**THE DELETERIOUS ASSOCIATION BETWEEN PROTON PUMP INHIBITORS AND PROSTATE CANCER SPECIFIC DEATH**

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**Abstract**

***Introduction***

Proton pump inhibitors (PPIs) are a commonly prescribed class of medications. Although in-vitro and in-vivo data have shown PPIs to have anti-tumor effects, more recent studies suggest an increased cancer risk in several solid organs. Pantoprazole, a specific PPI, has been shown to harbor a protective effect in human prostate cancer (PCa) cells. We aimed to investigate the effect of pantoprazole and other PPIs on PCa-specific death and other PCa outcomes.

***Materials & methods***

In this retrospective, population-based cohort study, data was incorporated from the Institute for Clinical and Evaluative Sciences to identify all men aged 66 and above with a history of a single negative prostate biopsy between 1994 and 2016. We used multivariable Cox regression models with time-dependent covariates, to assess the effect of PPIs on PCa diagnosis, androgen deprivation therapy (ADT) use, and PCa-specific death. All models included other medications with a putative effect on PCa. Furthermore, all models were adjusted for age, rurality index, comorbidity score, and study onset year.

***Results***

Overall, 21,512 men were included, with a mean follow-up time of 8.06 years (SD 5.44 years). A total of 10,999 patients (51.1%) used a PPI during the study period. A total of 5,187 patients (24.1%) were diagnosed with PCa, 2,043 patients (9.5%) were treated with ADT, and 805 patients (3.7%) died from PCa. Pantoprazole was associated with a 3% (95% CI 0.3%-6%) increased rate of being treated with ADT for every six months of cumulative use, while any use of all other PPIs was associated with a 39% (95% CI 18%-64%) increased PCa-specific mortality. No significant association was found to PCa diagnosis.

***Conclusion***

Upon validation of the potentially negative association of PPIs with PCa-specific death and ADT use, the expansive use of PPIs may need to be reassessed, especially in PCa patients.

**Introduction**

Prostate cancer (PCa) is the most commonly diagnosed cancer among Canadian males[1](#_ENREF_1). Approximately 60% of PCa develop in men older than 65, with an average age of 66[2](#_ENREF_2). In Canada, the five-year net survival for PCa is among the highest of all cancers at 95%[1](#_ENREF_1). In the US, survival for early-stage disease is almost 100% while being considerably lower for advanced cancers (stage IV) presenting with distant metastases at diagnosis (29%)[3](#_ENREF_3).

The high prevalence of PCa has led to tremendous interest in delaying disease progression and preventing PCa-specific death. Many medications have been previously assessed and were suggested to harbor a primary or secondary chemo-preventative effect. Some of the most well-studied medications include five alpha-reductase inhibitors (5ARIs)[4](#_ENREF_4), metformin[5](#_ENREF_5), and statins[6](#_ENREF_6).

However, another important class of medications are proton pump inhibitors (PPIs). These are one of the more commonly prescribed medications globally, used for gastroesophageal reflux and peptic ulcer disease[7](#_ENREF_7). PPIs inhibit gastric acid secretion by irreversibly binding and inhibiting the hydrogen/potassium ATPase enzyme in gastric parietal cells[8](#_ENREF_8). The effect of this group of medications has been assessed in several cancers, including gastric[9](#_ENREF_9), esophageal[10](#_ENREF_10), hepatic[11](#_ENREF_11), breast[12](#_ENREF_12), melanoma[12](#_ENREF_12), and PCa[12](#_ENREF_12). Some studies have shown PPIs to manifest anti-tumor effects[13](#_ENREF_13), but more recent studies have depicted contradicting results with an association between long-term PPI use and an increased risk of gastric[14](#_ENREF_14), colorectal[15](#_ENREF_15), pancreatic[16](#_ENREF_16), and PCa[7](#_ENREF_7).

Pantoprazole, one of the more commonly prescribed PPI, has been suggested to have a specific anti-tumor effect, influencing cancer cell apoptosis, metastasis, and autophagy[17](#_ENREF_17) (a regulated cell mechanism for removal of unnecessary components, and a known chemotherapy resistance mechanism). Pantoprazole specifically, has been suggested to enhance docetaxel activity against human PCa cells, in both in-vitro[18](#_ENREF_18) and in-vivo[19](#_ENREF_19) settings, by limiting autophagy.

These findings led us to investigate the effect of PPIs, and specifically the effect of pantoprazole on PCa-specific death and other PCa-associated outcomes, in a population-level based study. In addition to basic demographic data, we also included other medications with a putative effect on PCa. We hypothesized that pantoprazole and perhaps other PPIs, would decrease the rate of PCa-specific death over time.

**Methods**

This study was approved by the ethics board committee of the University of Toronto and University Heath Network. The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines[20](#_ENREF_20), and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data statement[21](#_ENREF_21). Administrative data housed at the Institute for Clinical and Evaluative Sciences (ICES) was used to perform a retrospective population-based cohort study. In the province of Ontario, a single government-funded health insurance system, the Ontario Health Insurance Plan (OHIP), is responsible for reimbursement of all essential medical care. This allows capture of the entire adult population and access to their anonymized data. Importantly, in Ontario, medication prescription is free available to everyone 65 years and older through the Ontario Drug Benefit (ODB) program. This allows accurate capture of all provided prescriptions in this population.

**Data sources**

Data was acquired from several specific datasets housed at ICES. These included the Ontario Cancer Registry (OCR), which was used to identify incident PCa cases, with a known accuracy of over 93%[22](#_ENREF_22); the registered persons database (RPDB) consisting of demographic information on persons registered under OHIP and persons who are eligible for the ODB program[23](#_ENREF_23); the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), consisting of in-patient hospitalization data[24](#_ENREF_24); the ODB database, including data on all drug prescription for patients older than 65[25](#_ENREF_25); the Ontario Laboratory Information System (OLIS), which harbors the results for approximately 95% of all laboratory tests conducted in Ontario[26](#_ENREF_26); and the Ontario office of the Registrar General (ORG), which consists of individual-level vital statistics data.

**Study design and participants**

A minimum age of 66 years was used as the cut-off for this study, to enable a one-year look-back period, confirming that no drug prescription of any of the analyzed medications was given between the age of 65 and 66. This ensured that all men analyzed in the study were medication-naïve. The study included all men aged 66 and older with a history of a single negative transrectal ultrasound-guided prostate biopsy (TRUS-Bx) in the province of Ontario between January 1st, 1994 and September 30th, 2016. To identify all relevant patients, we used OHIP billing codes for TRUS-Bx, and the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP) to make sure no record of PCa diagnosis, nor receipt of PCa-specific treatment existed within the three months after the biopsy. The codes used are detailed in Supplemental Table 1. Men with a history of a previous negative biopsy were chosen as part of a pre-screening method to include a ‘healthier’ population, seen fit to undergo a biopsy. A look-back window of minimum of three years, from January 1991 until the date of cohort entry was used to ascertain that included TRUS-Bxs were the first negative biopsies and that men had no previous PCa diagnosis. The index date (study onset time) was defined as the date 90 days after the first negative prostate biopsy, to ensure no PCa diagnosis was recorded. Patients were followed from the index date until one of four possible outcomes: a) Death, b) Last health services contact in Ontario, c) Becoming OHIP ineligible, or d) End of the study period (September 30th, 2016).

**Study outcomes**

Our primary outcome was PCa-specific death, examined as a time to event outcome. Secondary outcomes included use of androgen deprivation therapy (ADT), which served as a surrogate marker for advanced disease and PCa diagnosis.

**Study variables**

PCa-specific death was defined according to the primary reason of death noted on the death certificate. PCa diagnosis was defined as having either a record of PCa or having received PCa-specific treatment (radical prostatectomy, primary radiotherapy to the prostate or ADT). Data on additional medications with putative anti-cancer properties were acquired. These included medications for diabetes (metformin, insulin, sulfonylureas, thiazolidinediones), statins, 5ARIs, alpha-blockers, and glaucoma eye drops as a negative tracer drug. A detailed list of all medications analyzed is shown in appendix 1.

Additional collected variables included patient age categorized as (66-69, 70-74, 75-79, 80-84, and 85 and above), rurality index (continuous variable, with a higher number representing a more rural area)[27](#_ENREF_27), year of study entry (index year), and comorbidity status quantified with the Collapsed Ambulatory Diagnostic Groups (ADG) score (a continuous comorbidity variable derived from the Johns Hopkins Adjusted Clinical Groups System)[28](#_ENREF_28). The comorbidity score was captured with a three-year look-back period at study onset. Lastly, prostate-specific antigen (PSA) levels were collected as well but were available only from 2007.

**Statistical analyses**

Continuous variables were described using means and standard deviations (SD); categorical variables were characterized using proportions. We assessed the association between medication exposure and PC-specific death, ADT use, and PCa diagnosis. Multivariable Cox proportional hazard regression models with time-dependent exposure were used. The exposure to each medication was specified as a time-dependent variable (ever vs. never exposure at each time point during the follow-up, and the effect of the cumulative exposure to each medication per six-months of use) which was then associated with all outcomes of interest. All models were also adjusted for a priori selected covariates, treated as time-independent variables and using the values at study onset. These included the person’s age group, and the following continuous variables with log-linear effects: rurality index (0-100), index year (1994-2016) and the ADG comorbidity score. For PCa-specific death, we also included in the model all reported PCa-specific treatments (radical prostatectomy, primary radiotherapy, ADT). All assumptions underlying the models were assessed and no evidence of violations were found. All statistical tests were two-tailed, and a p-value of <0.05 was considered significant. All statistical analyses were performed using R software version 3.3.1.

**Sensitivity analyses**

Several preplanned sensitivity analyses were performed. As PSA levels were available only from 2007, we included this as a covariate in a subset analysis of patients enrolled in the study from 2007. If more than one PSA test was available, the median PSA for each patient was used. To assess for potential health utilization bias, we performed a tracer analysis, assessing the effects of PPIs on the occurrence of presbyopia.

**Results**

From 1994 until 2016, a total of 21,512 men 66 years or older with a history of a single negative prostate biopsy were identified. The mean follow-up time from the date of negative biopsy was 8.06 years (5.44 years). Table 1 depicts basic demographic data at study onset.

A total of 10,999 patients (51.1%) used a PPI during the study period (with 4,367 patients [20.3%] and 6,626 patients [30.8%], using pantoprazole and all ‘other PPIs’, respectively). Supplemental figure 1 depicts the use of all analyzed medications among the study patients. A total of 5,187 patients (24.1%) were diagnosed with PCa, 2,043 patients (9.5%) were treated with ADT, and 805 patients (3.7%) died from PCa. Figure 1 details these data stratified by age. Lastly, supplemental figure 2 depicts the various primary treatment modalities received by all PCa patients stratified by age.

When assessing the primary outcome of PC-specific death using a Cox proportional hazards model, Table 2 showed that all ‘other PPIs’ (excluding pantoprazole) were associated with a 39% (95% CI 18%-64%) increased PCa mortality, when modeled as ever vs. never use. Pantoprazole was associated with a 1.23 (95% CI 0.99-1.53) fold increased PCa mortality, but this was not statistically significant (p=0.056).

Table 3 showed that Pantoprazole was associated with a 3% (95% CI 0.3%-6%) increased rate of being treated with ADT per every six months of cumulative use. ‘Other PPIs’ were not associated with an increased rate of being treated with ADT. Furthermore, Table 4 showed no statistically significant association between pantoprazole and ‘other PPIs’ and PCa diagnosis. PSA levels could only be incorporated into the PCa diagnosis model, as in the other outcomes of interest, the number of events from 2007 and onwards was too small to analyze in a multivariable model.

Of note, 5ARIs were associated with a 44% (95% CI 25%-67%) and 9% (95% CI 6%-11%) increased rate of being treated with ADT, when modeled as ever. vs. never, and per six months of use, respectively. Additionally, increasing age, and rurality index, and a less contemporaneous study year onset were associated with a higher PCa mortality, rate of being treated with ADT, and being diagnosed with PCa. Increasing ADG comorbidity score was associated with an increased rate of being treated with ADT. Both primary radiotherapy to the prostate and primary ADT were associated with an increased PCa mortality (HR 1.86, 95% CI 1.52-2.28, and HR 4.36, 95% CI 3.56-5.33, respectively). In contrast, radical prostatectomy was associated with a protective effect (HR 0.47, 95% CI 0.31-0.72). Lastly, none of the other medications included in the models showed a negative association with any of the three outcomes examined. A focused assessment of each of these medications is beyond the scope of the present manuscript and will be considered elsewhere.

No identified association between PPIs or other medications and the tracer outcome of presbyopia (Supplemental Table 2) were found. Furthermore, we did not find an association between the tracer medication used (glaucoma eye drops) and any of the study outcomes.

**Discussion**

This study showed that during a mean follow-up of more than eight years, almost a quarter of men aged 66 years or older with a history of a single negative prostate biopsy, were diagnosed with PCa. A total of 9.5% were treated with ADT, and 3.7% died from PCa. More than half of the men were treated with a PPI during the study period. No association was found between PPIs and PCa diagnosis. However, any us of ‘other PPIs (excluding pantoprazole) was associated with a 39% increased PCa mortality. Any use of pantoprazole was associated with a 23% increased PCa mortality, although not reaching statistical significance level (p=0.056). In addition, for every six months of use, pantoprazole was associated with a 3% increased rate of being treated with ADT.

The validity of our datasets was supported by several findings: a) The lack of associations between presbyopia and all analyzed medications; b) The lack of association between glaucoma eye drops and any of the study’s outcomes; and c) The fact that the PCa diagnosis rate was similar to that found in a previous publication using ICES datasets and also showing a 23.7% PCa diagnosis rate[29](#_ENREF_29). Furthermore, the finding that 5ARIs increased the likelihood of ADT use, defined as a surrogate marker for advanced disease, is corroborated by data showing that pre-diagnostic use of 5ARIs is associated with worse cancer-specific outcomes; with patients using 5ARIS having higher Gleason scores, worse clinical-stage, and node-positive and metastatic disease[4](#_ENREF_4).

In 2016 two of the top 25 most commonly prescribed US medications were PPIs (omeprazole and pantoprazole), with more than 95 million yearly prescriptions combined for both[30](#_ENREF_30). PPIs are extremely prevalent and generally considered safe. However, in recent years, there has been some growing concerns with the various adverse effects resulting from long-term PPI use. These include increased risk of hip fracture, adverse cardiovascular events, and chronic kidney disease[31](#_ENREF_31), [32](#_ENREF_32). Furthermore, several animal models have shown that some PPIs promote carcinogenesis, including rat liver[33](#_ENREF_33), mice forestomach[34](#_ENREF_34), and induction of gastric adenocarcinoma in gerbils[35](#_ENREF_35). There have also been reports of increased rates of several malignancies in humans. These include gastric [9](#_ENREF_9), [36](#_ENREF_36), esophageal[10](#_ENREF_10), hepatic[11](#_ENREF_11), pancreatic[37](#_ENREF_37), colorectal[38](#_ENREF_38), and accumulating evidence that PPIs increase cancer-associated mortality[39](#_ENREF_39).

In PCa, there is evidence from basic science investigation suggesting that PPIs may be associated with worse PCa outcomes. First, PPIs have been shown to elevate the levels of chromogranin A in chemotherapy-naïve castrate-resistant PCa (CRPC) patients[40](#_ENREF_40). This may be associated with reduced overall survival in metastatic CRPC patients[41](#_ENREF_41). Second, PPIs exert survival, proliferative, and antiapoptotic effects in PCa cell lines and mice xenografted with androgen-sensitive human PCa cells[7](#_ENREF_7). PPIs cause these effects by inducing cell cycle progression, increasing oncoprotein expression (c-Myc), and the expression of the antiapoptotic protein (Bcl-2). Moreover, they activate proliferative pathways along with elevating PSA secretion and inhibiting prostate phosphatases[7](#_ENREF_7). Lastly, PPIs have also been shown to blunt the inhibitory action of docetaxel chemotherapy in androgen-sensitive human PCa cells[42](#_ENREF_42). To date, there has been insufficient data to assess these associations in a clinical setting. The present study demonstrates that these laboratory investigations may translate to the clinical context.

One other relevant consideration is the increasingly acknowledged role of the human microbiota and its complex relationship with its environment. The human microbiota are known to influence the metabolism, pharmacokinetics, and toxicity of many drugs and xenobiotics[43](#_ENREF_43), potentially influencing the effects of various anti-cancer treatments. Furthermore, the microbiota by itself may promote carcinogenesis, while cancer could, in turn, change the microenvironment and alter the microbiota composition[44](#_ENREF_44). When balanced, the microbiota serves as a protective factor for our body, but if in a state of dysbiosis, it does the exact opposite[45](#_ENREF_45). Although the specific role of the microbiota residing in the gastrointestinal and urinary tract and its role in PCa is far from clear, there is mounting evidence supporting its putative role in prostate health and PCa[46](#_ENREF_46). PCa patients have shown an increased prevalence of pro-inflammatory bacteria and uropathogens in the urinary tract[47](#_ENREF_47). Furthermore, hormonal therapies for PCa may alter the microbiota, influence clinical responses, and potentially modulate the antitumor effects of other therapies[44](#_ENREF_44). In PPI users, 20% of the gastrointestinal bacterial taxa were significantly different, compared with non-users[48](#_ENREF_48). This could theoretically result in increased carcinogenesis, worsening of PC-specific outcomes, and serve as a hypothesis of how PPIs alter the outcomes of PCa patients.

Only one other population-based study examined the chemopreventative effect of PPIs on PCa diagnosis[12](#_ENREF_12). In this Icelandic case-control study, the PPI use of 1,897 PCa patients was assessed and compared to age-matched population controls. The study did not find PPIs to have a chemopreventative effect on PCa diagnosis[12](#_ENREF_12), similar to our study. Importantly, the Icelandic study did not assess the effect of PPIs on ADT use or PCa-specific death. Other limitations of this study included the fact that all patients taking PPIs were included, both prevalent and incident users, making it difficult to ascertain the true effect of incident PPI use. Additionally, multivariable conditional logistic regression was used without using time-varying covariates, and no comorbidity or rurality data was available.

Our study’s strength lies in its large cohort of men, consisting of ‘real-world’ clinical data with relatively long follow-up time. To our knowledge, this is the only study specifically assessing the role of incident use of pantoprazole and all other PPIs on PCa-specific death and ADT use. However, the study does have several limitations. This was a retrospective population-based analysis with its inherent selection bias and health administrative database associated inaccuracies. Our data was limited to men older than 66, and it contained 20-year old data. We also lacked clinically important information regarding ethnicity, disease stage and grade, pertinent family history, and personal genetic risk factors. During the study period, some of the PPIs were available as low-dose over-the-counter medications, making it impossible to account for them. However, bearing in mind that these patients would not need to pay for a medication obtained by a prescription, it is safe to assume that over the counter exposure would not significantly bias the results. More importantly, it has been previously demonstrated that prescription claims data provide accurate estimation of association even though the prescribed medications are available over the counter[49](#_ENREF_49). We could also not account for the indication of PPI use. Additionally, for some patients ADT could have been given for local disease, as this has been done in the past, due to increasing age or significant comorbidities, making it a moot surrogate marker of advanced disease. Lastly, in such an analysis, there is always the risk of unaccounted residual confounding.

**Conclusions**

In PCa patients, use of pantoprazole and other PPIs showed an association with ADT use and increased PCa-specific mortality. The reported potential long-term impact of these medications on PCa outcomes need to be confirmed in additional studies. If these findings are validated, the broad use of PPIs needs to be reconsidered, especially in PCa patients.

**Abbreviations:**

5ARIs = Five alpha-reductase inhibitors

ADT = Androgen deprivation therapy

ADG = Ambulatory Diagnostic Groups

CIHI-DAD = Canadian Institute for Health Information Discharge Abstract Database

CRPC = Castrate resistant prostate cancer

ICES = Institute for Clinical and Evaluative Sciences

OAT = Organic anion transporters

OCR = Ontario cancer registry

ODB = Ontario drug benefit

OHIP = Ontario health insurance plan

OLIS = Ontario laboratory information system

ORG = Ontario office of the Registrar

RPDB = Registered persons database

PCa = Prostate cancer

PPI = Proton pump inhibitors

PSA = Prostate specific antigen

SD = Standard deviation

TRUS BX = Transrectal ultrasound guided prostate biopsy

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