Helicobacter pylori Infection and Development of Pancreatic Cancer

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Abstract

Background: **Infection with *Helicobacter pylori* is an established risk factor for gastric cancer. Results from two studies suggest that it may also be a risk factor for pancreatic cancer.**
Methods: **We conducted a nested case control study among 128,992 adult subscribers to the Kaiser Permanente Medical Care Program who had been enrolled in a multiphasic health checkup from 1964 to 1969. Serum collected during the checkup was maintained frozen, and subjects were followed for cancer. Cases consisted of 104 randomly selected subjects among 507 who developed pancreatic cancer in the cohort. Controls consisted of 262 pancreatic cancer–free subjects from a pool of 730 controls previously tested for studies conducted on this cohort. Controls were individually matched to cases on age, gender, race, site, and date of multiphasic health checkup. Control sera were compared with cases for antibodies to *H. pylori* and the CagA protein. The effects of smoking, alcohol consumption, obesity, and years of education were also investigated.**
Results: **Neither *H. pylori* [odds ratio (OR), 0.85; 95% confidence interval (95% CI), 0.49-1.48] nor its CagA protein (OR, 0.96; 95% CI, 0.48-1.92) was associated with subsequent development of pancreatic cancer. Smoking (OR, 2.09; 95% CI, 1.17-3.74) and greater number of years of education (OR, 2.13; 95% CI, 1.23-3.69) were risk factors for pancreatic cancer, whereas alcohol consumption and obesity were not.**
Conclusion: **Our results suggest that *H. pylori* infection is not associated with development of pancreatic cancer.** (Cancer Epidemiol Biomarkers Prev 2008; 17(5):1188–94)

Introduction

The American Cancer Society reports that 32,180 Americans (16,100 men and 16,080 women) were diagnosed with cancer of the pancreas during 2005 (1). The 5-year survival rate is ~4%, the worst in the United States for any malignancy, making pancreatic cancer the fourth leading cause of cancer death in the United States for both men and women.

Risk factors for pancreatic cancer are largely unknown. Besides older age and African American race, smoking and chronic pancreatitis have consistently been identified as risk factors for pancreatic cancer but account for only a small fraction of the cases, 23% and 3% to 4%, respectively (2). Despite an 18-fold increased risk in first-degree relatives of familial cases, genetic mutations, hereditary syndromes, and familial aggregation account for only 10% of cases (3). Other putative risk factors include obesity, type II diabetes, and consumption of smoked or processed meat, whereas fruits, vegetables, and vitamin C have been inversely associated with the malignancy.

In 1994, the bacterium *Helicobacter pylori* was declared a group 1 carcinogen by the IARC (4). Its causal association with gastric cancer and gastric lymphoma is widely accepted (5). Exploratory epidemiologic evidence from two case-control studies now suggests that *H. pylori* might be involved in the pathogenesis of pancreatic cancer as well. A 1998 case-control study of 92 Austrian pancreatic cancer patients found that *H. pylori* infection was more common among cases (65%) than among 27 healthy volunteers and 35 colorectal cancer patients [45% and 47%, respectively; odds ratio (OR) against pooled controls, 2.1; 95% confidence interval (95% CI), 1.1-4.1; ref. 6]. However, in the 20 histopathologic specimens investigated, *H. pylori* was absent not only from the malignant tissue but also from the ducts of surrounding normal pancreatic tissue, and no inflammatory reactions typically observed in *H. pylori* gastritis were found. In 2001, a nested case-control study of 121 exocrine pancreatic cancer cases and 226 cancer-free control subjects from a Finnish cohort of older male smokers found that 82% of cases were seropositive for *H. pylori* antibodies, compared with 73% of controls (OR, 1.87; 95% CI, 1.05-3.34; ref. 7). In this study, $CagA^+$ strains were associated with slightly greater odds of pancreatic cancer than the $CagA^-$ ones (OR, 2.01; 95% CI, 1.09-3.70 and OR, 1.65; 95% CI, 0.82-3.29, respectively). Authors have speculated that an excess of gastric acidity due to colonization of the gastric antrum might stimulate the pancreatic production of bicarbonate and secretin,

Received 2/27/08; accepted 2/27/08.

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doi:10.1158/1055-9965.EPI-08-0185

hence helping to induce hyperplasia and increased DNA synthesis in the ductal mucosa. Another hypothesis would be that *H. pylori* facilitates formation of mutagenic *N*-nitroso compounds in the stomach that ultimately have downstream carcinogenic effects (8).

To further investigate and potentially corroborate a possible association between *H. pylori* infection and subsequent development of pancreatic cancer, we conducted a nested case-control study in a well-characterized cohort of men and women from Northern California followed over several decades.

Design and Methods

Subjects. Between 1964 and 1969, 128,992 adult subscribers to the Kaiser Permanente Medical Care Program enrolled in a multiphasic health checkup program. Serum samples were collected during multiphasic health checkup visits and initially stored at −23°C. Since 1980, these sera have been stored at −40°C by the Orentreich Foundation for the Advancement of Science, Inc. Information available on multiphasic health checkup subjects included height, weight, sex, age, skin color, smoking status, drinking status, previously diagnosed diabetes, and education level. Hospitalization and tumor registry reports of the multiphasic health checkup cohort were monitored and routinely recorded. The Kaiser Permanente Medical Care Program reports to the Surveillance, Epidemiology, and End Results program, which reviews and confirms all reported cancer diagnoses. From enrollment until the year 2000, 507 cohort members developed pancreatic cancer, and 141 of these cases were randomly selected for this study. These cases were individually matched with controls from a pool of 730 control subjects from the multiphasic health checkup cohort previously studied by our research group in studies of gastric adenocarcinoma, gastric lymphoma, colon cancer, and myocardial infarction (Table 1; refs. 9-12). A priori power calculations showed that this sample size (141 cases and 730 unmatched controls) could detect an OR of 1.77 with a power of 80% and a two-sided type I error of 5% (13). After the matching process, 262 controls free of cancer and, with complete covariate information, were successfully matched to 104 cases on gender, age, self-determined skin color, date, and site of the multiphasic health checkup. Post-matching power calculations showed that this sample size (104 cases and 262 matched controls) could detect an OR of 2.5 with a power of 80% and a two-sided type I error of 5%. Reasons for not including the whole 141 selected cases in the study were as follows: One 61-year-old female case subject was missing race and site information and could not enter the matching process; six case subjects could not be matched with any control; and 30 cases were successively matched but were missing some covariate information.

Serology. For the control group, stored sera aliquots were shipped on dry ice at the time of each previous study to Stanford University where they were tested by workers who were blinded to their controls status. In 2001, stored aliquots for cases, along with 15 other control specimens with known serologic status from previous year's essays, were sent to Stanford University on dry ice in a blinded fashion. Case IDs were revealed to the investigators by the Orentreich Foundation after serologic testing was complete. Of note, among the 15 quality controls, there was 94% concordance between the assay results and those obtained using prior assays from our laboratory.

Serum samples for gastric carcinoma and gastric lymphoma controls were tested in 1990 and 1992, respectively, using an in-house ELISA with a sensitivity of 96% and a specificity of 76% when compared with 124 biopsy-confirmed serum samples from the United States, Latin America, and Asia (75 positive and 49 negative). The low specificity of the test was improved after adding antigens to Asian *H. pylori* strains. Serum samples for colon controls, heart controls, and for cases were tested in 1996, 2000, and 2001, respectively, using the improved in-house ELISA with a sensitivity of >90% and a specificity of 100% when compared with 56 biopsy-confirmed specimens. For each assay, the threshold for a positive ELISA was set as twice the mean value obtained from 15 known negative controls. The 15 negative controls and positive control were used to calibrate each run.

Serum IgG to a recombinant fragment of CagA (OraVax, Inc.) was analyzed by an in-house ELISA, as previously described (14, 15). Gastric, lymphoma, and colon controls were tested in 1996, whereas heart control and cases were tested in 2003.

To study the stability of serum antibodies over time, serum antibody results for *H. pylori* infection were compared among the different historical groups of controls with adjustment on length of storage (year of the multiphasic health checkup) and known freezing and thawing history. To assess effects of changes to ELISA over the years, 40 *H. pylori*–positive and 20 *H. pylori*–negative gastric control sera and 40 *H. pylori*–positive and 20 *H. pylori*–negative colon cancer controls were retested in 2001 using the newer ELISA.

Statistical Analysis. Statistical analysis was done with SAS 9.0 software. Univariate comparisons used the *t* test and Fisher exact test. ORs and 95% CIs were obtained by univariate and multivariate conditional logistic regression. The body mass index (BMI) was calculated as weight (kg) / [height (m)]^2 and categorized using clinically meaningful cutoffs (≥25, overweight; ≥30, obese). Combined effects of potential risk factors were explored with statistical tests for interaction (16).

A small fraction of those who tested negative for *H. pylori* were positive for CagA protein. In a separate analysis, those who tested positive for CagA were considered to be infected with *H. pylori*. For comparability to the previous nested case-control study from Finland, subset analyses were also done on males, White males, and White male smokers only (7).

Results

The mean time between each case subject's multiphasic health checkup and diagnosis of pancreatic cancer was 21.9 years (SD, 7.6 years). The mean age at diagnosis was 71.5 years (SD, 9.7 years). The characteristics of the cases and controls with respect to matching variables were similar (Table 2). The six cases who were excluded from the study because they could not be matched with any control were younger and only two of them were White;

Table 1. Demographic characteristics and risk factors for pancreatic cancer among original cases and pulled controls (before matching)

Variables	Total cases (n = 141)	Total controls (n = 730)	Controls from previous studies			
			Gastric lymphoma study 10 (n = 118)	Gastric carcinoma study 9 (n = 180)	Colon cancer study 11 (n = 228)	Heart study 32 (n = 204)
Gender,* n (%)						
Female	69 (49)	334 (46)	69 (58)	62 (34)	116 (51)	87 (43)
Male	72 (51)	395 (54)	49 (42)	117 (65)	112 (49)	117 (57)
Race,* n (%)						
Missing	1 (1)	4 (1)	0	0	3 (1)	1 (0)
Black	28 (20)	103 (14)	10 (8)	35 (19)	18 (8)	40 (20)
White	109 (77)	601 (82)	98 (83)	142 (79)	198 (87)	163 (80)
Other	3 (2)	22 (3)	10 (8)	3 (2)	9 (4)	0
Age at MHC,* y						
Mean (SD)	49 (10)	52 (10)	53 (13)	54 (11)	52 (9)	50 (8)
Year of MHC,* n (%)						
1964-1965	59 (42)	303 (42)	59 (50)	76 (42)	151 (66)	17 (8)
1966-1967	57 (40)	216 (30)	39 (33)	69 (38)	63 (28)	45 (22)
1968-1969	25 (18)	211 (28)	20 (17)	35 (20)	14 (6)	142 (70)
MHC location,* n (%)						
Missing	1 (1)	0	0	0	0	0
Oakland	74 (52)	372 (51)	64 (54)	92 (51)	107 (47)	109 (53)
San Francisco	66 (47)	358 (49)	54 (46)	88 (49)	121 (53)	95 (47)
Education, n (%)						
Missing	5 (4)	11 (2)	3 (2)	5 (3)	3 (1)	0
Less than high school	21 (15)	164 (22)	26 (22)	45 (25)	64 (28)	29 (14)
High/business school	47 (33)	289 (40)	54 (46)	59 (33)	103 (45)	73 (36)
College and beyond	25 (48)	266 (36)	35 (30)	71 (39)	58 (26)	102 (50)
Smoking, n (%)						
Missing	10 (7)	60 (8)	6 (5)	21 (12)	21 (9)	12 (6)
Never	32 (23)	279 (38)	46 (39)	58 (32)	99 (44)	76 (37)
Former	21 (15)	117 (16)	19 (16)	34 (19)	28 (12)	36 (18)
<1 pack/d	39 (28)	136 (19)	27 (23)	40 (22)	35 (15)	34 (17)
≥1 pack/d	39 (28)	138 (19)	20 (17)	27 (15)	45 (20)	46 (22)
Alcohol, n (%)						
Missing	12 (8)	96 (13)	15 (13)	27 (15)	35 (15)	19 (9)
Never	24 (17)	157 (21)	32 (27)	41 (23)	51 (23)	33 (16)
Former	4 (3)	19 (3)	4 (3)	6 (3)	7 (3)	2 (1)
<2 drinks/d	90 (64)	377 (52)	54 (46)	91 (51)	110 (48)	122 (60)
≥2 drinks/d	11 (8)	81 (11)	13 (11)	15 (8)	25 (11)	28 (14)
BMI, n (%)						
Missing	4 (3)	12 (2)	3 (2)	5 (3)	4 (2)	0
<25	72 (51)	368 (50)	60 (22)	80 (44)	120 (53)	108 (53)
≥25 and <30	50 (35)	270 (37)	40 (46)	75 (42)	80 (35)	75 (37)
≥30	15 (11)	80 (11)	15 (30)	20 (11)	24 (10)	21 (10)
H. pylori, n (%)						
Indeterminate	12 (9)	5 (1)	0	0	0	5 (2)
HP negative	62 (44)	277 (38)	46 (39)	74 (41)	74 (32)	83 (41)
HP positive	67 (48)	448 (61)	72 (61)	106 (59)	154 (68)	116 (57)
CagA, n (%)						
CagA negative	87 (62)	407 (56)	39 (33)	110 (61)	142 (62)	116 (57)
CagA positive	50 (35)	232 (32)	27 (23)	60 (33)	83 (36)	62 (30)

Abbreviations: MHC, multiphasic health checkup; HP, *H. pylori*.
*Matching variable in each of the previous studies.

half of them were *H. pylori* positive. The mean BMI (± SD) at the time of multiphasic health checkup visit was similar for cases and controls, 25.0 (± 3.8) and 25.2 (± 4.3), respectively (P = 0.5). When looking at the distribution of other risk factors, cases were more likely than controls to be smokers, well educated, and light drinkers (Table 2). In univariate analysis, BMI, alcohol consumption, previously diagnosed diabetes, and seropositivity to *H. pylori* or CagA were not significant predictors of pancreatic cancer, whereas smoking and greater years of education were (Table 3). Compared with nonsmokers, smokers and former smokers at the time of the multiphasic health checkup visit were more likely to develop pancreatic cancer; this effect was greater for heavy smokers (OR of 2.4 for ≥1 pack a day, and in a separate analysis, OR of 3.4 for ≥2 packs a day).

In a multivariate analysis, infection with *H. pylori* was not associated with pancreatic cancer (adjusted OR, 0.85; 95% CI, 0.49-1.48) whereas smoking and a greater number of years of education were found to have an independent positive association with the malignancy (Table 4). When systematically checked for combined effects of certain risk factors, a positive interaction was found between education and *H. pylori* infection for the

risk of pancreatic cancer (P for interaction = 0.02). In the less educated group, *H. pylori* infection was associated with a lower OR, and smoking was a stronger risk factor; in the more educated group, neither *H. pylori* nor smoking was significantly associated with the risk of cancer. However, with Bonferroni adjustment for multiple comparisons, the P value for interaction was no longer significant (corrected P = 0.12). No other combined effect of risk factors was found statistically significant.

Seropositivity for the CagA protein of *H. pylori* was not independently associated with pancreatic cancer, neither when compared with those who tested negative to both CagA and *H. pylori* (Table 4) nor when compared with those testing negative to only CagA protein (OR, 1.04; 95% CI, 0.59-1.83).

Among men and White men only, seropositivity for *H. pylori* or its CagA protein was not a significant risk factor for pancreatic cancer (Table 5); among White male smokers, however, the association of *H. pylori*, and especially its CagA protein, with pancreatic cancer was more pronounced but still not significant (OR, 1.56; 95% CI, 0.57-4.30 and OR, 2.59; 95% CI, 0.90-7.42, respectively).

No association was found between date of collection (as a marker for length of storage) and *H. pylori* positivity (in the multivariate model OR, 0.9; 95% CI, 0.9-1.1). Similarly, sera known to have been thawed were no more or less likely to be *H. pylori* positive (OR, 0.8; 95% CI, 0.3-2.5). To assess effects of changes to ELISA over the years, 40 *H. pylori*–positive and 20 *H. pylori*–negative gastric control sera and 40 *H. pylori*–positive and 20 *H. pylori*–negative colon cancer controls were retested using the newer ELISA. Nine of 40 (23%) gastric cancer controls, which originally tested positive (and were considered as positive in the study), retested as negative with the newer ELISA. Only 1 of 40 (3%) *H. pylori*–positive colon cancer controls retested as negative. None of the negative controls retested positive. Previously

Table 2. Demographic characteristics and risk factors for pancreatic cancer among selected pancreatic cases and matched controls

Variables	Cases, n = 104	Controls, n = 262	
Gender,* n (%)			
Female	53 (51.0)	132 (50.4)	
Male	51 (49.0)	130 (49.6)	
Race,* n (%)			
Black	20 (19.2)	35 (13.4)	
White	83 (79.8)	226 (86.2)	
Other	1 (1)	1 (0.4)	
Age at MHC,* y			
Mean (SD)	49.5 (9.2)	50.3 (8.8)	
Year of MHC,* n (%)			
1964-1965	37 (35.6)	101 (38.5)	
1966-1967	47 (45.2)	106 (40.5)	
1968-1969	20 (19.2)	55 (21.0)	
Site of MHC,* n (%)			
Oakland	54 (51.9)	130 (49.6)	
San Francisco	50 (48.1)	132 (50.4)	
Education, n (%)			
Less than high school	16 (15.4)	59 (22.5)	P = 0.01
High/business school	34 (32.7)	112 (42.7)	
College and beyond	54 (51.9)	91 (34.7)	
Smoking, n (%)			
Never	26 (25.0)	108 (41.2)	P = 0.03
Former	19 (18.3)	40 (15.3)	
<1 pack/d	29 (27.9)	59 (22.5)	
≥1 pack/d	30 (28.8)	54 (20.6)	
No amount stated	0 (0)	1 (0.4)	
Alcohol, n (%)			
Never	19 (18.3)	60 (22.9)	P = 0.04
Former	3 (2.9)	11 (4.2)	
<2 drinks/d	73 (70.2)	137 (52.3)	
≥2 drinks/d	6 (5.8)	33 (12.6)	
No amount stated	3 (2.9)	21 (8.0)	
BMI, n (%)			
<25	57 (54.8)	139 (53.1)	P = 0.9
≥25 and <30	36 (34.6)	96 (36.6)	
≥30	11 (10.6)	27 (10.3)	
Diabetes mellitus, n (%)			
Never diagnosed	101 (97.1)	253 (96.6)	P = 0.9
Ever diagnosed	3 (2.9)	9 (3.4)	
H. pylori, n (%)			
HP negative	53 (51.0)	107 (40.8)	P = 0.08
HP positive	51 (49.0)	155 (59.2)	
CagA protein, n (%)			
CagA negative	67 (64.4)	151 (57.6)	P = 0.7
CagA positive	33 (31.7)	83 (31.7)	
Indeterminate	4 (3.9)	28 (10.7)	

NOTE: P values for comparisons between cases and controls were obtained using χ^2 and Fisher exact tests for general association, testing the difference of distribution between cases and controls.
*Matching variable.

Table 3. Unadjusted ORs for the association between risk factors and subsequent development of pancreatic cancer

Risk factors	Unadjusted OR* (95% CI)	P
H. pylori IgG serology		
Negative	1.00	0.13
Positive	0.68 (0.41-1.12)	
H. pylori CagA serology †		
IgG negative and CagA negative	1.00	
IgG positive and CagA negative	0.85 (0.48-1.53)	0.60
IgG positive and CagA positive	0.88 (0.46-1.69)	0.70
BMI		
Normal (<25)	1.00	
Overweight (≥25 and <30)	0.95 (0.57-1.60)	0.87
Obese (≥30)	0.99 (0.44-2.25)	0.92
Cigarette smoking		
Never	1.00	
Former	2.32 (1.12-4.80)	0.02
<1 pack/d	2.06 (1.09-3.91)	0.03
≥1 pack/d	2.44 (1.26-4.73)	0.008
Education		
Less than high school	1.00	
High/business school	1.17 (0.57-2.40)	0.67
College and beyond	2.69 (1.30-5.56)	0.007
Alcohol consumption		
Never	1.00	
Former	0.88 (0.22-3.56)	0.86
≤2 drinks/d	1.93 (0.99-3.75)	0.05
>2 drinks/d	0.62 (0.21-1.85)	0.39
Diabetes mellitus		
Never diagnosed	1.00	
Ever diagnosed	0.93 (0.25-3.44)	0.91

*Unadjusted effects of the variables of interest were obtained by fitting a univariable conditional logistic regression model for each of the covariates. Twenty-four drinkers and one smoker with ''no amount stated'' have been excluded from this particular analysis.
†A separate analysis was conducted to test for the effect of *H. pylori* CagA protein. Six cases and three controls were both IgG negative and CagA positive; they were excluded from this separate CagA analysis. Redoing the analysis with these subjects counted as *H. pylori* positive gave similar results.

Table 4. Adjusted ORs for the association between risk factors and subsequent development of pancreatic cancer

Risk factors	Adjusted OR* (95% CI)	*P*
H. pylori IgG serology		
Negative	1.00	0.57
Positive	0.85 (0.49-1.48)	
H. pylori CagA serology †		
IgG negative and CagA negative	1.00	
CagA negative vs uninfected	1.01 (0.54-1.91)	0.96
CagA positive vs uninfected	0.96 (0.48-1.92)	0.91
Cigarette smoking		
Never	1.00	
Ever	2.09 (1.17-3.74)	0.01
Former	2.20 (1.04-4.63)	0.04
<1 packs/d	1.93 (1.01-3.73)	0.04
≥2 packs/d	2.43 (1.23-4.82)	0.01
Education		
Less than college	1.00	
College and beyond	2.13 (1.23-3.69)	0.01

*ORs obtained by conditional logistic regression and adjusted for the two other variables in the table. The variables BMI, alcohol consumption, and diabetes mellitus did not have any significant effect and were not kept in the final model.

†A separate multivariate analysis was conducted to test for the effect of the *H. pylori* CagA protein. Six cases and three controls were both IgG negative and CagA positive; they were excluded from this analysis. Redoing the analysis with these subjects counted as *H. pylori* positive gave similar results.

tested quality control sera sent by the Orentreich Foundation were tested along with case sera in a blinded fashion and had a 94% test-retest concordance.

Separate unmatched analysis using the initial 141 cases and 730 controls yielded similar results (OR, 0.75; 95% CI, 0.5-1.1) and showed that the association between *H. pylori* and pancreatic cancer was stable across comparison groups, suggesting that batch effects and minor changes in testing over time did not influence the results.

Discussion

In this nested case-control study conducted among a large Northern California-based cohort, subjects showing infection with *H. pylori* by seropositivity to it or its CagA protein were no more likely than uninfected subjects to develop pancreatic cancer. Two previous observational studies reported that infection with *H. pylori* might also be a risk factor for pancreatic cancer (6, 7). Our data do not confirm these suggestive results. An ongoing large cohort study being conducted in Sweden also has not yet found any such association and is in agreement with our negative findings (17).

Smoking, one of the few risk factors for pancreatic cancer consistently found in the literature, was also a noted risk factor in our study. Evidence linking alcohol consumption to cancer of the exocrine pancreas has been inconsistent, and our study, in agreement with a review by the IARC monograph, found no association with pancreatic cancer (18). Similarly, we found no association with BMI or with diabetes mellitus. Whereas the data of three recent large studies showed a significant positive association between BMI and cancer, the results of a 2003 meta-analysis showed a weak summary relative risk per unit increase in BMI of 1.02 (95% CI, 1.01-1.03), and the authors could not exclude the possibility of confounding (19-22). Another recent meta-analysis of 36 studies on the relation between type II diabetes and pancreatic cancer found an increased summary risk of 1.82 (95% CI, 1.66-1.89; ref. 23). The absence of effect seen in our study may be due to the low prevalence of diabetes mellitus compared with that of other risk factors or to our incapacity to distinguish between type I and type II diabetes.

Despite the matching process, cases and controls in the current study differed slightly in terms of race (19.2% Black among cases versus 13.4% among controls; Table 1). However, because African American race is one of the few known risk factors for pancreatic cancer and is also a risk factor for *H. pylori*, the resulting bias would have been toward a positive association, not against it.

Table 5. Adjusted ORs and 95% CIs for the association between risk factors and subsequent development of pancreatic cancer in various subgroups

Risk factors	OR* (95% CI)		
	Male subjects only	White male subjects only	White male smokers
H. pylori IgG serology			
Negative	1.00	1.00	1.00
Positive	0.69 (0.31-1.53)	0.80 (0.35-1.85)	0.85 (0.32-2.30)
H. pylori CagA serology †			
IgG negative and CagA negative	1.00	1.00	1.00
CagA negative vs uninfected	0.70 (0.25-1.91)	0.84 (0.29-2.46)	1.56 (0.57-4.30)
CagA positive vs uninfected	0.94 (0.38-2.36)	1.09 (0.38-3.11)	2.59 (0.90-7.42)
Cigarette smoking			
Never	1.00	1.00	NA
Ever	2.15 (0.83-5.57)	1.98 (0.74-5.34)	NA
Former	2.16 (0.66-7.04)	2.34 (0.72-7.59)	NA
<1 packs/d	2.00 (0.69-6.44)	1.69 (0.52-5.52)	NA
≥2 packs/d	2.39 (0.83-6.91)	2.00 (0.66-6.11)	NA
Education			
Less than college	1.00	1.00	1.00
College and beyond	1.47 (0.67-1.23)	2.17 (0.96-4.93)	2.00 (0.80-5.03)

Abbreviation: NA, not applicable.

*ORs obtained by conditional logistic regression and adjusted for the two other variables in the table.

†A separate multivariate analysis was conducted to test for the effect of the *H. pylori* CagA protein.

The relationship between socioeconomic status and pancreatic cancer remains unclear. Some studies, including a quite recent large prospective study, have found a positive association between higher socioeconomic status and pancreatic cancer, especially among women, whereas others have found inverse or no associations (24-27). Our study found a strong positive association between educational level and development of pancreatic cancer. The subjects recruited for our study all had identical access to medical care, and thus this association is not likely to be related to a diagnosis bias but rather to other unknown risk factors tied to educational level (e.g., diet), protective effect of previous contact with infectious agents other than *H. pylori*, and/or residual confounding (e.g., by smoking).

Strengths of our study include greater generalizability than previous studies, larger sample size, and decades of follow-up. Subjects were generally diverse in terms of age, gender, skin color, BMI, educational level, and smoking and alcohol consumption, all of which contributed to generalizability and allowed for greater ability to control for confounding in the analysis. Cases were randomly selected from incident pancreatic cancers in the multiphasic health checkup cohort. Controls were not primarily selected for this study but came from four previous studies where they had been selected to match previous cases of stomach adenocarcinoma, stomach lymphoma, colon cancer, and heart disease. In all of those studies, five variables (age, skin color, gender, year, and site of the multiphasic health checkup) were used to match cases and randomly selected controls, and the exact same matching variables were used in the present study, thereby suppressing the possibility of selection bias in the control group.

Our study has several limitations. First, the measured risk factors, including *H. pylori* infection status, were assessed only at the time of the multiphasic health checkup and might have subsequently changed. Such changes might unpredictably influence the associations found. Second, after the matching process, the study lost some of its power. It is therefore theoretically possible that a small true statistical association may have been missed. However, a separate unmatched analysis using the initial 141 cases and 730 controls (with enough power to detect similar associations than those found in previous studies) yielded null results, with a point estimate even lower than the null OR value of 1, consistently across control groups. Of greater concern is the difference between the two ELISA tests used for the different control groups. The low specificity of the early test may have resulted in a high false positive rate among the lymphoma and gastric cancer control subjects. The resulting overall bias would be against a positive association, and this is a concern because our study shows a null result when others have found positive results. We still believe our null results, however, for the following reasons: First, the lack of specificity issue only concerns two control groups of the four. Nevertheless, the *H. pylori*–positive rate does not differ significantly among control groups (Table 1). Second, even if half the positive test results among the gastric and lymphoma controls were false positive (more than twice the percentage suggested by the quality control results), the resulting crude OR would still be 1.02 and nonsignificant (95% CI, 0.65-1.61). In fact, it would take 100% error (suppose all the 56 controls from lymphoma and gastric studies who tested positive are false positive) to get a significant positive crude OR of 1.58 (95% CI, 1.00-2.50). Third, in separate unmatched analyses, the same null results have been consistently found when cases were analyzed against each control group. Finally, in a different study involving esophageal cancers and the same historical control groups, the same quality control concern made us start the study again using new matched controls that were shipped and tested with the more specific ELISA at the same time as the esophageal cases. Both esophageal studies (the first one using the same unmatched historical controls and the second one using matched new controls) found the same OR (28, 29). In summary, we acknowledge that the use of historical controls tested at different periods, some of them with a less specific ELISA, makes a definitive conclusion difficult to reach; the design of the study is not perfect. However, for us to have observed a positive association would have required such a difference in our serologic results too radical to be envisioned. Thus, we think that the null association found in this study reflects the truth in this large fairly representative U.S. cohort.

Considering the results of two previous studies investigating the association between *H. pylori* infection and pancreatic cancer, it is feasible that the relationship is not a simple one. It may be protective, deleterious, or null among different subsets of subjects, characterized by some still unrevealed genetic, immunologic, or environmental characteristic. For instance, a recent register-based retrospective cohort conducted in Sweden showed that the risk of pancreatic cancer was elevated in patients with gastric ulcer but not in patient with duodenal ulcer, contradicting the hypothesis that the presence of the bacteria per se contributes to malignancy. It is also possible that the current or previous studies are confounded by an unmeasured or poorly measured factor like socioeconomic status. For example, the small number of control subjects in the Austrian study prevented the authors to rigorously adjust for potential confounding variables (6). Finally, another possibility would be that previous findings were the consequence of a positive cross-reaction with another *Helicobacter* species, as hypothesized by Nilsson et al. (30), prevalent in some part of the world and not in others.

In conclusion, our study finds that infection with *H. pylori* is not a risk factor for development of pancreatic cancer. Additional factors such as occupational and environmental exposures, dietary habits, genetics, immunology, and site of infection might be warranted in subsequent studies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank Natalia Udaltsova and Shufang Yang for data management and serum testing, respectively, and Nancy P. Durr of Orentreich Foundation for the Advancement of Science for editorial assistance.

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