher in urban areas, where diet and lifestyle are similar to those in Western counties. Therefore, nutritional intake and lifestyle combined with *H. pylori* infection may have parallel effects in Eastern and Western populations[41,42]. In contrast, ESCC patients were mainly found in areas of Eastern developing countries, where nutrient absence and hot beverage intake are more universal than in Western populations. These different factors may influence the protective effect of *H. pylori* infection. Genetic factors, tumor biological characteristics and their complicated interactions with environmental factors may modulate risk

in ESCC.

Our study also showed that *H. pylori* infection is a strong protective factor against EAC, which is highly consistent with previous reports[4,43]. The underlying mechanism whereby *H. pylori* infection protects the esophagus has not been fully elucidated. *H. pylori* infection-related gastritis may result in lower gastric acid secretion[44]. Hypoacidity induced by atrophic gastritis has been proffered as one reason for this inverse association with EC. *H. pylori* infection reduced ghrelin synthesis in infected persons, which induced early satiety thereby preventing obesity and rapid gastric emptying, thus reducing the likelihood of gastroesophageal reflux, which may explain this protective effect[45].

Two other meta-analyses have summarized the relationship between *H. pylori* infection and EC risk[4,43]. The advantages of our meta-analysis are as follows: Compared with the previous two meta-analyses, the present study was much larger, with more than twice as many cancer cases as the earlier studies. In addition, several subgroup analyses were conducted to identify potential sources of heterogeneity. Secondly, according to our selection criteria, all the studies in our meta-analysis had acceptable quality and the cases and controls were collated from all included studies, which significantly increased the statistical power. Thirdly, our study suggested that *H. pylori* infection decreased the risk of ESCC. This study should be repeated which could be beneficial in detecting novel mechanisms to reduce the risk of EC. We also found that our study had several limitations. Heterogeneity for the ORs in ESCC was observed among the studies. This heterogeneity may be due to various factors, such as diversity in the population characteristics, differences in the number of cases and controls, *H. pylori* detection methods and study design. However, heterogeneity was eliminated in the Western population after stratifying by ethnicity. The variables used to adjust these values were not consistent across the studies, which may limit the reliability of the data. Too few studies were identified to allow for subgroup analysis by covariates. Subgroup analyses regarding other confounding factors such as age and gender were conducted in the present study, but did not reduce the heterogeneity in the Eastern population. Only one study focused on the relationship between *H. pylori* infection and EAC risk in Eastern subjects (OR = 0.32, 95%CI: 0.10-1.02) which was not statistically significant ($P = 0.05$). Further studies are required to confirm the protective role of *H. pylori*.

In conclusion, despite these limitations, our meta-analysis indicated that *H. pylori* infection may contribute to the decreased risk of EAC in the overall population and of ESCC in the Eastern population. To confirm our findings, further well-designed studies with large sample size and standardized laboratory methods in diverse ethnic populations should be performed to validate this association. The potential molecular mechanism of these protective effects should also be clarified to reduce the high morbidity caused by this malignancy.

COMMENTS

Background

Esophageal cancer is one of the most deadly malignancies. Many studies have explored the association between *Helicobacter pylori* (*H. pylori*) infection and esophageal cancer risk. However, the results were inconclusive and even controversial. Therefore, it is necessary to perform a meta-analysis in order to obtain a more precise evaluation of the relationship between *H. pylori* infection and esophageal cancer risk.

Research frontiers

H. pylori has been identified as a pathogen in gastric cancers. To date, there have been many case-control studies on the association between *H. pylori* infection and esophageal cancer risk, but few meta-analyses have been conducted on this topic.

Innovations and breakthroughs

This meta-analysis indicated that *H. pylori* infection might play a protective in esophageal squamous cell carcinoma (ESCC) risk in Eastern populations and in esophageal adenocarcinoma (EAC) risk in the overall population. Further studies are required to confirm these findings.

Applications

H. pylori infection is inversely associated with ESCC risk in Eastern populations and with EAC risk in the overall population. This meta-analysis provided a structured and systematic integration of information on the etiology of esophageal cancer, and the results may provide valuable information for researchers and clinicians.

Terminology

In cytotoxin-associated gene-A (CagA) positive strains of *H. pylori* the genome contains the cag pathogenicity island. This island includes approximately 31 putative genes, including CagA the gene that encodes the CagA protein strains that translocate the CagA protein into host cells and are significantly more likely to cause gastric cancer and other gastric diseases than CagA-negative strains.

Peer review

These researchers performed a meta-analysis to clarify the association between *H. pylori* infection and development of esophageal carcinoma. The results are very important and create other questions in mind that lead to further studies.

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