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## History of peptic ulcer disease and pancreatic cancer risk in men

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### Abstract

**Background & Aims**—Peptic ulcer disease has been associated with an increased risk of pancreatic cancer, but findings on this topic are inconsistent. We investigated the association between pancreatic cancer and the occurrence of gastric or duodenal ulcer in a large, United States cohort.

**Methods**—We analyzed data collected from 51,529 male health professionals in a prospective cohort study. History of peptic ulcer disease was assessed at baseline in 1986 and updated biennially thereafter. Relative risks (RRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models adjusting for smoking, body mass index, diabetes, and physical activity.

**Results**—During 18 years of follow-up, we observed 274 incident pancreatic cancer cases. Compared to those with report of no peptic ulcer disease, men with gastric ulcer had an increased risk of pancreatic cancer (RR, 1.83; 95% CI:1.13–2.97). Although the risk was highest for those with a diagnosis of gastric ulcer that was close in time to the cancer diagnosis (RR, 3.66; 95% CI:1.45–14.924), the risk remained significantly increased 10–19 years after gastric ulcer diagnosis (RR, 2.89; 95% CI:1.26–6.64). In contrast, duodenal ulcer was not associated with pancreatic cancer risk (RR, 1.15; 95% CI:0.78–1.71).

**Conclusions**—Gastric ulcer increases the risk of pancreatic cancer, whereas there does not appear to be an association between duodenal ulcers and pancreatic cancer.

### Introduction

Pancreatic cancer is a rapidly fatal neoplasm with little effective treatment. In 2008, approximately 37,680 new cases are expected to occur in the United States and about the same

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number of people are expected to die from it<sup>1</sup>. The etiology of this malignancy remains poorly understood.

In recent years, the inflammatory response, N-nitrosamine formation and excess gastric/duodenal acidity have been proposed to be involved in the development of pancreatic cancer. Chronic inflammatory conditions, including chronic pancreatitis<sup>2</sup>, obesity<sup>3</sup>, periodontal disease<sup>3</sup> and *H. pylori* infection<sup>4, 5</sup> have been associated with high risk of pancreatic cancer. Nitrosamines can induce pancreatic cancer in animals<sup>6</sup>, and products containing high levels of nitrosamines, such as tobacco smoke, increase the risk of pancreatic cancer in human<sup>7</sup>. Hyperacidity, an alternative potential mechanism, leads to an increase of secretin which appears to have trophic effect on pancreatic growth and accelerate the development of nitrosamine-induced pancreatic ductal adenocarcinoma in hamsters<sup>7, 8</sup>.

Gastric ulcer is primarily associated with corpus-predominant *H. pylori* gastritis, low acid production and subsequent high intragastric N-nitrosamine concentration, whereas duodenal ulcer is accompanied by antrum-predominant *H. pylori* gastritis, hyperacidity and relatively low intragastric nitrosamine levels<sup>9, 10</sup>. Therefore, the relation of pancreatic cancer to these two types of peptic ulcer may provide some clues into different potential biological mechanisms in pancreatic carcinogenesis.

Results from previous studies on the association between history of peptic ulcer and pancreatic cancer risk are inconsistent. Of 12 such studies, five showed an elevated risk among patients with gastric ulcer<sup>11</sup>, duodenal ulcer<sup>12</sup> or with ulcers in general<sup>13–15</sup>, with the relative risks ranging from 1.2 to 2.8<sup>11–15</sup>; while others did not confirm these associations<sup>16–22</sup>. Most of these studies were relatively small and only three had a prospective design<sup>11, 13, 16</sup>; retrospective studies are more prone to recall and selection bias as well as reverse causation. Most studies<sup>13–16, 18, 19, 22</sup> lacked information on the type of ulcer and half of the studies<sup>11, 12, 14, 15, 19, 20</sup> were not able to adjust for cigarette smoking, which is consistently associated with both peptic ulcer disease and pancreatic cancer. In addition, among these 12 studies, only one study has examined the time-dependent effect of ulcer occurrence on pancreatic cancer risk<sup>11</sup>.

Given our limited understanding of pancreatic cancer etiology, further investigation into the role of peptic ulcers in pancreatic carcinogenesis is warranted. We therefore investigated the association between peptic ulcer disease and pancreatic cancer in a large prospective cohort of health professionals with detailed and updated data on ulcer history and cigarette smoking.

## Materials and Methods

### Study Population

The Health Professionals Follow-Up Study (HPFS) was initiated in 1986 when 51,529 predominantly white men ages 40–75 years answered a detailed mailed questionnaire on medical history, current diet, and life style habits<sup>3</sup>. Participants in this cohort are dentists (57.6%), veterinarians (19.6%), pharmacists (8.1%), optometrists (7.3%), osteopathic physicians (4.3%), and podiatrists (3.1%) living in 50 United States states. Every 2 years, follow-up questionnaires were mailed to surviving cohort members to update data on potential risk factors and to identify newly diagnosed cases of various diseases, including the diagnosis of peptic ulcer and pancreatic cancer. Deaths of most members of this cohort were reported by family members or by the postal service in response to questionnaire mailings. In addition, the National Death Index was searched biennially for nonrespondents, which has been shown to have a sensitivity of 98%<sup>23</sup>. Through 2004, the total follow-up rate was nearly 90%. The study was approved by the institutional review board of the Harvard School of Public health.

## Pancreatic Cancer Ascertainment

We requested permission to review the medical records from men who reported a pancreatic cancer on the biennial questionnaires between the return of the 1986 questionnaire and December 31, 2004. If the primary or secondary cause of death on the death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records to confirm the diagnosis. All medical records had complete information on histology. Approximately 95% of pancreatic cancer cases were confirmed by medical records, and the remaining cases were confirmed by death certificate, physician, or a family member.

## Identification of Peptic Ulcers

At baseline, participants were asked whether they ever had any history of peptic ulcer and the type of ulcer with an approximate time of occurrence (categories included: before 1955, 1955–64, 1965–74, 1975–79, and 1980–86). In the 1988 follow-up questionnaire, participants were asked about the type of ulcers they had in the past two years and the time of occurrence for each type (categories included: before 1986, 1986, 1987 and 1988). For the following biennial follow-up questionnaires, gastric and duodenal ulcers were assessed as one question ‘Have you had gastric or duodenal ulcer?’ and the year of diagnosis was also reported (with a category for diagnoses before the present follow-up cycle). To distinguish gastric ulcer from duodenal ulcer for the follow-up questionnaires, we reviewed the relevant medical records for self-reported ulcers shortly after receiving the completed biennial questionnaires. We defined gastric/duodenal ulcer as confirmed by gastrointestinal endoscopy. Over the years, we were able to retrieve medical records for 56% of self-reported ulcers that occurred during follow-up, among which 77% were confirmed after medical record review. Self-reported ulcers with no medical records obtained or unconfirmed by medical records were classified as not having peptic ulcer disease (57% of the ulcers that were reported during 1988–2002). Because medical records were retrieved right after the return of the biennial questionnaires, i.e., before occurrence of pancreatic cancer, missing data on ulcer status is not likely to be related to the outcome. To confirm this, we used chi-square test for the follow-up ulcers to examine the relation between missing medical records and pancreatic cancer. The p value from chi-square test was not significant ( $p=0.30$ ).

Our primary analyses were based on self-reported ulcers that were diagnosed before 1986 (82%) and confirmed incident ulcers during 1988–2002 (18%).

## Smoking History and Other Risk Factors

In the baseline and the subsequent questionnaires, participants provided information on their smoking status, time since quitting and average number of cigarettes smoked daily. Total pack-years of smoking were calculated to incorporate all past smoking experience. One pack-year is equivalent to having smoked one pack or 20 cigarettes per day over a year.

We asked participants about history of diabetes and periodontal disease at baseline and in the follow-up questionnaires. We used baseline body mass index (BMI) which has been shown to be predictive for pancreatic cancer risk in this cohort<sup>3</sup>. We derived a score for physical activity as metabolic equivalent tasks (MET) per week (the caloric need per kilogram body weight per hour activity divided by the caloric need per kilogram per hour at rest) based on the 1986 questionnaire. We also collected information on race, geographic regions, height, nonsteroidal anti-inflammatory drug use (NSAIDs), H<sub>2</sub>-receptor antagonist use (cimetidine and ranitidine; as one question), multivitamin use, alcohol intake and dietary factors from the baseline questionnaires.

## Statistical Analysis

We excluded participants who died before 1986 (n=4), those who reported a baseline history of cancer other than nonmelanoma skin cancer (n=2081), those who were less than 35 years old at the enrollment (n=1) and those who later requested to be removed from the study (n=33). After these exclusions, 49410 individuals were eligible for the analysis. We computed person-years of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (Dec 31, 2004), whichever occurred first. We calculated relative risks (RRs) and 95% confidence intervals (CIs) using Cox proportional hazards models stratified by age (months) and calendar time (2 years).

We updated status of gastric/duodenal ulcer over each 2-year cycle. Once the diagnosis was made, the individual was considered to always have ulcer throughout the analysis because peptic ulcer is a chronic disease with frequent relapses. Because gastric ulcer and duodenal ulcer have different pathophysiologies<sup>9, 10</sup>, we analyzed these two types of ulcer separately. We computed relative risks comparing the incidence of pancreatic cancer among participants who ever had gastric/duodenal ulcer with the incidence among participants who never had peptic ulcers. We then compared the risk among individuals with gastric or duodenal ulcer only with the risk among those without ulcers. In addition, we calculated the relative risk for having both types of ulcer (1% of the cohort), which could be an indicator for severe ulcers.

Because the diagnosis and treatment of peptic ulcer disease have improved over the past decades, we categorized participants according to calendar time of ulcer diagnosis in 4 categories: before 1974, 1975–86, 1987–2002 and unknown date, to study the secular trend in risk associated with ulcer status. To examine the time-dependent effects of ulcers, we performed a latency analysis using a piecewise function<sup>24</sup>: we categorized years since first ulcer diagnosis into quartiles and used indicators for each quartile in the models. For ulcers identified by the baseline questionnaire, a midpoint value was assigned to each time period of ulcer diagnosis (except for ulcer before 1955 which was assigned 1950); for ulcers that occurred during follow-up, the date of ulcer diagnosis was extracted from medical records. The quartile cutpoints were based on the distribution of years since first ulcer diagnosis among ulcer patients. To examine whether the association varied by age at ulcer diagnosis, we additionally categorized participants according to the age at the first ulcer diagnosis. The cutpoints were based on the median age at the first ulcer diagnosis among ulcer patients.

We further conducted stratified analyses to assess the possibility of any residual confounding and effect modification by cigarette smoking (never/ever), which is a strong risk factor for both peptic ulcer disease and pancreatic cancer. Because antioxidant compounds, such as vitamins C and E, have ability to inhibit the nitrosamine formation<sup>25, 26</sup>, we investigated whether vitamins C and E would modify the association between peptic ulcer disease and pancreatic cancer risk. We examined peptic ulcers and pancreatic cancer risk by levels of vitamins C and E intakes (low/high, use median intake as the cutpoint). P values for interactions were calculated using the likelihood ratio test (LRT).

In sensitivity analyses, we conducted a 2-year lag analysis to rule out the possibility that subclinical pancreatic cancer had occurred before ulcer diagnosis. We started the follow-up from 1988 for ulcers diagnosed before 1986 and allowed a 2-year lag for ulcers diagnosed between 1986 and 2002, i.e., each person-year was classified according to the ulcer status 2 year ago. We also repeated our analyses by excluding pancreatic cancer cases that were not confirmed through medical records (5% of the cases).

In multivariate models, we adjusted for cigarette smoking (never; quit  $\geq 15$  years; quit  $< 15$  years,  $\leq 25$  pack-years; quit  $< 15$  years,  $> 25$  pack-years; current  $\leq 25$  pack-years; current  $> 25$

pack-years), diabetes (yes/no), BMI ( $\text{kg}/\text{m}^2$ , <18.5, 18.5 - <25, 25 - <30, 30 - <35, > 35, and missing), and physical activity (quintiles), as these are known to be either established or possible risk factors for pancreatic cancer. Gastric ulcer and duodenal ulcer were mutually adjusted, if applicable. We further adjusted for a number of covariates which have been shown to be associated with pancreatic cancer risk in some studies<sup>3</sup>, including race/ethnicity, geographic regions, height, periodontal disease, NSAIDs use, multivitamin use, total calories, and intakes of fruits and vegetables, alcohol, coffee, vitamin C, vitamin D, vitamin E, calcium and sucrose. For these variables, we only kept in the models those that altered the ulcer-pancreatic cancer relative risk estimates by 10% or more. We additionally adjusted for H2-blocker use to examine whether the effect of ulcers on pancreatic cancer risk was mediated through H2-blockers, because H2-receptor antagonists such as Tagamet (cimetidine) and Zantac (ranitidine) have been used for the treatment of peptic ulcers since the late 1970s. An indicator variable for missing values of each covariate was created.

Most recently, we found an association between ABO blood group pancreatic cancer<sup>27</sup>. Because a link between blood type and peptic ulcer disease has been suggested for almost 50 years<sup>28</sup>, we further adjusted for blood groups (A, B, AB, and O) in the multivariate models. The follow-up for this additional analysis started from 1996 as blood type was assessed in the 1996 questionnaire.

The effect of misclassification of the self-reported baseline ulcers was evaluated by the method developed by Zucker and Spiegelman<sup>29</sup>, using data on follow-up ulcers as the validation. The positive predicted value (PPV) for this analysis was 0.77 and we assumed that individuals who never reported ulcer history were truly without peptic ulcer disease, i.e., negative predicted value (NPV) was 1. This assumption is likely to be valid given that participants were asked about ulcer history repeatedly in 8 follow-up questionnaires (1988–2002), and ulcer would be picked up if any one of them showed ulcer diagnosis. We further conducted a sensitivity analysis with NPV changing from 0.99 to 0.85. The results remained unchanged.

SAS statistical software (version 9.1; SAS Institute, Inc, Cary, NC) was used for all analyses. All statistical tests were two-sided; *P* values less than 0.05 were considered statistically significant.

## Results

With 798475 person-years accrued over 18 years of follow-up, 274 men were diagnosed with pancreatic cancer. At baseline, 3% of the participants reported ever having gastric ulcer, 6% reported ever having duodenal ulcer and 0.8% reported having both gastric and duodenal ulcer. Men with gastric ulcer were generally similar to men with duodenal ulcer. Compared to those without ulcers, individuals who reported history of peptic ulcer disease were more likely to be current smokers, had higher cigarette use (pack-years) and NSAID use, and less likely to exercise (Table 1).

Using self-reported data at baseline and updated data confirmed by medical records, we examined the relation of gastric ulcer or duodenal ulcer to the risk of pancreatic cancer. Gastric ulcer and duodenal ulcer were mutually adjusted in the models. Compared with those who never had ulcers, men who ever had gastric ulcers experienced a significant elevation in risk of pancreatic cancer (Table 2: age-adjusted RR, 1.88; 95% CI, 1.17 – 3.03). After additionally adjusting for smoking, history of diabetes, BMI and physical activity, the relative risk was similar and remained significantly increased (multivariable RR, 1.83; 95% CI, 1.13 – 2.97). In contrast, duodenal ulcer was not significantly associated with pancreatic cancer risk (multivariable RR, 1.15; 95% CI, 0.78 – 1.71). Similar findings were observed in the 2-year



lag analysis (for gastric ulcer: multivariable RR, 1.77; 95% CI, 1.09 – 2.88; for duodenal ulcer, multivariable RR, 1.24; 95% CI, 0.82 – 1.87).

We further computed the relative risks of pancreatic cancer for having gastric ulcer only, duodenal ulcer only, or both ulcers. Men with gastric ulcer only had an increased, albeit not statistically significant, risk of pancreatic cancer (11 pancreatic cancer cases; 17554 person-years; multivariable RR, 1.48; 95% CI, 0.79 – 2.77); men with duodenal ulcer only did not have increased risk (21 pancreatic cancer cases; 43323 person-years; multivariable RR, 1.02; 95% CI, 0.65 – 1.61); and men who had both ulcers had the highest risk (9 pancreatic cancer cases; 7030 person-years; multivariable RR, 2.85; 95% CI, 1.44 – 5.64).

We then examined the time-dependent effect of peptic ulcer disease on pancreatic cancer risk. Due to the substantial overlap between gastric ulcer and duodenal ulcer among pancreatic cancer cases, we had very limited power to examine the time-dependent effect for those with only gastric ulcer or for those with only duodenal ulcer. Therefore, we compared men who ever had gastric/duodenal ulcers with those who never had ulcers. In order to ensure the validity of the estimates, gastric ulcer and duodenal ulcer were mutually adjusted in the models. We categorized ulcers according to calendar time of diagnosis and found a 3-fold increase in risk among men who had gastric ulcer during 1975–1986 or after 1987. In contrast, gastric ulcer that occurred before 1974 was not related to risk of pancreatic cancer (Table 2). When examining years since first ulcer diagnosis, we observed that risk was highest for individuals within 10 years since a gastric ulcer diagnosis (multivariable RR, 3.66; 95% CI, 1.45 – 9.24) (Table 2). However, the risk remained significantly elevated 10–19 years after ulcer diagnosis (multivariable RR, 2.89; 95% CI, 1.26 – 6.64). The association between gastric ulcer and pancreatic cancer risk was more pronounced when gastric ulcer was diagnosed after age 40 (Table 2: multivariable RR, 2.39; 95% CI, 1.34 – 4.27).

In subgroup analyses, the association between gastric ulcer and pancreatic cancer risk was stronger among never smokers (Table 3: multivariable RR, 2.34; 95% CI, 1.05 – 5.20) and among those with low intakes of vitamin C (multivariable RR, 2.38; 95% CI, 1.26 – 4.50) and vitamin E (multivariable RR, 2.10; 95% CI, 1.03 – 4.27). However, none of the P values for interaction were statistically significant.

In contrast, duodenal ulcer was not related to pancreatic cancer when we examined time components of ulcer occurrence (Table 2) or in the subgroup analyses by smoking status (Table 3). Duodenal ulcer was not significantly associated with pancreatic cancer risk at any levels of vitamin C/E intake (Table 3).

To evaluate the effect of misclassification of the self-reported baseline ulcers, we performed the misclassification analysis. Correction for misclassification of baseline ulcers strengthened the association with gastric ulcer: the multivariable RR comparing men with history of gastric ulcer before 1986 versus men without ulcer history before 1986 changed from 1.69 (95% CI, 0.99–2.87) to 2.66 (95% CI, 1.05–6.76) after correction for measurement error. In contrast, the RR of duodenal ulcer at baseline remained statistically insignificant after measurement error correction (before correction: RR, 1.09; 95% CI, 0.71–1.65; after correction: RR, 1.59; 95% CI, 0.86–2.91).

Results remained unchanged when we additionally adjusted for other potential confounders, including race/ethnicity, geographic regions, height, periodontal disease, NSAID use, multivitamin use and dietary factors (fruits and vegetables, sucrose, vitamin C, vitamin D, vitamin E, calcium, and total calories) (data not shown). At baseline, only 20% of men with an ulcer history reported use of H<sub>2</sub>-receptor antagonists and these men did not have a higher risk of pancreatic cancer (P=0.30). Further control for H<sub>2</sub> blocker use did not alter the observed associations with gastric ulcer or duodenal ulcer. Similarly, blood type had little impact on

relative risk estimates (data not shown). We also obtained similar results when excluding pancreatic cancer cases with missing medical records (5% of cases) (data not shown).

## Discussion

In our study, gastric ulcer was associated with an increase in risk of pancreatic cancer. The elevated risk persisted 10–19 years after gastric ulcer diagnosis. In contrast, duodenal ulcer was not associated with pancreatic cancer risk.

The positive relation between gastric ulcer and pancreatic cancer risk might be explained by excess nitrosamine formation associated with gastric ulcer. Nitrosamines induce pancreatic cancer in animals and are considered potential human pancreatic carcinogens<sup>6</sup>. Tobacco smoke, a strong risk factor of pancreatic cancer, contain high levels of nitrosamines<sup>7</sup>. Besides exogenous exposure from cigarette smoke, the main source of human exposure to nitrosamines comes from endogenous formation by a number of bacterial strains in the oral cavity and the gastrointestinal tract<sup>30</sup>. Periodontal disease and *H. pylori* infection have been hypothesized to influence pancreatic carcinogenesis through greater endogenous nitrosation<sup>3, 30</sup>. Another piece of evidence supporting nitrosamine hypothesis comes from a strong association between gastrectomy and pancreatic cancer risk. Patients who had undergone partial gastric resection for benign conditions such as peptic ulcer disease have extremely high concentration of intragastric nitrosamines<sup>10</sup>, probably due to bacterial overgrowth secondary to postoperative hypochlorhydria; these individuals also have increased pancreatic cancer risk 20 or more years after the surgery<sup>20, 31–33</sup>. Gastric ulcer patients have low acid output<sup>9</sup> and the neutral pH allows for bacterial colonization and nitrosation<sup>10, 34</sup> which leads to elevated intragastric nitrosamine concentrations. It is possible that bacterially catalyzed nitrosamines are transported via the bloodstream to the organs (such as pancreas) where they could induce DNA damage, stimulate DNA synthesis and eventually cause tumor development<sup>35, 36</sup>. A previous analysis in the HPFS 3, which demonstrated an increase risk of bladder cancer with gastric ulcer, also suggests that gastric ulcer might be a source of nitrosamines and hereby involved in carcinogenesis. In addition, we observed in the present study that high intakes of vitamin C and E, two blockers of nitrosamine formation, may have attenuated the positive association of gastric ulcer with pancreatic cancer.

An alternative explanation for the association between gastric ulcer and pancreatic cancer risk might be the inflammatory response related to *H. pylori* infection and the ulcer healing process. Chronic inflammation involves generation of pro-inflammatory cytokines that can be delivered through the circulation, which might contribute to pancreatic carcinogenesis<sup>37</sup>. Since the majority of ulcer patients are infected with *H. pylori* and ulcer healing is an inflammatory process<sup>38</sup>, gastric ulcers may lead to systemic inflammation by increasing secretion of inflammatory mediators and thereby increase risk of pancreatic cancer. However duodenal ulcer, also involving inflammation, was not associated with risk of pancreatic cancer in our study, but gastric ulcer and duodenal ulcer have different pathophysiologies<sup>9</sup> and therefore might have different inflammatory response patterns. Although no evidence so far showed differences in the inflammatory response between these two ulcers, we can not entirely rule out the possibility that inflammatory response is partly responsible for the increased risk with gastric ulcer, since there is not much research being conducted to examine differences in inflammatory response patterns of these two ulcers and there are still so many unanswered questions in terms of biological mechanisms.

Unlike gastric ulcer, duodenal ulcer is largely a disease of acid hypersecretion<sup>9</sup>. Because duodenal ulcer was not related to risk of pancreatic cancer in the present study, hyperacidity is not likely to play a crucial role in the initiation of pancreatic cancer.



Similar results were found in a large cohort study conducted in Sweden<sup>11</sup>. In that register-based study, gastric ulcer but not duodenal ulcer was associated with a modest increase in risk of pancreatic cancer. After a peak in risk during the first 2 years of follow-up (RR, 4.8; 95% CI, 4.2 – 5.5), gastric ulcer was associated with 20% (95% CI, 1.1 – 1.4) excess risk for pancreatic cancer during year 3–38 of follow-up. The risk increased with follow-up duration and reached 1.5 after 10 years (p value for trend test=0.03). However, they were not able to adjust for cigarette smoking, a potential confounding factor which could bias estimates upwards. Several case-control studies<sup>12, 17, 20, 21</sup> also had information on the types of ulcer and examined their associations with the risk. No associations were found with gastric ulcer<sup>12, 17, 20, 21</sup> and most observed null associations with duodenal ulcer<sup>17, 20, 21</sup>, with one exception<sup>12</sup>.

The strengths of the present study included a relatively large number of cases of pancreatic cancer, a long follow-up duration, the assessment of the time-dependent effect of ulcer occurrence, and extensive information on potential confounders. The repeated measurement on ulcer occurrence was an advantage because it allowed for the opportunity to account for changes in ulcer status over time. The cohort design and relatively complete follow-up minimized selection bias in this study.

One of the major concerns of the study was that ulcer diagnoses were self-reported. Misclassification of ulcer location (gastric versus duodenal) or confusion with other gastrointestinal diseases, such as gastritis and duodenitis, was possible. However, men in this cohort were health professionals and have been shown in this cohort to accurately report many medical conditions<sup>3, 39</sup>. Self-reporting of ulcer occurrence was reasonably accurate in the cohort: among men for whom we were able to retrieve medical records during 1988–2002, only 23% of the self-reported ulcers were rejected after medical record review. Conceptually, even if reported gastric ulcers were mixed with gastritis, the findings still support evidence for the inflammation and nitrosamine hypotheses, because gastritis is also accompanied by an inflammatory response and nitrosamine formation<sup>40, 41</sup>. In addition, the relative risk estimates for ulcers diagnosed between 1987–2002, which were confirmed by endoscopy, were similar to those in the primary analysis which combined self-reported baseline ulcers and confirmed follow-up ulcers. Furthermore, ulcer misclassification in this study is likely to be nondifferential given the prospective design, leading to underestimation of the true association given the binary exposure. Our misclassification analysis showed that the association with gastric ulcer was strengthened after correction for measurement error; therefore, misclassification of ulcer location is unlikely to explain the positive association with gastric ulcer we found in the primary analysis. Nonetheless, non-differential misclassification due to remote recall of ulcer occurrence and lack of endoscopic equipment at that time remained an alternative explanation for the lack of significant association among men who had gastric ulcer before 1974 or before age 40 or among men with gastric ulcer followed for more than 20 years.

Another concern is that by the time that peptic ulcers were diagnosed, pancreatic cancer might have had already existed given its insidious onset and non-specific early symptoms. It is also possible that peptic ulcers were an early symptom or consequence of pancreatic cancer. To rule out the reverse temporal relationship, we conducted a sensitivity analysis by excluding the first 2 years of follow-up because pancreatic cancer is a fast-growing malignancy with a median survival of less than 5 months. The results were not materially changed. In addition, the risk of pancreatic cancer remained significantly elevated 10–19 years after gastric ulcer diagnosis.

Antacids, H<sub>2</sub> receptor antagonists and proton-pump inhibitors are the main treatment for peptic ulcers and may mediate the effects of ulcers on pancreatic cancer. In the primary analysis, we found no association of H<sub>2</sub>-blocker use with pancreatic cancer and the risk estimates remained unchanged after adjusting for H<sub>2</sub>-receptor antagonists, indicating that the ulcer effects are not

mediated by these drugs. Although we cannot control for antacids due to lack of information, they would not be able to explain the divergent effects observed with two types of ulcers because antacids are used indiscriminately for gastric and duodenal ulcers. Proton-pump inhibitors were not introduced into clinical practice until 1988, thus they are not likely to be responsible for any associations found before baseline.

Because of the substantial overlap between gastric ulcer and duodenal ulcer among pancreatic cancer cases, we had very limited power to estimate the risk and examine the time-dependent effect for those with only gastric ulcer (11 pancreatic cancer cases) or for those with only duodenal ulcer (21 pancreatic cancer cases). For most analyses, the exposure was ever having gastric/duodenal ulcer, i.e., individuals with both ulcers (9 pancreatic cancer cases) were included in the gastric ulcer group and in the duodenal ulcer group. Although gastric ulcer and duodenal ulcer were mutually adjusted, it might not be enough and the observed associations could partially reflect greater exposure where both ulcers occurred.

Residual confounding is probably of minor importance because risk estimates were similar for age-adjusted models and multivariable models. Particularly, the observed positive association with gastric ulcer was not likely to be due to confounding by cigarette smoking because the association remained significantly elevated among never smokers. The association among ever smokers was weaker probably because of the high background level of nitrosamines from smoke in these individuals. Unmeasured confounding by potential risk factors for pancreatic cancer, including history of chronic pancreatitis, family history of pancreatic cancer and low socioeconomic status, cannot be completely ruled out. However, the prevalence of chronic pancreatitis in the general population is very low, ranging from 0.04 to 5% in different geographic regions<sup>42</sup>, and its relation with peptic ulcers remains unclear. Similarly, family history of pancreatic cancer is uncommon and no evidence has linked it to peptic ulcer disease. Although socioeconomic status may be related to both ulcer and pancreatic cancer, our cohort is relatively homogeneous with all the members being health professionals.

In conclusion, gastric ulcer was strongly associated with pancreatic cancer risk in our study, suggesting that intragastric N-nitrosamine formation might be an important mechanism in pancreatic carcinogenesis. Lack of association for duodenal ulcer, on the other hand, is consistent with a less crucial role of hyperacidity in the development of pancreatic cancer.

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**Table 1**Baseline Characteristics According to Baseline Ulcer Status <sup>a</sup>

Characteristic	No ulcers	Gastric ulcer	Duodenal ulcer
No. of individuals	45417	1425 <sup>b</sup>	2980 <sup>b</sup>
Age, y	54.5	54.8	54.8
Race			
White, %	90.7	89.4	90.2
African American, %	1.0	1.3	1.0
Other, %	8.3	9.3	8.8
BMI, kg/m <sup>2</sup>	25.5	25.8	25.6
Physical activity, MET-h/week	21.2	17.8	19.0
History of diabetes, %	3.2	3.0	3.3
History of periodontal disease, %	15.8	17.7	18.3
Smoking status			
Current smokers, %	9.3	15.2	14.2
Pack-years of cigarettes <sup>c</sup>	26.2	31.7	30.4
Alcohol, g/day	11.3	11.1	11.2
Multivitamin use, %	41.6	44.2	42.2
NSAID use, %	35.1	44.4	39.4

<sup>a</sup> All variables (except age) were age-standardized.

<sup>b</sup> Included 412 individuals who had both gastric ulcer and duodenal ulcer.

<sup>c</sup> Pack-years were calculated for former and current smokers only.

**Table 2**

History of Gastric/Duodenal Ulcer and Risk of Pancreatic Cancer <sup>a</sup>

Peptic ulcer disease <sup>b</sup>	Cases <sup>c</sup>	Person-years	Age-adjusted RR (95% CI)	Multivariable RR (95% CI) <sup>d</sup>
<b>None</b>	233	730568	1.0 (referent)	1.0 (referent)
<b>Gastric Ulcer</b>				
Ever	20	24584	1.88 (1.17 – 3.03)	1.83 (1.13 – 2.97)
Calendar years of ulcer diagnosis				
Before 1974	7	11313	1.36 (0.63 – 2.93)	1.27 (0.58 – 2.79)
1975–1986	8	8024	2.99 (1.45 – 6.16)	2.94 (1.42 – 6.08)
1987–2002	4	2128	3.03 (1.09 – 8.43)	3.15 (1.12 – 8.83)
Years since first ulcer diagnosis <sup>e</sup>				
<10	5	3452	3.69 (1.47 – 9.24)	3.66 (1.45 – 9.24)
10–19	6	5848	2.97 (1.30 – 6.79)	2.89 (1.26 – 6.64)
20–29	4	4830	2.28 (0.83 – 6.27)	2.29 (0.83 – 6.33)
>30	4	7249	0.98 (0.36 – 2.70)	0.91 (0.32 – 2.55)
Age at first ulcer diagnosis <sup>f</sup>				
<40	6	10451	1.63 (0.70 – 3.75)	1.50 (0.64 – 3.52)
>40	13	11022	2.39 (1.34 – 4.25)	2.39 (1.34 – 4.27)
<b>Duodenal Ulcer</b>				
Ever	30	50353	1.22 (0.83 – 1.81)	1.15 (0.78 – 1.71)
Calendar years of ulcer diagnosis				
Before 1974	19	33614	1.16 (0.72 – 1.86)	1.11 (0.69 – 1.78)
1975–1986	4	9912	1.01 (0.37 – 2.76)	0.90 (0.33 – 2.47)
1987–2002	3	3126	1.74 (0.54 – 5.62)	1.74 (0.54 – 5.65)
Years since first ulcer diagnosis <sup>e</sup>				
<20	7	12817	1.42 (0.66 – 3.07)	1.35 (0.62 – 2.93)
20–29	2	10594	0.51 (0.13 – 2.05)	0.45 (0.11 – 1.81)
30–39	7	11375	1.36 (0.63 – 2.93)	1.28 (0.59 – 2.77)
>40	10	11871	1.24 (0.65 – 2.37)	1.22 (0.64 – 2.34)
Age at first ulcer diagnosis <sup>f</sup>				
<35	12	23330	1.33 (0.74 – 2.40)	1.32 (0.73 – 2.39)
>35	14	23331	1.06 (0.61 – 1.86)	0.97 (0.56 – 1.70)

<sup>a</sup>Ulcer history was first assessed at baseline in 1986 and updated biennially thereafter. RR = relative risk; CI = confidence interval.

<sup>b</sup>Individuals who had both gastric ulcer and duodenal ulcer (n=412) were included in gastric ulcer and duodenal ulcer groups. Gastric ulcer and duodenal ulcer were mutually adjusted in all the models.

<sup>c</sup>Exposed cases do not add up to 20 (gastric ulcer) or 30 (duodenal ulcer) due to missing information on date of ulcer diagnosis.

<sup>d</sup>Adjusted for age, smoking (never; quit ≥ 15 years; quit <15 years, ≤ 25 pack-years; quit <15 years, >25 pack-years; current ≤ 25 pack-years; current >25 pack-years), diabetes (yes/no), BMI (kg/m<sup>2</sup>, <18.5, 18.5 - <25, 25 - <30, 30 - <35, >35, and missing) and physical activity (quintiles).

<sup>e</sup>Cutpoints based on quartiles of years since first ulcer diagnosis among gastric/duodenal ulcer patients.



<sup>f</sup>Cutpoints based on median age of ulcer diagnosis among gastric/duodenal ulcer patients.

**Table 3**

History of Peptic Ulcer Disease and Risk of Pancreatic Cancer, by Smoking Status and Intakes of Vitamin C and E <sup>a</sup>

	Cases	Person-years	Multivariable RR (95% CI) <sup>b</sup>	P-value, test for interaction <sup>c</sup>
Gastric ulcer				
Never smokers	8	9652	2.34 (1.05 – 5.20)	0.46
Ever smokers	12	14931	1.64 (0.86 – 3.12)	
Low vitamin C intake <sup>d</sup>	12	11947	2.38 (1.26 – 4.50)	0.18
High vitamin C intake	7	11828	1.44 (0.63 – 3.31)	
Low vitamin E intake <sup>d</sup>	10	11100	2.10 (1.03 – 4.27)	0.38
High vitamin E intake	9	12675	1.40 (0.67 – 2.96)	
Duodenal ulcer				
Never smokers	11	19492	1.35 (0.69 – 2.66)	0.85
Ever smokers	19	30861	1.11 (0.67 – 1.84)	
Low vitamin C intake <sup>d</sup>	21	24757	1.64 (0.99 – 2.72)	0.04
High vitamin C intake	9	24086	0.71 (0.35 – 1.46)	
Low vitamin E intake <sup>d</sup>	14	23081	1.40 (0.76 – 2.57)	0.70
High vitamin E intake	16	25762	1.11 (0.64 – 1.93)	

<sup>a</sup>History of peptic ulcer disease and cigarette smoking was first assessed at baseline in 1986 and updated biennially thereafter. Intakes of vitamin C and E were obtained from baseline questionnaires. Individuals who had both gastric ulcer and duodenal ulcer (n=412) were included in gastric ulcer and duodenal ulcer to increase power. RR = relative risk; CI = confidence interval.

<sup>b</sup>Referent was the incidence of pancreatic cancer among participants without peptic ulcer disease in each category defined by smoking status, vitamin C intake or vitamin E intake. Multivariable Models were adjusted for age, smoking (never; quit  $\geq$  15 years; quit <15 years,  $\leq$  25 pack-years; quit <15 years, >25 pack-years; current  $\leq$  25 pack-years; current >25 pack-years), diabetes (yes/no), BMI (kg/m<sup>2</sup>, <18.5, 18.5 - <25, 25 - <30, 30 - <35, >35, and missing) and physical activity (quintiles). Gastric ulcer and duodenal ulcer were mutually adjusted.

<sup>c</sup>Test for interaction was conducted using the likelihood ratio test (LRT).

<sup>d</sup>Cutpoints based on median intakes among all participants: vitamin C (227 mg/day) and vitamin E (9.4 mg/day). Analyses were conducted among the participants who provided sufficient dietary data to estimate vitamin intakes (47602 participants, 257 cases).