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Serum Pepsinogen level, Atrophic Gastritis and the Risk of Incident Pancreatic Cancer – a Prospective Cohort Study

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Abstract

Background—Pancreatic cancer is a highly fatal disease without screening tests. Studies have suggested possible etiologic similarities between gastric and pancreatic cancers. Atrophic gastritis, a pre-malignant condition for gastric cancer, is characterized by low serum pepsinogen I (SPGI) level. We hypothesized that low SPGI level may be associated with an increased risk of pancreatic cancer and be a useful biomarker for the disease.

Methods—Our analytic cohort included 20,962 participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) who had SPGI level measured. Of these, 1,663 (7.9%) subjects had low SPGI levels (<25 μg/l) and were invited for gastroscopy which was completed in 1,059 (63.7%) participants. Atrophic gastritis was histologically-confirmed in 1,006 (95.0%) subjects. We used Cox proportional hazards regression to calculate the hazard ratios (HR) and 95% confidence intervals (CI) for pancreatic cancer.

Results—During follow-up of up to 16.3 years (mean=10.8 years; 226,325 person-years), 227 incident pancreatic cancers were diagnosed. The incidence rates were 9.9, 11.3, and 12.7 per 10,000 person-years of follow-up for participants with normal pepsinogen level (≥25 μg/l), low pepsinogen level and histologically-confirmed atrophic gastritis, respectively. Compared to subjects with normal pepsinogen levels, there was no statistically significant increased risk of pancreatic cancer among subjects with low pepsinogen level (Adjusted HR=1.01; 95%CI: 0.63–

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1.62) or those with histologically-confirmed atrophic gastritis (Adjusted HR=1.13; 95%CI: 0.66–1.95).

Conclusions—Atrophic gastritis, serological or histological, is not associated with increased risk of pancreatic cancer. These findings do not provide any evidence for potential usefulness of SPGI for pancreatic cancer screening.

Keywords

Serum pepsinogen; atrophic gastritis; pancreatic cancer

INTRODUCTION

Pancreatic cancer is a highly fatal disease and patients usually present at advanced stages of disease. The suggested risk factors for pancreatic cancer include smoking, family history of pancreatic cancer, diabetes mellitus and chronic pancreatitis.[1,2] To date, there is no established screening test or useful biomarker for the disease.

Some studies have suggested possible etiologic similarities between gastric and pancreatic cancers with the finding that some pancreatic cancers express markers of gastrointestinal epithelial cells.[3] Positive associations between gastric ulcers and sub-total gastrectomy for ulcer disease and pancreatic cancer have been reported.[4–7] *Helicobacter pylori* (*H. pylori*) seropositivity was also associated with a significant elevated risk of pancreatic cancer [8,9] and *Helicobacter* species DNA have also been isolated from pancreatic cancer tissue.[10,11] Furthermore, pepsinogen expression by pancreatic cancer cells was found in 38% of well-differentiated, resectable cancers and portends a better overall survival compared to others without the expression.[12] Gastrin, a gastrointestinal peptide, has also been shown to have a proliferative effect on pancreatic cancer cells. [13]

Atrophic gastritis is a chronic condition characterized by gastric inflammation, gland loss, mucosa thinning and epithelial cell regeneration and replacement. It results from multiple etiologies including autoimmune pernicious anemia, chronic *H. pylori* infections and possibly, long-term proton pump inhibitor therapy.[14–16] It is characterized by hypergastrinemia and low serum pepsinogen levels. This raises a possibility that factors that lead to atrophic gastritis may be associated with the development of pancreatic cancer. Another potential mechanism is that the low acid production that occurs with atrophic gastritis results in a change of pH in the stomach and bacterial overload. Bacterial metabolism of nitrates promotes the generation of carcinogenic nitroso-compounds which may be associated with an increased risk of pancreatic cancer.[17] To our knowledge, no previous study has evaluated the relationship between atrophic gastritis and pancreatic cancer.

We hypothesized that atrophic gastritis confirmed histologically or by low serum pepsinogen I (SPGI) level as its biomarker, may be associated with an increased risk of pancreatic cancer and provide a potential clinical utility for SPGI in pancreatic cancer screening. We tested this hypothesis in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a large, long-term prospective study of male smokers, who, given their smoking history, were at elevated risk of pancreatic cancer.

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METHODS

ATBC study

The details of the rationale, design, and results of the ATBC have been published. 18,19 In brief, the ATBC was a randomized, double-blind, placebo-controlled, 2 × 2 factorial design, primary prevention trial that tested whether supplementation with alpha-tocopherol and/or beta-carotene could reduce the incidence of lung and other cancers. A total of 29,133 male smokers, aged 50–69 and living in southwestern Finland were recruited from 1985 to 1988. Exclusion criteria included a history of malignancy other than non-melanoma skin cancer, severe angina on exertion, chronic renal insufficiency, liver cirrhosis, chronic alcoholism, or other medical conditions that might limit long-term participation; or if they were receiving anticoagulant therapy or used supplements containing vitamin E (>20 mg/day), vitamin A (>20 000 IU/day), or beta carotene (>6 mg/day). The intervention was terminated on April 30, 1993, but the participants continue to be followed as a cohort. The ATBC study was approved by the institutional review boards of the National Cancer Institute, Bethesda, Maryland and the National Public Health Institute, Helsinki, Finland. All subjects gave written informed consent.

At the pre-randomization baseline visit, study participants completed questionnaires on demographic characteristics and provided information regarding their medical, dietary, and smoking history. Their weights and heights were measured by trained study staff. Blood samples were collected from participants at two time points: at baseline (1985–1988) and 3 years after randomization. The sera were stored at −70°C.

In 1991, three to six years after baseline, an additional questionnaire on certain risk factors for cancer such as family history of specific cancers, history of ulcers and gastrectomy was mailed to the participants still in trial. The questionnaire was returned at the next follow-up visit when a nurse verified its completion (n = 20,931).

Study subjects and serum pepsinogen measurement

SPGI measurement was performed on all available and sufficient blood samples from the follow-up blood draw (n = 21,188). Of these, 226 subjects were censored (221 subjects were dead, 2 subjects dropped out of ATBC, and 3 subject were alive but had personal history of pancreatic cancer) before the SPGI assay was completed and were therefore excluded from this analysis. Our final cohort is comprised of 20,962 participants who had the SPGI assay on their follow-up blood draw and were still in the ATBC and free of pancreatic cancer at the time of SPGI assay (Figure).

SPGI measurements were performed in two laboratories. Serum samples for 6,112 (29.2%) subjects were assayed in Dr Samloff's laboratory at the University of California, Los Angeles, California from 1989–1991, but because this laboratory was damaged during the 1991 earthquake in California, the serum samples for the remaining 14,850 subjects (70.8%) were assayed in Dr Härkönen's laboratory at the University of Helsinki, Helsinki, Finland from 1992–1993. The analyses were done by radioimmunoassay methods. A low SPGI level was defined as <25 μg/l.20¯22

Gastroscopy

A total of 1,663 subjects had low SPGI and were invited for gastroscopy but 604 (36.3%) subjects refused, did not respond, or were ineligible for gastroscopy because of health reasons (mostly due to coronary artery disease). Therefore, gastroscopy was performed on 1,059 (63.7%) subjects (Figure). The procedures were performed within two months of the SPGI assay by gastrointestinal endoscopists in a standard manner. Routine biopsy specimens

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were taken under direct visualization as follows: one from the distal and one from the proximal antrum along the lesser curvature, two from the middle of the body of the stomach, and one from the anterior and one from the posterior wall (total of 6 routine biopsies). In addition, multiple biopsy specimens were taken from all endoscopically abnormal lesions (local color changes, ulcers, scars, abnormal folds, polypoid lesions, and tumors).

Histological diagnosis of atrophic gastritis

Histopathologic diagnoses of all specimens were classified using the Sydney System.23 Two trial pathologists with expertise in gastrointestinal oncology evaluated the specimens and classified the subjects based on the most severe histopathologic change: no atrophy, atrophic gastritis (mild, moderate, and severe), dysplasia (mild, moderate, and severe), and malignant (adenocarcinoma and carcinoid).

For our primary analysis, we categorized subjects only by the absence or presence of atrophic gastritis, irrespective of the severity. Among the 1,059 subjects who underwent gastroscopy, 53 (5.0%) had no evidence of atrophic gastritis in their biopsy samples whereas 1,006 (95.0%) had histologically-confirmed atrophic gastritis. In a sensitivity analysis we limited our histological atrophic gastritis group to the 731 participants with mild, moderate, or severe atrophy (excluding the 275 with dysplasia or malignancy) and repeated our analysis. This was because of the possibility that subjects with findings of dysplasia or worse lesions from gastroscopy may modify their lifestyles which in turn may modify their risk of pancreatic cancer

Outcome assessment

Pancreatic cancer cases were identified from the Finnish Cancer Registry, which provides almost 100% case ascertainment in Finland.24 For cases diagnosed through April 1999, medical records were reviewed centrally by one or two study oncologists for diagnostic confirmation. Information on pancreatic cancer cases diagnosed since May 1999 through April 2005 was derived only from the Finnish Cancer Registry. Deaths were identified from the National Death Registry, a branch of Statistics Finland.

Statistical analysis

We compared those with low SPGI (< 25 μg/l) and those with histologically-confirmed atrophic gastritis to a reference group of participants with normal SPGI (≥25 μg/l). We used chi-square tests to compare the proportions of dichotomous variables and Wilcoxon rank-sum tests to compare the rank distribution of the continuous variables because several of the continuous variables were not normally distributed.

We defined the start of follow-up as the date of the SPGI assay. We chose this as our start date rather than the date of blood draw because we were interested in participants with histologically-confirmed atrophic gastritis from gastroscopy (the gold standard for atrophic gastritis) as our main analysis. The gastroscopy was generally performed within 2 months of SPGI assay. Therefore, since subjects with normal SPGI was the comparison group for our analyses, using the date of SPGI assay provided a comparable beginning of follow up for this cohort. Subjects were censored at death (from any cause), at diagnosis of pancreatic cancer, or at the end of follow-up for this study (April 30, 2005), whichever came first. The number of person-years each participant contributed to the cohort served as the underlying time metric.

We determined the incidence rate of pancreatic cancer among participants with normal SPGI (reference group), low SPGI, and subjects with histologically-confirmed atrophic gastritis. We used Cox proportional hazards regression to calculate the hazard ratios (HR) and 95%

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confidence intervals (CI) for incident pancreatic cancer; comparing the second and the third groups with the reference group. The proportional hazard assumption was tested using likelihood-ratio tests. We used two Cox multivariate models. All models were controlled for smoking because smoking is a putative risk factor for pancreatic cancer. In model 1 (the parsimonious model), we kept only variables that were true confounders (i.e. associated with both pepsinogen concentrations and pancreatic cancer and changed the risk estimates by >10 %). Only age fulfilled these criteria. In model 2 (*a priori* model), we retained *a priori* factors that have been suggested in the literature to be risk factors for pancreatic cancer. The variables are: age, body mass index, cigarettes smoking, personal history of diabetes mellitus and pancreatitis, family history of pancreatic cancer and dietary fat, folate and energy. In order to assess the effect of any prevalent subclinical disease at the time of SPGI measurement, we also repeated our analysis and excluded the first one, three, and five years of follow-up.

Although the randomization assignment was not a confounder in our study, we performed a sensitivity analysis in which we restricted our cohort to only participants in the placebo arm and repeated our analysis. We used Stata ® statistical software version 9 (College Station, Texas) for all analyses. All reported P-values correspond to two-sided tests.

RESULTS

Baseline characteristics of participants

Table 1 shows the baseline characteristics of the 20,962 participants included in the analytic cohort (Figure). The subjects were evenly distributed by randomization assignment. The mean age of the cohort was 56.9 years and 16.4% of the subjects had junior high school education or higher. The mean smoking duration was 35.5 years and number of cigarettes smoked per day was 20.2. A total of 530 (3.1%) subjects had a family history of pancreatic cancer while 653 (3.3%) subjects had a history of partial gastrectomy. When compared to participants with normal SPGI, those with atrophic gastritis were older; smoked for longer duration; had less alcohol use; and were more likely to have a family history of stomach cancer and a personal medical history of peptic ulcer disease and partial gastrectomy. However, they had lower body mass indices and were less likely to have formal education beyond junior high school (all P-values <0.01). Participants with low SPGI or atrophic gastritis did not differ from those with normal SPGI by marital status, family history of pancreatic cancer or self-reported history of pancreatitis or diabetes mellitus.

Among the subjects with low SPGI, those who underwent gastroscopy and biopsy (n = 1,059) were comparable to those who did not (n = 604) except that non-participants were slightly older (mean age 59.5 versus 58.5 years, P < 0.001); had longer duration of smoking (38.6 versus 36.7 years, P < 0.001); had less formal education (junior high school or higher: 7.5% versus 11.1%, P = 0.015); and were less likely to be married (80.0% versus 84.1%, P = 0.031). There were no differences in the prevalence of family history of pancreatic cancer (1.6% versus 3.1%, P = 0.101) or gastric cancer (15.7% versus 19.3%, P = 0.108) between the two groups.

Incident pancreatic cancer by serum pepsinogen level or histologically-confirmed atrophic gastritis

A total of 227 pancreatic cancers were diagnosed during a follow-up period up to 16.3 years (mean = 10.8 years; 226,325 person-years of follow-up). The proportional hazard assumption was satisfied (P value ≥ 0.36 for all analytic models). The incidence rate for pancreatic cancer was 9.9 per 10,000 person-years of follow-up for subjects with normal SPGI and 11.3 per 10,000 person-years of follow-up for subjects with low SPGI level (Table

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2). There was no association between low SPGI level and incident pancreatic cancer: (HR = 1.01; 95%CI: 0.63–1.62) for the parsimonious model and (HR = 1.04; 95%CI: 0.60–1.80) for the *a priori* model.

The incidence rate of pancreatic cancer was 12.7 per 10,000 person-years of follow-up among subjects with histologically-confirmed atrophic gastritis (Table 2). There was no increased risk of pancreatic cancer for both the parsimonious model (HR = 1.13; 95%CI: 0.66–1.95) and *a priori* model (HR = 1.11; 95%CI: 0.58–2.11) compared to those with normal SPGI level. There was no meaningful difference in risk estimates for the association between either SPGI or histologically confirmed atrophic gastritis and pancreatic cancer when the initial one, three or five years of follow-up were excluded (data not shown).

Sensitivity analyses

We also restricted our analysis of histologically-confirmed atrophic gastritis to only subjects with mild, moderate, or severe atrophic gastritis without evidence of dysplasia or malignancy (n = 731). These participants were followed for a mean duration of 11.0 years (range 0.8–16.3 years) for a total 8,086 person-years of follow-up. A total of twelve cases of pancreatic cancer were diagnosed among these participants for an incidence rate of 14.8 per 10,000 person-years of follow-up. When compared with subjects with normal SPGI, there was no association between this alternate definition of histological atrophic gastritis and pancreatic cancer in both analytical models: (HR = 1.35; 95%CI: 0.75–2.43) for the parsimonious model and (HR = 1.25; 95%CI: 0.61–2.55) for the *a priori* model.

In another sensitivity analysis, we limited our cohort to the placebo arm of the ATBC trial (n = 5,239; pancreatic cancer cases = 61), and repeated our analysis. The inferences were unchanged. When compared with subjects with normal SPGI, there was no association between low SPGI level and pancreatic cancer: (HR = 1.08; 95%CI: 0.43–2.71) for the parsimonious model and (HR = 1.24; 95%CI: 0.44–3.50) for the *a priori* model. Similarly, there was no association between histologically-confirmed atrophic gastritis and pancreatic cancer: (HR = 1.01; 95%CI: 0.31–3.23) for the parsimonious model and (HR = 1.41; 95%CI: 0.43–4.60) for the *a priori* model.

DISCUSSION

We did not observe any association between atrophic gastritis whether diagnosed serologically or histologically, and pancreatic cancer in our cohort study with long-term follow-up. We assessed atrophic gastritis using low SPGI level as a biomarker and by histopathology following gastroscopy. To the best of our knowledge, no previous study has evaluated this relationship; therefore, we have no studies with which to directly compare our findings.

There have been, however, studies that examine the relationship between other gastrointestinal conditions and pancreatic cancer risk. A recent retrospective cohort study involving 81,379 subjects with gastric ulcer and 61,548 subjects with duodenal ulcer 4 reported an increased risk of pancreatic cancer among hospitalized patients with gastric ulcer (Standardized Incidence ratio (SIR) = 1.2; 95% CI: 1.1–1.4) but not with duodenal ulcer (SIR = 1.1; 95% CI: 0.9–1.3). The authors also reported an increased risk of pancreatic cancer among subjects who underwent surgery for peptic ulcer (SIR = 1.5; 95% CI: 1.2–1.9). However, this study was registry-based, limited to hospitalized patients, and the authors could not adjust for the effect of smoking. Of note, neither a history of peptic ulcer disease (HR=0.98; 95%CI: 0.69–1.39) nor a history of partial gastrectomy (HR=1.63; 95%CI: 0.89–3.00) was significantly associated with incident pancreatic cancer in our study.

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We have previously evaluated the relationship between *H. pylori* infection and pancreatic cancer in a nested case-control study in this cohort 8 and determined that *H. pylori* infection was associated with an increased pancreatic cancer risk (OR = 1.87 [95% CI = 1.05 – 3.34]; particularly cytotoxin-associated gene-A-positive (CagA+) strains (OR = 2.01 [95% CI = 1.09 – 3.70]). However, a recent study involving 104 cases of pancreatic cancer and 262 cancer-free control subjects within Kaiser Permanente Medical Care Program evaluated the association between *H. pylori* infection and pancreatic cancer. 25 The authors reported that neither *H. pylori* seropositivity (OR = 0.85; 95% CI = 0.49 – 1.48) nor its CagA+ strains (OR = 0.96; 95% CI = 0.48 – 1.92) was associated with subsequent development of pancreatic cancer overall. However, a non-significant elevated risk was observed among male smokers for CagA+ strains (OR=2.59, 95% CI 0.90–7.42) compared to *H. pylori* negative controls. It is unclear why these two studies differed in their findings. It is possible that the positive association between *H. pylori* and pancreatic cancer could be due to extra-gastric or systemic effect of *H. pylori* or was due to uncontrolled confounding.

Our study had a number of strengths. The study population was from a very large, prospective study with up to 16 years of follow-up. Furthermore, information related to risk, particularly atrophic gastritis diagnosis, was gathered prior to cancer diagnosis. We assessed atrophic gastritis using SPGI level as well as histopathological diagnosis following gastroscopy, which is the gold standard. Our case ascertainment was from a detailed, reliable, and population-based registry that covered a population with relatively low migration, and therefore was considered complete.

However, our study has limitations. Participants in the ATBC were all male smokers and our findings may not be generalizable to non-smokers and women. Another potential limitation of our study is misclassification of exposure. Some participants with SPGI levels ≥ 25 μg/L may have some degree of gastric atrophy which we did not identify since we did not perform gastroscopy on all participants. Also, as our study demonstrated, some individuals with SPGI <25 μg/L did not have atrophic gastritis on histology. Furthermore, we do not have additional repeated measures of SPGI during follow up, and it is possible that the atrophic gastritis status of participants may have changed over time. This non-differential misclassification would be expected to influence our findings towards null. However, in a population - based study from Finland, 26 SPGI was < 25 μg/L in 80% of subjects with severe atrophic corpus gastritis, but in only 2.1% of those without atrophic gastritis. It is noteworthy that we assessed the effect of possible misclassification in our study: assuming that the true prevalence of atrophic gastritis is 8% in the non-cases (as in our study), and the true risk estimate is approximately 2, a 50% misclassification of atrophic gastritis into the non-exposed group would only reduce the estimate to 1.96 and a 90% misclassification would reduce it to 1.68, whereas the unadjusted HR = 1.15 in our study. Therefore, we feel that the effect of such a misclassification is minimal and would not explain the lack of association in our study.

In conclusion, our large prospective cohort study did not demonstrate an increased risk of pancreatic cancer with atrophic gastritis in a high risk population of male smokers, and we did not find any evidence that low SPGI level is a potentially useful biomarker for screening for pancreatic cancer. Furthermore, our study suggests that the direct gastric effect of potential risk factors for pancreatic cancer may not be related to subsequent risk of the disease.

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Abbreviations in this paper

ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CI	Confidence interval
HR	Hazard ratio
SPGI	Serum pepsinogen 1

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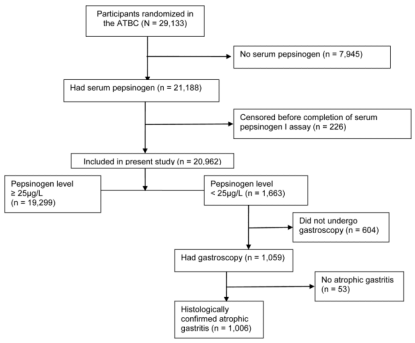

Figure.
Diagram of flow of participants through the study

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Table 1

Baseline characteristics of subjects by serum pepsinogen I levels and histologically confirmed atrophic gastritis

Baseline characteristics	All participants n = 20,962	Normal serum pepsinogen 1 level (≥ 25μg/L) n = 19,299	Low serum pepsinogen 1 level (< 25μg/L) n = 1,663	P value*	Histologically-confirmed atrophic gastritis n =1,006	P value†
Random assignment						
Placebo	5,239 (25.0)	4,846 (25.1)	393 (23.6)	0.206	237(23.6)	0.335
Alpha-tocopherol (AT)	5,253 (25.1)	4,845 (25.1)	408 (24.5)		244 (24.3)	
Beta-carotene (BC)	5,226 (24.9)	4,814 (24.9)	412 (24.8)		251 (25.0)	
Both (AT+BC)	5,244 (25.0)	4,794 (24.8)	450 (27.1)		274 (27.2)	
Mean age in years (SD)	56.9 (5.0)	56.8 (4.9)	58.9 (5.1)	<0.001	58.6 (5.2)	<0.001
Junior high school education or more, n (%)	3,444 (16.4)	3,281 (17.0)	163 (9.8)	<0.001	111 (11.0)	<0.001
Married, n (%)	17,361 (82.8)	15,987 (82.8)	1,374 (82.6)	0.822	848 (84.3)	0.232
Mean body mass index kg/m^2(SD)	26.3 (3.7)	26.4 (3.7)	25.8 (3.8)	<0.001	25.8 (3.7)	<0.001
Smoking history						
Duration, years (SD)	35.5 (8.4)	35.3 (8.4)	37.4 (8.7)	<0.001	36.8 (9.0)	<0.001
Cigarettes smoked/day (SD)	20.2 (8.8)	20.3 (8.9)	19.4 (8.0)	<0.001	19.3 (7.9)	<0.001
Self-reported medical history						
Pancreatitis, n (%)	260 (1.2)	240 (1.2)	20 (1.2)	0.885	9 (0.9)	0.327
Diabetes mellitus, n (%)	812 (3.9)	738 (3.8)	74 (4.5)	0.204	42 (4.2)	0.572
Gallstones, n (%)	1,151 (5.5)	1,058 (5.5)	93 (5.6)	0.85	45 (4.5)	0.169
Peptic ulcer disease, n (%)	3,496 (16.7)	3,131 (16.2)	365 (22.0)	<0.001	202 (20.1)	0.001
Partial gastrectomy, n (%)	653 (3.3)	449 (2.5)	204 (13.0)	<0.001	119 (12.2)	<0.001
Family cancer history						
Pancreatic cancer, n (%)	530 (3.1)	496 (3.1)	34 (2.6)	0.291	25 (3.0)	0.886
Stomach cancer, n (%)	2,316 (13.3)	2,076 (13.0)	240 (18.1)	<0.001	164 (19.6)	<0.001
Dietary intake						
Alcohol use, g/d, (SD)	17.3 (20.2)	17.4 (20.3)	16.0 (19.7)	<0.001	15.7 (18.9)	0.008
Coffee consumption, g/d, (SD)	614.5 (348.0)	613.3 (346.9)	629.3 (360.2)	0.083	625.8 (345.0)	0.126
Energy, kcal/d	2,824.7 (775.6)	2,823.3 (775.2)	2,841.2 (781.0)	0.464	2843.4 (767.7)	0.403
Total fat intake, g/d	35.6 (5.4)	35.6 (5.4)	35.7 (5.6)	0.652	35.7 (5.4)	0.952

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Baseline characteristics	All participants n = 20,962	Normal serum pepsinogen 1 level (≥ 25μg/L) n = 19,299	Low serum pepsinogen 1 level (< 25μg/L) n = 1,663	P value*	Histologically-confirmed atrophic gastritis n =1,006	P value†
Saturated fat intake, g/d	18.4 (4.7)	18.4 (4.7)	18.6 (4.8)	0.038	18.4 (4.8)	0.922
Folate intake, μg/d	121.2 (20.7)	121.3 (20.8)	120.1 (20.2)	0.032	120.4 (19.6)	0.242

*For comparison between participants with normal versus low serum pepsinogen levels

†For comparison between participants with normal serum pepsinogen levels versus histologically-confirmed atrophic gastritis

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Table 2

Incident pancreatic cancer in relation to atrophic gastritis

	Normal serum pepsinogen1 level (≥ 25μg/L) n = 19,299	**Low serum pepsinogen1 level (< 25μg/L) n = 1,663**	**Histologically- confirmed atrophic gastritis n = 1,006**
Number of pancreatic cancers diagnosed	208	19	14
Mean duration of follow-up, years (range)	10.85 (0.00 – 16.26)	10.15 (0.08 – 16.26)	10.97 (0.54 – 16.26)
Person-years of follow-up	209,451	16,874	11,034
Incidence rate/10,000 person-years of follow-up	9.9	11.3	12.7
Incidence rate ratio (95% CI)	Reference	1.13 (0.67 – 1.82)	1.28 (0.69 – 2.19)
Univariate model, HR (95% CI)	Reference	1.15 (0.72 – 1.84)	1.28 (0.75 – 2.20)
Age-adjusted model, HR (95% CI)	Reference	1.00 (0.62 – 1.61)	1.12 (0.65 – 1.93)
Multivariate model 1, HR (95% CI) [1]	Reference	1.01 (0.63 – 1.62)	1.13 (0.66 – 1.95)
Multivariate model 2, HR (95% CI) [2]	Reference	1.04 (0.60 – 1.80)	1.11 (0.58–2.11)

[1] Model 1 = Parsimonious model with only established confounders (age and smoking).

[2] Model 2 = *A priori* model including factors associated with pancreatic cancer in the literature (age, body mass index, smoking, history of diabetes mellitus, history of pancreatitis, family history of pancreatic cancer and dietary fat, folate and energy).