

ORIGINAL ARTICLE

Association between *Helicobacter pylori* Infection and Pancreatic Cancer. A Cumulative Meta-Analysis

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ABSTRACT

Context Infection with *Helicobacter pylori* (*H. pylori*) has been implicated in the etiopathogenesis of various malignant conditions. Notwithstanding, its etiological association with pancreatic cancer remains inconclusive. Studies focusing on the relationship between *H. pylori* infection and pancreatic cancer risk have yielded conflicting results. **Objective** The aim of this study was to obtain a reliable estimate of the risk of *H. pylori* infection in causing pancreatic cancer, by performing a meta-analysis of the existing observational studies evaluating the association. **Methods/Statistics** Observational studies comparing the prevalence of *H. pylori* infection in patients with pancreatic cancer and healthy controls, conducted in adult populations and published in all languages, were identified through systematic search in the MEDLINE and EMBASE up to April 2010. *H. pylori* infection was confirmed by serological testing using an antigen-specific enzyme-linked immunosorbent assay. Pooled adjusted odds ratios (AOR) and associated 95% confidence intervals (CI) were obtained by using a DerSimonian and Laird random-effects model. **Results** Six studies involving a total of 2,335 patients met our eligibility criteria. A significant association between *H. pylori* seropositivity and development of pancreatic cancer (AOR 1.38, 95% CI: 1.08-1.75; P=0.009) was seen. No significant association was seen on pooled analysis of the three studies assessing the relationship between cytotoxin-associated gene A (CagA) positivity and pancreatic cancer. A cumulative meta-analysis suggested a reducing, albeit statistically significant association as the evidence was accumulated. **Conclusions** The pooled data suggests an association between infection with *H. pylori* and the development of pancreatic cancer. Further research is needed to confirm our findings.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death in men and women in United States, with an estimated 42,470 new cases and 35,240 deaths in 2009 [1]. There is no effective screening diagnostics; therefore, most patients present with metastatic or advanced disease, not amenable to surgery. Due to the paucity of effective therapeutic options, pancreatic cancer has one of the highest mortality rates of all cancers and a median survival of only 3-6 months [2]. Thus, identification of modifiable risk factors and an effective primary prevention appear critical to reduce the incidence of this aggressive malignancy.

Notwithstanding, the risk factors for pancreatic cancer remain largely unknown. Older age and cigarette smoking are consistently reported associations that are commonly accepted [3]. Other potential risk factors include African-American race, chronic pancreatitis, obesity, type 2 diabetes mellitus, and consumption of smoked or processed meat. Genetic mutations, hereditary syndromes and familial aggregation may account for approximately 5-10% of cases [4]. During the last decade the causal role of *Helicobacter pylori* (*H. pylori*) in the pathogenesis of peptic ulcer disease has been firmly established [5]. Its etiological association with gastric cancer and gastric lymphoma has also been demonstrated [6].

Some epidemiologic evidence suggests that *H. pylori* might be involved in the pathogenesis of pancreatic cancer, although the results have not been consistent across the studies [7, 8, 9, 10, 11, 12]. Risch *et al.* reported a pooled analysis of these studies in 2010 suggesting a positive association between *H. pylori* and pancreatic cancer [11]. However, no methods were included in this report and the data they used from prior studies was inconsistent. Thus, we performed an updated meta-analysis of relevant clinical studies as well as a cumulative meta-analysis in order to

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Abbreviations AOR: adjusted odds ratio; CagA: cytotoxin-associated gene A

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determine the nature of the association between pancreatic cancer and *H. pylori* and to see how the evidence accumulated and if the conclusions may have shifted over time.

METHODS

Data Sources and Searches

We performed a systematic review of the published literature according to the “Meta-Analyses of Observational Studies in Epidemiology” guidelines to identify all studies that provided an effect estimate for a potential association between pancreatic cancer and *H. pylori* [13]. Two authors (G.T. and A.P.) independently conducted MEDLINE search (1966 to April 2010) and EMBASE (1990 to April 2010) for all relevant articles. We also manually searched references from studies or reviews and major gastroenterology meeting abstracts through March 2010. The following medical subject headings (MeSH) or keywords were used: pancreatic cancer, pancreatic tumor, pancreatic neoplasm, *Helicobacter pylori*, *H. pylori*, *Campylobacter pylori*, and peptic ulcer disease. Citations were limited to those published in the English language.

Study Selection

Two independent reviewers assessed studies for inclusion in a parallel manner using “priori-defined criteria”. To assess the potential association, we selected observational (case control, cohort and cross-sectional) studies for inclusion if they: 1) were conducted in adult population, defined as patients greater than 18 years of age; 2) included patients with exocrine pancreatic carcinoma as confirmed by biopsy; 3) diagnosed *H. pylori* infection by serological testing, including using an antigen-specific enzyme-linked immunosorbent assay (ELISA); 4) included a control group; and 5) reported data on incidence of *H. pylori* infection in patients with and without pancreatic cancer.

Data Extraction and Quality Assessment

Two reviewers (G.T. and A.P.) used a standardized data extraction tool to independently extract study data. Data obtained from each study included study design, inclusion and exclusion criteria, methodological quality criteria, study population, baseline patient characteristics, diagnostic method of pancreatic cancer, and data related to the primary outcomes. We resolved the few encountered disagreements by mutual discussion and, if required, by consulting a third investigator (W.L.B.).

The quality of the individual studies included in this review was assessed independently by two investigators. Quality criteria included the similarity of groups at baseline, methods for selecting participants, methods for measuring exposure variables, extent to which valid primary outcomes were described, as well as analytic methods for control-group matching and control confounding. Each study was given a quality

rating of good, fair or poor, based on their risk of bias using the above stated criteria.

Data Synthesis and Analysis

The primary outcome of this analysis was the prevalence of pancreatic cancer in patients with *H. pylori* infection compared with controls. Pooled adjusted odds ratios (AOR) and associated 95% confidence intervals (CI) were obtained by using a DerSimonian and Laird random-effects model [14]. In addition, we conducted a cumulative meta-analysis whereby studies were pooled chronologically by year of publication, starting with the earliest. Statistical heterogeneity among studies was assessed by using the I^2 statistic, with significant heterogeneity defined as an $I^2 < 50\%$ [15]. We evaluated the presence of publication and related bias by using funnel plots and Egger test [16]. Statistics were performed using Comprehensive Meta-Analysis, Version 2 (Biostat, Englewood, NJ, USA). A P value of less than 0.05 was considered statistically significant.

Certain host and genetic factors can modify the likelihood of acquisition and persistence of *H. pylori* infection, which may overturn the balance towards carcinogenesis. Cytotoxin-associated gene A positive (CagA+) strains have been demonstrated to have a greater propensity for inflammation, ulceration and malignant transformation. They have been implicated in etiopathogenesis of gastric cancer [17]. The presence of these strains, but also vacA s1+, vacA m1+ and babA2+ *H. pylori* strains, may increase the risk of malignant transformation in subjects with a positive family history and/or proinflammatory polymorphisms of the interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-alpha) genes [17]. Early-life social environment, along with the presence of *H. pylori* virulent strains, may play a significant role in the development of malignancy five to eight decades later [18, 19]. A subgroup analysis was therefore performed to investigate the relationship between antibodies to CagA antigens and exocrine pancreatic cancer.

RESULTS

Results of Primary Literature Review

Our initial search strategy yielded 32 potential citations for inclusion. Two other additional records were identified through other sources. Of those, 25 were excluded through review of the abstracts due to either not being a report involving human subjects (n=5) or an observational study (n=8), or not evaluating the presence of *H. pylori* infection (n=12) leaving 9 articles for full publication review. Out of these, two studies were excluded because no patients with pancreatic neoplasms were involved and an additional study by Kosunen *et al.* [20], which was included in the earlier-published meta-analysis by Risch *et al.* [11], was excluded from our analysis due to the lack of reliable data on pancreatic cancer; therefore, a total of 6 observational studies (n=2,335 patients) met our eligibility requirements (Figure 1) [7, 8, 9, 10, 11, 12].

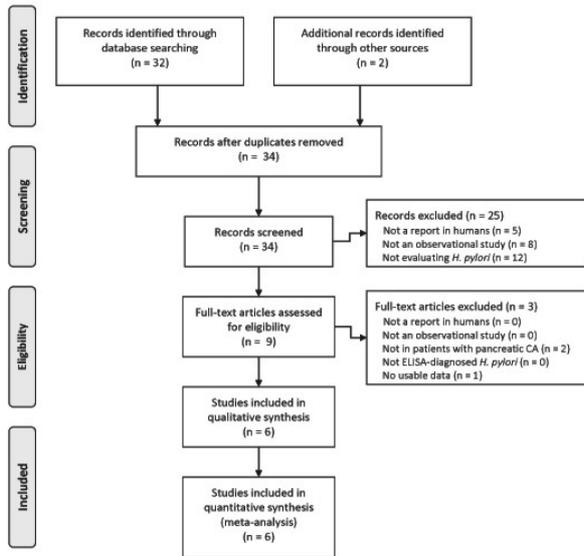


Figure 1. Literature search and selection.

Study Characteristics

The characteristics of the included studies are summarized in Table 1. The number of study subjects ranged from 90 to 1,063, with mean/median ages ranging from 47.5 to 68 years. The proportion of males ranged from 49.5% to 100%. All of the included studies confirmed *H. pylori* seropositivity using serological analysis. The studies by Raderer *et al.* [7], Risch *et al.* [11], and Wadstrom *et al.* [12] had a case-control design, while the others were nested case-control studies [8, 9, 10]. Four of the studies were rated as fair quality [7, 8, 10, 11], one as good quality [9], and one which was published only in abstract form as poor quality [12]. The studies differed somewhat in the covariates that were controlled for within the multivariate analysis. All of the studies, except one [12] had analysis adjusted for smoking history, four adjusted for age [7, 8, 9, 11], three adjusted for sex [7, 9, 11], and one each adjusted for BMI [9], alcohol use [9], educational level [10], and ELISA plate number [11].

Table 1. Characteristics of included studies.

Author, year (Country)	Study Design	Cases No.	Controls No.	Age (years)	Males No.	<i>H. pylori</i> test method	CagA positive No.	Study quality
Raderer, 1998 (Austria) [7]	Case-control	92	27 ^a	58 vs. 56 ^b	65 (54.6%)	Serology (ELISA)	NR	Fair
Stolzenberg, 2001 (USA) [8]	Nested case-control	121	226	64 (50-76) ^c	347 (100%)	Serology (ELISA)	118 (54.2%)	Fair
Wadstrom, 2004 (Sweden) [12]	Case-control	45	45	NR	NR	Serology	NR	Poor ^g
Lindkvist, 2008 (Sweden) [9]	Nested case-control	87	263	60.7 ^d	245 (70.0%)	Serology (ELISA)	NR	Good
de Martel, 2008 (USA) [10]	Nested case-control	104	262	71.5±9.7 ^e	181 (49.5%)	Serology (ELISA)	116 (31.7%)	Fair
Risch, 2010 (USA) [11]	Case-control	373	690	68.3 vs. 66.9 ^f	605 (56.9%)	Serology (ELISA)	163 (15.3%)	Fair

^a Control group included patients with colorectal cancer and normal subjects

^b Median ages for the case and control groups, respectively

^c Median and range ages at cancer diagnosis

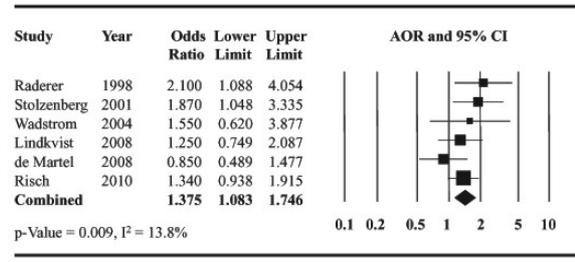
^d Mean age

^e Mean±SD age

^f Mean ages at interview for the case and control groups, respectively

^g Published in abstract form

CagA: cytotoxin-associated gene A; ELISA; enzyme-linked immunosorbent assay; No.: number of cases; NR: not reported



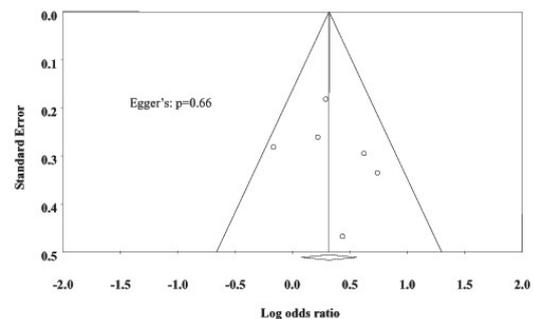
AOR = adjusted odds ratio, CI = confidence interval

The squares represent individual studies and the size of the square represents the weight given to each study in the meta-analysis. Error bars represent 95% CIs. The diamond represents the combined results. The solid vertical line extending upwards from 1 is the null value.

Figure 2. Forest plot of pooled adjusted odds ratio.

Synthesis of Results

Our meta-analysis of one good-quality [9], four fair-quality [7, 8, 10, 11], and one poor quality [12] observational studies showed a significant association between *H. pylori* seropositivity and development of pancreatic cancer (AOR 1.38, 95% CI: 1.08-1.75; P=0.009) (Figure 2). No significant statistical heterogeneity was seen (I²=13.8%). Visual inspection of the funnel plot (Figure 3) could not rule out the possibility of publication bias, however Egger's weighted regression analysis suggested a low likelihood (P=0.662). When the three observational studies [8, 10, 11], out of the four with fair-quality, that



The circles represent each study included in the analysis. They are plotted with effect size on the X axis and the variance on the Y axis. Studies are generally clustered around the mean effect size (vertical line). The pattern should ultimately resemble an inverted funnel. If publication bias was present, the studies would be asymmetrically scattered around the effect size.

Figure 3. Funnel plot analysis.

reported CagA positive status were pooled, no significant association was seen (AOR 1.14, 95% CI: 0.66-1.97; P=0.639).

The cumulative meta-analysis demonstrated that, as studies were published, the association between *H. pylori* and pancreatic cancer remained statistically significant although the point estimate has been reducing over time (Figure 4). The publication of the most recent study by Risch *et al.* [11] did not change the point estimate much and may signal a plateau in the evidence, although additional studies will be required.

DISCUSSION

In this study, we used meta-analytic techniques to evaluate for a possible etiological association between *H. pylori* infection, a preventable risk factor, and pancreatic cancer. Our updated pooled analysis of 6 studies, evaluating a total of 2,335 patients, found a significant association between the presence of *H. pylori* infection and pancreatic cancer (AOR 1.38, 95% CI: 1.08-1.75). Our conclusions are similar to those made by Risch *et al.* [11] although we reported more detailed methodology. Additionally, the findings of our cumulative meta-analysis suggested that the strength of this association is reducing over time although is staying statistically significant. This suggests that future studies with more diverse patient populations and larger sample sizes are required to further confirm our findings. It should be pointed out that all of the currently available evidence, including the current report, arises from observational studies and suggest only that an association between *H. pylori* infection and pancreatic cancer may exist. Studies showing causality are currently not available but are required. Interestingly, besides its proven association with gastric cancer, previous meta-analyses demonstrated positive associations between *H. pylori* infection and the development of colorectal [21], hepatocellular [22], lung [23] and laryngeal cancers [24]. Conversely, *H. pylori* infection was suggested to be protective against esophageal cancer [25]. The precise mechanism by which *H. pylori* contributes to carcinogenesis has not yet been elucidated. Several theories have been proposed to explain the potential association between *H. pylori* infection and pancreatic cancer. Thus, Nilsson *et al.* [26] detected the 16S ribosomal DNA of

gastric *H. pylori* as well as other enteric *Helicobacter* species in 75% of tissue samples obtained from patients with pancreatic cancer, as compared with none in the corresponding control group. They theorized that proinflammatory cytokines, reactive oxygen species and other inflammatory mediators associated with chronic *H. pylori* infection may induce tissue inflammation, increasing genomic DNA damage and cell proliferation. This may lead to an inactivation of tumor-suppressor genes, further facilitating the malignant transformation of pancreatic cells [26]. Takayama *et al.* [27] suggested that *H. pylori* infection of human pancreatic cells may enhance their malignant potential in a similar fashion to the gastric cell carcinogenesis. Significant increases in serum levels of IL-8 and VEGF were seen in *H. pylori* infected gastric cancer patients [28, 29]. These molecules are known to promote angiogenesis, growth and metastasis of human malignancies. Additionally, activities of nuclear factor-kB, activator protein-1, and serum response element of human pancreatic cancer cells were shown to be increased by the *H. pylori* infection [27]. Moreover, the CagA protein was introduced into the pancreatic cancer cells by the *H. pylori* infection, which further accentuated serum response element activation. Overall, they demonstrated that *H. pylori* infection leads to increases in inflammatory cytokine and angiogenic factor secretion, ultimately culminating in malignant transformation of the utilized pancreatic cell line [27].

The prevalence of *H. pylori* colonization of the gastrointestinal tract is especially high in developing countries as well as in individuals of lower socio-economic strata and older persons. Another hypothesis suggested that this gastric antral colonization by *H. pylori* is associated with increased gastric acid output, leading to uninhibited secretin release from the duodenum [30]. This causes an increased basal pancreatic bicarbonate output and enhanced DNA synthesis, resulting in ductal hyperplasia and later malignancy [30]. Further secretin stimulation has also been proven to accelerate the development and frequency of pancreatic tumors induced by nitrosamines in hamster models [31].

A third hypothetical pathway involves the *H. pylori* colonization of the gastric corpus which results in a loss of parietal cells, a decrease in gastric acid output, and basal hypergastrinemia [31]. The resulting hypoacidity facilitates bacterial overgrowth and increased production of N-nitroso compounds, which can be activated in the ductal epithelium after transportation to the pancreas by the circulation. This is further supported by the observation of pernicious anemia commonly associated with pancreatic cancer [32]. Further *H. pylori* induced gastritis causes a reduced absorption of anti oxidants such as vitamin C [33]. Recent studies show that there is an increased risk of pancreatic cancer in patients with gastric ulcer, but not duodenal ulcer bolstering this hypothesis [34]. Lastly, there appears to be a number of similarities

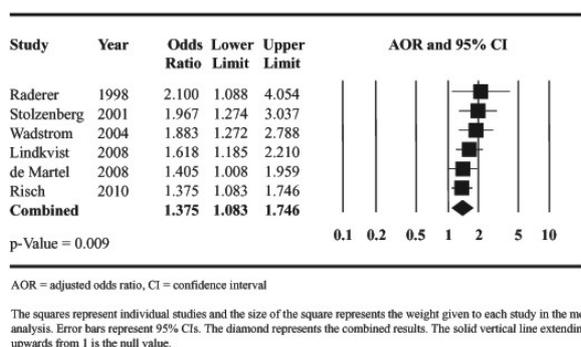


Figure 4. Cumulative meta-analysis results.

between gastric cancer and pancreatic cancer in terms of epidemiologic and possible etiologic cofactors involved in the two malignancies. These include diets deficient in fresh fruits and vegetables, cigarette smoking, poor socio-economic status, which have also been associated with the *H. pylori* infection itself [7].

We also realize that our study has several limitations. Our primary endpoint included pooled data of adjusted OR pulled from the included studies. The variables used to adjust these values were not consistent across studies, which may limit the reliability of the data. Too few studies were identified to allow for subgroup analysis by covariates. Second, as with any meta-analysis, the potential for publication bias is a concern. As such, the results of our study must be interpreted in the context of its possibility. However, visual inspection of the funnel plots were did not identify any significant publication bias. This is further strengthened by the non-significant findings using Egger's weighted regression statistic. Lastly, although a statistically significant association between *H. pylori* and pancreatic cancer was seen in our pooled analysis, the AOR is relatively modest. Some epidemiologists have suggested that an odds ratio of greater than 2 is required for clinical relevance. Since the AOR we found was 1.38, the clinical relevance of the association could be debated. This should not discount the association; rather justify the need for causative future studies.

In conclusion, our updated and cumulative meta-analysis of six studies suggests an association between *H. pylori* infection and the development of pancreatic cancer. Further studies with larger sample sizes evaluating this relationship are warranted to confirm our findings and to unearth the potential underlying mechanisms.

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Disclosures None

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