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Running Title: Proton Pump inhibitors and pancreatic cancer

Blánaid Hicks [1], Søren Friis [2, 3], Anton Pottegård [4]

[1] Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland.

[2] Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark

[3] Department of Public Health, Copenhagen University, Copenhagen, Denmark

[4] Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark

Correspondence:

Dr Blánaid Hicks

Centre for Public Health, ICSB,

Royal Victoria Hospital

Belfast, N. Ireland,

BT12 6BA

E-mail: B.Hicks@qub.ac.uk

Phone: +44 (0)28 9063 5009

Key Points:

- Preclinical studies suggest that proton pump inhibitors may increase the risk of pancreatic cancer, however, the epidemiologic evidence is sparse and equivocal.
- In this study, use of proton pump inhibitors was not associated with an increased risk of pancreatic cancer.
- A neutral association was also seen between use of histamine-2-receptor antagonists and pancreatic cancer risk.

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ABSTRACT

Purpose

Preclinical studies have suggested that proton pump inhibitors (PPIs) may increase pancreatic cancer risk, however, epidemiological studies are few, and the results are conflicting. This spurred us to evaluate whether PPI use is associated with an increased risk of pancreatic cancer in a large population-based study.

Methods

We conducted a nationwide case-control study using data from Danish demographic and healthcare registries. All patients (n=6,921) with a first cancer diagnosis of pancreatic cancer between 2000 and 2015 were identified from the Danish Cancer Registry and age-, sex-, and calendar-matched 1:20 to population controls using risk set sampling. Conditional logistic regression was applied to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for potential confounders. In secondary analyses, we examined dose-response patterns and associations with individual PPIs as well as with histamine-2-receptor antagonists.

Results

Ever use of PPIs occurred among 27.8% of 6,921 pancreatic cancer cases and 25.4% of 34,695 matched controls, yielding a neutral adjusted OR of 1.04 (95% CI 0.97–1.11). ORs were also close to unity in analyses of high-use of PPIs (≥1,000 DDDs; OR, 0.92 95%CI 0.80-1.07). There was no evidence of a dose-response relationship, with ORs close to unity across categories, including for those with the highest cumulative use (>2000 DDDs; OR, 1.03 95%CI 0.84-1.26). Analyses of subgroups as well as individual types of PPI and of histamine-2-receptor antagonists use also returned neutral associations.

Conclusions

In this large nationwide case-control study, PPI use was not associated with an increased risk of pancreatic cancer.

INTRODUCTION

Proton pump inhibitors (PPIs) are used predominantly for the treatment of gastrointestinal disorders, including gastroesophageal reflux disease (GERD). PPI use is increasing dramatically[1] and concerns have been raised about their overutilization and risks of potential adverse effects,[2] including the potential increased risk of pancreatic cancer.[3]

Two hypotheses have been suggested for the potential carcinogenic effect of PPIs in pancreatic cancer, relating to increased production of gastrin [4] and gastric hypoacidity.[5] Few observational studies have examined the association between PPI use and risk of pancreatic cancer, reporting equivocal results. One study reported strong associations between both short-term and intermediate-term (initiation 12-24 months prior to diagnosis) users and pancreatic cancer risk; however, these associations were prone to reverse causality bias. Still, the increased risk persisted among long-term (first prescription >24 months before index date) users (HR,1.85; 95%CI 1.67-2.06).[3] In contrast, additional studies reported null associations with PPI use and pancreatic cancer risk.[6,7]

Prompted by the conflicting evidence, we used detailed data from the Danish nationwide demographic and health registries to investigate the association between PPI use and pancreatic cancer risk.

MATERIALS AND METHODS

Data Sources

We performed a nested-case control analysis based on the nationwide registry data including: the Danish Cancer Registry,[8] the National Prescription Registry,[9] the National Patient Registry,[10] Registers in Statistics Denmark on educational level and the Civil Registration System.[11] Supplementary Material provides a detailed description of these registries (**Appendix A**) with codes for diagnoses, drug exposure and covariates (**Appendix B**). All linkages were performed by Statistics Denmark.

Case Selection

From the Danish Cancer Registry, we identified cases as all patients with a primary diagnosis of histologically verified pancreatic ductal adenocarcinoma between January 1st 2000 and December 31st 2015. The date of diagnosis was defined as the index date. We excluded patients outside the range of 18-85 years at the index date and patients who resided outside of Denmark within 10 years prior to the index date, ensuring at least 10 years exposure period. We excluded patients with a history of cancer (excluding non-melanoma skin cancers) and familial pancreatic syndromes (hereditary breast and ovarian cancer syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome and Li-Fraumeni syndrome).

Control Selection

Controls were selected using risk set sampling. For each case, we selected 20 controls matched by sex, age and calendar time, applying the same selection criteria as for cases.

Index dates for control participants were identical to that of corresponding cases. Subjects were eligible for sampling as controls before they became cases.

Exposure definition

Based on prescriptions dispensed since 1995, ever-use of PPIs (including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole) was defined as having filled at least one prescription for a PPI prior to the index date. High levels of PPI use were defined as filled prescriptions equivalent to ≥1000 defined daily doses (DDDs), corresponding to approximately 3 years of cumulative use, e.g., 20,000 mg of omeprazole or 30,000 mg of lansoprazole. Prescriptions filled within two years prior to the index period were disregarded to allow for a minimum of latency time and to minimize reverse causality.

Potential Confounders

Potential confounders included a prior diagnoses of diabetes, alcohol-related diseases, chronic obstructive pulmonary disorder (COPD), chronic pancreatitis, gallstones, peptic ulcer, helicobacter pylori infection, or hepatitis B and C infection, use of low-dose aspirin, NSAIDs, statins or HRT (with concomitant drug use defined as ≥2 prescriptions), Charlson Comorbidity Index (CCI) score (0 low; 1-2 medium; ≥3 high) and highest achieved education (basic, medium, higher or unknown). For all covariates, information within two years prior to the index date was disregarded.

Statistical Analyses

We used conditional logistic regression to calculate ORs and 95% confidence intervals (CIs) for pancreatic cancer associated with PPI use, adjusting for the above confounders. Secondary analyses evaluated the presence of a potential dose-response association, stratifying cumulative PPI use by predefined categories, i.e., 1-99 DDDs, 100-499 DDDs, 500-999 DDDs, 1000-2000 DDDs, and >2000 DDDs. We calculated ORs for pancreatic cancer risk for individual types of PPIs. Never use of PPI served as the reference category in all analyses of PPI use.

We repeated the main analyses for histamine-2-receptor antagonists (never use constituted the reference group), as these agents have similar indications to PPIs and also have the capacity to induce hypergastrinemia.[12]

Subgroup and Sensitivity Analyses

We preformed subgroup analyses by age, gender, stage at diagnosis (i.e. localized or non-localized), calendar year and no history of diabetes (as patients with diabetes experience an increased risk of pancreatic cancer).[13] Finally, analyses varied the lag time between zero and five years in 6-month intervals.

All analyses were performed using STATA Release 14.1 (StataCorp, College Station, TX, USA). This study was approved by The Danish Data Protection Agency and Statistics Denmark's Scientific Board.

RESULTS

We identified 10,592 cases of pancreatic ductal adenocarcinoma. Following

exclusions (**Supplementary Figure 1**), 6,921 cases were matched to 34,605 cancer-free

controls. Overall, 27.8 % of cases and 25.4% of controls filled a prescription for PPIs.

Compared to controls, cases had higher prevalence of comorbid conditions, including

diabetes, higher comorbidity score, and more frequent use of concomitant drugs, including

NSAIDs and statins. Other characteristics were similar between cases and controls

(**Supplementary Table 1**).

Compared with non-use, ever use of PPIs yielded an age-, sex-, and calendar-period-

adjusted (by design) OR for pancreatic cancer of 1.13 (95%CI 1.07-1.20) and for high-use an

OR of 1.09 (95%CI 0.95-1.25). In multivariable analyses, the ORs were attenuated for ever-

use (OR, 1.04 95%CI 0.97-1.11) and high-use (OR, 0.92 95%CI 0.80-1.07). Analyses

defining PPI use according to cumulative DDDs revealed no apparent dose-response

relationship. Analyses stratified by individual PPI drugs did not alter associations materially

(**Table 1**).

Secondary analyses examining the association between H2RAs and pancreatic cancer

risk, yielded ORs close to unity for ever use (OR, 1.02 95%CI 0.94-1.11) and high use (OR,

0.90 95%CI 0.68-1.20), with no evidence of a dose-response (**Supplementary Table 2**).

In analyses stratifying by pre-defined subgroups associations with PPI use and

pancreatic cancer risk remained largely similar (**Table 2**). Sensitivity analyses varying the

length of exposure lag time revealed a marked increase in OR when removing the lag (OR,

1.51 95%CI 1.31-1.73), while all ORs were close to unity when applying lag-time periods

between 6 and 60 months (**Supplementary Table 3).**

DISSCUSSION

In this large nationwide case-control study, we found no evidence of an association between PPI use and pancreatic cancer risk. Similar neutral associations were found in analyses of the association between H2RA use and pancreatic cancer risk.

The results of this study are compatible with those from two previous studies, which reported null associations with ever use of PPIs and pancreatic cancer.[6,7] Contrastingly, an additional study reported an increased risk of pancreatic cancer with PPI use.[3] The strongest associations were seen with short-term use (OR, 10.42 95%CI 9.26–11.73) however the increased risk persisted among long-term users (OR, 1.85; 95%CI 1.67-2.06). The results of this study are likely attributable to reverse causality, i.e., initiation or discontinuation of PPIs occurring as a consequence of symptoms of yet undiagnosed pancreatic cancer. [13] Indeed, we also observed elevated ORs when removing the 2-year lag period, however, estimates returned to unity when we applied a 6-month lag period. The authors also failed to account for the apparent crucial latency period, which appears to have had substantial influence on the study results.

Strengths and Limitations

This study was large and extended over a long study period with almost complete population coverage. Furthermore, pancreatic cancer cases were identified from the Danish Cancer Registry, which has accurate and almost complete registration of incident cancer.[8] Histological verification of the pancreatic cancer cases further enhanced case validity. Additionally, the use of the Danish National Prescription Registry ensured complete and high-quality assessment of prescription drug use up to a maximum of 20 years of drug exposure history.[9]

This study also had some limitations. We lacked information on anthropometric measures and smoking status, which are established risk factors for pancreatic cancer.[14] However, we adjusted for COPD as a crude measure of heavy smoking. Moreover, confounding by both body mass index and smoking would result in an overestimation of the association between PPI use and pancreatic cancer risk, and thus given our null findings, provides some reassurance. Secondly, this study included only pancreatic ductal adenocarcinoma thus we cannot exclude associations with rare subtypes of pancreatic cancer (e.g. acinar cell carcinoma or pancreatic neuroendocrine tumours). Finally, we were unable to account for over-the-counter use of PPIs; however, this accounts for only approximately 2% of PPI use in Denmark[1,15], and typically represents sporadic use, due to lower initial pricing of prescription drugs and reimbursement by the Danish Health National Service.[15]

In summary, we found no evidence of an association between the use of PPIs and pancreatic cancer risk. Results remained consistent across subgroup and in sensitivity analyses. This study should provide some reassurance to both patients and clinicians.

ACKNOWLEDGMENTS

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Table 1 Association between PPI use and risk of pancreatic cancer.

Subgroup	Cases	Controls	Adjusted OR (95% CI)[†]	Adjusted OR (95% CI)[‡]
Non-use	4,998	25,809	1.00 (ref.)	1.00 (ref.)
Ever use	1,923	8,796	1.13 (1.07-1.20)	1.04 (0.97-1.11)
High-use (≥1000 DDDs)	293	1,392	1.09 (0.95-1.25)	0.92 (0.80-1.07)
Cumulative use (DDDs)				
1-99	964	4,573	1.09 (1.01-1.18)	1.02 (0.94-1.10)
100-499	478	2,095	1.19 (1.07-1.33)	1.07 (0.95-1.21)
500-999	188	736	1.36 (1.15-1.62)	1.18 (0.98-1.41)
1000-2000	135	719	0.93 (0.77-1.14)	0.78 (0.63-0.96)
>2000	158	673	1.24 (1.03-1.50)	1.03 (0.84-1.26)
Test for trend	1,923	8,796	P=0.53	P=0.76
Individual PPIs (High Use ≥1000 DDDs)				
Esomeprazole	68	315	1.11 (0.85-1.45)	0.96 (0.73-1.27)
Omeprazole	101	483	1.06 (0.85-1.33)	0.92 (0.73-1.15)
Pantoprazole	41	212	1.01 (0.72-1.43)	0.89 (0.63-1.26)
Lansoprazole	82	345	1.21 (0.95-1.55)	1.06 (0.82-1.36)

Abbreviations: OR, Odds ratio; CI, confidence interval; DDD, defined daily dose
[†]Adjusted for age, gender, and calendar time (by design).
[‡] Fully adjusted model, additionally adjusting for prior diagnoses of diabetes, alcohol-related disease, COPD, chronic pancreatitis, gallstones, peptic ulcer, helicobacter pylori infection, hepatitis B and C infection; use of low-dose aspirin, NSAIDs, statins or HRT; Charlson comorbidity Index (CCI) score (0 low; 1-2 medium; ≥3 high); highest achieved education (basic, medium, higher or unknown).

Table 2 Association between high use of PPI and risk of pancreatic cancer by patient subgroup

Subgroup	Cases Exposed /unexposed	Controls Exposed /unexposed	Adjusted OR (95%CI)[†]	Adjusted OR (95%CI)[‡]
Age				
< 50 years	(n<5)	16 / 1,375	(-)	(-)
50-60 years	46 / 919	123 / 4,879	1.79 (1.25-2.56)	1.27 (0.85-1.91)
60-75 years	171 / 2,826	798 / 14,697	1.15 (0.96-1.38)	0.95 (0.78-1.15)
75+ years	73 / 987	455 / 4,858	0.78 (0.59-1.01)	0.74 (0.55-1.00)
Sex				
Male	145 / 2,730	689 / 13,900	1.06 (0.88-1.29)	0.96 (0.78-1.18)
Female	148 / 2,268	703 / 11,909	1.12 (0.92-1.36)	0.87 (0.70-1.08)
Stage				
Localized	32 / 579	164 / 3,044	0.98 (0.65-1.48)	0.88 (0.56-1.37)
Non-localized	186 / 3,566	914 / 18,288	1.05 (0.89-1.25)	0.89 (0.74-1.08)
No history of diabetes	220 / 4,453	1,175 / 24,066	1.01 (0.86-1.18)	0.89 (0.75-1.05)
Calendar year				
2004-2007	34 / 1,661	188 / 8,531	0.98 (0.67-1.43)	0.80 (0.53-1.20)
2008-2011	83 / 1,715	398 / 8,806	1.04 (0.81-1.34)	0.92 (0.70-1.21)
2012-2015	176 / 1,622	806 / 8,472	1.14 (0.95-1.37)	1.01 (0.82-1.23)

Abbreviations: OR, odds ratio; CI, confidence intervals
[†]Adjusted for age, gender, and calendar time (by design).
[‡]Fully adjusted model, additionally adjusting for prior diagnoses of diabetes, alcohol-related disease, COPD, chronic pancreatitis, gallstones, peptic ulcer, helicobacter pylori infection, or hepatitis B and C infection; use of low-dose aspirin, NSAIDs, statins or HRT; Charlson comorbidity Index (CCI) score (0 low; 1-2 medium; ≥3 high); highest achieved education (basic, medium, higher or unknown).