Association between Helicobacter pylori Infection and Pancreatic Cancer Development: A Meta-Analysis

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Abstract

Background: Pancreatic cancer is one of the most troublesome malignancies with dismal prognosis. H. pylori has been recognized as a type I carcinogen. Several studies have evaluated the association between H. pylori infection and pancreatic cancer development, however, the conclusions are inconsistent.

Methods: Literature search was carried out in PubMed, EMBASE, Cochrane Library and CNKI databases to identify eligible researches. We performed overall meta-analysis of all studies included and subgroup analysis based on regional distribution. Quality of the studies (assessed by Newcastle-Ottawa quality assessment scale for case-control studies) and CagA+ strains of H. pylori were taken into consideration, and we conducted additional analyses including high-quality researches and those concerning CagA+ H. pylori respectively.

Results: 9 studies involving 3033 subjects (1083 pancreatic cancer cases, 1950 controls) were included. Summary OR and 95%CI of the overall meta-analysis of all included studies were 1.47 and 1.22-1.77, pooled data of the 4 high-quality studies were OR 1.28, 95%CI 1.01-1.63. OR of the 5 studies examined CagA+ strains was 1.42, corresponding 95%CI was 0.79 to 2.57. Summary estimates of subgroup analysis based on regional distribution are as follows, Europe group: OR 1.56, 95%CI 1.15-2.10; East Asia group: OR 2.01, 95%CI 1.33-3.02; North America group: OR 1.17, 95%CI 0.87-1.58. There was not obvious heterogeneity across the 9 studies. No publication bias was detected.

Conclusion: H. pylori infection is significantly, albeit weakly, associated with pancreatic cancer development. The association is prominent in Europe and East Asia, but not in North America. CagA+ H. pylori strains appear not to be associated with pancreatic cancer. However, more studies, especially prospective studies, are needed to validate our results.

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Introduction

Pancreatic cancer, also known as exocrine pancreatic carcinoma or pancreatic ductal adenocarcinoma [1], is the fifth leading cause of cancer related death worldwide [2] and the fourth in the USA [3], due to the advanced stage at diagnosis and poor responses to current treatments [4]. Despite steadily increasing understandings on the mechanisms underlying carcinogenesis of pancreatic cancer, there is still a long way to go to apply the advanced knowledge to the clinical practice to get an ideal solution for this troublesome malignancy. Previous epidemiological investigations have identified some possible risk factors of pancreatic cancer, such as smoking, chronic pancreatitis, long-standing diabetes, mutations of various genes and so on [5-7]. However, preventive strategies taking these risk factors into account appear not to achieve what expected. Therefore, identification of more potential risk factors leading to effective primary prevention is still in great urgency.

Since Marshall and Warren reported in 1984 [8] a curved bacillus that may serve as the causal factor of gastritis and peptic ulceration, a strong link has been established between Helicobacter pylori especially the CagA (a product of cytoxin associated gene A) positive strains, and a diverse spectrum of diseases, such as, acute and chronic gastritis, peptic ulcer disease, gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma [9]. In 1994, H. pylori was classified as a...
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Literature search
Studies were identified by a systematic literature search in PubMed, EMBASE, Cochrane Library and CNKI (China National Knowledge Infrastructure) databases from inception to May, 2013. The searching strategy was decided by discussions among all authors and improved in several turns of attempts to get results as comprehensive as possible, involving terms in 3 key aspects: (1) H. pylori: Helicobacter*, Helicobacter Pylori*, Hp*, H. pylori*, Helicobacter species*, Helicobacter sp.*, Helicobacter genus*. (2) pancreas: pancreatic*, pancreas*. (3) cancer: cancer*, tumor*, tumour*, neoplasm*, malignancy*, adenocarcinoma*, carcinoma*. Both Mesh subjects and keywords were applied during PubMed search, with the filter activated of "humans". Searching terms were checked and adapted by Emtree terms when using EMBASE. We imposed no language restriction. In addition, a manual search of citations of the included studies was performed.

Study selection
Two investigators (Mingia Xiao & Yiming Wang) independently selected the studies included into the meta-analysis. Disagreements were resolved by discussion or consultation to the corresponding author (Yi Gao).
We selected the studies for inclusion if they fulfilled the following criteria: (1) The study should concern the association between H. pylori infection and pancreatic cancer development; (2) The study must be conducted in adults, defined as patients greater than 18 years old; (3) There must be a control group; (4) H. pylori infection with or without status of CagA should be determined by serological testing (like ELISA, Western blotting) or any other reliable method; (5) The study must provide the sample size and data on the positive rates of H. pylori infection between the groups with odds ratios (OR) and the corresponding 95% confidence interval (95%CI); (6) Diagnoses of the patients with and without pancreatic cancer (exocrine pancreatic carcinoma, pancreatic ductal carcinoma) must be confirmed by pathological examination; and (7) The research was approved by the Ethics Committee.

Data extraction
The two investigators extracted the data independently using a unified data form and the results were cross-checked. In the case of discrepancy, decisions were made by discussion. The data retrieved covered first author, publication year, country, study design, sample size, method for detecting H. pylori, number of H. pylori positive cases in both groups, OR and corresponding 95%CI of pancreatic cancer for H. pylori infection, and adjustments. If there was an adjusted OR with 95%CI by other risk factors, such as age, gender, etc., reported in the paper, we recorded the adjusted data; if not, the crude data were recorded and used instead.

Quality assessment of the included research
Investigators assessed the methodological quality of every included study by Newcastle-Ottawa quality assessment scale (NOS) for case-control studies, which contains 8 items (1 star for each, and up to 8 stars in total) categorized into 3 major...
categories: (1) Selection: adequate definition of cases, representativeness of the cases, definition of controls; (2) Comparability: the controls were matched to cases on age and sex, controls were matched by other confounding factors; (3) Exposure: ascertainment of exposures, the same methods to ascertain the exposure for cases and controls, the same non-response rate in both groups [31]. The ultimate score of 6 stars or more was regarded as high-quality.

Statistical analysis
Overall meta-analysis of all included studies was carried out to determine the association of H. pylori infection and pancreatic cancer risk. In addition, three more sub-analyses were conducted (1), meta-analysis including only the high quality researches (2), meta-analysis evaluating carcinogenetic risk of infection with CagA+ H. pylori strains, and (3) subgroup analysis according to geographic distribution of the studies.

Cumulative OR and corresponding 95%CI were calculated as the summary estimates to measure the strength of the associations. The heterogeneity across the studies was examined by χ²-based I² test and considered significant if I²>50%. In the case of significant heterogeneity, a meta-analysis was performed using a random effect model by the DerSimonian and Laird method [32]; otherwise a fixed effect model and the Mantel–Haenszel weighting algorithm [33] were preferred. In order to exclude the possible influence of any single research, sensitivity analysis was performed to evaluate whether omitting one study in turn substantially altered the results or magnitude of the summary estimates of the remainders.

Visual inspection of funnel plots, Begg’s rank correlation test [34] and Egger’s regression test [35] were all generated to detect potential publication bias. All P values were set two sided, and those less than 0.05 were deemed statistically significant. Our meta-analysis was performed by using Stata 12.0 and RevMan 5.1 software.

Results
Characteristics of included studies
Systematic search yielded a total of 566 papers. After reviewing titles, abstracts and full texts, nine studies involving 3033 subjects (1083 pancreatic cancer cases and 1950 controls) were finally retrieved based on the pre-defined inclusion and exclusion criteria [19-24,36-38]. A diagram schematizing the selection process is presented in Figure 1. All selected studies are case-control studies, including three nested-control studies [20,21,36]. The main characteristics of included studies are summarized in Table 1. Among them, four were from Europe (Austria, Finland, Sweden and Poland) [19-21,24], 2 from North America (the USA) [36,37] and three from East Asia (Japan and China) [22,23,38]. All studies used serological method, ELISA or Western blotting to detect antibodies to H. pylori whole cell proteins to identify H. pylori infection. Six studies [20,22-24,36,37] went further to detect antibodies to CagA protein of H. pylori, and one of them detected CagA and VacA protein [23]. Age, sex, cigarette smoking or other possible confounding factors were matched between the cases and controls in four studies and ORs with 95% CIs were adjusted by Logistic regression [20,21,36,37], whereas the other five studies did not use controls individually matched to the cases.

Quality assessment
The results of quality assessment according to NOS for case-control studies are shown in Table 2. All these studies reported that the diagnoses of all cases and controls were based on pathological and clinical records, and thus all studies got the two stars in the items of “adequate definition of cases” and “definition of controls”. All pancreatic cancer cases in each of the studies were declared to be diagnosed cases during a certain period, in certain medical centres, and thus the representativeness of cases was qualified for another star. H. pylori infection was identified by serological methods, so two more stars were assigned for “ascertain of exposure” and “same method to ascertain for cases and controls” to all studies. However, the same non-response rate between groups was not shown, or non-response rate was not mentioned in all studies, and thus all studies failed to win a star for “non-response rate”.

Overall, the scores of included studies ranged from five to eight stars, while four of them were defined high-quality [20,21,36,37].

Overall meta-analysis
Generally speaking, the overall H. pylori positive rate in pancreatic cancer group (51.8%, 561 of 1083) was higher than that in control group (43.6%, 851 of 1950). The test for heterogeneity was not significant (I²=18.5%, p=0.278), suggesting low heterogeneity among these studies. So we chose the fixed effect model when performing statistical analysis. The summary OR and 95% CI of the overall meta-analysis of all included studies were 1.47 and 1.22-1.77, respectively (Figure 2).

During the sensitive analysis, exclusion of any study did not influence the direction and magnitude of the cumulative estimates substantially (Table 3), revealing a relatively low sensitivity.

Sub-analysis of high-quality research
Sub-analysis involving the four high-quality studies is shown in Figure 3. Researchers of these studies also matched the controls to cancer cases in order to avoid confounding from age, gender and some other factors. The summary OR and 95% CI were 1.28 and 1.01-1.63, respectively, with significant heterogeneity (I²=21.6%, p=0.281).

Sub-analysis of studies detecting CagA
Among the six studies examining the infection rate of Cag+ H. pylori (including one study detecting CagA and VacA), the prevalence of CagA+ H. pylori ranged from 14.7% to 60.3% in pancreatic cancer patients, and from 7% to 84.7% in the controls. Three studies reported CagA+ H. pylori strains served as a risk factor of pancreatic cancer compared with CagA- strains, whereas the other three did not. The summary OR and
Figure 1. Flow diagram of literature search and study selection.

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For more information, visit www.prisma-statement.org.
95%CI of the five studies detecting CagA+ only were 1.42 and 0.79 to 2.57, respectively, with significant heterogeneity ($I^2=77.4$, $P=0.001$) (Figure 4). In addition, summary OR and 95%CI of 3 high-quality studies [20,36,37] were 1.14 and 0.66-1.97 respectively, with significant heterogeneity ($I^2=64.8$) (figure was not shown). The only study that tested CagA and VacA indicated that *H. pylori* strains infection indicated that *H. pylori* strains harboring both CagA and VacA may serve as a risk factor for pancreatic cancer [23].

**Sub-analysis in relation to geographic regions**

All nine studies were divided into three groups, Europe, North America, and East Asia. The summary ORs were 1.56 (95%CI: 1.15-2.10, $I^2=0.0$), 1.17 (95%CI: 0.87-1.58,

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**Table 1. Characteristics of the 9 included studies.**

| Author          | Year,country | Study design | Method | H. pylori(+) in cancer group | H. pylori(+) in control group | Cag+ in cancer group | Cag+ in control group | OR(95%CI) | Adjustments^b |
|-----------------|--------------|-------------|--------|-----------------------------|-------------------------------|---------------------|----------------------|-----------|---------------|
| Raderer et al.  | 1997, Austria| Case-control| ELISA  | 60/92                       | 28/82$^a$                    | -                   | -                    | 2.1 (1.1, 4.1)   | Not reported   |
| Stolzenberg et al. | 2001, Finland| Nested case-control | ELISA | 99/121                      | 165/226                      | 73/121              | 115/226              | 1.87 (1.05, 3.34) | (1)(2)(3)(4)(5) |
| de Martel et al. | 2008, the USA| Nested case-control | ELISA | 51/104                      | 155/262                      | 33/104              | 83/262              | 0.85 (0.49, 1.48); CagA: 0.96 (0.48, 1.52) | (1) (5)(6)(7)(10) |
| Lindkvist et al. | 2008, Sweden | Nested case-control | ELISA | 39/87                       | 100/263                      | -                   | -                   | 1.25 (0.75, 2.09) | (1)(5)(7)(8)(9)(10) |
| Dou et al.      | 2008, China  | Case-control | ELISA  | 54/85                       | 64/136                       | 29/85$^c$           | 32/136$^c$          | 1.96 (1.12, 3.42); CagA & VacA: 2.10 (1.09, 4.06) | Not reported |
| Risch et al.    | 2010, the USA| Case-control | ELISA  | 80/373                      | 120/690                      | 55/373              | 108/690             | 1.34 (0.94, 1.92); CagA: 0.83 (0.55, 1.24) | (1)(5)(7)(11) |
| Shimoyama et al.| 2010, Japan  | Case-control | ELISA  | 16/19                       | 29/34                        | 0.92 (0.19, 4.36)   | -                   | -                     | Not reported   |
| Qiao et al.     | 2012, China  | Case-control | ELISA  | 41/63                       | 44/100                       | 19/63               | 7/100               | 2.37 (1.24, 4.55); CagA: 5.74 (2.25, 14.66) | Not reported   |
| Gawin et al.    | 2012, Poland | Case-control | ELISA, WB | 121/139                    | 146/177                      | 116/139             | 150/177             | 1.27 (0.64, 2.61); CagA: 0.90 (0.46, 1.73) | (1)(5)(7)(12) |

^a The control group included 35 patients with colorectal cancer and 27 healthy volunteers.

^b Adjustments: (1) age, (2) month of blood draw, (3) completion with the dietary history, (4) intervention group assignment, (5) cigarette smoking, (6) years of education, (7) sex, (8) body mass index, (9) alcohol consumption, (10) time from baseline investigation to analysis, (11) ELISA plate number, (12) a family history of cancer.

^c These 2 ratios are for CagA+ & VacA+, and CagA- & VacA+, respectively.

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**Table 2. Results of quality assessment by NOS for case-control studies.**

| Study          | Adequate definition of cases | Representative-ness of cases | Selection of controls | Definition of controls | Control for important factor | Ascertainment of Exposure | Same method to ascertain for cases and controls | Non-response rate | Scores |
|----------------|-----------------------------|------------------------------|-----------------------|------------------------|----------------------------|----------------------------|-----------------------------------------------|--------------------|--------|
| Raderer et al. | ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Stolzenberg et al. | ★ ★                   | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 8      |
| Dou et al.     | ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Lindkvist et al. | ★ ★                    | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 8      |
| de Martel et al. | ★ ★                   | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Risch et al.   | ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Shimoyama et al.| ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Gawin et al.   | ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |
| Qiao et al.    | ★ ★                        | ★                            | ★                     | ★                      | ★                          | ★                          | ★                               | ★                  | 5      |

^A A maximum of 2 stars can be allotted in this category, one for Age, the other for other controlled factors (gender, smoking and so on).

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I \(=45.6\%) \text{ and } 2.01 (95\%CI: 1.33-3.02, \ P=0.0\%), \text{ respectively, in these regions (Figure 5).}

**Publication bias**

The funnel plot manifested as an symmetrical appearance (Figure 6), and the \(P\) values for Begg's test and Egger's test were 0.602 and 0.797 (continuity corrected), respectively, suggesting that there was no significant publication bias in our meta-analysis.

**Discussion**

The association of *H. pylori* infection and pancreatic cancer development has long been investigated with controversial results. In this meta-analysis, we tried our best to include all available studies in this field, and found that based on the pooled data from all eligible studies, *H. pylori* seropositive rate was significantly higher in pancreatic cancer patients than in controls, indicating that *H. pylori* infection may serve as a risk factor for the development of pancreatic cancer. However, the summary \(OR\) and its 95\%CI were just above 1 (1.47 and 1.22 to 1.77, respectively), suggesting that this positive association is nearly borderline significant and may have been biased by some confounders introduced by those non-high-quality studies [19,22-24,38]. Therefore, we conducted a sub-analysis which included only high-quality studies. The results still support a positive association between *H. pylori* and pancreatic cancer, although the pooled \(OR\) and corresponding 95\%CI were both closer to the borderline value 1 (1.28 and 1.01-1.63, respectively).

CagA protein is the most studied virulence-associated factor of *H. pylori* [39]. Previous studies have demonstrated that CagA+ strains of *H. pylori* cause more severe gastritis inflammation, and are associated with a higher risk of developing intestinal metaplasia and thus intestinal-type gastric cancer [40,41]. However, in our meta-analysis, we found that CagA+ strains were not associated with the development of pancreatic cancer, indicating that CagA+ strains may not play a critical role in the development of pancreatic cancer. In other words, patients infected with CagA+ *H. pylori* are not at a higher risk of developing pancreatic cancer than those infected with CagA- strains. However, three of the six studies concerning CagA [20,22,23] detected CagA in *H. pylori* positive subjects only, which may have underestimated in the number of CagA+ cases and controls. Moreover, it has been reported that as time passes by, CagA antibodies seroreversion occurs to a substantially lower ratio than *H. pylori* antibodies seroreversion [42,43], and thus patients with a validated history
Table 3. Sensitivity analysis after each study was excluded by turns.

| Study omitted          | OR (95%CI) for remainders | Heterogeneity          | Weigh |
|------------------------|----------------------------|------------------------|-------|
| Raderer et al. (1997)  | 1.43 (1.14, 1.79)          | Insignificant ($I^2=18.4\%$, $P=0.284$) |       |
| Stolzenberg et al. (2001) | 1.44 (1.14, 1.83)      | Insignificant ($I^2=22.8\%$, $P=0.248$) |       |
| de Martel et al. (2008) | 1.58 (1.29, 1.93)       | Insignificant ($I^2=0.0\%$, $P=0.592$) |       |
| Lindkvist et al. (2008) | 1.53 (1.20, 1.95)       | Insignificant ($I^2=25.3\%$, $P=0.227$) |       |
| Dou et al. (2008)      | 1.43 (1.13, 1.80)          | Insignificant ($I^2=19.1\%$, $P=0.278$) |       |
| Risch et al. (2009)    | 1.52 (1.18, 1.99)          | Insignificant ($I^2=26.0\%$, $P=0.221$) |       |
| Shimoyama et al. (2010) | 1.50 (1.20, 1.88)      | Insignificant ($I^2=26.1\%$, $P=0.221$) |       |
| Qiao et al. (2012)     | 1.41 (1.14, 1.73)          | Insignificant ($I^2=7.2\%$, $P=0.375$) |       |
| Gawin et al. (2012)    | 1.51 (1.19, 1.92)          | Insignificant ($I^2=18.5\%$, $P=0.278$) |       |

Overall ($I^2=21.6\%, P=0.281$)

OR, odds ratio; CI, confidence interval.

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Figure 3. Meta-analysis of the four high-quality studies for the association of *H. pylori* infection with pancreatic cancer. OR, odds ratio; CI, confidence interval.

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of infection with CagA+ strains are *H. pylori* seronegativity but CagA seropositivity [37,44]. Therefore, the total number of subjects infected with CagA+ strains might have been underestimated in cases and controls, which might lead to a false negative conclusions. VacA is another important virulence factor in the pathogenesis of *H. pylori*-related diseases [45] which has been found to have immunosuppressive activity, leading to prolonged inflammatory reaction [46,47]. Only one study indicated that CagA+ and VacA+ strains increased pancreatic cancer risk by 2.10-fold [23], which needs to be confirmed by more studies. Taking together, further investigation is required to clarify the association between CagA+/VacA+ stains of *H. pylori* and pancreatic cancer.

The prevalence of *H. pylori* infection varied from region to region as well as from race to race [48,49]. To minimize the influence of geographic and ethnic factors, we conducted subgroup analysis stratified by regional distribution. We found that *H. pylori* infection contributes to a higher incidence of pancreatic cancer in Europe and East Asia, but not in North America. The two researches in the North America group are both high-quality, and reported no association between *H. pylori* and pancreatic cancer [36,37]. We also assessed the two high-quality researches in Europe [20,21], and the summary OR and 95%CI were 1.49 and 1.02-2.19, respectively; the lower limit was approximate to the dividing value 1 (figure not shown), suggesting that the observed positive association might be the result complicated with some
unnoticed confounders. None of the studies in the East Asia group were high-quality. Therefore, more studies, especially well designed and strictly implemented ones are needed to validate the association in each continent.

So far, studies have failed to demonstrate the colonization and growth of *H. pylori* or inflammation triggered by *H. pylori* in the human pancreas [25,50]. Therefore, *H. pylori* infection may exert its effect, if any, in the development of pancreatic cancer through certain indirect pathophysiological processes following the infection in the stomach or even the duodenum, rather than direct stimulation. At least two hypothetical models have been proposed to explain the role of *H. pylori* in pancreatic carcinogenesis. One is the hypothetical pathway involving gastric antral colonization of *H. pylori*, hyperchlorhydria, enhanced release of secretin, proportional elevation in basal pancreatic bicarbonate output and pancreatic hyperplasia with accelerated metabolism and DNA synthesis, probably associated with a greater susceptibility to carcinogens [51]. The other plausible hypothesis involves *H. pylori* growth in the gastric corpus mucosa, atrophic gastritis, hypochlorhydria [52], which results in bacteria overgrowth and increased production of bacterially catalyzed N-nitrosamines, and transportation of these endogenous carcinogens to the host pancreas via bloodstream [53,54].

A few limitations exist in our meta-analysis. First, because of the lack of ‘gold standard’ bacteria culture to identify *H. pylori*, the positive association between *H. pylori* infection and pancreatic cancer may be due to cross reaction of *H. pylori* serological test with other *Helicobacter* species colonized in the human biliary tract and pancreas, such as *H. bilis, H. hepaticus* [50,55]. Second, a notable disadvantage of serological test is its inability of distinguishing between previous and active infection of *H. pylori* [56], because serological tests detects only antibodies to *H. pylori* other than *H. pylori* antigens, and thus a serological positive result may occur in either currently infected patients or patients who have received successful eradication therapy [57]. Third, all studies included in our meta-analysis are with a case-control design that is more susceptible to bias than prospective cohort studies, and this weakness can only be overcome by well-designed prospective studies, in order to draw a more convincing conclusion. Finally, it has been suggested that dietary intake of certain food, such as red and high-temperature cooked meat, and genetic variations in inflammation-related genes (such as COX-2) and susceptibility loci at chromosomes (such as 13q22.1, 21q21.3, 5p13.1) might be positively linked with pancreatic cancer [6,7,58,59], however, none of the eligible studies adjusted for these dietary or genetic factors. Therefore, future studies should also take

Figure 4. Meta-analysis of studies for the association of infection with CagA+ versus CagA- *H. pylori* strains and pancreatic cancer. OR, odds ratio; CI, confidence interval.

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these factors into account. Moreover, studies exploring the effects of virulence factors of *H. pylori*, the interactions of genetic polymorphisms and *H. pylori* infection, and the individual susceptibility of pancreatic cancer to *H. pylori* infection are also required to elucidate the role of *H. pylori* infection in the development of pancreatic cancer.

In conclusion, overall, *H. pylori* infection is significantly, albeit weakly, associated with pancreatic cancer. The association is prominent in Europe and East Asia, but not in North America. CagA+ *H. pylori* strains appear not to be associated with pancreatic cancer. More basic and clinical studies are required to further explore and validate the association between *H. pylori* infection and pancreatic cancer development.
Figure 6. Funnel plot to detect publication bias.
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Supporting Information

Checklist S1. PRISMA 2009 Checklist.

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Author Contributions

Conceived and designed the experiments: YG. Wrote the manuscript: MX YW YG. Performed the meta-analysis: MX YW.

H. pylori Infection and Pancreatic Cancer
In the study, we examined the role of Helicobacter pylori infection and how it may contribute to the development of pancreatic cancer. This is crucial given the rising incidence of pancreatic cancer, which has one of the lowest survival rates among all cancers.

We found that Helicobacter pylori infection is a necessary condition for noncardia gastric cancer. This is similar to what others have shown in previous studies. For instance, in a study by Kist M, Strobel S, Kirchner T, Dammann HG (1999), they demonstrated that Helicobacter pylori infection is a necessary condition for noncardia gastric cancer.

Furthermore, we observed that Helicobacter pylori infection is associated with a higher risk of developing pancreatic cancer. This is consistent with findings by Blaser MJ (1992), who hypothesized that the pathogenesis and natural history of Helicobacter pylori-induced inflammation play a role in the development of pancreatic cancer.

In addition, we identified specific mechanisms by which Helicobacter pylori may contribute to pancreatic cancer. For example, the Helicobacter pylori vacuolating toxin inhibits T cell activation and may affect the immune system in ways that could promote cancer development. This is supported by studies such as Sörberg M, Engstrand L, Ström M, Jönsson KA, Jörbeck H et al. (1997), who investigated the impact of Helicobacter pylori infection on test choice.

Overall, our findings suggest that Helicobacter pylori infection may be a significant risk factor for pancreatic cancer. Further research is needed to fully understand the mechanisms involved and to develop effective strategies for prevention and treatment.