RESEARCH ARTICLE

Helicobacter pylori and Pancreatic Cancer Risk: a Meta-analysis Based on 2,049 Cases and 2,861 Controls

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Abstract

Aim: *Helicobacter pylori* (***H. pylori***) **have been considered as a risk factor for many cancers. We conducted this meta-analysis to clarify the association between *H. pylori* infection and the risk of pancreatic cancer. Methods: We searched the Medicine/Pubmed and Embase databases, studies about the association between *H. pylori* infection and pancreatic cancer published up to Jan.2014 were included. Finally, a total of 9 studies were used for this a meta-analysis. The odds ratios (ORs) and 95% confidence interval (95%CI) of *H. pylori* infection on pancreatic cancer with respect to control groups were evaluated. Two authors independently assessed the methodological quality and extracted data. This meta-analysis was conducted using software, state (version 12.0) to investigate heterogeneity among individual studies and to summarize the studies. Using the fixed-effects or random-effects model, depending on the absence or presence of significant heterogeneity. Sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omitting a single study each time. Publication bias was evaluated by funnel plot, using Egger's and Begg's tests. Results: There was no significant association between *H. pylori* infection and pancreatic cancer risk in the summary ORs,(OR=1.06, 95%CI: 0.74-1.37) through the random-effect method, but heterogeneity among studies was significant (I^2=58.9%), so we put the studies into two subgraphs (eastern and western). The results about western (OR=1.14 95%CI:0.89, 1.40) showed heterogeneity among the western countries of I^2=6.6%, with no significant association between Hp+ and pancreatic cancer, but the eastern countries (OR=0.62, 95%CI:0.49, 0.76), I^2=0, suggested that decreasing pancreas-cancer risk in subjects with Hp+ infection. Simultaneously, 7 studies examined CagA+ strains was (OR=0.84 95%CI:0.63, 1.04), I^2=36% with the random-effect method, subgraphs indicated that CagA+ could decrease the risk of pancreatic cancer in the eastern subjects (OR=0.66, 95%CI:0.52-0.80), but the association was not statistically significant in the western subjects (OR=0.95, 95%CI:0.73, 1.16). Conclusion: Hp+ and CagA+ infection are associated with a decreased risk of pancreatic cancer in eastern populations but have no significant associations in western countries.**

Keywords: *Helicobacter pylori* - pancreatic cancer - risk - meta-analysis

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Introduction

Pancreatic cancer is one of the most dismal malignancies. Lack of highly sensitive and specific test and the early symptoms, it is difficult to early discovery, diagnosis and treatment. The International Agency for Research on Cancer reported that 278684 new cases and 266669 deaths of this disease occurred worldwide in 2008. Pancreatic cancer was the thirteenth leading cause of cancer mortality and the seventh leading cause of incidence among both men and women (Chen et al., 2013), yet the etiology of pancreatic cancer is not well understood. Cigarette smoking continues to be identified as a strong established risk factor (Iodice et al., 2008; Lynch et al., 2009; Maisonneuve et al., 2010), and more recently, obesity has been consistently associated with increased the risk (Larsson et al., 2007; Arslan et al., 2010; Aune et al., 2012). Recent literature suggests that heavy alcohol intake (Tramacere et al., 2010; Lucenteforte et al., 2012), non-O blood type (Iodice et al., 2010) modestly increase pancreatic cancer risk. Although diabetes (Ben et al., 2011; Li et al., 2011) and pancreatitis (Raimondi et al., 2010; Duell et al., 2012; Olson, 2012) increase risk, diabetes may also be an early manifestation (Ben et al., 2011; Magruder et al., 2011), and pancreatitis is extremely rare. But whether Hp infection is the risk of pancreatic cancer is controversial.

H. pylori is a helical-shaped Gram negative bacterium and has been identified as the major causative agent of various benign and malignant digestive tract diseases (Handa et al., 2011), such as gastric cancer and gastric lymphoma (Correa et al., 2007). but the association Hp infection and pancreatic cancer is inconsistent, a meta-analysis from Guru Trikudanathan et al (2011)

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including 6 case-controls indicates that a significant association between the presence of *H. pylori* infection and pancreatic cancer (AOR 1.38, 95% CI: 1.08-1.75). Another meta-analysis from Mingjia Xiao (2013) including 9 case-controls also suggests that *H. pylori* infection is significantly, albeit weakly, associated with pancreatic cancer development. but recently another two large sample size: Guoqin Yu et al (2013) including 700 subjects manifested that *H. pylori* was not a risk factor for pancreatic cancer; other one observational study in taking 1555 subjects indicated that *H. pylori* colonization may have diverse effects on cancer risk, depending on the organism strain type as well as on the particular cancer site. In order to further clarify the association hp infection and pancreatic cancer. Therefore, an updated meta-analysis was performed which included all eligible studies to evaluate the association between *H. pylori* infection and pancreatic cancer risk.

Materials and Methods

Search strategy

We initially identified all articles which tested the association between *H. pylori* infection and pancreatic cancer by searching the Medicine/PubMed Embase databases up to Jan. 2014 using the following MeSH terms and keywords: "Helicopter pylori" [MeSH] OR (Campylobacter pylori) OR (*H. pylori*) OR (Hp) AND ("pancreatic Neoplasms" [MeSH] OR (pancreatic cancer) OR pancreatic carcinoma) OR (pancreatic adenocarcinoma) OR (pancreatic Cancer) OR (pancreas Cancer) OR (pancreatic Neoplasms) OR (Neoplasms, pancreas) OR (carcinoma of pancreas) OR (pancreas tumor). We did not restrict the languages. Two authors reviewed the search results to reduce the possibility of missing the published papers. For data missing, we contacted the authors for the relevant information.

Study selection

Inclusion criteria: (i) Studies on the association between *H. pylori* infection and pancreatic cancer risk ; (ii) Subjects more than 18 years old; (iii) Hp+ infection by serological testing like ELISA, westerning blotting or another reliable methods; (iiii) The pancreatic cancer diagnoses and the sources of cases and controls should be stated. The studies excluded in this meta-analysis was mainly for the following reasons: lacking a normal control group, reviews, letters, only abstract, the research design being not scientific and reasonable, and including repeated data. A total of 9 papers met the eligible criterias and were included in the present study (Raderer et al., 1997; Stolzenberg-Solomon et al., 2001; Lindkvist et al., 2008; de Martel et al., 2008; Rish et al., 2010; Shimoyama et al., 2010; Gawin et al., 2012; Yu et al., 2013; Xiao et al., 2014).

Data extraction

Two reviewers independently extracted the following data for each eligible study: authors, year of publications, country of participants, study design. Pylori detection method, number of Cases and controls including Hp+ and CagA+, the matched and the adjusted factors with the adjusted OR 95%CI including Hp+ and CagA+.The data were extracted and registered independently by two investigators (Yin Wang, FU-Cheng Zhang), Any disagreements were resolved by a third investigator (Yao-Jun Wang), who participated in the discussion and made the ultimate decision.

Quality assessment

Two reviewers independently assessed the quality of the included studies with the Newcastle–Ottawa Scale (NOS) , which consists of three parameters of quality: selection, comparability and exposure assessment. The NOS assigns a maximum score of 4 for selection, 2 for comparability, and 3 for exposure. So, a score of 9 is the highest and reflects the highest quality. Disagreements were resolved by the third one. The NOS evaluation tool included:

(1) Selection
Is the case definition adequate?
Representativeness of the cases
Selection of Controls
Definition of Controls
(2) Comparability
Comparability of cases and controls on the basis of the design or analysis
(3) Exposure
Ascertainment of exposure
Same method of ascertainment for cases and controls
Non-Response rate

Statistical analysis

The data on *H. pylori* positive results in the case and control groups were summarized OR and 95%CI to assess the association between *H. pylori* infection and pancreatic cancer risk. Heterogeneity was quantified evaluated using the Q statistic and the I^2 statistic, this statistic yields results ranged from 0 to 100% (I^2 = 0-25%, no heterogeneity; I^2 = 25-50%, moderate heterogeneity; I^2 = 50-75%, large heterogeneity; and I^2 = 75-100%, extreme heterogeneity) (Higgins et al., 2003). If heterogeneity existed, the random-effects model was used; otherwise, the fixed-effects model was used. The potential publication bias was assessed graphically using Begg's and egger's test and funnel plots. All analyses were performed with STATA software (version 12.0).

Results

Eligible studies

About 562 papers after duplicated initially, finally 9 studies including a total of 2049 cases and 2861 controls were identified, a flow chart for the study selection is shown in Figure1, among the studies, there were 7 studies on western populations, 2 papers on eastern populations , adjusted ORs with corresponding 95%CI were reported in 7 studies. The selected study characteristics are summarized in Table 1, there are 6 studies on high quality (NOS score higher than 6), and the quality assessment of all the published studies was shown in Table 2.

Table 1. Characteristics of the 9 Studies Included in the Meta-analysis

Auhtor	Study area	Year	studystype	Method	case		control		matched / adjusted	controls	adjustments	OR(95%CI)
					Hp+	CagA+	Hp+	CagA+				
Raderer et al.	Austria	1997	Case-control	ELISA	60/92	-	28/62	-	yes/no	sex and age	---	H.pylori:2.1(1.1,4.1)
Stolzenberg et al.	Finland	2001	Nested case control	ELISA					yes/yes	the same as adjustments	age,month of blood draw, completion of dietary history,study center,intervention group assignment	H.pylori:1.87(1.05, 3.34);
de Martel et al.	the USA	2008	Nested case control	ELISA	51/104	33/104	115/262	83/262	yes/yes	age, gender, race, site, date of multiphasic health checkup	BMI, alcohol consumption, diabetes mellitus	H.pylori:0.85(0.49, 1.48); CagA:0.96(0.48,1.92)
Lindkvist et al.	Sweden	2008	Nested case control	ELISA	39/87	-	100/263	-	yes/yes	age, gender, time for baseline investigation	age,sex,BMI,Hp serology status, smoking status,alcohol consumption, time from baseline investigation to analysis	H.pylori:1.25(0.75, 2.09)
Risch et al.	the USA	2010	Case-control	ELISA	80/373	55/373	120/690	108/690	yes/yes	sex and age	age,sex,years of cigarette smoking,ELISA plate number	H.pylori:1.34(0.94, 1.92); CagA:0.83(0.55,1.24)
Shimoyama et al.	Japan	2010	Case-control	western blot	16/19	-	29/34	-	no/no	--	--	0.92(0.19,4.36)
Gawin et al.	Poland	2012	Case-control	ELISA	121/139	116/139	146/177	150/177	yes/yes	sex,age et al.	age.cigarette smoking.sex.time from baseline investigation to analysis"	H.pylori:1.27(0.64, 2.61); CagA:0.90(0.46,1.73)
Guoqin Yu et al.	Finland	2013	Nested case control	multiplex	325/353	258/353	328/353	258/353	yes/yes	date of baseline serum-collection, age,follow up time	age,number of cigarettes per day and years smoked	H.pylori:0.86(0.49,1.51); CagA:1.00(0.71,1.42)
Harvey A Risch et al.	China	2013	Case–control	ELISA	233/761	442/761	327/794	537/794v	yes/yes	age and gender	age and gender, BMI, cigarette smoking	H.pylori:0.62(0.50,0.77); CagA:0.66(0.53,0.81)

Test of heterogeneity

According to the Figure 2a and Figure 3, we analysized the heterogeneity of all 9 studies on Hp+ and 7 studies on CagA+, the Q statistic was significant (P<0.01)and the I^2 statistic showed a high variation (Hp+ I^2=58.9%), (CagA+ I^2=36%). so a random effect model was used for further analysis (Figure 2a. Figure3 and table3).

Hp infection and pancreatic cancer risk

Because of heterogeneity significantly, in this meta-analysis, we all used random-effects model. The association between Hp infection and pancreatic cancer risk is shown in Figure 2a and table 3, the results suggested that hp+ in the pooled ORs (OR=1.06, 95%CI:0.74-1.37)showed no significant association between Hp+ and pancreatic cancer, and the same as result in the western countries (OR=1.14, 95%CI:0.89, 1.40), but in the eastern counties showed decreasing the cancer risk (OR=0.62, 95%CI:0.49, 0.76). when high quality studies and adjusted studies were analyzed respectively, the combined OR for the association between Hp infection and pancreatic cancer risk was (OR=1.00, 95%CI:0.66, 1.33), (OR=1.01, 95%CI0.70, 1.33), showed no significant association between Hp+ and pancreatic cancer.

The association between CagA+ stains and pancreatic cancer was also evaluated among the 7 studies (Figure 3 and table3). The overall OR was 0.84 (95%CI: 0.63-1.04) and showed moderate heterogeneity among the studies (I^2= 36.0%, P= 0.167). This moderate heterogeneity may be caused partly by regional or ethnic differences, as heterogeneity values may weaken during location subgroup analysis. Similarly, CagA+ strains of infection may decrease the risk of pancreatic cancer in Eastern subjects (OR = 0.66, 95%CI: 0.52-0.80), but not in Western subjects (OR = 0.95, 95%CI: 0.73-1.16), and we also analysized the high quality studies and adjusted studies , respectively, the results suggested that high quality studies: (OR=0.85, 95%CI:0.85-1.08), adjusted studies (OR=0.84, 95%CI:0.63-1.04) all showed no significant association between CagA+ and pancreatic cancer.

Sensitivity analysis and publication bias:

Sensitivity analysis was performed

Table 2.Results of Quality Assessment by NOS for Case-Control Studies

Study	Selection	Comparability	Exposure	total scores
Raderer et al.	3	0	2	5
Stolzenberg et al.	4	2	2	8
Lindkvist et al.	4	2	2	8
de Martel et al.	4	2	2	8
Risch et al.	4	2	2	8
Shimoyama et al.	3	0	2	5
Gawin et al.	3	0	2	5
Guoqin Yu et al.	4	2	2	8
HA.Risch1 et al.	4	2	2	8

Table 3. Meta-analysis of the H.pylori Infection on the Risk of Pancreatic Cancer

	studies	P	I^2	Overall OR (95%CI)
pancreatic cancer case/control (2049/2861)				
all studies	9	0.013	58.90%	1.06 (0.74, 1.37)
Eastern	2	0.778	0	0.62 (0.49, 0.78)
Western	7	0.378	6.60%	1.14 (0.89, 1.40)
High qualites	6	0.01	66.90%	1.00 (0.66, 1.33)
Adjusted studies	7	0.012	63.10%	1.01 (0.70, 1.33)
CagA+	6	0.167	36.00%	0.84 (0.63, 1.04)
Eastern	1	……	……	0.66 (0.52, 0.80)
Western	5	0.541	0	0.95 (0.73, 1.16)
High qualites	5	0.108	47.20%	0.85 (0.61, 1.08)
Adjusted studies	6	0.167	36%	0.84 (0.63, 1.04)

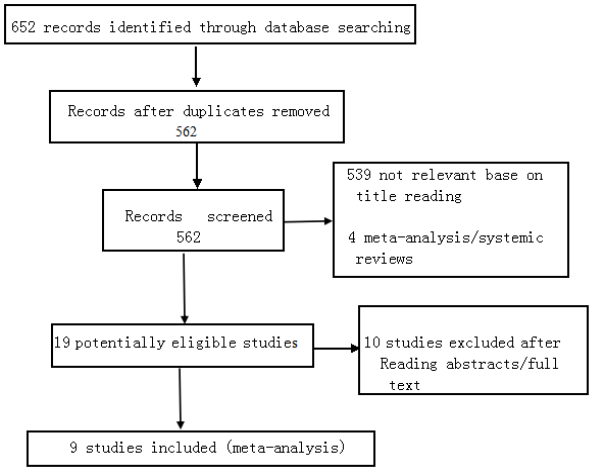

Figure 1. Summary of the Studies Selection Process

to assess the influence of each individual study on the pooled ORs by omitting a single study each time, the result indicated that the main result was robustness and no substantial change in the corresponding pooled OR (Figure 4) was observed. Begg's funnel plot and Egger's test were performed to assess publication bias. Begg's funnel plots were symmetrical (Figure 2b), and the *P* values for pancreatic cancer were 0.466>0.05. The statistical results still did not show publication bias using Egger's test, and the *P* values for pancreatic cancer were 0.06>0.05, Therefore, there was no significant publication bias in the eligible studies.

Discussion

As we all know, Hp infection can obviously increase the risk incidence of gastric cancer. But with other cancers,

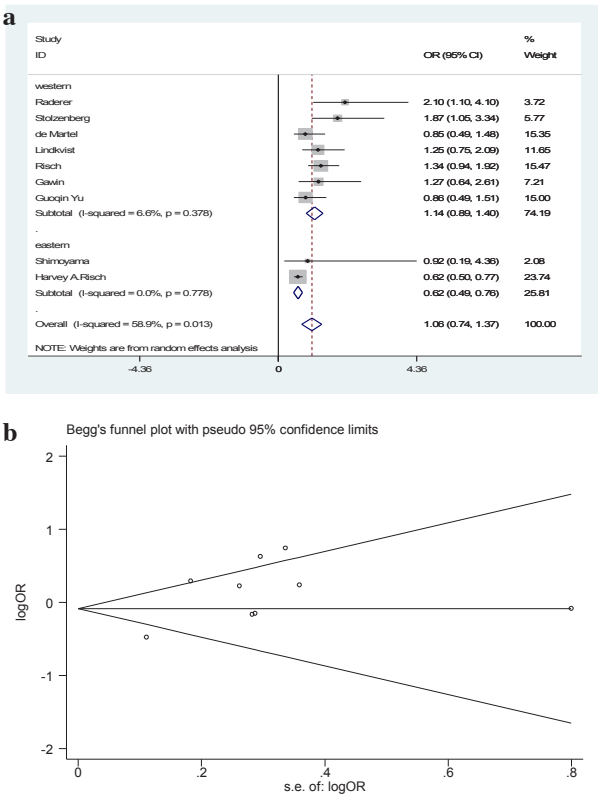

Figure 2a Forest Plot of the Association Between *H. pylori* Infection and Pancreatic Carcinoma; 2b, Begg's Funnel Plot of the Association Between *H. pylori* Infection and Pancreatic Carcinoma

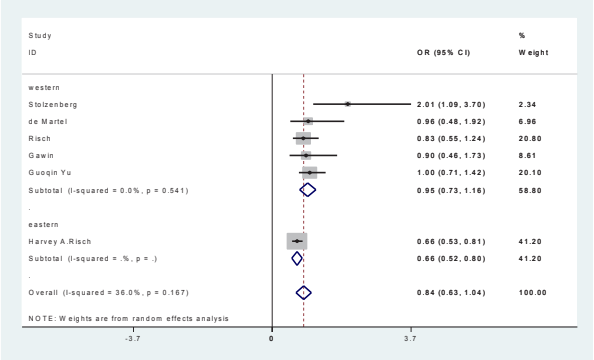

Figure 3. Meta-analysis with a Random-effect Model for the Association between CagA+ and Pancreatic Cancer

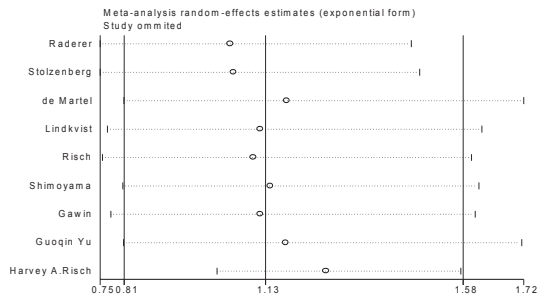

Figure 4. Sensitivity Analysis was Performed to Assess the Influence of Each Individual Study on the Pooled ORs

for example, whether the Hp infection is association with the colorectal adenoma and adenocarcinoma, there is an updated meta-analysis about *Helicobacter pylori* Infection

and the Risk of colorectal adenoma and adenocarcinoma, the result indicated that twenty-two studies were included in this meta-analysis, and the odds ratio for the association between *H. pylori* infection and colorectal cancer was 1.49 (95% confidence interval 1.30-1.72). The pooled data suggested *H. pylori* infection indeed increases the risk of colorectal adenoma and adenocarcinoma (Chen et al., 2013).

In our present study, we collected all available, published studies and performed a meta-analysis to examine the association between *H. pylori* infection and the risk of pancreatic cancer. 9 studies were critically reviewed to clarify the controversial results from previous reports. Our meta-analysis showed that *H. pylori* infection significantly decreased the risk of pancreatic cancer in

eastern populations, but no significant association on total studies and western countries. About the CagA+, in the stratified analysis of the study location, no significant association between CagA+ and pancreatic cancer risk in Western subjects was found. However, we observed a significant association between CagA+ and the risk of pancreatic cancer in East Asian populations.

The results of this meta-analysis suggested that colonization of the stomach with CagA positive strains of H.Pylori may protect against pancreatic cancer in eastern counties. For this phenomenon, there are several probable explanations. Firstly, probably the different regions, race and live conditions may influence the Hp in the humans' body, and then caused the significant discrepancy among the western and eastern counties. Secondly, It is also possible that different risk associations may be conveyed by Western versus Asian CagA-positive strains (Loh et al., 2011), which differ in their virulence properties according to C-terminus variation in the CagA protein (Higashi et al., 2002; Atherton et al., 2009) and in associations between CagA-seropositivity and expression of other virulence factors such as VacA (Peek et al., 2002). thirdly, Hp may reduce pancreatic cancer risk by decreasing the stimulates appetite (Wren et al., 2007). A reduction in the level of ghrelin may lead to lower rates of obesity, an important risk factor for pancreatic cancer. Last, the protective association of *H. pylori* with pancreatic cancer in eastern countries may be part of a broader phenomenon. The long history of co-existence of this organism with humans, despite its disease-causing potential, may suggested that *H. pylori* also has some beneficial effects to humans (Blaser, 2006), including possible roles in reducing diarrheal diseases and asthma (Chen et al., 2007; Blaser et al., 2008; Chen et al., 2008).

Two other meta-analyses have summarized the relationship between *H. pylori* infection and pancreatic cancer risk (Trikudanathan et al., 2011; Xiao et al., 2013). The advantages of our meta-analysis are as follows: Compared with the previous two meta-analyses, the present study was much larger, with more than about twice as many cancer cases as the earlier studies, We excluded several of the studies used in the previous meta-analysis because the low quality and without the matched adjusted factors; and we included several additional recent large sample size studies. In addition, several subgroup analyses were conducted to identify potential sources of heterogeneity. We also used the high quality and the adjusted studies as the subgraphs in order to strength the results robust. Secondly, according to our selection criteria, all the studies in our meta-analysis had acceptable quality and the cases and controls were collated from all included studies, which significantly increased the statistical power. Thirdly, our study suggested that *H. pylori* infection decreased the risk of pancreatic cancer in the eastern countries. This study should be repeated which could be beneficial in detecting novel mechanisms to reduce the risk of pancreatic cancer. We also found that our study had several limitations. Heterogeneity for the ORs in Hp infection was observed among the studies. This heterogeneity may be due to various factors, such as diversity in the population characteristics, differences in the number of cases and controls, *H. pylori* detection methods and study design. However, heterogeneity was eliminated populations after stratifying by ethnicity. The variables used to adjust these values were not consistent across the studies, which may limit the reliability of the data. Too few studies were identified to allow for subgroup analysis by covariates. Subgroup analyses regarding other confounding factors such as age and gender were conducted in the present study. Only two studies focused on the relationship between *H. pylori* infection and pancreatic cancer risk in Eastern subjects (OR = 0.66, 95%CI: 0.52-0.80) which was statistically significant (*P*= 0.05). Further studies are required to confirm the protective role of H.pylori.

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

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