Original Article

The relationship between *Helicobacter pylori* and pancreatic cancer: a meta-analysis

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Background: The relationship between *Helicobacter pylori* (*H. pylori*, HP) infection and pancreatic cancer would be investigated in this article.

Methods: All cohort studies and case-control studies about *H. pylori* infection and pancreatic cancer up to October 2021 were searched in the databases of PubMed, Embase and Cochrane. The combined odds ratio (OR) and 95% confidence interval (CI) were calculated by R 4.1.0 software. Funnel plot and Egger test were used to evaluate publication bias.

Results: A total of 17 studies which included 8 case-control studies, 5 nested case-control studies, and 4 cohort studies were included in this study, and the results of this article have confirmed that the *H. pylori* infection was significantly correlated with the occurrence of pancreatic cancer (OR =1.30, 95% CI: 1.02–1.64), especially in economically underdeveloped areas (OR =2.10, 95% CI: 1.44–3.05). However, negative results were obtained in the relationship between CagA + *H. pylori* and pancreatic cancer. Similarly, we also did not find an association between vacuolating cytotoxin gene A-positive strains (VacA-positive *H. pylori*) and pancreatic cancer. The heterogeneity of this study was significant. Through a sensitivity analysis by the leave-one-out method, we found the results remained unchanged on the whole but the correlation between *H. pylori* infection and the occurrence of pancreatic cancer in the Asian population was significant. The tests for funnel plot asymmetry indicated that there might be obvious publication bias in this study. After carrying out the Egger test, we proved the existence of the publication bias in this study, which could have a certain impact on the results.

Discussion: Based on the currently available data, we confirm that *H. pylori* infection can increase the incidence of pancreatic cancer in general. CagA/VacA-positive *H. pylori* infection is not associated with the incidence of pancreatic cancer. *H. pylori* infection is significantly associated with the incidence of pancreatic cancer in economically underdeveloped areas, while the relationship between *H. pylori* infection and the incidence of pancreatic cancer in the Asian population is uncertain. In addition, more high-quality studies are needed to be included to confirm this conclusion.

Keywords: Pancreatic cancer; *Helicobacter pylori* (*H. pylori*); cytotoxin-associated gene A (CagA); vacuolating cytotoxin gene A (VacA); meta-analysis

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Introduction

Pancreatic cancer is a type of tumor with highly malignant and invasive gastrointestinal. Most patients were diagnosed as advanced due to a lack of typical clinical manifestations. Because of concealment, low surgical rate, insensitivity to radiotherapy and chemotherapy, and it has resulted in unsatisfactory treatment effects and short survival time. It was reported that the 5-year overall survival rate of pancreatic cancer patients was only 9% (1). Therefore, the prevention of etiological factors become an important measure for the prevention and treatment of pancreatic cancer. The occurrence of pancreatic cancer was associated with various factors, among which smoking was the clearest risk factor. Chronic pancreatitis and long-term type 2 diabetes were also associated with increased risks of pancreatic cancer, but were not the main causes of this disease (2). The last several years have seen increased interest in the association between bacteria and pancreatic cancer. Carriage of certain bacteria in the oral cavity (e.g., *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Streptococcus sp.*), gut [e.g., *Helicobacter pylori* (*H. pylori*, HP), *Synergistetes*, *Proteobacteria*], and pancreas (e.g., Fusobacterium sp., Enterobacteriaceae, Pseudomonadaceae) has been associated with an increased risk of developing pancreatic cancer (3). On this basis, several studies have proposed that *H. pylori* might be associated with the occurrence of pancreatic cancer (4-12). Some studies suggested that there was no obvious correlation between the two as a whole, but different subgroup of *H. pylori* infection might be significantly associated with the occurrence of pancreatic cancer (13-17). In addition, there remained some problems in the past seven meta-analyses. Due to the limited number of studies, although publication bias tests have been carried out, they were still not sure that there was no publication bias in their studies. The quality of cohort studies was regarded to be higher than the case-control studies, but only two studies have been included in the cohort study for analysis. This meta-analysis was necessary due to the relationship between the two was not clear so far. This article would include more research data to look for newer and stronger evidence to explore the relationship between *H. pylori* infection and pancreatic cancer further. We present the following article in accordance with the PRISMA reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2803/rc).

Methods

Literature search

PubMed, Embase, and Cochrane databases were searched for all literature on *H. pylori* infection and the occurrence of pancreatic cancer from inception to October 2021, as well as references and abstracts of gastroenterology meetings. Here is an example of the retrieval strategy in PubMed: ("Pancreatic Neoplasms"[Mesh] OR "Neoplasm, Pancreatic"[Title/Abstract] OR "Pancreatic Neoplasm"[Title/Abstract] OR "Pancreas Neoplasms"[Title/Abstract] OR "Neoplasm, Pancreas"[Title/Abstract] OR "Neoplasms, Pancreas"[Title/Abstract] OR "Pancreas Neoplasm"[Title/Abstract] OR "Neoplasms, Pancreatic"[Title/Abstract] OR "Cancer of Pancreas"[Title/Abstract] OR "Pancreas Cancers"[Title/Abstract] OR "Pancreas Cancer"[Title/Abstract] OR "Cancer, Pancreas"[Title/Abstract] OR "Cancers, Pancreas"[Title/Abstract] OR "Pancreatic Cancer"[Title/Abstract] OR "Cancer, Pancreatic"[Title/Abstract] OR "Cancers, Pancreatic"[Title/Abstract] OR "Pancreatic Cancers"[Title/Abstract] OR "Cancer of the Pancreas"[Title/Abstract]) AND ("Helicobacter pylori"[Mesh] OR "Helicobacter nemestrinae"[Title/Abstract] OR "Campylobacter pylori"[Title/Abstract] OR "Campylobacter pylori subsp. Pylori"[Title/Abstract] OR "Campylobacter pyloridis"[Title/Abstract] OR "Gastritis, Atrophic"[Mesh] OR "Atrophic Gastritides"[Title/Abstract] OR "Atrophic Gastritis"[Title/Abstract] OR "Gastritides, Atrophic"[Title/Abstract]).

Inclusion criteria

(I) The content of the study was about the relationship between *H. pylori* and pancreatic cancer. (II) The type of study was a case-control study or cohort study. (III) NOS (Newcastle-Ottawa Scale) score >3 points. (IV) The diagnostic method of pancreatic cancer and *H. pylori* (such as serological test, breath test and gastroscopic biopsy) must be illustrated and the diagnosis must be clear. (V) The odds ratios (OR) and 95% confidence interval (CI) should be given in the study directly or could be calculated from the original data.

Exclusion criteria

(I) Study without a control group. (II) The study that could not extract data effectively. (III) The study only had abstracts without full text. (IV) Animal study and case report. (V) The study that did not explain the detection the

method of *H. pylori* infection. (VI) The study whose sample size was too small.

Quality assessment and data extraction

Two investigators reviewed studies independently according to the above strategies, and strictly followed the inclusion and exclusion criteria to select eligible studies that met the retrieval conditions. For the divergent literature, it was decided whether to include it or not through discussion or consultation with the third researcher. For the lack of information in the literature, the original author was contacted as possible to supplement it. If the original author could not be contacted successfully, it would be decided whether or not to rule out according to the impact on the study. The NOS scoring criteria was used to evaluate the quality of the included studies. The information extracted from the studies includes: title, first author, time of publication, type of study, area, detection method of *H. pylori*, sample size, *H. pylori* infection rate, prevalence rate of pancreatic cancer, cytotoxin-associated gene A (CagA) positive rate and OR and 95% CI in observation group and control group. The data would be displayed in a tabular form.

Statistical methods

All data were analyzed with the R 4.1.0 meta package. The combined OR and 95% CI were calculated to compare the correlation between them. If OR >1, it was considered that HP infection promoted the occurrence of pancreatic cancer. If OR <1, it indicated that HP infection reduced the incidence of pancreatic cancer; 95% CI containing 1 equals P <0.05, which represented the result did not have statistical significance. Heterogeneity tests were used to assess the heterogeneity of studies, and the I^2 statistic represented the significant degree of heterogeneity. We stipulated that P<0.1 was statistically significant. When I^2>50%, it was considered that there was significant heterogeneity between studies, and the random effect model would be used. When I^2<50%, there was no obvious heterogeneity within studies, and the fixed effect model was adopted. The possible sources of heterogeneity were estimated by sensitivity-analysis, and the possible sources of heterogeneity were analyzed by subgroup-analysis. By carrying out the funnel plots and Egger test to examine whether publication bias existed. It indicated that the existence of publication bias was possible if P<0.05. In this study, all statistical tests were bilateral tests.

Results

Study retrieval results

Through extensive review and strict compliance with the inclusion criteria, a total of 17 articles met the inclusion criteria and were included in this study (*Figure 1*), including 8 case-control studies (3,790 subjects, 1,705 in the case group and 2,085 in the control group), 5 nested case-control studies (2,665 subjects, 1,113 in the case group and 1,552 in the control group) and 4 cohort studies (69,625 subjects, 29,346 in the case group and 40,279 in the control group). The basic information of each study was shown in *Table 1*, and the data extraction results were shown in *Tables 2*,*3*.

H. pylori infection and pancreatic cancer

An overall meta-analysis and three subgroup-analysis were carried out for the included studies. Meta-analysis results showed that *H. pylori* infection was generally associated with the occurrence of pancreatic cancer (OR =1.30; 95% CI: 1.02–1.64; P=0.03) (*Figure 2*). Heterogeneity test results indicated that the included studies had significant heterogeneity (I^2=75%; P<0.01), so the random effect model should be selected. Subgroup-analysis was carried out to explore the source of heterogeneity due to the significant heterogeneity between studies, which could improve the credibility of this study.

Considering that there were great differences in the research methods and quality of each type of study, we divided this study into three groups according to the type of study (*Figure 3*). They were case-control group, nested case-control group and cohort study group. The results of the subgroup-analysis showed that there was significant heterogeneity in the case-control group (I^2=83%; P<0.01), and the difference was statistically significant. *H. pylori* infection was not associated with pancreatic cancer in the case-control group (OR =1.40; 95% CI: 0.91–2.15). The nested case-control group also had heterogeneity (I^2=51%; P=0.08), and the difference was statistically significant. *H. pylori* infection was not associated with pancreatic cancer in the nested case-control group (OR =1.01; 95% CI: 0.76–1.34). In the cohort study group, the heterogeneity was also significant (I^2=65%; P=0.04). The difference was statistically significant. It showed that *H. pylori* infection had no connection with pancreatic cancer in the nested case-control group (OR =1.70; 95% CI: 1.00–2.91). To sum up, these three types of studies all suggested that *H. pylori* infection had no relation to the occurrence of pancreatic

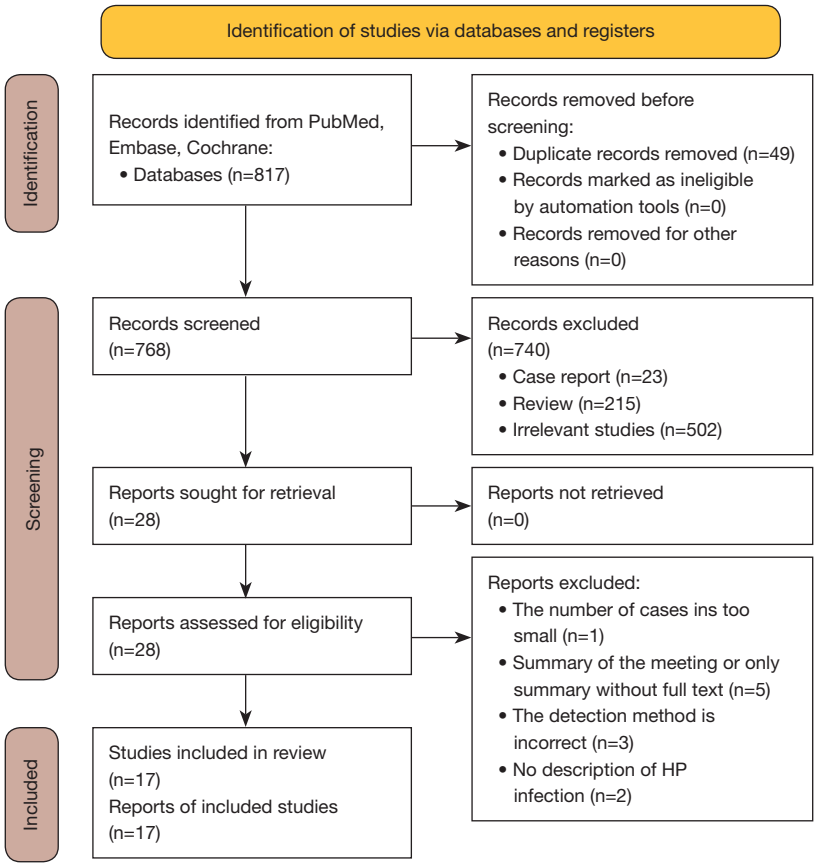

Figure 1 Flow diagram of literature screening. HP, *Helicobacter pylori*.

cancer. Since there was still high heterogeneity in these three subgroups, the research type was not the main source of heterogeneity.

We believed that the infectivity and toxicity of *H. pylori* might be related to the economic level of the region (27), the subgroup analysis of the research data was carried out again according to the regional economic level (*Figure 4*). We regarded Europe, North America and parts of Asia (such as Japan, as well as Shanghai and Taiwan in China) as developed areas, and the rest as non-developed areas. The results of subgroup-analysis showed that there was a significant correlation between *H. pylori* infection and pancreatic cancer in economically undeveloped areas (OR =2.10; 95% CI: 1.44–3.05), while *H. pylori* infection was not associated with pancreatic cancer in developed areas (OR =1.17; 95% CI: 0.92–1.50). However, the developed areas group still had high intra-group heterogeneity.

The living environment and habits of people in different regions were quite different, which could be the result of the significant heterogeneity in developed areas group. For this reason, we divided all the studies into three subgroups according to the continent the study came from. They were the Asian group, European group and North American group (*Figure 5*). The results of the subgroup-analysis showed that there existed heterogeneity in the North American group, and the difference was statistically significant (I^2=63%; P=0.04). In this group, we did not observe the connection between *H. pylori* infection and pancreatic cancer (OR =1.04; 95% CI: 0.66–1.63). There was significant heterogeneity in the Asia group, and the difference was statistically significant (I^2=89%; P<0.01). It didn't show the relation between *H. pylori* infection and pancreatic cancer in the Asian group (OR =1.61; 95% CI: 0.90–2.90). The European group didn't show significant heterogeneity (I^2=36%; P=0.15). Similarly, this group indicated that *H. pylori* had nothing to do with pancreatic cancer (OR =1.15; 95% CI: 0.96–1.37). In a word, there was no association between *H. pylori* infection and the incidence of pancreatic cancer in the three regions, but the Asia group had significant heterogeneity (I^2=89%), which might

Table 1 Basic characteristics of the included studies

Author	Type	Method[a]	Region	CagA[b]	NOS	Conclusion[c]
Permuth (18)	Case control study	Multiple serological	USA	Yes	8	Nonsupport
Geng (4)	Case control study	ELISA	China	Yes	6	Support+
Huang (19)	Nested case-control study	ELISA	EU	Yes	7	Nonsupport
Ai (5)	Case control study	ELISA	China	Yes	6	Support+
Risch (7)	Case control study	ELISA	China	Yes	8	Support–
Yu (20)	Nested case-control study	Multiple serological	Finland	NA	8	Nonsupport
Gawin (21)	Case control study	ELISA	Poland	Yes	7	Nonsupport
Risch (8)	Case control study	ELISA	USA	Yes	8	Support+
Lindkvist (22)	Nested case-control study	ELISA	Sweden	NA	8	Nonsupport
Dou (9)	Case control study	ELISA	China	Yes	5	Support+
de Martel (23)	Nested case-control study	ELISA	USA	Yes	8	Nonsupport
Stolzenberg-Solomon (10)	Nested case-control study	ELISA	Finland	Yes	8	Support+
Raderer (11)	Case control study	ELISA	Austria	NA	6	Support+
Hirabayashi (24)	Prospective cohort study	ELISA	Japan	NA	8	Nonsupport
Chen XZ (25)	Prospective cohort study	ELISA	Germany	Yes	8	Nonsupport
Hsu (6)	Retrospective cohort study	Endoscopy	China TW	NA	8	Support+
Chen Y (26)	Prospective cohort study	ELISA	USA	Yes	8	Nonsupport

[a], the detection of *Helicobacter pylori*; [b], it showed whether the study had detected serum CagA; [c], it showed studies' conclusion. Support+, Serum CagA positive *H. pylori* infection increases the incidence of pancreatic cancer. Support–, Serum CagA negative *H. pylori* infection increases the incidence of pancreatic cancer. Nonsupport, *H. pylori* infection is not associated with pancreatic cancer. CagA, cytotoxin-associated gene A; NOS, Newcastle-Ottawa Scale.

be the main source of overall heterogeneity. Therefore, this result was still not convincing due to the unexplained heterogeneity. Furthermore, after carrying out a sensitivity-analysis by the leave-one-out method, we found that Risch's study was the main factor for the increase in heterogeneity (*Figure 6*). After being eliminated, the I^2 statistic was reduced to 58%. The overall results did not change significantly, while partial results of subgroup-analysis changed. When we carried out a subgroup-analysis according to the type of study, the I^2 statistic in the case-control group decreased to 22% (P=0.26), which indicated that there was no significant heterogeneity in the group. Case-control studies showed that *H. pylori* infection was related to pancreatic (OR =1.52; 95% CI: 1.24–1.88). When the subgroup-analysis is carried out according to the regional economic level, the result is stable. When the subgroup-analysis was carried out according to the continent, the results of the Asia group were reversed, which indicated that *H. pylori* infection could be significantly associated with pancreatic cancer in the Asian population (I^2=63%; P=0.03; OR =1.95; 95% CI: 1.24–3.07).

CagA-positive H. pylori infection and pancreatic cancer

CagA antibody was detected in seven case-control studies, four nested case-control studies and 1 cohort study, with a total of 15,146 subjects. The result of the meta-analysis showed that there was no significant association between CagA-positive *H. pylori* infection and pancreatic cancer on the whole (I^2=44%; OR =0.90; 95% CI: 0.80–1.01) (*Figure 7*).

VacA-positive H. pylori infection and pancreatic cancer

To further study the relationship between the subtype of *H. pylori* and pancreatic cancer, we explored whether VacA-positive *H. pylori* infection could promote the occurrence of pancreatic cancer. Two case-control studies and 1 nested case-control study were included, with a total of 1,086 subjects. We did not find the significant association

Table 2 Data extraction from case-control studies and nested case-control studies

Study	Sample	Case group			Control group		
		HP+[a]	HP−[b]	N[c]	HP+	HP−	N
Permuth	262	13	118	131	16	115	131
Geng	138	47	21	68	34	36	70
Huang	896	196	250	448	206	241	448
Ai	116	36	20	56	28	32	60
Risch	1,555	233	528	761	327	467	794
Yu	706	325	28	353	328	25	353
Gawin	316	121	18	139	146	31	177
Risch	1,063	80	293	373	120	570	690
Lindkvist	350	39	48	87	100	163	263
Dou	221	54	31	85	64	72	136
de Martel	366	51	53	104	155	107	262
Stolzenberg-Solomon	347	99	22	121	165	61	226
Raderer	119	60	32	92	12	15	27

[a], the number of patients with *H. pylori* infection; [b], the number of patients without *H. pylori* infection; [c], overall number of patients. HP, *Helicobacter pylori*.

Table 3 Data extraction from cohort studies

Study	Sample	Case group		Control group	
		HP[a]	PC[b]	HP	PC
Hirabayashi	20,116	13,752	83	6,364	36
Chen X	9,504	4,738	27	4,766	19
Hsu	30,110	6,022	11	24,088	11
Chen Y	9,895	4,834	15	5,061	8

[a], the number of patients with *H. pylori* infection; [b], the number of patients who developed pancreatic cancer. HP, *Helicobacter pylori*; PC, pancreatic cancer.

between VacA-positive *H. pylori* infection and pancreatic cancer (I^2=0%; OR =0.94; 95% CI: 0.71–1.25) (*Figure 8*).

Assessment of publication bias

A funnel plot was used to evaluate the publication bias of the included studies. The funnel plot was asymmetric on both sides, which indicated the existence of publication bias (*Figures 9,10*). Egger tests (P<0.05) also showed that there was a possibility of publication bias in this study. We used the trim and filling method to assess the impact of publication bias on this article. Seven additional studies were added to the trim and filling method and the results were consistent with this article. It was proved that although publication bias affected this study, the results were still robust.

Discussion

Since the discovery of *H. pylori*, researchers have devoted themselves to studying its pathological significance in humans. It is clear that *H. pylori* infection is associated with a variety of gastric diseases, such as gastric ulcers, chronic atrophic gastritis, gastric cancer, gastric lymphoma and so on (28). CagA and VacA are the critical virulence factors of *H. pylori*, which can regulate the host's immune response to help *H. pylor*'s survival, and induce the formation of acidic vacuoles in the cytoplasm of gastric epithelial cells *in vivo*, as well as in permanent cell lines or primary epithelial cells (29,30). With further research, the researchers have found that *H. pylori* can colonize not only in gastric mucosa, but also in other digestive organs (31). Therefore, *H. pylori* infection might promote the occurrence of other non-gastric diseases, such as pancreatic cancer, colorectal cancer (32), liver cancer (33) and cholangiocarcinoma (34). In addition to digestive diseases, researchers have also found that

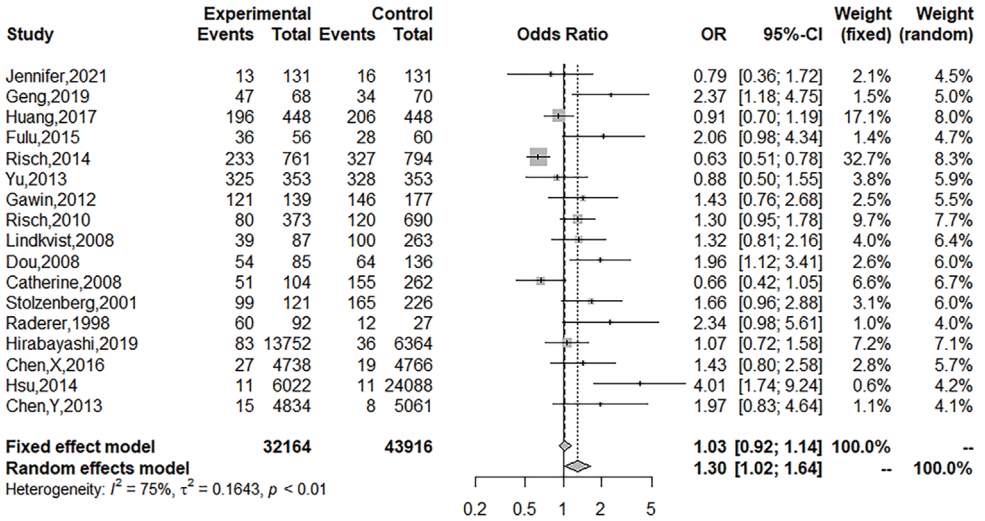

Figure 2 Meta-analysis forest plot of the relationship between *H. pylori* infection and pancreatic cancer. Using random effects model (I^2=75%). OR =1.30, 95% CI: 1.02–1.64. OR, odds ratio; CI, confidence interval.

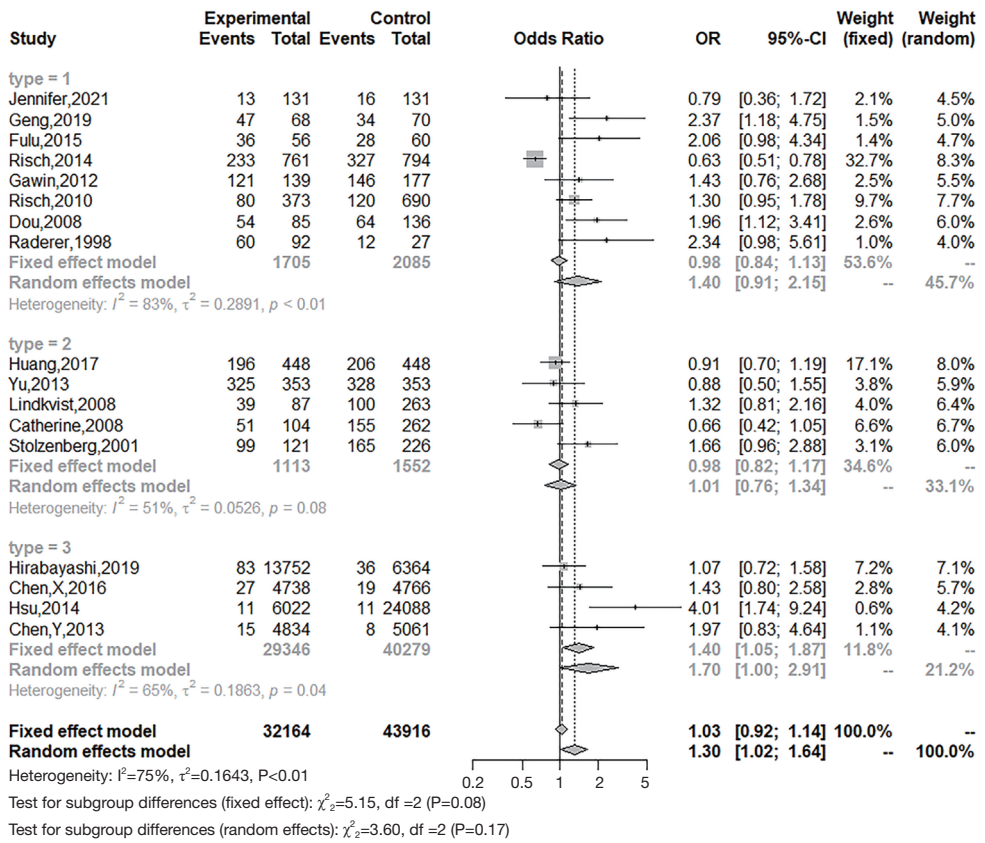

Figure 3 Subgroup-analysis forest plot of the relationship between *H. pylori* infection and pancreatic cancer (study type). Type =1: case-control study. Using random effects model (I^2=83%). OR =1.40, 95% CI: 0.91–2.15; Type =2: nested case-control study. Using random effects model (I^2=51%). OR =1.01, 95% CI: 0.76–1.34; Type =3: cohort study. Using random effects model (I^2=65%). OR =1.70, 95% CI: 1.00–2.91. OR, odds ratio; CI, confidence interval.

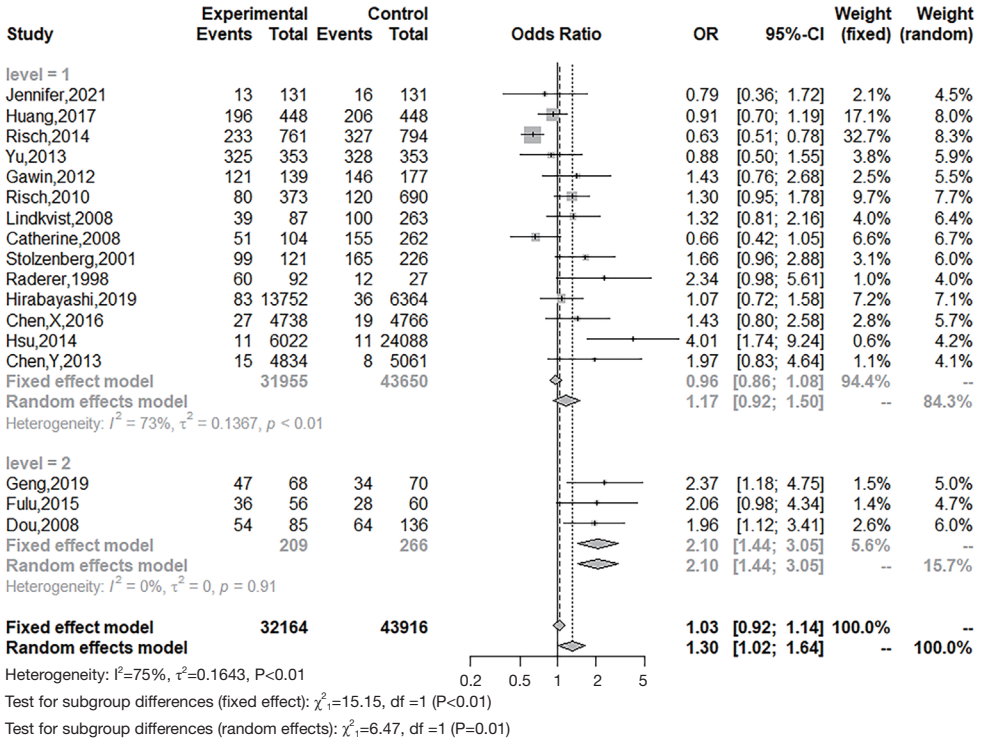

Figure 4 Subgroup-analysis forest plot of the relationship between *H. pylori* infection and pancreatic cancer (economic level). Level =1: economically developed areas. Using random effects model (I^2=73%). OR =1.17, 95% CI: 0.92–1.50; Level =2: economically underdeveloped areas. Using fixed effect model (I^2=0%). OR =2.10, 95% CI: 1.44–3.05. OR, odds ratio; CI, confidence interval.

H. pylori seropositive may be associated with some respiratory diseases, but there is no clear evidence to prove the reliability of this link due to the limited quality and quantity of research (35). Although many studies have been carried out, there is still no definite conclusion as to whether *H. pylori* is related to the occurrence of pancreatic cancer or not. There have been several meta-analyses of the relationship between *H. pylori* infection and pancreatic cancer previously (12-17,36), but the conclusions are controversial. To explore the correlation between the two fully, our study included more updated samples and various types of studies, such as case-control studies, nested case-control studies, prospective cohort studies and retrospective cohort studies.

Our meta-analysis confirmed that there was an overall association between *H. pylori* infection and pancreatic cancer, and this correlation would become more significant in underdeveloped areas. We have not confirmed that *H. pylori* infection was associated with pancreatic cancer in the Asian population. However, we observed that *H. pylori* infection significantly increased the possibility of pancreatic cancer in the Asian population after a sensitivity-analysis by the leave-one-out method. Therefore, the association between *H. pylori* infection and pancreatic cancer in the Asian population remained uncertain. In addition, although several studies have shown that CagA-seropositive *H. pylori* infection could promote the occurrence of pancreatic cancer, our studies indicated that CagA-positive *H. pylori* infection was not associated with the occurrence of pancreatic cancer. We further explored the relationship of the VacA- positive *H. pylori* infection and pancreatic cancer, but did not find a statistical significance between them. Due to the significant heterogeneity among the included studies, subgroup-analysis and sensitivity-analysis were carried out to find the source of heterogeneity. The results of the subgroup-analysis have shown that there existed heterogeneity among all subgroups. Sensitivity-analysis have found that Risch's study led to the increase of heterogeneity in our study, but it was not the main factor for the increase of heterogeneity. Even if excluding Risch's study, our study still had significant heterogeneity (I^2=57%). After a review of all studies, we have found that there were two studies whose included population were smokers (10,20). Smokers tended to have a higher incidence of *H. pylori*

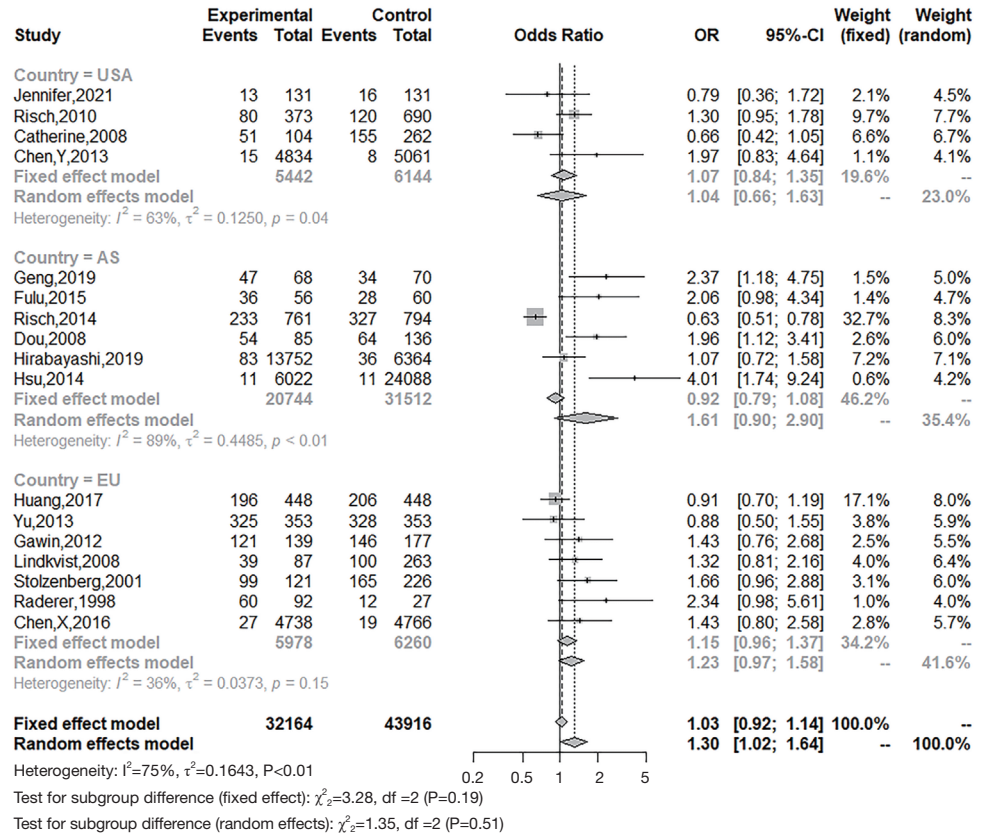

Figure 5 Subgroup-analysis forest plot of the relationship between *H. pylori* infection and pancreatic cancer (region). USA = America. Using random effects model (I^2=63%). OR =1.04, 95% CI: 0.66–1.63; AS = Asian region. Using random effects model (I^2=89%). OR =1.61, 95% CI: 0.90–2.90; EU = European region. Using fixed effect model (I^2=36%). OR =1.15, 95% CI: 0.96–1.37. OR, odds ratio; CI, confidence interval.

infection (37,38) and a higher incidence of pancreatic cancer (39) compared with non-smokers, which made patients in this study have a higher incidence of pancreatic cancer than in other studies. In addition, two studies used various serological tests to detect *H. pylori* antibodies (18,20), and it was regarded as *H. pylori* infection only if more than 4 antibodies were seropositive. However, most of the studies detected IgG or IgM antibodies of *H. pylori* directly. It was considered as *H. pylori* infection when either of them was seropositive. As a result, the *H. pylori* infection rate in these two studies might be lower than that in other studies. The number of *H. pylori* seronegative but CagA-positive in Risch's study was more than that in other studies. The main reason might be that different researchers have different methods of *H. pylori* typing. Some studies tested serum CagA in all patients, while others only tested CagA in *H. pylori*-positive patients, resulting in some *H. pylori*-negative but CagA-positive patients not counted as CagA-positive. In the study, Risch pointed out that the appreciable fraction of CagA-positive individuals *H. pylori* seronegative. Therefore, we believed that the significant heterogeneity might be caused by many factors, which may be related to the particularity of each study population (including race, living standard, smoking, etc.) and the differences between different studies (including testing methods, testing population, research quality, etc.). Although it did not affect the overall outcome, the relationship between *H. pylori* infection and pancreatic cancer in the Asian population needed to be treated with caution.

The mechanism by which *H. pylori* may cause pancreatic cancer is still unclear so far. A study showed that *H. pylori* could induce pancreatic cancer through ascending gastric infection or retrograde metastasis of the small intestine, based on the identification of peptide AIP1e7 in a small number of patients with pancreatic cancer, which was homologous to the amino acid sequence of PBP of *H. pylori* (40). Nilsson

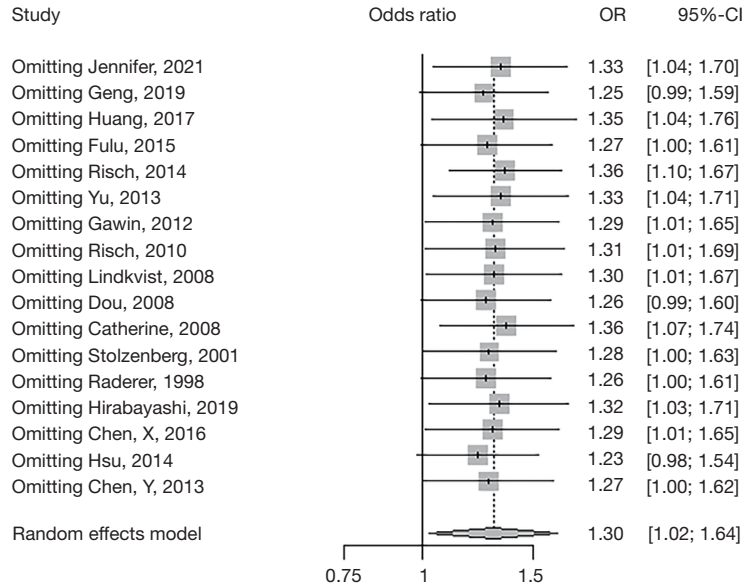

Figure 6 Sensitivity-analysis forest plot of the relationship between *H. pylori* infection and pancreatic cancer. For each study, the estimates of OR and 95% CI were plotted with a box and a horizontal line. Closed diamond indicates pooled OR and 95% CI. OR, odds ratio; CI, confidence interval.

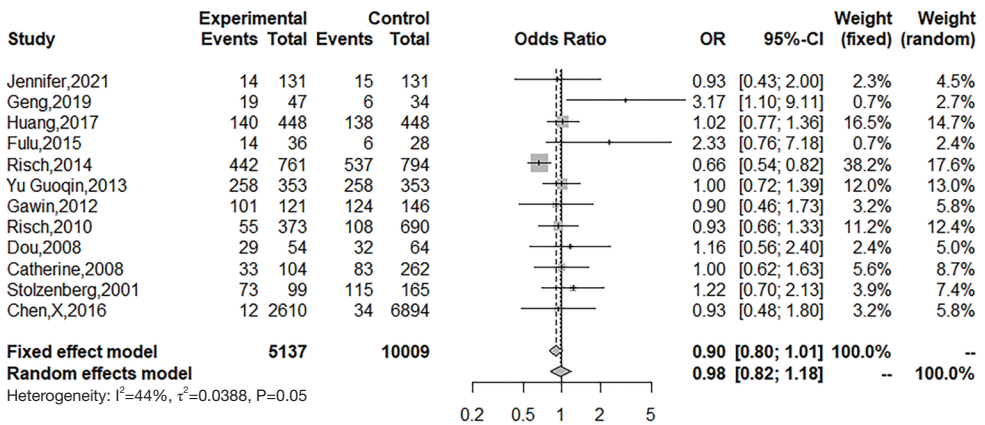

Figure 7 Meta-analysis forest plot of the relationship between cytotoxin-associated gene A positive *H. pylori* infection and pancreatic cancer. Using fixed effect model (I^2=44%). OR =0.90, 95% CI: 0.80–1.01. OR, odds ratio; CI, confidence interval.

et al. (41) detected *H. pylori* DNA in pancreatic tumor and/or surrounding tissues of 60% of pancreatic cancer patients, and suggesting that *H. pylori* might cause pancreatic cancer by directly infecting pancreatic tissue. Takayama *et al.* (42) found that the secretion of interleukin-8 (IL-8) and vascular endothelial growth factor (VEGF) in pancreatic cells would increase after *H. pylori* infection, as well as the activities of proliferation factors (including NF-kappaB, AP-1 and SRE) related to pancreatic carcinogenesis increased, thus enhancing the malignant potential of pancreatic cells, which may be one of the important mechanisms of pancreatic cancer caused by *H. pylori*. Risch *et al.* (43) believed that smoking and food-derived N-nitrosamines were important factors leading to pancreatic cancer, and the colonization of *H. pylori* in the stomach could enhance this carcinogenic effect. In addition, ABO genotype/phenotypic status could affect the biological behavior of *H. pylori* and ultimately enhance the carcinogenicity of pancreatic cancer exposed to

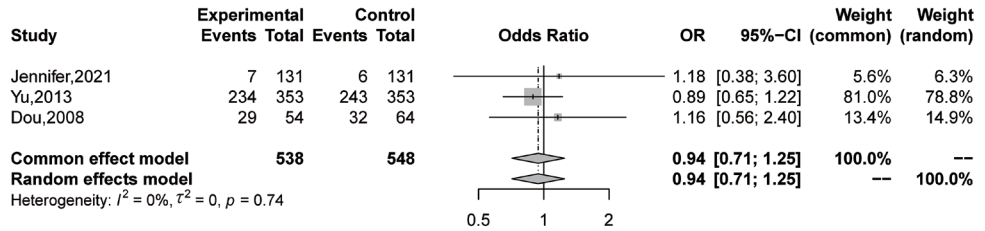

Figure 8 Meta-analysis forest plot of the relationship between vacuolating cytotoxin gene A positive *H. pylori* infection and pancreatic cancer. Using fixed effect model (I^2=0%). OR =0.94, 95% CI: 0.71–1.25. OR, odds ratio; CI, confidence interval.

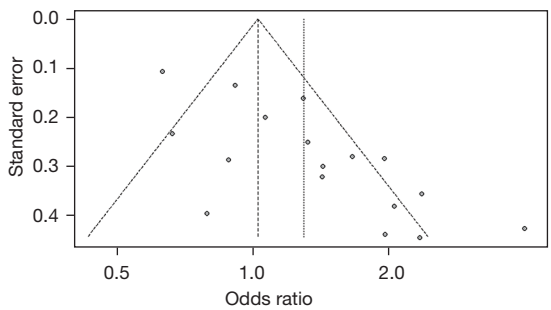

Figure 9 Funnel plot of the relationship between *H. pylori* infection and pancreatic cancer.

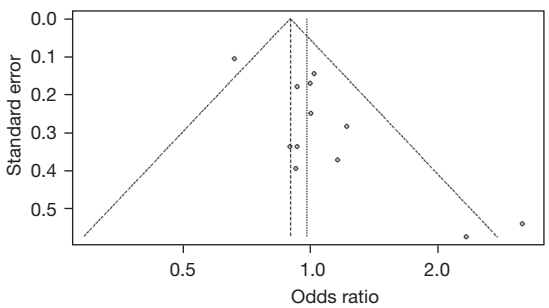

Figure 10 Funnel plot of the relationship between cytotoxin-associated gene A positive *H. pylori* infection and pancreatic cancer.

N-nitrosamines associated with diet and smoking, resulting in the risk of pancreatic cancer. A new study showed that there was a significant correlation between *H. pylori* infection and the expression of mucin family MUC4. MUC4 might be a potential action site in pancreatic cancer caused by *H. pylori* (44). To sum up, pancreatic cancer caused by *H. pylori* might be the result of the synergistic effect of multiple mechanisms, so a great number of studies are still needed to explore all possible carcinogenic mechanisms.

The limitations of our study were the existence of significant heterogeneity and publication bias. The reasons for publication bias were mostly due to the omission of included studies in meta-analysis, the bias of small sample studies, and the difficulty of publishing negative results. We believed that a possible source of publication bias in our study was due to the quality of previous retrospective analysis and meta-analysis follow-up studies, despite being more robust, might not be published due to repetition, while articles with negative results, might be more difficult to be published due to its contradictory narrative. Another source of publication bias in our study was the inclusion of studies that used small sample-size. Therefore, studies that draw similar results might be difficult to publish because of repeated conclusions, while articles with negative results were more likely to be inconsistent with the mainstream conclusions and thus get published opportunities. In addition, this study included more small sample studies, which may also lead to publication bias. Therefore, more high-quality cohort studies and case-control studies are needed to confirm the correctness of this conclusion. In addition, more and more in-depth basic studies should be carried out to clarify the specific mechanism of pancreatic cancer caused by *H. pylori* and to provide a stronger theoretical basis for the existence of this link from an etiological point of view.

Conclusions

Our study confirmed that *H. pylori* infection was generally associated with pancreatic cancer, and this correlation would become more significant in economically underdeveloped areas. Although have not confirmed that *H. pylori* infection was associated with pancreatic cancer in the Asian population, we observed that *H. pylori* infection significantly increased the possibility of pancreatic cancer in the Asian population after sensitivity-analysis, suggesting that the results were not stable. In addition, we did not observe the evidence which

could prove the association between CagA/VacA-positive *H. pylori* infection and the occurrence of pancreatic cancer.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2803/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2803/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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