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Helicobacter pylori infection, chronic corpus atrophic gastritis and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: a nested case-control study

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Abstract

The association between *H. pylori* infection and pancreatic cancer risk remains controversial. We conducted a nested case-control study with 448 pancreatic cancer cases and their individually matched control subjects, based on the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, to determine whether there was an altered pancreatic cancer risk associated with *H. pylori* infection and chronic corpus atrophic gastritis. Conditional logistic regression models were applied to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs), adjusted for matching factors and other potential confounders. Our results showed that pancreatic cancer risk was neither associated with *H. pylori* seropositivity (OR=0.96; 95% CI: 0.70, 1.31) nor CagA seropositivity (OR=1.07; 95% CI: 0.77, 1.48). We also did not find any excess risk among individuals seropositive for *H. pylori* but seronegative for CagA, compared with

the group seronegative for both antibodies (OR=0.94; 95% CI: 0.63, 1.38). However, we found that chronic corpus atrophic gastritis was non-significantly associated with an increased pancreatic cancer risk (OR=1.35; 95% CI: 0.77, 2.37), and although based on small numbers, the excess risk was particularly marked among individuals seronegative for both *H. pylori* and CagA (OR=5.66; 95% CI: 1.59, 20.19, *p* value for interaction < 0.01). Our findings provided evidence supporting the null association between *H. pylori* infection and pancreatic cancer risk in western European populations. However, the suggested association between chronic corpus atrophic gastritis and pancreatic cancer risk warrants independent verification in future studies, and, if confirmed, further studies on the underlying mechanisms.

Keywords

H. pylori infection; chronic corpus atrophic gastritis; pancreatic cancer risk; nested case-control study; EPIC cohort

Introduction

Pancreatic cancer is one of the most devastating malignancies and has the lowest five-year survival proportion[1–4]. It ranks the fourth or fifth leading cause of cancer-related death for men and women in developed countries[2], and it is estimated to become the second leading cause of cancer-related death in the U.S. by 2020[5]. Established risk factors include old age, male sex, tobacco smoking, chronic pancreatitis, type 2 diabetes mellitus, obesity and a family history of pancreatic cancer[6]. Besides, ABO blood type has recently also been proposed as a risk factor for pancreatic cancer[7], although the first study to explore this association was conducted half a century ago in the context of examination between ABO blood types and multiple malignant diseases[8]. Yet, the etiology of pancreatic cancer is not fully understood as the identified risk factors explain only around 40% of all pancreatic cancer cases in the UK[9]. Further search for its etiological factors and understanding of the related mechanisms are urgently needed.

Helicobacter pylori (H. pylori), a group I carcinogen defined by IARC[10], has been established and widely accepted to play an important role in the development of noncardia gastric cancer[10, 11]. One type of *H. pylori* strains contains a gene associated with cytotoxin expression, namely CagA positive *H. pylori*. The *CagA* gene was found to lead to enhanced inflammatory responses and an increased risk for gastric cancer[12, 13]. However, results from previous epidemiologic studies on its association with pancreatic cancer are inconsistent. One meta-analysis containing four European studies showed a pooled 56% excess pancreatic cancer risk among *H. pylori* infected individuals[14], but another meta-analysis with seven studies from Western countries did not confirm this association[15]. However, a recent meta-analysis study suggested that an increased risk of pancreatic cancer among individuals of CagA-negative *H. pylori* seropositivity[16]. Nevertheless, the prevalence of *H. pylori* infection and distribution of strains (CagA+ or CagA-) vary greatly throughout the world, with a higher prevalence of overall infection and CagA+ strains predominantly in Asia compared with the U.S. and Europe.

Chronic corpus atrophic gastritis is a precursor lesion of gastric cancer and is characterized by long-term chronic gastric inflammation. Autoimmune pernicious anemia, chronic *H. pylori* infection and long period proton pump inhibitor therapy are identified as risk factors of chronic corpus atrophic gastritis[17–19]. We hypothesized that chronic corpus atrophic gastritis may be associated with an increased pancreatic cancer risk, through a stomach low-acid-production mechanism that may subsequently entail bacterial overgrowth and enhance accumulation of N-nitrosamines.

To further examine the associations between *H. pylori* infection, chronic corpus atrophic gastritis and pancreatic cancer risk, we conducted a case-control study nested within the large European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

Methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large cohort study that enrolled 520,000 apparently healthy volunteers, age 25 to 70, from 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Norway, Sweden, and the United Kingdom) from 1992 to 2000. Details in study design, population and baseline data collection have been described previously[20]. The study was approved by Institutional Ethics Review Board of each participating center, and each participant provided informed consent. This specific project was further approved by the Regional Ethics Review Board in Stockholm, Sweden.

Ascertainment of cases and control selection

Follow-up of subject to detect cancer incidence was based on population cancer registers in Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. In the other three countries (France, Germany and Greece), a combined approach was employed including linkage to health insurance records, cancer and pathology registers, and active follow-up of study participants and their next-of-kin. All the mortality data was provided by regional or national registers. All the participants were followed from their recruitment to a cancer diagnosis, death, emigration, or the end of follow-up (Dec, 2006), whichever occurred first.

Until the end of 2006, a total of 578 first incident pancreatic cancer cases were identified according to International Classification of Diseases, 10th Revision (ICD-10, C25.0–25.3, 25.7–25.9). Due to the different etiology, endocrine pancreatic tumor (ICD -O-3 C25.4, histologic type and morphology codes 8150, 8151, 8153, 8155, 8240 and 8246) were not included in this study. We further excluded individuals without blood samples, leaving a total of 448 cases in the final analysis. By using an incidence density sampling procedure, each identified case was individually matched with one control that was alive and free of cancer at the time when the index case was diagnosed. The matching factors included study center, sex, age (±3 years), date (±3 months), time (±2 h), and fasting status (<3h, 3–6h or >6 after the last meal) at blood collection.

Biomarkers and exposure assessment

Determination of H. pylori serostatus—Seroprevalence of anti-*H. pylori* antibodies was determined by enzyme-linked immunosorbent assay (ELISA) using the commercial *H. pylori* IgG kit from Biohit (Helsinki, Finland). The enzyme immunounits (EIU) were calculated as following: sample EIU= [mean optical density (OD) value of sample-mean OD value of blank]/[mean OD value of calibrator-mean OD value of blank]*100; A value of 30 EIU or more was considered as positive.

Determination of CagA serostatus—Seroprevalence of anti-CagA antibodies was determined by ELISA using the commercial *H. pylori* p120 (CagA) IgG kit from Ravo Diagnostika GmbH (Freiburg, Germany). The EIU were calculated as following: sample EIU= [mean OD value of sample-mean OD value of blank]/[mean OD value of calibrator-mean OD value of blank]*unit value of calibrator; A value of 7.5 EIU or more was considered as positive.

Determination of pepsinogen I and pepsinogen II levels—Serum levels of pepsinogen I and II were determined by pepsinogen I and pepsinogen II ELISA kits from Biohit (Helsinki, Finland). A calibration curve was generated to calculate the pepsinogen I or II concentration. A pepsinogen I level < 25 μg/l or pepsinogen I/II <3 was considered as presence of chronic corpus atrophic gastritis[21].

For quality control, the laboratory staff was blinded to the case/control status and in each plate duplicate internal control serum samples were added. All the tested samples, including positive control, calibration samples and internal control samples, yielded titer values well within their appropriate ranges; coefficients of variation calculated from values of the internal controls, were 9.7% for *H. pylori*, 10.3% for CagA, 5.0% for pepsinogen I and 7.9% for pepsinogen II assay, respectively.

Determination of ABO blood group—The common ABO blood type was determined by genotyping 2 known SNPs, rs505922 and rs8176746, which are correlated with the O and B alleles, respectively[7].

Statistical analysis

Differences of baseline characteristics between cases and control subjects were tested by paired t-test for continuous variables, and by McNemar's test or generalized McNemar's test for categorical variables. We used a conditional logistic regression model with stratified case-control risk sets to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between *H. pylori* infection, Cag A seropositivity, chronic corpus atrophic gastritis and pancreatic cancer risk. The crude conditional logistic regression models were inherently adjusted for the matching factors (mentioned above). We further considered smoking status (never, former or current), diabetes mellitus status (no or yes), height, and waist-to-hip ratio, a proxy of central obesity, as potential confounders and adjusted them in the models.

To estimate blood group stratum-specific effects, a 4-category new variable was generated by combining two dichotomous variables, i.e. *H. pylori*/CagA seropositivity (*H. pylori*– and CagA– vs *H. pylori* + or CagA+) and blood group (O vs non-O); dummy variables were then created and entered into regression models. The effect of *H. pylori*/CagA seropositivity on pancreatic cancer risk in O or non-O blood group strata was estimated by using different reference groups. To examine whether the association between *H. pylori* and/or CagA serostatus and pancreatic cancer was significantly modified by ABO blood group (O vs non-O blood type), a multiplicative interaction term was introduced into the regression model and *p* value for the interaction term was derived from a Wald test. Similarly the stratum-specific effects of chronic corpus atrophic gastritis by *H. pylori*/CagA serostatus were estimated, and the interaction between these two variables was examined. Again, in order to explore the modification effect of smoking (never vs ever) for the association between *H. pylori* /CagA serostatus and pancreatic cancer risk, the interaction term between these two variables was introduced into the regression model and *p* value was derived.

Socioeconomic status (SES) might also be a potential confounder that is both related to *H. pylori* infection and pancreatic cancer risk. We further performed a sensitivity analysis by adjusting SES in the models. The highest achieved educational level, which was classified into four categories (primary education or less, vocational secondary education, other secondary education, college or university), was used as the proxy for SES.

To check the influence of reverse causation bias, a sensitivity analysis was further performed by excluding cases (and their matched controls) who were diagnosed within the first two years of follow-up. In order to minimize the influence of non-fasting status of blood samples, we conducted another sensitivity analysis by only including case patients and their matched controls with the fasting status of more than six hours since the last meal to blood collection.

All statistical analyses were conducted using the Statistical Analysis System (SAS) software package, version 9.3 (SAS Institute Inc., Cary, NC, USA). All statistical tests were two-sided and statistical significance level was set at the 5% level.

Results

The mean age at recruitment was 57.8 years for both cases and control subjects. Cases did not significantly differ from control subjects for height and waist-to-hip ratio. In contrast, compared to control subjects, cases were more likely to be current smokers and tended to have a history of diabetes at baseline of recruitment. Female pancreatic cancer cases had a significantly higher weight compared to their corresponding controls. Overall, the prevalence of *H. pylori* seropositivity, CagA seropositivity and serologically defined chronic corpus atrophic gastritis did not differ significantly between cases and control subjects (Table 1).

Based on the crude models, our results showed that pancreatic cancer risk was neither associated with *H. pylori* seropositivity (OR=0.91; 95% CI: 0.68, 1.21) nor CagA seropositivity (OR=1.02; 95% CI: 0.76, 1.38). Further adjustment for potential confounding

factors including height, waist-to-hip ratio, smoking status (never, former or current) and diabetes mellitus status (no or yes) had a negligible effect on the associations (Table 2). We did not find any association between pancreatic cancer risk and *H. pylori*/CagA seropositivity, in either never smokers or ever smokers (*p* value for interaction = 0.11, fully-adjusted model) (data not shown).

In the combined analysis of *H. pylori* and CagA serostatus, compared with those seronegative for both *H. pylori* and CagA, the OR was close to unity for those seropositive for either *H. pylori* or CagA (OR=0.99; 95%CI: 0.73, 1.35, fully-adjusted model). The null associations were consistent across subgroups with different combinations of *H. pylori* and CagA serostatus (Table 2). In the sub-analysis among those with complete ABO blood type information (278 cases and their matched controls), we further performed a combined analysis of *H. pylori*/CagA serostatus and ABO blood type. We did not observe any excess risk of pancreatic cancer related to *H. pylori*/CagA seropositivity, in either O or non-O blood group (*p* value for interaction = 0.46, fully-adjusted model) (Table 2).

On the contrary, our results indicated that chronic corpus atrophic gastritis was positively, although not statistically significantly, associated with pancreatic cancer risk (OR=1.35; 95% CI: 0.77, 2.37, fully-adjusted model). To examine the modification effect of *H. pylori* infection on the association between chronic corpus atrophic gastritis and pancreatic cancer risk, we further performed stratified analyses and found that the positive association was confined to the stratum seronegative for both *H. pylori* and CagA (OR=5.66, 95% CI: 1.59, 20.19, *p* value for interaction < 0.01, fully-adjusted model) (Table 3).

In the sensitivity analysis by further adjusting for SES in the models, the results did not change notably (data not shown). In another sensitivity analysis to examine the influence of reverse causation bias, we excluded pancreatic cancer cases identified within two years of follow-up and their matched controls (N=83 case-control pairs), the results did not alter appreciably (data not shown). Similarly, including only the case-control sets with fasting status of more than six hours since the last meal in the analysis, the results did not change remarkably (data not shown).

Discussion

This case-control study nested within a large European prospective cohort study showed no evidence supporting the association between *H. pylori* infection (indicated by either *H. pylori* seropositivity or CagA seropositivity, or a combination of both) and pancreatic cancer risk. The lack of association was still evident in stratified analysis by ABO blood type. Although based on small numbers, our results provided some support that severe chronic corpus atrophic gastritis, defined by serological pepsinogen levels, might be associated with an increased pancreatic cancer risk.

A number of previous studies have addressed the potential association between *H. pylori* infection and pancreatic cancer risk. The first study was a hospital-based case-control study reported in 1998[22], including 92 pancreatic cancer cases and 62 controls (35 colorectal cancer patients and 27 healthy volunteers), in which a 2-fold excess risk of pancreatic cancer

was associated with *H. pylori* seropositivity. This positive association was later confirmed by a case-control study nested within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention cohort and the association seemed to be stronger for CagA seropositivity[23]. However, in two later population-based case-control studies conducted in the U.S. and China[24, 25], excess risk of pancreatic cancer was found to be associated with CagA-negative *H. pylori* infection only, in particular among those with non-O blood type[24]. In a Swedish case-control study nested within a prospective cohort, although overall *H. pylori* seropositivity was not associated with pancreatic cancer risk, positive associations were observed among never-smokers or low alcohol consumers[26]. The small numbers of cases in stratified analyses, however, cautioned interpretation of the findings. In contrast to the above-mentioned positive associations, three studies reported null associations between *H. pylori* seropositivity and pancreatic cancer[27–29]. In the two case-control studies nested within prospective cohort studies in the U.S. and Finland, neither *H. pylori* nor CagA was associated with pancreatic cancer development[27, 28]. Of note, the study in Finland[28] was an updated report based on extended follow-up of the same study cohort, from which a significant positive association was reported in 2001[23]. In a small clinical study conducted in Japan, the authors found that *H. pylori* seroprevalence was similar between pancreatic cancer cases and controls[29]. Discrepancies of results reported in previous studies may be explained by small sample size, various study designs and study populations, different methods of assessment of *H. pylori* infection, unmeasured confounders, and differential joint effects of environmental and/or genetic factors.

Various underlying mechanisms have been proposed to explain the potential association between *H. pylori* infection and pancreatic cancer risk. One plausible mechanism involves antral colonization of *H. pylori* which may lead to an excess of gastric acidity, that can stimulate uninhibited secretin release from the duodenum and induce basal pancreatic ductal bicarbonate output. This will in turn result in pancreatic ductular hyperplasia through increased DNA synthesis[30]. Another potential mechanism, in contrast to an excess of gastric acidity, is related to the sequential pathologic alterations during the gastric cancer carcinogenesis. It has been proposed that the long-term pathogenesis process after gastric colonization of *H. pylori* usually goes via chronic superficial gastritis, chronic atrophic gastritis, metaplasia and dysplasia[31]. The development of multifocal atrophic gastritis may cause a loss of parietal cells, leading to a hypo- or achlorhydria and basal hypergastrinemia, which subsequently entails the bacterial overgrowth and enhances *N*-nitrosation catalyzation[32]; through the blood stream circulation, the *N*-nitrosamines may transport to the pancreas, and the carcinogens may be activated on the ductal epithelium[33]. The latter hypoacidity mechanism is supported by a register-based Swedish study[34], in which an elevated pancreatic cancer risk was observed among patients with gastric ulcer, but not among those with duodenal ulcer. Duodenal ulcer is related to antral colonization of *H. pylori* and hyperchlorhydria, whereas gastric ulcer is linked to infection on the gastric corpus with normo- or hypochlorhydria. Another supportive evidence for the hypoacidity mechanism comes from the observed excess risk of pancreatic cancer among patients with pernicious anemia which is characterized by long-term hypo- or achlorhydria[35, 36]. Although not conclusive, our results tended to support the above-mentioned hypoacidity mechanism.

Few studies have directly examined the association between chronic corpus atrophic gastritis and pancreatic cancer risk. In a Finnish study on male smokers, the authors found that neither low pepsinogen level nor histologically confirmed atrophic gastritis was associated with subsequent pancreatic cancer risk[37]. However, in our study, we found a significant positive association between chronic corpus atrophic gastritis and pancreatic cancer in the stratum seronegative for both *H. pylori* and CagA, but not in the stratum seropositive for *H. pylori* or CagA. Given the very small number of study subjects in the seronegative stratum (only three controls with chronic corpus atrophic gastritis), caution is needed in interpreting this finding. One possible explanation may be due to that in the seronegative stratum, chronic corpus atrophic gastritis might be more severe. In addition, previous studies have found that long-term advanced chronic corpus atrophic gastritis might result in clearance of *H. pylori* colonization of the stomach mucosa, and in turn result in lower antibodies against the bacterium[38, 39]. However, we still cannot rule out the possibility that the observed positive association was explained by chance, given the relatively small sample size in this subgroup. Confirmatory studies are warranted to reexamine this association.

The strengths of this study include a prospective study design with prediagnostic blood samples collected, highly complete follow-up and availability of detailed information of potential confounding factors. However, our findings should be interpreted carefully due to several limitations. Misclassification of exposures of interest, such as *H. pylori* infection and presence of chronic corpus atrophic gastritis, might exist, although it is most likely to be non-differential, as we had to rely on measuring serum antibodies against *H. pylori*/CagA and pepsinogen I/II levels. For chronic corpus atrophic gastritis, the ‘gold standard’ of diagnosis is based on histopathological examination which requires biopsies during an upper gastrointestinal endoscopy examination, but this is impossible to apply in large-scale epidemiological studies. In addition, we used ABO rs505922 to determinate O blood alleles. Although it has high linkage disequilibrium with rs8176719, it still cannot be a complete replacement for the functional variant of rs8176719[40]. Therefore, the genotyping measurement error might exist and result in non-differential misclassification of O and non-O blood type in the present study.

In conclusion, neither *H. pylori* seropositivity nor CagA status was directly associated with pancreatic cancer risk. The lack of association remained consistent regardless of ABO blood type. However, we found some supportive evidence that chronic corpus atrophic gastritis might be associated with a higher pancreatic cancer risk, especially among *H. pylori* seronegative group. Future studies are warranted to verify this observation, and if confirmed, to further explore the underlying mechanisms.

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References

1. Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for pancreatic cancer across the world. HPB (Oxford). 2008; 10:58–62. [PubMed: 18695761]
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015; 65:87–108. [PubMed: 25651787]
3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9–29. [PubMed: 24399786]
4. Lepage C, Capocaccia R, Hackl M, Lemmens V, Molina E, Pierannunzio D, Sant M, Trama A, Faivre J, Grouph E-W. Survival in patients with primary liver cancer, gallbladder and extrahepatic biliary tract cancer and pancreatic cancer in Europe 1999–2007: Results of EUROCARE-5. Eur J Cancer. 2015
5. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014; 74:2913–21. [PubMed: 24840647]
6. Maisonneuve P, Lowenfels AB. Risk factors for pancreatic cancer: a summary review of meta-analytical studies. Int J Epidemiol. 2015; 44:186–98. [PubMed: 25502106]
7. Wolpin BM, Kraft P, Gross M, Helzlsouer K, Bueno-de-Mesquita HB, Steplowski E, Stolzenberg-Solomon RZ, Arslan AA, Jacobs EJ, Lacroix A, Petersen G, Zheng W, et al. Pancreatic cancer risk and ABO blood group alleles: results from the pancreatic cancer cohort consortium. Cancer Res. 2010; 70:1015–23. [PubMed: 20103627]
8. Case J, Raeburn C, Walther WW. Blood-groups in relation to malignant diseases. Lancet. 1956; 271:970–2. [PubMed: 13368566]
9. Parkin DM, Boyd L, Walker LC. 16. The fraction of cancer attributable to lifestyle and environmental factors in the UK in 2010. Br J Cancer. 2011; 105(Suppl 2):S77–81. [PubMed: 22158327]
10. Humans IWGotEoCRt. Biological agents. Volume 100 B. A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer. 2012; 100:1–441.
11. Adami, HOHD., Trichopoulos, D. Textbook of Cancer Epidemiology – 2nd Ed, Chapter: Stomach cancer. Nyrén, O., Adami, HO., editors. Oxford University Press; New York: 2008. p. 239-374.
12. Parsonnet J, Friedman GD, Orentreich N, Vogelman H. Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. Gut. 1997; 40:297–301. [PubMed: 9135515]
13. Huang JQ, Zheng GF, Sumanac K, Irvine EJ, Hunt RH. Meta-analysis of the relationship between cagA seropositivity and gastric cancer. Gastroenterology. 2003; 125:1636–44. [PubMed: 14724815]
14. Xiao M, Wang Y, Gao Y. Association between Helicobacter pylori infection and pancreatic cancer development: a meta-analysis. PLoS One. 2013; 8:e75559. [PubMed: 24086571]
15. Wang Y, Zhang FC, Wang YJ. Helicobacter pylori and pancreatic cancer risk: a meta- analysis based on 2,049 cases and 2,861 controls. Asian Pac J Cancer Prev. 2014; 15:4449–54. [PubMed: 24969867]
16. Schulte A, Pandeya N, Fawcett J, Fritschi L, Risch HA, Webb PM, Whiteman DC, Neale RE. Association between Helicobacter pylori and pancreatic cancer risk: a meta-analysis. Cancer Causes Control. 2015

17. Kuipers EJ. Proton pump inhibitors and gastric neoplasia. Gut. 2006; 55:1217–21. [PubMed: 16905689]
18. El-Zimaity H. Gastritis and gastric atrophy. Curr Opin Gastroenterol. 2008; 24:682–6. [PubMed: 19122515]
19. de Vries AC, Kuipers EJ. Epidemiology of premalignant gastric lesions: implications for the development of screening and surveillance strategies. Helicobacter. 2007; 12(Suppl 2):22–31. [PubMed: 17991173]
20. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondiere UR, Hemon B, Casagrande C, Vignat J, Overvad K, Tjonneland A, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. Public Health Nutr. 2002; 5:1113–24. [PubMed: 12639222]
21. Storskrubb T, Aro P, Ronkainen J, Sipponen P, Nyhlin H, Talley NJ, Engstrand L, Stolte M, Vieth M, Walker M, Agreus L. Serum biomarkers provide an accurate method for diagnosis of atrophic gastritis in a general population: The Kalixanda study. Scand J Gastroenterol. 2008; 43:1448–55. [PubMed: 18663663]
22. Raderer M, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, Hejna M, Scheithauer W. Association between Helicobacter pylori infection and pancreatic cancer. Oncology. 1998; 55:16–9. [PubMed: 9428370]
23. Stolzenberg-Solomon RZ, Blaser MJ, Limburg PJ, Perez-Perez G, Taylor PR, Virtamo J, Albanes D. Study A. Helicobacter pylori seropositivity as a risk factor for pancreatic cancer. J Natl Cancer Inst. 2001; 93:937–41. [PubMed: 11416115]
24. Risch HA, Yu H, Lu L, Kidd MS. ABO blood group, Helicobacter pylori seropositivity, and risk of pancreatic cancer: a case-control study. J Natl Cancer Inst. 2010; 102:502–5. [PubMed: 20181960]
25. Risch HA, Lu L, Kidd MS, Wang J, Zhang W, Ni Q, Gao YT, Yu H. Helicobacter pylori Seropositivities and Risk of Pancreatic Carcinoma. Cancer Epidemiol Biomarkers Prev. 2013
26. Lindkvist B, Johansen D, Borgstrom A, Manjer J. A prospective study of Helicobacter pylori in relation to the risk for pancreatic cancer. BMC Cancer. 2008; 8:321. [PubMed: 18986545]
27. de Martel C, Llosa AE, Friedman GD, Vogelman JH, Orentreich N, Stolzenberg-Solomon RZ, Parsonnet J. Helicobacter pylori infection and development of pancreatic cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17:1188–94. [PubMed: 18483341]
28. Yu G, Murphy G, Michel A, Weinstein SJ, Mannisto S, Albanes D, Pawlita M, Stolzenberg-Solomon RZ. Seropositivity to Helicobacter pylori and Risk of Pancreatic Cancer. Cancer Epidemiol Biomarkers Prev. 2013; 22:2416–9. [PubMed: 24089457]
29. Shimoyama T, Takahashi R, Abe D, Mizuki I, Endo T, Fukuda S. Serological analysis of Helicobacter hepaticus infection in patients with biliary and pancreatic diseases. J Gastroenterol Hepatol. 2010; 25(Suppl 1):S86–9. [PubMed: 20586873]
30. Risch HA. Etiology of pancreatic cancer, with a hypothesis concerning the role of N-nitroso compounds and excess gastric acidity. J Natl Cancer Inst. 2003; 95:948–60. [PubMed: 12837831]
31. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992; 52:6735–40. [PubMed: 1458460]
32. Houben GM, Stockbrugger RW. Bacteria in the aetio-pathogenesis of gastric cancer: a review. Scand J Gastroenterol Suppl. 1995; 212:13–8. [PubMed: 8578226]
33. Anderson, KEPJ., Mack, TM. Pancreatic cancer. In: Schotenfeld, D., Fraumeni, JFJ., editors. Cancer Epidemiology and Prevention. New York: Oxford University Press; 1996. p. 725-771.
34. Luo J, Nordenvall C, Nyren O, Adami HO, Permert J, Ye W. The risk of pancreatic cancer in patients with gastric or duodenal ulcer disease. Int J Cancer. 2007; 120:368–72. [PubMed: 17044024]
35. Borch K, Kullman E, Hallhagen S, Ledin T, Ihse I. Increased incidence of pancreatic neoplasia in pernicious anemia. World J Surg. 1988; 12:866–70. [PubMed: 3250137]
36. Hsing AW, Hansson LE, McLaughlin JK, Nyren O, Blot WJ, Ekbom A, Fraumeni JF Jr. Pernicious anemia and subsequent cancer. A population-based cohort study. Cancer. 1993; 71:745–50. [PubMed: 8431855]

37. Laiyemo AO, Kamangar F, Marcus PM, Taylor PR, Virtamo J, Albanes D, Stolzenberg-Solomon RZ. Serum pepsinogen level, atrophic gastritis and the risk of incident pancreatic cancer--a prospective cohort study. Cancer Epidemiol. 2009; 33:368–73. [PubMed: 19800305]

38. Weck MN, Gao L, Brenner H. Helicobacter pylori infection and chronic atrophic gastritis: associations according to severity of disease. Epidemiology. 2009; 20:569–74. [PubMed: 19404195]

39. Ye W, Held M, Enroth H, Kraaz W, Engstrand L, Nyren O. Histology and culture results among subjects with antibodies to CagA but no evidence of Helicobacter pylori infection with IgG ELISA. Scand J Gastroenterol. 2005; 40:312–8. [PubMed: 15932172]

40. Duell EJ, Bonet C, Munoz X, Lujan-Barroso L, Weiderpass E, Boutron-Ruault MC, Racine A, Severi G, Canzian F, Rizzato C, Boeing H, Overvad K, et al. Variation at ABO histo-blood group and FUT loci and diffuse and intestinal gastric cancer risk in a European population. Int J Cancer. 2015; 136:880–93. [PubMed: 24947433]

What is new?

The association between *H. pylori* infection and pancreatic cancer risk remains controversial. In this nested case-control study of 448 pancreatic cancer cases and individually matched controls, our findings provided evidence supporting the null association between *H. pylori* infection and pancreatic cancer risk in western European populations. However, we found some supportive evidence that chronic corpus atrophic gastritis might be associated with a higher pancreatic cancer risk, especially among *H. pylori* seronegative group.

Table 1

Baseline characteristics of cases with pancreatic cancer and control subjects[1]

Factor	Controls (*N*=448)	Cases (*N*=448)	*P*-value[2]
Age at recruitment (years, mean ± SD)	57.8 ± 7.8	57.8 ± 7.8	matched
Sex, *n* (%)			matched
Male	213	213	
Female	235	235	
Age at blood collection (±3 years)	58.0 ± 7.8	58.0 ± 7.8	matched
Fasting status, *n* (%)			matched
Fasting (≥6 h)	104 (23.2)	112 (25.0)	
In between (3–6 h)	69 (15.4)	68 (15.2)	
Not-fasting (<3 h)	172 (38.4)	172 (38.4)	
Unknown	103(23.0)	96 (21.4)	
Height (cm, mean ± SD)			
Male	175.1 ± 7.6	174.6 ± 7.3	0.68
Female	161.4 ± 7.0	162.2 ± 6.5	0.19
Weight (kg, mean ± SD)			
Male	82.1 ± 12.6	81.7 ± 11.7	0.69
Female	65.6 ± 11.0	69.5 ± 13.3	0.0004
Waist to hip ratio (mean ± SD)			
Male	0.95 ± 0.06	0.95 ± 0.06	0.62
Female	0.81 ± 0.06	0.81 ± 0.07	0.15
Smoking status (%)			
Never	194 (43.3)	165 (36.8)	
Former	153 (34.2)	140 (31.3)	
Current	96 (21.4)	138 (30.8)	0.002
Unknown	5	5	
History of diabetes mellitus (%)			
No	409 (95.6)	397 (92.8)	
Yes	19 (4.4)	31 (7.2)	0.09
Unknown	20	20	
Pepsinogen I, *n* (%)			
Low (<25)	14 (3.2)	20 (4.5)	
High (≥25)	427 (96.8)	422 (95.5)	0.29
Missing	7	6	
Pepsinogen I/II, *n* (%)			
Low (<3)	25 (5.7)	28 (6.3)	
High (>3)	416 (94.3)	414 (93.7)	0.66
Missing	7	6	
H. pylori, *n* (%)			
HP negative	241 (53.9)	250 (56.1)	
HP positive	206 (46.1)	196 (44.0)	0.50

Factor		Controls (*N*=448)	Cases (*N*=448)	*P*-value[2]
	Missing	1	2	
CagA, *n* (%)				
	CagA negative	306 (68.9)	302 (68.3)	
	CagA positive	138 (31.1)	140 (31.7)	0.88
	Missing	4	6	

[1] Cases and control subjects were 1:1 matched on center, sex, age at blood collection (±3 years), date of blood donation (±3 months), time of blood donation (±2 h), and fasting status (<3h, 3–6h or >6 after the last meal).

[2] *P* values were derived from paired *t* test for continuous variable, and from McNemar's test or generalized McNemar's test for categorical variables.

Table 2

Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) for pancreatic cancer risk according to *H. pylori* serology: a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

	Control subjects	Case patients	Crude model[1]		Adjusted model[2]	
	N, %	*N*, %	OR	95% CI	OR	95% CI
***H. pylori* serology**						
Negative	241 (53.9)	250 (56.0)	1.00		1.00	
Positive	206 (46.1)	196 (44.0)	0.91	0.68, 1.21	0.96	0.70, 1.31
CagA serology						
Negative	306 (68.9)	302 (68.3)	1.00		1.00	
Positive	138 (31.1)	140 (31.7)	1.02	0.76, 1.38	1.07	0.77, 1.48
***H. pylori* and CagA serology**						
***H. pylori*−, CagA−**	214 (48.3)	218 (49.5)	1.00		1.00	
***H. pylori*+ or CagA+**	231 (51.9)	224 (50.7)	0.94	0.70, 1.25	0.99	0.73, 1.35
***H. pylori*−, CagA+**	25 (5.6)	28 (6.4)	1.11	0.61, 2.02	1.14	0.59, 2.22
***H. pylori*+, CagA−**	91 (20.5)	82 (18.6)	0.88	0.61, 1.27	0.94	0.63, 1.38
***H. pylori*+, CagA+**	113 (25.5)	112 (25.4)	0.96	0.68, 1.37	1.04	0.63, 1.38
Sub-analysis stratified by ABO blood group (*N*=278, case-control pairs)						
O blood group						
***H. pylori*−, CagA−**	59 (21.2)	49 (17.6)	1.00		1.00	
***H. pylori*+ or CagA+**	52 (18.7)	45 (16.2)	1.06	0.57, 1.96	1.17	0.60, 2.30
Non-O blood type						
***H. pylori*−, CagA−,**	76 (27.3)	86 (30.9)	1.00		1.00	
***H. pylori*+ or CagA+**	91 (32.7)	98 (35.3)	0.94	0.60, 1.46	0.86	0.54, 1.38

[1]Crude conditional logistic regression model was inherently adjusted for the matching factors, including study center, sex, age at blood collection (±3 years), date of blood donation (±3 months), time of blood donation (±2 h), and fasting status (<3h, 3–6h or >6 after the last meal).

[2]Adjusted conditional logistic regression model was inherently controlled for the matching factors, and was further adjusted for height, waist-to-hip ratio, smoking status (never, former or current) and diabetes mellitus status (no or yes).

Table 3

Association between serologically determined chronic corpus atrophic gastritis and risk of pancreatic cancer: a case-control study nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort.

	Control subjects	Cases	Crude model[1]		Adjusted model[2]	
	N, %	*N*, %	OR	95% CI	OR	95% CI
Chronic corpus atrophic gastritis[3]						
No	415 (94.1)	407 (92.1)	1.00		1.00	
Yes	26 (5.9)	35 (7.9)	1.39	0.81, 2.38	1.35	0.77, 2.37
Stratifying by *H. pylori* and CagA serostatus						
***H. pylori*+ or CagA+**						
Chronic corpus atrophic gastritis (no)	204 (46.5)	202 (46.1)	1.00		1.00	
Chronic corpus atrophic gastritis (yes)	22 (5.0)	18 (4.1)	0.88	0.45, 1.72	0.85	0.42, 1.72
***H. pylori*− and CagA−**						
Chronic corpus atrophic gastritis (no)	210 (47.8)	202 (46.1)	1.00		1.00	
Chronic corpus atrophic gastritis (yes)	3 (0.7)	16 (3.7)	5.29	1.53, 18.23	5.66	1.59, 20.19

[1] Crude conditional logistic regression model was inherently adjusted for the matching factors, including study center, sex, age at blood collection (±3 years), date of blood donation (±3 months), time of blood donation (±2 h), and fasting status (<3h, 3–6h or >6 after the last meal).

[2] Adjusted conditional logistic regression model was inherently controlled for the matching factors, and was further adjusted for height, waist-to-hip ratio, smoking status (never, former or current) and diabetes mellitus status (no or yes).

[3] Chronic corpus atrophic gastritis was defined as pepsinogen I <25 μl/l or pepsinogen I/II<3.