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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.

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Authorship Contribution Statement

Re: Proton pump inhibitor use on pancreatic cancer risk and survival: a case-control and cohort study

1. Drs. Yang, Boursi and Kearns each made substantial contributions to all aspects of this study, including conception and design, acquisition of data, analysis and interpretation of data
2. Drs. Yang, Boursi and Kearns jointly drafted the initial version of the manuscript and subsequently critically revised the manuscript for important intellectual content. They also jointly revised the manuscript for the resubmission.
3. Drs. Yang, Boursi and Kearns give final approval of the version to be published.

Results—The case-control study included 4,113 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.

Keywords

pancreatic cancer; proton pump inhibitor; risk; survival; epidemiology

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 enterochromaffin-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).

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 is entered using a standardized protocol and is 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. The 183-day lag was implemented in order to ensure that only incident pancreatic cancer cases were included (40).

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 this data set 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. The follow-up period started on the pancreatic cancer diagnosis date and ended on the date of death recorded in the THIN database, or the earliest of the following: transferring out of practice or end of THIN follow-up.

2.4.5 Statistical analysis—The survival analysis was performed using a multivariate Cox regression analysis, which estimated hazard ratios (HRs) and 95% CI. All p-values were two-sided and values <0.05 were considered significant. Analyses were adjusted as described above.

3. Results

The nested-case-control study included 4,113 patients with pancreatic cancer and 16,072 matched controls. The prevalence of PPI use (active or former) was greater in individuals with a diagnosis of pancreatic cancer, with 52.9% (2175 of 4113 patients) of cases being active users compared to 26.2% (4217 of 16072 patients) of controls and 43.8% (1801 of 4113 patients) of cases being never users compared to 72.0% (11576 of 16072 patients) of controls. As expected, cases were more likely to be obese, smokers, use alcohol, or have a diagnosis of diabetes (Table 1).

All PPI exposure categories were associated with the risk of pancreatic cancer in our unadjusted conditional logistic regression analysis (Table 2). Short-term, active users had the largest OR (10.60, 95% CI 9.36–11.79) while former users (OR 3.54, 95% CI 2.83, 4.43), intermediate-term (OR 2.54, 95% CI 2.16, 3.00), and long-term active users (OR 1.94, 95% CI 1.74, 2.14) all had lower but significantly elevated risks when compared to non-users. When adjusted for diabetes, obesity, alcohol use and smoking, the results were largely unchanged (Table 2). When duration of PPI use was analyzed as a continuous variable, individuals with pancreatic cancer had a significantly shorter duration of use compared to controls (2.47 vs. 4.14 years, OR 0.85, 95% CI 0.83–0.87).

With regard to the association between PPI use and survival after pancreatic cancer, the unadjusted values showed that only short-term active users experienced a significant increase in death rate (HR 1.11, 95% CI 1.02–1.21). Results were nearly identical when adjusted for diabetes, smoking, alcohol use and obesity (Table 3).

4. Discussion

We evaluated the effect of PPI exposure on both pancreatic cancer risk and survival in a large, population-based study of more than 4,000 incident pancreatic cancer cases. We found PPI use to be associated with pancreatic cancer risk in our population regardless of the duration of PPI therapy. In our retrospective cohort study on PPI and pancreatic cancer survival, only short-term, active PPI users had a modestly increased mortality risk (1.11, 95% CI 1.02–1.21). Our findings are the first population-level study with results in accordance with the compelling link between hypergastrinemia and pancreatic cancer seen *in vitro* and in animal models. Although the only other large epidemiologic study to evaluate the link between PPI therapy and pancreatic cancer found no association (33), the time period during which this study collected data (between 1995 and 2006) may not include the dramatic increase in PPI use seen in recent years. This pervious study also included far fewer cases compared to our study (1,141 compared to 4, 113) (33).

Of note, the duration of PPI use was significantly shorter when comparing cases to controls (2.47 vs. 4.14 years, OR 0.85, 95% CI 0.83–0.87), likely representing a component of reverse causality. Some cases may have been started on PPI therapy for non-specific symptoms related to pancreatic cancer prior to cancer diagnosis. We accounted for this possible bias in our study design looking at different timing of PPI initiation. The elevated OR in all patients taking PPI, even starting >24 months prior to pancreatic cancer diagnosis

argues against reverse causality as the main explanation for our results and suggests that PPIs themselves might increase the risk of pancreatic cancer to some degree. However, even in case of reverse causality, a new PPI prescription may serve as an indicator for an individual at higher risk for pancreatic cancer, even among individuals without known predisposing factors. The decreased survival among short term PPI users may be related to the fact that GI symptoms often represent a later stage of pancreatic cancer (49). However in the current study we lacked staging information, thus we were unable to test this hypothesis.

Our study had several strengths. It included a large number of incident pancreatic cases from a population-representative cohort. The exposure and outcome data from the THIN database were complete and accurate. Being a general practice electronic medical records system, THIN captures complete information on chronic medication use. Furthermore, the diagnosis of pancreatic cancer in THIN has been validated previously. Our study also has a duration of follow-up sufficient to capture incident cases of pancreatic cancer in spite of its long latency period (50). Potential limitations of our study include: generalizability (the THIN database is only generalizable to the UK population) and a lack of dosing information. However, inconsistent adherence to prescribed regimens or over-the-counter PPI use that fell outside our analysis would likely bias results towards the null.

In summary, while epidemiological data has been variable, our study shows a significant association between PPI use and pancreatic cancer although part of this association is secondary to reverse causality and non-specific abdominal symptoms prior to pancreatic cancer diagnosis. These data require confirmation in future studies, but they are consistent with the effect of gastrin on the pancreas and pancreatic cancer cells demonstrated in *in vitro* and animal models. The potential association between long-term PPI therapy and the risk of pancreatic cancer adds another reason for the judicious prescribing of PPI therapy in general. As many as two-thirds of hospitalized patients are prescribed PPIs without an appropriate indication (51) and furthermore are often continued on PPIs after discharge without an indication (52). On the other hand, our retrospective cohort study among pancreatic cancer patients seems to suggest that these patients should not be deprived of the benefit of PPI therapy if they have acid-related symptoms.

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Highlights

- -Hypergastrinemia is mechanistically linked to pancreatic cancer risk.
- -Proton pump inhibitors (PPIs) cause hypergastrinemia.
- PPIs may be associated with an increased risk of pancreatic cancer.
- -PPI use is not associated with survival in pancreatic cancer patients.
- -PPIs should be prescribed judiciously but not withheld in patients with pancreatic cancer.

Table 1

Characteristics of pancreatic cancer cases and controls.

	Cases	Controls	ORs	(95% CI)
n (%)	4113 (20.4)	16072 (79.6)		
age (mean+/− SD) yrs	70.9 +/− 11.5	71.1 +/− 11.4		
Gender (n, % female)	1,999 (48.6)	7,794 (48.5)		
obesity(n, %)[1]	861 (20.9) *	3013 (18.7)	1.15	(1.06–1.26)
smoking(n, %)[2]	2053 (49.9) **	6625 (41.22)	1.52	(1.41–1.64)
alcohol use (n, %)[3]	2135 (51.9) **	7706 (48.0)	1.23	(1.13–1.34)
diabetes (n,%)[4]	931 (22.6) **	1598 (9.9)	2.74	(2.50–3.01)
most recent PPI prescription (mean+/− SD)[5]	1.51+/− 0.85	1.54+/− 0.79	1	(0.94–1.06)
Duration of follow-up (year+/− SD)	6.33+/− 4.09	6.36 +/− 4.10	0.99	(0.68–1.45)
Duration of PPI use (year+/− SD)	2.47+/− 3.07	4.14 +/− 3.19	0.85	(0.83–0.87)

n, number of patients; yrs, years; SD, standard deviation; ORs, Odds Ratios; 95% CI, 95% Confidence Intervals;

[1] BMI >30 mg/kg2;

[2] lifetime smoker;

[3] lifetime alcohol use;

[4] READ code for diabetes;

[5] years prior to index date;

* p= 0.001;

** p=<0.0001

Table 2

PPI exposure and pancreatic cancer risk

	Cases/Controls N= (4113/16072)	Crude OR (95%CI)	adjusted[1] OR (95% CI)
Never users	1801/11,576		
Former users	137/279	3.54 (2.83–4.43)	3.36 (2.67–4.22)
Short-term, active users	1109/705	10.50 (9.36–11.79)	10.42 (9.26–11.73)
Intermediate-term, active users	243/629	2.54 (2.16–3.00)	2.47 (2.09–2.92)
Long-term, active users	823/2883	1.94 (1.75–2.14)	1.85 (1.67–2.06)

N=, number of individuals; OR, odds ratio; 95% CI, 95% confidence interval;

[1]Adjusted for: diabetes, smoking, alcohol use and obesity

Stratification:

1. former users: most recent PPI prescription >6 months prior to index date
2. active users: most recent PPI prescription < 6 months prior to index date
    a. short-term, active users: first prescription <12 months before the index date
    b. intermediate-term, active users: first prescription 12 –24 months before the index date
    c. long-term, active users: first prescription >24 months before index date

Table 3

The effect of PPI use on survival in patients with pancreatic cancer

	Crude HR (95%CI)	adjusted[1] HR (95% CI)
Former users	1.15 (0.94–1.40)	1.12 (0.92–1.37)
Short-term, active users	1.11 (1.02–1.21)	1.11 (1.02–1.21)
Intermediate-term, active users	0.96 (0.82–1.11)	0.95 (0.82–1.11)
Long-term, active users	1.03 (0.94–1.14)	1.02 (0.93–1.13)

N=, number of individuals; HR, hazard ratio; 95% CI, 95% confidence interval;

[1]Adjusted for: diabetes, smoking, alcohol use and obesity

Stratification:

1. former users: most recent PPI prescription >6 months prior to index date
2. active users: most recent PPI prescription < 6 months prior to index date
    a. short-term, active users: first prescription <12 months before the index date
    b. intermediate-term, active users: first prescription 12 – 24 months before the index date
    c. long-term, active users: first prescription >24 months before index date