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ARTICLE

Clinical Research

The deleterious association between proton pump inhibitors and prostate cancer-specific mortality – a population-based cohort study

Hanan Goldberg[1,2,3,4] · Faizan K. Mohsin[5] · Refik Saskin[4] · Girish S. Kulkarni[1,4] · Alejandro Berlin[6] · Miran Kenk[1] · Christopher J. D. Wallis[1,7] · Thenappan Chandrasekar[8] · Zachary Klaassen[9,10] · Olli Saarela[5] · Linda Penn[11] · Shabbir M. H. Alibhai[2,12] · Neil Fleshner[1,2]

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Abstract

Background Proton pump inhibitors (PPIs) are commonly prescribed medications that have been shown to have contradicting effects on cancer. We aimed to investigate the effect of pantoprazole and other PPIs on prostate cancer (PCa) specific mortality (PCSM), use of androgen deprivation therapy (ADT), and PCa diagnosis using a large Canadian population-based cohort.

Methods We identified 21,512 men aged ≥ 66, with a history of a single negative prostate biopsy and no previous use of any of the analyzed medications between 1994 and 2016. Multivariable Cox regression models with time-dependent covariates were used to assess the associations of PPIs with PCa outcomes. All models included other medications with a putative chemopreventative effect on PCa-outcomes, and were adjusted for age, rurality, comorbidity, and study inclusion year.

Results Over a mean follow-up of 8.06 years (SD 5.44 years), 10,999 patients (51.1%) used a PPI, 5187 patients (24.1%) had PCa, 2043 patients (9.5%) were treated with ADT, and 805 patients (3.7%) died from PCa. For every 6 months of cumulative use, pantoprazole was associated with a 3.0% (95% CI 0.3–6.0%) increased rate of ADT use, while any use of other PPIs was associated with a 39.0% (95% CI 18.0–64.0%) increased risk of PCSM. No association was found with PCa diagnosis.

Conclusions Upon validation of the potentially negative association of PPIs with PCa, PPI use may need to be reassessed in PCa patients.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among Canadian males [1]. Approximately 60% of

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✉ Hanan Goldberg
gohanan@gmail.com

1 Division of Urology, Department of Surgical Oncology, Princess Margaret Cancer Centre, University Health Network and the University of Toronto, Toronto, ON, Canada

2 Institute of Medical Science, University of Toronto, Toronto, ON, Canada

3 Department of Urology, SUNY Upstate Medical University, Syracuse, NY, USA

4 Institute for Clinical Evaluative Sciences, Toronto, ON, Canada

5 Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada

6 Department of Radiation Oncology, University of Toronto; and Techna Institute, University Health Network, Toronto, ON, Canada

7 Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA

8 Department of Urology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

9 Division of Urology, Department of Surgery, Medical College of Georgia, Augusta University, Augusta, GA, USA

10 Georgia Cancer Center, Augusta, GA, USA

11 Department of Medical Biophysics, University of Toronto, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada

12 Department of Medicine, University Health Network and University of Toronto, Toronto, ON, Canada

PCa develop in men older than 65, with an average age of 66 [2].

The high prevalence of PCa has led to tremendous interest in delaying disease progression and preventing PCa-specific mortality (PCSM). Many medications have been previously assessed and were suggested to harbor a primary or secondary chemo-preventative effect, including 5-alpha-reductase inhibitors (5ARIs) [3], metformin [4], and statins [5].

Another important class of medications is proton pump inhibitors (PPIs). These are one of the more commonly prescribed medications globally, used for gastroesophageal reflux and peptic-ulcer disease [6]. PPIs inhibit gastric acid secretion by irreversibly binding and inhibiting the hydrogen/potassium ATPase enzyme in gastric parietal cells [7]. The effect of these medications was assessed in several cancers, including gastric [8], esophageal [9], hepatic [10], breast [11], melanoma [11], and PCa [11]. Some studies have shown PPIs to manifest antitumor effects [12], but more recent studies have depicted contradicting results with an association between long-term PPI use and an increased risk of gastric [13, 14], colorectal [15], pancreatic [16], and PCa [6].

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

These findings led us to investigate the effect of PPIs, and specifically pantoprazole on PCSM and other PCa-associated outcomes, in a population-level based study. We hypothesized that pantoprazole, and other PPIs would decrease the rate of PCSM overtime.

Methods

This study was approved by the ethics board committee of the University of Toronto. (protocol reference number 34486). The study was reported according to Strengthening the Reporting of Observational Studies in Epidemiology guidelines [20], and Reporting of Studies Conducted Using Observational Routinely-Collected Health Data statement [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 freely 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 were acquired from several datasets housed at ICES [22] and detailed in supplemental Table 1. The included data contained demographic, comorbidity, medication prescription, cancer diagnosis, and vital status details. The data for each patient from these databases is linkable using a unique encoded identifier.

Study design and participants

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 before the age of 66, essentially making sure all men included in our analysis never took any of the analyzed medications before age 66 and study inclusion. All men included in the study had a history of a single negative transrectal ultrasound-guided prostate biopsy (TRUS-BX) between January 1st, 1994 and September 30th, 2016. This was done as a pre-screening method to include a 'healthier' population, seen fit to undergo a biopsy, and include only men at risk to develop PCa. To identify all relevant patients, we used OHIP billing codes for TRUS-BX, and the specific Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures codes (Supplemental Table 2) to make sure no record of PCa diagnosis, nor receipt of PCa-specific treatment existed within the three months after the biopsy. A look-back window of a 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. Patients were followed from the index date, which was defined as three months following the date of the first negative prostate biopsy. Follow-up continued until either: (a) Death, (b) Last health services contact in Ontario, (c) Becoming OHIP ineligible, or (d) End of the study period.

Study outcomes

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

Study variables

PCSM was defined according to the primary reason of mortality 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 primary ADT). Data on additional medications with putative anti-cancer properties were acquired. These included diabetes medications (metformin, insulin, sulfonylureas, thiazolidinediones), statins, 5ARIs, and alpha blockers. Glaucoma eye drops served 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 years and above. This was not a continuous variable, as per the registry guidelines to maintain patient anonymity), rurality index (continuous variable, with a higher number representing a more rural area, year of study inclusion (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) [23]. Lastly, prostate-specific antigen (PSA) levels, available only from 2007, were collected as well.

Statistical analyses

Continuous variables were described using means and standard deviations (SD); categorical variables were characterized using proportions. Using multivariable Cox proportional hazard regression models with time-dependent exposure for each cause-specific hazard, we assessed the association between medication exposure and three distinct outcomes, including PCSM, ADT use, and PCa diagnosis. Two types of analyses were performed. In the first analysis (ever vs. never exposure), the exposure to each medication was modeled as a time-dependent binary variable with a patient's status being unexposed for the duration of the follow-up where they had not initiated the particular medication, and becoming exposed after they had first initiated the medication (ever vs never exposure at each time point during the follow-up). Therefore, the reference category are the patients who never took any medication. In the second analysis (cumulative exposure), we modeled medication exposure as a time-dependent variable but with time split into six-month intervals, to see the effect of the six-month incremental increase in exposure. The same analyses with the same models as in the ever vs. never models were performed, except that the exposure status for all the medications were replaced by the cumulative time exposed to the medications. Since medication exposure was treated as a continuous variable with six-month time intervals there was no reference category. In addition to PPIs, all models included other putative chemopreventative medications including hydrophobic and hydrophilic statins, 5ARIs, alpha blockers, and common diabetic medications (metformin, insulin, sulphonylurea, and thiazolidinediones) and the tracer drug, glaucoma eye drops. All medications were analyzed in the same manner. Using the values at study onset, additional *a priori* covariates were adjusted for and included age group, rurality index (0–100), index year (1994–2016) and the ADG comorbidity score. For the PCSM model, we also included all reported PCa-specific treatments. For the models assessing PCSM and ADT use, only men diagnosed with PCa were evaluated and the time of origin was PCa diagnosis. The proportionality and log-linearity assumptions underlying the models were assessed using residual-based diagnostics, and no 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 with a limited timeframe of one year from the first negative biopsy date. 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 TRUS-Bx and no previous use of any of the analyzed medications were identified. The mean follow-up time (SD) was 8.06 years (5.44 years). Table 1 depicts basic demographic data at study inclusion stratified by PPI use. A total of 10,999 patients (51.1%) used a PPI during the study period (with 4377 patients [20.3%] and 6622 patients [30.8%], using pantoprazole and all 'other PPIs', respectively). Supplemental Fig. 1 depicts the use of all analyzed medications among the study patients. A total of 5187 patients (24.1%) were diagnosed with PCa, 2043 patients (9.5%) were treated with ADT, and 805 patients (3.7%) died from PCa. Figure 1 details these data stratified by age. Lastly, Supplementary Fig. 2 depicts the various primary treatment modalities stratified by age.

Table 2 assessed the primary outcome of PCSM using a Cox proportional hazards model with time-dependent exposure. All 'other PPIs' (excluding pantoprazole) were associated with a 39% (95% CI 18–64%) increased PCSM,

when modeled as ever vs. never use. Table 3 showed that every six months of cumulative use of pantoprazole was associated with a 3% (95% CI 0.3–6%) increased hazard of being treated with ADT. Lastly, 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.

Of note, 5ARIs were associated with a 44% (95% CI 25–67%) and 9% (95% CI 6–11%) increased hazard of being treated with ADT, when modeled as ever. vs. never, and per six months of use, respectively (Supplemental Table 3). Additionally, increasing age and rurality index, and an earlier study inclusion year were associated with a higher PCSM, likelihood 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 PCSM (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). Supplemental Table 3 demonstrates the associations of all analyzed medications. A focused assessment of each of these medications and especially the ones with a protective effect is beyond the scope of the present manuscript and will be considered elsewhere.

No identified association between any PPI or other medications and the tracer outcome of presbyopia (Supplemental Table 4) were found. Furthermore, no association between the tracer medication used (glaucoma eye drops) and any of the study outcomes were found.

Table 1 Basic demographic characteristics of all patients.

	Pantoprazole users	*All Other PPI users*	*No PPI users*
Number of men, (%)	4377 (20.3%)	6622 (30.8%)	12,755 (59.3%)
Time-period, n (%)			
1994–2000	4263 (64.4%)	5277 (60.3%)	6854 (53.7%)
2001–2007	2050 (31%)	2866 (32.7%)	3768 (29.5%)
2008–2014	309 (4.7%)	614 (7.0%)	2133 (16.7%)
Age category, n (%)			
66–69	1983 (45.3%)	2717 (41%)	4816 (37.8%)
70–74	1564 (35.7%)	2397 (36.2%)	4330 (33.9%)
75–79	631 (14.4%)	1117 (16.9%)	2304 (18.1%)
80–84	164 (3.7%)	326 (4.9%)	929 (7.3%)
≥85	35 (0.8%)	65 (1.0%)	376 (2.9%)
Mean Rurality index (SD)	11.75 (17.06)	11.54 (17.58)	11.53 (17.36)
Mean ADG score, (SD)	18.52 (10.92)	19.17 (11.21)	19.05 (11.92)
Prostate cancer diagnosis rate, n (%)	1244 (28.4%)	1821 (27.5%)	2778 (21.8%)
Prostate cancer treatment			
AS/WW/No treatment	246 (5.6%)	417 (6.3%)	909 (7.1%)
Primary ADT	350 (8.0%)	541 (8.2%)	752 (5.9%)
Radiotherapy to the prostate +/–	460 (10.5%)	598 (9.0%)	696 (5.5%)
ADT	188 (4.3%)	265 (4.0%)	421 (3.3%)
Radical prostatectomy			
Glaucoma eye drops use, n (%)	354 (8.1%)	538 (8.1%)	775 (6.1%)

ADT androgen deprivation therapy, *ADG* Johns Hopkins' Aggregated Diagnosis Groups comorbidity score, *AS* active surveillance, *PPI* proton pump inhibitors, *SD* standard deviation, *WW* watchful waiting.

Discussion

This study showed that during a mean follow-up of more than eight years, almost a quarter of the men

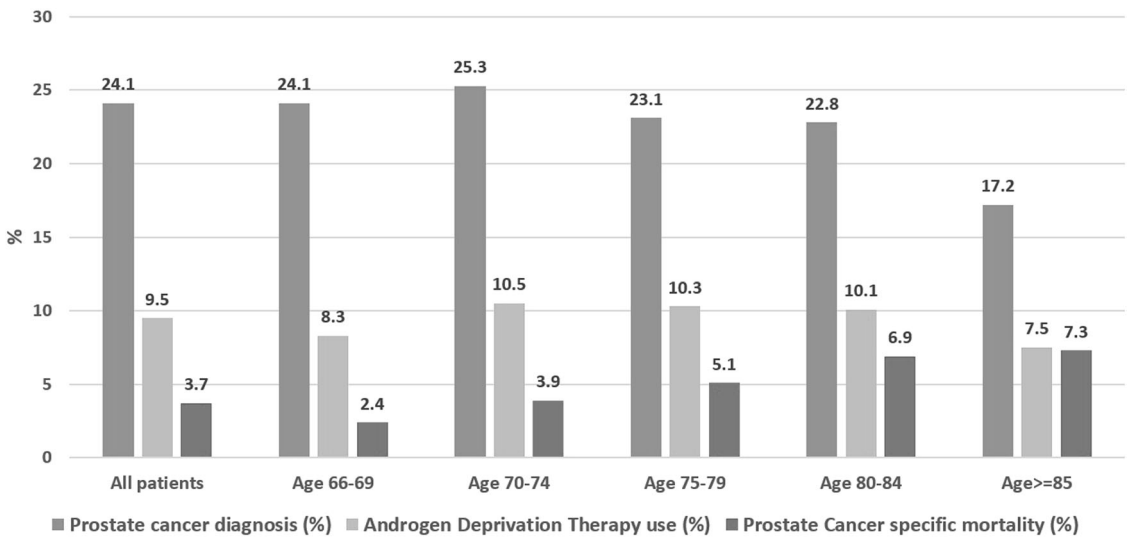

Fig. 1 Prostate cancer diagnosis, treatment and mortality rates. Percentage of prostate cancer diagnosis (out of entire study population), any use of androgen deprivation therapy, and prostate cancer-specific mortality, stratified by age.

Table 2 Cox proportional hazards multivariable regression model predicting the risk of prostate cancer-specific mortality with medications modeled as ever vs. never and cumulative 6 months usage.

	Ever vs. never		Cumulative 6 months	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age Category (reference 66–69 years)				
70–74 years	1.38 (1.14–1.68)	0.0009	1.4 (1.15–1.71)	0.0005
75–79 years	2.41 (1.93–3.02)	<0.0001	2.47 (1.98–3.09)	<0.0001
80–84 years	4.18 (3.12–5.59)	<0.0001	4.3 (3.22–5.74)	<0.0001
≥85 years	6.9 (4.38–10.86)	<0.0001	7.09 (4.5–11.15)	<0.0001
ADG score (continuous variable)	1.004 (0.997–1.01)	0.2	1.005 (0.998–1.01)	0.1
Rurality index (continuous variable)	1.004 (1.001–1.008)	0.01	1.004 (1.001–1.008)	0.013
Index year (continuous variable)	0.9 (0.87–0.92)	<0.0001	0.91 (0.88–0.93)	<0.0001
Prostate cancer treatment (reference no treatment)				
Primary radiotherapy	1.86 (1.52–2.28)	<0.0001	1.94 (1.59–2.38)	<0.0001
Radical prostatectomy	0.47 (0.31–0.72)	<0.0001	0.44 (0.29–0.66)	0.0001
Primary ADT	4.36 (3.56–5.33)	<0.0001	4.42 (3.61–5.41)	<0.0001
Pantoprazole treatment vs. no treatment	1.23 (0.99–1.53)	0.056	0.987 (0.944–1.03)	0.57
Treatment with all other proton pump inhibitors vs. no treatment	1.39 (1.18–1.64)	<0.0001	1.009 (0.977–1.02)	0.94
Glaucoma eye drops treatment vs. no treatment	1.05 (0.79–1.4)	0.71	0.99 (0.92–1.06)	0.827

All models also included usage of statins, alpha blockers, 5-alpha-reductse inhibitors, metformin, insulin, sulphonylurea, and thiazolidinediones.

ADG Johns Hopkins' Aggregated Diagnosis Groups comorbidity score, *ADT* androgen deprivation therapy, *PSA* prostate-specific antigen.

Table 3 Cox proportional hazards multivariable regression model assessing the likelihood of being treated with androgen deprivation therapy with medications modeled as ever vs. never and cumulative 6 months usage.

	Ever vs. never		Cumulative 6 months	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age category (reference 66–69 years)				
70–74 years	1.47 (1.35–1.6)	<0.0001	1.47 (1.35–1.6)	<0.0001
75–79 years	2.04 (1.85–2.26)	<0.0001	2.04 (1.84–2.2)	<0.0001
80–84 years	2.7 (2.33–3.12)	<0.0001	2.71 (2.35–3.14)	<0.0001
≥85 years	3.449 (2.658–4.47)	<0.0001	3.47 (2.68–4.51)	<0.0001
ADG score (continuous variable)	1.005 (1.002–1.008)	0.001	1.005 (1.002–1.008)	0.001
Rurality index (continuous variable)	1.0019 (1.000–1.0037)	0.046	1.001 (1.0001–1.003)	0.04
Index year (continuous variable)	0.963 (0.954–0.972)	<0.0001	0.96 (0.954–0.97)	<0.0001
Pantoprazole treatment vs. no treatment	1.15 (0.978–1.35)	0.088	1.03 (1.003–1.06)	0.031
Treatment with all other proton pump inhibitors vs. no treatment	0.977 (0.871–1.09)	0.692	0.981 (0.959–1.003)	0.099
Glaucoma eye drops treatment vs. no treatment	0.894 (0.728–1.098)	0.287	0.976 (0.91–1.04)	0.49

All models also included usage of statins, alpha blockers, 5-alpha-reductase-inhibitors, metformin, insulin, sulphonylurea, and thiazolidinediones.

ADG Johns Hopkins' Aggregated Diagnosis Groups comorbidity score, *PSA* prostate-specific antigen.

above the age of 66 with a previous history of a single negative TRUS-BX were diagnosed with PCa. 9.5% were treated with ADT, and 3.7% died from PCa. More than half of the men were treated with a PPI. No association was found between PPIs and PCa diagnosis. However, unexpectedly, any use of PPIs (excluding pantoprazole) was associated with a 39% increased PCSM, and any use of pantoprazole was associated with a 23% increased PCSM, although not reaching statistical significance ($p = 0.056$). Also, for every six months of use, pantoprazole was associated with a 3% increased rate of being treated with ADT.

Table 4 Cox proportional hazards multivariable regression model assessing the risk of being diagnosed with prostate cancer with medications modeled as ever vs. never and cumulative 6 months usage.

	Ever vs. never		Cumulative 6 months		Ever vs. never (with PSA [>2007])	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age category (reference 66–69 years)						
70–74 years	1.07 (1.005–1.14)	0.032	1.0728 (1.0073–1.14)	0.028	1.19 (0.91–1.557)	0.188
75–79 years	1.04 (0.967–1.13)	0.246	1.05 (0.969–1.13)	0.22	0.91 (0.59–1.39)	0.66
80–84 years	1.222 (1.08–1.38)	0.001	1.22 (1.086–1.38)	0.001	0.6 (0.22–1.64)	0.32
≥85 years	1.157 (0.924–1.44)	0.2	1.16 (0.926–1.45)	0.19	1.3 (0.36–4.68)	0.68
ADG score (continuous variable)	0.999 (0.997–1.002)	0.87	0.999 (0.997–1.002)	0.87	1.008 (0.99–1.02)	0.169
Rurality index (continuous variable)	1.004 (1.003–1.006)	<0.0001	1.004 (1.003–1.006)	<0.0001	1.003 (0.996–1.011)	0.31
Index year (continuous variable)	0.98 (0.974–0.986)	<0.0001	0.979 (0.973–0.985)	<0.0001	1.18 (1.1–1.26)	<0.0001
PSA (continuous variable)	–	–	–	-	1.002 (1.001–1.004)	<0.0001
Pantoprazole treatment vs. no treatment	1.07 (0.929–1.253)	0.314	1.02 (0.993–1.05)	0.064	1.06 (0.631–1.79)	0.81
Treatment with all other proton pump inhibitors vs. no treatment	0.95 (0.86–1.04)	0.313	0.991 (0.97–1.01)	0.41	1.344 (0.873–2.069)	0.17
Glaucoma eye drops treatment vs. no treatment	0.960 (0.81–1.16)	0.736	0.988 (0.93–1.05)	0.71	1.76 (0.9–3.47)	0.0984

All models also included usage of statins, alpha blockers, 5-alpha-reductase-inhibitors, metformin, insulin, sulphonylurea, and thiazolidinediones.
ADG Johns Hopkins' Aggregated Diagnosis Groups comorbidity score, *PSA* prostate-specific antigen.

The validity of our analyses was supported by: (a) The lack of associations between presbyopia and all medications; (b) The lack of association between glaucoma eye-drops and all study outcomes; (c) The PCa diagnosis rate was similar to that found in a previous publication using a similar population from ICES datasets (23.7%) [24]; and (d) The finding that 5ARIs increased the hazard of ADT use is corroborated by data showing that pre-diagnostic use of 5ARIs is associated with worse cancer-specific outcomes; with higher Gleason scores and worse clinical-stage [3].

In 2016 two of the 25 most commonly prescribed US medications were PPIs (omeprazole and pantoprazole), with more than 95 million yearly prescriptions combined for both [25]. PPIs are extremely prevalent and considered safe. However, recently, there has been some growing concerns with adverse effects resulting from long-term PPI use. These include increased risk of hip fracture, adverse cardiovascular events, chronic kidney disease [26, 27] and mortality resulting from cardiovascular and chronic kidney disease [14]. Furthermore, several animal models have shown that some PPIs promote carcinogenesis, including rat liver [28], and mouse forestomach [29]. There have also been reports of increased human malignancy rates, including gastric [8], esophageal [9], hepatic [10], pancreatic [30], and colorectal [31].

Basic science investigations suggested that PPIs may be associated with worse PCa outcomes. First, PPIs have been shown to elevate chromogranin A levels in chemotherapy-naïve castrate-resistant PCa patients, which may be associated with reduced overall survival [32]. Second, PPIs exert survival, proliferative, and antiapoptotic effects in PCa cell-lines and mice xenografted with androgen-sensitive human PCa cells [6]. PPIs cause these effects by inducing cell cycle progression, increasing oncoprotein (c-Myc) and antiapoptotic protein (Bcl-2) expression. Moreover, they activate proliferative pathways along with elevating PSA secretion and inhibiting prostate phosphatases [6]. Lastly, PPIs also blunt the inhibitory action of docetaxel in androgen-sensitive human PCa cells [33]. The present study demonstrates that these laboratory investigations may translate to 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 is known to influence the metabolism, pharmacokinetics, and toxicity of many drugs and xenobiotics [34], 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 [35]. When balanced, the microbiota protects our body, but if in a state of dysbiosis, it can have a harmful effect. Although the specific role of the microbiota residing in the gastrointestinal and urinary-tract is still unclear, there is mounting evidence supporting its putative role in PCa [36]. PCa patients have shown an increased prevalence of pro-inflammatory bacteria and uropathogens in the urinary-tract [37]. Furthermore, hormonal therapies for PCa may alter the microbiota, influence clinical

responses, and potentially modulate the antitumor effects of other therapies [35]. In PPI users, 20% of the gastrointestinal bacterial taxa were significantly different, compared with non-users [38]. This could theoretically result in increased carcinogenesis, worsening of PC-specific outcomes, and serve as a hypothesis of how PPIs alter PCa outcomes.

When assessing the published clinical evidence, only one other population-based study examined the chemopreventative effect of PPIs on PCa diagnosis [11]. In this recent case-control study, the PPI use by 1897 PCa patients was compared to age-matched population controls. The authors did not find PPIs to have a chemopreventative effect on PCa diagnosis (OR 1.12, 95% CI: 1.00–1.25) [11]. However, this study did not assess the effect of PPIs on ADT use or PCSM. Other limitations included the fact that all patients taking PPIs, both prevalent and incident users were included, making it difficult to ascertain the true effect of incident PPI use. Additionally, the authors used multivariable conditional logistic regression without time-varying covariates, and no comorbidity or rurality data was available.

Our study's strength lies in its large cohort, consisting of 'real-world' data with long follow-up time. To our knowledge, this is the only study specifically assessing the role of incident use of pantoprazole and other PPIs on PCSM and ADT use. However, several limitations are noteworthy. 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 lacked information regarding ethnicity, disease stage and grade, pertinent family history, personal genetic risk factors, and the reasons for TRUS-BX referral. Medication prescription is not synonymous with actual administration of the medications, as some patients may have been prescribed but not actually taking the medication. In contrast, 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, and if anything, would simply dilute the observed associated harm of PPI use, making our estimates conservative. More importantly, it has been previously demonstrated that prescription claims data provide an accurate estimation of association even though the prescribed medications are available over-the-counter [39]. 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 previously done, due to increasing age or significant comorbidities, making it a moot surrogate marker of advanced disease. Moreover, surgery, as opposed to other treatment modalities, had a protective association with PCSM, most likely explained by the fact that patients with less aggressive disease were referred for surgery, and not since radiotherapy and ADT are not effective therapies. In the sensitivity analysis of patients with PSA data, only patients from the year 2007 were analyzed, resulting in only 2773 men (12.9% of all men) being analyzed, with only 267 events of PCa diagnosis occurring (as compared to 5148 events in the original analysis including all men). This drastic reduction in the number of events has most likely resulted in the differing results of the sensitivity analysis model. Lastly, in such analyses, 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 PCSM. 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 in PCa patients needs to be reconsidered.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References

1. CCSsACoCS. Canadian Cancer Statistics 2018. 2018. http://www.cancer.ca/Canadian-Cancer-Statistics-2018-EN.
2. CoAC S. Key Statistics for Prostate Cancer. 2019. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html.

3. Sarkar RR, Parsons JK, Bryant AK, Ryan ST, Kader AK, McKay RR, et al. Association of treatment with 5alpha-reductase inhibitors with time to diagnosis and mortality in prostate cancer. JAMA Intern Med. 2019;179:812–9.
4. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst. 2013;105:1123–31.
5. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin use and reduced cancer-related mortality. N. Engl J Med. 2012;367:1792–802.
6. Gesmundo I, Di Blasio L, Banfi D, Villanova T, Fanciulli A, Favaro E, et al. Proton pump inhibitors promote the growth of androgen-sensitive prostate cancer cells through ErbB2, ERK1/2, PI3K/Akt, GSK-3beta signaling and inhibition of cellular prostatic acid phosphatase. Cancer Lett. 2019;449:252–62.
7. Klinkenberg-Knol EC, Nelis F, Dent J, Snel P, Mitchell B, Prichard P, et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease: efficacy, safety, and influence on gastric mucosa. Gastroenterology. 2000;118:661–9.
8. Brusselaers N, Wahlin K, Engstrand L, Lagergren J. Maintenance therapy with proton pump inhibitors and risk of gastric cancer: a nationwide population-based cohort study in Sweden. BMJ Open. 2017;7:e017739.
9. Brusselaers N, Engstrand L, Lagergren J. Maintenance proton pump inhibition therapy and risk of oesophageal cancer. Cancer Epidemiol. 2018;53:172–7.
10. Tran KT, McMenamin UC, Proton pump inhibitor histamine-2 receptor antagon use risk liver cancer two population-based studies. 2018;48:55–64.
11. Halfdanarson OO, Fall K, Ogmundsdottir MH, Lund SH, Steingrimsson E, Ogmundsdottir HM, et al. Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control study. Pharmacoepidemiology drug Saf. 2019;28:471–8.
12. Canitano A, Iessi E, Spugnini EP, Federici C, Fais S. Proton pump inhibitors induce a caspase-independent antitumor effect against human multiple myeloma. Cancer Lett. 2016;376:278–83.
13. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut. 2018;67:28–35.
14. Xie Y, Bowe B, Yan Y, Xian H, Li T, Al-Aly Z. Estimates of all cause mortality and cause specific mortality associated with proton pump inhibitors among US veterans: cohort study. BMJ. 2019;365:l1580.
15. Soriano LC, Soriano-Gabarró M, García Rodríguez LA. Trends in the contemporary incidence of colorectal cancer and patient characteristics in the United Kingdom: a population-based cohort study using The Health Improvement Network. BMC Cancer. 2018;18:402.
16. Kearns MD, Boursi B, Yang YX. Proton pump inhibitors on pancreatic cancer risk and survival. Cancer Epidemiol. 2017;46:80–4.
17. Cao Y, Chen M, Tang D, Yan H, Ding X, Zhou F, et al. The proton pump inhibitor pantoprazole disrupts protein degradation systems and sensitizes cancer cells to death under various stresses. Cell Death Dis. 2018;9:604.
18. Tan Q, Joshua AM, Saggar JK, Yu M, Wang M, Kanga N, et al. Effect of pantoprazole to enhance activity of docetaxel against human tumour xenografts by inhibiting autophagy. Br J cancer. 2015;112:832–40.
19. Hansen AR, Tannock IF, Templeton A, Chen E, Evans A, Knox J, et al. Pantoprazole affecting docetaxel resistance pathways via autophagy (PANDORA): phase II trial of high dose pantoprazole (autophagy inhibitor) with docetaxel in metastatic castration-resistant prostate cancer (mCRPC). Oncologist. 2019;24:1188–94.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573–7.
21. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12:e1001885.
22. Institute of Clinical Evaluative Sciences Homepage. 2019. http://www.ices.on.ca.
23. The Johns Hopkins ACG (R) System version 10.0.
24. Sayyid RK, Alibhai SMH, Sutradhar R, Eberg M, Fung K, Klaassen Z, et al. Population-based outcomes of men with a single negative prostate biopsy: importance of continued follow-up among older patients. Urologic Oncol. 2019;37:298.e19–.e27.
25. The Top 300 of 2019. 2019. www.clincalc.com.
26. Malfertheiner P, Kandulski A, Venerito M. Proton-pump inhibitors: understanding the complications and risks. Nat Rev Gastroenterol Hepatol. 2017;14:697–710.
27. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017;153:35–48.
28. Hayashi H, Taniai E, Morita R, Hayashi M, Nakamura D, Wakita A, et al. Enhanced liver tumor promotion but not liver initiation activity in rats subjected to combined administration of omeprazole and beta-naphthoflavone. J toxicological Sci. 2012;37:969–85.
29. Huang L, Qi DJ, He W, Xu AM. Omeprazole promotes carcinogenesis of fore-stomach in mice with co-stimulation of nitrosamine. Oncotarget. 2017;8:70332–44.
30. Peng YC, Lin CL, Hsu WY, Lu IT, Yeh HZ, Chang CS, et al. Proton Pump inhibitor use is associated with risk of pancreatic cancer: a nested case-control study. Dose Response. 2018;16:1559325818803283.
31. Hwang IC, Chang J, Park SM. Emerging hazard effects of proton pump inhibitor on the risk of colorectal cancer in low-risk populations: a Korean nationwide prospective cohort study. PloS ONE. 2017;12:e0189114.
32. Giridhar KV, Sanhueza C, Hillman DW, Alkhateeb H, Carlson R, Tan W, et al. Serum chromogranin-A-based prognosis in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2018;21:431–7.
33. Quinn DI, Sandler HM, Horvath LG, Goldkorn A, Eastham JA. The evolution of chemotherapy for the treatment of prostate cancer. Ann Oncol: Off J Eur Soc Med Oncol. 2017;28:2658–69.
34. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. Nat Rev Microbiol. 2016;14:273–87.
35. Sfanos KS, Markowski MC, Peiffer LB, Ernst SE, White JR, Pienta KJ, et al. Compositional differences in gastrointestinal microbiota in prostate cancer patients treated with androgen axis-targeted therapies. Prostate Cancer Prostatic Dis. 2018;21:539–48.
36. Porter CM, Shrestha E, Peiffer LB, Sfanos KS. The microbiome in prostate inflammation and prostate cancer. Prostate Cancer Prostatic Dis. 2018;21:345–54.
37. Shrestha E, White JR, Yu SH, Kulac I, Ertunc O, De Marzo AM, et al. Profiling the urinary microbiome in men with positive versus negative biopsies for prostate cancer. J Urol. 2018;199:161–71.
38. Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DPY, Fu J, et al. The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes. 2017;8:351–8.
39. Yood MU, Campbell UB, Rothman KJ, Jick SS, Lang J, Wells KE, et al. Using prescription claims data for drugs available over-the-counter (OTC). Pharmacoepidemiol Drug Saf. 2007;16:961–8.