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Helicobacter pylori infection, atrophic gastritis, and pancreatic cancer risk

A meta-analysis of prospective epidemiologic studies

Hong Liu, MM[a], Yue-Tong Chen, MB[b], Rui Wang, BN[c], Xin-Zu Chen, MD, PhD[d,*]

Abstract

Background: To investigate the associations of *Helicobacter pylori* (Hp) infection and atrophic gastritis (AG) with pancreatic cancer risk.

Methods: A literature search in PubMed was performed up to July 2017. Only prospective cohort and nested case–control studies enrolling cancer-free participants were eligible. Incident pancreatic cancer cases were ascertained during the follow-up. The risks of pancreatic cancer were compared between persons infected and noninfected with Hp, or between those with and without AG status at baseline. Odds ratios (ORs) or hazard ratios were combined. Subgroup and sensitivity analyses were performed, and publication bias was estimated.

Results: Three cohort studies and 6 nested case–control studies, including 65,155 observations, were analyzed. The meta-analyses did not confirm the association between pancreatic cancer risk and Hp infection (OR = 1.09, 95% confidence interval [CI] = 0.81–1.47) or AG status (OR = 1.18, 95% CI = 0.80–1.72). However, particular subpopulations potentially had increased risks of pancreatic cancer. Cytotoxin-associated gene A (CagA)-negative strains of Hp might be a causative factor of pancreatic cancer (OR = 1.30, 95% CI = 1.05–1.62), but a sensitivity analysis by leave-one-out method did not fully warrant it (OR = 1.20, 95% CI = 0.93–1.56). In 1 nested case–control study, AG at stomach corpus in Hp-negative subpopulation might have increased risk of pancreatic cancer, but with a poor test power = 0.56. Publication biases were nonsignificant in the present meta-analysis.

Conclusion: Based on current prospective epidemiologic studies, the linkage of pancreatic cancer to Hp infection or AG status was not warranted on the whole. Nevertheless, prospective studies only focusing on those specific subpopulations are further required to obtain better power.

Abbreviations: AG = atrophic gastritis, CagA = cytotoxin-associated gene A, CI = confidence interval, Hp = *Helicobacter pylori*, HR = hazard ratio, OR = odds ratio.

Keywords: atrophic gastritis, cytotoxin-associated gene A, epidemiology, *Helicobacter pylori*, pancreatic cancer

1. Introduction

Pancreatic cancer is still one of the leading causes of cancer-related death globally.[1,2] The prognosis of pancreatic cancer is fairly poor, because it is usually diagnosed at advanced stage.[3] By now, there is no established prevention program of pancreatic cancer worldwide. Thus, it is meaningful to understand the etiology of pancreatic cancer and investigate the potential approaches to prevention and prediction of pancreatic cancer. The etiology of pancreatic cancer has been widely and extensively researched, and around two-thirds of the major risk factors may be modifiable and predictable.[4] Some studies demonstrated the similar potential risk factors might be coexposed between pancreatic and gastric cancers.[5–7]

There were several meta-analyses that evaluated the association between *Helicobacter pylori* (Hp) infection and pancreatic cancer risk, but with inconsistent results (Table 1).[8–14] Particularly, a meta-analysis based on 5 prospective nested

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[a] Department of Integrated Traditional Chinese and Western Medicine, [b] Intensive Care Unit, [c] Nursing Section, Department of Gastroenterology, [d] Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China.

[*] Correspondence: Xin-Zu Chen, Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Guo Xue Xiang 37, Chengdu 610041, Sichuan Province, China (e-mail: chen_xz_wch_scu@126.com).

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Table 1

Brief summary of current meta-analyses on the associations between Hp infection and pancreatic cancer risk.

Meta-analysis	Year	Studies	Observations	Hp infection		
				Overall	CagA+	CagA−
Guo et al[8]	2016	8	2757	Harmful	Not analyzed	Not analyzed
Chen et al[9]	2015	5	3681	Null	Null	Harmful
Schulte et al[10]	2015	11	36,035	Null	Protective	Harmful
Wang et al[11]	2014	9	4910	Protective	Protective	Not analyzed
Xiao et al[12]	2013	9	3033	Harmful	Null	Not analyzed
Trikudanathan et al[13]	2011	6	2335	Harmful	Null	Not analyzed
Risch et al[14]	2010	7	34,314	Harmful	Not analyzed	Not analyzed

CagA = cytotoxin-associated gene A, Hp = *Helicobacter pylori*.

case–control studies previously found a potential causative association between the cytotoxin-associated gene A-negative (CagA−) strains and pancreatic cancer risk.[9] In contrast, the CagA-positive (CagA+) strains did not correlate with pancreatic cancer risk. However, the limited sample size and the absence of prospective cohort studies were certain limitations of the meta-analysis. Additionally, atrophic gastritis (AG) is potentially linked with the progression from Hp-related gastritis.[15,16] Serological biomarkers, pepsinogen I/II, may well predict the AG status.[17,18] Whether this precancerous lesion is simultaneously predictive for pancreatic cancer risk remains pending. Aforementioned meta-analysis was performed based on a literature search up to September 2014 and only focusing on Hp infection other than AG status. The present updated meta-analysis was therefore warranted and aimed to achieve more robust evidence to understand the linkage between the pancreatic cancer risk and Hp infection or AG status as well.

2. Methods

2.1. Literature search

The PubMed database was searched up to July 16, 2017 through the strategy: "English"[Language] AND ("pancreatic neoplasms"[MeSH Terms] OR ("pancreatic"[All Fields] AND "neoplasms"[All Fields]) OR "pancreatic neoplasms"[All Fields] OR ("pancreatic"[All Fields] AND "cancer"[All Fields]) OR "pancreatic cancer"[All Fields]) AND ("gastritis, atrophic"[MeSH Terms] OR ("gastritis"[All Fields] AND "atrophic"[All Fields]) OR "atrophic gastritis"[All Fields] OR ("atrophic"[All Fields] AND "gastritis"[All Fields]) OR "helicobacter pylori"[MeSH Terms] OR ("helicobacter"[All Fields] AND "pylori"[All Fields]) OR "helicobacter pylori"[All Fields]). The eligible language of publication was English only.

2.2. Eligibility, selection, and data retrieval

The eligible study design should be prospective cohort study or nested case–control study based on a certain prospective cohort study. Cancer-free participants at baseline were enrolled. Incident pancreatic cancer cases were ascertained during the follow-up periods. Either serological or histological examination of Hp infection or AG status was acceptable. The risks of pancreatic cancer were compared between persons infected and noninfected with Hp, as well as between with and without AG status at baseline. There was no limit of sex, age, and ethnicity of participants.

The literature selection of this update was performed by 2 independent reviewers (CYT and WR). The titles and abstracts were browsed as primary selection, and full-texts of potentially eligible studies were assessed as secondary selection. The detailed information of study and prevalence data were extracted by the 2 reviewer in the double-check manner. Prevalence data included sample sizes, events, and proportions. The estimates of effect size were also extracted, including either odds ratios (ORs) or hazard ratios (HRs) and their 95% confidence intervals (CIs). The procedures of this meta-analysis were performed according to the PRISMA 2009 standards, and a PRISMA flow diagram was drawn.[19]

2.3. Statistics

The Cochrane Review Manager (RevMan) 5.3 software was used for statistical analysis.[20] The module of generic inverse variance was used for an effect estimate. The ratios and their lower limits of 95% CIs were used to calculate their standard errors (SE). ORs or HRs were combined by fixed or random effect model where suitable, and their 95% CIs were also calculated. The 2-sided *P* values for the combined ratios less than .05 were considered as statistically significant. Subgroup analysis on Hp was performed through stratifying CagA serostatus as CagA+ and CagA−. The overall serostatus of AG between pancreatic cancer patients and controls were initially combined in a meta-analysis. Although, because of the heterogeneous methods of stratification, it was unable to perform additional pooling subgroup analysis, regarding the diagnostic methods, severity of AG, or synchronous serostatus of Hp and CagA. Instead, a narrative summary of available ORs or HRs in different subgroups was presented. I^2 was estimated to evaluate the heterogeneity of each meta-analysis. If the *P* values of heterogeneity test less than .1, the random effect model should be considered. Funnel plots were drawn by the STATA 12.0 software to observe and evaluate the publication bias.[21] Both the Begg rank correlation test with continuity corrected and Egger linear regression test were used. Any *P* value less than .05 of Begg test or Egger test was considered as existence of publication bias. In Egger test, the intercept and its 95% CI were estimated. The leave-one-out method was always used in the sensitivity analysis for those meta-analyses pooling more than 2 studies. When result interpretation based on or related to a single study, the value of test power ($1-\beta$) was estimated by the PASS 11 software.[22] The category of 2 independent proportions to test inequality was selected, and parameter module of proportions was used for calculation. Two-sided Z test (pooled) was provided with $\alpha = 0.05$. If the power less than 0.80, the result was considered as potentially unreliable.

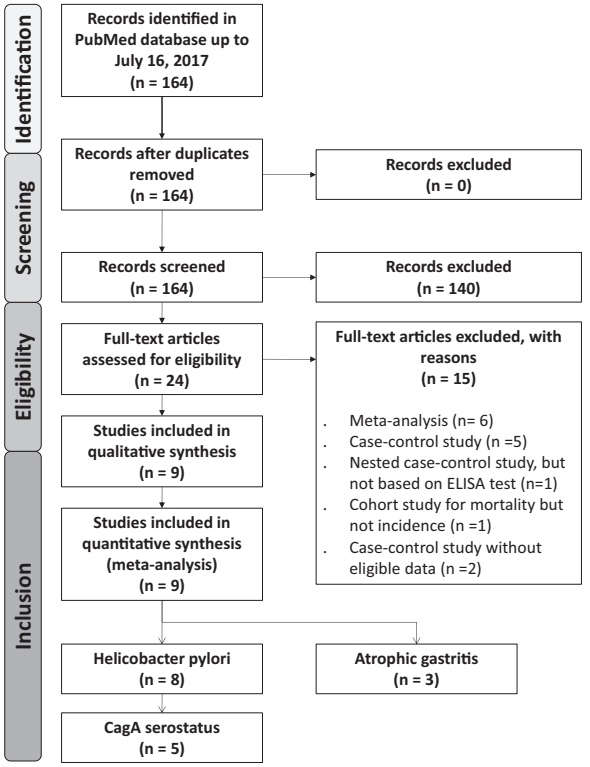

Figure 1. Flow diagram of literature search, screening, and selection.

2.4. Ethics

The ethical approval was not necessary due to the nature of research based on literature.

3. Results

3.1. Helicobacter pylori and pancreatic cancer

Six nested case–control studies (4577 observations),[14,23–27] 1 prospective cohort study (9506 observations),[28] and 1 case–-cohort study (30,110 observations)[29] were included (Fig. 1). In total, 44,193 observations were analyzed. The general information of the included nested case–control and cohort studies were shown in Tables 2 and 3, respectively.

As a whole, the Hp infection was not associated with the pancreatic cancer risk (OR = 1.09, 95% CI 0.81–1.47, $P = .58$) by random effect model (Fig. 2A). Sensitivity analysis was performed by combining 2 cohort studies (Fig. 2B),[28,29] and also found a nonsignificant but tendentious association (OR = 1.61, 95% CI 0.97–2.67, $P = .07$). Sensitivity analyses by leave-one-out method did not alter the results also (data not shown).

Subgroup analysis was performed by classifying the Hp infection into CagA+ and CagA− strains. There were 5 studies additionally classifying the CagA serostatus.[14,23,26–28] CagA+ strains (Hp+/CagA+) might not be associated with the pancreatic cancer risk (OR = 0.99, 95% CI 0.63–1.56, $P = .96$) by random effect model (Fig. 3A). In contrast, the infection with CagA− strains (Hp+/CagA−) might induce the increased risk of pancreatic cancer (OR = 1.30, 95% CI 1.05–1.62, $P = .02$) by fixed effect model (Fig. 3B). However, sensitivity analyses by leave-one-out method found when only the study by Risch et al[14] was excluded, the association between CagA− strains and pancreatic cancer risk became nonsignificant (OR = 1.20, 95% CI 0.93–1.56, $P = .17$) (Fig. 3C) (other data not shown). The estimated power (1–β) of the study Risch et al[14] was merely = 0.59.

3.2. Atrophic gastritis and pancreatic cancer

Two cohort studies and 1 nested case–control study investigated the associations of AG status with pancreatic cancer risk, and 31,364 observations were analyzed (Tables 2, 3).[27,28,30] As a whole, the AG status was not associated with pancreatic cancer risk (OR = 1.18, 95% CI 0.80–1.72, $P = .40$) (Fig. 4A). The leave-one-out sensitivity analysis did not find different results (data not shown). Narratively, the diagnostic methods and severity grading of AG were not associated with pancreatic cancer risk (Fig. 4B). Moreover, the serostatus of Hp might differ the AG-associated risk of pancreatic cancer. Huang et al[27] found AG at stomach corpus might increase the risk of pancreatic cancer in the Hp-negative subpopulation (Hp−/CagA−), but with the estimated power (1–β) = 0.56 (other data not shown).

3.3. Publication bias estimate

The publication bias was observed by the funnel plots and regression plots (Fig. 5). There was no obvious publication bias according to the Begg tests and Egger tests, with the only exception of the comparison between Hp+/CagA+ and Hp− (a marginal bias by Egger test, intercept = 4.52, 95% CI 0.26–8.77, $P = .043$).

4. Discussion

This updated meta-analysis only included prospective epidemiologic studies and greatly expands the sample size. On the whole, the findings did not confirm the linkage of pancreatic cancer risk to either Hp infection or AG status. However, particular subpopulations were found to potentially have increased risks of pancreatic cancer. CagA− strains of Hp might be a causative factor of pancreatic cancer, but the sensitivity analysis did not fully confirm it. In 1 nested case–control study, AG at stomach corpus in the Hp-negative subpopulation might increase the risk of pancreatic cancer, but with a poor test power.

Hp has been defined by World Health Organization as a class I carcinogenic pathogen for gastric cancer,[31,32] while recent researches demonstrated the potential associations between Hp infection and extragastric malignancies, including colorectal and pancreatic cancer.[33–37] The CagA is known as a common virulent factor of Hp.[15] The presence of CagA (CagA+) was found to be significantly associated with increased risk of gastric cancer, while CagA− strains might not.[28] It underlines the usefulness of screening the CagA serostatus and identifying the high-risk subpopulation, who may subsequently be treated to prevent gastric cancer in a personalization manner.[38] Therefore, it is reasonable why more studies investigated the linkage between Hp infection and extragastric cancers, for the sake of potential predictive and preventive effect from Hp screening and eradication in a population framework.[39]

Interestingly, some previous evidence indicated CagA− Hp strains might be a causative factor for pancreatic cancer.[9,10] In this case, the subpopulation infected with CagA− strains may also be considered as candidates for the Hp eradication. This finding is a good challenge to the indication for the Hp eradication, regarding the prevention of not only gastric cancer but also pancreatic cancer. It is the additional evidence

Table 2

General information of included nested case–control studies.

Study	Region of population	Enrollment period	Pancreatic cancer cases			Cancer-free controls		
			Source	Number	Age (mean, y)	Source	Number	Age (mean, y)
Stolzenberg-Slolmon 2001[23]	Finland	1985–1988	Finnish Cancer Registry, and ABTC study, a primary prevention trial	121	58.0	ABTC study, a primary prevention trial	226	58.0
de Martel 2008[24]	U.S.	1964–1969	Kaiser Permanente Medical Care Program	104	49.5	A pool of cancer-free controls from other studies	262	50.3
Lindkvist 2008[25]	Sweden	1974–1999	Malmö Preventive Project cohort database to the Swedish Cancer Registry	87	47.9	Malmö Preventive Project cohort database to the Swedish Cancer Registry	263	47.5
Risch 2010[14]	U.S.	2005–2009	30 general hospitals across Connecticut, U.S.	373	66.9	Resident in Connecticut	690	68.3
Risch 2014[26]	China	2006–2011	Shanghai Cancer Institute	761	64.9	Shanghai Residents Registry	794	64.9
Huang 2017[27]	10 European countries	1992–2000	EPIC cohort study	448	57.8	EPIC cohort study	448	57.8

Study	Matching factor	Laboratory work	Serum storage	Tests
Stolzenberg-Slolmon 2001[23]	Age, baseline date, completion of questionnaire, study center, and intervention group	National Cancer Institute, U.S.	−70 °C	Hp: ELISA (in-house); CagA: ELISA (Peptide Therapeutics, Cambridge, MA)
de Martel 2008[24]	Age, gender, skin color, baseline date, and site of health checkup	Stanford University, U.S.	Intially stored at −23 °C, and since 1980 at −40 °C by Orentreich Foundation for the Advancement of Science, Inc.	Hp: ELISA (in-house); CagA: ELISA (OraVax, Inc.)
Lindkvist 2008[25]	Age, baseline date	Malmö University Hospital, Sweden	−20 °C in a biological specimen bank	Hp: ELISA (in-house)
Risch 2010[14]	Age, gender, and baseline date	Yale University School of Medicine, U.S.	Transported on freeze packs within 4 h to lab, and stored immediately at −80 °C until analysis	Hp: ELISA (Diagnostic Automation, Inc, Calabasas, CA); CagA: ELISA (Inverness Medical Deutschland GmbH)
Risch 2014[26]	Age, gender, and baseline date	Yale School of Public Health, U.S.	On-ice transported to specimen processing laboratory of Shanghai Cancer Institute, frozen at −80 °C, shipped to Yale in thick Styrofoam boxes with dry ice and air courier, and then stored at −80 °C	Hp: ELISA (Scanlisa HM-CAP, Scimedx Corp.); CagA: ELISA (RavoDiagnostika p120, Alere GmbH)
Huang 2017[27]	Study center, sex, age, date, time, and fasting status at blood collection	Unspecified	Mostly in liquid nitrogen at IARC or the central EPIC	Hp: ELISA (Biohit, Helsinki, Finland); CagA: ELISA (RavoDiagnostika GmbH, Freiburg, Germany); Pepsinogen: ELISA (Biohit, Helsinki, Finland)

CagA = cytotoxin-associated gene A, ELISA = enzyme-linked immunosorbent assay, Hp = *Helicobacter pylori*.

supporting the Kyoto global consensus on the necessity to treat all Hp positive individuals, regardless of CagA serostatus.[40]

However, additional evidence showed diverse results of the association between pancreatic cancer risk and Hp infection (Table 1). Most of the meta-analyses included those small-scaled retrospective case–control studies.[41–46] It may largely impair the robustness of power. An excluded nested case–control study did not classify CagA− status into Hp+/CagA− and Hp−/CagA−, and found no significant difference of pancreatic cancer risks between CagA+ and CagA− serostatus.[47] On the other hand, the present updated meta-analysis based on all prospective studies did not confirm the linkage of pancreatic cancer risk to Hp infection and CagA serostatus. Therefore, the goal of translation of the Hp screening and eradication into the prediction and prevention of pancreatic cancer is unable to be achieved at this moment. Therefore, further high-quality epidemiologic studies

Table 3

General information of included cohort studies.

Study	Population	Enrollment period	Number	Age, y	Exposure	Laboratory work	Tests
Laiyemo 2009[30]	ATBC trial in southwestern Finland	1985–1988	20,962	50–69	AG	University of California, and then University of Helsinki	Serological Pepsinogen: radioimmunoassay methods; Histological: gastroscopy by Sydney system
Hsu 2014[29]	NHI Research Database (NHIRD) in Taiwan	2000–2009	Hp: 6022 Control: 24,088	51.1 ± 15.4 51.0 ± 15.5	Hp	Unspecified	Pathological or microscopic findings by endoscopies
Chen 2016[28]	ESTHER cohort in Germany	2000–2002	9506	50–75	Hp; AG	German Cancer Research Center	Serological Hp and CagA: ELISA (ravo H. Pylori Diagnostika, Freiburg, Germany); Pepsinogen: ELISA (Biohit, Helsinki, Finland)

AG = atrophic gastritis, CagA = cytotoxin-associated gene A, ELISA = enzyme-linked immunosorbent assay, Hp = *Helicobacter pylori*.

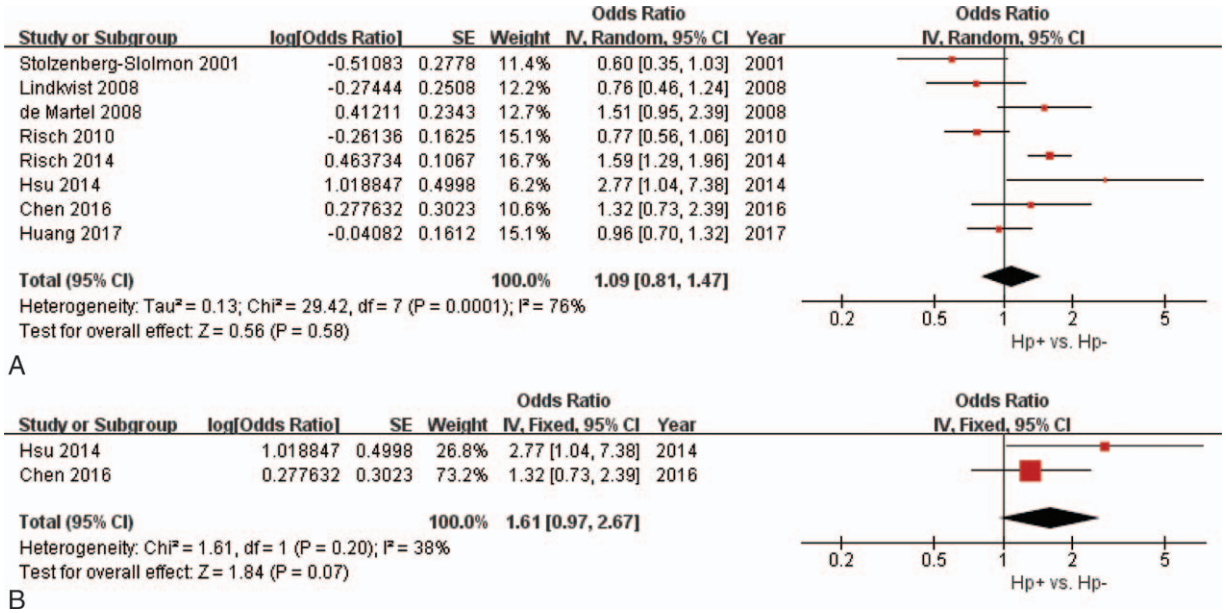

Figure 2. Meta-analyses on the risks of pancreatic cancer between *Helicobacter pylori* (Hp)+ and Hp− subpopulations: (A) overall pooling estimate; (B) sensitivity analysis based on 2 prospective cohort studies.

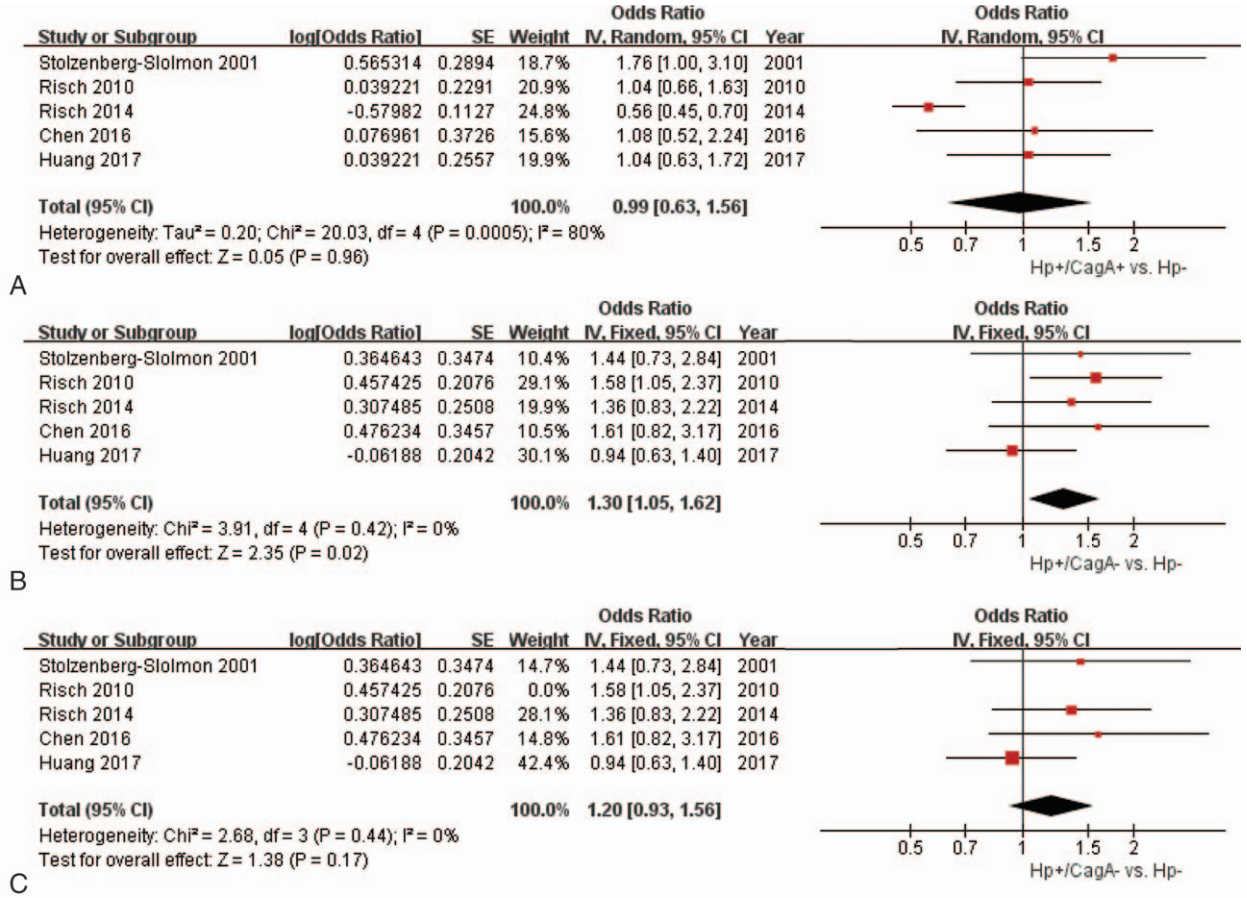

Figure 3. Meta-analyses on the risks of pancreatic cancer according to the CagA serostatus: (A) Hp+/CagA+ versus Hp−; (B) Hp+/CagA− versus Hp−; (C) sensitivity analysis by leave-one-out method for Hp+/CagA− versus Hp−. CagA = cytotoxin-associated gene A, Hp = *Helicobacter pylori*.

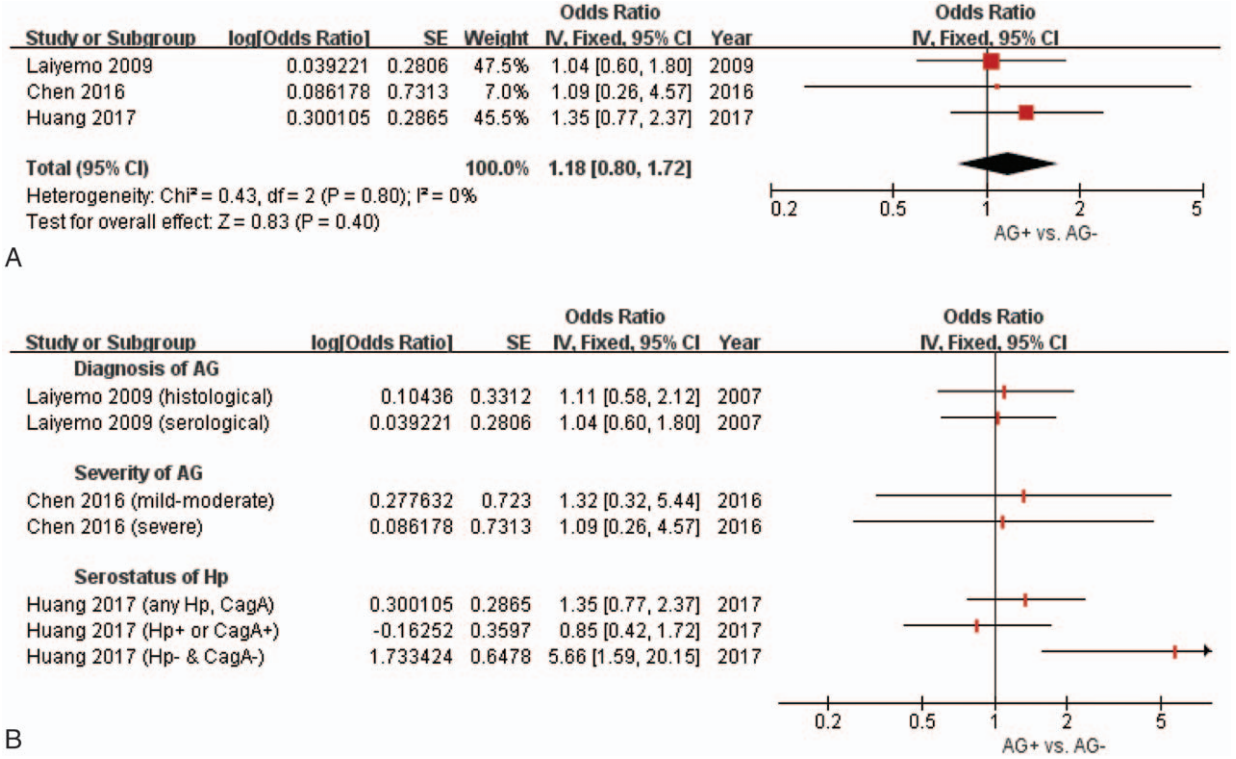

Figure 4. (A) Meta-analysis on the risks of pancreatic cancer according to the atrophic gastritis (AG) status; (B) narrative demonstration of subgroups of AG status.

focusing on the subpopulation infected with CagA− strains are required to obtain stronger power and more reliable suggestion. Besides, this epidemiologic finding warrants further biological investigations to reveal the mechanism behind the potential association of CagA− Hp with the pancreatic cancer risk.

AG is a precancerous lesion of gastric cancer, and possibly resulted from chronic Hp infection and related mucosal inflammation.[48,49] Serological biomarkers, pepsinogen I/II and gastrin-17, have been accepted to diagnose AG, by good consistence with the biopsy.[50,51] Truan et al[52] found the pepsinogen was expressed in 38% of well differentiated, resectable pancreatic cancers. Smith et al[53] found the gastrin, a gastrointestinal peptide, had a proliferative effect on pancreatic cancer cells. Therefore, it was hypothesized that the causative factors of AG might lead to pancreatic cancer development, or biomarkers of AG might also predict pancreatic cancer risk.[30] Nevertheless, to date, the epidemiologic evidence is still sparse to clarify the linkage of pancreatic cancer to AG and its biomarkers. Particularly, 2 population-based cohort studies did not support the hypothesis.[28,30] Although Huang et al[27] found the potential association between AG at stomach corpus and pancreatic cancer in the subpopulation infected with Hp +/CagA− strains, the test power was inadequate to avoid type II error. Namely, current evidence does not support the hypothesis and warrants further prospective studies to understand this issue.

The strengths of this updated meta-analysis mainly involve all prospective studies and greatly expanded the sample size compared to the previous. According to the Oxford 2011 levels of evidence,[54] the cohort studies and nested case–control studies had better quality and higher level than the small-scaled retrospective case–control studies. The measurement of exposure factors, Hp and AG, at the baselines was able to rule out the inverse causation. In spite of that, a better study design should be a randomized controlled trial to identify the effectiveness of Hp eradication on preventing pancreatic cancer development. Because of difference study design, the HRs of cohort studies were additionally combined in a subgroup analysis, other than ORs of nested case–control studies. Besides, the interpretation of results is fully referred to the leave-one-out sensitivity analysis with caution, as well as the estimate of test power for individual study.

On the other hand, several limitations need carefully consider. First, a small proportion of Hp−/CagA+ serostatus represented the former infection of Hp,[55] and this misclassification was unable to be ruled out in some included studies of the present meta-analysis. Second, the test power of individual study in subgroup analysis was inadequate for a confirmative conclusion. For example, only 46 incident pancreatic cancer were ascertained in the ESTHER cohort study.[28] Third, the number of included studies for meta-analysis was limited, and publication bias might not be reliably estimated. Forth, the present meta-analysis only included the studies published in English, so the language bias should be considered with caution. We performed additional search with the alteration in publication language filter, limit to the non-English field. One Polish case–control study, out of 21 citations, compared Hp and CagA serostatus between pancreatic cancer patients and controls.[44] The Polish study found null results that neither Hp nor CagA serostatus was associated with pancreatic cancer, and these findings were consistent with our major conclusion. Therefore, we supposed that the language bias might be minor and not alter the judgment.

In conclusion, based on current available prospective epidemiologic studies, meta-analysis may not warrant the linkage between pancreatic cancer risk and Hp infection or AG on the whole.

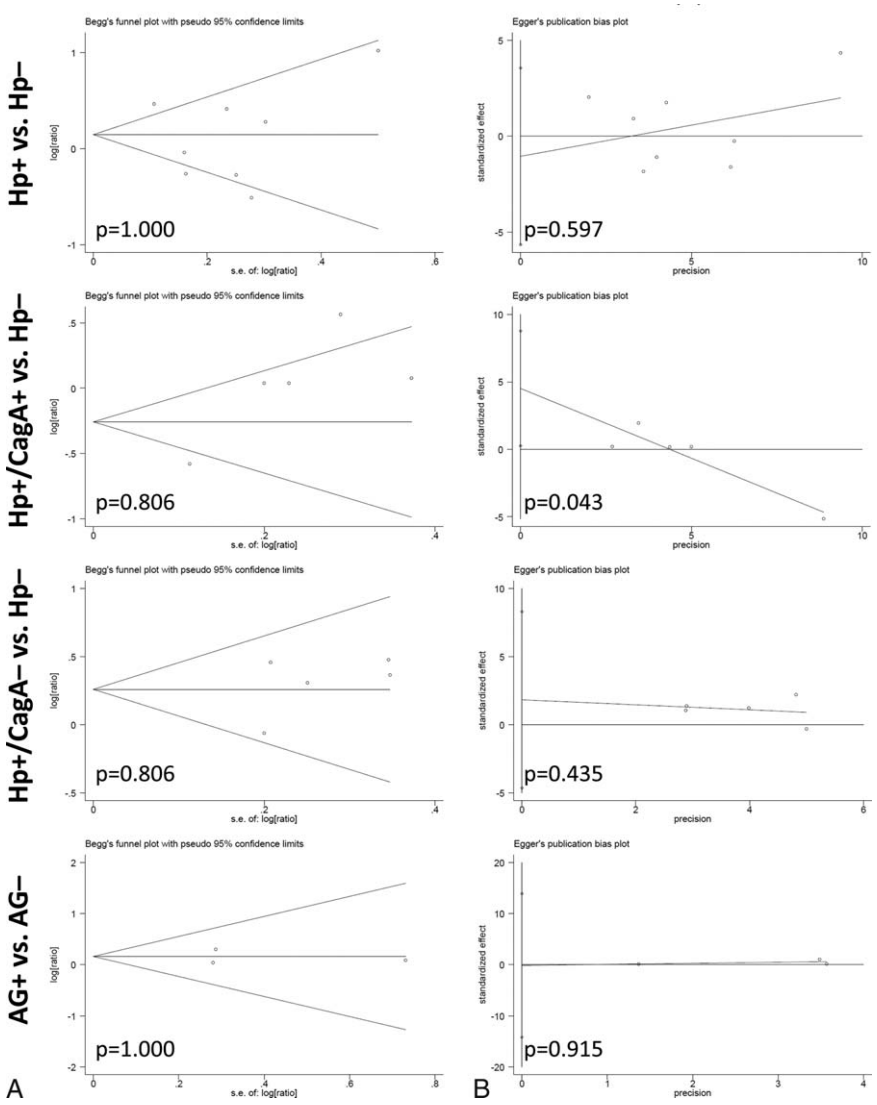

Figure 5. Estimated publication biases of meta-analyses: (A) Begg funnel plots; (B) Egger regression plots.

Nevertheless, prospective studies only focusing on those specific subpopulations are further required to obtain better power.

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