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Proton pump inhibitors on pancreatic cancer risk and survival

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ABSTRACT

Background: Hypergastrinemia may promote the development and progression of pancreatic cancer. Proton pump inhibitor (PPI) therapy is known to cause hypergastrinemia. We sought to determine the association between PPI therapy and the risk of developing pancreatic cancer as well as survival following pancreatic cancer diagnosis.

Methods: We conducted a nested case-control study and a retrospective cohort study in The Health Improvement Network (THIN), a medical records database representative of the UK population. In the case-control study, each patient with incident pancreatic cancer was matched with up to four controls based on age, sex, practice site and both duration and calendar time of follow-up using incidence density sampling. The odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer risk associated with PPI use were estimated using multivariable conditional logistic regression. The retrospective cohort study compared the survival of pancreatic cancer patients according to their PPI exposure at the time of diagnosis. The effect of PPI use on pancreatic cancer survival was assessed using a multivariable Cox regression analysis.

Results: The case-control study included 4113 cases and 16,072 matched controls. PPI use was more prevalent in cases than controls (53% vs. 26% active users). Adjusting for diabetes, smoking, alcohol use and BMI, PPI users including both former users and active users with longer cumulative PPI use had a higher risk of pancreatic cancer compared to non-users. When assessing survival following pancreatic cancer diagnosis, only short-term, active users had a modest decrease in survival.

Conclusions: Long-term PPI therapy may be associated with pancreatic cancer risk. While PPI users recently started on treatment had a slightly worse survival, this result likely is from reverse causation.

1. Introduction

Proton pump inhibitors (PPIs), which are among the most prescribed medications worldwide [1], may influence the risk of gastrointestinal (GI) malignancies, including pancreatic cancer. The mechanism through which PPIs may increase cancer risk is related to the pathway by which they provide therapeutic benefit; PPIs inactivate the H+/K+ ATPase (or proton pump) on parietal cells in the stomach, thus reducing gastric acid secretion. Acid suppression creates a strong stimulus for gastrin (a trophic factor) production by G cells [2] in nearly all patients on long-term PPI therapy [3,4]. Hypergastrinemia may be associated with entero-chromaffin-like (ECL) cell hyperplasia [5] and tumorogenesis [6–9], gastric tumors [10–12] and Barrett's epithelium [13] in *in vitro* and animal models. Gastrin has been shown to stimulate the growth of human pancreatic cancer cells in cultures [3,14–17] and pancreatic tumors transplanted into nude mice [18]. These effects are likely mediated through the gastrin receptor, which has been found on human pancreatic cancer cells [19]. Gastrin-receptor antagonists prevent growth of pancreatic cancer cells [18] and gastrazole, a gastrin inhibitor, increased survival time as a cancer treatment in a small number of patients [20] (though this was refuted in another study [21]). Furthermore, successful antibody production to gastrin (following exposure to a diphtheria toxoid-coupled vaccine) was associated with survival benefits in patients with in pancreatic cancer [22] and colorectal cancer [23].

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In spite of a highly suggestive mechanism demonstrated in experimental models linking PPI use and increased gastrin levels to GI cancers, the results of epidemiologic studies have been mixed; several studies showed increased rates of gastric cancer among PPI users [24–26] while other studies found no link between acid suppression and gastric cancers [27,28], colorectal cancer [29–32] or pancreatic cancer [33]. In this study, we evaluated the impact of PPI use on both the risk of pancreatic cancer and survival after diagnosis in a large, population-based cohort. Elucidating the association between pancreatic cancer and PPI use could help advance our understanding of the pathogenesis of pancreatic cancer, specifically regarding the role of gastrin. It would also provide important data to help patients and prescribers weigh the risk and benefit of long-term PPI therapy.

2. Materials and methods

2.1. Study design

We conducted a nested case-control study to determine the effect of PPI exposure on pancreatic cancer risk and a retrospective cohort study to evaluate the impact of PPI use on survival in subjects with pancreatic cancer.

2.2. Data source

The Health Improvement Network (THIN) is a medical records database that contains records from approximately 10 million patients treated in >570 general practices in the UK. Its population has been shown to be representative of the general population of the UK [34]. General practitioners have been trained to record their medical diagnoses as READ codes [35] using the Vision general practice computer system (In Practice Systems, London, UK) for the collection of THIN data. The data are entered using a standardized protocol and are routinely analyzed for quality control [34,36]. In our study, we searched for medical diagnoses (e.g. pancreatic cancer, diabetes, alcohol use) using specific READ diagnostic codes [37], and PPI prescriptions were identified using multiplex codes. A recent study in THIN showed that 97% of the incident pancreatic cancer cases identified using READ codes was confirmed based on manual chart review [38].

2.3. The effect of PPI on pancreatic cancer risk, a case-control study

2.3.1. Study population

All patients receiving care from a practitioner using THIN between 1995 and 2013 were potentially eligible for inclusion. Subjects with a diagnosis of inflammatory bowel disease, familial pancreatic cancer syndromes or age below 40 years old at the time of diagnosis were excluded in order to focus on an average risk population. Patients without acceptable medical records (i.e., patients with incomplete documentation or out of sequence date of birth, registration date, date of death, or date of exit from the database) were also excluded.

2.3.2. Cases

Cases were individuals with at least one READ code for pancreatic cancer recorded >183 days after they were either enrolled in a THIN practice [34,39] or that the practice started using Vision software, whichever was later. The 183-day lag was implemented in order to ensure that only incident pancreatic cancer cases were included [40].

2.3.3. Controls

Up to 4 controls were matched with each case using incidence density sampling [41] based on: age, sex, practice site and both duration and calendar time of follow-up. The controls were assigned the same index date as their matched cases.

2.3.4. Exposure

The exposure of interest was PPI use prior to index date. Individuals without a multiplex code for a PPI were considered unexposed. Reverse causation can occur in case-control studies when a treatment administered for the first symptoms of a disease can appear to cause that disease. We attempted to capture the effect of this bias by stratifying groups based on the timing of their PPI prescriptions prior to pancreatic cancer diagnosis: former users (most recent PPI prescription >6 months prior to index date) and active users (most recent PPI prescription <6 months prior to index date). Active users were further separated into: 1) short-term, active users (first prescription <12 months before the index date), 2) intermediate-term, active users (first prescription between 12 and 24 months before the index date) and 3) long-term, active users (first prescription >24 months before index date).

2.3.5. Covariates and confounders

We examined a list of variables known or suspected to affect pancreatic cancer risk (e.g., type 2 diabetes [42], cigarette smoking [43], alcohol use [44,45]) and potential confounders associated with both pancreatic cancer and PPI use (i.e., obesity [46–48]). All variables were measured prior to the index date and defined as follows: obesity (BMI > 30 mg/kg^2), smoking and alcohol use (as identified by the presence of diagnosis codes entered into THIN by providers). Additional data regarding amount of use (for example number of cigarettes or alcoholic drinks per day) were not extracted given concerns over completeness of such information and small numbers of individuals in each category. We adjusted our analyses for these variables.

2.3.6. Statistical analysis

The baseline characteristics of cases and controls were compared using Pearson's chi-squared test for categorical variables and Student's *t*-test for continuous variables. The association between PPI use and the risk of pancreatic cancer was assessed using univariate and multivariable conditional logistic regressions to estimate odds ratios (ORs) and 95% confidence intervals (CI). All p-values were two-sided and values <0.05 were considered significant.

2.4. The effect of PPI use on pancreatic cancer risk, a retrospective cohort study

2.4.1. Study population

All individuals from the above case-control study with at least one READ code for pancreatic cancer 183 days after they were either enrolled in the clinic or that the practice started using Vision computer system/software were included.

2.4.2. Exposure

PPI exposure status at the time of the pancreatic cancer diagnosis was categorized using the same approach as the nested case-control study as 1) former users, 2) short-term, active users, 3) intermediate-term, active users, 4) long-term, active users and 5) non-users.

2.4.3. Covariates and confounders

History of smoking, alcohol use, diabetes and obesity were examined in this population as defined above.

2.4.4. Outcomes

This study evaluated survival following pancreatic cancer diagnosis in groups that were exposed and unexposed to PPIs.