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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, 1663 (7.9%) subjects had low SPGI levels (<25 μg/l) and were invited for gastroscopy which was completed in 1059 (63.7%) participants. Atrophic gastritis was histologically confirmed in 1006 (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: 0.63–1.62) 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.

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1. 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

☆ An abstract from the study was presented as a poster presentation at the 73rd Annual Scientific Meeting of the American College of Gastroenterology, Orlando, Florida in October 2008.

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI, confidence interval; HR, hazard ratio; SPGI, serum pepsinogen 1.

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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.

2. Methods

2.1. 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, 3–6 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).

2.2. 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 subjects 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 (Fig. 1).

SPGI measurements were performed in two laboratories. Serum samples for 6112 (29.2%) subjects were assayed in Dr Samloff's laboratory at the University of California, Los Angeles, California from 1989 to 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 to 1993. The analyses were done by radioimmunoassay methods. A low SPGI level was defined as <25 μg/l [20–22].

2.3. Gastroscopy

A total of 1663 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 1059 (63.7%) subjects (Fig. 1). The procedures were performed within 2 months of the SPGI assay by gastrointestinal endoscopists in a standard manner. Routine biopsy specimens 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 six 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).

2.4. 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 1059 subjects who underwent gastroscopy, 53 (5.0%) had no evidence of atrophic gastritis in their biopsy samples whereas 1006 (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.

2.5. Outcome assessment

Pancreatic cancer cases were identified from the Finnish Cancer Registry, which provides almost 100% case ascertainment in