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Original Article

Helicobacter pylori Infection and Risk of Cardia Gastric Cancer in Asian Countries: A Systematic Review and Meta-analysis

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Abstract

Background and objectives: The incidence of cardia gastric cancer (CGC) is rising worldwide, particularly in East Asia. There has been a debate over whether *Helicobacter pylori* (*H. pylori*) constitutes a risk factor for CGC. This study aimed to evaluate the relative risk of *H. pylori* infection and CGC in Asian countries.

Methods: Relevant studies examining *H. pylori* and CGC were searched in PubMed, Embase, and Web of Science from their inception to June 30, 2024. Either a random-effect model or a fixed-effect model was used to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). Sensitivity analyses and assessments of publication bias were performed. The stability of results was evaluated in cases where publication bias was detected.

Results: A total of 24 studies were included in the meta-analysis. A significant association between *H. pylori* and CGC was observed (OR = 2.20, 95% CI 1.73–2.80). In a subgroup analysis of different countries, a significant association was observed in East Asian countries, including China (OR = 2.12, 95% CI 1.63–2.77), Japan (OR = 2.21, 95% CI 1.16–4.20), and Korea (OR = 2.36, 95% CI 1.58–3.54), but not in Iran (OR = 1.48, 95% CI 0.77–2.84). The pooled OR from five prospective cohort studies revealed a strong association between *H. pylori* and CGC (OR = 2.32, 95% CI 1.47–3.66).

Conclusions: East Asia bears a significant burden of *H. pylori*-related CGC. A clear association between *H. pylori* infection and CGC was observed in this region.

Introduction

According to statistical sources, there were more than 960,000 new cases of gastric cancer worldwide in 2022, with about 660,000 fatalities. Gastric cancer is the fifth most prevalent malignancy and the fifth leading cause of cancer-related death globally. It can be divided into two subsites based on anatomical location: cardia gastric cancer (CGC) and non-cardia gastric cancer (NCGC).[1] East Asia has the highest incidence of CGC in the world, and the incidence continues to show an upward trend.[2]

East Asia has a 54.1% overall *Helicobacter pylori* (*H. pylori*) infection rate, which is significantly higher than that of other regions. Furthermore, this region bears a high burden of gastric cancer related to *H. pylori* infection.[3] Several studies have identified a substantial connection between *H. pylori* infection and NCGC.[4] Correa described the progression from *H. pylori* infection, chronic gastritis, chronic atrophic gastritis, intestinal metaplasia, and atypical hyperplasia to cancer, a pathway widely recognized in NCGC.[5] Additionally, *H. pylori* eradication therapy has been shown to reduce the incidence of gastric cancer and related mortality.[6] However, the relationship between *H. pylori* and CGC has remained controversial due to the unique anatomical position of CGC. A previous meta-analysis found a positive correlation in East Asia (odds ratio (OR) = 2.9, 95% confidence interval (CI) 2.3–2.6) and a negative correlation in the West (OR = 0.8, 95% CI 0.6–1.0).[4] A recent multicenter prospective case-control study of 500,000 Chinese individuals found that at least 78% of NCGC

Keywords: Cardia gastric cancer; *Helicobacter pylori*; Risk factor; East Asia; Meta-analysis; Systematic review.

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and 62% of CGC can be attributed to *H. pylori*.[7] However, the latest meta-analysis included studies on duplicate populations, which may have affected the results.[4] Therefore, our goal was to more convincingly evaluate the relative risk of *H. pylori* infection and CGC in Asian populations.

Materials and methods

Search strategy

This systematic review and meta-analysis, registered in PROSPERO (CRD42023432339), was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement.[8] All relevant studies were retrieved from three databases, including PubMed, Embase, and Web of Science, from their inception up to June 30, 2024. The following search terms were utilized: ("cardia" OR "proximal" OR "esophagogastric junction" OR "gastroesophageal junction") AND ("neoplasm" OR "tumor" OR "cancer" OR "neoplasia" OR "carcinoma" OR "adenocarcinoma") AND ("*helicobacter pylori*" OR "*helicobacter nemestrinae*" OR "*campylobacter pylori*" OR "*H. pylori*"). The detailed search strategy is provided in Table S1. Additionally, reference lists of relevant studies were checked to identify additional eligible studies. Two collaborators independently retrieved and evaluated the included studies, with disagreements resolved through consensus.

Inclusion and exclusion

All studies investigating the association between *H. pylori* infection and CGC in Asian populations were considered for screening. *H. pylori* detection methods included histology, rapid urease testing, culture, serology, or carbon-urea breath testing. The inclusion criteria were carefully defined: (1) the study type included case-control, cross-sectional, or cohort studies; (2) the exposure variable was *H. pylori* infection; (3) the case group involved CGC, and the control group was free of gastric cancer; (4) the population was from Asian countries; (5) studies provided sufficient data to estimate ORs or risk ratios; and (6) studies were published in English with full text available. We attempted to exclude other types of gastroesophageal junction carcinoma, such as distal esophageal adenocarcinoma. Case reports, letters, comments, reviews, and duplicate publications were excluded.

Data extraction

Two authors extracted detailed information from each included study, including the first author, publication year, country, patient characteristics (age, sex), study design (study type, follow-up time, method of *H. pylori* detection), definition of CGC, and details of the case and control groups (sample size, *H. pylori* infection status, outcomes).

Quality assessment and risk of bias

The methodological quality of eligible studies was independently assessed by two authors using the Newcastle-Ottawa Scale for case-control and cohort studies. Studies with scores ranging from seven to nine points were considered high quality. The risk of bias was assessed using ROBINS-E, a tool for non-randomized exposure studies, across several domains, including confounding, participant selection, exposure measurement, post-exposure interventions, missing data, outcome measurement, and selection of reported results.[9] A study was considered to have a high risk of bias if bias was present in at least one of the seven domains.

Statistical analysis

Pooled ORs with 95% CIs were calculated to assess the association between *H. pylori* and CGC. The model used was based on heterogeneity results, which were analyzed using the chi-squared (χ^2) test (Cochran's Q) and the inconsistency index (I^2). A random-effect model was employed when significant heterogeneity was identified (χ^2 $P < 0.05$ or $I^2 > 50\%$); otherwise, a fixed-effect model was applied. The aim of our analysis was to investigate the association between *H. pylori* infection and the risk of CGC. Subgroup analyses were conducted to explore effect modification based on study-level factors such as country, detection time of *H. pylori*, publication year, and duration of follow-up. Sensitivity analyses were performed to explore potential sources of heterogeneity. Publication bias was evaluated using funnel plots (Begg's and Egger's regression tests). All analyses were performed using Review Manager V.5.4 and STATA 15, with statistical significance defined as $P < 0.05$.

Results

Literature search and study characteristics

The PRISMA flowchart is presented in Figure 1. The preliminary literature search yielded a total of 4,308 articles from PubMed, Embase, and Web of Science. After removing 1,829 duplicates and excluding 2,393 unrelated articles based on title and abstract screening, 86 studies remained for full-text review. Finally, 24 full-text articles were included in the final analysis,[7,10–32] after excluding six studies that used duplicate populations.[33–38] The analysis involved 2,529 CGC cases and 52,556 control subjects. The study populations of the 24 included studies were from Asian countries (eight in China, nine in Japan, five in Korea, and two in Iran). The characteristics and quality scores of the eligible articles are shown in Table 1. Using the ROBINS-E risk of bias tool, three studies were rated as high risk of bias, six as moderate risk, and the remainder as low risk (Fig. 2).

Pooled data

The pooled OR for the association between *H. pylori* and CGC in Asian countries was 2.20 (95% CI 1.73–2.80), with significant heterogeneity (I^2 = 66%, $P < 0.001$), based on a random-effect model (Fig. 3).

Subgroup analysis

Stratification by country

The included studies were from Asian countries. A significant association between *H. pylori* and CGC was observed in East Asian countries, including China (OR = 2.12 [95% CI 1.63–2.77], I^2 = 58%, $P < 0.001$), Japan (OR = 2.21 [95% CI 1.16–4.20], I^2 = 78%, $P = 0.02$), and Korea (OR = 2.36 [95% CI 1.58–3.54], I^2 = 15%, $P < 0.01$), but not in Iran (OR = 1.48 [95% CI 0.77–2.84], I^2 = 0%, $P = 0.24$) (Fig. 4a).

Stratification by detection time of *H. pylori*

It is possible that *H. pylori* infection could be cleared as the cancer progresses.[39,40] Identifying the status of *H. pylori* before malignancy develops can help reduce false-negative results to some extent. Seven articles, including five cohort studies and two nested case-control studies, detected the status of *H. pylori* before the onset of CGC. A comparable correlation was observed regardless of *H. pylori* detection time (OR = 2.03 [95% CI 1.32–3.12], I^2 = 69%,

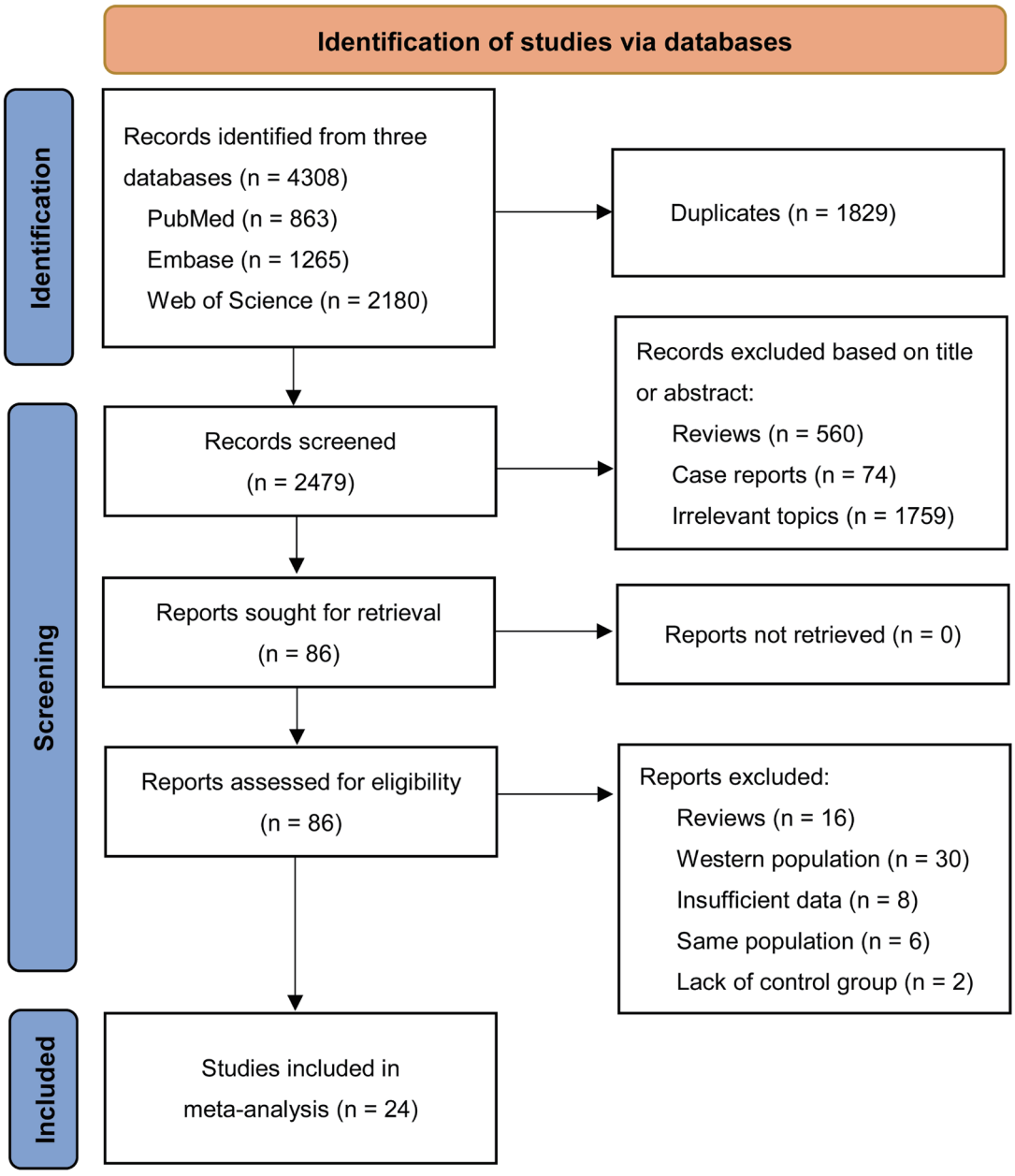


Fig. 1. Flowchart of the systematic search and selection process.

P = 0.001; OR = 2.27 [95% CI 1.67–3.09], I^2 = 66%, P < 0.001) (Fig. 4b).

Stratification by publication time

Between 1990–2000 and 2000–2010, there was a significant association between *H. pylori* and CGC (OR = 2.83 [95% CI 1.55–5.19], I^2 = 58%, P < 0.001; OR = 2.10 [95% CI 1.55–2.86], I^2 = 48%, P < 0.001). However, the pooled studies published from 2010 to 2020 showed no correlation (OR = 1.56 [95% CI 0.73–3.32], I^2 = 72%, P = 0.25) (Fig. 5a).

Stratification by follow-up time

Seven of the studies were retrospective or prospective cohort studies, with five being prospective studies with a follow-up period of more than five years. The pooled data analysis of five studies revealed a notable association between *H. pylori* and CGC (OR = 2.32 [95% CI 1.47–3.66], I^2 = 75%, P < 0.001), while no correlation was seen in two studies with follow-ups of less than five years (OR = 0.94 [95% CI 0.36–2.46], I^2 = 0%, P = 0.90) (Fig. 5b).

Publication bias and sensitivity analysis

Publication bias was evaluated using Begg's and Egger's tests. No substantial publication bias was observed (P-value of Begg's test = 0.980, P-value of Egger's test = 0.503) (Fig. S1). Furthermore, visual inspection of the funnel plot shapes revealed no significant evidence of asymmetry among the studies (Fig. 6). The study by

Table 1. Characteristics of 24 studies

First author	Year	Country	Design	Study period	Median follow-up (year)	H.pylori method	Age (year)	Male (%)	Number of CGC/ control	Definition of CGC	NOS
Chen[10]	2009	Taiwan, China	case-control	2000–2009	–	ELISA	CGC: 64.53 ± 2.17 Control: 63.27 ± 1.73	100 100	41/205	within 5mm to GEJ	8
Cho[11]	2010	Korea	case-control	2003.6–2007.4	–	ELISA	Case: 58.1 ± 12.0 Control: 53.0 ± 7.0	68.8 50.0	216/562	within 2cm distal to GEJ	8
Derakhshan[12]	2008	Iran	case-control	–	–	ELISA	CGC: 63.8 ± 7.1 Control:matched	69.8 –	53/53	within 2cm distal to GEJ	7
Gao[13]	2022	China	case-control	2010–2014	–	Immunoblot	CGC: 69.3 ± 7.9 Control: 66.3 ± 8.71	67.9 69.1	349/1,859	within 5cm to GEJ	8
Horii[14]	2011	Japan	case-control	2000.8–2009.1	–	histology/RUT/ELISA	CGC: 68.7 ± 9.5 Control: 61.7 ± 8.3	87.0 93.5	23/46	within 2cm to GEJ	8
Inoue[15]	2020	Japan	cohort	1993–1994	18	ELISA	56.7 ± 8.3	Case: 62.2 Control: 37.7	50/1,8511	anatomical position	7
Kamangar[16]	2007	China	case-cohort	1985–2001	10	ELISA	CGC: 55.5 ± 7.7 Control: 51.9 ± 8.9	60.3 45.3	582/992	proximal 3cm of the stomach	8
Kato[17]	2004	Japan	case-control	–	–	ELISA	–	–	86/6,578	–	7
Kikuchi[18]	1995	Japan	case-control	1988–1992	–	ELISA	GC: 20–40 Control: 15–44	45.7 43.6	35/203	–	7
Kikuchi[19]	2000	Japan	case-control	1993.6–1995.7	–	ELISA	matched	GC: 66.1 Control: 51.3	186/1,007	upper third of stomach	7
Kim[20]	1997	Korea	case-control	1994	–	histology/RUT	GC: 57.3 Control: 56.9	65 61.9	12/160	anatomical position	6
Kim[21]	2012	Korea	case-control	2003.6–2011.2	–	histology/RUT/ ELISA/tissue culture	Case: 60.3 ± 12.3 Control: 55.9 ± 11.9	67.3 33.7	60/270	within 2cm below GEJ	8
Komoto[22]	1998	Japan	case-control	1991–1996	–	ELISA	GC: 64.9 ± 1.2 Control: 62.4 ± 1.1	78.10 matched	14/105	within 20mm distal to GEJ	8
Lee[23]	1998	Korea	case-control	1992–1995	–	RUT	GC: 54.4 Control: 40.5	67.4 71.7	17/113	anatomical position	7
Shakeri[24]	2015	Iran	case-control	2004.12–2011.12	–	ELISA,multiplex serology	CGC: 66.3 ± 11.1 Mcontrol: 64.5 ± 9.1	78.2 77.2	142/276	-	8
Shibata[25]	1996	Japan	case-control	–	–	histology	GC: 62 Control: 61.8	74 74	5/50	upper third of stomach	6
Shin[26]	2005	Korea	nested case-control	1993–1999	2.6	ELISA	Cases: 63.0 Control:matched	66 matched	6/24	–	8

(continued)

Table 1. *(continued)*

First author	Year	Country	Design	Study period	Median follow-up (year)	H.pylori method	Age (year)	Male (%)	Number of CGC/ control	Definition of CGC	NOS
Suzuki[27]	2007	Japan	nested case-control	1970.1–2001.12	2	ELISA	CGC: 70 ± 11 Control: –	54.5 58.9	22/1,042	–	7
Wu[28]	2009	Taiwan, China	case-control	2000–2007	–	ELISA	GC: 63.2 ± 13.5 Control: 40.2 ± 6.2	62.8 51.6	29/395	within 3cm distal to GEJ	8
Xie[29]	2020	China	cross-sectional	2014.1–2016.6	–	13C	CGC: 62.65 ± 5.27 Control: 53.30 ± 7.94	41.96 60.87	23/1,225	–	8
Yamaoka[30]	1999	Japan	case-control	–	–	ELISA	GC: 64.5 Control: matched	72.7 matched	23/23	cardia and fundus	6
Yan[32]	2024	China	case-cohort	2015–2017	6.3	13C	54.7	41.8	76/18,233	–	8
Yang[7]	2021	China	case-cohort	2004.6–2008.7	10.1	Immunoblot	CGC: 61.2 ± 8.6 Control: 59.1 ± 9.9	75.0 69.0	436/500	–	8
Yuan[31]	1999	China	case-cohort	1986–1989	5.2	ELISA	GC: 63.4 ± 5.6 Control: matched	–	43/124	–	8

CGC, cardia gastric cancer; ELISA, enzyme linked immunosorbent assay; GC, gastric cancer; GEJ, gastroesophageal junction; NOS, Newcastle-Ottawa Scale; RUT, rapid urease test.

Fig. 2. Assessment of risk of bias using the ROBINS-E.

Kikuchi *et al*.[19] deviated from the line of symmetry, which could be attributed to the study population being primarily composed of patients under the age of 40. We assessed the contribution of each study to the overall pooled OR through a leave-one-out sensitivity

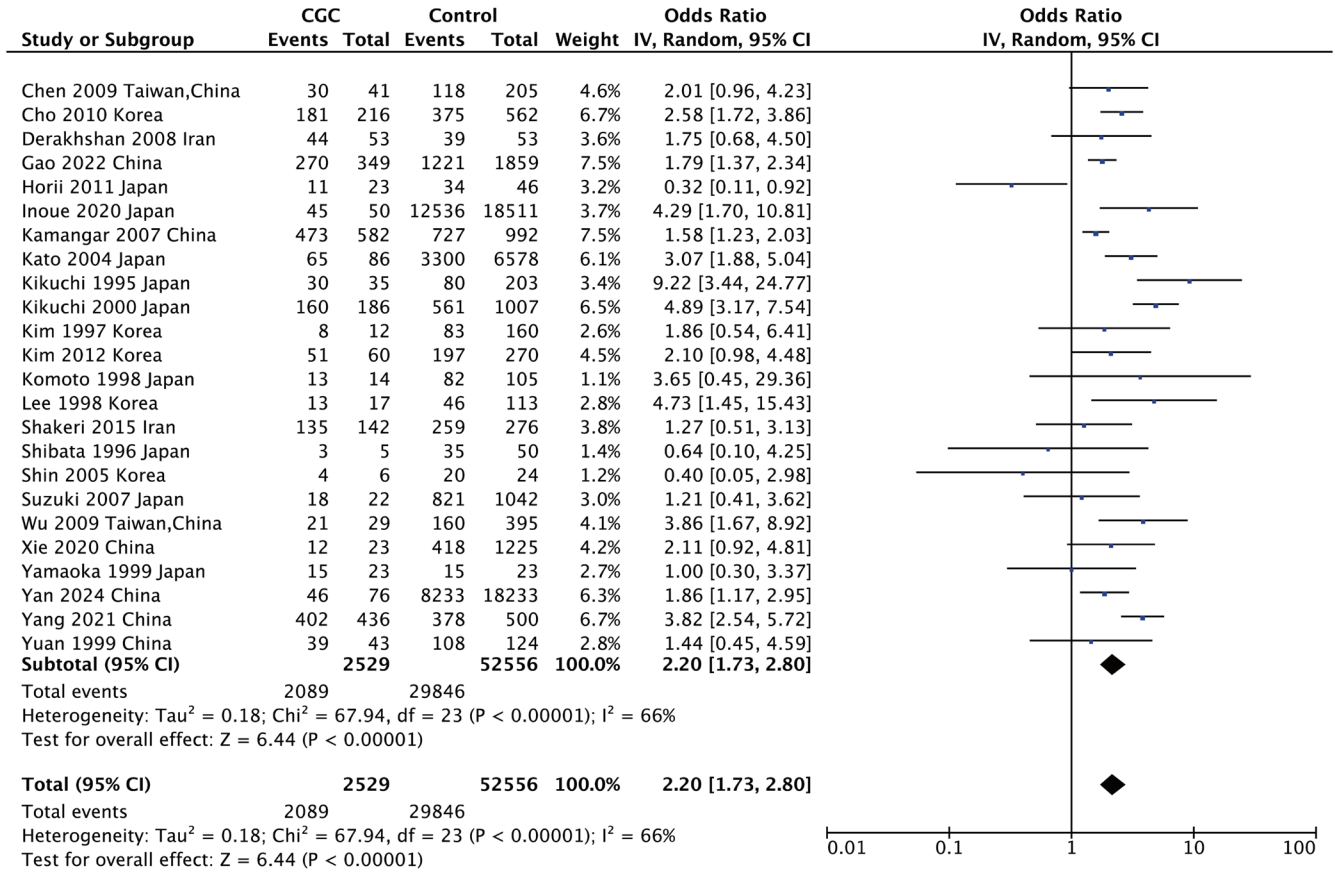


Fig. 3. Forest plot for *Helicobacter pylori* infection among cardia gastric cancer. CI, confidence interval; IV, inverse variance.

analysis. The stability of the results was confirmed, as no single study significantly influenced the pooled OR (Fig. 7). When combined with the results of the subgroup analysis, the heterogeneity was attributed to various factors, including differences in the definition of CGC, study population, and *H. pylori* detection methods.

Discussion

The incidence rate of CGC is increasing in Asian countries. The proportion of CGC in Japan has risen from 2.3% to 10.0% in recent years.[41] In high-incidence areas of China, the rate can reach 50/100,000.[42] The risk factors and etiology of CGC are debatable but appear to be related to geography and ethnicity. Previous studies have yielded contradictory conclusions about the relationship between *H. pylori* and CGC.[4,43–46] Han *et al*.[4] conducted a meta-analysis that demonstrated a significant association between *H. pylori* infection and CGC in East Asia, but the analysis included studies using duplicated populations. Moreover, the most recent meta-analysis by Gu *et al*.[47] completed the literature search in December 2021. Recent papers could significantly affect these conclusions. Therefore, we updated the literature and excluded studies using duplicated populations to analyze any new associations between *H. pylori* and CGC in Asia.

A total of 24 studies were included in our meta-analysis. The *H. pylori* infection rate in CGC cases was 2.20 times greater than that in the control group, confirming that *H. pylori* is a clear risk factor for CGC. At the same time, we conducted a subgroup analysis for different countries. The outcomes revealed that infected individuals from East Asia (China, Japan, and Korea) had a twofold higher risk of developing CGC than the control group, whereas no correlation was found in Iran. Our analysis only included two Western Asia-related studies from Iran. Western Asia has much lower age-standardized incidence rates of stomach and esophageal malignancies than Eastern Asia, which ranks first.[48] Additionally, several previous studies confirmed a null or negative correlation between *H. pylori* and CGC in Western populations or low-incidence regions.[4,43,44,46] Hence, a positive association between *H. pylori* and CGC was only observed in East Asia.

Because of the unique location of the esophagogastric junction (GEJ), CGC is likely a heterogeneous tumor originating from different mucosal types. Internationally, various definitions and classification standards exist. The Siewert classification, proposed in 1987 and extensively used, refers to adenocarcinomas located within 5 cm of the GEJ, including type I (located 1 to 5 cm above the GEJ), type II (located 1 cm above to 2 cm below the GEJ), and type III (located 2 to 5 cm below the GEJ).[49] The Kyoto International Consensus Report in 2022 stated that adenocarcinomas within 1 cm of the GEJ should be classified as "cardia cancer".[50] Several studies have found geographical variations in the pathogenesis of CGC. In the West, it is often associated with excessive gastric acid damage caused by gastroesophageal reflux disease, similar to esophageal adenocarcinoma. In East Asia, CGC is associated with gastric mucosal atrophy induced by *H. pylori* infection, similar to distal gastric cancer.[12,51,52] Urabe *et al*.[53] demonstrated

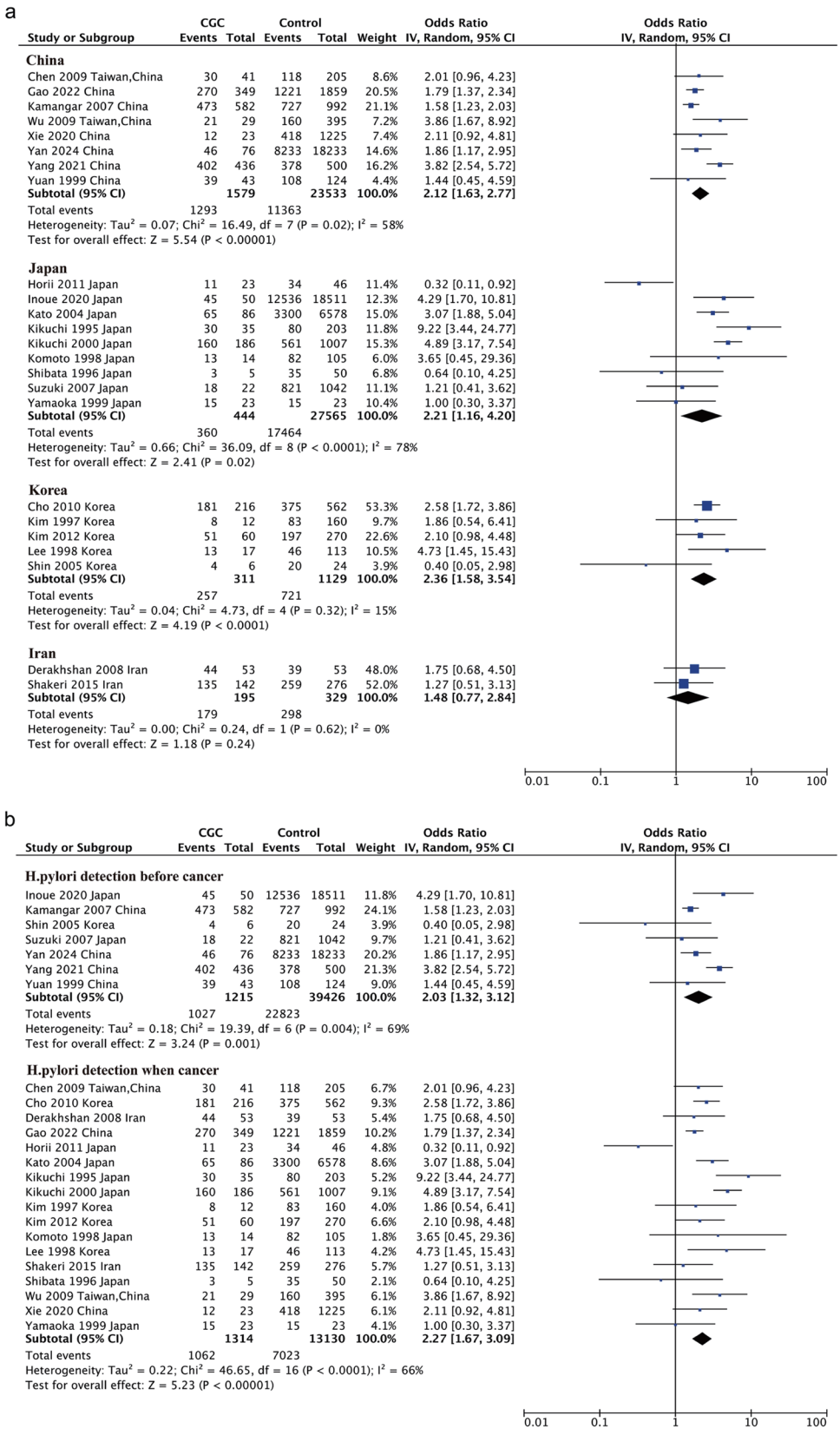
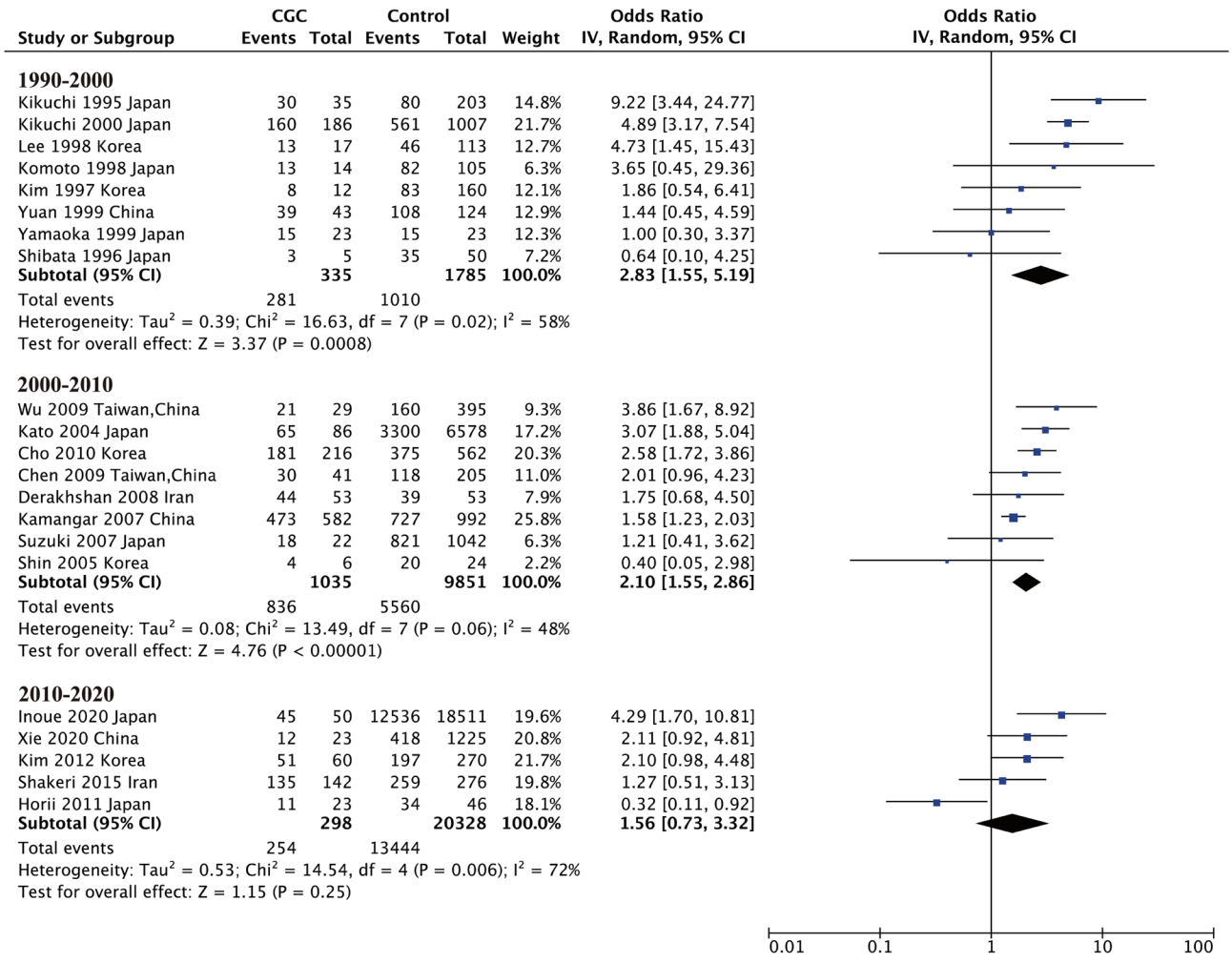


Fig. 4. Subgroup analysis (a) by countries; (b) by detection time of *Helicobacter pylori*. CGC, cardia gastric cancer; CI, confidence interval; IV, inverse variance,

a



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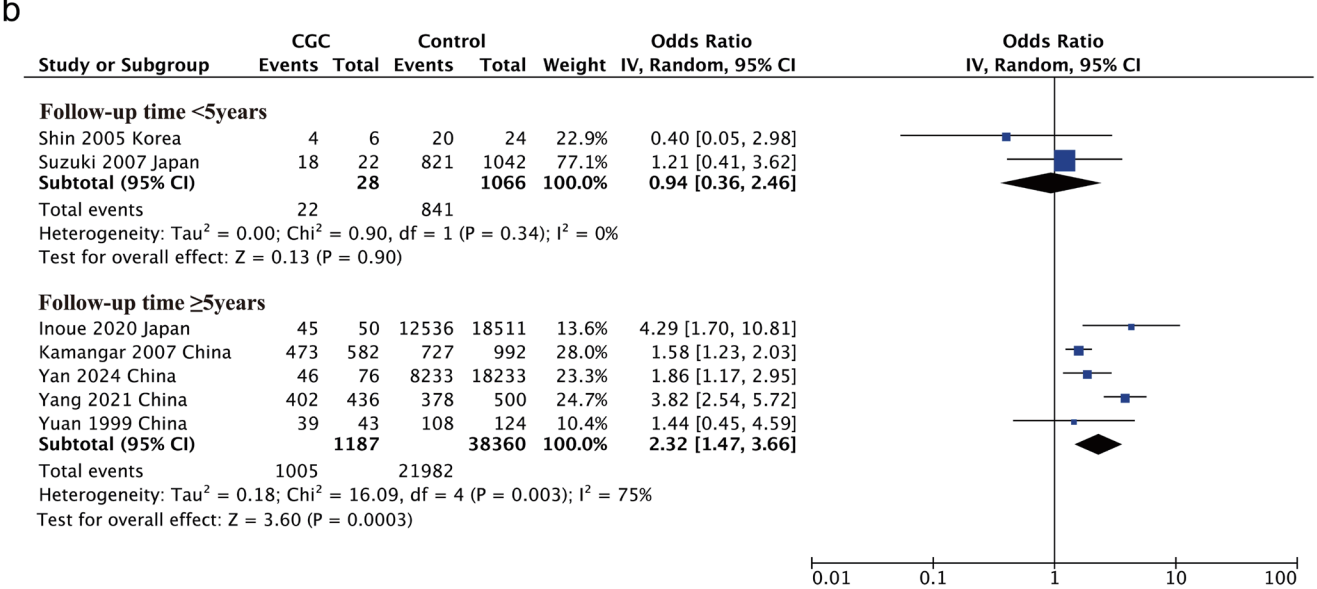

Fig. 5. Subgroup analysis (a) by publication time; (b) by duration of follow-up time. CGC, cardia gastric cancer; CI, confidence interval; IV, inverse variance.

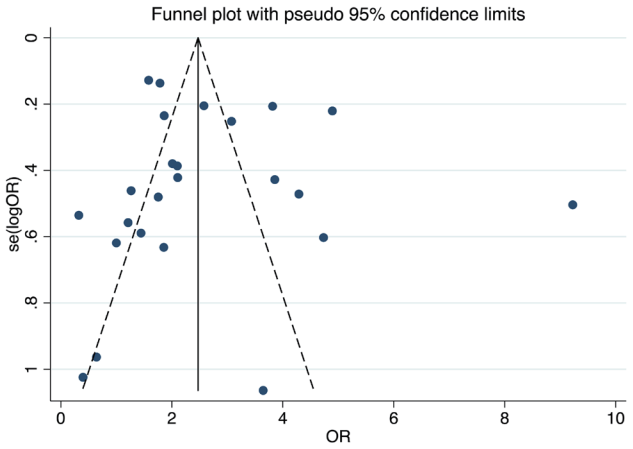

Fig. 6. Funnel plot. OR, odds ratio.

that gastric cancers and type III adenocarcinoma of the esophagogastric junction had a similar background mucosal type. Based on survey data from three high-incidence areas in China, the long-term morbidity and mortality risk of CGC increased as the severity of cardia mucosal lesions increased. Trend analysis revealed a positive correlation between the degree of mucosal lesions and the *H. pylori* infection rate.[54] To summarize, severe mucosal atrophy and intestinal metaplasia increase the risk of CGC to some extent. The question of whether its occurrence and development follow the path of Correa needs further exploration. Additionally, the strain type of *H. pylori* and host susceptibility also play roles in the complex process of carcinogenesis. Current clinical research has found that compared to NCGC, CGC tends to present at a later pTNM stage and has worse clinical outcomes.[55] Therefore, identifying risk factors, performing early screening, and implementing interventions are critical in clinical practice.

In addition, the accuracy of *H. pylori* status is affected by various factors. The first issue involves methodological limitations. In one prospective study, the relationship between *H. pylori* and the risk of NCGC assessed by immunoblot was more than threefold higher than that assessed by ELISA (enzyme linked immunosorbent assay),[56] indicating that detection techniques have different sensitivity levels. Secondly, anti-*H. pylori* therapy for atrophic gastritis prior to malignancy should be considered. Moreover, both histological infection and serological antibody titers of *H. pylori* may be cleared or decreased as cancer progresses.[39] As a result, the *H. pylori* infection rate may be underestimated due to the factors described above. We performed a subgroup analysis based on the detection time of *H. pylori* and found that there was a consistent correlation regardless of detection time, and heterogeneity was not primarily due to this factor. The results from five prospective cohort studies appear to be more reliable. We did not conduct a subgroup analysis of different detection methods because only a few studies employed the immunoblot method.

This meta-analysis has certain limitations. First, although we performed sensitivity analysis to evaluate the stability of the results, the source of heterogeneity remains somewhat difficult to explain. At least half of the studies contributed to the heterogeneity. On the one hand, the criteria for CGC in various studies have not been standardized, resulting in heterogeneity in study populations. Second, various methods were used to detect *H. pylori*. Studies focusing on younger patients may also have contributed to the heterogeneity. Third, the majority of the included studies were retrospective case-control studies, which are subject to selection bias

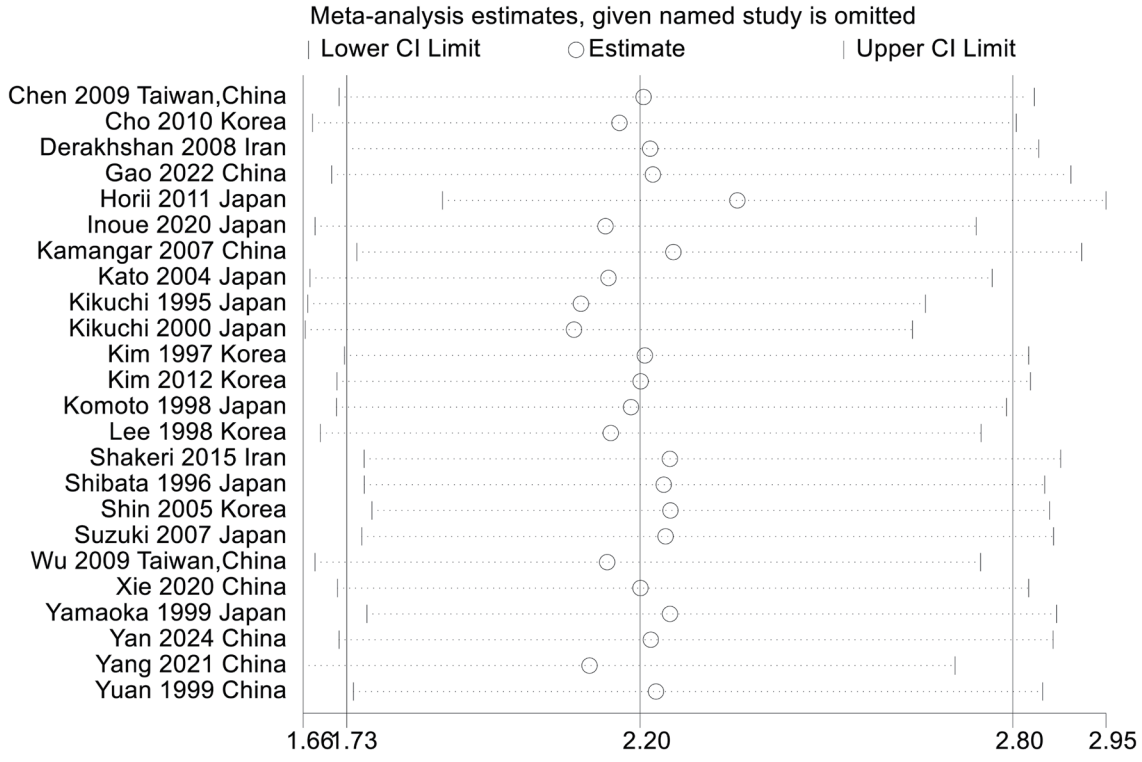

Fig. 7. Sensitivity analysis. CI, confidence interval.

and confounding variables. Although most studies were matched by age and gender, other risk factors, including diet, smoking, alcohol consumption, gastroesophageal reflux disease, and gastrointestinal ulcers, may confound the relationship between *H. pylori* and CGC.[57] Additional adjustments are required for these risk variables. Furthermore, our conclusions primarily focus on East Asian populations due to the lack of sufficient information from countries outside East Asia. Despite the constraints of our study, we updated the latest relevant literature. In addition, we identified and excluded studies using duplicate population cohorts, compared to a prior meta-analysis.[4] In summary, *H. pylori* infection is a risk factor for CGC in East Asia. It is meaningful to conduct early detection and intervention.

Conclusions

East Asia bears a significant burden of CGC, where a positive association between *H. pylori* infection and CGC has been observed. We anticipate the development of more reliable endoscopic techniques and pathology diagnostics to better identify the origin of cancer in the gastroesophageal junction area. Additionally, more valuable prospective cohort studies and randomized controlled trials are needed. Identification of risk factors and early intervention are critical for reducing the incidence of CGC.

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None.

Conflict of interest

One of the authors, Prof. Ruihua Shi has been an associate editor of *Cancer Screening and Prevention* since March 2022. There are no other conflicts of interest regarding the publication of this paper.

Author contributions

Material preparation, data collection, and analysis (YNZ, YD), writing of the first draft of the manuscript (YNZ). All authors contributed to the study's conception and design and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data sharing statement

The datasets used in support of the findings of this study are available from the corresponding author at ruihuashi@126.com upon request.

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