A study of the association between *Helicobacter pylori* infection type and pancreatic cancer risk: A systematic review and meta-analysis

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Abstract. Pancreatic cancer is a highly invasive malignant tumor with a complex pathogenesis that makes early diagnosis challenging. The potential association between *Helicobacter pylori* infection and pancreatic cancer risk has been noted; however, the available results are still highly divergent. The aim of the present study was to systematically evaluate the association between different types of *H. pylori* infection and pancreatic cancer risk as well as to explore the possible causes. A systematic search was conducted using the PubMed, Embase and Cochrane Library databases up to August 2023. The literature quality was evaluated using the Newcastle-Ottawa Scale. All studies that met the criteria were included in the overall meta-analysis to calculate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In addition, subgroup analyses were performed based on factors such as diagnostic criteria for *H. pylori* infection, study region, type of study design and CagA status. The effect of publication bias on the quantitative synthesis results was assessed using the trim-and-fill analysis, and sensitivity analyses were used to verify the robustness of the quantitative synthesis results. A total of 17 studies involving 67,910 participants, including 64,372 controls and 3,538 patients with pancreatic cancer, were included in the present study. The overall analysis showed that no significant association was observed between *H. pylori* infection and pancreatic cancer risk (OR, 1.15; 95% CI, 0.93-1.41). Further subgroup analyses, which did not consider the effects of study quality, diagnostic criteria, geographical distribution and the type of study design, did not produce new findings that contradicted the results of the overall analysis. $CagA^+$ *H. pylori* infection did not significantly affect the risk of pancreatic cancer (OR, 0.95; 95% CI, 0.78-1.16), whereas $CagA^-$ *H. pylori* infection may be a possible risk factor for pancreatic cancer (OR, 1.24; 95% CI, 1.004-1.541). The *H. pylori* infection did not significantly increase the risk of pancreatic cancer. However, it is noteworthy that $CagA^-$ *H. pylori* infection could be a potential factor that elevated the risk of pancreatic cancer.

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Introduction

Helicobacter pylori is a bacterium that is capable of thriving at the low oxygen and acidic conditions of the stomach, and infection is closely related to various gastrointestinal disorders, such as peptic ulcer disease and non-ulcer dyspepsia. (1). The bacterium produces the enzyme, urease, which decomposes urea to generate ammonia thereby neutralizing the surrounding acid and facilitating its survival in the highly acidic stomach mucosa (2). This property notably contributes to the issue of drug resistance of *H. pylori*, and the application of novel nanomaterials for the treatment of drug-resistant bacteria represents a promising avenue (3-5). The risk associated with *H. pylori* infection stems from its ability to induce chronic inflammation, which is a significant factor in tumorigenesis. Chronic inflammation can lead to genetic mutations in gastric mucosal cells and increase the risk of gastric cancer (6). In recent years, with the in-depth research on the association between *H. pylori* infection and cancer, increasing evidence suggests that *H. pylori* infection is not only associated with the development of gastric cancer, but also potentially associated with other types of cancer such as pancreatic cancer (7,8).

Pancreatic cancer is a highly malignant tumor characterized by subtle early symptoms that can be easily overlooked or misdiagnosed resulting in a mid-to-late stage diagnosis and a missed opportunity for the most effective treatment (9). In

addition, the complex biological behavior of pancreatic cancer makes it a challenging tumor to treat (10). According to the 2022 Global Cancer Statistics, there were ~511,000 new cases of pancreatic cancer and 467,000 pancreatic cancer-associated deaths. Pancreatic cancer has one of the worst prognoses, ranking sixth among the causes of cancer-related deaths in both men and women, and accounting for ~5% of all cancer-related deaths worldwide. The incidence is approximately four times higher in countries with a higher Human Development Index (HDI) compared with those with a lower HDI (11).

The etiology of pancreatic cancer is complex and is not yet fully understood. Existing studies suggested that pancreatic cancer may be associated with several factors such as genetic factors, dietary factors, smoking, alcoholism, chronic pancreatitis, pancreatic stones, obesity and metabolic syndrome. Among them, mutations in BRCA1, BRCA2 and CDKN2A are associated with an increased risk of pancreatic cancer (12,13). Smoking and alcohol abuse may lead to DNA damage and gene mutations in pancreatic cells and are therefore considered to be important risk factors for pancreatic cancer (14).

Although the etiology of pancreatic cancer has not yet been fully elucidated, the potential carcinogenic role of *H. pylori* infection has attracted increased attention from researchers. There have been numerous attempts to study the association between *H. pylori* infection and pancreatic cancer risk. However, the studies have revealed notable heterogeneity and even contradictory results (15). Huang *et al* (16) conducted a nested case-control study of 448 pancreatic cancer cases and 447 individually matched control subjects; the authors demonstrated that there was no marked association between *H. pylori* infection and pancreatic cancer risk in Western European populations [odds ratio (OR), 0.96; 95% confidence interval (CI), 0.70-1.31]. By contrast, in a population-based case-control study, Risch *et al* (17) found an association between pancreatic cancer and $CagA^-$ *H. pylori* colonization, especially for individuals in the non-O blood group (OR, 2.78; 95% CI, 1.49-5.20). Even meta-analyses that combined several studies have shown varying results. A meta-analysis by Xiao *et al* (18) showed a notable association between *H. pylori* infection and pancreatic cancer development in Europe and East Asia, but this association was weak in North America. A meta-analysis by Zhou *et al* (19) indicated that there was no sufficient evidence to support an association between *H. pylori* infection and increased risk of pancreatic cancer, with similar results for the $CagA^+$ *H. pylori* infection subgroup. A quantitative synthesis of 10 studies conducted by Schulte *et al* (20) revealed that $CagA^+$ *H. pylori* infection may be a protective factor for pancreatic cancer development (OR, 0.78; 95% CI, 0.67-0.91), whereas $CagA^-$ strain infection may be a potential risk factor (OR, 1.30; 95% CI, 1.02-1.65). This heterogeneity may stem from a variety of factors, including differences in study design, region, ethnicity, *H. pylori* strains, inconsistencies in diagnostic criteria for pancreatic cancer and limitations in sample size.

Given the limitations and uncertainties of existing studies, additional in-depth and systematic studies are necessary. The present review aimed to collect additional abundant and standardized data, including prospective and retrospective studies, through rigorous inclusion criteria and more comprehensive statistical analyses to overcome the controversies and limitations in the existing studies and to clarify the association between *H. pylori* infection and the risk of pancreatic cancer, providing new ideas for the prevention and management strategies of pancreatic cancer and *H. pylori* infection.

Materials and methods

Registration protocol. The present review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (21) and was registered on PROSPERO (https://www.crd.york.ac.uk/prospero/; registration no. CRD42024520782) to ensure the completeness and traceability of the study design, analysis and results. The registration information includes the study purpose, study design, key indicators and the plan for data collection and analysis.

Search strategy. The PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/) and Cochrane Library (https://www.cochranelibrary.com/) databases were searched, and the search scope was confined to studies published from the inception of the database up to August 31st, 2023. When searching PubMed, subject terms were selected according to the Medical Subject Headings (MeSH) subject term list, and when searching Embase, Emtree was used to check and adjust the terms. The pattern of subject terms plus free words were used while searching, and the terms were mainly from the fields of pancreatic cancer and *H. pylori*. For example, the following search strategy was used in the PubMed database: [('*Helicobacter pylori*' (MeSH Terms) OR '*helicobacter pylori*' (All Fields) OR '*H. pylori*' (All Fields)] AND ['Pancreatic neoplasms' (MeSH Terms) OR 'pancreatic neoplasms' (All Fields) OR 'pancreatic cancer' (All Fields) OR 'pancreatic adenocarcinoma' (All Fields)] AND ['1,000/1/1' (Date-Publication) : '2023/8/31' (Date-Publication)]. The search terms used in the Embase and Cochrane Library databases were similar to those used in PubMed. The search strategy was developed after discussion among all authors and modified by several rounds of adjustments. In addition, a manual citation search was performed on the included studies.

Inclusion and exclusion criteria. The inclusion criteria were as follows: i) Case-control or cohort study; ii) human study object; iii) investigation of the relationship between *H. pylori* infection and pancreatic cancer risk; iv) *H. pylori* infection with or without $CagA^+$ status as determined by serology [such as enzyme linked immunosorbent assay (ELISA) or western blotting] or any other reliable method; v) diagnosis of pancreatic cancer (exocrine pancreatic cancer or pancreatic duct cancer) pathologically confirmed or from reliable documentation; vi) available detailed data on the status of *H. pylori* infection in pancreatic cancer cases and control groups; and vii) literature published in the English language.

The exclusion criteria were as follows: i) Unavailable abstracts or full texts; ii) unavailable detailed data such as positive rate of *H. pylori* infection status; iii) study types such as reviews, conferences, guidelines and meta-analyses; iv) topic unrelated to the association between *H. pylori* infection and pancreatic cancer risk; v) low quality studies such as those with a too small a sample size or notable flaws in the study

design; vi) study data overlapped with data from other studies; and vii) outcome indicators unrelated to pancreatic cancer.

Two authors read the literature separately and selected the studies strictly according to the aforementioned inclusion and exclusion criteria. Differences were resolved through discussion.

Data extraction. Data extraction was separately performed by two authors with a unified data table. The results were cross-checked and differences were resolved through discussion. Data were extracted based on first author, publication year, study location, study design type, sample size, mean age, diagnostic criteria for *H. pylori* infection and pancreatic cancer, as well as CagA status.

Literature quality evaluation. The quality of the methodology section of the included studies was assessed according to the Newcastle-Ottawa Scale (NOS) (22). This scale is applicable to case-control and cohort studies. The contents of the evaluation can be divided into three categories: i) Selection of the study population: Definition of cases, representativeness of case groups, selection of controls and definition of controls; ii) comparability: Comparability between the control and case groups; and iii) exposure: Determination of exposure, consistency of exposure determination methods between groups and the non-response rate. The evaluation was completed according to the scores of these items. The item for between-group comparability can be awarded 2 points, while other items receive 1 point each, with a maximum possible score of 9 points. The higher the score, the higher the quality of the methodology section of the assessed study. A score of >7 was considered to indicate a high-quality study in the present analysis.

Statistical analysis. Stata (version 14.0; https://www.stata.com/) was used for statistical analysis. An overall meta-analysis of all included studies was performed to determine the association between *H. pylori* infection and pancreatic cancer risk. In addition, several subgroup analyses were performed, including a meta-analysis that included only high-quality studies, and subgroup analyses sorted by study design, geographical distribution and diagnostic criteria for *H. pylori* infection. Subgroup analyses of the association between $CagA^+$ *H. pylori* infection and $CagA^-$ *H. pylori* infection were also conducted.

OR was used as the combined effect size. OR and 95% CI were used as statistical measures of the strength of association. Heterogeneity between studies was measured by the I^2 value based on χ^2 tests, and the heterogeneity was considered to be significant if I^2 was >50% (23). Considering that there is always heterogeneity in intervention effects across multiple studies from different groups and geographical locations, a random effects model was used to calculate the combined effect sizes. The funnel plot method, Begg's rank correlation and Egger's linear regression test were used to detect potential publication bias. P<0.05 was considered to indicate a statistically significant publication bias (24,25). The effect of publication bias on the merged results was assessed using the trim and fill method (26). Leave-one-out sensitivity analyses were performed to check the robustness of the combined results and to avoid a significant influence of extreme data from a single study on the combined results.

Results

Literature search and characteristics of the included studies. The search of the three databases (PubMed, Embase and Cochrane Library) and the manual citation search yielded 1,024 articles, leaving 906 articles after screening for duplicates. Further screening of titles, abstracts and full text yielded 17 suitable articles for the present study (16,17,20,27-40). The selection process is shown in Fig. 1. These studies involved 67,910 participants (3,358 patients with pancreatic cancer and 64,372 control group members) and included 9 case-control studies, 5 nested case-control studies and 3 cohort studies. Of these studies, 7 were conducted in Asia, 5 in Europe, 4 in North America and 1 in Oceania. The sample size range of the studies was 53-30,110 (Table I). Additionally, 16 studies used serological markers as the diagnostic criteria for *H. pylori* infection, and only Hsu *et al* (36) used histopathological examination to diagnose *H. pylori* infection. This histopathological approach may depend largely on the level of expertise of the examiner and may not identify previous infection. A total of 11 studies further tested for CagA antibodies, while 1 study employed multiple serology to simultaneously test for CagA, Vacuolating Cytotoxin A (VacA) and other virulence factors (31).

It is noteworthy that the study populations of Stolzenberg-Solomon *et al* (27) and Yu *et al* (41) were both derived from the Finnish ATBC cohort study, which was designed to identify the role of α-tocopherol or β-carotene in reducing cancer incidence in male smokers. The study by Yu *et al* (41) had a larger sample size and a longer follow-up period but was not group-matched according to interventions in the ATBC study, indicating that the results may have been influenced by interventions in the ATBC cohort study. Therefore, the study by Stolzenberg-Solomon *et al* (27) was finally included in the present analysis. Some meta-analyses included both articles (19) indicating that there was likely some duplication in the study population which could affect the credibility of the results.

Literature quality evaluation. The NOS scores of the 17 included studies ranged from 4 to 8, with an mean score of 6.8. The results of the literature quality assessment are presented in Table I. A total of 12 studies were determined to be high quality based on the NOS scores.

Overall analysis. All 17 studies were included in the analysis. The heterogeneity test showed a significant heterogeneity among studies (I^2=72.1%; P<0.001; Fig. 2). The results of the meta-analysis suggested that *H. pylori* infection was not significantly associated with the risk of pancreatic cancer (OR, 1.15; 95% CI, 0.93-1.41; Fig. 2). A leave-one-out sensitivity analysis was performed to verify the reliability of the combined results. The findings indicated that the combined results were stable and not affected by the extremes of a single study (Fig. 3).

Subgroup analyses. To explore potential sources of heterogeneity and identify key factors influencing the combined results, subgroup analyses were conducted, where studies were grouped and analyzed based on their quality, geographical region, study design, diagnostic criteria and the subtype of *H. pylori*.

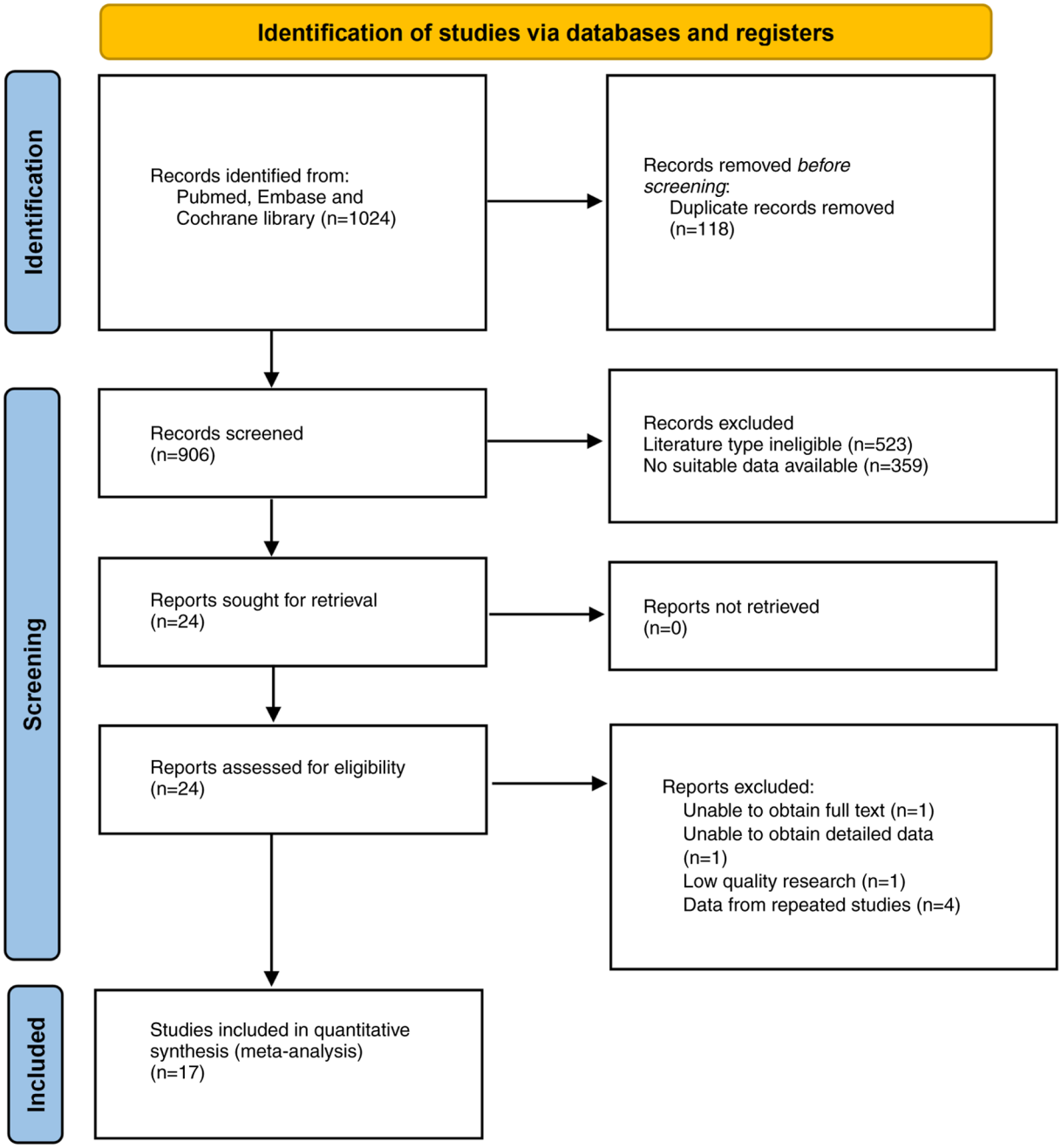

Figure 1. Literature search and study selection flowchart following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines.

Subgroup analysis of high-quality studies. To reduce the potential impact of low-quality studies on the combined outcomes, only 12 high-quality studies (16,17,20,27-35) were included in this subgroup. The heterogeneity of this subgroup was still significant (I^2=73.3%; P<0.001). The analysis showed no significant association between *H. pylori* infection and pancreatic cancer risk (OR, 1.06; 95% CI, 0.86-1.31; Fig. S1). However, in this subgroup, the results were closer to the line of null effect and their 95% CIs were narrower.

Subgroup analysis on study region. All 17 studies were grouped according to the region of the study population. Among them, 7 studies were assigned to the Asian group, 5 studies to the European group, 4 studies to the North American group and 1 study to the Oceania group. The results in the European group (OR, 1.28; 95% CI, 0.95-1.72), the Asian group (OR, 1.34; 95% CI, 0.77-2.34) and the Oceania group (OR, 1.05; 95% CI, 0.79-1.40) suggested that *H. pylori* infection was a risk factor for pancreatic cancer (Fig. S2). By contrast, in North America (OR, 0.92; 95% CI, 0.69-1.23), *H. pylori* infection was a protective factor for pancreatic cancer. However, none of these associations were statistically significant, which may suggest that there were small regional differences in the association between *H. pylori* infection and pancreatic cancer, but that these differences did not have a decisive effect.

Subgroup analysis on study design. The types of the studies included were case-control studies, nested case-control studies and cohort studies, which may have different implementation pathways and levels of evidence in evidence-based medicine. Therefore, the studies were analyzed in subgroups according to study design to identify potential sources of

Table I. Main characteristics of included studies in the meta-analysis.

First author, year	Region	Mean age or age range[a]	Study design	*H. pylori* (+) in cancer group, n	*H. pylori* (-) in cancer group, n	*H. pylori* (+) in control group, n	*H. pylori* (-) in cancer group, n	Sample size, n	*H. pylori* detection method	Ascertainment of pancreatic cancer	NOS score	(Refs.)
Raderer *et al*, 1998	Europe	21-85	Case-control	60	32	13	14	119	ELISA	Histopathological diagnosis	7	(33)
Stolzenberg-Solomon *et al*, 2001	Europe	50-69	Nested case-control	99	22	165	61	347	ELISA	Histopathological diagnosis	8	(27)
de Martel *et al*, 2008	North America	49.5/50.3	Nested case-control	51	53	155	107	366	ELISA	Tumor registry reports	7	(30)
Lindkvist *et al*, 2008	Europe	47.9/47.5	Nested case-control	39	48	100	163	350	ELISA	Diagnostic histopathology or imaging	8	(34)
Risch *et al*, 2010	North America	66.9/68.3	Case-control	80	293	120	570	1,063	ELISA	Medical report	7	(17)
Shimoyama *et al*, 2010	Asia	66.9/61.6	Case-control	16	3	29	5	53	E-plate[b]	-	4	(38)
Hsu *et al*, 2014	Asia	51.1/51.0	Cohort	11	11	6,011	24,077	30,110	Pathological diagnosis	Tumor registry reports	5	(36)
Risch *et al*, 2014	Asia	64.9/64.9	Case-control	233	528	327	467	1,555	ELISA	Medical report	8	(29)
Ai *et al*, 2015	Asia	56.8/54.6	Case-control	31	25	16	44	116	ELISA	Histopathology or clinical diagnosis	7	(35)
Schulte *et al*, 2015	Oceania	66.5/67.4	Case-control	113	443	119	489	1,164	ELISA	Histopathology or clinical diagnosis	8	(20)
Chen *et al*, 2016	Europe	50-75	Cohort	27	19	4,738	4,766	9,550	ELISA	Tumor registry reports	6	(37)
Huang *et al*, 2017	Europe	57.8	Nested case-control	196	250	206	241	893	ELISA	Tumor registry reports	8	(16)
Hirabayashi *et al*, 2019	Asia	40-69	Cohort	83	36	13,669	6,328	20,116	ELISA	Tumor registry reports	7	(32)
Permuth *et al*, 2021	North America	67.6/59.0	Case-control	13	118	16	115	262	Multiplex serology[c]	Histopathological diagnosis	8	(31)
Laya *et al*, 2022	Asia	55.85/53.21	Case-control	34	27	42	52	155	ELISA	Diagnostic histopathology or imaging	5	(39)
Osaki *et al*, 2022	Asia	68.8/73.6	Case-control	20	39	11	14	84	ELISA	-	4	(40)
Lee *et al*, 2023	North America	63.9/62	Nested case-control	150	335	377	745	1,607	ELISA	Medical report	8	(28)

[a]Presented as the mean age of case group/mean age of control group or the age range. [b]A new serological test kit (38). [c]Positivity was defined as being positive for at least 4 of the 15 proteins measured (Cad, Cagδ, CagM, CagA, Catalase, HcpC, HP0231, HP0305, HpaA, HyuA, GroEL, NapA, HP1564, VacA and UreA) (31). NOS, Newcastle-Ottawa Scale; ELISA, enzyme linked immunosorbent assay.

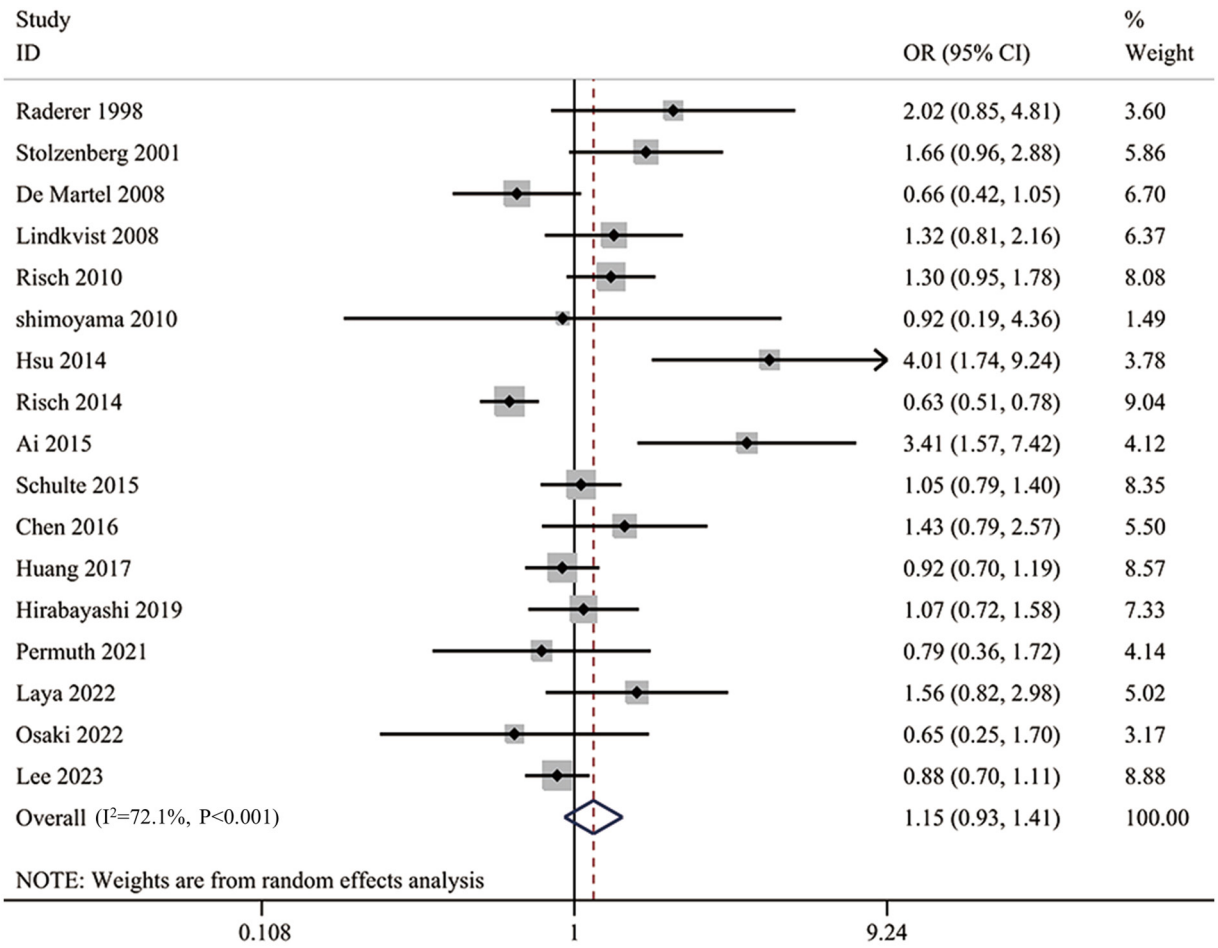

Figure 2. Forest plot of the overall meta-analysis of the association between *Helicobacter pylori* infection and the risk of pancreatic cancer. OR, odds ratio; CI, confidence interval.

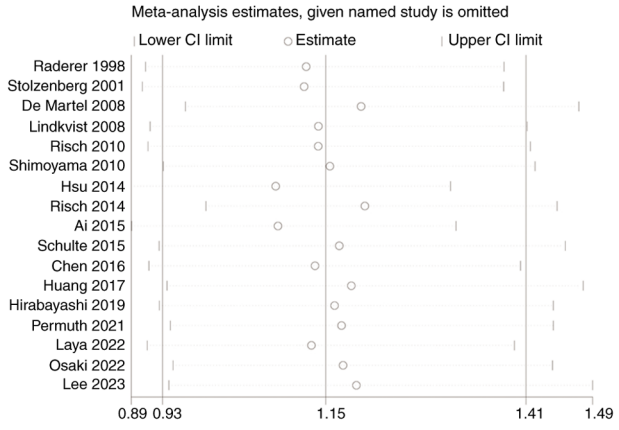

Figure 3. Sensitivity analysis of the overall meta-analysis of the association between *Helicobacter pylori* infection and the risk of pancreatic cancer. CI, confidence interval.

heterogeneity (42,43). The analysis showed that there was no significant difference between the results of the case-control study group (OR, 1.07; 95% CI, 0.78-1.48), the nested case-control study group (OR, 1.05; 95% CI, 0.82-1.34) and the cohort study group (OR, 1.68; 95% CI, 0.86-3.29), which suggests that study design may not be a major source of heterogeneity (Fig. S3).

Subgroup analysis on diagnostic criteria. The original studies employed a variety of diagnostic methods for *H. pylori* infection. Therefore, the original studies were analyzed in groups based on the diagnostic criteria. A total of 14 studies used ELISA-based Hp-IgG positivity as a diagnostic criterion for *H. pylori* infection, and the analysis of this group still suggested no significant association between *H. pylori* infection and the risk of pancreatic cancer (OR, 1.10; 95% CI, 0.90-1.35; Fig. S4). By contrast, the remaining three diagnostic methods (E-Plate, multiple serology and histopathology) had all been used in a single study and had limited significance for a combined analysis.

Subgroup analysis of CagA⁺ H. pylori infection. CagA is a crucial virulence factor of *H. pylori* that is associated with tumorigenic risk and CagA⁺ *H. pylori* is typically considered to possess higher virulence (6). A total of 11 studies (9 studies using ELISA, 1 using an immunoblot test and 1 using multiple serology) additionally examined the CagA status of *H. pylori*, all of which were included in the present subgroup. The result showed no significant association between CagA⁺ *H. pylori* infection and the risk of pancreatic cancer (OR, 0.95; 95% CI, 0.78-1.16; Fig. S5). However, the diagnostic criteria for CagA⁺ *H. pylori* infection varied among studies. For example, a study in the United States in 2023 determined CagA positivity based on the detection of CagA only (28), whereas a cohort study in Germany in 2016 interpreted the results of CagA testing on

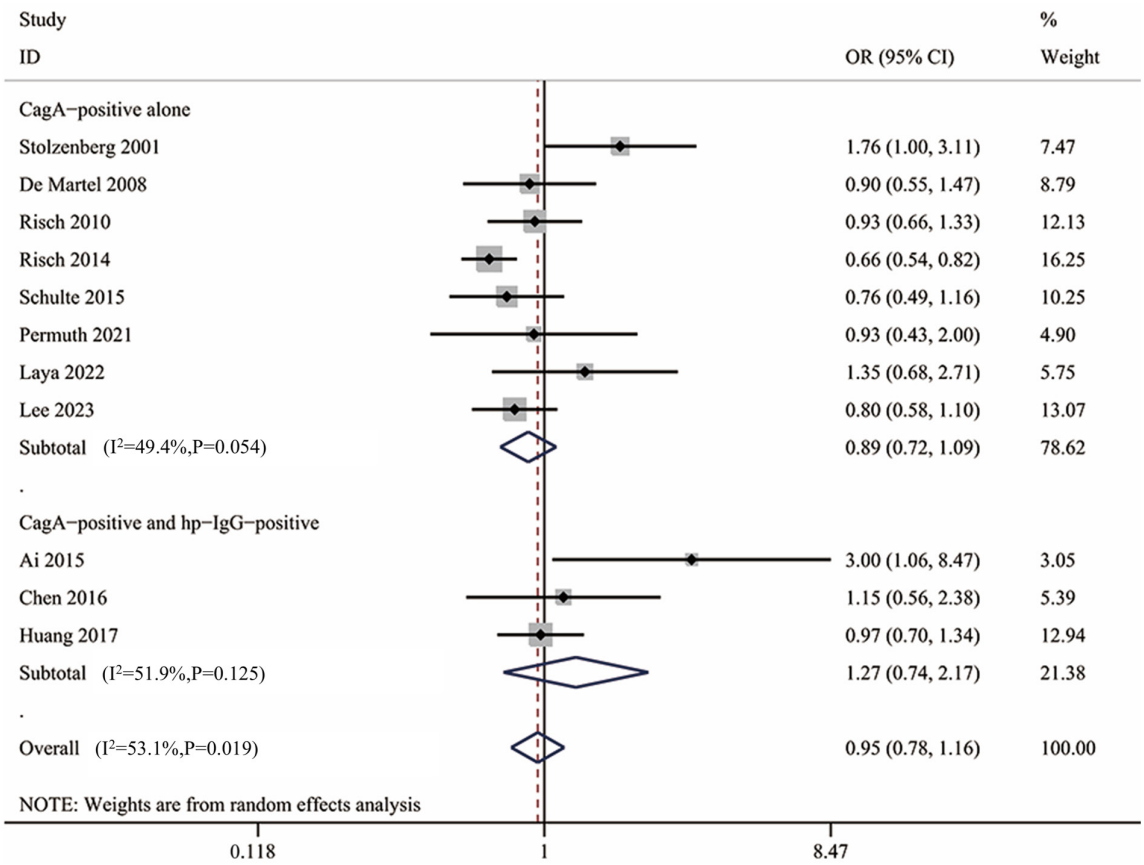

Figure 4. Forest plot of the diagnostic criteria subgroup analysis of the association between CagA⁺ *Helicobacter pylori* infection and the risk of pancreatic cancer. OR, odds ratio; CI, confidence interval.

the basis of Hp-IgG positivity (37). The different diagnostic criteria likely affected the reliability of the results. For both diagnostic criteria, a subgroup analysis was performed, although no significant association was found in both the CagA⁺ group alone (OR, 0.89; 95% CI, 0.72-1.09) and the Hp-IgG⁺ + CagA⁺ group (OR, 1.27; 95% CI, 0.74-2.17) (Fig. 4). Therefore, the conclusions did not change. In this subgroup, further subgroup analyses were performed based on quality, study region and study design, but none yielded meaningful results (data not shown). The results of the subgroup analysis of CagA⁺ *H. pylori* infection were reliable and not abnormally affected by a single extreme result, as demonstrated by sensitivity analysis (Fig. S6).

Subgroup analysis of CagA⁻ H. pylori infection. A total of 7 studies additionally analyzed CagA⁻ *H. pylori* infection, all of which were included in the subgroup analysis. The test for heterogeneity indicated that inter-study heterogeneity was not significant (I^2=42.4%; P=0.108; Fig. 5). The quantitative synthesis results showed that CagA⁻ *H. pylori* infection was associated with the risk of pancreatic cancer (OR, 1.24; 95% CI, 1.00-1.54; Fig. 5). The results suggested that CagA⁻ *H. pylori* infection could be a risk factor for pancreatic cancer. However, the corresponding sensitivity analysis suggested that this result was not very stable (Fig. S7).

Publication bias. The funnel plot results were slightly asymmetric (Fig. S8). Begg's test did not identify publication bias (P=0.077), but Egger's test suggested some publication bias (P=0.014). The trim and fill analysis allows the modelling of results that may be absent due to publication bias, thus assessing the impact of publication bias on the results and providing an adjusted effect value. A trim-and-fill analysis was performed, and the results showed that no studies were trimmed or filled (Fig. 6), and the adjusted results were consistent with the original results. The results demonstrated that there was no significant publication bias and its influence on the results of the meta-analysis was weak.

Discussion

Although the potential oncogenic role of *H. pylori* infection has received widespread attention, its association with pancreatic cancer risk is unclear and study findings are controversial. The present study aimed to examine the existing literature and assess the association between different types of *H. pylori* infection and pancreatic cancer risk and to explore possible causes.

In the present study, the predetermined inclusion and exclusion criteria were strictly followed to select high-quality original studies. By excluding non-compliant or low-quality literature and including those studies that met the criteria, the present study enhances the generalizability of the selected research population and the universality of the research conclusions. In addition, the selected original studies included a variety of study types, such as case-control, nested case-control and cohort studies, providing a multidimensional perspective

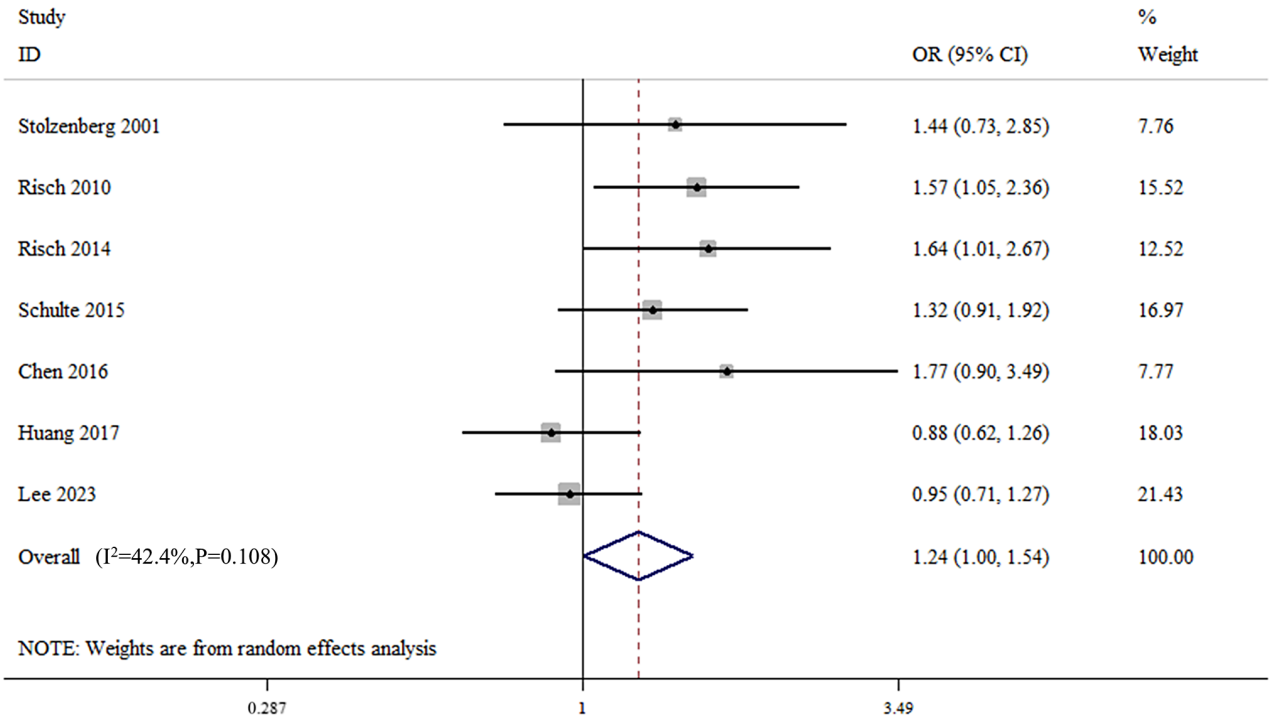

Figure 5. Forest plot of the meta-analysis of the association between CagA- *Helicobacter pylori* infection and the risk of pancreatic cancer. OR, odds ratio; CI, confidence interval.

that contributed to a comprehensive assessment of the association between *H. pylori* infection and pancreatic cancer risk. The largest sample size to date (a total of 67,910 subjects) was included, which notably enhanced the statistical efficacy of the present meta-analysis and reduced randomization error, thus providing more robust and reliable conclusions.

For statistical analysis, a comprehensive analytical strategy was used to investigate the complex relationship between *H. pylori* infection and pancreatic cancer risk. Through subgroup analyses, the effects of study region, design, diagnostic criteria and CagA status on the results were examined, which helped to identify potential heterogeneity among different subgroups and provide valuable clues for future studies. In addition, to ensure the robustness of the findings, sensitivity analyses were further performed to assess the impact of individual studies on the overall effect estimates and the trim-and-fill method was employed to adjust for potential publication bias. The use of these analytical tools has increased the confidence in the study's conclusions.

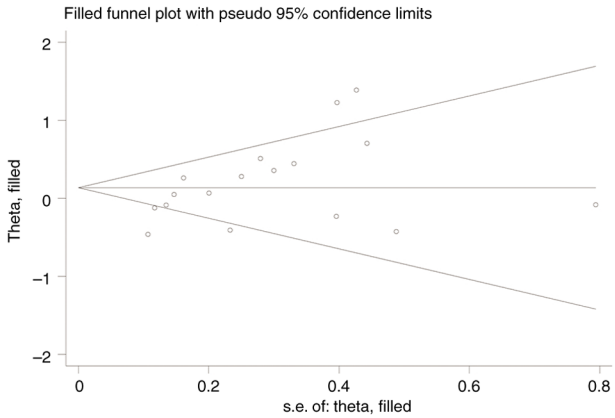

Figure 6. Trim-and-fill analysis based on the overall meta-analysis of the association between *Helicobacter pylori* infection and the risk of pancreatic cancer. s.e., standard error.

The present analysis showed no significant association between *H. pylori* infection and pancreatic cancer risk (OR, 1.15; 95% CI, 0.93-1.41). Although there was some publication bias and significant heterogeneity, the result of the sensitivity analysis and the trim-and-fill analysis demonstrated that the results are stable and reliable. Meta-analyses by Zhou *et al* (19) and Schulte *et al* (20) also showed similar results. Trikudanathan *et al* (44) and Xiao *et al* (18) included 6 and 9 original studies, respectively, and their results suggested a statistically significant association between *H. pylori* infection and pancreatic cancer risk (OR, 1.38; 95% CI, 1.08-1.75 and OR, 1.47; 95% CI, 1.22-1.77, respectively). However, building on their original study, several newly published papers were also included in the present study, including 3 cohort studies, which enhanced the credibility of the results. Xiao *et al* (18) also performed a subgroup analysis of high-quality studies, in which 4 original studies that were considered high-quality were analyzed and found statistically significant results (OR, 1.28; 95% CI, 1.01-1.63). Although this result still suggested that *H. pylori* infection was a risk factor, the OR and 95% CI of the high-quality subgroup were closer to 1 compared with the results of their overall analysis (OR, 1.47; 95% CI, 1.22-1.77), suggesting that the results of the overall analysis were somewhat influenced by the other studies. By contrast, the high-quality subgroup analysis in the present study involved 12 articles, including all 4 articles used by Xiao *et al* (18) and 8 new high-quality articles. The results suggested no significant association between *H. pylori* infection and pancreatic cancer

risk (OR, 1.06; 95% CI, 0.86-1.31), consistent with the results of the overall analysis of the present study. Similarly, the OR and 95% CI of the high-quality subgroup analysis were closer to 1 than those of the overall analysis.

Regional subgroup analyses were performed in the present study, and no statistically significant results were found in the European, Asian or North American groups. The results of the study by Zhou *et al* (19) are consistent with the findings of the present study. By contrast, Xiao *et al* (18) found statistically significant results in the European and East Asian groups (OR, 1.56; 95% CI, 1.15-2.10 and OR, 2.01; 95% CI, 1.33-3.02, respectively). Compared with the study by Xiao *et al*, the regional subgroup analyses in the present study additionally included 8 newly published articles (including 3 cohort studies) and did not include 3 studies published in languages other than English. Consequently, the regional subgroup analyses in the present study incorporated more recent data and larger sample sizes.

Subgroup analyses on the diagnostic criteria and study design did not reveal significant heterogeneity between groups. Of the four diagnostic methods for *H. pylori* infection included in the present study, three were used in only 1 study. Therefore, interpretation of diagnostic criteria subgroup results were limited by sample size.

CagA protein is an important virulence factor of *H. pylori*. CagA interferes with cell signal transduction by binding to various receptors of host cells, thus affecting cell proliferation, migration and apoptosis (6). The present study comprehensively analyzed the role of the CagA protein based on existing data, and the findings indicated no significant association between $CagA^+$ *H. pylori* infection and the risk of pancreatic cancer. Certain previous meta-analyses corroborate this finding (18,19). $CagA^-$ *H. pylori* infection was significantly associated with the risk of pancreatic cancer (OR, 1.24; 95% CI, 1.00-1.54) in the present study. Compared with the study of Zhou *et al* (19) (OR, 1.22; 95% CI, 1.00-1.49), the present study additionally included a 2016 cohort study from Germany (37) and a 2023 nested case-control study from the United States (28). By introducing these 2 new original studies, narrower confidence intervals were obtained and therefore the results showed statistical significance. In terms of $CagA^-$ *H. pylori* infection, several meta-analyses are consistent with the findings of the present study (20,37,45), but the present study had the largest sample size and the narrowest confidence intervals. However, the corresponding sensitivity analysis showed that the combined results were not very stable. After several critical studies were excluded individually (17,20,29,37), the results were no longer statistically significant.

VacA is also a major virulence factor produced by *H. pylori*. As a cytotoxin, VacA can interact with host cell membranes to form transmembrane channels that disrupt membrane integrity. This damage results in the leakage of intracellular material and loss of cellular function, which in turn may trigger cell death (46,47). This mechanism of VacA makes it one of the key factors related to *H. pylori* infection, gastric mucosal injury and inflammation. However, only 1 study examined VacA status, and therefore quantitative synthetic analyses could not be performed in the present study (31).

The association between $CagA^-$ *H. pylori* infection and pancreatic cancer risk may involve multiple biological mechanisms. First, *H. pylori* infection itself may cause damage to pancreatic cells through a chronic inflammatory response, and this inflammatory environment may promote the development of pancreatic cancer. Chronic inflammation is recognized as an important cancer-promoting factor that can lead to DNA damage, cell proliferation and immune escape, thereby increasing the risk of pancreatic cancer (48,49). For example, a study found that *H. pylori* infection was associated with elevated markers of inflammation in patients with pancreatic cancer, suggesting that inflammation may play a role in the development of pancreatic cancer (18). *H. pylori* infection may elevate inflammation levels and promote β-catenin accumulation by inducing spermine oxidase, which metabolizes the polyamine, spermine, into spermidine and H_2O_2 (50). There is evidence that gastric polyamine levels are positively associated with gastritis in *H. pylori*-infected gerbils (51). An association between colonic spermidine levels and histological damage was also observed in a wild-type mouse model of *Citrobacter rodentium* infection (52). The Wnt/β-catenin signaling pathway is pivotal in carcinogenesis (53,54). *H. pylori* induces nuclear accumulation of β-catenin in gastric epithelial cells, facilitating the development of cells exhibiting cancer stem cell-like characteristics (55).

Second, *H. pylori* infection may affect the immune surveillance and immune escape mechanisms of pancreatic cancer by affecting the immune microenvironment of the pancreas and altering the distribution and function of immune cells (6). It has been shown that *H. pylori* infection has the capacity to upregulate the expression of indoleamine 2,3-dioxygenase in macrophages, thereby inducing M2 polarization (56). M2 macrophages promote cancer initiation and malignant progression by enhancing angiogenesis and increasing tumor migration, invasion and intravasation, while also inhibiting antitumor immunity (57). Guo *et al* (58) showed that M2 macrophages shield tumor-initiating cells from immune elimination and are essential for tumorigenesis. In addition, M2 macrophages are able to promote tumor cell colonization and growth by regulating the interaction between tumor cells and surrounding cells, as well as by remodeling the stroma surrounding tumor cells (59).

H. pylori infection is also associated with oxidative stress and extensive DNA damage related to chronic inflammation (60). It is well known that *H. pylori* causes neutrophil infiltration and elevated *de novo* synthesis of reactive oxygen species (ROS) by epithelial cells both *in vivo* and *in vitro* (61,62). ROS are oxygen-containing chemicals that are highly reactive in living organisms and, under normal physiological conditions, they are produced by cellular metabolism and are involved in cell signaling processes (63,64). In turn, the increase in ROS leads to DNA damage and genetic instability and may even activate tumorigenic signals (64-66). Hardbower *et al* (60) inhibited DNA damage induced by oxidative stress in mouse and gerbil models infected by *H. pylori*, which were found to exhibit a decrease in heterotopic hyperplasia and carcinoma.

$CagA^-$ *H. pylori* infection exhibits enhanced survivability in highly acidic conditions, which may mean that these strains are more likely to infect or colonize highly acidic individuals (67). The highly acidic trait coupled with infection by *H. pylori* may induce a strong stimulation of the pancreas (68,69). Pancreatic cells found in a highly secretory active state for a long period

are more prone to malignancy (70,71). Contrary to $CagA^-$ strains, $CagA^+$ strains are generally considered to be more virulent and capable of inducing more severe gastric mucosal atrophy, intestinal epithelial hyperplasia and inflammatory cell infiltration (72). Consequently, a reduction in gastric acidity may be more prevalent among the long-term effects of $CagA^+$ *H. pylori*, which may instead alleviate the burden on pancreatic cells. This may explain why $CagA^-$ *H. pylori* infection is more dangerous in terms of pancreatic cancer risk. Moreover, in addition to CagA and VacA, *H. pylori* possesses an extensive array of virulence factors, including dupA, iceA and htrA (73-75). Subgroup analysis based only on CagA status overlooks the role of these virulence factors, and taking these virulence factors into account helps to explain the relationship between *H. pylori* infection and pancreatic cancer more scientifically.

Lifestyle and genetic susceptibility are also significant factors influencing pancreatic cancer risk (13). For instance, smoking, high BMI and diabetes are often regarded as risk factors for pancreatic cancer (76-78), while mutations of various genes (such as CDKN2A, BRCA2, ATM and BRCA1) have been shown to be associated with pancreatic cancer (79,80). Certain studies matched for fundamental confounders such as age, sex, smoking and alcohol intake, thereby eliminating their influence on the results (16,27). Nonetheless, regarding dietary structure and genetic susceptibility, which are more difficult indicators to count, only a few studies have controlled their distribution across groups (20,31). Therefore, more high-quality studies are required to elucidate the association between *H. pylori* infection and pancreatic cancer risk.

The present study also has some limitations. High-performance assays for *H. pylori* infection, such as tissue culture and nested PCR (81), were infrequently employed in the studies included in the analysis, and the majority of original studies used serology for diagnosing *H. pylori* infection, which is among the most prevalent diagnostic procedures (82,83). The lesions resulting from *H. pylori* infection exhibit marked variability across individuals (84,85). The extent of chronic inflammation due to *H. pylori* infection was not assessed, nor were the changes in the acidity of the stomach (which stimulates the pancreas) in the case of diagnosis using serology. This deficiency reveals the shortcomings in the degree of refinement of the subgroups of *H. pylori* infection. Furthermore, studies have demonstrated that the conversion rate of serum CagA antibodies was considerably lower than that of Hp-IgG antibodies, and that the inclusion of CagA antibodies in the diagnostic criteria could facilitate the detection of remote *H. pylori* infection with greater efficacy (86,87). Therefore, some studies have chosen to use the results of CagA antibodies to correct for the results of Hp-IgG antibodies (17,20,27-29). However, some studies neglected to do so, and some did not test for CagA antibodies, which likely contributed to the underestimation of the *H. pylori* infected population. In the case-control studies covered in the present study, there was often a long interval between specimen collection and testing, and it has been found that the level of serologic markers might change after prolonged storage (30), which could be avoided by higher-quality study designs.

As only one of the original studies included tested VacA status using multiple serological methods (31), it was not possible to perform a meta-analysis on the association between VacA and pancreatic cancer risk. Furthermore, since the original studies included in the present study included just 3 cohort studies (32,36,37), the degree of evidence for the original data should be raised. The emergence of more rigorously designed studies with higher levels of evidence will help to address these issues.

In conclusion, the results of the present study suggested that *H. pylori* infection, including $CagA^+$ *H. pylori* infection, did not significantly increase the risk of pancreatic cancer. However, $CagA^-$ *H. pylori* infection is a risk factor that warrants caution. Although study region, diagnostic methods, study design and virulence of strains all had some impact on the results, this impact did not affect the conclusions.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MZ, CQ and CX conceived of the study; MZ, CQ, CX and WX participated in the design of the study; CQ and ZZ participated in data collection; CQ, XS and XW analyzed and interpreted the data; CQ and CX drafted the manuscript; CX revised and edited the manuscript. MZ and WX confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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