
Helicobacter pylori Seropositivity as a Risk Factor for Pancreatic Cancer

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Background: Pancreatic cancer is among the most fatal cancers worldwide and one for which few preventable risk factors have been established. Gastric carriage of *Helicobacter pylori*, particularly cytotoxin-associated gene-A-positive (CagA+) strains, is known to be a risk factor for peptic ulcer disease and gastric cancer and may have a similar etiologic relationship with pancreatic cancer. **Methods:** We investigated the association of *H. pylori* carriage and exocrine pancreatic cancer in a nested case-control study within the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort of 29 133 male Finnish smokers aged 50–69 years at baseline. Case subjects (n = 121) were matched on date of baseline serum collection, study center, age, trial intervention, and completion of the dietary questionnaire to 226 control subjects who were alive at the time the matching case subject was diagnosed and who remained free of cancer, during up to 10 years of follow-up. Levels of immunoglobulin G antibodies to *H. pylori* whole-cell and CagA+ antigens from stored baseline serum were measured by enzyme-linked immunosorbent assay. Smoking-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by use of conditional logistic regression. Statistical tests were two-sided. **Results:** Seroprevalence of *H. pylori* was 82% and 73% among case and control subjects, respectively. Compared with seronegative subjects, those with *H. pylori* or CagA+ strains were at statistically significantly elevated risk of pancreatic cancer (OR = 1.87 [95% CI = 1.05 to 3.34]; OR = 2.01 [95% CI = 1.09 to 3.70], respectively). **Conclusions:** Our findings support a possible role for *H. pylori* carriage in the development of exocrine pancreatic cancer. [J Natl Cancer Inst 2001;93:937–41]

Exocrine pancreatic cancer is among the most fatal cancers worldwide and one for which few preventable risk factors have been established (e.g., smoking) (1). Gastric carriage of *Helicobacter pylori* is known to be a risk factor for peptic ulcer disease (2), gastric cancer (2), and mucosa-associated lymphoid tissue lymphoma (3), with cytotoxin-associated gene-A-positive (CagA+) strains having a greater propensity for inflammation, ulceration, and malignancy (2). Furthermore, a history of gastrectomy for benign conditions such as peptic ulcer disease has been associated with increased pancreatic cancer risk 20 or more years after surgery (4,5), suggesting a possible relationship between *H. pylori* and pancreatic carcinogenesis that is supported by one case-control study (6).

From 1985 through 1988, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study (7), a randomized controlled trial of α -tocopherol and β -carotene supplementation for the prevention of cancer, collected and stored serum for 29 133 participants. We conducted a nested, prospective case-control investigation of the relationship between antibodies to *H. pylori* whole-cell (WC) and CagA antigens and exocrine pancreatic cancer to determine whether carriage of *H. pylori* or particular strains was associated with risk of acquiring the tumor.

SUBJECTS AND METHODS

Study Population

The ATBC Study was a double-blind, placebo-controlled, 2 × 2 factorial design primary prevention trial that tested whether α -tocopherol or β -carotene could reduce the incidence of cancer among male smokers. Study rationale, design, and methods have been described previously (7,8). From 1985 through 1988, a total of 29 133 eligible men in southwestern Finland, aged 50–69 years, who smoked at least five cigarettes per day, were randomly assigned to receive either active supplements or placebo. Men were excluded from the study if they had a history of malignancy other than nonmelanoma cancer of the skin or carcinoma *in situ*, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, or other medical conditions that might limit long-term participation, if they were receiving anticoagulant therapy, or if they used supplements containing vitamin E (>20 mg/day), vitamin A (>20 000 IU/day), or β -carotene (>6 mg/day). All of the study participants provided written informed consent before randomization, and the study was approved by the institutional review boards of both the National Public Health Institute (Helsinki, Finland) and the U.S. National Cancer Institute (Bethesda, MD).

Participants completed questionnaires on general

background characteristics, including medical, smoking, and dietary histories during their prerandomization baseline visit. Diet was assessed with a validated self-administered dietary history questionnaire that determined the frequency of consumption and the usual portion size of 276 food items during the past year, with the use of a color-picture booklet as a guide for portion size (9). The dropout rate during the trial was similar (30.1%–31.3%) for all four treatment groups (α -tocopherol, β -carotene, ATBC, and placebo) (7).

Ascertainment of Case Subjects and Control Subjects

All cases of pancreatic cancer diagnosed from January 1985 through December 1995 were identified through the Finnish Cancer Registry and death certificates. The Finnish Cancer Registry provides almost 100% case ascertainment in Finland (10,11). Medical records were reviewed centrally by two study oncologists (7) and the histopathologic and cytologic specimens by one or two pathologist(s) for diagnostic confirmation (7). Only cases confirmed by the study physicians as incident primary malignant neoplasms of the exocrine pancreas (International Classification of Diseases, 9th Revision [ICD-9]-157 (12), excluding islet cell carcinomas, ICD-9-157.4) were included in this analysis (n = 130). The interval between baseline serum collection and diagnosis was up to 10 years (median follow-up time, 4.6 years [range, 0.06–10 years]), and the median age at diagnosis was 64 years (range, 50–76 years).

Control subjects were selected from among ATBC Study participants who were alive at the time the matching case subject was diagnosed and free from cancer (except nonmelanoma skin cancer) as of December 1995. Two control subjects were matched to each case subject by age (± 5 years), month of baseline blood draw, completion of dietary history, study center, and intervention group assignment.

Of the 130 pancreatic cancer case subjects and the 260 matched control subjects, 123 case subjects and 239 control subjects had sufficient baseline serum for measurement of *H. pylori* WC and CagA strains; of these, 121 case subjects had matched control sub-

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jects (n = 226). Thirty-one percent, 16%, 27%, and 26% of the case and control subjects were in the placebo, β -carotene alone, α -tocopherol alone, and α -tocopherol/ β -carotene intervention groups, respectively.

Biomarkers

Fasting serum was collected at the prerandomization baseline visit and stored at -70°C . Frozen baseline serum samples for both case and control subjects were assayed for antibodies to *H. pylori* WC and CagA antigen with previously described and validated methods (13–15). Serology for immunoglobulin G (IgG) antibodies to *H. pylori* WC was determined by antigen-specific enzyme-linked immunosorbent assay (ELISA), which was prepared from a pool of sonicates of WC antigens from five different clinical *H. pylori* isolates (13,15). Serum IgG-specific antibodies to the CagA antigen were determined by ELISA by use of a purified truncated recombinant protein (orv220) from *Escherichia coli* (Peptide Therapeutics, Cambridge, MA). Serum samples were diluted 1 : 800 and 1 : 100, respectively, for the *H. pylori* WC and CagA antigen determinations, and optical density for each was calculated from the mean reading of duplicate assays of the same sera, run on separate days. Individuals were considered to be seropositive if the optical density of the IgG antibodies for *H. pylori* WC was greater than or equal to 1.0 or for CagA was greater than or equal to 0.35. Overall disagreement for *H. pylori* classification between the first and second run was 8%. For those samples with discordant *H. pylori* classification between the duplicate assays, a third run was performed. After the third assay, the assay with the greatest variation from the other two assays was discarded, and the results of the remaining two assays were averaged. The sensitivity and specificity for the *H. pylori* WC assay are both more than 92% (13) and for the CagA assay are 94% and 93%, respectively (14).

Case and control specimens were handled in the same standard manner, and the laboratory was blinded to case–control status. Matched serum case and control samples were analyzed consecutively as triplets within batches, and blinded replicate quality-control phantom samples (one *H. pylori*-seropositive and one -seronegative subject) were placed toward the beginning and end of each batch, constituting approximately 10% of each batch. The intrabatch and interbatch coefficients of variation were 8.6% and 19.6%, respectively, for the *H. pylori* WC assay and 8.2% and 26.6%, respectively, for the CagA assay. The high interbatch coefficient of variation for *H. pylori* WC and CagA could potentially lead to misclassification of the exposure and influence risk estimates. However, the percent agreement for classifying *H. pylori* seropositivity based on cut points for the blinded repeated samples was 100%.

Previously measured serum nutrients were evaluated as confounders of the main effects. Baseline serum α -tocopherol and β -carotene were measured for all of the participants in the ATBC Study by high-performance liquid chromatography (7), and serum total homocysteine, folate, pyridoxal-5'-phosphate, and vitamin B₁₂ were measured for subjects in this substudy, with the methods described previously (16).

Statistical Analysis

H. pylori serology was defined as negative (having antibodies to neither WC nor CagA antigens), positive (having antibodies to WC and/or CagA+ antigens), positive with CagA-negative (CagA–) strain (having antibodies to WC but not to CagA+ antigen), or positive with CagA+ strains (having antibodies to CagA+ antigen). A small proportion of subjects were *H. pylori* WC negative and CagA+ (three case subjects, ~2.5%; eight control subjects, ~3.5%), and these were combined with those who were *H. pylori* WC positive and CagA+ to form the CagA+ category. Other relevant variables examined as potential confounders were age; smoking history; educational level; history of diabetes, ulcer (peptic or duodenal), pancreatitis, or gallstones; dietary nutrients (energy, protein, carbohydrate, fat, saturated fat, fiber, carotenoids, vitamins C, E, B₆, and B₁₂, folate, methionine, sodium, nitrate, and nitrite); foods (fruit, citrus fruit, vegetables [fresh, cooked and cruciferous], roots, legumes, sausages, and cold cuts); alcohol and coffee intake; and serum nutrients (α -tocopherol, β -carotene, folate, vitamin B₁₂, pyridoxal-5'-phosphate, and total homocysteine).

Dietary nutrients highly associated with energy were energy adjusted by use of the residual method described by Willett and Stampfer (17), and nutrients not normally distributed were log-transformed for energy adjustment. Selected characteristics of the case and control subjects (and by *H. pylori* serology among the control subjects) were compared with the use of nonparametric Wilcoxon rank-sum and chi-squared tests. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals for pancreatic cancer with subjects testing negative for *H. pylori* as the reference category; indicator variables for *H. pylori* positive with CagA+ and positive with CagA– categories were included in the model. Multivariable models were developed by individually adding covariates to the model; continuous variables were included in the models if they were associated with both the disease and the risk factor, had a chi-squared *P* value of less than or equal to .20 in the full model, and changed the risk estimate by greater than or equal to 10%.

All statistical analyses were performed by use of Statistical Analysis Software (SAS) software (SAS Institute, Inc., Cary, NC). All statistical tests were two-tailed and were considered to be statistically significant at the .05 level. Because case and control subjects were matched, the median values, proportions, and risk estimates (including those labeled as crude) should be interpreted as being adjusted for the matching factors.

RESULTS

Compared with control subjects, case subjects smoked statistically significantly more pack-years ($P = .03$) and had statistically significantly lower serum folate ($P = .03$), pyridoxal-5'-phosphate ($P = .009$), and α -tocopherol ($P = .007$) concentrations (Table 1). Case subjects did not statistically significantly differ from control subjects with respect to other nutrients and foods. *H. pylori* seropositivity tended to be associated with a history of

ulcer disease and CagA+ strains associated with a history of ulcer disease and gallstones (Table 2), although the associations were not statistically significant. In addition, subjects with *H. pylori* tended to have lower intake of fiber, vegetables, roots, potatoes, carotenoids, vitamin C, folate, vitamin B₆, and nitrite, as well as lower serum folate, vitamin B₁₂, and vitamin B₆ (data not shown).

Case subjects were somewhat more likely than control subjects to have *H. pylori* (82% versus 73%; $P = .07$) and CagA+ strains (60% versus 51%; $P = .05$) (Table 3). Men testing positive for *H. pylori* were nearly twice as likely to have developed pancreatic cancer as those who did not (Table 3), with the association becoming stronger and statistically significant after adjustment for years of smoking. This relationship appeared stronger for CagA+ than for CagA– strains (Table 3). These relationships were similar for tumors located in the head, body, and tail of the pancreas and when early follow-up cancers (i.e., those diagnosed within the first 2 years) were excluded. Educational level, dietary nutrients, alcohol and coffee intake, nutritional status, and disease history status did not confound our results.

DISCUSSION

To our knowledge, this is the first prospective study to observe a statistically significant relationship between carriage of *H. pylori* and pancreatic cancer. The risk appeared to be the greatest for those with the CagA+ strains, which is consistent with its greater virulence and carcinogenic potential, and thus propensity to cause disease in humans (18), including a stronger observed relationship with gastric cancer.

Our results are consistent with the only published case–control study (6) to our knowledge that has examined *H. pylori* and pancreatic cancer. That study found greater *H. pylori* seropositivity among 92 pancreatic cancer case subjects (65%) than among 62 control subjects (45%; control subjects had either colorectal cancer or no disease) and showed a similar significant doubling of risk. In that study, there was no evidence of inflammation or *H. pylori* colonization in the pancreatic tumor or surrounding tissue in a small subset of 20 specimens (6), a finding consistent with processes occurring in the stomach whereby *H. pylori* disappears as chronic atrophic gastritis and extensive

Table 1. Selected baseline characteristics of case and control subjects (median and interquartile range or proportion)

Characteristic	Case subjects (n = 121)	Control subjects (n = 226)	Two-sided P*
Age, y (range)	58 (56–63)	58 (55–63)	.79
Primary school education or less, %†	80	80	.99‡
Living in a city, %	48	42	.34‡
History of, %			
Peptic or duodenal ulcer	18	24	.19‡
Pancreatitis	1.7	1.8	1.00§
Gallstones	5.0	5.8	.76‡
Diabetes mellitus	9.1	4.9	.12‡
Smoking habits			
Total cigarettes smoked/day (range)	20 (15–25)	20 (12–25)	.18
Years of smoking, y (range)	40 (33–44)	39 (32–43)	.09
Pack-years (range)	38 (26–50)	35 (22–45)	.03
Energy intake, kcal/day (range)	2566 (2145–3010)	2666 (2234–3201)	.10
Alcohol intake, g/day (range)	8.3 (2.4–22.9)	11.9 (2.9–27.8)	.28
Coffee intake, g/day (range)	600 (440–660)	550 (330–700)	.42
Serum folate, ng/mL (range)	3.55 (2.91–4.24)	3.73 (3.08–4.95)	.05
Serum pyridoxal-5'-phosphate, pmol/mL (range)	26.7 (21.2–39.0)	31.9 (23.3–45.9)	.009
Serum α -tocopherol, cholesterol adjusted, mg/L (range)	11.2 (9.7–12.8)	12 (10.6–13.2)	.006

*Wilcoxon rank sum test, except where indicated.

†Sixth to 8th grade education or less.

‡Chi-squared test.

§Fisher's exact test.

||Pack-years = number of packs smoked per day \times number of years.**Table 2.** Selected characteristics of control subjects by *Helicobacter pylori* and cytotoxin-associated gene-A (CagA) strain serology (median and interquartile range or proportion)

Characteristic	<i>H. pylori</i> serology			Two-sided P†	
	Negative (n = 61)	Positive* (n = 165)	Positive with CagA+ (n = 115)	Negative versus positive	Negative versus CagA+
Age, y (range)	58 (55–62)	58 (55–63)	59 (56–63)	.71	.26
Body mass index (range)‡	26.8 (24.5–28.2)	25.7 (23.6–28.4)	25.9 (23.7–28.8)	.24	.37
History of, %					
Peptic or duodenal ulcer	16.4	27.3	27.8	.09	.09§
Pancreatitis	0	2.4	3.0	.58§	.55
Gallstones	1.6	7.3	9.6	.19§	.06
Diabetes mellitus	6.6	4.2	2.6	.49§	.24
Elementary school education or less, %	75	82	83	.28	.17§
Living in a city, %	43	42	39	.91	.65§
Smoking habits					
Years of smoking (range)	38 (33–43)	38 (32–43)	40 (33–43)	.67	.87
Total cigarettes smoked/day (range)	20 (13–25)	20 (12–25)	20 (12–25)	.51	.52
Pack-years (range)	38 (22–48)	34 (22–44)	35 (22–45)	.27	.44
Alcohol intake, g/day (range)	18.3 (5.3–26.2)	10.7 (2.3–28.2)	10.7 (1.8–30.3)	.16	.14
Coffee intake, g/day (range)	550 (420–660)	600 (330–750)	660 (440–750)	.39	.19

*Positive for *H. pylori* whole cell and/or CagA+.

†Wilcoxon rank sum test, except where indicated.

‡Body mass index = weight in kilograms/height in meters squared.

§Chi-squared test.

||Fisher's exact test.

||Pack-years = number of packs smoked per day \times number of years.

intestinal metaplasia replace normal mucosae (2).

H. pylori has been implicated as a carcinogenic factor for noncardia gastric cancer and causes a persistent inflammatory-proliferative state that evolves from

chronic superficial gastritis to precancerous atrophic gastritis, metaplasia, and dysplasia (2). Given recent evidence that chronic pancreatitis has been associated with pancreatic cancer (19), pathologic consequences of *H. pylori* similar to those

observed in gastric tissue could also be postulated for the pancreas. Two studies (20,21), limited by small sample sizes and in populations with low *H. pylori* seroprevalence, have not shown a difference in the seroprevalence of antibodies to *H.*

Table 3. Crude* and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer and *Helicobacter pylori* and cytotoxin-associated gene-A (CagA) strain serology

<i>H. pylori</i> serology	Case subjects		Control subjects		Crude OR* (95% CI)	Adjusted OR* [†] (95% CI)
	No.	%	No.	%		
Negative	22	18	61	27	1.00 (referent)	1.00 (referent)
Positive [‡]	99	82	165	73	1.71 (0.97–3.01)	1.87 (1.05–3.34)
Positive with CagA-§	26	21	50	22	1.48 (0.75–2.91)	1.65 (0.82–3.29)
Positive with CagA+	73	60	115	51	1.85 (1.02–3.36)	2.01 (1.09–3.70)

*Interpreted as adjusted for the matching factors (age, month of blood draw, completion of dietary history, study center, and intervention group assignment).

[†]Additionally adjusted for years smoked.

[‡]Positive for *H. pylori* whole cell and/or CagA+.

§Compared with *H. pylori* negative and adjusted for *H. pylori* positive with CagA+.

||Compared with *H. pylori* negative and adjusted for *H. pylori* positive with CagA-.

pylori between subjects with and without chronic pancreatitis. However, to investigate the observation that subjects with chronic pancreatitis have a high prevalence of duodenal ulcers (22–24), Niemann et al. (25) showed a significantly higher *H. pylori* seroprevalence in subjects with chronic pancreatitis complicated by duodenal ulcer compared with control subjects with nonorganic abdominal pain ($P = .002$) or subjects with chronic pancreatitis without duodenal ulcer ($P = .04$) but not compared with control subjects with simple duodenal ulcer without pancreatitis. With regard to adjacent organs, *H. pylori* has an established role in the etiology of duodenal ulcer (26) and has been identified in liver biopsy specimens of patients with biliary inflammation (27). Whether or not pancreatic colonization by *H. pylori* exists is unknown and perhaps should be examined in asymptomatic subjects. Other possible mechanisms for the association between *H. pylori* and pancreatic cancer include changes in gastrin (increased secretion) and somatostatin (low number of antral somatostatin cells) resulting from *H. pylori* gastritis (28–31). For example, elevated gastrin could stimulate pancreatic growth (32), with associated proliferation potentially increasing the susceptibility of the pancreas to carcinogens, and diminished somatostatin could also allow for increased pancreatic cancer growth (33). Pernicious anemia, a condition marked by hypergastrinemia, has been associated with pancreatic cancer (34,35). Alternatively, the increased formation of *N*-nitroso compounds produced by hypochlorhydria-related gastric bacterial overgrowth could be another carcinogenic mechanism. Finally, *H. pylori*, especially CagA+ status, may represent a marker of another gastrointestinal colonizing or in-

fecting organism that may be a risk factor for pancreatic cancer.

In our study, persons with prior cholelithiasis or peptic ulcer disease were more likely to be seropositive for *H. pylori* and CagA+ strains, although the proportion who had a history of either disease was small and the number of case and control subjects with the conditions did not statistically significantly differ. Cholecystectomy (1,36) and duodenal ulcer disease (37) diagnosed up to 20 years earlier have been associated with subsequent pancreatic cancer, although for neither diagnosis are the data consistent (36,37). Subjects who were seropositive for *H. pylori* are often asymptomatic—i.e., without dyspeptic symptoms (38). Combined with the current findings, such studies suggest that persons with *H. pylori* could have subclinical inflammation or disease.

In conclusion, our study suggests that *H. pylori* carriage may be a risk factor for pancreatic cancer. Strengths of this study include the prospective nature of the blood collection (i.e., 1–10 years before diagnosis of the cancer), a relatively large sample size, and a control group derived from the same study cohort. The associations between *H. pylori* and CagA+ strains and pancreatic cancer are temporally related, biologically plausible, and similar to associations observed for cancer of the stomach. Because the subjects in this study were male smokers, our findings may not be generalizable to other nonsmoking populations, and caution is justified in the interpretation of our results. Our observed associations became stronger after controlling for years of smoking, however, and are in accord with those seen in the other published case-control study (6). Evaluation of this relationship in additional studies appears warranted to confirm or refute our find-

ings and to understand potential mechanisms.

REFERENCES

- (1) Anderson KE, Potter JD, Mack TM. Pancreatic cancer. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 2nd ed. New York (NY): Oxford University Press; 1996. p. 725–71.
- (2) Forman D. *Helicobacter pylori* infection and cancer. Br Med Bull 1998;54:71–8.
- (3) Go MF, Smoot DT. *Helicobacter pylori*, gastric MALT lymphoma, and adenocarcinoma of the stomach. Semin Gastrointest Dis 2000;11:134–41.
- (4) Tersmette AC, Offerhaus GJ, Giardiello FM, Tersmette KW, Vandenbroucke JP, Tytgat GN. Occurrence of non-gastric cancer in the digestive tract after remote partial gastrectomy: analysis of an Amsterdam cohort. Int J Cancer 1990;46:792–5.
- (5) Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. J Natl Cancer Inst 1986;76:49–60.
- (6) Raderer M, Wrba F, Kornek G, Maca T, Koller DY, Weinlaender G, et al. Association between *Helicobacter pylori* infection and pancreatic cancer. Oncology 1998;55:16–9.
- (7) The ATBC Cancer Prevention Study Group. The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study: design, methods, participant characteristics, and compliance. Ann Epidemiol 1994;4:1–10.
- (8) The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. N Engl J Med 1994;330:1029–35.
- (9) Pietinen P, Hartman AM, Haapa E, Rasanen L, Haapakoski J, Palmgren J, et al. Reproducibility and validity of dietary assessment instruments. I. A self-administered food use questionnaire with a portion size picture booklet. Am J Epidemiol 1988;128:655–66.
- (10) Kyllonen LE, Teppo L, Lehtonen M. Completeness and accuracy of registration of colorectal cancer in Finland. Ann Chir Gynaecol 1987;76:185–90.
- (11) Pukkala E. Use of record linkage in small-area studies. In: Elliott P, Cuzick J, English D, Stern R, editors. Geographical and environmental epidemiology: methods for small-area studies. New York (NY): Oxford University Press; 1992. p. 125–31.
- (12) Physician ICD-9-CM. Salt Lake City (UT): Medicode, Inc.; 1997.
- (13) Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. Intrafamilial clustering of *Helicobacter pylori* infection. N Engl J Med 1990;322:359–63.
- (14) Blaser MJ, Perez-Perez GI, Kleanthous H, Cover TL, Peek RM, Chyou PH, et al. Infection with *Helicobacter pylori* strains possessing cagA is associated with an increased risk of developing adenocarcinoma of the stomach. Cancer Res 1995;55:2111–5.
- (15) Morris AJ, Ali MR, Nicholson GI, Perez-Perez GI, Blaser MJ. Long-term follow-up of volun-

- tary ingestion of *Helicobacter pylori*. *Ann Intern Med* 1991;114:662-3.
- (16) Stolzenberg-Solomon RZ, Albanes D, Nieto FJ, Hartman TJ, Tangrea JA, Rautalahti M, et al. Pancreatic cancer risk and nutrition-related methyl-group availability indicators in male smokers. *J Natl Cancer Inst* 1999;91:535-41.
- (17) Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;124:17-27.
- (18) Blaser MJ. The interaction of cag+ *Helicobacter pylori* strains with their hosts. In: Hunt RH, Tytgut GN, editors. *Helicobacter pylori*, basic mechanisms to clinical cure. Dordrecht (The Netherlands): Kluwer Academic Publishers; 1998. p. 27-32.
- (19) Lowenfels AB, Maisonneuve P, Lankisch PG. Chronic pancreatitis and other risk factors for pancreatic cancer. *Gastroenterol Clin North Am* 1999;28:673-85.
- (20) Manes G, Dominguez-Munoz JE, Hackelsberger A, Leodolter A, Rossner A, Malfertheiner P. Prevalence of *Helicobacter pylori* infection and gastric mucosal abnormalities in chronic pancreatitis. *Am J Gastroenterol* 1998;93:1097-100.
- (21) Savarino V, Mela GS, Zentilin P, Mansi C, Mele MR, Pandolfo N, et al. Circadian gastric acidity and *Helicobacter pylori* infection in patients with chronic pancreatitis. *Dig Dis Sci* 2000;45:1079-83.
- (22) James O, Agnew JE, Bouchier IA. Chronic pancreatitis in England: a changing picture? *Br Med J* 1974;2:34-8.
- (23) Dreiling DA, Naqvi MA. Peptic ulcer diathesis in patients with chronic pancreatitis. *Am J Gastroenterol* 1969;51:503-10.
- (24) Schulze S, Thorsgaard Pedersen N, Jorgensen MJ, Mollmann KM, Rune SJ. Association between duodenal bulb ulceration and reduced exocrine pancreatic function. *Gut* 1983;24:781-3.
- (25) Niemann T, Larsen S, Mouritsen EA, Thorsgaard N. *Helicobacter pylori* infection in patients with chronic pancreatitis and duodenal ulcer. *Scand J Gastroenterol* 1997;32:1201-3.
- (26) Parsonnet J. *Helicobacter pylori*. *Infect Dis Clin North Am* 1998;12:185-97.
- (27) Nilsson HO, Taneera J, Castedal M, Glatz E, Olsson R, Wadstrom T. Identification of *Helicobacter pylori* and other *Helicobacter* species by PCR, hybridization, and partial DNA sequencing in human liver samples from patients with primary sclerosing cholangitis or primary biliary cirrhosis. *J Clin Microbiol* 2000;38:1072-6.
- (28) Tham TC, Chen L, Dennison N, Johnston CF, Collins JS, Ardill JE, et al. Effect of *Helicobacter pylori* eradication on antral somatostatin cell density in humans. *Eur J Gastroenterol Hepatol* 1998;10:289-91.
- (29) Park SM, Lee HR, Kim JG, Park JW, Jung G, Han SH, et al. Effect of *Helicobacter pylori* infection on antral gastrin and somatostatin cells and on serum gastrin concentrations. *Korean J Intern Med* 1999;14:15-20.
- (30) Larsson LI. Developmental biology of gastrin and somatostatin cells in the antropyloric mucosa of the stomach. *Microsc Res Tech* 2000;48:272-81.
- (31) Fisher WE, Muscarella P, Boros LG, Schirmer WJ. Gastrointestinal hormones as potential adjuvant treatment of exocrine pancreatic adenocarcinoma. *Int J Pancreatol* 1998;24:169-80.
- (32) Chu M, Kullman E, Rehfeld JF, Borch K. Effect of chronic endogenous hypergastrinaemia on pancreatic growth and carcinogenesis in the hamster. *Gut* 1997;40:536-40.
- (33) Redding TW, Schally AV. Inhibition of growth of pancreatic carcinomas in animal models by analogs of hypothalamic hormones. *Proc Natl Acad Sci U S A* 1984;81:248-52.
- (34) Hsing AW, Hansson LE, McLaughlin JK, Nyren O, Blot WJ, Ekobom A, et al. Pernicious anemia and subsequent cancer. A population-based cohort study. *Cancer* 1993;71:745-50.
- (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.
- (36) Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe KD, Swanson GM, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. *Br J Cancer* 1999;80:1830-7.
- (37) Mills PK, Beeson WL, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer* 1988;61:2578-85.
- (38) Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. *Gastroenterology* 1992;102:41-6.

NOTES

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