Research Article

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Helicobacter pylori Seropositivities and Risk of Pancreatic Carcinoma

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Abstract

Background: Pathophysiologic actions of *Helicobacter pylori* colonization on gastric acidity have been hypothesized to modulate the effect of pancreatic carcinogens, through CagA-negative organism strain type, hyperchlorhydria and increased risk of pancreatic cancer, or CagA-positive strain, hypochlorhydria and decreased risk of pancreatic cancer. We aimed to determine *H. pylori* strain–specific associations with pancreatic cancer in a population in which colonization by CagA-positive strains is common.

Methods: We carried out a large population-based case–control study of pancreatic carcinoma in Shanghai, China. Venipuncture specimens were obtained from a representative sample of 761 case patients and 794 randomly selected control subjects matched by category of age and gender. Antibody seropositivity for *H. pylori* and its virulence protein CagA were determined by commercial enzyme-linked immunosorbent IgG assays.

Results: Compared with individuals seronegative for both *H. pylori* and CagA, decreased pancreas-cancer risk was seen for CagA seropositivity [adjusted OR, 0.68; 95% confidence interval (CI), 0.54–0.84], whereas some increased risk was suggested for CagA-negative *H. pylori* seropositivity (OR, 1.28; 95% CI, 0.76–2.13). No risk interactions were observed between CagA seropositivity and gender, cigarette smoking, or age-21 body mass index.

Conclusions: Similar to what has been seen in animal models, our results provide suggestive evidence in humans for the involvement of gastric acidity, through its bidirectional modification according to colonization by *H. pylori* CagA strain type, in the risk of pancreatic carcinoma.

Impact: *H. pylori* colonization may have diverse effects on cancer risk, depending on the organism strain type as well as on the particular cancer site. *Cancer Epidemiol Biomarkers Prev; 23(1); 172–8. ©2013 AACR.*

Introduction

Pancreatic cancer, one of the most aggressive and highly fatal cancers, has been dramatically increasing in incidence in China over the last 30 years. In urban Shanghai, average annual age-adjusted incidence rates (per 10^5) have risen among men from 3.7 in 1973 to 11.2 in 2000, and among women from 3.2 to 10.9 (1), beginning to approach rates seen in U.S. Whites. Over the same period, incidence rates of pancreatic cancer among individuals of Chinese ancestry in California have remained at about 80% of the rates in Whites. Factors explaining why the rates in Chinese may be lower than those in whites have not been determined.

In humans, risk factors for pancreatic cancer include gastric colonization by *Helicobacter pylori*, dietary intake of *N*-nitrosamines or of nitrites that form gastric *N*-nitrosamines, and cigarette smoking, which also supplies *N*-nitrosamines (2). Pathophysiologic actions of *H. pylori* colonization on gastric acidity have been suggested to modulate the pancreatic carcinogenic effect of *N*-nitrosamines or other carcinogens via hyperchlorhydria and increased risk of pancreatic cancer, or hypochlorhydria and decreased risk (2). In a study of *H. pylori* colonization and risk of pancreatic cancer in Connecticut, in which CagA-negative strains of the organism are comparable in frequency with CagA-positive ones (3), significantly increased risk was associated with seropositivity for CagA-negative strain and weakly decreased risk for CagA-positive strain (3), supporting the hypothesis of altered gastric acidity and risk because of the well-established contrasting effects of CagA-positive and -negative *H. pylori* strains associated with chronic gastric hypo- and hyperchlorhydria, respectively (4). To examine this theory in a population with substantially different *H. pylori* colonization—where upwards of 70% of older individuals

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are colonized, overwhelmingly (95%) by CagA-positive strains—we undertook a population-based case–control study of pancreatic cancer in urban Shanghai, China.

Materials and Methods

Participants

All study participants were Shanghai residents ages 35 to 79 years. An "instant case reporting system" of networked staff identified potential cases in the 37 major hospitals of Shanghai in which most individuals with pancreatic cancer are diagnosed and receive care. Between December 2006 and January 2011, we identified 1,241 newly diagnosed patients reported to the Shanghai Cancer Institute. Of these, 149 had died, refused to participate, or were unable to be contacted; the remaining 1,092 (88%) patients were recruited into the study. All relevant hospital records, pathology reports and slides, and/or imaging materials were obtained for later review of case eligibility by an expert panel of study pathologists and clinicians. Among the 1,092 patients, 200 were excluded because of diagnoses of benign, nonpancreatic, or nonadenocarcinoma tumors, leaving 892 patients with confirmed pancreatic cancer for analysis.

Over the same period, representative population control subjects were randomly selected from the Shanghai Residents Registry files according to categories of frequency matching by gender and age group. The Residents Registry enumerates all permanent residents of Shanghai. Contact was attempted for 1,653 candidates. Among those selected, 94 had been diagnosed with malignant diseases and 30 were deceased (all ineligible), 462 refused to participate, and the remaining 1,067 were recruited as controls (70% participation of eligible subjects). The study was approved by the institutional human subjects review boards of the Shanghai Cancer Institute (Shanghai, China) and Yale University (New Haven, CT).

Serologic evaluation

Participants signed informed consent, followed by in-person interview and phlebotomy. Blood samples were obtained from 761 cases (85%) and 794 controls (74%). The samples (on ice) were transported immediately after interview to the Shanghai Cancer Institute specimen processing laboratory, where they were promptly centrifuged, aliquoted into standard components, and frozen at −80°C. After the study received export approval from the Chinese National Office for the Management of Human Genetic Resources, the aliquot samples were packed in thick Styrofoam boxes with large quantities of dry ice and air-courier shipped to our laboratories at Yale. The still-frozen aliquots were then stored at −80°C until analysis. Before their shipment to the United States, all study biosamples were labeled with identifying numbers bearing no relation to any personal identifying information, thus protecting participant anonymity.

Commercial IgG ELISA kits were used for the determination of plasma seropositivity for *H. pylori* (Scanlisa HM-CAP; Scimedx Corp.) and for CagA-positive *H. pylori* strain (Ravo Diagnostika p120; Alere GmbH). In Shanghai subjects, the HM-CAP assay has measured sensitivity of 97% and specificity of 88% compared with urea breath test/histology (5, 6). The widely used p120 CagA assay has measured sensitivity of 88% and specificity of 100% (7). All study subjects were tested for both assays. Plasma samples blinded for case–control status were analyzed in duplicate along with calibration and quality-control samples in each assay plate. Titer values for all the quality-control samples were well within their appropriate ranges; coefficients of variation for the calibration samples averaged 2.7% for *H. pylori* and 2.3% for CagA ELISAs. Seropositivity was assigned for calculated titer levels exceeding the manufacturers' recommended thresholds of 2.2 (HM-CAP) and 7.5 (p120 CagA) units. In colonized normal adults, over the lifetime, natural *H. pylori* IgG seroreversion occurs substantially more frequently than CagA seroreversion (8–10). We therefore considered CagA seropositivity to indicate history of colonization by CagA-positive strains of *H. pylori*, whether or not *H. pylori* seropositivity was also found.

Statistical analysis

For analyses of seropositivity with risk of pancreatic cancer, unconditional logistic regression methods were used to estimate ORs and their 95% confidence intervals (CIs). All analyses were adjusted for continuous terms of interview age, age-21 body mass index (BMI), and years of cigarette smoking, and a dichotomous term for gender. The GLIM computer program was used for calculations (11). All P values are two-sided and based on $\times 2$ differences in model log-likelihoods referred to the χ^2 distribution.

Results

Comparability of participants

Among our Shanghai study subjects, controls were comparable with cases on age, gender, and education (Table 1). History of cigarette smoking and regular alcohol use differed very slightly, whereas average BMI (weight/height^2) at the age of 21 years showed a statistical though not appreciable difference between cases and controls (Table 1). Cases and controls had similar BMI based on reported usual weight later in life during adulthood. The distributions of these factors were very similar comparing all interviewed subjects with the 761 cases and 794 controls that provided blood samples (data not shown).

Associations with Risk of Pancreatic Cancer

Associations with risk of pancreatic cancer according to *H. pylori* seropositivity and for CagA-positive and -negative *H. pylori* strains are shown in various models in Table 2. Both *H. pylori* and CagA seropositivity were associated with significantly decreased risk. In contrast,

Table 1. Characteristics of pancreatic cancer case patients and normal population control subjects in urban Shanghai, China, 2006–2011

	Cases (%)[a]	Controls (%)[a]	*P*[b]
Total number	761	794	
Age at interview, y			
Mean (SD)	64.9 (9.6)	64.9 (9.9)	0.99
Range	36.7–80.0	35.4–80.0	
Gender			
Males	435 (57.2)	460 (57.9)	0.74
Females	326 (42.8)	334 (42.1)	
Education			
Primary school or lower	146 (19.2)	142 (17.9)	0.21[c]
Middle-high school	445 (58.5)	498 (62.7)	
College or higher	170 (22.3)	154 (19.4)	
Regular alcohol use			
No	418 (54.9)	398 (50.1)	0.058
Yes	343 (45.1)	396 (49.9)	
Tobacco use			
Never smoker	428 (56.3)	458 (57.7)	0.55[c]
Former smoker	97 (12.7)	109 (13.7)	
Current smoker	236 (31.0)	227 (28.6)	
Cigarettes, years of smoking, mean (SD)			
Among former smokers	29.2 (14.5)	30.2 (12.5)	0.76[d]
Among current smokers	36.5 (10.5)	36.0 (10.5)	
BMI[e] at age 21 years, mean (SD)			
Males	20.6 (2.30)	20.2 (2.02)	$3.9{\cdot}10^{-5}$ [d]
Females	20.5 (2.50)	19.9 (2.34)	
BMI[e] based on usual adult weight, mean (SD)			
Males	23.7 (3.07)	23.4 (3.10)	0.13[d]
Females	23.3 (3.39)	23.0 (3.08)	

[a]Values are numbers (percentages) of participants unless indicated otherwise.
[b]*P* values calculated by χ^2 for categorical variables (gender, education, regular alcohol use, tobacco use) and as trends by unconditional logistic regression for continuous variables (age at interview, years of smoking, BMI at age 21 years).
[c]*P* value based on two degrees of freedom for the test of homogeneity across three categories.
[d]*P* value based on two degrees of freedom for simultaneous continuous trends in both strata.
[e]BMI, weight/height^2 (kg/m^2).

CagA-negative *H. pylori* seropositivity, although not as common, was associated with significantly increased risk compared with non–CagA-negative *H. pylori* seropositivity (model 4). The association with CagA seropositivity remained about the same, whereas that with CagA-negative *H. pylori* seropositivity was attenuated somewhat when both factors were included in the same model with respect to a common reference group seronegative for both strain types (model 5). No risk interactions were observed between CagA seropositivity and gender ($P = 0.47$), cigarette smoking ($P = 0.62$), or age-21 BMI ($P = 0.28$). Among *H. pylori* seropositive subjects, both for cases and controls, *H. pylori* serotiters were similar for CagA-seropositive versus CagA-seronegative individuals: mean (SD) 3.40 (0.90) versus 3.44 (1.05) for cases and 3.63 (1.13) versus 3.74 (1.11) for controls, respectively.

Discussion

Strengths and limitations

Because of the very high disease mortality, case–control studies of pancreatic cancer typically have very low case participation fractions compared with studies of other cancer sites, allowing for the possibility that sampled cases may not represent the general features of the disease. An important strength of our study was the involvement of networked staff in each of the 37 major Shanghai hospitals involved in the diagnosis and care of individuals with pancreatic cancer. This instant reporting network yielded the participation of 88% of eligible cases, perhaps the largest participation fraction of any pancreatic cancer case–control study to our knowledge. Our study also achieved a 70% participation fraction for controls, which is comparable with control participation in many

Table 2. Association between *H. pylori* seropositivity and risk of pancreatic cancer in urban Shanghai, China, 2006–2011[a]

Model	Risk factors	Case patients = 761 (%)	Control subjects = 794 (%)	Adjusted OR (95% CI)[b]	*P*
1	*H. pylori*$^{-}$[c]	528 (69.4)	467 (58.8)	Ref	
	H. pylori^{+}	233 (30.6)	327 (41.2)	0.62 (0.50–0.77)	0.000011
2	CagA^{-}[d]	319 (41.9)	257 (32.4)	Ref	
	CagA^{+}	442 (58.1)	537 (67.6)	0.66 (0.53–0.81)	0.000096
3	CagA^{-}, *H. pylori*$^{+}$[e]	43 (5.7)	28 (3.5)	Ref	
	CagA^{+}, *H. pylori*$^{+}$	190 (25.0)	299 (37.7)	0.41 (0.24–0.68)	0.00058
4	*H. pylori*$^{-}$ or CagA^{+}	718 (94.3)	766 (96.5)	Ref	
	H. pylori^{+}, CagA^{-}	43 (5.7)	28 (3.5)	1.65 (1.01–2.70)	0.046
5	*H. pylori*$^{-}$, CagA^{-}	276 (36.3)	229 (28.8)	Ref	
	H. pylori^{+}, CagA^{-}	43 (5.7)	28 (3.5)	1.28 (0.76–2.13)	0.35
	CagA^{+}	442 (58.1)	537 (67.6)	0.68 (0.54–0.84)	0.00052

[a]Unconditional logistic regression models used to obtain ORs and 95% CIs. Each model in the table includes the one or two risk factors shown. All *P* values are two-sided.

[b]All models were adjusted for age at interview (continuous), gender (dichotomous), BMI at the age of 21 years (weight/height^2, kg/m^2, continuous), and years of cigarette smoking (continuous).

[c]The HM-CAP *H. pylori* assay titer was considered positive above the manufacturer's threshold of 2.2 units. The greater natural seroreversion of *H. pylori* than CagA titers over adult life accounts for the appreciable fraction of CagA-positive individuals *H. pylori* seronegative (8–10).

[d]The CagA titer was considered positive above the manufacturer's threshold of 7.5 units.

[e]Additionally adjusted for *H. pylori* serostatus.

published high-quality case–control studies. Among our study participants, we obtained blood specimens from 85% of cases and 74% of controls which, in combination with the subject participation fractions and the sensitivity and specificity of the ELISA assays, could allow for some degree of potential misclassification and expected reduced magnitudes of association. However, on a number of characteristics, the study subjects that provided blood specimens were observed to be very similar to all enrolled subjects, and we did observe statistically significant associations, although their magnitudes may be underestimates.

A second consideration is that we obtained case–subject biospecimens after cancer diagnosis, creating the theoretical possibility that seropositivity could have changed because of effects of tumor development. However, it seems unlikely that effects of reverse causality can explain our findings. Biosamples from all cases in our Shanghai study and most in our previous Connecticut study were obtained before treatment, removing chemotherapy as an explanation. Although immune senescence occurs with aging, our controls were matched to cases on age and age was included in all regression model adjustments. Any hypothetical effect that a developing pancreatic cancer might have on general immune function would be expected to apply equally to serotiters of antibodies to CagA-positive and CagA-negative strains of *H. pylori*. Among our *H. pylori* seropositive Shanghai subjects, *H. pylori* serotiters were similar for CagA-seropositive versus CagA-seronegative individuals, both for cases and controls. A parallel similar pattern was seen for our Connecticut subjects. Because our association results were in opposite directions for CagA^{+} versus *H. pylori*$^{+}$ CagA^{-} subjects, a general increase or decrease in immune seroreactivity caused by tumor development cannot be an explanation.

A superficially paradoxical finding in our data is that CagA seropositivity is more frequent than *H. pylori* seropositivity, the latter of which should reflect colonization by CagA-positive strains. With these seroassays, some individuals test *H. pylori*-seronegative but CagA-positive, a finding seen in most other studies, although perhaps not to the degree of our present data. Although possible test error of our HM-CAP assay could have contributed to this difference, over adulthood natural *H. pylori* whole-cell IgG seroreversion occurs more frequently than CagA seroreversion (10); thus, at least some older individuals can show whole-cell seronegativity but CagA-seropositivity. If test error of the HM-CAP assay is appreciable in our Shanghai subjects, then the magnitude of our observed association with CagA-negative *H. pylori* seropositivity would likely be an underestimate.

Interpretation of findings

Helicobacter pylori colonization differs appreciably between the United States and China. In the United States, over the last century and particularly after World War II, general increases in standards of living and development of suburban lifestyles with reduced

population densities have led to significant declines in frequency of colonization by *H. pylori* (12). Whereas the overwhelming majority of colonized individuals in China carry CagA-positive strains (e.g., 95% of seropositive controls in the present study), a smaller fraction of colonized persons in the United States do so (65% of seropositive controls in our Connecticut study; ref. 3), and, according to our data, seropositivity as a whole among adults is much lower in the United States than in China, 24% versus 71%, respectively. Thus, a superficial examination of risk of pancreatic cancer in the two countries, according to *H. pylori* whole-cell seropositivity, leads to very different results (OR, 0.62 in Shanghai; OR, 1.34 in Connecticut; ref. 3) because the CagA-positive and CagA-negative organism strains behave very differently from each other and comprise highly different fractions of colonized individuals in the two populations.

However, in examining colonization by CagA-positive and CagA-negative strain types separately, the present study is supported by the results of our earlier Connecticut work (3). In both studies, CagA seropositivity was associated with reduced risks (OR, 0.66 in Shanghai and OR, 0.77 in Connecticut; ref. 3), the former highly statistically significant. In contrast, CagA-negative *H. pylori* seropositivity was associated with increased risks in both studies: OR, 1.65 in Shanghai; OR, 1.68 in Connecticut (3). When both CagA seropositivity and CagA-negative *H. pylori* seropositivity were simultaneously included in the same regression models, the effect on risk for CagA seropositivity was unchanged in the Shanghai study and that for CagA-negative *H. pylori* seropositivity was unchanged in the Connecticut study, both remaining significant, whereas the remaining factor in each study changed toward unity.

Seven previous, although smaller, studies have examined the *H. pylori* association with pancreatic cancer. Four of these studies did not determine CagA seropositivity (13–16), and while providing some evidence for increased risk associated with *H. pylori* seropositivity [ORs (95% CIs) = 2.1 (1.1–4.1), 1.55 (0.62–3.88), 1.42 (1.13–1.79), and 1.25 (0.75–2.09), respectively], they do not help to distinguish risk differences between CagA-positive and CagA-negative *H. pylori* strains as seen in our Shanghai and Connecticut studies. A recent case–control study in Poland (17) found nonsignificantly increased risk for *H. pylori* seropositivity both overall (OR, 1.27; 95% CI, 0.64–2.61) and among CagA-negative *H. pylori* seropositive subjects (OR, 1.57; 95% CI, 0.68–3.62), and slightly decreased risk for CagA-seropositive individuals (OR, 0.90; 95% CI, 0.46–1.73), a risk pattern very similar to that in our Connecticut study. The remaining two studies were of prospective cohorts in Finland (18) and California (19) that obtained blood samples on average 4.6 and 22 years before diagnosis, respectively. The Finland study, involving 121 cases and 226 controls, not only found increased risk for *H. pylori* seropositivity (OR, 1.87; 95% CI, 1.05−3.34) but also for CagA seropositivity (OR, 2.01; 95% CI, 1.09–3.70; ref. 18). The California study, involving 104 cases and 262 controls, observed no risk associations for either CagA-negative or CagA-positive *H. pylori* seropositivity (OR, 1.01; 95% CI, 0.54−1.91; OR, 0.96; 95% CI, 0.48−1.92, respectively; ref. 19). In the latter study, control samples were analyzed with different *H. pylori* assays in two batches about 6 to 8 years apart. Of the 40 samples seropositive by the original ELISA, 9 (23%) tested negative with the newer ELISA. This raises the possibility that the null findings might have been influenced by the characteristics of the two custom ELISAs used. However, it is also possible that with nonnegligible rates of *H. pylori* and CagA seroreversion (8–10), assays of serum samples obtained 22 years before diagnosis may yield different results from those obtained 4.6 years before diagnosis or at diagnosis. It is also possible that different risk associations may be conveyed by Western versus Asian CagA-positive strains (20), which differ in their virulence properties according to C-terminus variation in the CagA protein (21, 22) and in associations between CagA-seropositivity and expression of other virulence factors such as VacA (23).

Overall, the present large study and its consistency with the results of our previous large study provide indirect evidence for the involvement of gastric acidity and its bidirectional modification according to *H. pylori* CagA strain type in the risk of pancreatic cancer. In contrast to other *Helicobacter* species, *H. pylori* does not colonize the pancreas in normal individuals and thus has no direct proximal effect on the pancreatic ductal epithelium (13, 24–26). Gastric colonization by CagA-negative *H. pylori* is associated with antral-predominant gastritis and hyperchlorhydria, whereas colonization by CagA-positive *H. pylori* is associated with corpus atrophic gastritis and hypo- or achlorhydria (2, 4). Apart from colonization of the gastric corpus versus the antrum and corresponding inflammatory sequelae and atrophy, for the pancreas the major clinical pathophysiologic difference between CagA-positive and CagA-negative *H. pylori* colonization is the chronic reduced versus increased gastric acid production, respectively (4). Eradication of *H. pylori* in patients with duodenal ulcer (i.e., CagA-negative strains) returns their hyperchlorhydria to normal acidity (27, 28), whereas eradication of CagA-positive *H. pylori* in patients with corpus atrophic gastritis returns their hypo- or achlorhydria to normal (29). Gastric acidity drives pancreatic ductal cell bicarbonate and fluid secretion (2). This mechanism allows *H. pylori* resident in the stomach to affect functioning of the pancreatic ductular epithelium. In the hamster *N*-nitrosamine model of pancreatic cancer, chronic excess production of pancreatic bicarbonate and fluid significantly potentiates the development of ductular cell dysplasia and frank ductular adenocarcinoma (30). Thus, although other mechanisms are possible, it is reasonable to suggest that differential modification of chronic gastric acidity by CagA-negative versus CagA-positive strains of *H. pylori* may be involved in modulating the risk of pancreatic cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for the analyses and the interpretation of the data presented in this study. No funders and sponsors of the study had any involvement in the design of the study; the collection, analysis, or interpretation of the data; the writing of the article; or the decision to submit the article for publication.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.A. Risch, L. Lu, J. Wang, W. Zhang, Q. Ni, Y.-T. Gao, H. Yu
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