Proton pump inhibitor use among adults

Mapping the landscape of PPI use and exploring its effect on cancer risk and mortality

Óskar Örn Hálfdánarson

Thesis for the degree of Philosophiae Doctor

Supervisor:
Helga Zoëga

Advisors:
Eiríkur Steingrímsson and Helga M. Ögmundsdóttir

Doctoral committee:
Margrét H. Ögmundsdóttir and Katja Fall

March 2019

UNIVERSITY OF ICELAND
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

Notkun prótónupumpuhemla á Íslandi

Kortlagning PPI notkunar og möguleg áhrif hennar á krabbameinsáhættu og lifun

Óskar Örn Hálfdánarson

Ritgerð til doktorsgráðu

Umsjónarkennari:
Helga Zoëga

Leiðbeinendur:
Eiríkur Steingrímsson og Helga M. Ögmundsdóttir

Doktorsnefnd:
Margrét H. Ögmundsdóttir og Katja Fall

Mars 2019

UNIVERSITY OF ICELAND
SCHOOL OF HEALTH SCIENCES
FACULTY OF MEDICINE

ISBN 978-9935-9421-7-3

Printing by Háskólaprent.

Reykjavik, Iceland 2019

The road to wisdom?

Well, it´s plain
and simple to express.
Err and err and err again,
but less and less and less.

- Piet Hein

Ágrip

Inngangur og markmið: Prótónupumpuhemlar (PPI) eru sýrubindandi lyf sem eru almennt notuð við meðferð á ýmsum magasýrusjúkdómum. Notkun PPI lyfja er útbreidd á heimsvísu og sú umtalsverða aukning sem hefur orðið á notkun þeirra hefur verið gagnrýnd í ljósi mögulegrar ofnotkunar og óvissu sem ríkir um mögulegar skaðlegar aukaverkanir. Sýrubindandi virkni PPI hefur verið talin hafa möguleg krabbameinshindrandi áhrif vegna hæfni þeirra til að hindra virkni sérhæfðra sýruseytandi ensíma. Talið er að slík ensím taki þátt í myndun á súru utanfrumuumhverfi krabbameinsfruma.

Markmið okkar var nota lýðgrundaða gagnagrunna á Íslandi til að I) kortleggja notkun PPI lyfja meðal fullorðinna einstaklinga á Íslandi, II) meta áhættu PPI notenda á því að greinast með brjóstakrabbamein, blöðruhálskirtilskrabbamein, eða sortuæxli í húð, og III) meta möguleg verndandi áhrif PPI lyfjanotkunar á lifun sjúklinga með blöðruhálskirtils–krabbamein.

Aðferðir: Rannsókn I var lyfjanotkunarrannsókn þar sem við lýstum notkun PPI lyfja á árunum milli 2003 og 2015. Við áætluðum árlegt nýgengi og algengi PPI notkunar, lengd PPI lyfjameðferðar og samhliða notkun lyfja sem geta haft í för með sér blæðingar í meltingarvegi. Rannsókn II var tilfella-viðmiðsrannsókn þar sem tilfellin voru einstaklingar sem greindust með brjóstakrabbamein, blöðruhálskirtilskrabbamein og sortuæxli á milli 2005 og 2014. Hvert og eitt krabbameinstilfelli pöruðum við saman við allt upp að 10 viðmið eftir almanaksári, fæðingarári, og kyni. Við áætluðum PPI notkun þátttakenda, þ.e. hvort leyst hefði verið út að minnsta kosti eina PPI lyfjaávísun, hvort notkun væri ≥1000 skilgreindum dagskömmtum (DDDs) og heildarnotkun og reiknuðum út gagnlíkindahlutföll (ORs) og 95% öryggisbil (CIs) fyrir áhættuna á því greinast. Rannsókn III var hóprannsókn þar sem einstaklingar á aldursbilinu 40 til 85 ára sem greindust með krabbamein í blöðruhálskirtli á milli 2007 og 2012 mynduðu rannsóknarhópinn. Við áætluðum upphaf PPI notkunar (fyrir eða eftir greiningu), heildarnotkun og lagskiptum eftir klínískri stigun. PPI notkun var meðhöndluð sem tímaháð breyta og Cox aðhvarfsgreining var notuð til að reikna út hættuhlutfall (HRs) fyrir dauða af völdum blöðruhálskirtilskrabbameins annars vegar og dauða af öllum orsökum hins vegar með 95% öryggismörkum (CI).

Niðurstöður: Niðurstöður úr rannsókn I sýndu að heildarnotkun PPI lyfja á Íslandi fór ört vaxandi á rannsóknartímabilinu. Þótt nýgengi hafi haldist stöðugt jókst algengi PPI notkunar úr 8.5 á hverja 100 einstaklinga árið 2003 yfir í 15.5 á hverja 100 einstaklinga árið 2015. Ennfremur, reyndist algengi hækka með hækkandi aldri og 22% sjúklinga var enn að nota PPI einu ári eftir að meðferð hófst.

Niðurstöður úr rannsókn II bentu ekki til þess að PPI notkun hafi í áhrif á krabbameinsáhættu (ORs 1.03; 95% CI: 0.92-1.16 fyrir brjóstakrabbamein, 1.12; 95% CI: 1.00-1.25 fyrir blöðruhálskirtilskrabbamein og 0.84; 95% CI: 0.69-1.12 fyrir sortuæxli). Sömuleiðis virtist PPI notkun ≥1000 DDDs ekki hafa áhrif (OR 0.97; 95% CI: 0.78-1.19 fyrir brjóstakrabbamein, 1.20; 95% CI: 0.99-1.47 fyrir blöðruhálskirtilskrabbamein, og 0.59; 95% CI: 0.40-1.13 fyrir sortuæxli). Niðurstöður okkar bentu ekki til þess að tengsl væru á milli heildarnotkunar á PPI og áhættunnar á því að greinast með brjóstakrabbamein, blöðruhálskirtilskrabbamein, eða sortuæxli.

Niðurstöður úr rannsókn III bentu ekki til þess að PPI notkun eftir greiningu hefði áhrif á líkur á dauða af völdum blöðruhálskirtilskrabbameins (HR 0.88; 95% CI: 0.52-1.48) eða dauða af öllum orsökum (HR 1.02; 95% CI: 0.73-1.43). Upphaf PPI notkunar virtist ekki hafa áhrif, en HRs fyrir dauða af völdum blöðruhálskirtilskrabbameins voru 0.45 (95% CI: 0.21-0.98) meðal sjúklinga sem notuðu PPI lyf samfellt bæði fyrir og eftir greiningu og 1.12 (95% CI: 0.61-2.08) á meðal nýrra PPI notenda. HRs fyrir dauða af öllum orsökum voru 0.67 (95% CI: 0.43-1.04) á meðal sjúklinga sem notuðu PPI samfellt og 1.25 (95% CI: 0.82-1.92) á meðal nýrra PPI notanda. Lagskipting eftir heildarnotkun PPI lyfja og klínískri stigun leiddi ekki ljós tölfræðilega marktækt samband á milli PPI notkunar og lifunar.

Ályktun: Niðurstöður verkefnisins benda til þess að PPI notkun hafi aukist umtalsvert á Íslandi yfir síðasta áratuginn; sér í lagi hjá eldri einstaklingum. Þar að auki er stór hluti sjúklinga meðhöndlaður lengur en mælt er með í klínískum leiðbeiningum fyrir lyfin. Niðurstöður okkar benda hvorki til þess að PPI notkun hafi áhrif á áhættu á brjóstakrabbameini, blöðruhálskirtils–krabbameini, eða sortuæxlum, né að hún hafi áhrif á lifun meðal sjúklinga með krabbamein í blöðruhálskirtli.

Lykilorð:
Prótónupumpuhemlar, lyfjafaraldsfræði, krabbamein, sýruseyting, lýðgrunduð rannsókn

Abstract

Background and aims: Proton pump inhibitors (PPIs) are commonly prescribed drugs that are used to treat acid-related disorders of the gastrointestinal tract. Over the last decade, PPI use has repeatedly been shown to be increasing worldwide, causing concerns due to reports of unsubstantiated long-term use and potential adverse effects. However, PPIs have also been suggested to promote antineoplastic effects in certain cancer settings via inhibition of specialized proton pumps. These proton pumps are involved in pH regulation in eukaryotic cells and believed to act as facilitators for the acidification of the tumor microenvironment (TME).

Our aim was to use the population-based resources available to us in Iceland I) to assess the utilization of PPIs among the adult outpatient population residing in Iceland, II) to explore the potential of PPIs possessing an antineoplastic effect by estimating the risk among PPI users of being diagnosed with a first-time breast cancer, prostate cancer, or malignant melanoma, and III) to assess the potential influence of post-diagnosis PPI use on mortality among prostate cancer patients.

Materials and methods: In study I, a drug utilization study, we investigated changes in overall PPI use between 2003 and 2015 among the adult outpatient population in Iceland. We estimated changes in annual incidence and prevalence, duration of PPI treatment, and the concurrent use of ulcerogenic drugs. In study II, a nested case-control study, we identified incident cases of breast cancer, prostate cancer, and malignant melanoma between 2005 and 2014. For each case, up to 10 controls were matched on birth-year, sex, and calendar year using risk-set sampling. Assessing ever use, high use, and cumulative use of PPIs, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) using conditional logistic regression. In study III, a cohort study, we identified patients diagnosed with prostate cancer between 2007 and 2012 among adult residents of Iceland aged between 40 and 85 years. PPI use was modelled in a time-dependent manner. Assessing post-diagnosis use, timing of use, cumulative use and stratifying by clinical stage we estimated the associations with prostate-cancer specific and all-cause mortality using Cox proportional hazard regression models and 95% CIs.

Results: In study I, we observed a marked increase in outpatient PPI use over the last decade. Although the annual incidence remained fairly stable between 2003 and 2015, the annual prevalence estimates rose from 8.5 per 100 persons in 2003 to 15.5 per 100 persons in 2015. Furthermore, we found that prevalence increased with age and that 22% of patients were still being treated with PPIs one year after treatment initiation.

In study II, we observed the following adjusted odds ratios (ORs) associated with ever use and high use of PPIs, respectively: 1.03 (95% CI: 0.92-1.16) and 0.97 (95% CI: 0.78-1.19) for breast cancer, 1.12 (95% CI: 1.00-1.25) and 1.20 (95% CI: 0.99-1.47) for prostate cancer, 0.84 (95% CI: 0.69-1.12) and 0.59 (95% CI: 0.40-1.13) for malignant melanoma. In secondary analyses, we did not observe a pattern consistent with a dose-response relationship for these three cancer types.

In study III, we did not observe a statistically significant association between post-diagnosis PPI use and prostate cancer-specific mortality (HR 0.88; 95% CI: 0.52-1.48) or all-cause mortality (HR 1.02; 95% CI: 0.73-1.43). In secondary analyses, stratification by timing of use yielded adjusted HRs of 0.45 (95% CI: 0.21-0.98) among continuous PPI users and 1.12 (95% CI: 0.61-2.08) among new PPI users for prostate cancer-specific mortality. For all-cause mortality, we observed adjusted HRs of 0.67 (95% CI: 0.43-1.04) and 1.25 (95% CI: 0.82-1.92) among continuous users and new users, respectively. Stratification by cumulative dose and clinical stage did not reveal a statistically significant association with post-diagnosis PPI use for the mortality outcomes of interest.

Conclusions: In conclusion, our observations indicate that PPI use in Iceland has increased considerably over the last decade; especially among older adults. Additionally, a high proportion of patients were treated for longer periods than clinical guidelines recommend. Furthermore, our findings do not support a chemopreventive role of PPIs in attenuating the risk of being diagnosed with a first-time breast cancer, prostate cancer, or malignant melanoma. Finally, our results do not indicate that post-diagnosis PPI use influences mortality among prostate cancer patients.

Keywords:

Proton pump inhibitors, pharmacoepidemiology, population-based, cancer, V-ATPase

Acknowledgements

As is often the case, the best part a project like this is the people you meet along the way. I have been lucky enough during the past 3 ½ years to have had the opportunity to meet and work around people who have supported and inspired me throughout. The work presented within this thesis rests on the shoulders of those mentioned below.

Thank you to **Helga Zoëga**, my mentor and overall terrific human being, for our endless hours of discussions between continents, introducing me to the field of pharmacoepidemiology and widening my perspective. Her endless source of positivity, knowledge and willingness to navigate me through this process was essential.

Thank you to my wonderful advisors, **Eiríkur Steingrímsson** and **Helga M. Ögmundsdóttir**, for giving me the opportunity to work on this project and their limitless support and sound guidance.

Thank you to my doctoral committee, **Margrét H. Ögmundsdóttir** and **Katja Fall** for their willingness to guide me through this. Our countless encouraging and stimulating discussions will keep me going for a long time.

Thank you to **Sigrún Helga Lund**, for lighting my way through the statistical jungle. Her enthusiasm for the project played a critical role in leading me through the maze.

Thank you to my other co-authors, **Anton Pottegard** and **Einar Stefán Björnsson**, for their invaluable contribution to my growth as a professional. I would especially like to extend my eternal gratitude to Anton for his willingness to educate a pharmacoepidemiological novice like myself and for his lightning-quick responses to all of my queries.

Thank you to **Dóra R. Ólafsdóttir**, for always being willing to assist me with everything, no matter what. Without her, I would not have made it this far.

Thank you to all my wonderful co-workers at the Centre of Public Health Sciences, **Unnur Anna Valdimarsdóttir**, **Thor Aspelund**, **Arna Hauksdóttir** and **Kristjana Einarsdóttir** for providing me with such a fun place to work. Special gratitude must go towards **Álfheiður**, **Emma**, **Maríanna**, **Sæmi**, **Villi**, **Elli**, **Sigrún**, **Hildur**, **Edda**, **Jóhanna**, **Hrönn**, **Harpa**, **Eva**, **Heiðrún**, **Agnes**, **Rebekka**, **Ásdís**, **Sara**, and all the others. They say that each day is only as

good as the company you keep while drinking your morning coffee. Thanks for making this such a joyful experience.

Thank you to **Sara**, **Valerie**, **Rami**, **Kimberley**, **Diahann**, **Josue**, **Ásgeir** and all of the other people in and around the Steingrímsson lab and Læknagarður for their support and company during the first years of this project.

Thank you to **Guðrún Kristín Guðfinnsdóttir** and **Kristinn Jónsson** at the Directorate of Health for all of their help with acquiring and linking the data. Guðrún Kristín deserves a big thank you for her patience in answering the endless amount of emails I sent her way while working on this project.

Thank you to **Laufey Tryggvadóttir**, **Guðríður Helga Ólafsdóttir** and **Helgi Birgisson** at the Icelandic Cancer Registry for providing data and always being willing to assisst and answer my questions.

Thank you to **Ólafur Baldursson**, **Jakob Jóhannsson**, **Erna Karlsdóttir**, **Sif Sumarliðadóttir**, **Garðar Mýrdal**, **Helga Bjarnadóttir** and **Íris Jónbjörnsdóttir** at Landspítali – the National University Hospital of Iceland for all of their help. They were able to make a complex process simple with their kindness and generosity.

Thank you to **Ellert Magnússon** and **Rúnar Guðlaugsson** at the Icelandic Medicines Agency for their time and help in providing wholesale data on drug use for this project.

A very special thank you to my **family and friends** for their unconditional support and love during these last years. To my late grandfather and namesake I would just like to say this: Now I think I am done.

To my **parents**: Everything is because of you. I am glad that you guys are my mom and dad.

And to **Halla**: The vocabulary of the world is not deep enough to provide me with adequate words to express my gratitude. Simply put: I would not have been able to do this without you. Thank you for making most days brighter and every day better.

Thank you all from the bottom of my heart. The next round is on me!

Contents

List of abbreviations

ADP	Adenosine diphosphate
ATC	Anatomical Therapeutic Chemical Classification
ATP	Adenosine triphosphate
BMI	Body Mass Index
CI	Confidence Interval
DDD	Defined Daily Dose
ER	Estrogen Receptor
GERD	Gastroesophageal Reflux Disease
H^+-K^+-ATPase	Hydrogen Potassium ATPase
HER2	Human Epidermal Growth Factor Receptor 2
HIC	High Income Country
HR	Hazard Ratio
ICD	International Classification of Diseases
LMICs	Low and Middle Income Countries
NCSP	NOMESCO Classification of Surgical Procedures
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
PPC	Proportion of Patients Covered
PPI	Proton Pump Inhibitor
PR	Progesterone Receptor
PSA	Prostate Specific Antigen
PUD	Peptic Ulcer Disease
RCT	Randomized Clinical Trial
SES	Socioeconomic Status
TME	Tumor Microenvironment
TNM	Tumor Node Metastasis
V-ATPase	Vacuolar H^+-ATPase
WHO	World Health Organization

List of figures

List of tables

List of original papers

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals:

I. Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, Lund SH, Ogmundsdottir MH, Steingrímsson E, Ogmundsdottir HM, Zoëga H. *Proton-pump inhibitors among adults: a nationwide drug-utilization study*. Therapeutic Advances in Gastroenterology 2018; 11: 1-11.

II. Hálfdánarson ÓÖ, Fall K, Ogmundsdottir MH, Lund SH, Steingrímsson E, Ogmundsdottir HM, Zoëga H. *Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control* study. Pharmacoepidemiology and Drug Safety 2018; 1-8.

III. Hálfdánarson ÓÖ, Pottegård A, Lund SH, Ogmundsdottir MH, Ogmundsdottir HM, Zoëga H. *Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer*. Submitted.

Declaration of contribution

In close collaboration with his supervisor, Óskar Örn Hálfdánarson, planned and designed the research work of papers I – III. Óskar Örn applied for the appropriate ethical and research approvals, conducted the statistical analyses for all three studies, drafted each manuscript, and wrote this thesis under the sound guidance of his doctoral committee.

1 Introduction

A rapid increase in proton pump inhibitor (PPI) use has in recent years given rise to concerns about the appropriateness of their use and potential adverse effects that might stem from staying on PPI treatment for extended durations of time (Batuwitage et al., 2007). Given the high usage of these drugs it is important to determine all potentially associated safety considerations for their use; both adverse and beneficial. Due to their inherent function as acid inhibitors, PPIs have been proposed to be able to function as potential antineoplastic agents by promoting pH homeostasis in certain cancer settings (Luciani et al., 2004).

In this PhD project, we explore the landscape of PPI use among the adult population in Iceland, evaluate the risk of incident diagnoses of breast cancer, prostate cancer, and malignant melanoma among PPI users, and finally aim to determine whether PPI use influences mortality among prostate cancer patients.

1.1 Pharmacoepidemiology

Pharmacoepidemiology is a rather young discipline that can be seen to bridge the research areas of clinical pharmacology and epidemiology. It is defined as the study of the use of drugs and their consequent effects, both beneficial and adverse, in large numbers of individuals (Strom et al., 2012). Pharmacoepidemiology emerged from the need to address increasing concerns of adverse effects by developing methods to assess the safety profiles of drugs. These concerns were compounded by events such as the “thalidomide disaster” which took place around 1960, where rare birth defects could be traced back to the fetus being exposed to thalidomide via maternal use of the drug during pregnancy (Strom et al., 2012).

Pharmaceutical drugs are extensively evaluated in pre-clinical and clinical phases prior to marketing and randomized controlled trials (RCTs) are considered to be the gold standard when it comes to estimating the effectiveness of the drugs under study (Akobeng, 2005). However, RCTs are not always applicable when estimating the safety of a drug, such as when the adverse effects are rare or take a long time to develop. Furthermore, the small sample sizes often seen in RCTs tend to be relatively homogenous. Thus, they are not always comparable to the general population, making it

hard to predict the overall real-world benefits and risks of a particular drug (Strom et al., 2012; Vandenbroucke, 2004). Furthermore, in addition to pre-marketing clinical trials being limited by duration, extent, and patient characteristics, there are valuable insights to be gained from observational studies that are conducted in the post-marketing phase. In fact, they can sometimes reveal previously undetected beneficial or adverse effects and they can also test the effectiveness of drugs under different conditions and within patient populations that were not adequately represented in pre-marketing clinical trials (Guess, 2005). Pharmacoepidemiological studies are therefore able to provide further insight into the safety profiles and effectiveness of previously marketed drugs due to the possibility of greater follow-up and the tracking of real-world drug use and prescription patterns within large populations (Strom & Tugwell, 1990).

A key aspect of pharmacoepidemiological research is the availability of relevant data on drug use. Since its advent, pharmacoepidemiology has developed hand in hand with technological advancements. The growth of medical databases has led to ever-increasing amounts of data that previously were collected and compiled in a time-consuming manner (Wettermark, 2013). For instance, in the Nordic countries population-based registries have been established in each country that cover the majority of all dispensed drugs within their populations (Furu et al., 2010). However, although the amount of available data has increased considerably over the years, there are still several methodological challenges that arise and need to be considered when data on drug use is utilized in pharmacoepidemiological studies.

1.1.1 Nationwide prescription registries in the Nordic countries

High-quality data sources are essential for registry-based research in the field of pharmacoepidemiology. A crucial component of such data sources is the ablility to be able to compile and store data on an individual level, using a personal identification number that is unique to every individual for each record entry. Regional databases that collected individual-level data in specific regions of Sweden (Boethius & Wiman, 1977) and Denmark (Hallas et al., 2017), were important precursors of the national level prescription registries of today. With the ushering in of the computer age, it became possible to efficiently collect individual-level data on every filled prescription from pharmacies within entire countries. Today, all five Nordic countries have established centralized databases that cover each country‘s entire population that hold information on individual-level data on dispensed drugs dating back

to 1994 in Denmark (Pottegård et al., 2016b) and Finland (Klaukka, 2009), 2003 in Iceland, 2004 in Norway, and 2005 in Sweden (Furu et al., 2010; Wettermark et al., 2007).

There are a lot of similarites between the Nordic prescription registries. First, the data structure is the same and the variables are categorized based on their nature, i.e. whether the data is related to the patient, the prescriber, the drug, or the pharmacy (Furu et al., 2010). Second, the parliaments in the respective countries have given informed consent on behalf of their populations for everyone to be included in the national health registries (Rosén, 2002). Third, the prescription databases are all based on personal identification numbers that are unique to every resident of each country. Personal identification numbers are important because they allow the data to be linked to other national registries that hold data on other variables, potential outcomes and confounding factors, which then facilitates the study of potential effects of drug exposures (Wettermark et al., 2013). Due to the similarities between the Nordic countries, and their shared history and cultural ties, and their frequent collaborations in general, cross-national pooling of pharmacoepidemiological data for research purposes is an intriguing prospect. Such collaborative efforts have several potential benefits, such as allowing for assessment of possible variations between countries, strengthening research competencies, and increasing the sample size of studies. Taken together, the national prescription databases in the Nordic countries cover around 27 million individuals. Thus, the Nordic countries are well placed to collaborate on high-quality pharmacoepidemiological studies with large underlying populations (Wettermark et al., 2013).

However, there are also some challenges that come along with combining cross-national data. While the healthcare systems and access to data on exposures and outcomes are similar between countries (Furu et al., 2010), there can be some administrative and logistic challenges that come with the combining the data in one place. Furthermore, even small differences in the record-linking process and access to clinical variables can cause some difficulties when performing studies where the focus is on the outcome of drug therapy, although descriptive cross-national drug utilization studies might be easier to carry out (Wettermark et al., 2013).

Even though the Nordic prescription registries cover entire national populations, allow for linkage of data with other relevant registries such as cancer registries, cause-of-death registries, population registries, and inpatient registries and contain vast amounts of data on dispensed drugs,

they do not include information on the underlying indications behind each prescription nor the prescribed daily dose, which is a limiting factor for some pharmacoepidemiological studies. Furthermore, the prescription registries do not contain information on the majority of non-prescription over-the-counter (OTC) drugs, which is a potential cause of misclassification bias (Furu et al., 2010).

All in all, the nature of the Nordic prescription registries allows the Nordic countries to collaborate on high-quality population-based, cross-national pharmacoepidemiological studies. Such collaborations may enhance the field of public health by contributing to a deeper understanding of real-world drug use and raising awareness on previously unknown effects of drugs, thus promoting the development of safer and more effective treatment protocols. Today, studies that are based on the Nordic prescription registries have paved the way for new knowledge on drug utilization and effectiveness, and have increased the safety of prescription drug use in the society (Wettermark et al., 2013).

1.1.2 ATC/DDD drug classifiation system

The Anatomical Therapeutic Chemical Classification System (ATC) with Defined Daily Doses (DDD) was devoleped in Norway as a modified and extended version of a previous classification system, used by the European Pharmaceutical Market Research Association (EphMRA). This system is recommended by the World Health Organization (WHO) as the international standard for drug utilization studies. The DDD is a measuring unit based on the assumed average maintenance dose per day for a drug that is being used for its main indication in adults. It is a unit that is technical in nature and was originally developed for use in drug utilization studies where it is important to have a clear and stable classification system, as well as a standardized unit of measurement, when presenting and comparing statistics of drug consumption at an international level. The DDD unit should not be assumed to necessarily reflect actual prescribed dosages, since those can drastically vary based on individual characteristics of the patients and other considerations (WHO, 2018). The Nordic prescription registries utilize the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) classification to classify the prescription drugs that are recorded in the registries.

The basis of the ATC/DDD system is its five level hierarchial classification of the active substances of the drugs that are being classified. The first level of classification is based on organ or system on which the drugs act, and has

14 distinct anatomical/pharmacological groups. The remaining levels (2nd – 5th) break down the ATC main groups and categorizes them based on their chemical, pharmacological, and therapeutic proporties (WHO, 2018).

1.1.3 Biases in pharmacoepidemiological studies

Observational studies in the field of pharmacoepidemiology are subject to some of the same biases as epidemiological studies in general. These include systematic errors such as selection bias and information bias. Selection bias occurs when the selection of study participants is not representative of the total population. This bias makes it impossible to conclude anything meaningful in a larger context from a study suffering from this bias (Guess, 2005). In pharmacoepidemiological studies, selection bias can be avoided by utilizing information on drug exposure from large data sources, such as the Nordic prescription registries, that cover entire populations (Wettermark et al., 2013). Information bias is a result of the inaccurate collection of information relating to the study subjects. These inaccuracies tend to cause misclassification of some of the important variable under study relating to exposures, outcomes, or covariates (Guess, 2005). As an example, studies that require patients to recall previous exposure to specific drugs might be subject to misclassifation of the information provided. Also, misclassification in pharmacoepidemiological studies might stem from prescription registries not containing information on OTC drug use where a patient might be misclassified as unexposed due to an OTC purchase of a drug.

Confounding is another common bias in epidemiological studies that is an important source of concern. It is a consequence of an imbalance in the distribution of important patient characteristics between exposed and unexposed subjects (Suissa, 2009). A confounding factor is not situated in the causal pathway between the exposure and outcome of interest but has a strong association with the exposure and is a risk factor for the outcome. If confounding is not adequately dealt with in study design or the analysis phase, then it will bias the effect of the exposure on the outcome under study. The ways in which to control for a confounder in the analysis phase might include stratification, standardization, multivariable regression, and the application of a propensity score, while restriction and matching might be used to control for confounding in study design (Klungel et al., 2004). A prerequisite for confounder adjustment is that the confounding factor is measured. However, it might also be the case that it is poorly measured, or

unmeasured, in which case we refer to such factors as unmeasured, unobserved, or residual confounders (Uddin et al., 2016).

Confounding by indication is another form of confounding bias that is especially relevant when discussing potential biases in pharmacoepidemiological studies. A medical intervention such as drug use is usually supported by an underlying clinical indication based on specific symptoms displayed by a patient. This type of bias is of special concern when the indication itself increases the risk of the outcome that is being studied (Guess, 2005). Examples of studies where confounding by indication was an issue include a study examining the use of calcium channel blockers and the risk of myocardial infarction (Psaty et al., 1995), and studies on PPI use and the risk of gastric cancer (Poulsen et al., 2009); where the underlying indication for drug use is a risk factor for both the exposure and outcome. Another type of bias is protopathic bias, sometimes also referred to as reverse causality or reverse causation. As the name suggests, reverse causation occurs when the outcome precedes and leads to the exposure of interest, i.e. the exposure does not cause the outcome but rather the outcome causes the exposure (Guess, 2005).

Cohort studies are an important observational study design and frequently used in pharmacoepidemiology. One bias that has been frequently seen to arise in pharmacoepidemiological cohort studies is a form of time-related bias called immortal time bias, where an exposure to a drug is determined based on filled prescriptions during follow-up (Suissa, 2007). The concept of immortal time indicates that there is a period during follow-up, often from the moment of cohort entry until an exposure definition has been met, during which a specific end point, i.e. death or another study outcome, is by definition unable to occur (Levesque et al., 2010). In other words, in order to be exposed to a drug, a patient would have been required to survive this time period in order to receive a prescription. Therefore, misclassification of the exposure during the immortal time period, or exclusion of this period altogether, can then give rise to immortal time bias. By failing to appropriately account for the immortal time as an unexposed period of time, the results of an analysis, comparing exposed subjects to those that are unexposed, will ultimately give rise to an effect estimate that will be biased downward. In the context of pharmacoepidemiology, this would provide an artificial association that would, if the bias goes undetected, result in a false conclusion of a drug providing a protective effect in relation to a given outcome. This happens, in essence, because the follow-up time of exposed subjects contains a period of time where they are artificially protected, i.e. they are unable to experience

the study outcome until they become exposed (Suissa, 2007). There are however several ways to circumvent the issue of immortal time bias. One option would be to avoid a time-fixed definition of exposure by conducting a time-dependent cohort analysis, where the immortal time is correctly classified as an unexposed period (Weberpals et al., 2016). Another time-related bias can stem from the failure of accounting for the lengthy period of time that usually passess during carcinogenesis and the latency of potential drug effects (Suissa & Azoulay, 2012). One approach to address this potential bias in the study design by implementing a period of lag-time within which exposure should be disregarded (Pottegård et al., 2017). Another option is to exclude patients who experience the event of interest within the lag-period (Suissa & Azoulay, 2012).

Finally, an alternative study design that could be used to avoid immortal time bias is to use a time matched nested case-control design (Suissa, 2013). Case-control studies themselves can be subject to a form of time-related bias, i.e. time-window bias, that arises if the exposure opportunity times among cases and controls are not comparable (Suissa et al., 2011). However, this bias can be circumvented by ensuring that both cases and controls have a similar exposure opportunity time.

1.1.4 Studying drug-cancer associations in pharmacoepidemiology

Cancer is sometimes referred to as a family of diseases, i.e. not one but many diseases, displaying several different faces, all characterized by an uncontrolled and abnormal growth of cells (Mukherjee, 2011). Cancers are complex and heterogenous and their development within the human body contains multiple different stages such as initiation, promotion, and progression of cancerous growth, the invasion of cancer cells from a site of origin into adjacent tissues, and the spread of malignant cells to regional lymph nodes and beyond; forming secondary tumors in other organs (Hanahan & Weinberg, 2011). Thus, carcinogenesis can be a very long process; in some types of cancer it can take up to 20-30 years before they become detectable and clinical symptoms appear (Umar et al., 2012).

Several observational studies have established that exposure to certain pharmaceutical drugs has the potential to either increase or decrease the risk of a cancer related outcome (Drew et al., 2016; Dubach et al., 1991; Jensen et al., 1989). However, the long developmental period of cancer growth provides a challenge in elucidating the real effect of drug exposure on cancer development since it is highly unlikely that drug initiation would have an

immediate impact on the manifestation of cancer, encouraging the use of lag-time in data analysis (Pottegård et al., 2017).

Pharmacoepidemiological studies on drug-cancer associations are an important area of research that has the potential to have a significant public health importance, especially as time passes and more and more high-quality data on exposures and outcomes become available. It is vitally important to identify drugs, often widely used, that either exhibit a potential carcinogenic effect or are associated with a potential beneficial effect. This applies to establishing an association between drug exposure and cancer incidence, as well as on cancer mortality. Furthermore, pharmacoepidemiological studies are valuable when it comes to establishing that a drug does not exhibit a carcinogenic effect, which holds a significant value.

1.1.4.1 Assessment of drug exposure

For exposure assessment it is important to keep in mind that drug exposure does not usually occur in one single treatment episode. Rather, in many cases drug use is characterized by continuous starts and stops, often over a long period of time. This makes it important to obtain detailed individual-level drug history so that the exposure variable can be handled appropriately, i.e. in a time-dependent manner allowing researchers to account for the changes in exposure status over a long period of time (Pottegård et al., 2017). Therefore, data sources, such as the Nordic prescription registries which can contain information on the use of prescription drugs over a long time-period, provide an excellent source of exposure information for drug-related cancer studies. From these registries, one should be able to obtain information on the initiation of exposure and the duration of use. The prescribed dose for each prescription is an important piece of information to be able to estimate cumulative exposure, a crucial variable for dose-response analyses. Although the prescribed dose is not always available from prescription registries, a comparable variable like the number of dispensed DDDs could be obtained which allows for the approximation of the duration of each prescription.

Drug exposure that affects cancer development, exerts its effect within a given period that can be defined as a ‘risk period’ for a particular drug. This could be the time from exposure until the manifestation of cancer, i.e. the induction period, or the time from manifestation of cancer until diagnosis, i.e. the latency period. In observational studies, it is customary to refer to the time that passes from the initiation of drug exposure until the ascertainment of outcome as latency, since actual induction and latency periods cannot be accurately identified (Pinheiro et al., 2016). A drug that contributes to

initiation of the first steps of cancerous growth, i.e. an initiator, would elicit its effect prior to carcinogenesis. Considering the long period of cancer growth mentioned previously, assessing the exposure to such a drug would require a significant period of recorded drug use. On the other hand, assessing the effect of a promoter, i.e. a drug whose cancer related function it is to promote the growth of a tumor that is already established within a given tissue, might require a shorter period of recorded drug use. Although it might also require a long period of recorded drug use depending on the nature of its effect. However, whether a drug is categorized as an initiator or a promoter; whether its latency period is thought to be long or short; whether its effect is chemopreventive or carcinogenic, it is extremely difficult, and almost impossible, to accurately determine the exact moment when a drug elicits its effect in this context. Which in turn makes it challenging to define a relevant exposure window for suspected drug related associations with cancer (Pottegård et al., 2017).

Due to the long period of cancer growth and latency of drug effects, the use of lag-time in observational studies on drug-cancer associations has been recommended, as mentioned above. This is because drug exposure that is initiated shortly before a cancer diagnosis, should not realistically be expected to have had a carcinogenic or chemopreventive effect. Additionally, it should be considered that, although a patient may have discontinued drug treatment, there might be a period of time after that discontinuation might be influenced by the drug exposure. Furthermore, the implementation of a lag-time might counteract the potential effect of reverse causation (Pottegård et al., 2017).

1.1.4.2 Ascertainment of cancer outcome

Individual-level information on cancer incidence for ascertainment of outcome is a requirement for studies on potential drug-cancer associations. Population-based nationwide registries, e.g. the Nordic cancer registries (Pukkala et al., 2018), are generally the preferred choice of data source and is considered the gold standard for obtaining the necessary information on each cancer diagnosis (Pinheiro et al., 2016).

Bearing in mind the heterogenic nature of cancer (Hanahan & Weinberg, 2011), even when tumors residing within the same organ are compared, the clustering of all cancers into one group in an analysis on drug-cancer associations should be avoided. Any associations observed for ‘cancer overall’ is likely driven by an effect on higher incidence cancers (Pottegård et al., 2017). Therefore, separating different cancer types by International

Classification of Diseases (ICD) codes, or tumor sites, is recommended. It might even be argued that a further separation might be desirable in some organs, e.g. by histological subtype, although that might not always be feasible (Pottegård et al., 2017).

1.2 Proton pump inhibitors

Proton pump inhibitors (PPIs) are a class of drugs that inhibit acid secretion by forming a covalent bond with their target; cysteine residues on the gastric hydrogen potassium ATPase (H^+-K^+-ATPase). The H^+-K^+-ATPase, also known as the gastric acid pump, is a proton pump that can be found in the canalicular membrane of parietal cells of the stomach (Sachs et al., 1995). Omeprazole, the first PPI substance, became commercially available in 1989 and since then several other PPI substances have been introduced (Strand et al., 2017). Other PPI substances with a marketing licence in Iceland include pantoprazole, lansoprazole, rabeprazole, and esomeprazole.

PPIs are effective in the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD) (Dent et al., 2005; Lundell et al., 2009; Mahon et al., 2005; Mehta et al., 2006) and have also been shown to be useful if included in the treatment of *Helicobacter pylory* infection, which is a risk factor for ulcer bleeding (Yuan et al., 2013). Furthermore, PPIs are considered effective in treating non-steroidal anti-inflammatory drug (NSAID) associated ulcers and can be used for prophylaxis treatment among patients taking NSAIDs and low-dose aspirin (Scheiman, 2013). Clinical guidelines generally recommend treatment durations of 4 to 12 weeks, although the duration of therapy can depend on the severity of symptoms (NICE, 2018; Scarpignato & Blandizzi, 2016).

PPIs are prodrugs, i.e. they remain inactive after intake until they are absorbed in the small intestines and carried to acidic environments, e.g. the acidic secretory canaliculi of a parietal cell, where they undergo two protonations that render them active and able to react with the active form of the H^+-K^+-ATPase, situated in the canalicular membrane of a parietal cell (Sachs et al., 2006). The serum half-life of PPIs is one to two hours, which is relatively short. Therefore, to maximize their effectiveness, clinical instructions recommend pre-prandial intake since canaliculi expression of H^+-K^+-ATPases is activated in response to a meal; a prerequisite for the covalent binding of PPIs and subsequent inhibition of the proton pump activity (Strand et al., 2017).

Their potency and clinical effectiveness as acid inhibitors, accompanied by their excellent safety profile, has led PPIs to becoming the mainstay in treatment of upper gastrointestinal related disorders (Strand et al., 2017). PPIs are therefore widely prescribed, and their use has been increasing over time in a number of populations and patient groups (Ksiądzyna et al., 2015; Moriarty et al., 2016; Pottegård et al., 2016a; Wallerstedt et al., 2017). Although they are considered to be safe, the increased use and elevated popularity has given rise to concerns related to reported adverse effects that might be associated with their use, i.e. increased risk of bone fractures (Zhou et al., 2016), kidney disease (Lazarus et al., 2016), microscopic colitis (Law et al., 2017), hypomagnesemia (Cheungpasitporn et al., 2015), *Clostridium dificile* infection (Naito et al., 2018), and chronic liver disease (Llorente et al., 2017). Additionally, stepping down from PPI have been shown to be a cause of rebound acid hypersecretion following discontinued use (Lødrup et al., 2013; Waldum et al., 1996). Additionally, inappropriate PPI use and overprescribing, driven by vague indications and unsubstantiated long-term use have been reported as a cause of concern in relation to the use of PPIs (Batuwitage et al., 2007; Grant et al., 2006; Ladd et al., 2014; Naunton et al., 2000), especially among the elderly (Cahir et al., 2010; Moriarty et al., 2016). Furthermore, there have also been reports on the potential drug-drug interactions associated with metabolic inhibition of drugs that are coadministered together with some PPI substances (Hagymási et al., 2011).

There is an ongoing debate over the long-term use of PPIs and whether they might possess a carcinogenic potential and therefore increase cancer risk, especially in digestive organs. However, the question whether PPIs are associated with increased risk of gastrointestinal related cancer is complex due to the nature of symptoms and underlying indications for PPI use. Observational studies examining this issue have not provided a definitive conclusion and many of the studies reporting an association with increased risk might be prone to reverse causation (Kearns et al., 2017), confounding by indication (Poulsen et al., 2009; Rodriguez et al., 2006; Tamim et al., 2008), or time-related biases (Cheung et al., 2017; Suissa & Suissa, 2018).

Although H^+-K^+-ATPases are their main original target, PPIs are potent inhibitors of acid secretion in general and have been reported to also inhibit the activity of another type of proton pump that controls the intracellular and extracellular pH of cells and cellular compartments; the vacuolar H^+-ATPase (V-ATPase) (Ikemura et al., 2017; Moriyama et al., 1993; Sabolic et al., 1994).

1.3 Vacuolar H^+-ATPase

1.3.1 Structure and function

The V-ATPase is a complex multisubunit ATP-dependent proton pump that operates through a rotary mechanism and is involved in the regulation of intracellular and extracellular pH (Forgac, 2007). It is a highly conserved membrane-bound enzyme in eukaryotic cells made up of several subunits that are arranged into two domains; the peripheral V1 domain, and the integral V0 membrane domain. The V1 domain is responsible for ATP hydrolysis while the V0 domain has a role to play in the translocation of protons across the membrane (Nishi & Forgac, 2002). Eight subunits, A-H, make up the V1 domain while the V0 domain is composed of the a, d, e, c, c´/Ac45 and c´´ subunits (Wilkens et al., 2005). It has been shown that the two domains do reversibly disassociate, resulting in the inhibition of the ATPase activity of the V1 domain, which is an important regulatory mechanism of the activity of the V-ATPase (Cotter et al., 2015b).

The V-ATPase is found in a variety of cellular membranes and of importance to the diversity of their biological functions is the ATP-dependent proton transport from the cytoplasm and across cellular membranes; either into intracellular compartments or the extracellular space (Nishi & Forgac, 2002). Within intracellular membranes, V-ATPases function in various cellular processes such as receptor endocytosis and vesicular trafficking of lysosomal enzymes (Pamarthy et al., 2018). Additionally, the V-ATPase serves a critical role in regulating pH within digestive organelles, such as lysosomes, and securing the acidic pH that is required for the activation of digestive enzymes within these organelles (Forgac, 2007). V-ATPases have also been shown to be expressed in the plasma membrane of various specialized cells where they function to acidify the external environments by facilititating the transport of protons from the cytosol and across the plasma membrane. This function of plasma membrane V-ATPases in specialized cells such as renal intercalated cells, osteoclasts, and clear cells of the epididymis, is critical for maintaining pH homeostasis via acid secretion into the renal tubule, bone resorption, and sperm maturation, respectively (Breton & Brown, 2013; Marshansky et al., 2014). Furthermore, overexpression of the V-ATPase has been observed in the plasma membrane of tumor cells and their presence there is believed to contribute to the acidification of the tumor microenvironment (TME) (Stransky et al., 2016; Webb et al., 2011).

1.3.2 Extracellular acidification

Growth promoting metabolic alterations are emerging as one of the hallmarks of cancer (Hanahan & Weinberg, 2011). Driven by increased expression of the glucose transporter GLUT1, which facilitates the transport of glucose through the plasma membrane, there is a marked increase in the uptake of glucose in proliferating tumor cells, compared to non-proliferating normal tissue (Lunt & Vander Heiden, 2011; Pavlova & Thompson, 2016). In the presence of oxygen (O_2), normal cells convert glucose to pyruvate, via glycolysis, and the pyruvate is then processed further to produce ATP via oxidative phosphorylation in the mitochondria, while surplus pyruvate is converted to lactate in the cytoplasm (DeBerardinis & Chandel, 2016). A characteristic of cancer cells is their ability to be able to shift away from oxidative phosphorylation, even in the presence of O_2, by reprogramming their metabolism of glucose and increasing the rate of glycolysis; a metabolic switch that is generally termed “aerobic glycolysis” or “the Warburg effect” (Hanahan & Weinberg, 2011; Warburg, 1956). The metabolic switch along with the increased consumption of glucose results in a higher glycolytic rate which leads to the accumulation of lactate and protons within the cytoplasm (Chen et al., 2007; Gladden, 2004). To avoid intracellular acidification, the cells seem to adapt to this accumulation by increasing the activity of membrane-bound proteins that are involved in pH regulation, such as NA^+/H^+ exchangers (NHE), carbonic anhydrases (CAs), bicarbonate transporters (HCO_3-transporters), monocarboxylate transporters (MCTs), and V-ATPases (Granja et al., 2017). This creates a reversed pH gradient by facilitating the extrusion of protons across the plasma membrane, or into internal vacuoles, thus promoting alkalization of the cytoplasm and acidification of the extracellular environment (Webb et al., 2011). The increased acidity disrupts pH homeostasis in the TME and creates an environment within the tumor tissue that is believed to enhance invasiveness, metastatic behavior, and drug resistance (Martínez-Zaguilán et al., 1996; Rofstad et al., 2006; Spugnini et al., 2015; Wachsberger et al., 1997). Furthermore, it has recently been reported that exposure to low pH in the extracellular environment, in prostate cancer cells and a model of lung metastasis, resulted in prolonged mobility of cancer cells which eventually leads to establishment of distant metastases (Riemann et al., 2016).

A potential role of V-ATPases in regulating pH in various human cancer cells was initially suggested in 1993 (Martinez-Zaguilan et al., 1993). Invasive breast cancer cells were later reported to exhibit enhanced V-ATPase activity at their plasma membrane, compared to poorly metastatic BC cells

(Sennoune et al., 2004). As of today, several studies have reported that plasmalemmal V-ATPase activity is elevated in a number of cancer types, including breast cancer (Capecci & Forgac, 2013; Cotter et al., 2015a; Hinton et al., 2009), prostate cancer (Michel et al., 2013; Riemann et al., 2016), and melanoma (Nishisho et al., 2011).

1.3.3 Inhibition of V-ATPase function in cancer

Given the mounting evidence suggesting that enhanced V-ATPase activity correlates with cancer cell invasion and migration, metastasis, and drug resistance, all major attributes of a malignant phenotype, inhibitors of V-ATPase activity have been increasingly studied as potential therapeutic candidates that could hinder progression to malignancy and multidrug resistance. A number of studies, both *in vitro* and *in vivo*, have shown that V-ATPase inhibition reduces invasion and migration. Knockdown of subunit C of the V-ATPase V1 domain in a mouse xenograft model of breast cancer was shown to inhibit tumor growth and metastatic tendencies (Feng et al., 2013). Also, knockdown of subunit a3 inhibited metastasis in a mouse model of melanoma (Nishisho et al., 2011). Treatment with V-ATPase specific inhibitors, such as archazolid and bafilomycin, have also been shown to reduce BC tumor growth *in vivo* (Schneider et al., 2015) and significantly inhibit the invasive behaviour of highly metastatic BC cells (Sennoune et al., 2004). Furthermore, exposure to bafilomycin A and concanamycin A, another V-ATPase specific inhibitor, has been shown to significantly reduce invasion of prostate cancer cells *in vitro* (Michel et al., 2013). However, since V-ATPase specific inhibition involves a high degree of toxicity for normal cells, due to the ubiquitous expression of V-ATPase, other avenues have increasingly been explored with regard to clinical applications (Iessi et al., 2017). As previously mentioned, and depicted in Figure 1, PPIs have been shown to exhibit an affinity for V-ATPases (Moriyama et al., 1993; Sabolic et al., 1994) and one of the first studies to demonstrate their potential efficacy in anticancer therapy reported that pre-treatment with PPIs in vitro enhanced the effect of chemotherapeutic agents in cancer cells derived from human melanoma, adenocarcinoma, and lymphoma (Luciani et al., 2004). The same study also reported that oral pre-treatment with omeprazole enhanced cisplatin sensitivity *in vivo*, using a mouse xenograft melanoma model (Luciani et al., 2004) and pre-treatment with lansoprazole was recently reported to increase the efficacy of paclitaxel, a chemotherapeutic agent, in the treatment of human melanoma (Azzarito et al., 2015). Additionally, PPIs have been reported to inhibit proliferation and inducing tumor cell death of melanoma cells *in vitro*, while also reducing tumor growth in mice engrafted with human melanoma cells (De Milito et al., 2010).

The therapeutic benefit of PPIs in tandem with chemotherapy have also been evaluated in studies among human cancer patients. One of those studies reported that pre-treatment with PPIs, among patients with osteosarcomas, increased the effectiveness of neoadjuvant chemotherapy (Ferrari et al., 2013). Furthermore, a phase II clinical study performed among patients with metastatic breast cancer, showed that intermittent treatment

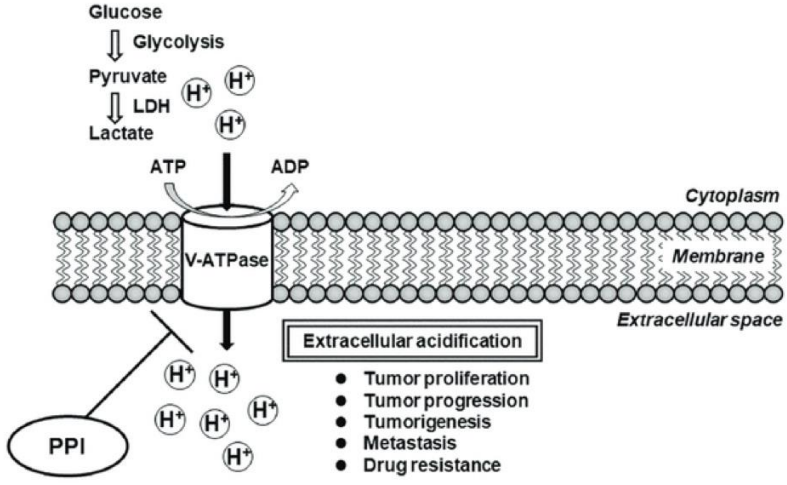


Figure 1. A schematic overview of the potential therapeutic benefits of PPI inhibition of V-ATPase, which has been reported to promote alkalization of the tumor microenvironment. PPI inhibition is thought to prevent tumor progression and drug resistance, which is otherwise induced by extracellular acidification. Figure adjusted from Ikemura et al., 2017.

with high-dose PPIs increased the efficacy of chemotherapy in breast cancer patients with a metastatic disease (Wang et al., 2015). However, a recent Danish observational study reported that PPI use was associated with increased mortality among patients diagnosed with any cancer, as well as certain site specific cancer types such as breast cancer and prostate cancer (Tvingsholm et al., 2018).

1.4 Epidemiology of breast cancer, prostate cancer, and malignant melanoma

1.4.1 Breast cancer

On a global scale, it is estimated that in 2018 there will be approximately 2.1 million diagnosed cases of incident female breast cancer, making it the most

commonly diagnosed cancer among women (Bray et al., 2018). There is however a considerable diversity in incidence rates when the underlying numbers are examined on a regional level, with the highest rates being observed in Australia/New Zealand, North America, and Europe (excluding Eastern Europe) and the lowest in South Central Asia, Middle Africa, and Eastern Africa (Bray et al., 2018). Generally, although breast cancer incidence rates in many low- and middle-income countries (LMICs) have been steadily increasing, high income countries (HICs) tend to have the highest incidence (Torre et al., 2016). In the case of female breast cancer, this in part reflects a varying degree of access to early detection programs, i.e. screening as well as differences in the prevalence of established risk factors; reproductive and hormonal factors that have been shown to increase breast cancer risk, such as long menstrual history, nulliparity, late age at first birth, recent use of oral contraceptives, and hormone replacement therapy, while breastfeeding has been shown to be a protective factor (Jemal et al., 2011; Torre et al., 2016). Other risk factors include age, family history of the disease and inherited mutations (e.g. *BRCA1*, *BRCA2*), obesity in postmenopausal women, alcohol use, low socio-economic status, and physical inactivity (Barnard et al., 2015; Ginsburg et al., 2017; Torre et al., 2016).

As well as being the most commonly diagnosed cancer, breast cancer is also the leading cause of cancer related death among women worldwide (Bray et al., 2018; Torre et al., 2016). Overall, there is less variation in the age-standardized rates for mortality compared to incidence but unlike that pattern the breast cancer mortality rate has actually been decreasing in many HICs while simultaneously increasing in some LMICs, likely due to restricted access to early detection and treatment accompanied by increasing prevalence of risk factors (Bray et al., 2018; Torre et al., 2016). On a specific population level, in 2016 the age-standardized incidence rate of female breast cancer in the Icelandic population was 85.5 per 100.000 persons and the mortality rate was 15.8 per 100.000 persons (Laufey Tryggvadottir et al., 2018).

Given the fact that breast cancer is a highly heterogenous disease there have been endeavors to characterize individual tumors based on tumor size, lymph node and metastasis status (TNM), and histological grade (Provenzano et al., 2018). Additionally, tumors are also clinically categorized and grouped by their varying expression of the estrogen receptor (ER), progesterone receptor (PR), and the *neu* oncogene (HER2), thus creating three distinct tumor subgroups, i.e. the ER positive group, the HER2

amplified group, and the triple negative/basal-like group, which lacks expression of ER, PR, and HER2 (Koboldt et al., 2012; Slamon et al., 1987). Furthermore, at the turn of the last century, studies reporting on the outcome of hierarchical clustering analyses of gene expression profiling within breast tumors revealed expression patterns that would come to define the intrinsic molecular subtypes, categorized as the luminal A, luminal B, HER2 overexpressing, and basal-like subtypes (Perou et al., 2000; Sørlie et al., 2001, 2003). Clinical practice guidelines recommend that factors such as histological type, grade, TNM staging, ER and PR status, HER2 gene expression, and the molecular intrinsic subtypes should be considered when estimating prognosis and for the purposes of treatment decision making (Rakha et al., 2010; Senkus et al., 2015).

1.4.2 Prostate cancer

According to global cancer statistics, it is estimated that a total of 1.3 million incident cases of prostate cancer will be diagnosed in 2018 and it is the most frequently diagnosed cancer type in 105 out of 185 countries listed in the GLOBOCAN estimates for 2018, making it the second most commonly diagnosed cancer among men worldwide after lung cancer (Bray et al., 2018). The prevalence of prostate cancer is especially high in HICs, where one in six among those that have reached the age of 79 years are expected to be diagnosed with the disease, compared to one in 47 in LMICs (Global Burden of Disease Cancer Collaboration et al., 2017).

With regard to mortality on a global scale, prostate cancer is the fifth most common cause of cancer related death and counter to the incidence pattern the mortality rate reveals itself to be higher in LMICs compared to HICs (Bray et al., 2018; Pernar et al., 2018). Within the Icelandic population, the age-standardized incidence and mortality rates were 79.5 and 15.0 per 100.000 persons in 2016, respectively (Laufey Tryggvadottir et al., 2018). Prostate cancer risk is heavily influenced by age, with rising incidence estimates generally observed with increasing age (Laufey Tryggvadottir et al., 2018).

There is a considerable degree of variation in the global pattern of prostate cancer incidence. This is in part due to varying levels of prostate-specific antigen (PSA) screening between individual countries (Pernar et al., 2018). PSA screenings were intensively used after they became commercially available in the late 20th century accompanied by a rapid increase in incidence rates and a shift in diagnostic patterns, reflected in a higher proportion of patients being diagnosed with localized disease and at an earlier age (Etzioni et al., 2008; Hassanipour-Azgomi et al., 2016;

Seamonds et al., 1986). However, a variation in incidence predating the use of PSA tests hints that the observed differences in the number of new cases between countries cannot be entirely due to PSA screening variability, emphasizing the effect of potential lifestyle-related differences and other factors that might modulate prostate cancer risk, such as age, family history of the disease and ethnicity (Brawley, 2012; Pernar et al., 2018).

Prostate cancer is a biologically heterogenous disease and pathologically complex. The identification of specific prognostic determinants has therefore proven to be quite cumbersome. However, there are several clinical and pathological characteristics that have been investigated as potential prognostic factors. These factors, measured around the time of diagnosis, include Gleason score, TNM status, and PSA levels as measured at diagnosis (Martin et al., 2011).

1.4.3 Malignant melanoma

Malignant melanoma is one of the deadliest forms of skin cancer. Worldwide, it is estimated that around 287 thousand new cases will be diagnosed and about 60 thousand melanoma related deaths will occur in 2018 (Bray et al., 2018). There is a considerable variation in both incidence and mortality rates when different countries and regions are compared. In 2012, the lowest incidence, in both men and women, of melanoma was observed to be under 0.5 per 100.000 persons in South-Eastern and South-Central Asia while the highest incidence was seen to be 40.3 per 100.000 persons and 30.5 per 100.000 persons in Australia and New Zealand, respectively. Meanwhile, in North-America and Northern- and Western-Europe incidence rates over 10 per 100.000 persons were observed (Ferlay et al., 2015). The regions that are most affected by this cancer are those that inhabit predominantly fair-skinned populations. In 2012, the age-standardized mortality rates ranged from 0.1 per 100.000 persons in South-East Asia to 4.7 per 100.000 persons in New Zealand (Schadendorf et al., 2018). In the Icelandic population, the age-standardized incidence rates in 2012 were 9.1 and 13.3 per 100.000 persons among men and women, respectively. The estimated age-standardized mortality rates in Iceland were under 3 per 100.000 persons among both sexes (Laufey Tryggvadottir et al., 2018).

Established risk factors that are known to enhance the risk of malignant melanoma include ultraviolet radiation and subsequent sunburns following sun exposure or use of indoor sunbeds (Boniol et al., 2012; Gandini et al., 2011), a personal or family history of the disease as well as the presence of melanocytic birthmarks (Berwick et al., 2009), high socioeconomic status

(SES) (Jiang et al., 2015), and certain phenotypic characteristics such as having fair skin that has a tendency to freckle, light eye color, and light hair color (Berwick et al., 2009).

2 Aims

The overarching aim of this study was to use the population-based resources available in Iceland to assess the use of proton pump inhibitors among the adult outpatient population in Iceland, explore whether PPIs possess a chemopreventive effect on malignant melanoma, breast or prostate cancer, and to assess a potential antineoplastic effect of PPI use on mortality among prostate cancer patients.

2.1 Study I – Proton-pump inhibitors among adults

The aim of our first study was to provide evidence of real-world use of PPIs in Iceland between 2003 and 2015. Specifically, we set out to determine overall use of PPIs by individual PPI substance and specialty of the prescribing physician. Furthermore, our objective was to determine the annual prevalence and incidence of PPI use, treatment duration and the proportion of PPI use that could be associated with gastroprotection.

2.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

The aim of our second study was to examine a potential preventive role of PPI use by testing the association between exposure to PPIs and the risk of being diagnosed with a first-time malignant melanoma, breast or prostate cancer among the adult population in Iceland between 2005 and 2014.

2.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

The aim of our third study was to explore whether PPI use decreases prostate-cancer specific and all-cause mortality among patients that were diagnosed with a first-time prostate cancer between 2007 and 2012.

3 Materials and methods

The following chapters give an overview of the data sources, study designs, and methods that we used in this PhD project. A more detailed description of the materials and methods that were used in each of the separate studies can be found within the original publications.

3.1 Data sources

3.1.1 The Icelandic Medicines Registry

The Icelandic Medicines Registry is an important resource for Icelandic pharmacoepidemiological studies that is maintained by the Directorate of Health ("The Directorate of Health," 2018). It was established in 2005 and contains individual-level information on all filled prescriptions to the outpatient population in Iceland from January 1, 2003 onwards with a completeness in the range between 91% to 98%. Since 2010 the Medicines Registry has also contained information on dispensed prescription drugs within Icelandic nursing homes (Furu et al., 2010).

We used data from the Medicines Registry in all three studies. For each filled PPI prescription by the outpatient population we received information on the name of the drug, ATC code, date of dispensing, number of dispensed DDDs, specialty of the prescribing physician, location of the pharmacy where a prescription for a PPI drug was filled, number of tablets dispensed and tablet strength in milligrams. For study III we also retrieved information on the number of distinct medications, down to the fourth ATC level, that were dispensed to a patient in the 12 months prior to an incident diagnosis of prostate cancer to be used as medication-based comorbidity.

3.1.2 The Icelandic Cancer Registry

The Icelandic Cancer Registry (Laufey Tryggvadottir et al., 2018) was established in 1954 and is maintained by the Icelandic Cancer Society under the authority of the Directorate of Health. The Cancer Registry is a population-based registry that contains information on every cancer diagnosis in Iceland since 1955 with 99% completeness (Sigurdardottir et al., 2012). Each diagnosis is currently coded according to the 10th revision of the ICD (ICD-10). Previous diagnoses coded based on earlier ICD revisions have been converted to ICD-10 to facilitate reporting and communication of the data (Sigurdardottir et al., 2012).

We used data from the Cancer Registry for studies II and III. For each diagnosis of interest, we obtained information on the date of diagnosis, ICD-10 code, morphological code, clinical stage, number of previous cancer diagnoses, and age at diagnosis. For study III, we additionally retrieved information on Gleason score for prostate cancer patients.

Systematic collection of information regarding TNM pathological staging was initiated at the Cancer Registry in 2011 (Sigurdardottir et al., 2012). Therefore, for the period between 2003 and 2015 there was a considerable amount of missing information on TNM staging for breast cancer and malignant melanoma. For prostate cancer, information on TNM staging has been collected for diagnoses of prostate cancer dating back to 1998 in a collaboration between the Cancer Registry and urologists operating in Iceland.

3.1.3 The Icelandic Cause of Death Registry

The Icelandic Cause of Death Registry is a centralized national registry that is maintained by the Directorate of Health. It contains mortality data for the Icelandic population categorized according to the ICD-10 system (World Health Organization, 2016). This includes data on date of death and the main underlying cause of death for each deceased individual. For study III, we obtained information on the underlying causes of death, enabling us to identify prostate cancer-specific mortality within our cohort of prostate cancer patients.

3.1.4 Landspitali – The National University Hospital of Iceland

Landspitali – The National University Hospital of Iceland is supervised by the Directorate of Health and is the leading hospital in Iceland, providing health care to patients from all health districts in Iceland. For study III we obtained information on chemotherapy, radiotherapy, and relevant surgical operations categorized according to the NOMESCO Classification of Surgical Procedures (NCSP). For surgical operations, data were available from 2003 onwards. For chemotherapy and radiotherapy, complete data were available from 2007 onwards. These variables were obtained from Electronic Health Records that were accessed through the Clinical Data Warehouse at the hospital.

3.1.5 Other data sources

For all of our studies (I-III) the Icelandic Population Register provided us with information on year of people´s birth, month of birth, sex, residency, migration

status and date of death (if appropriate). These variables were collected for every resident of Iceland during the relevant study periods, both Icelandic and foreign.

PPIs were not available in Iceland as OTC drugs prior to February 1, 2009. The Icelandic Medicines Agency ("Icelandic Medicines Agency," 2018) provided us with data on wholesale statistics of PPI drugs which allowed us to determine the annual proportion of OTC PPI use from 2009 onwards.

Table 1 lists basic information about each study that we conducted that is included in this thesis.

3.2 Study design and population

3.2.1 Study I – Proton-pump inhibitors among adults

This was a nationwide population-based drug utilization study covering the entire adult population residing in Iceland from January 1, 2003 through December 31, 2015. Over the study period 313,296 individuals constituted our study population; a dynamic cohort where individuals could enter the cohort once they reached 19 years or immigrated to Iceland and left the cohort if they emigrated from Iceland. We obtained data on outpatient PPI use from the Medicines Registry while the Population Registry provided demographic information on the study population.

3.2.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

This was a population-based matched case-control study nested within the adult population of Iceland, which amounted to 220,512 individuals during the study period. Individuals were required to have resided in Iceland from January 1, 2003 to be eligible for inclusion in the study. Those with a previous history of cancer were excluded. Incident cases of breast cancer (N = 1739; ICD-10: C50), prostate cancer (N = 1897; ICD-10: C61), and malignant melanoma (N = 385; ICD-10: C43) that were diagnosed between January 1, 2005 and December 31, 2014 were identified using data from the Cancer Registry. For each case, we selected up to 10 controls from the underlying population that were matched on birth year and sex using risk-set-sampling. The Medicines Registry provided us with data on outpatient PPI use while we obtained demographic information from the Population Register.

Table 1. The studies included in this thesis, the study periods, size of study populations, and data sources that were used.

Study	Title	Study period	Study population (N)	Study design	Data sources
I	Proton-pump inhibitors among adults: a nationwide drug-utilization study	2003 - 2015	313,296	Population-based cohort study	Icelandic Medicines Registry, Icelandic Population Registry
II	Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control study	2005 - 2014	19,129 BC cases and controls, 20,865 PC cases and controls, 4235 MM cases and controls	Population-based nested case-control study	Icelandic Cancer Registry, Icelandic Medicines Registry, Icelandic Population Registry
III	Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer	2007 - 2015	1058	Population-based cohort study	Icelandic Cancer Registry, Icelandic Medicines Registry, Icelandic Population Registry, Icelandic Cause Death Register, Landspitali - the National University Hospital of Iceland

Abbreviations: BC, breast cancer; PC, prostate cancer; MM, malignant melanoma

3.2.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

Using nationwide data from Icelandic health registries we conducted a population-based cohort study. We identified eligible patients that received a first-time diagnosis of prostate cancer (N = 1058; ICD-10: C61) between January 1, 2007 and December 31, 2012 using data from the Cancer Registry. To be eligible for inclusion patients had to be 18 years or older, were required to have resided in Iceland at the start of follow-up and had to have survived the first 12 months following their diagnosis. Outpatient use of PPIs was assessed from January 1, 2003 through December 31, 2015 using data from the Medicines Registry. Data from the cancer registry and the medicines registry were then linked together with the Population Register, the Causes of Death Registry, and data from Landspitali – the National University Hospital of Iceland using unique personal identification numbers. The primary outcomes in study III were prostate cancer-specific mortality (ICD-10: C61) and all-cause mortality. Patients were followed from 12 months after their diagnosis until their date of death, date of emigration or the end of the study period.

3.3 Assessment of exposure and ascertainment of outcome

We obtained data on PPI drug exposure from the Medicines Registry. Every drug we assessed was defined according to the World Health Organization anatomical therapeutic chemical/defined daily doses (ATC/DDD) classification (WHO, 2018). In all studies (I-III), we considered PPI use as the primary exposure and we defined PPIs as those drugs belonging to the ATC-group A02BC (*Proton pump inhibitors*). The four PPI substances that were prescribed to the outpatient population in Iceland during our study periods are listed in Table 2, as well as our classification of higher and lower doses based on tablet strength in milligrams (mg).

3.3.1 Study I – Proton-pump inhibitors among adults

When estimating prevalence and incidence (per 100 persons) in study I, we defined PPI use as at least one PPI dispensing within the relevant calendar year. We used the National Institute for Health and Care Excellence (NICE) clinical guidelines (NICE, 2018) to define PPI dose strengths (in mg) as either higher or lower dose by defining standard and double doses as higher-dose PPIs and low doses as lower-dose PPIs (Table 2).

Table 2. Proton pump inhibitor substances that were prescribed to the outpatient population in Iceland between 2003 and 2015.

Drug	ATC	DDD (mg)	Available package sizes in Iceland (mg)	Lower dose (mg)	Higher dose (mg)
Omeprazole	A02BC01	20	10, 20, 40	10	20, 40
Lansoprazole	A02BC03	30	15, 30	15	30
Rabeprazole	A02BC04	20	10, 20	10	20
Esomeprazole	A02BC05	30	10, 20, 40	10	20, 40

3.3.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

In the main analysis of study II, we defined patients as PPI users if they received at least one PPI dispensing prior to index date. We implemented a lag-time where we disregarded filled prescriptions within the 24 months prior to index date. Furthermore, we performed secondary analyses stratified by high use, cumulative dose, and cumulative duration. Additionally, we adjusted observed risk estimates for NSAID use, defined as at least two filled prescriptions prior to index date. We required NSAID users to have received at least two filled prescriptions rather than one since our objective was to approximate longer-term use which has been linked with concurrent use of PPIs. The primary outcome of study II was a registered diagnosis in the Cancer Registry of breast cancer (ICD-10: C50), prostate cancer (ICD-10: C61) or malignant melanoma (ICD-10: C43).

3.3.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

In study III, we focused on the use of PPIs after prostate cancer diagnosis. Individuals that received at least two filled PPI prescription following their diagnosis were defined as post-diagnosis users. PPI exposure was modelled in a time-dependent manner where patients were considered to be unexposed until they had received a second PPI prescription, after which they were considered to be exposed for the remainder of follow-up. Exposed person-time was lagged for 12 months after the exposure criteria was met. We then assessed post-diagnosis PPI use in varying ways in several secondary and sensitivity analyses as described in paper 3. The primary outcome of study III was prostate cancer-specific death (ICD-10: C61) but we also assessed death from all causes as a secondary outcome.

3.4 Data analysis

In studies II and III, we analyzed each cancer type separately. R version 3.4.2 ("R: The R Project for Statistical Computing," 2018) and RStudio ("RStudio – Open source and enterprise-ready professional software for R," 2018) were used in all analyses for studies I-III.

3.4.1 Study I – Proton-pump inhibitors among adults

We measured overall use of PPIs as the total amount of dispensed DDDs during the study period stratified by calendar year, PPI substance, and specialty of the prescribing physician. We defined annual prevalence of PPI use as the number of adult individuals who filled at least one PPI prescription within each calendar year per 100 persons in the adult population. Further, we performed a sensitivity analysis after redefining prevalence use as the total number of adults filling at least two PPI prescriptions within a relevant calendar year. We defined annual incidence of PPI use as the number of adults who were dispensed their first PPI drug, after a 24-month period of no PPI dispensing, per 100 persons in the adult population.

We estimated the duration of each PPI prescription assuming a daily intake of one tablet and added a grace period of 108 days to account for irregular use. We then used the 'Proportion of Patients Covered' (PPC) method (Rasmussen et al., 2018) to estimate the duration of PPI treatment for each incident PPI user over a 5-year period from their first PPI prescription. The duration analysis was stratified by age, dose strength, and sex. Additionally, we examined the distribution of dispensed DDDs and tablets over a 5-year period following the start of an initial treatment episode. Lastly, we explored the proportion of PPI use that might be attributable to gastroprotection by measuring concurrent use of drugs that have been shown to increase the risk of gastrointestinal complications.

3.4.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

To estimate the association between PPI use and an incident diagnosis of breast cancer, prostate cancer or malignant melanoma, we compared the risk among cases and controls, matched on birth-year and sex, using conditional logistic regression to calculate the relevant odds ratios (ORs) and 95% confidence intervals (CIs). Figure 2 gives an overview of the main analysis. In subgroup analyses, we stratified the data based on high-use, cumulative dose, cumulative duration of PPI use, and calendar period. All analyses were adjusted for NSAID use prior to index date.

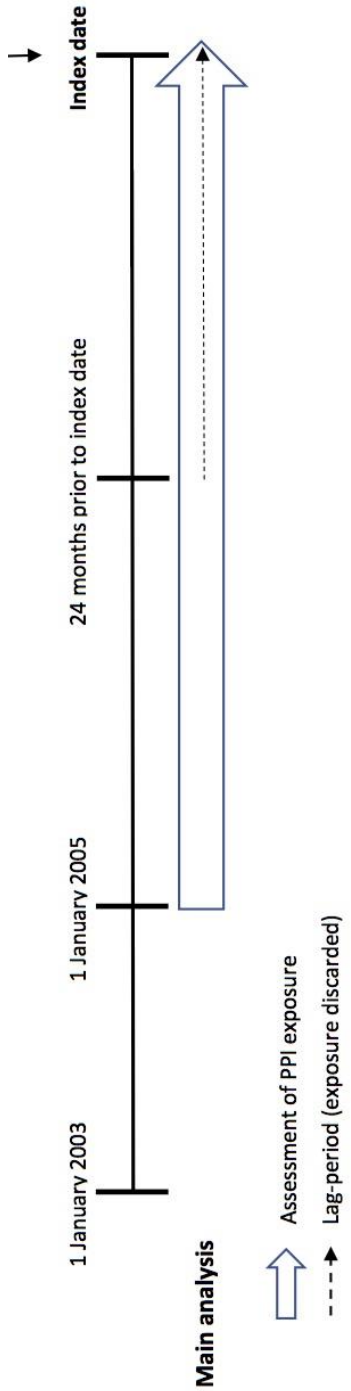


Figure 2. An overview of the main analysis of study II.

Additionally, we performed several sensitivity analyses to assess the effect of different definitions of a lag-period prior to index date (24 months in the main analysis). Furthermore, we also repeated the main analyses employing a new-user design rather than a prevalent user design. Finally, we performed a post-hoc supplementary analysis considering clinical stage at diagnosis among prostate cancer patients.

3.4.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

We used Cox proportional hazard models to estimate hazard ratios (HRs) with 95% CIs of prostate cancer-specific mortality and all-cause mortality associated with PPI use. All models included adjustment for age at diagnosis, calendar year, clinical stage, Gleason score, radiotherapy, prostate cancer surgery, cancer drug treatment, and medication-based comorbidity. In the main analysis, PPI exposure was considered as a time-dependent covariate. Additionally, we performed secondary analyses by timing of use, clinical stage, and cumulative dose. We performed three sensitivity analyses to assess our original definition of PPI exposure. A graphical overview of the main analysis is given in Figure 3.

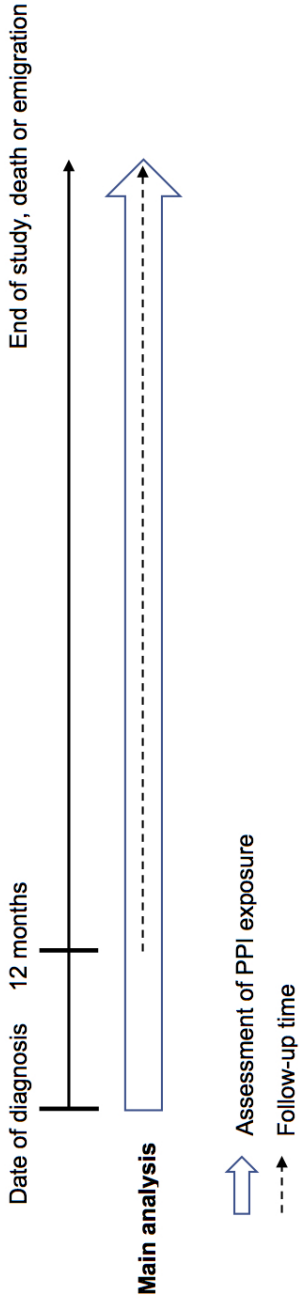


Figure 3. An overview of the main analysis of study III.

3.5 Ethical considerations

We received authorization for all three studies from the National Bioethics Committee and the Data Protection Authority in Iceland. In all instances, personal identification numbers were encrypted by the data manager at the Directorate of Health and we, the researchers, did not at any stage have access to identifiable personal information. Following are the licenses we were granted by the relevant Icelandic authorities.

We obtained ethical approvals from the National Bioethics Committee and the Data Protection Authority October 27, 2015 for studies I and II (reference number VSNb2015080004/03.03). Reprint of the original documents can be found in Appendix A.

For study III we obtained ethical approvals from the National Bioethics Committee and the Data Protection Authority on September 6, 2016 (reference number VSNb2016080001/03.01). Reprint of the original document can be found in Appendix B.

All of our three studies were observational and based on nationwide registry data. Thus, they did not require us to obtain informed consent from the study population.

4 Results

4.1 Study I – Proton-pump inhibitors among adults

In this study, we observed an increase in total PPI use from 3.5 million dispensed DDDs in 2003 to 10.7 million dispensed DDDs in 2015. We found that the majority of all DDDs that were dispensed in this period were prescribed by primary care physicians. Esomeprazole was the most commonly prescribed PPI substance early on in the study period but after 2009 omeprazole became the most commonly prescribed substance. There was an overall increase in annual prevalence of PPI use over time. In 2003 we observed a prevalence of 8.5 per 100 persons while by 2015 it had increased to 15.5 per 100 persons. We did not observe a similar increase when estimating the annual incidence, which we found to be 3.3 per 100 persons in 2005 and 4.1 per 100 persons in 2015. We observed that the prevalence increased with age and was higher among females than among males. After redefining prevalent use for the purposes of a sensitivity analysis we observed that the prevalance estimates decreased somewhat compared with the estimates from the main analysis, i.e. rising from 5.4 per 100 persons in 2003 to 11.0 per 100 persons in 2014 (Figure 4).

Using the PPC method to estimate the duration of PPI treatment among incident PPI users by age and initial dose strength, we found that the duration of treatment tended to be longer among older patients and among patients that started their initial PPI treatment on higher doses. When looking at the proportion of PPI use that might have been attributed to gastroprotection, we observed that the proportion of patients concurrently using PPIs and NSAIDs decreased over time while the opposite was true of concurrent use of PPIs and oral anticoagulants, PPIs and acetylsalicylic acid, and PPIs and platelet inhibitors.

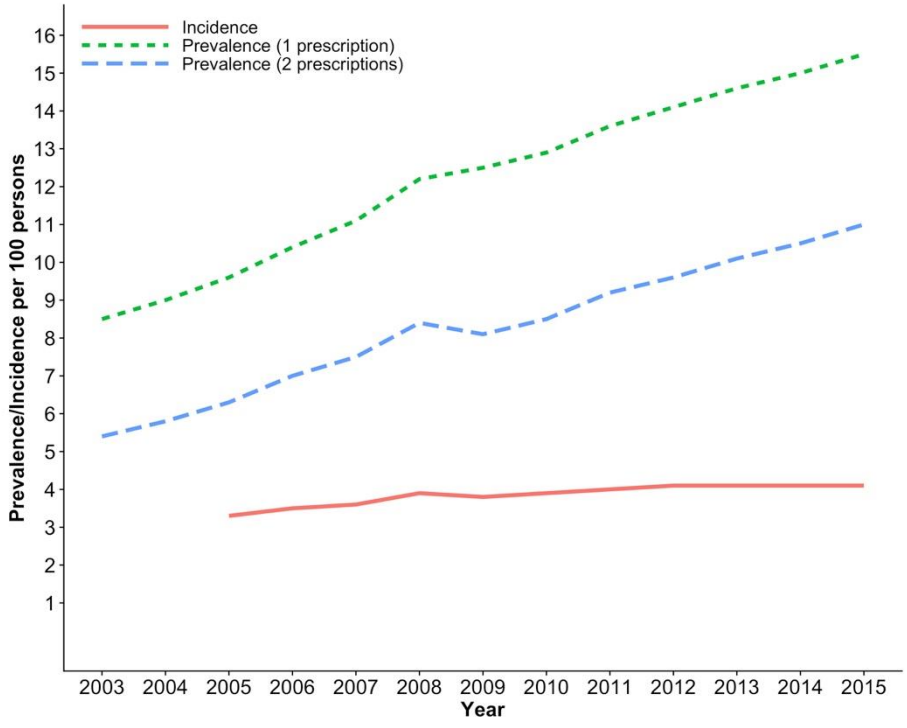


Figure 4. Annual incidence and prevalence (per 100 persons) of proton pump inhibitor use among adults in Iceland. Displaying prevalence estimates from both main and sensitivity analyses.

4.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

4.2.1 Ever use and high use of PPIs

In our analyses of ever use of PPIs, comparing it to non-use, we observed adjusted ORs of 1.03 (95% CI: 0.92-1.16), 1.12 (95% CI: 1.00-1.25), and 0.84 (95% CI: 0.69-1.12) for breast cancer, prostate cancer, and malignant melanoma, respectively. For high use of PPIs, we observed an adjusted OR of 0.97 (95% CI: 0.78-1.19) for breast cancer, 1.20 (95% CI: 0.99-1.47) for prostate cancer, and 0.59 (95% CI: 0.40-1.13) for malignant melanoma.

4.2.2 Cumulative use of PPIs

We further explored cumulative use of PPIs by stratifying by cumulative dose in DDDs and cumulative duration in years for all three cancer types. We observed that individual ORs were elevated, with a marginally statistically

significant association for prostate cancer, indicating a potential increase in risk for patients that used over 1096 DDDs (1.26 (95% CI: 1.02-1.55)) and those that were exposed for 1-5 years (1.22 (95% CI: 1.04-1.42)). Additionally, for malignant melanoma we observed ORs that indicated a marginally significant association with decreased risk among patients consuming between 365 and 730 DDDs (0.37 (95% CI: 0.15-0.93)) and those using PPIs for a duration of 1-5 years (0.57 (95% CI: 0.36-0.91)). However, the patterns we observed did not indicate a dose-response relationship for any of the cancer types (see Figure 5 and Figure 6).

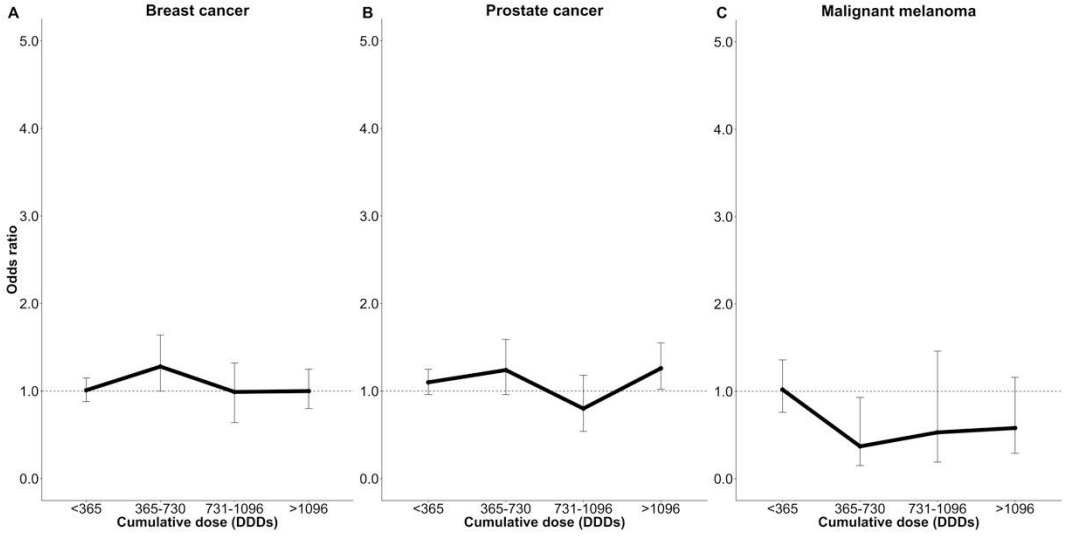


Figure 5. The observed pattern between cumulative PPI dose and risk of breast cancer (A), prostate cancer (B), and malignant melanoma (C).

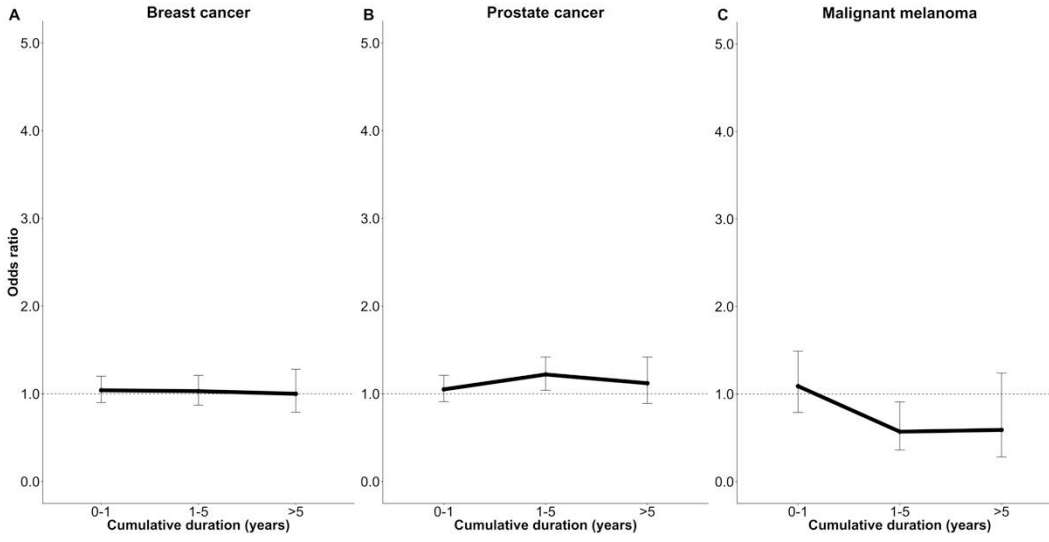


Figure 6. The observed pattern between cumulative duration of PPI use and risk of breast cancer (A), prostate cancer (B), and malignant melanoma (C).

4.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

In the main analysis of study III, we observed adjusted HRs of 0.88 (95% CI: 0.52-1.48) and 1.02 (95% CI: 0.73–1.43) for prostate cancer-specific and all-cause mortality, respectively. Thus, our results did not indicate that post-diagnosis PPI use was associated with increased, or decreased, prostate cancer-specific or all-cause mortality. When we stratified our analysis by timing of PPI use we observed adjusted HRs of 0.45 (95% CI: 0.21-0.98) for prostate-cancer specific mortality and 0.67 (95% CI: 0.43-1.04) for all-cause mortality among continuous PPI users, while we observed adjusted HRs of 1.12 (95% CI: 0.61-2.08) for prostate-cancer specific mortality and 1.25 (95% CI: 0.82-1.92) for all-cause mortality among new PPI users. Stratification by clinical stage yielded an adjusted HR of 0.50 (95% CI: 0.22-1.16) among patients with localized disease and 1.00 (95% CI: 0.44-2.27) among patients with non-localized disease. For cumulative PPI use, analyses of prostate cancer-specific mortality yielded adjusted HRs of 0.91 (95% CI: 0.43-1.90) for cumulative use of 1-365 DDDs and 0.86 (95% CI: 0.45-1.61) for >365 DDDs. For all-cause mortality we observed adjusted HRs of 1.19 (95% CI: 0.76-1.87) and 0.91 (95% CI: 0.61-1.37) for cumulative use of 1-365 DDDs and >365 DDDs, respectively.

Figure 7 gives a visual overview of the results from study III for analyses of prostate cancer-specific mortality.

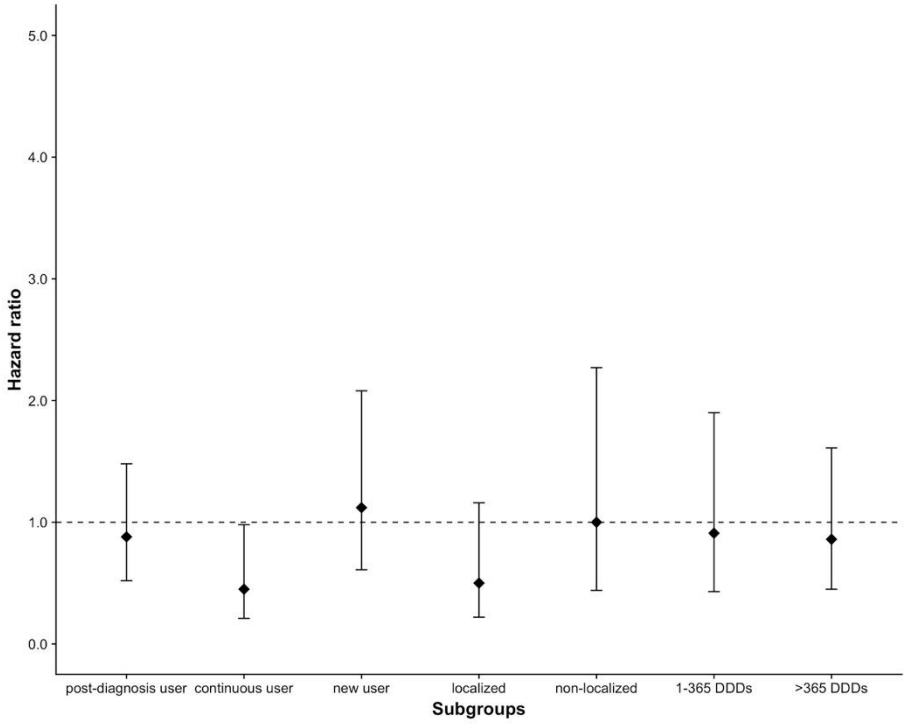


Figure 7. Adjusted hazard ratios and 95% confidence intervals for prostate cancer-specific mortality among PPI user subgroups from the main analysis (post-diagnosis users) and secondary analyses (stratified by timing of use, clinical stage, and cumulative use).

5 Discussion

5.1 Main findings

Overall, we found that PPI use is widespread within the Icelandic population and that it has increased considerably over the past decade. Additionally, patients seem to be treated for longer durations than is generally recommended by clinical guidelines. The findings of our studies do not support a chemopreventive role of PPI use when it comes to the risk of being diagnosed with an incident breast cancer, prostate cancer, or malignant melanoma. Furthermore, our results do not indicate that post-diagnosis PPI use decreases mortality among prostate cancer patients.

5.2 General discussion

5.2.1 Study I – Proton-pump inhibitors among adults

We made an effort to map the landscape of PPI use within the adult Icelandic population by conducting a nationwide population-based drug utilization study. In line with findings from comparable populations (Haastrup et al., 2014; Pottegård et al., 2016a; Wallerstedt et al., 2017), our results indicate that overall use of PPIs increased considerably during the study period. In 2015, the total use of PPIs within the population had reached 10.7 million dispensed DDDs; an increase of 7.2 million DDDs when compared to the 3.5 million DDDs dispensed in 2003. We found that the rising use over time was driven in large part by a surge in prescriptions from primary care physicians, which accounted for 60% of the overall increase in sold DDDs. There are several possible explanations for this considerable rise in PPI use. First, it might be due to changes in the incidence of underlying clinical indications, e.g. increasing incidence of GERD. Unfortunately, the Medicines Registry does not contain information on the underlying indication for each prescription, which made this difficult to assess. Nonetheless, should this be the case we might expect that to be reflected to some degree in either the prescribing pattern among gastroenterologists or in our estimates of annual incidence, or in both. However, prescriptions issued by gastroenterologists only accounted for 6% of the overall increase in PPI use. Furthermore, we only observed a modest rise in annual incidence during the study period while we found that there was a marked increase in annual prevalence which seems to suggest that the elevated PPI use was driven by rising use among

current users, rather than a surge in the number of new users. Second, it could be that PPIs were increasingly used for prophylactic purposes. However, we found that there were actually fewer PPI users concurrently using ulcerogenic drugs in 2015 (36.2%) than in 2003 (37.6%).

As is discussed in more detail in paper I, our analyses of duration of PPI treatment revealed that 22% of patients were still using PPIs one year after starting their initial treatment and that a higher proportion of older patients stayed on treatment for longer durations compared to younger patients. In general, the observed treatment duration among a considerable proportion of patients were longer than is generally recommended by clinical guidelines (NICE, 2018). However, we were unable to determine whether these prolonged durations of PPI treatment reflected more severe symptoms of appropriate underlying indications. The popularity of PPIs has led to some speculations that their general tolerability and good safety profile might be contributing factors to their potential overuse in some quarters, due to patients receiving prescriptions for PPIs without a clear diagnosis (Heidelbaugh et al., 2012). For example, one US study found that among patients receiving antisecretory treatment for more than 90 days, around 39% did not have a documented upper GI diagnosis (PUD, GERD, dyspepsia, or a combination of the three) (Jacobson et al., 2003). Additionally, the appropriateness of long-term PPI use has been questioned in some cases amid concerns that patients might be receiving repeat PPI prescriptions with automatic renewals, without their symptoms being reevaluated, which is likely to encourage unsubstantiated long-term use (Batuwitage et al., 2007). It has been reported in other studies that many long-term PPI users do not meet with their general practitioner (GP) regularly to discuss their treatment (Krol, Muris, Schattenberg, Grol, & Wensing, 2004). Furthermore, when they do meet, the expected duration of PPI treatment is not necessarily discussed (Haastrup et al., 2014; Krol et al., 2004). As with any drug treatment, it is important that PPI therapy is based on reliable information and appropriate indications.

5.2.2 Study II – Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma

The continuous rise of PPIs since they originally became available approximately 30 years ago has stimulated the conversation around the potential links between long-term PPI use and certain adverse effects, e.g. an increased risk of kidney disease (Lazarus et al., 2016), bone fractures (Zhou et al., 2016), hypomagnesemia (Cheungpasitporn et al., 2015), Clostridium

difficile infection (Naito et al., 2018), microscopic colitis (Law et al., 2017), chronic liver disease (Llorente et al., 2017), as well as changes in the composition of the intestinal microbiota (Marlicz et al., 2014). Furthermore, there have also been some reports that have focused on PPI use in association with cancer outcomes. Specifically, they have focused on cancers related to the digestive tract with conflicting results and some of them are likely to be influenced by confounding by indication (Poulsen et al., 2009; Rodriguez et al., 2006; Tamim et al., 2008), reverse causation (Kearns et al., 2017), and time-related biases (Cheung et al., 2017; Suissa & Suissa, 2018).

The emphasis in most observational studies to date has been on gastrointestinal-related cancers and the potential of PPIs to enhance cancer risk. The focus of our cancer-related studies however, narrowed in on the potential beneficial effects of using PPIs in relation to cancer. Therefore, the underlying hypothesis of studies II and III was that PPI use had a potential preventive role in the context of cancer risk and mortality. We decided to exclude gastrointestinal-related cancers from our studies, due to the high probability of confounding by indication and reverse causation in this context. Rather, we decided to focus our attention on three cancers that were not as likely to be subject to these biases, i.e. breast cancer, prostate cancer, and malignant melanoma; cancer types that have been studied previously both in vitro and in vivo where PPIs were shown to exhibit antineoplastic effects (De Milito et al., 2010; Katara et al., 2016; Marino et al., 2010; Michel et al., 2013; Schneider et al., 2015). Furthermore, breast cancer, in women, and prostate cancer, in men, are commonly diagnosed cancer types; a meaningful consideration given the size of the Icelandic population and the importance of elucidating exposures that could influence disease risk.

The biological plausibility of PPIs having a preventive role in a cancer setting, centers on their function as potent acid inhibitors. As has been discussed previously, although not specifically designed to do so, PPIs are able to bind to proton pumps of the V-ATPase type. The V-ATPase has been shown to play a part in promoting acidification of the tumor microenvironment by facilitating a flow of protons through the plasma membrane. Our underlying hypotheses therefore rest on the assumptions that, in the context of the human body, the PPIs are consumed and then absorbed into the circulation where they are then distributed to cancer sites where the extracellular acidity would have to be acidic enough to attract and activate the PPIs. There they would have to bind the V-ATPases and inhibit the extrusion of protons out into the extracellular environment. However, as presented in

paper II, our findings do not support the hypothesis that PPIs possess a chemopreventive effect in the context of breast cancer, prostate cancer, and malignant melanoma.

As we discussed in paper II, if PPIs actually do possess a chemopreventive effect in these cancers, our results could be explained by a number of reasons. First, it could be that several other proteins participate in regulating pH-levels within the cancer cells. Thus, V-ATPase inhibition in itself might not be enough to cut off the flow of protons into the extracellular environment. Second, the pH-level where these tumors are growing might not be low enough for the PPIs to accumulate at the target sites. PPIs are weak bases that are inactive upon consumption but become active in acidic environments. It has been postulated that PPIs selective accumulate in the acidic space of the secretory canaliculus of parietal cells of the stomach (Shin & Kim, 2013). The reason for this selective accumulation is that weak bases like the PPIs require a pH < 4.0, which is not found in another region of the body (Shin et al., 2004). Therefore, for the PPIs to accumulate at tumor sites and be activated, the pH would have to be below 4.0. Although the TME around cancer cells has been shown to be acidic compared to the external environment of normal cells, the acidity is only thought to reach pH values around 6.0 (Gatenby & Gillies, 2004), which might not be enough to attract the PPIs to these sites.

Whether the acidity in tumors that are progressing to a metastatic state might reach lower pH values than 6.0 is unclear. Interestingly, highly metastatic cancer cells have been shown to exhibit an increased expression of V-ATPase (Nishisho et al., 2011; Sennoune et al., 2004), which might indicate increased TME acidity in advanced tumors. Although our post-hoc analysis, where we stratified prostate cancer patients by clinical stage, did not return conclusive results, it would be interesting to examine this matter systematically with an increased sample size.

5.2.3 Study III – Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

Results from a phase II clinical trial among patients with metastatic breast cancer reported that intermittent high-dose treatment with esomeprazole was associated with increased responsiveness in patients receiving chemotherapy (Wang et al., 2015). Initially, influenced in part by the findings of Wang et al., our aim was to include breast cancer patients in this study. However, the Cancer Registry unfortunately did not contain information on clinical stage among breast cancer patients before 2011. Since clinical stage

is a crucially important prognostic variable, we eventually decided to focus our attention solely on prostate cancer patients in this study. Furthermore, when we originally conceived of this study our aim was to focus on a longer study period, i.e. from 2004 through 2012. However, since the Clinical Data Warehouse at Landspitali hospital did not possess exhaustive information for all patients on chemotherapy and radiotherapy prior to 2007, we decided to adjust the study period accordingly. Furthermore, our initial efforts to conduct secondary analyses stratified by PPI substance as well as PPI pre-treatment among patients receiving chemotherapy were thwarted by the small sample size and eventual low numbers in some of the subgroups.

The association between PPI use and mortality among prostate cancer patients has not been studied extensively in other observational studies. In fact, to our knowledge, the only other study to look into this matter is the study by Tvingsholm et al. (Tvingsholm et al., 2018). Although not solely focused on prognosis among prostate cancer patients, they observed significantly increased prostate cancer-specific mortality among post-diagnosis users of PPIs compared with non-users, in their analyses of selected cancer sites. Motivated by these conflicting results, the previously reported antineoplastic activity of PPIs on prostate cancer cells, and the high incidence of prostate cancer overall, we sought to explore whether PPI use would be associated with mortality among prostate cancer patients. As in study II, our hypothesis was based on the biological plausibility that PPI use might have a beneficial effect; in this case by improving survival among exposed patients. However, our findings did not support this hypothesis.

Our observations of null associations between PPI use and prostate cancer-specific and all-cause mortality is in contrast with the findings of Tvingsholm et al., i.e. that PPI use is associated with increased mortality risk among prostate cancer patients. In their study, Tvingsholm et al. found that the increased mortality they observed seemed to be exclusively associated with new users, while the increased risk was not observed among continuous users (Tvingsholm et al., 2018). Their results seem to suggest that there is some unmeasured confounding at play, since the increased mortality is only observed among patients that start their PPI use after they are diagnosed with prostate cancer. One would think, that if PPI use increased the risk of mortality among post-diagnosis users, that this would also be observed among continuous users, who had been using PPIs for longer durations and consumed a greater cumulative quantity of the drugs. In our study, although we observed lower adjusted HRs for prostate cancer-specific mortality among continuous users of PPIs, compared with new PPI users, our findings did not

indicate that initiating PPI use after diagnosis was associated with excess mortality.

As in study II, the biological rationale for the potential antineoplastic role of PPIs in cancers, via their inhibitory function of acid secretion, depends on a number of factors that have to align for them to be able to have their proposed effect within the human body, i.e. accumulate at the cancer sites and promote the alkalization of the TME. As it stands, the evidence from these observational studies do not suggest that the PPIs are able to elicit these effects. In the context of mortality among cancer patients, the possibility of pre-treatment with PPIs being able to increase the effectiveness of chemotherapy might be best suited to be studied in the controlled surroundings of a RCT or in a well-controlled observational study that is able to account for possible confounding by other diseases likely to increase mortality.

5.3 Studies II and III – Potential biases

In studies II and III, there were several biases we had to take into account. A more detailed overview of these biases, and others, is given in chapter 1.1.1, which focuses on biases in pharmacoepidemiological studies. Here, we discuss the biases we encountered in our two outcome studies.

5.3.1 Immortal time bias

A simple definition of immortal time is that it refers to a period of follow-up in a cohort during which the outcome of interest is not able to occur (Levesque et al., 2010). Immortal time bias in pharmacoepidemiological research has been shown to be increasingly common, e.g. in a paper by Suissa this bias was identified in 20 observational studies that were studying drug-related effects of commonly used prescription drugs (Suissa, 2007). If unaccounted for, this bias will invariably skew the results of studies on drug effects so that they are likely to suggest a highly protective role of the drug under study relating to a given outcome, e.g. an incident cancer diagnosis. Another manifestation of this bias, in the context of mortality, was observed in a study whose results suggested that Academy Award winners are likely to live longer than their peers that never receive the prestigious award (Redelmeier & Singh, 2001; Sylvestre et al., 2006).

Both in study II and study III, immortal time bias was an issue that we needed to deal with in our study designs. This was especially important, given the underlying hypothesis, because immortal time bias was likely to

skew the resulting estimates from our analyses downward, thereby likely creating a false sense of a protective drug effect. In fact, before we implemented the nested case-control design in study II, we set up a cohort study where the study population consisted of the entire adult population in Iceland. Using that design, we compared those that had ever used PPIs to those that had never used PPIs. Additionally, we performed a secondary analysis where we estimated the effect of cumulative duration of use in a Cox regression analysis (0-3 months, 3-6 months, 6-24 months, 24-60 months, >60 months). Our observations, heavily influenced by immortal time bias and presented in appendix C, highlight the importance of averting this bias. Otherwise, we might have falsely concluded that PPIs possess a chemopreventive effect in all three cancer types.

5.3.2 Time-window bias

Although observational cohort studies have been shown to be susceptible to certain time-related biases, the same cannot be said about studies using the case-control study design. In a paper by Suissa et al (Suissa et al., 2011), the authors investigated the results of a case-control study claiming that statin use drastically reduces lung cancer risk by 45% (Khurana et al., 2007). What Suissa and colleagues found was that the results from the lung cancer study could be explained by a bias referred to as “time-window bias” (Suissa et al., 2011). This bias arises when there is an imbalance in the length of exposure opportunity time between cases and controls, because a patient with a shorter exposure opportunity time is, by definition, not as likely to be exposed to a specific drug, than a patient with a longer exposure opportunity time.

In study II, we ensured that cases and controls would have similar opportunities to become exposed by restricting the underlying study population to those individuals that had resided in the Iceland from January 1, 2003. As presented in Table 1 of paper II, this resulted in a comparable exposure opportunity time between cases and controls, allowing us to avoid time-window bias.

5.3.3 Reverse causation (protopathic bias)

Reverse causation in pharmacoepidemiology refers to a situation where drug use is initiated as a response to initial symptoms caused by a disease that is still undiagnosed when drug use is started. In the context of study II for example, this bias might lead to false conclusions on the association between PPIs and cancer risk, i.e. that PPI use increases cancer risk when in reality the cancer “causes” the PPI use. Reverse causation can be dealt with by

implementing a lag-period within which all drug exposure is disregarded, i.e. within a time period of a given length prior to the cancer diagnosis (Pottegård & Hallas, 2017).

In study II, we implemented various lag-periods in several sensitivity analyses, ranging from 0-24 months using 6-month intervals. As results from these analyses show, reverse causation was not really a problem in study II. This might be due to these three cancers not causing physical symptoms that are likely to lead to the initiation of PPI treatment. To this point, we repeated our main analyses from study II and looked at the effect of implementing different lag-periods when assessing the association between PPI use and gastric cancer risk (ICD-10: C16.0-C16.9). As the results presented in Table 3 show, removing the lag-period yielded a higher risk estimate, indicating that the results are likely influenced by reverse causation. Although we performed this analysis on the association between PPI use and gastric cancer, we do not want to conclude anything from the observed results since these analyses were mainly done to explore the effect of implementing different lag-periods, where the underlying symptoms from an undiagnosed tumor were likely to influence initiation of PPI treatment. These observations should encourage the implementation of various lag-periods in pharmacoepidemiological studies exploring the association between drug use and cancer.

Table 3. Associations between proton pump inhibitor use and gastric cancer, with varying length of lag-time implemented.

Gastric cancer: Ever use *vs.* Never use			
Lag-time (months)	**No. of cases**	**No. of controls**	**Adjusted OR‡**
0	154 (64.4)	855 (35.8)	3.61 (2.70 - 4.83)
6	93 (38.9)	809 (33.9)	1.26 (0.95 - 1.68)
12	84 (35.1)	766 (32.1)	1.16 (0.86 - 1.56)
18	80 (33.5)	724 (30.3)	1.17 (0.87 - 1.58)
24	72 (30.1)	676 (28.3)	1.10 (0.80 - 1.49)

Prescribing patterns among patients that are close to death likely reflect worsening physical conditions and PPIs are commonly prescribed to a patient with a life-limiting medical diagnosis (McNeil et al., 2016). In study III, we therefore lagged the exposure by 12 months, following the date that patients met the exposure criteria, to limit the influence of changing prescribing patterns nearing end of life. In a sensitivity analysis where we removed the

lag-period, the observed increase in mortality indicates that without the exposure lag, our results would likely have been influenced by reverse causation (Table 4).

Table 4. Cox proportional hazard regression models for the associations between post-diagnosis PPI use and prostate cancer-specific and all-cause mortality, without lagging the exposure.

PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Prostate cancer-specific mortality				
Non-use	49	3854	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	49	1059	3.69 (2.48 - 5.50)	3.95 (2.59 - 6.02)
All-cause mortality				
Non-use	123	3854	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	80	1059	2.34 (1.76 - 3.10)	2.29 (1.71 - 3.08)

Abbreviations: HR, hazard ratio; CI, confidence interval
[b]Adjusted for age at diagnosis
[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

5.4 Strengths and limitations

The most important overall strength of our studies involved nationwide data sources of high quality allowing us, e.g. through the Icelandic Medicines Registry, to assess PPI use among the entire Icelandic adult population and, e.g. through the Icelandic Cancer Registry, to identify all of the cancer diagnoses in Iceland relevant for our studies. Furthermore, the nature of how the data were collected for each data source, independently from one another, allowed our analyses to be carried out without us having to worry about recall bias; a bias that can be problematic if e.g. survey data were used to assess prior drug use. Lastly, the time-varying nature of our analyses in studies II and III enabled us to avoid time-related biases which likely would have skewed our results, leading us to draw false conclusions.

Our studies also had several overall limitations that we were unable to avoid. First, and perhaps most importantly, we lacked information about the underlying reason for PPI use which limited our ability to assess the appropriateness of PPI use in study I and further limited our ability to address potential confounding factors in studies II and III that might have influenced our results. To address the potential of confounding by indication influencing our results in studies II and III, we considered performing analyses using H2RA use as an active comparator, i.e. to compare the observed association for PPIs with the association for another drug used to treat the same clinical condition. However, this was not a feasible option due to the low-level of H2RA use in our underlying study population. In 2014 the total amount of sold H2RA, measured in DDDs, was 387,584 DDDs, out of which 245,375 DDDs were sold OTC. That amounts to 63.3% of the total amount of sold

H2RA drugs during that year. For comparison, there were 10,866,604 DDDs of PPIs sold in 2014, out of which 9.4% were sold OTC.

Second, we were unable to obtain information on individual-level risk factors such as body-mass-index (BMI), SES, alcohol use, smoking, and disease-based comorbidities. The lack of adjustment for these variables might have contributed to some level of unmeasured confounding influencing our results in studies II and III.

Third, information on PPI use before 2003 was unknown which might be a source of misclassification bias. Further, PPIs and NSAIDs are available OTC in pharmacies in Iceland which might have resulted in some misclassification of their use. However, as mentioned in study I the overall OTC use of PPIs, our primary exposure in all three studies, never exceeded 10% of the total use of PPIs after they became available OTC on February 1, 2009. Nevertheless, it cannot be completely ruled out that misclassification of PPI use might have biased the results from studies II and III towards the null.

Fourth, another potential source of misclassification bias might stem from the fact that the Medicines Registry only contains information on outpatient PPI use, leaving us in the dark about their use within hospitals. PPIs have been shown to be used extensively among hospitalized patients, with reports of approximately 50% of inpatients being prescribed PPIs during their stay within the hospital setting. This might have influenced our results to some degree, especially in study III where a higher proportion of patients likely entered the inpatient setting at some point following their diagnosis. Fifth, we lacked information on exact dosing regimens for the PPI prescriptions which forced us to assume a daily intake of either one tablet or one DDD, although it is likely that patients with more severe symptoms might have had a higher daily intake. In study I, this would have further allowed us to evaluate the appropriateness of PPI use. If a high proportion of patients consumed a higher daily dose than one tablet/DDD that would potentially affect our estimates of treatment duration in studies I and II.

Sixth, as in all registry-based studies on drug use we had to assume that patients receiving a dispensing for a drug do actually take them. It remains likely that some patients that receive PPIs only take them occasionally and on-demand. In fact, our observation in study I of lowered prevalence estimates, when prevalent use was redefined by requiring two filled prescriptions rather than one, supports the idea that a number of PPI users can probably be referred to as ‘occasional users’. Seventh, the Icelandic Medicines Registry did not contain information on PPI use within nursing

homes until 2010, which might have resulted in PPI use being somewhat underestimated before that time, since the prevalence of PPI use was shown to increase with age.

Eighth, the length of our study periods in studies II and III were limited in part by the information that was available to use. In study II, we were limited by the fact that the Medicines Registry only started in 2003 and to be able to implement a 24-month lag-period we had to limit the start of the study period to the year 2005. In study III, we were limited by the lack of comprehensive information from Landspitali hospital on chemo- and radiotherapy prior to 2007, forcing us to limit the study period to 2007-2012. Additionally, because we only had information on clinical stage prior to 2011 for prostate cancer diagnoses, we were unable to include breast cancer patients in study III, as we initially intended.

Finally, one of our original aims was to assess the mortality among patients that received PPIs prior to chemotherapy but this turned out to be infeasible due to the small sample size of patients receiving chemotherapy. Therefore, it is clear that studies II and III would benefit greatly from an increased period of follow-up time. Finally, despite our best efforts, we cannot entirely exclude the possibility that the aforementioned biases in chapter 5.3 might have influenced our results to some degree, although our precautions should have substantially limited their effect on our study results.

6 Conclusions and future studies

Our findings suggest that overall PPI use has increased considerably since 2003, driven by a substantial increase of prescriptions in primary care. Our results indicate that the observed increase was mainly due to increased use among current users, especially among the elderly. Furthermore, our observations of extended treatment durations, often on higher doses and well beyond the recommended duration of PPI treatment according to clinical guidelines, should encourage future studies to explore the appropriateness of the extensive PPI use observed in Iceland in this study.

Overall our findings do not support our hypothesis that PPIs possess antineoplastic properties. Specifically, our results do not suggest a chemopreventive role of PPIs in breast cancer, prostate cancer, or malignant melanoma. Future studies on PPI use and cancer risk should focus on clinical stage and whether PPIs influence the risk of being diagnosed with a metastatic disease, given the evidence of increased plasmalemmal V-ATPase expression in metastatic cancer cells. Furthermore, our results do not indicate that post-diagnosis PPI use is associated with decreased mortality among prostate cancer patients. Future observational studies on PPI use and mortality among cancer patients should focus on whether pre-treatment with PPIs among patients receiving chemotherapy influences mortality, possibly by enhancing the chemotherapeutic effect. However, due to the high level of PPI use among cancer patients, likely with various indications, confounding by indication likely needs to be addressed; perhaps by stratifying by underlying clinical indications.

References

Akobeng, A. K. (2005). Understanding randomised controlled trials. *Archives of Disease in Childhood*, *90*(8), 840–844. https://doi.org/10.1136/adc.2004.058222

Azzarito, T., Venturi, G., Cesolini, A., & Fais, S. (2015). Lansoprazole induces sensitivity to suboptimal doses of paclitaxel in human melanoma. *Cancer Letters*, *356*(2), 697–703. https://doi.org/10.1016/j.canlet.2014.10.017

Barnard, M. E., Boeke, C. E., & Tamimi, R. M. (2015). Established breast cancer risk factors and risk of intrinsic tumor subtypes. *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, *1856*(1), 73–85. https://doi.org/10.1016/j.bbcan.2015.06.002

Batuwitage, B. T., Kingham, J. G. C., Morgan, N. E., & Bartlett, R. L. (2007). Inappropriate prescribing of proton pump inhibitors in primary care. *Postgraduate Medical Journal*, *83*(975), 66–68. https://doi.org/10.1136/pgmj.2006.051151

Berwick, M., Erdei, E., & Hay, J. (2009). Melanoma Epidemiology and Public Health. *Dermatologic Clinics*, *27*(2), 205–214. https://doi.org/10.1016/j.det.2008.12.002

Boethius, G., & Wiman, F. (1977). Recording of drug prescriptions in the county of Jämtland, Sweden: I. Methodological aspects. *European Journal of Clinical Pharmacology*, *12*(1), 31–35. https://doi.org/10.1007/BF00561402

Boniol, M., Autier, P., Boyle, P., & Gandini, S. (2012). Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. *BMJ*, *345*(jul24 2), e4757–e4757. https://doi.org/10.1136/bmj.e4757

Brawley, O. W. (2012). Prostate cancer epidemiology in the United States. *World Journal of Urology*, *30*(2), 195–200. https://doi.org/10.1007/s00345-012-0824-2

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries: Global Cancer Statistics 2018. *CA: A Cancer Journal for Clinicians*. https://doi.org/10.3322/caac.21492

Breton, S., & Brown, D. (2013). Regulation of Luminal Acidification by the V-ATPase. *Physiology*, *28*(5), 318–329. https://doi.org/10.1152/physiol.00007.2013

Cahir, C., Fahey, T., Teeling, M., Teljeur, C., Feely, J., & Bennett, K. (2010). Potentially inappropriate prescribing and cost outcomes for older people: a national population study. *British Journal of Clinical Pharmacology*, *69*(5), 543–552. https://doi.org/10.1111/j.1365-2125.2010.03628.x

Capecci, J., & Forgac, M. (2013). The Function of Vacuolar ATPase (V-ATPase) a Subunit Isoforms in Invasiveness of MCF10a and MCF10CA1a Human Breast Cancer Cells. *Journal of Biological Chemistry*, *288*(45), 32731–32741. https://doi.org/10.1074/jbc.M113.503771

Chen, Z., Lu, W., Garcia-Prieto, C., & Huang, P. (2007). The Warburg effect and its cancer therapeutic implications. *Journal of Bioenergetics and Biomembranes*, *39*(3), 267–274. https://doi.org/10.1007/s10863-007-9086-x

Cheung, K. S., Chan, E. W., Wong, A. Y. S., Chen, L., Wong, I. C. K., & Leung, W. K. (2017). Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut*. https://doi.org/10.1136/gutjnl-2017-314605

Cheungpasitporn, W., Thongprayoon, C., Kittanamongkolchai, W., Srivali, N., Edmonds, P. J., Ungprasert, P., O'Corragain, O. A., Korpaisarn, S., & Erickson, S. B. (2015). Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of obser–vational studies. *Renal Failure*, *37*(7), 1237–1241. https://doi.org/10.3109/0886022X.2015.1057800

Cotter, K., Capecci, J., Sennoune, S., Huss, M., Maier, M., Martinez-Zaguilan, R., & Forgac, M. (2015a). Activity of Plasma Membrane V-ATPases Is Critical for the Invasion of MDA-MB231 Breast Cancer Cells. *Journal of Biological Chemistry*, *290*(6), 3680–3692. https://doi.org/10.1074/jbc.M114.611210

Cotter, K., Stransky, L., McGuire, C., & Forgac, M. (2015b). Recent Insights into the Structure, Regulation, and Function of the V-ATPases. *Trends in Biochemical Sciences*, *40*(10), 611–622. https://doi.org/10.1016/j.tibs.2015.08.005

De Milito, A., Canese, R., Marino, M. L., Borghi, M., Iero, M., Villa, A., Venturi, G., Lozupone, F., Iessi, E., Logozzi, M., Mina, P. D., Santinami, M., Rodolfo, M., Podo, F., Rivoltini, L., & Fais, S. (2010). pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. *International Journal of Cancer*, *127*(1), 207–219. https://doi.org/10.1002/ijc.25009

DeBerardinis, R. J., & Chandel, N. S. (2016). Fundamentals of cancer metabolism. *Science Advances*, *2*(5), e1600200. https://doi.org/10.1126/sciadv.1600200

Dent, J., El-Serag, H. B., Wallander, M.-A., & Johansson, S. (2005). Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut*, *54*(5), 710–717. https://doi.org/10.1136/gut.2004.051821

Drew, D. A., Cao, Y., & Chan, A. T. (2016). Aspirin and colorectal cancer: the promise of precision chemoprevention. *Nature Reviews Cancer*, *16*(3), 173–186. https://doi.org/10.1038/nrc.2016.4

Dubach, U. C., Rosner, B., & Stürmer, T. (1991). An Epidemiologic Study of Abuse of Analgesic Drugs: Effects of Phenacetin and Salicylate on Mortality and Cardiovascular Morbidity (1968 to 1987). *New England Journal of Medicine*, *324*(3), 155–160. https://doi.org/10.1056/NEJM199101173240304

Etzioni, R., Gulati, R., Falcon, S., & Penson, D. F. (2008). Impact of PSA Screening on the Incidence of Advanced Stage Prostate Cancer in the United States: A Surveillance Modeling Approach. *Medical Decision Making*, *28*(3), 323–331. https://doi.org/10.1177/0272989X07312719

Feng, S., Zhu, G., McConnell, M., Deng, L., Zhao, Q., Wu, M., Zhou, Q., Wang, J., Qi, J., Li, Y.-P., & Chen, W. (2013). Silencing of Atp6v1c1 Prevents Breast Cancer Growth and Bone Metastasis. *International Journal of Biological Sciences*, *9*(8), 853–862. https://doi.org/10.7150/ijbs.6030

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012: Globocan 2012. *International Journal of Cancer*, *136*(5), E359–E386. https://doi.org/10.1002/ijc.29210

Ferrari, S., Perut, F., Fagioli, F., Brach Del Prever, A., Meazza, C., Parafioriti, A., Picci, P., Gambarotti, M., Avnet, S., Baldini, N., & Fais, S. (2013). Proton pump inhibitor chemosensitization in human osteosarcoma: from the bench to the patients' bed. *Journal of Translational Medicine*, *11*(1), 268. https://doi.org/10.1186/1479-5876-11-268

Forgac, M. (2007). Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology. *Nature Reviews Molecular Cell Biology*, *8*(11), 917–929. https://doi.org/10.1038/nrm2272

Furu, K., Wettermark, B., Andersen, M., Martikainen, J. E., Almarsdottir, A. B., & SÃ¸rensen, H. T. (2010). The Nordic Countries as a Cohort for Pharmacoepidemiological Research. *Basic & Clinical Pharmacology & Toxicology*, *106*(2), 86–94. https://doi.org/10.1111/j.1742-7843.2009.00494.x

Gandini, S., Autier, P., & Boniol, M. (2011). Reviews on sun exposure and artificial light and melanoma. *Progress in Biophysics and Molecular Biology*, *107*(3), 362–366. https://doi.org/10.1016/j.pbiomolbio.2011.09.011

Gatenby, R. A., & Gillies, R. J. (2004). Why do cancers have high aerobic glycolysis? *Nature Reviews Cancer*, *4*(11), 891–899. https://doi.org/10.1038/nrc1478

Ginsburg, O., Bray, F., Coleman, M. P., Vanderpuye, V., Eniu, A., Kotha, S. R., Sarker, M., Huong, T. T., Allemani, C., Dvaladze, A., Gralow, J., Yeates, K., Taylor, C., Oomman, N., Krishnan, S., Sullivan, R., Kombe, D., Blas, M. M., Parham, G., Kassami, N., & Conteh, L. (2017). The global burden of women's cancers: a grand challenge in global health. *The Lancet*, *389*(10071), 847–860. https://doi.org/10.1016/S0140-6736(16)31392-7

Gladden, L. B. (2004). Lactate metabolism: a new paradigm for the third millennium: Lactate metabolism. *The Journal of Physiology*, *558*(1), 5–30. https://doi.org/10.1113/jphysiol.2003.058701

Global Burden of Disease Cancer Collaboration, Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H., Dicker, D. J., Chimed-Orchir, O., Dandona, R., Dandona, L., Fleming, T., Forouzanfar, M. H., Hancock, J., Hay, R. J., Hunter-Merrill, R., Huynh, C., Hosgood, H. D., Johnson, C. O., Jonas, J. B., Khubchandani, J., Kumar, G. A., Kutz, M., Lan, Q., Larson, H. J., Liang, X., Lim, S. S., Lopez, A. D., MacIntyre, M. F., Marczak, L., Marquez, N., Mokdad, A. H., Pinho, C., Pourmalek, F., Salomon, J. A., Sanabria, J. R., Sandar, L., Sartorius, B., Schwartz, S. M., Shackelford, K. A., Shibuya, K., Stanaway, J., Steiner, C., Sun, J., Takahashi, K., Vollset, S. E., Vos, T., Wagner, J. A., Wang, H., Westerman, R., Zeeb, H., Zoeckler, L., Abd-Allah, F., Ahmed, M. B., Alabed, S., Alam, N. K., Aldhahri, S. F., Alem, G., Alemayohu, M. A., Ali, R., Al-Raddadi, R., Amare, A., Amoako, Y., Artaman, A., Asayesh, H., Atnafu, N., Awasthi, A., Saleem, H. B., Barac, A., Bedi, N., Bensenor, I., Berhane, A., Bernabé, E., Betsu, B., Binagwaho, A., Boneya, D., Campos-Nonato, I., Castañeda-Orjuela, C., Catalá-López, F., Chiang, P., Chibueze, C., Chitheer, A., Choi, J.-Y., Cowie, B., Damtew, S., das Neves, J., Dey, S., Dharmaratne, S., Dhillon, P., Ding, E., Driscoll, T., Ekwueme, D., Endries, A. Y., Farvid, M., Farzadfar, F., Fernandes, J., Fischer, F., G/hiwot, T. T., Gebru, A., Gopalani, S., Hailu, A., Horino, M., Horita, N., Husseini, A., Huybrechts, I., Inoue, M., Islami, F., Jakovljevic, M., James, S., Javanbakht, M., Jee, S. H., Kasaeian, A., Kedir, M. S., Khader, Y. S., Khang, Y.-H., Kim, D., Leigh, J., Linn, S., Lunevicius, R., El Razek, H. M. A., Malekzadeh, R., Malta, D. C., Marcenes, W., Markos, D., Melaku, Y. A., Meles, K. G., Mendoza, W., Mengiste, D. T., Meretoja,

T. J., Miller, T. R., Mohammad, K. A., Mohammadi, A., Mohammed, S., Moradi-Lakeh, M., Nagel, G., Nand, D., Le Nguyen, Q., Nolte, S., Ogbo, F. A., Oladimeji, K. E., Oren, E., Pa, M., Park, E.-K., Pereira, D. M., Plass, D., Qorbani, M., Radfar, A., Rafay, A., Rahman, M., Rana, S. M., Søreide, K., Satpathy, M., Sawhney, M., Sepanlou, S. G., Shaikh, M. A., She, J., Shiue, I., Shore, H. R., Shrime, M. G., So, S., Soneji, S., Stathopoulou, V., Stroumpoulis, K., Sufiyan, M. B., Sykes, B. L., Tabarés-Seisdedos, R., Tadese, F., Tedla, B. A., Tessema, G. A., Thakur, J. S., Tran, B. X., Ukwaja, K. N., Uzochukwu, B. S. C., Vlassov, V. V., Weiderpass, E., Wubshet Terefe, M., Yebyo, H. G., Yimam, H. H., Yonemoto, N., Younis, M. Z., Yu, C., Zaidi, Z., Zaki, M. E. S., Zenebe, Z. M., Murray, C. J. L., & Naghavi, M. (2017). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncology*, *3*(4), 524. https://doi.org/10.1001/jamaoncol.2016.5688

Granja, S., Tavares-Valente, D., Queirós, O., & Baltazar, F. (2017). Value of pH regulators in the diagnosis, prognosis and treatment of cancer. *Seminars in Cancer Biology*, *43*, 17–34. https://doi.org/10.1016/j.semcancer.2016.12.003

Grant, K., Al-Adhami, N., Tordoff, J., Livesey, J., Barbezat, G., & Reith, D. (2006). Continuation of proton pump inhibitors from hospital to community. *Pharmacy World & Science: PWS*, *28*(4), 189–193. https://doi.org/10.1007/s11096-006-9028-4

Guess, H. A. (2005). Pharmacoepidemiology, Adverse and Beneficial Effects. In P. Armitage & T. Colton (Eds.), *Encyclopedia of Biostatistics*. Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/0470011815.b2a04034

Haastrup, P., Paulsen, M. S., Zwisler, J. E., Begtrup, L. M., Hansen, J. M., Rasmussen, S., & Jarbøl, D. E. (2014). Rapidly increasing prescribing of proton pump inhibitors in primary care despite interventions: A nationwide observational study. *European Journal of General Practice*, *20*(4), 290–293. https://doi.org/10.3109/13814788.2014.905535

Hagymási, K., Müllner, K., Herszényi, L., & Tulassay, Z. (2011). Update on the pharmacogenomics of proton pump inhibitors. *Pharma–cogenomics*, *12*(6), 873–888. https://doi.org/10.2217/ pgs.11.4

Hallas, J., Hellfritzsch, M., Rix, M., Olesen, M., Reilev, M., & Pottegård, A. (2017). Odense Pharmacoepidemiological Database: A Review of Use and Content. *Basic & Clinical Pharmacology & Toxicology*, *120*(5), 419–425. https://doi.org/10.1111/bcpt.12764

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of Cancer: The Next Generation. *Cell*, *144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Hassanipour-Azgomi, S., Mohammadian-Hafshejani, A., Ghoncheh, M., Towhidi, F., Jamehshorani, S., & Salehiniya, H. (2016). Incidence and mortality of prostate cancer and their relationship with the Human Development Index worldwide. *Prostate International*, *4*(3), 118–124. https://doi.org/10.1016/j.prnil.2016.07.001

Heidelbaugh, J. J., Kim, A. H., Chang, R., & Walker, P. C. (2012). Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therapeutic Advances in Gastroenterology*, *5*(4), 219–232. https://doi.org/10.1177/1756283X12437358

Hinton, A., Sennoune, S. R., Bond, S., Fang, M., Reuveni, M., Sahagian, G. G., Jay, D., Martinez-Zaguilan, R., & Forgac, M. (2009). Function of a subunit isoforms of the V-ATPase in pH homeostasis and in vitro invasion of MDA-MB231 human breast cancer cells. *The Journal of Biological Chemistry*, *284*(24), 16400–16408. https://doi.org/10.1074/jbc.M901201200

Icelandic Medicines Agency. (2018). Retrieved November 28, 2018, from https://www.ima.is

Iessi, E., Logozzi, M., Mizzoni, D., Di Raimo, R., Supuran, C., & Fais, S. (2017). Rethinking the Combination of Proton Exchanger Inhibitors in Cancer Therapy. *Metabolites*, *8*(1), 2. https://doi.org/10.3390/metabo8010002

Ikemura, K., Hiramatsu, S., & Okuda, M. (2017). Drug Repositioning of Proton Pump Inhibitors for Enhanced Efficacy and Safety of Cancer Chemotherapy. *Frontiers in Pharmacology*, *8*. https://doi.org/10.3389/fphar.2017.00911

Jacobson, B. C., Ferris, T. G., Shea, T. L., Mahlis, E. M., Lee, T. H., & Wang, T. C. (2003). Who is using chronic acid suppression therapy and why? *The American Journal of Gastroenterology*, *98*(1), 51–58. https://doi.org/10.1111/j.1572-0241.2003.07186.x

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, *61*(2), 69–90. https://doi.org/10.3322/caac.20107

Jensen, O. M., Knudsen, J. B., Tomasson, H., & Sørensen, B. L. (1989). The Copenhagen case-control study of renal pelvis and ureter cancer: role of analgesics. *International Journal of Cancer*, *44*(6), 965–968.

Jiang, A. J., Rambhatla, P. V., & Eide, M. J. (2015). Socioeconomic and lifestyle factors and melanoma: a systematic review. *British Journal of Dermatology*, *172*(4), 885–915. https://doi.org/10.1111/bjd.13500

Katara, G. K., Kulshrestha, A., Jaiswal, M. K., Pamarthy, S., Gilman-Sachs, A., & Beaman, K. D. (2016). Inhibition of vacuolar ATPase subunit in tumor cells delays tumor growth by decreasing the essential macrophage population in the tumor microenvironment. *Oncogene*, *35*(8), 1058–1065. https://doi.org/10.1038/onc.2015.159

Kearns, M. D., Boursi, B., & Yang, Y.-X. (2017). Proton pump inhibitors on pancreatic cancer risk and survival. *Cancer Epidemiology*, *46*, 80–84. https://doi.org/10.1016/j.canep.2016.12.006

Khurana, V., Bejjanki, H. R., Caldito, G., & Owens, M. W. (2007). Statins Reduce the Risk of Lung Cancer in Humans. *Chest*, *131*(5), 1282–1288. https://doi.org/10.1378/chest.06-0931

Klaukka, T. (2009). The Finnish database on drug utilisation. *Norsk Epidemiologi*, *11*(1). https://doi.org/10.5324/nje.v11i1.529

Klungel, O. H., Martens, E. P., Psaty, B. M., Grobbee, D. E., Sullivan, S. D., Stricker, B. H. C., Leufkens, H. G. M., & de Boer, A. (2004). Methods to assess intended effects of drug treatment in observational studies are reviewed. *Journal of Clinical Epidemiology*, *57*(12), 1223–1231. https://doi.org/10.1016/j.jclinepi.2004.03.011

Koboldt, D. C., Fulton, R. S., McLellan, M. D., Schmidt, H., Kalicki-Veizer, J., McMichael, J. F., Fulton, L. L., Dooling, D. J., Ding, L., Mardis, E. R., Wilson, R. K., Ally, A., Balasundaram, M., Butterfield, Y. S. N., Carlsen, R., Carter, C., Chu, A., Chuah, E., Chun, H.-J. E., Coope, R. J. N., Dhalla, N., Guin, R., Hirst, C., Hirst, M., Holt, R. A., Lee, D., Li, H. I., Mayo, M., Moore, R. A., Mungall, A. J., Pleasance, E., Gordon Robertson, A., Schein, J. E., Shafiei, A., Sipahimalani, P., Slobodan, J. R., Stoll, D., Tam, A., Thiessen, N., Varhol, R. J., Wye, N., Zeng, T., Zhao, Y., Birol, I., Jones, S. J. M., Marra, M. A., Cherniack, A. D., Saksena, G., Onofrio, R. C., Pho, N. H., Carter, S. L., Schumacher, S. E., Tabak, B., Hernandez, B., Gentry, J., Nguyen, H., Crenshaw, A., Ardlie, K., Beroukhim, R., Winckler, W., Getz, G., Gabriel, S. B., Meyerson, M., Chin, L., Park, P. J., Kucherlapati, R., Hoadley, K. A., Todd Auman, J., Fan, C., Turman, Y. J., Shi, Y., Li, L., Topal, M. D., He, X., Chao, H.-H., Prat, A., Silva, G. O., Iglesia, M. D., Zhao, W., Usary, J., Berg, J. S., Adams, M., Booker, J., Wu, J., Gulabani, A., Bodenheimer, T., Hoyle, A. P., Simons, J. V., Soloway, M. G., Mose, L. E., Jefferys, S. R., Balu, S., Parker, J. S., Neil Hayes, D., Perou, C. M., Malik, S., Mahurkar, S., Shen, H., Weisenberger, D. J., Triche Jr, T., Lai, P. H., Bootwalla, M. S., Maglinte, D. T., Berman, B. P., Van Den Berg, D. J., Baylin, S. B., Laird, P. W., Creighton, C. J., Donehower, L. A., Getz, G., Noble, M., Voet, D., Saksena, G., Gehlenborg, N., DiCara, D., Zhang, J., Zhang, H., Wu, C.-J., Yingchun Liu, S., Lawrence, M. S., Zou, L., Sivachenko, A., Lin, P., Stojanov, P., Jing, R., Cho, J., Sinha, R., Park, R. W., Nazaire, M.-D., Robinson, J., Thorvaldsdottir, H., Mesirov, J., Park, P. J., Chin, L.,

Reynolds, S., Kreisberg, R. B., Bernard, B., Bressler, R., Erkkila, T., Lin, J., Thorsson, V., Zhang, W., Shmulevich, I., Ciriello, G., Weinhold, N., Schultz, N., Gao, J., Cerami, E., Gross, B., Jacobsen, A., Sinha, R., Arman Aksoy, B., Antipin, Y., Reva, B., Shen, R., Taylor, B. S., Ladanyi, M., Sander, C., Anur, P., Spellman, P. T., Lu, Y., Liu, W., Verhaak, R. R. G., Mills, G. B., Akbani, R., Zhang, N., Broom, B. M., Casasent, T. D., Wakefield, C., Unruh, A. K., Baggerly, K., Coombes, K., Weinstein, J. N., Haussler, D., Benz, C. C., Stuart, J. M., Benz, S. C., Zhu, J., Szeto, C. C., Scott, G. K., Yau, C., Paull, E. O., Carlin, D., Wong, C., Sokolov, A., Thusberg, J., Mooney, S., Ng, S., Goldstein, T. C., Ellrott, K., Grifford, M., Wilks, C., Ma, S., Craft, B., Yan, C., Hu, Y., Meerzaman, D., Gastier-Foster, J. M., Bowen, J., Ramirez, N. C., Black, A. D., XPATH ERROR: unknown variable “tname”., R. E., White, P., Zmuda, E. J., Frick, J., Lichtenberg, T. M., Brookens, R., George, M. M., Gerken, M. A., Harper, H. A., Leraas, K. M., Wise, L. J., Tabler, T. R., McAllister, C., Barr, T., Hart-Kothari, M., Tarvin, K., Saller, C., Sandusky, G., Mitchell, C., Iacocca, M. V., Brown, J., Rabeno, B., Czerwinski, C., Petrelli, N., Dolzhansky, O., Abramov, M., Voronina, O., Potapova, O., Marks, J. R., Suchorska, W. M., Murawa, D., Kycler, W., Ibbs, M., Korski, K., Spychała, A., Murawa, P., Brzeziński, J. J., Perz, H., Łaźniak, R., Teresiak, M., Tatka, H., Leporowska, E., Bogusz-Czerniewicz, M., Malicki, J., Mackiewicz, A., Wiznerowicz, M., Van Le, X., Kohl, B., Viet Tien, N., Thorp, R., Van Bang, N., Sussman, H., Duc Phu, B., Hajek, R., Phi Hung, N., Viet The Phuong, T., Quyet Thang, H., Zaki Khan, K., Penny, R., Mallery, D., Curley, E., Shelton, C., Yena, P., Ingle, J. N., Couch, F. J., Lingle, W. L., King, T. A., Maria Gonzalez-Angulo, A., Mills, G. B., Dyer, M. D., Liu, S., Meng, X., Patangan, M., Waldman, F., Stöppler, H., Kimryn Rathmell, W., Thorne, L., Huang, M., Boice, L., Hill, A., Morrison, C., Gaudioso, C., Bshara, W., Daily, K., Egea, S. C., Pegram, M. D., Gomez-Fernandez, C., Dhir, R., Bhargava, R., Brufsky, A., Shriver, C. D., Hooke, J. A., Leigh Campbell, J., Mural, R. J., Hu, H., Somiari, S., Larson, C., Deyarmin, B., Kvecher, L., Kovatich, A. J., Ellis, M. J., King, T. A., Hu, H., Couch, F. J., Mural, R. J., Stricker, T., White, K., Olopade, O., Ingle, J. N., Luo, C., Chen, Y., Marks, J. R., Waldman, F., Wiznerowicz, M., Bose, R., Chang, L.-W., Beck, A. H., Maria Gonzalez-Angulo, A., Pihl, T., Jensen, M., Sfeir, R., Kahn, A., Chu, A., Kothiyal, P., Wang, Z., Snyder, E., Pontius, J., Ayala, B., Backus, M., Walton, J., Baboud, J., Berton, D., Nicholls, M., Srinivasan, D., Raman, R., Girshik, S., Kigonya, P., Alonso, S., Sanbhadti, R., Barletta, S., Pot, D., Sheth, M., Demchok, J. A., Mills Shaw, K. R., Yang, L., Eley, G., Ferguson, M. L., Tarnuzzer, R. W., Zhang, J., Dillon, L. A. L., Buetow, K., Fielding, P., Ozenberger, B. A., Guyer, M. S., Sofia, H. J., & Palchik, J. D. (2012). Comprehensive molecular

portraits of human breast tumours. *Nature*, *490*(7418), 61–70. https://doi.org/10.1038/nature11412

Krol, N., Wensing, M., Haaijer-Ruskamp, F., Muris, J. W. M., Numans, M. E., Schattenberg, G., Balen, J., & Grol, R. (2004). Patient-directed strategy to reduce prescribing for patients with dyspepsia in general practice: a randomized trial. *Alimentary Pharmacology and Therapeutics*, *19*(8), 917–922. https://doi.org/10.1111/j.1365-2036.2004.01928.x

Ksiądzyna, D., Szeląg, A., & Paradowski, L. (2015). Overuse of proton pump inhibitors. *Polish Archives of Internal Medicine*, *125*(4), 289–298. https://doi.org/10.20452/pamw.2790

Ladd, A. M., Panagopoulos, G., Cohen, J., Mar, N., & Graham, R. (2014). Potential costs of inappropriate use of proton pump inhibitors. *The American Journal of the Medical Sciences*, *347*(6), 446–451. https://doi.org/10.1097/MAJ.0b013e31829f87d5

Laufey Tryggvadottir, Elinborg J. Olafsdottir, & Helgi Birgisson. (2018). Icelandic Cancer Registry at Icelandic Cancer Society. Retrieved September 19, 2018, from http://www.cancerregistry.is

Law, E. H., Badowski, M., Hung, Y.-T., Weems, K., Sanchez, A., & Lee, T. A. (2017). Association Between Proton Pump Inhibitors and Microscopic Colitis. *The Annals of Pharmacotherapy*, *51*(3), 253–263. https://doi.org/10.1177/1060028016673859

Lazarus, B., Chen, Y., Wilson, F. P., Sang, Y., Chang, A. R., Coresh, J., & Grams, M. E. (2016). Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Internal Medicine*, *176*(2), 238–246. https://doi.org/10.1001/jamainternmed.2015.7193

Levesque, L. E., Hanley, J. A., Kezouh, A., & Suissa, S. (2010). Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*, *340*(mar12 1), b5087–b5087. https://doi.org/10.1136/bmj.b5087

Llorente, C., Jepsen, P., Inamine, T., Wang, L., Bluemel, S., Wang, H. J., Loomba, R., Bajaj, J. S., Schubert, M. L., Sikaroodi, M., Gillevet, P. M., Xu, J., Kisseleva, T., Ho, S. B., DePew, J., Du, X., Sørensen, H. T., Vilstrup, H., Nelson, K. E., Brenner, D. A., Fouts, D. E., & Schnabl, B. (2017). Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal Enterococcus. *Nature Communications*, *8*(1). https://doi.org/10.1038/s41467-017-00796-x

Lødrup, A. B., Reimer, C., & Bytzer, P. (2013). Systematic review: symptoms of rebound acid hypersecretion following proton pump inhibitor treatment. *Scandinavian Journal of Gastroenterology*, *48*(5), 515–522. https://doi.org/10.3109/00365521.2012.746395

Luciani, F., Spada, M., De Milito, A., Molinari, A., Rivoltini, L., Montinaro, A., Marra, M., Lugini, L., Logozzi, M., Lozupone, F., Federici, C., Iessi, E., Parmiani, G., Arancia, G., Belardelli, F., & Fais, S. (2004). Effect of Proton Pump Inhibitor Pretreatment on Resistance of Solid Tumors to Cytotoxic Drugs. *JNCI Journal of the National Cancer Institute*, *96*(22), 1702–1713. https://doi.org/10.1093/jnci/djh305

Lundell, L., Miettinen, P., Myrvold, H. E., Hatlebakk, J. G., Wallin, L., Engström, C., Julkunen, R., Montgomery, M., Malm, A., Lind, T., Walan, A., & Nordic GERD Study Group. (2009). Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clinical Gastroenterology and Hepatology: The Official Clinical Practice Journal of the American Gastroenterological Association*, *7*(12), 1292–1298; quiz 1260. https://doi.org/10.1016/j.cgh.2009.05.021

Lunt, S. Y., & Vander Heiden, M. G. (2011). Aerobic Glycolysis: Meeting the Metabolic Requirements of Cell Proliferation. *Annual Review of Cell and Developmental Biology*, *27*(1), 441–464. https://doi.org/10.1146/annurev-cellbio-092910-154237

Mahon, D., Rhodes, M., Decadt, B., Hindmarsh, A., Lowndes, R., Beckingham, I., Koo, B., & Newcombe, R. G. (2005). Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *The British Journal of Surgery*, *92*(6), 695–699. https://doi.org/10.1002/bjs.4934

Marino, M. L., Fais, S., Djavaheri-Mergny, M., Villa, A., Meschini, S., Lozupone, F., Venturi, G., Della Mina, P., Pattingre, S., Rivoltini, L., Codogno, P., & De Milito, A. (2010). Proton pump inhibition induces autophagy as a survival mechanism following oxidative stress in human melanoma cells. *Cell Death & Disease*, *1*(10), e87–e87. https://doi.org/10.1038/cddis.2010.67

Marlicz, W., Łoniewski, I., Grimes, D. S., & Quigley, E. M. (2014). Nonsteroidal Anti-inflammatory Drugs, Proton Pump Inhibitors, and Gastrointestinal Injury: Contrasting Interactions in the Stomach and Small Intestine. *Mayo Clinic Proceedings*, *89*(12), 1699–1709. https://doi.org/10.1016/j.mayocp.2014.07.015

Marshansky, V., Rubinstein, J. L., & Grüber, G. (2014). Eukaryotic V-ATPase: novel structural findings and functional insights. *Biochimica Et Biophysica Acta*, *1837*(6), 857–879. https://doi.org/10.1016/j.bbabio.2014.01.018

Martin, N. E., Mucci, L. A., Loda, M., & DePinho, R. A. (2011). Prognostic Determinants in Prostate Cancer: *The Cancer Journal*, *17*(6), 429–437. https://doi.org/10.1097/PPO.0b013e31823b042c

Martinez-Zaguilan, R., Lynch, R. M., Martinez, G. M., & Gillies, R. J. (1993). Vacuolar-type H(+)-ATPases are functionally expressed in plasma membranes of human tumor cells. *American Journal of Physiology-Cell Physiology*, *265*(4), C1015–C1029. https://doi.org/10.1152/ajpcell.1993.265.4.C1015

Martínez-Zaguilán, R., Seftor, E. A., Seftor, R. E., Chu, Y. W., Gillies, R. J., & Hendrix, M. J. (1996). Acidic pH enhances the invasive behavior of human melanoma cells. *Clinical & Experimental Metastasis*, *14*(2), 176–186.

McNeil, M. J., Kamal, A. H., Kutner, J. S., Ritchie, C. S., & Abernethy, A. P. (2016). The Burden of Polypharmacy in Patients Near the End of Life. *Journal of Pain and Symptom Management*, *51*(2), 178-183.e2. https://doi.org/10.1016/j.jpainsymman.2015.09.003

Mehta, S., Bennett, J., Mahon, D., & Rhodes, M. (2006). Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: Seven-year follow-up. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract*, *10*(9), 1312–1316; discussion 1316-1317. https://doi.org/10.1016/j.gassur.2006.07.010

Michel, V., Licon-Munoz, Y., Trujillo, K., Bisoffi, M., & Parra, K. J. (2013). Inhibitors of vacuolar ATPase proton pumps inhibit human prostate cancer cell invasion and prostate-specific antigen expression and secretion. *International Journal of Cancer*, *132*(2), E1–E10. https://doi.org/10.1002/ijc.27811

Moriarty, F., Bennett, K., Cahir, C., & Fahey, T. (2016). Characterizing Potentially Inappropriate Prescribing of Proton Pump Inhibitors in Older People in Primary Care in Ireland from 1997 to 2012. *Journal of the American Geriatrics Society*, *64*(12), e291–e296. https://doi.org/10.1111/jgs.14528

Moriyama, Y., Patel, V., Ueda, I., & Futai, M. (1993). Evidence for a Common Binding-Site for Omeprazole and N-Ethylmaleimide in Subunit A of Chromaffin Granule Vacuolar-Type H+-ATPase. *Biochemical and Biophysical Research Communications*, *196*(2), 699–706. https://doi.org/10.1006/bbrc.1993.2306

Mukherjee, S. (2011). *The emperor of all maladies: a biography of cancer* (1st Scribner trade paperback ed). New York: Scribner.

Naito, Y., Kashiwagi, K., Takagi, T., Andoh, A., & Inoue, R. (2018). Intestinal Dysbiosis Secondary to Proton-Pump Inhibitor Use. *Digestion*, *97*(2), 195–204. https://doi.org/10.1159/000481813

Naunton, M., Peterson, G. M., & Bleasel, M. D. (2000). Overuse of proton pump inhibitors. *Journal of Clinical Pharmacy and Therapeutics*, *25*(5), 333–340.

NICE. (2018). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management | Guidance and guidelines | NICE. Retrieved November 22, 2017, from https://www.nice.org.uk/guidance/cg184

Nishi, T., & Forgac, M. (2002). The vacuolar (H+)-ATPases — nature's most versatile proton pumps. *Nature Reviews Molecular Cell Biology*, *3*(2), 94–103. https://doi.org/10.1038/nrm729

Nishisho, T., Hata, K., Nakanishi, M., Morita, Y., Sun-Wada, G.-H., Wada, Y., Yasui, N., & Yoneda, T. (2011). The a3 isoform vacuolar type H^+-ATPase promotes distant metastasis in the mouse B16 melanoma cells. *Molecular Cancer Research: MCR*, *9*(7), 845–855. https://doi.org/10.1158/1541-7786.MCR-10-0449

Pamarthy, S., Kulshrestha, A., Katara, G. K., & Beaman, K. D. (2018). The curious case of vacuolar ATPase: regulation of signaling pathways. *Molecular Cancer*, *17*(1). https://doi.org/10.1186/s12943-018-0811-3

Pavlova, N. N., & Thompson, C. B. (2016). The Emerging Hallmarks of Cancer Metabolism. *Cell Metabolism*, *23*(1), 27–47. https://doi.org/10.1016/j.cmet.2015.12.006

Pernar, C. H., Ebot, E. M., Wilson, K. M., & Mucci, L. A. (2018). The Epidemiology of Prostate Cancer. *Cold Spring Harbor Perspectives in Medicine*, a030361. https://doi.org/10.1101/cshperspect.a030361

Perou, C. M., Sørlie, T., Eisen, M. B., van de Rijn, M., Jeffrey, S. S., Rees, C. A., Pollack, J. R., Ross, D. T., Johnsen, H., Akslen, L. A., Fluge, Ø., Pergamenschikov, A., Williams, C., Zhu, S. X., Lønning, P. E., Børresen-Dale, A.-L., Brown, P. O., & Botstein, D. (2000). Molecular portraits of human breast tumours. *Nature*, *406*(6797), 747–752. https://doi.org/10.1038/35021093

Pinheiro, S. P., Rivera, D. R., Graham, D. J., Freedman, A. N., Major, J. M., Penberthy, L., Levenson, M., Bradley, M. C., Wong, H.-L., & Ouellet-Hellstrom, R. (2016). Challenges in evaluating cancer as a clinical outcome in postapproval studies of drug safety. *Annals of Epidemiology*, *26*(11), 735–740. https://doi.org/10.1016/j.annepidem.2016.04.012

Pottegård, A., Broe, A., Hallas, J., de Muckadell, O. B. S., Lassen, A. T., & Lødrup, A. B. (2016a). Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. *Therapeutic Advances in Gastroenterology*, *9*(5), 671–678. https://doi.org/10.1177/ 1756283X16650156

Pottegård, A., Friis, S., Stürmer, T., Hallas, J., & Bahmanyar, S. (2017). Considerations for Pharmacoepidemiological Studies of Drug-Cancer Associations. *Basic & Clinical Pharmacology & Toxicology*. https://doi.org/10.1111/bcpt.12946

Pottegård, A., & Hallas, J. (2017). New use of prescription drugs prior to a cancer diagnosis: Use of Prescription Drugs Prior to Cancer Diagnosis. *Pharmacoepidemiology and Drug Safety*, *26*(2), 223–227. https://doi.org/10.1002/pds.4145

Pottegård, A., Schmidt, S. A. J., Wallach-Kildemoes, H., Sørensen, H. T., Hallas, J., & Schmidt, M. (2016b). Data Resource Profile: The Danish National Prescription Registry. *International Journal of Epidemiology*, dyw213. https://doi.org/10.1093/ije/dyw213

Poulsen, A. H., Christensen, S., McLaughlin, J. K., Thomsen, R. W., Sørensen, H. T., Olsen, J. H., & Friis, S. (2009). Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. *British Journal of Cancer*, *100*(9), 1503–1507. https://doi.org/10.1038/sj.bjc.6605024

Provenzano, E., Ulaner, G. A., & Chin, S.-F. (2018). Molecular Classification of Breast Cancer. *PET Clinics*, *13*(3), 325–338. https://doi.org/10.1016/j.cpet.2018.02.004

Psaty, B. M., Heckbert, S. R., Koepsell, T. D., Siscovick, D. S., Raghunathan, T. E., Weiss, N. S., Rosendaal, F. R., Lemaitre, R. N., Smith, N. L., & Wahl, P. W. (1995). The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*, *274*(8), 620–625.

Pukkala, E., Engholm, G., Højsgaard Schmidt, L. K., Storm, H., Khan, S., Lambe, M., Pettersson, D., Ólafsdóttir, E., Tryggvadóttir, L., Hakanen, T., Malila, N., Virtanen, A., Johannesen, T. B., Larønningen, S., & Ursin, G. (2018). Nordic Cancer Registries – an overview of their procedures and data comparability. *Acta Oncologica*, *57*(4), 440–455. https://doi.org/10.1080/0284186X.2017.1407039

R: The R Project for Statistical Computing. (2018). Retrieved May 21, 2018, from https://www.r-project.org/

Rakha, E. A., Reis-Filho, J. S., Baehner, F., Dabbs, D. J., Decker, T., Eusebi, V., Fox, S. B., Ichihara, S., Jacquemier, J., Lakhani, S. R., Palacios, J., Richardson, A. L., Schnitt, S. J., Schmitt, F. C., Tan, P.-H., Tse, G. M., Badve, S., & Ellis, I. O. (2010). Breast cancer prognostic classification in the molecular era: the role of histological grade. *Breast Cancer Research*, *12*(4). https://doi.org/10.1186/bcr2607

Rasmussen, L., Pratt, N., Hansen, M. R., Hallas, J., & Pottegård, A. (2018). Using the “proportion of patients covered” and the Kaplan-Meier survival analysis to describe treatment persistence. *Pharmacoepidemiology and Drug Safety*, *27*(8), 867–871. https://doi.org/10.1002/pds.4582

Redelmeier, D. A., & Singh, S. M. (2001). Survival in Academy Award-winning actors and actresses. *Annals of Internal Medicine*, *134*(10), 955–962.

Riemann, A., Schneider, B., Gündel, D., Stock, C., Gekle, M., & Thews, O. (2016). Acidosis Promotes Metastasis Formation by Enhancing Tumor Cell Motility. In C. E. Elwell, T. S. Leung, & D. K. Harrison (Eds.), *Oxygen Transport to Tissue XXXVII* (Vol. 876, pp. 215–220). New York, NY: Springer New York. https://doi.org/10.1007/978-1-4939-3023-4_27

Rodriguez, L. A. G., Lagergren, J., & Lindblad, M. (2006). Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut*, *55*(11), 1538–1544. https://doi.org/10.1136/gut.2005.086579

Rofstad, E. K., Mathiesen, B., Kindem, K., & Galappathi, K. (2006). Acidic Extracellular pH Promotes Experimental Metastasis of Human Melanoma Cells in Athymic Nude Mice. *Cancer Research*, *66*(13), 6699–6707. https://doi.org/10.1158/0008-5472.CAN-06-0983

Rosén, M. (2002). National Health Data Registers: a Nordic heritage to public health. *Scandinavian Journal of Public Health*, *30*(2), 81–85. https://doi.org/10.1080/140349401753683444

RStudio – Open source and enterprise-ready professional software for R. (2018). Retrieved November 18, 2018, from https://www.rstudio.com/

Sabolic, I., Brown, D., Verbavatz, J. M., & Kleinman, J. (1994). H(+)-ATPases of renal cortical and medullary endosomes are differentially sensitive to Sch-28080 and omeprazole. *American Journal of Physiology-Renal Physiology*, *266*(6), F868–F877. https://doi.org/10.1152/ajprenal.1994.266.6.F868

Sachs, G., Shin, J. M., Briving, C., Wallmark, B., & Hersey, S. (1995). The Pharmacology of the Gastric Acid Pump: The H+,K+ ATPase. *Annual Review of Pharmacology and Toxicology*, *35*(1), 277–305. https://doi.org/10.1146/annurev.pa.35.040195.001425

Sachs, G., Shin, J. M., & Howden, C. W. (2006). Review article: the clinical pharmacology of proton pump inhibitors. *Alimentary Pharmacology and Therapeutics*, *23*(s2), 2–8. https://doi.org/10.1111/j.1365-2036.2006.02943.x

Scarpignato, C., & Blandizzi, C. (2016). Effective and safe proton pump inhibitor therapy in acid-related diseases – A position paper addressing benefits and potential harms of acid suppression. *BMC Medicine*, *14*(1). https://doi.org/10.1186/s12916-016-0718-z

Schadendorf, D., van Akkooi, A. C. J., Berking, C., Griewank, K. G., Gutzmer, R., Hauschild, A., Stang, A., Roesch, A., & Ugurel, S. (2018).

Melanoma. *The Lancet*, *392*(10151), 971–984. https://doi.org/10.1016/S0140-6736(18)31559-9

Scheiman, J. M. (2013). The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Research & Therapy*, *15*(Suppl 3), S5. https://doi.org/10.1186/ar4177

Schneider, L. S., von Schwarzenberg, K., Lehr, T., Ulrich, M., Kubisch-Dohmen, R., Liebl, J., Trauner, D., Menche, D., & Vollmar, A. M. (2015). Vacuolar-ATPase Inhibition Blocks Iron Metabolism to Mediate Therapeutic Effects in Breast Cancer. *Cancer Research*, *75*(14), 2863–2874. https://doi.org/10.1158/0008-5472.CAN-14-2097

Seamonds, B., Yang, N., Anderson, K., Whitaker, B., Shaw, L. M., & Bollinger, J. R. (1986). Evaluation of prostate-specific antigen and prosttic acid phosphatase as prostate cancer markers. *Urology*, *28*(6), 472–479. https://doi.org/10.1016/0090-4295(86)90146-9

Senkus, E., Kyriakides, S., Ohno, S., Penault-Llorca, F., Poortmans, P., Rutgers, E., Zackrisson, S., & Cardoso, F. (2015). Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *26*(suppl 5), v8–v30. https://doi.org/10.1093/annonc/mdv298

Sennoune, S. R., Bakunts, K., Martínez, G. M., Chua-Tuan, J. L., Kebir, Y., Attaya, M. N., & Martínez-Zaguilán, R. (2004). Vacuolar H+-ATPase in human breast cancer cells with distinct metastatic potential: distribution and functional activity. *American Journal of Physiology. Cell Physiology*, *286*(6), C1443-1452. https://doi.org/10.1152/ajpcell.00407.2003

Shin, J. M., Cho, Y. M., & Sachs, G. (2004). Chemistry of Covalent Inhibition of the Gastric (H^+, K^+)-ATPase by Proton Pump Inhibitors. *Journal of the American Chemical Society*, *126*(25), 7800–7811. https://doi.org/10.1021/ja049607w

Shin, J. M., & Kim, N. (2013). Pharmacokinetics and Pharmacodynamics of the Proton Pump Inhibitors. *Journal of Neurogastroenterology and Motility*, *19*(1), 25–35. https://doi.org/10.5056/jnm.2013.19.1.25

Sigurdardottir, L. G., Jonasson, J. G., Stefansdottir, S., Jonsdottir, A., Olafsdottir, G. H., Olafsdottir, E. J., & Tryggvadottir, L. (2012). Data quality at the Icelandic Cancer Registry: comparability, validity, timeliness and completeness. *Acta Oncologica (Stockholm, Sweden)*, *51*(7), 880–889. https://doi.org/10.3109/0284186X.2012.698751

Slamon, D., Clark, G., Wong, S., Levin, W., Ullrich, A., & McGuire, W. (1987). Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science*, *235*(4785), 177–182. https://doi.org/10.1126/science.3798106

Sørlie, T., Perou, C. M., Tibshirani, R., Aas, T., Geisler, S., Johnsen, H., Hastie, T., Eisen, M. B., van de Rijn, M., Jeffrey, S. S., Thorsen, T., Quist, H., Matese, J. C., Brown, P. O., Botstein, D., Lonning, P. E., & Borresen-Dale, A.-L. (2001). Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proceedings of the National Academy of Sciences*, *98*(19), 10869–10874. https://doi.org/10.1073/pnas.191367098

Sørlie, T., Tibshirani, R., Parker, J., Hastie, T., Marron, J. S., Nobel, A., Deng, S., Johnsen, H., Pesich, R., Geisler, S., Demeter, J., Perou, C. M., Lønning, P. E., Brown, P. O., Børresen-Dale, A.-L., & Botstein, D. (2003). Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proceedings of the National Academy of Sciences*, *100*(14), 8418–8423. https://doi.org/10.1073/pnas.0932692100

Spugnini, E. P., Sonveaux, P., Stock, C., Perez-Sayans, M., De Milito, A., Avnet, S., Garcìa, A. G., Harguindey, S., & Fais, S. (2015). Proton channels and exchangers in cancer. *Biochimica et Biophysica Acta (BBA) - Biomembranes*, *1848*(10), 2715–2726. https://doi.org/10.1016/j.bbamem.2014.10.015

Strand, D. S., Kim, D., & Peura, D. A. (2017). 25 Years of Proton Pump Inhibitors: A Comprehensive Review. *Gut and Liver*, *11*(1), 27–37. https://doi.org/10.5009/gnl15502

Stransky, L., Cotter, K., & Forgac, M. (2016). The Function of V-ATPases in Cancer. *Physiological Reviews*, *96*(3), 1071–1091. https://doi.org/10.1152/physrev.00035.2015

Strom, B. L., Kimmel, S. E., & Hennessy, S. (Eds.). (2012). *Pharmacoepide–miology* (5. ed). Chichester: Wiley-Blackwell.

Strom, B. L., & Tugwell, P. (1990). Pharmacoepidemiology: current status, prospects, and problems. *Annals of Internal Medicine*, *113*(3), 179–181.

Suissa, S. (2007). Immortal time bias in observational studies of drug effects. *Pharmacoepidemiology and Drug Safety*, *16*(3), 241–249. https://doi.org/10.1002/pds.1357

Suissa, S. (2009). Statistical methods in pharmacoepidemiology: advances and challenges*. *Statistical Methods in Medical Research*, *18*(1), 3–6. https://doi.org/10.1177/0962280208099879

Suissa, S. (2013). Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. In B. L. Strom & S. E. Kimmel (Eds.), *Textbook of Pharmacoepidemiology* (pp. 383–395). West Sussex, England: John Wiley & Sons, Ltd,. https://doi.org/10.1002/9781118707999.ch26

Suissa, S., & Azoulay, L. (2012). Metformin and the Risk of Cancer: Time-related biases in observational studies. *Diabetes Care*, *35*(12), 2665–2673. https://doi.org/10.2337/dc12-0788

Suissa, S., Dell'Aniello, S., Vahey, S., & Renoux, C. (2011). Time-window Bias in Case-control Studies: Statins and Lung Cancer. *Epidemiology*, *22*(2), 228–231. https://doi.org/10.1097/EDE.0b013e3182093a0f

Suissa, S., & Suissa, A. (2018). Proton-pump inhibitors and increased gastric cancer risk: time-related biases. *Gut*, gutjnl-2017-315729. https://doi.org/10.1136/gutjnl-2017-315729

Sylvestre, M.-P., Huszti, E., & Hanley, J. A. (2006). Do OSCAR winners live longer than less successful peers? A reanalysis of the evidence. *Annals of Internal Medicine*, *145*(5), 361–363; discussion 392.

Tamim, H., Duranceau, A., Chen, L.-Q., & Lelorier, J. (2008). Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case-control study. *Drug Safety*, *31*(8), 675–684.

The Directorate of Health. (2018). Retrieved November 28, 2018, from https://www.landlaeknir.is/english/

Torre, L. A., Siegel, R. L., Ward, E. M., & Jemal, A. (2016). Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiology Biomarkers & Prevention*, *25*(1), 16–27. https://doi.org/10.1158/1055-9965.EPI-15-0578

Tvingsholm, S. A., Dehlendorff, C., Østerlind, K., Friis, S., & Jäättelä, M. (2018). Proton pump inhibitor use and cancer mortality: Proton pump inhibitors and cancer. *International Journal of Cancer*, *143*(6), 1315–1326. https://doi.org/10.1002/ijc.31529

Uddin, M. J., Groenwold, R. H. H., Ali, M. S., de Boer, A., Roes, K. C. B., Chowdhury, M. A. B., & Klungel, O. H. (2016). Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. *International Journal of Clinical Pharmacy*. https://doi.org/10.1007/s11096-016-0299-0

Umar, A., Dunn, B. K., & Greenwald, P. (2012). Future directions in cancer prevention. *Nature Reviews Cancer*, *12*(12), 835–848. https://doi.org/10.1038/nrc3397

Vandenbroucke, J. P. (2004). When are observational studies as credible as randomised trials? *The Lancet*, *363*(9422), 1728–1731. https://doi.org/10.1016/S0140-6736(04)16261-2

Wachsberger, P. R., Landry, J., Storck, C., Davis, K., O'Hara, M. D., Owen, C. S., Leeper, D. B., & Coss, R. A. (1997). Mammalian cells adapted to growth at pH 6.7 have elevated HSP27 levels and are resistant to cisplatin. *International Journal of Hyperthermia: The Official Journal*

of European Society for Hyperthermic Oncology, North American Hyperthermia Group, *13*(3), 251–255; discussion 257-259.

Waldum, H. L., Arnestad, J. S., Brenna, E., Eide, I., Syversen, U., & Sandvik, A. K. (1996). Marked increase in gastric acid secretory capacity after omeprazole treatment. *Gut*, *39*(5), 649–653.

Wallerstedt, S. M., Fastbom, J., Linke, J., & Vitols, S. (2017). Long-term use of proton pump inhibitors and prevalence of disease- and drug-related reasons for gastroprotection-a cross-sectional population-based study. *Pharmacoepidemiology and Drug Safety*, *26*(1), 9–16. https://doi.org/10.1002/pds.4135

Wang, B.-Y., Zhang, J., Wang, J.-L., Sun, S., Wang, Z.-H., Wang, L.-P., Zhang, Q.-L., Lv, F.-F., Cao, E.-Y., Shao, Z.-M., Fais, S., & Hu, X.-C. (2015). Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. *Journal of Experimental & Clinical Cancer Research*, *34*(1). https://doi.org/10.1186/s13046-015-0194-x

Warburg, O. (1956). On the Origin of Cancer Cells. *Science*, *123*(3191), 309–314. https://doi.org/10.1126/science.123.3191.309

Webb, B. A., Chimenti, M., Jacobson, M. P., & Barber, D. L. (2011). Dysregulated pH: a perfect storm for cancer progression. *Nature Reviews. Cancer*, *11*(9), 671–677. https://doi.org/10.1038/nrc3110

Weberpals, J., Jansen, L., Carr, P. R., Hoffmeister, M., & Brenner, H. (2016). Beta blockers and cancer prognosis – The role of immortal time bias: A systematic review and meta-analysis. *Cancer Treatment Reviews*, *47*, 1–11. https://doi.org/10.1016/j.ctrv.2016.04.004

Wettermark, B. (2013). The intriguing future of pharmacoepidemiology. *European Journal of Clinical Pharmacology*, *69*(S1), 43–51. https://doi.org/10.1007/s00228-013-1496-6

Wettermark, B., Hammar, N., MichaelFored, C., Leimanis, A., Otterblad Olausson, P., Bergman, U., Persson, I., Sundström, A., Westerholm, B., & Rosén, M. (2007). The new Swedish Prescribed Drug Register—Opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiology and Drug Safety*, *16*(7), 726–735. https://doi.org/10.1002/pds.1294

Wettermark, B., Zoëga, H., Furu, K., Korhonen, M., Hallas, J., Nørgaard, M., Almarsdottir, A., Andersen, M., Andersson Sundell, K., Bergman, U., Helin-Salmivaara, A., Hoffmann, M., Kieler, H., Martikainen, J., Mortensen, M., Petzold, M., Wallach-Kildemoes, H., Wallin, C., & Sørensen, H. (2013). The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. *Pharmacoepidemiology and Drug Safety*, *22*(7), 691–699. https://doi.org/10.1002/pds.3457

WHO. (2018, May 28). WHOCC - ATC/DDD Index. Retrieved May 28, 2018, from https://www.whocc.no/atc_ddd_index/

Wilkens, S., Zhang, Z., & Zheng, Y. (2005). A structural model of the vacuolar ATPase from transmission electron microscopy. *Micron*, *36*(2), 109–126. https://doi.org/10.1016/j.micron.2004.10.002

World Health Organization. (2016). *International statistical classification of diseases and related health problems: 10th revision ICD-10*. Geneva: World Health Organization.

Yuan, Y., Ford, A. C., Khan, K. J., Gisbert, J. P., Forman, D., Leontiadis, G. I., Tse, F., Calvet, X., Fallone, C., Fischbach, L., Oderda, G., Bazzoli, F., & Moayyedi, P. (2013). Optimum duration of regimens for *Helicobacter pylori* eradication. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD008337.pub2

Zhou, B., Huang, Y., Li, H., Sun, W., & Liu, J. (2016). Proton-pump inhibitors and risk of fractures: an update meta-analysis. *Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*, *27*(1), 339–347. https://doi.org/10.1007/s00198-015-3365-x

Original publications

Paper I

Therapeutic Advances in Gastroenterology

Original Research

Proton-pump inhibitors among adults: a nationwide drug-utilization study

Óskar Ö. Hálfdánarson, Anton Pottegård, Einar S. Björnsson, Sigrún H. Lund, Margret H. Ogmundsdottir, Eiríkur Steingrímsson, Helga M. Ogmundsdottir and Helga Zoega

Ther Adv Gastroenterol

2018, Vol. 11: 1–11

DOI: 10.1177/1756284818777943

Abstract

Background: The use of proton-pump inhibitors (PPIs) has grown worldwide, and there are concerns about increased unsubstantiated long-term use. The aim of the study was to describe the real-world use of PPIs over the past decade in an entire national population.

Methods: This was a nationwide population-based drug-utilization study. Patterns of outpatient PPI use among adults in Iceland between 2003 and 2015 were investigated, including annual incidence and prevalence, duration of use, and dose of tablet used (lower *versus* higher), as well as the proportion of PPI use attributable to gastroprotection.

Results: We observed 1,372,790 prescription fills over the entire study period, of which 95% were for higher-dose PPIs. Annual incidence remained stable across time (3.3–4.1 per 100 persons per year), while the annual prevalence increased from 8.5 per 100 persons to 15.5 per 100 persons. Prevalence increased with patient age and was higher among women than men. Duration of treatment increased with patients' age (36% of users over 80 years remained on treatment after 1 year compared with 13% of users aged 19–39 years), and was longer among those initiating on a higher dose compared with a lower dose. The proportion of PPI users concurrently using nonsteroidal anti-inflammatory drugs decreased over the study period, while the proportion concurrently using acetylsalicylic acid, oral anticoagulants, or platelet inhibitors increased.

Conclusions: In this nationwide study, a considerable increase in overall outpatient use of PPIs over a 13-year period was observed, particularly among older adults. Patients were increasingly treated for longer durations than recommended by clinical guidelines and mainly with higher doses.

Keywords: incidence, nationwide, pharmacoepidemiology, prevalence, proton-pump inhibitors, treatment duration

Received: 12 February 2018; revised manuscript accepted: 25 April 2018.

Correspondence to:
Óskar Örn Hálfdánarson
Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Sturlugata 8, 101 Reykjavík, Iceland
ooh@hi.is

Anton Pottegård
Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark

Einar S. Björnsson
Department of Internal Medicine, The National University Hospital of Iceland, Reykjavik, Iceland, and Faculty of Medicine, University of Iceland, Reykjavik, Iceland

Sigrún H. Lund
Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

Margret H. Ogmundsdottir
Eiríkur Steingrímsson
Department of Biochemistry and Molecular Biology, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

Helga M. Ogmundsdottir
Cancer Research Laboratory, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

Helga Zoega
Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland, and Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales, Sydney, New South Wales, Australia

Introduction

Proton-pump inhibitors (PPIs) are commonly prescribed for several acid-related disorders,[1] such as gastroesophageal reflux disease (GORD) and peptic ulcer disease.[2–5] These drugs are also effective in treating ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and as prophylactic treatment for patients on NSAIDs and low-dose aspirin.[6–10] Recommended doses and duration of PPI treatment vary by indications. Clinical guidelines rarely recommend PPI treatment for more than 8–12 weeks.[11,12] High-dose treatment is recommended when initiating therapy for GORD and peptic ulcer disease, while low-dose treatment is generally regarded as a maintenance therapy for recovering patients.[12]

PPIs are generally considered safe.[13] However, their use has been associated with increased risks of adverse events, such as bone fractures,[14] kidney disease,[15] microscopic colitis,[16] and hypomagnesemia.[17] Use of PPIs has also been suggested to cause changes in the composition of the intestinal

microbiota, increasing the risk of *Clostridium difficile* infection[18] and chronic liver disease.[19] Although PPIs have been shown to minimize NSAID-related adverse effects in the stomach, recent evidence suggests that PPIs might cause changes in the composition of the small intestinal microbiota, augmenting unwanted adverse effects of NSAIDs in the small intestines.[20] Furthermore, discontinuation of PPI treatment has been linked to acid hypersecretion[21] and the development of dyspeptic symptoms in healthy volunteers.[22]

PPIs have had undisputed effects on the treatment of symptoms related to excessive acid secretion, but concerns are growing about inappropriate indications and potential overuse, both within hospitals and in the primary-care setting.[23–26] These concerns are compounded by observations of increased long-term use especially in elderly populations,[27–29] where overprescribing has been associated with increased morbidity and mortality.[30]

In light of these concerns, we aimed to provide data on real-world use of PPIs, and changes thereof, across the past decade in an entire national population. Specifically, we aimed to determine patterns of use by patient and prescriber characteristics, including treatment duration contrasting between higher- and lower-dose PPIs. Furthermore, we described the proportion of PPI use attributable to gastroprotection.

Methods

This was an observational drug-utilization study describing the use of PPIs among the adult Icelandic population (19 years or older) during the period 1 January 2003 through to 31 December 2015.

Data sources

The Icelandic Medicines Registry (IMR) contains individual information on all dispensed prescription drugs in outpatient care in Iceland since 1 January 2003. We received information from the IMR on PPI dispensing during the study period. As of 2010, the IMR also contained information on dispensed prescription drugs within nursing homes in Iceland.[31,32] Completeness of the IMR ranged from 91% to 98% of all dispensed prescription drugs for the study years. Information on wholesale statistics of PPIs was provided by the Icelandic Medicines Agency.[33]

The Icelandic Population Register provided information about all citizens, Icelandic and foreign, residing in Iceland during the study period, including data on month and year of birth, sex, residency at 1 January 2003, migration status, and date of death (if appropriate).

Using personal identification numbers, unique to every individual residing in Iceland, we linked together the variables from these two registries.

Study drugs

The drugs of interest were classified according to the World Health Organization anatomical therapeutic chemical/defined daily doses (ATC/DDD) classification.[34] During the study period, four PPI substances were prescribed in Iceland: omeprazole (A02BC01), lansoprazole (A02BC03), rabeprazole (A02BC04), and esomeprazole (A02BC05). We further categorized each PPI type by available tablet strengths in milligrams as higher or lower dose. In the National Institute for Health and Care Excellence (NICE) clinical guidelines, PPI doses (in mg) are defined as standard/full dose, double dose, or low dose.[12] In the current study, standard and double doses were defined as higher-dose PPIs and low doses as lower-dose PPIs (Table 1).

On 1 February 2009, PPIs became available as over-the-counter (OTC) products in Iceland. However, the majority of PPIs during the study period were obtained by prescription rather than OTC, with OTC sales ranging from 1% in 2009 to 10% in 2015 of the total dispensed DDDs in these years (Supplementary Table S1).

Information on the indication for the prescription of PPIs was not available in the IMR. We explored potential reasons for PPI use by assessing the proportion of use attributable to gastroprotection, that is, concurrent use of PPIs with acetylsalicylic acid (ATC codes: B01AC06, N02BA01, B01AC30), NSAIDs (ATC codes: M01, excluding M01AX), oral anticoagulants (ATC codes: B01AA, B01AE, B01AF, B01AX06), and platelet inhibitors (B01AC04, B01AC07, B01AC22, B01AC24, B01AC30).

Analysis

We presented overall use of PPIs in Iceland as the total number of dispensed DDDs to the adult population stratified by calendar year, PPI substance,

Table 1. Proton-pump inhibitors and tablet strengths dispensed to adults in Iceland in 2003–2015.

PPI	ATC	DDD (mg)	Lower dose (mg)*	Higher dose (mg)*
Omeprazole	A02BC01	20	10	20, 40
Lansoprazole	A02BC03	30	15	30
Rabeprazole	A02BC04	20	10	20
Esomeprazole	A02BC05	30	10	20, 40

*National Institute for Health and Care Excellence clinical guidelines define PPI doses as standard/full dose, double dose or low dose.[12] Here we categorize low PPI doses as lower-dose PPIs while standard and double doses are categorized as higher-dose PPIs. ATC, anatomical therapeutic chemical; DDD, defined daily dose, PPI, proton-pump inhibitor.

and specialty of the prescribing physician (primary care, gastroenterology, and other specialties).

Annual prevalence (per 100 persons) of PPI use was defined as the number of adult individuals who filled at least one prescription in the relevant calendar year (2003–2015) divided by the total adult population residing in Iceland on 1 July of that year. Further we reported the sex- and age-specific prevalence of PPI use in 2015, the last year of the study period (by 1-year age intervals between ages 19–39 years and 80+ years). As a sensitivity analysis, we repeated the analysis of annual prevalence requiring at least two filled PPI prescriptions in the relevant calendar year to be classified as a prevalent user.

Annual incidence (per 100 persons per year) of PPI use was defined as the number of adult individuals who, during the relevant calendar year (2005–2015), filled their first PPI prescription after a period of 24 months during which no PPI prescriptions were filled, divided by the total adult population residing in Iceland on 1 July of that year.

To describe the duration of PPI use we used the 'proportion of patients covered' method, which estimates the proportion of subjects that are alive and covered by treatment on a given day after the initiation of an incidence treatment episode. For each patient, we estimated duration of each filled prescription based on days' supply, assuming one tablet as a daily dose. We allowed for a grace period of 108 days (2 × the median number of days between dispensing, that is, the number of days by which 50% of the population had received a subsequent dispensing), to account for irregular prescription fills and added to the duration of each prescription. If a patient did not fill a new prescription within this time we considered them to have discontinued their PPI treatment. They could then later re-enter the user population upon initiating a new treatment episode. We followed incident PPI users for 5 years, from the date of their first PPI prescription (day 0), and calculated the proportion of patients covered by dividing the number of users that were using the drug at day X (defined by 30-day intervals) by the number of people who were still alive and had not migrated at day X. Furthermore, to assess differences in treatment duration by patient age or by their prescribed PPI dose, we stratified the duration analysis by age (19–39, 40–49, 50–59, 60–69, 70–79, 80+ years), dose strength (higher *versus* lower), and sex. In addition, we explored the distribution in number of dispensed DDDs and tablets in the first 5 years after start of initial treatment episode (0–99, 100–199, 200–299, 300–399, 400–499, 500–599, 600–699, 700–799, 800–899, 900–999, $\geqslant$ 1000).

To assess concurrent use of selected drugs (ATC codes: M01 [excluding M01AX], B01AC06, N02BA01, B01AC30, B01AA, B01AE, B01AF, B01AX06, B01AC04, B01AC07, B01AC22, B01AC24, and B01AC30), we calculated the proportion (%) of prevalent PPI users in each study year who also filled prescriptions for these drugs within 90 days leading up to a PPI prescription fill. To assess the pattern of concurrent use among different age groups we performed a stratified analysis by age (19–39, 40–64, 65+ years).

All analyses were performed using R version 3.4.2[35] and RStudio.[36] The study was approved by the National Bioethics Committee in Iceland (study reference number: VSNb2015080004/03.03). As the study was based on national registry data, we did not obtain informed consent from individuals

in the study population. All personal information was encrypted and de-identified prior to analysis.

Results

We observed 1,372,790 prescription fills for PPIs over the entire study period. The vast majority (95%) were higher-dose prescriptions. Among 313,296 individuals constituting our source population, a total of 101,909 (33%) filled at least one PPI prescription, including 56,252 women (55%) and 45,657 men (45%). The mean age at first prescription fill was 46 years (interquartile range 30–60). We observed a median of three PPI prescription fills per patient (interquartile range 1–15). The median number of days between prescription fills was 54.

During the study period, there was an increase in total PPI use, measured as the number of dispensed DDDs, from 3.5 million DDDs dispensed in 2003 to 10.7 million DDDs dispensed in 2015 (Figure 1a). Primary-care physicians prescribed the majority (60%) of all dispensed DDDs during the study period, whereas gastroenterologists prescribed 11% and physicians of other specialties prescribed 29%. Prior to 2009, esomeprazole was the most commonly prescribed drug among all specialties. Although esomeprazole remained the PPI of choice among gastroenterologists, omeprazole became the most commonly prescribed PPI thereafter among nongastroenterologists (Figure 1b–d).

Figure 2 shows an increase in annual prevalence of PPI use with calendar time, from 8.5 per 100 persons in 2003 to 15.5 per 100 persons in 2015. Meanwhile, the incidence of PPI use ranged from 3.3 per 100 persons in 2005 to 4.1 per 100 persons in 2015. A more stringent measure of annual prevalence, requiring at least two prescription fills within a relevant year, yielded a prevalence of 5.4 per 100 persons in 2003 to 11.0 per 100 persons in 2015 (Supplementary Figure S1). Prevalence of PPI use was higher among women than men and increased with patient age (Figure 3).

We identified 74,973 incident PPI users in our study population, which we then followed for 5 years to estimate the proportion of users still on treatment over time. Figure 4(a) shows the estimated treatment duration stratified by patient age. The proportion of patients still on PPI treatment after 1 year was highest among those over 80 years of age, (36%) and lowest in those aged 19–39 years (13%). After 5 years, the proportion was highest in those aged 70–79 years (20%) and lowest among the youngest, 19–39 years (7%). The majority of patients filled fewer than 200 DDDs/tablets during the first 5 years after starting PPI treatment (Supplementary Figure S2).

Figure 4(b) shows PPI treatment duration among incident PPI users stratified by strength of PPI dose at treatment initiation. Of the 74,973 incident users, 70,720 (94%) initiated on higher-dose PPIs and 4240 (6%) on lower-dose PPIs. The proportion of patients still treated with the same dose after 1 year was greater among those prescribed higher- (21%) than lower-dose PPIs (9%). The proportion of patients still on the same dose was 13% *versus* 2% after 5 years, respectively on higher- *versus* lower-dose PPIs. Duration of treatment by PPI dose strength was nearly identical for both sexes (Supplementary Figure S3).

We observed a slight decrease in the proportion of PPI users concurrently using drugs that have been shown to be ulcerogenic or increase the risk of bleeding, from 38% in 2003 to 36% in 2015 (Figure 5). The proportion of PPI users concurrently using NSAIDs decreased from 33% in 2003 to 24% in 2015. We observed an increase in concurrent use of oral anticoagulants (3–6%), acetylsalicylic acid (5–8%), and other platelet inhibitors (2–3%). The proportion of PPI users concurrently treated with any of these four drugs was highest among those aged over 65 years (47% in 2003, 47% in 2015) and lowest among the youngest aged 19–39 years (21% in 2003, 17% in 2015) (Supplementary Figure S4).

Discussion

In this study, which covered all PPI dispensing in an entire national population over 13 years, we observed widespread and increasing use of PPIs, especially among the elderly. Primary-care physicians prescribed the vast majority of dispensed PPIs in our study data. While the number of new users remained relatively stable over time, the results suggested that patients were increasingly treated for longer durations than recommended by clinical guidelines and mainly with higher-dose PPIs.

The rising prevalence of PPI use across time observed in our study is in line with recently

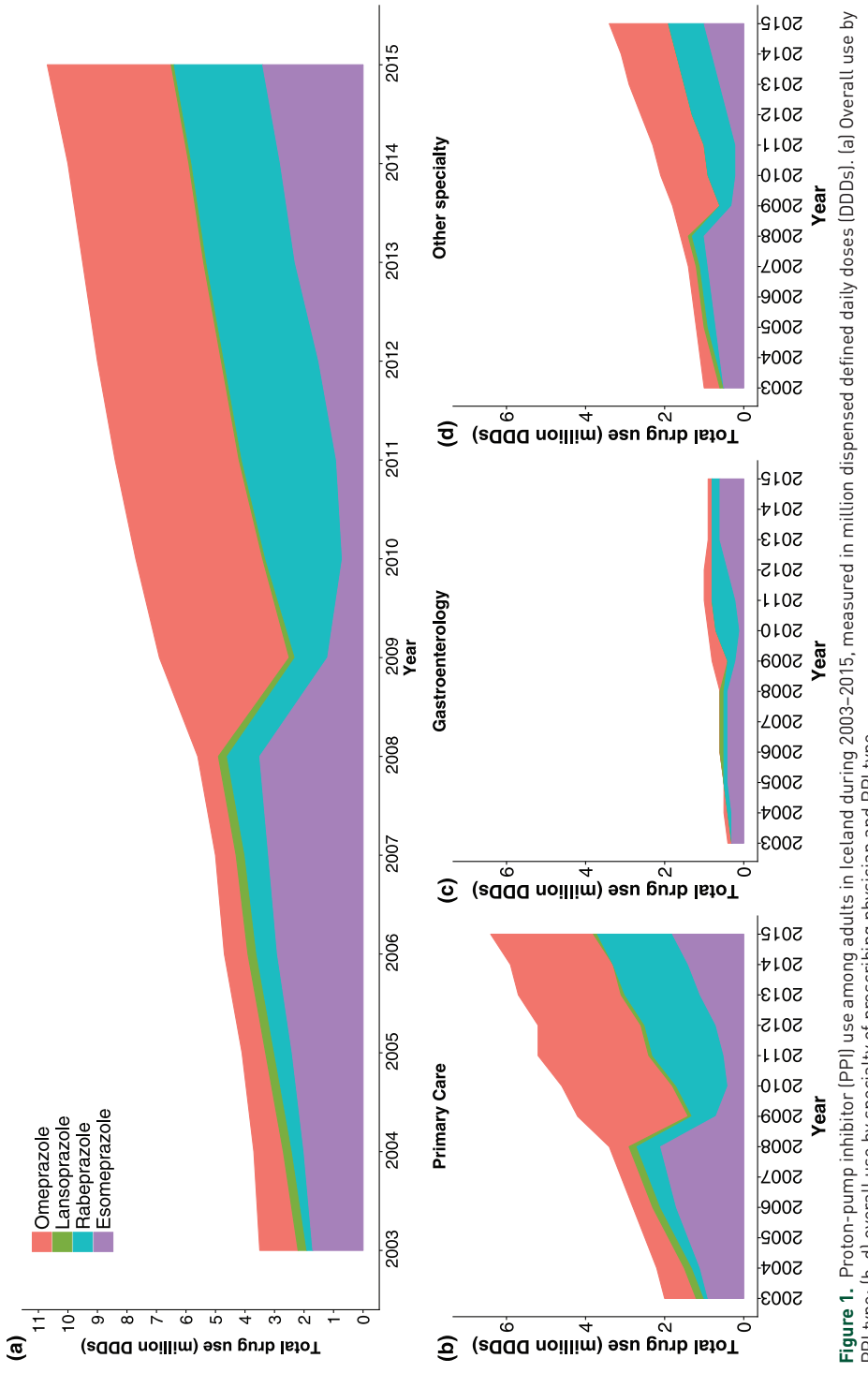


Figure 1. Proton-pump inhibitor (PPI) use among adults in Iceland during 2003–2015, measured in million dispensed defined daily doses (DDDs). (a) Overall use by PPI type; (b–d) overall use by specialty of prescribing physician and PPI type.

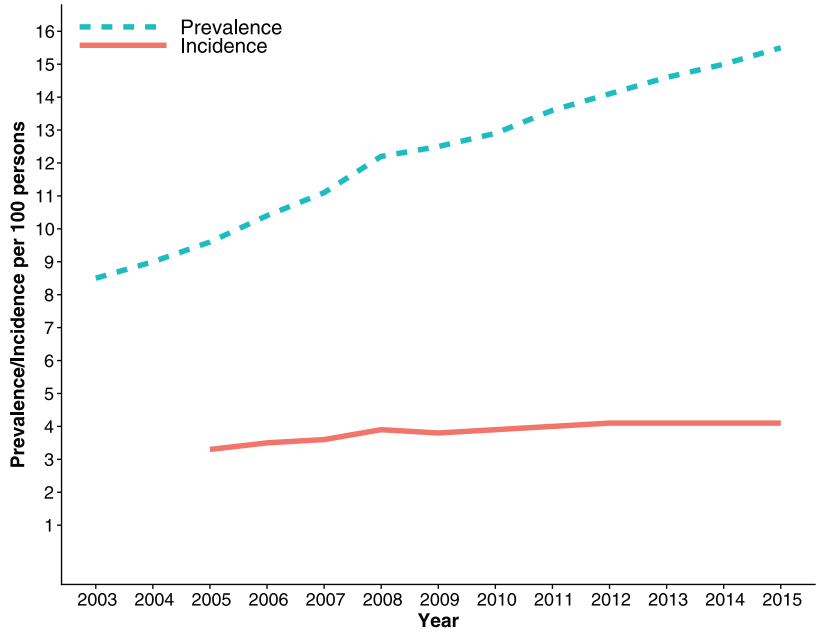


Figure 2. Annual prevalence and incidence (per 100 persons) of proton-pump inhibitor use among adults in Iceland.

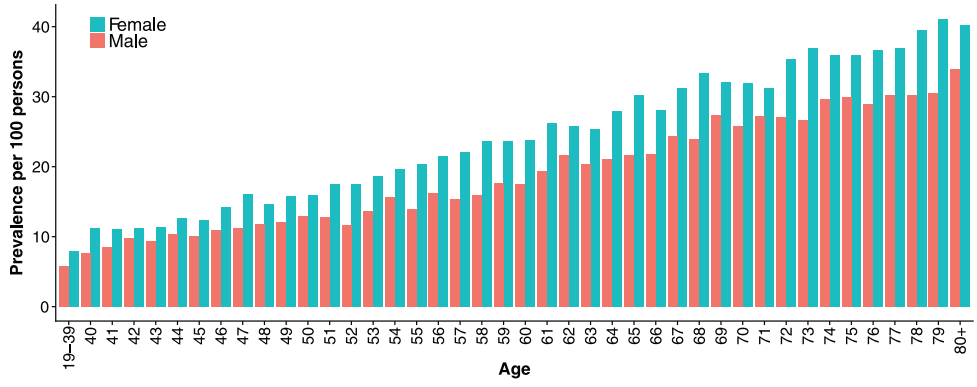


Figure 3. Age- and sex-specific prevalence of proton-pump inhibitor use among adults in Iceland in 2015.

published reports in comparable populations.[27,29,37] However, the prevalence in Iceland in 2015 was more than twice that observed among adults in Denmark in 2014 (15.5% *versus* 7.4%). GORD is the most common indication for PPIs with an estimated prevalence of 9–26% in European populations.[38] Although our use estimates were within this range, we were unable to draw definitive conclusions on the appropriateness of PPI use in Iceland as we did not have information on the indications for which PPIs were prescribed nor data on the prevalence of GORD or other underlying conditions in the population.

Inappropriate use of PPIs in the outpatient setting, for example, in the form of inappropriate

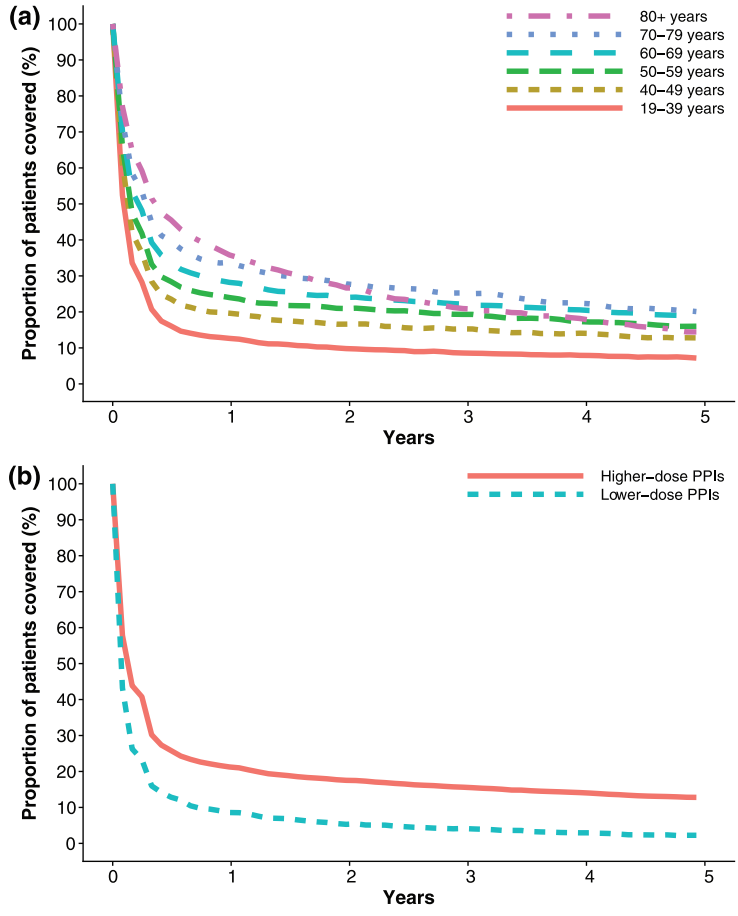


Figure 4. Duration of PPI treatment among incident users: (a) by age; (b) by initial dose strength of the proton-pump inhibitors (PPIs), measured as the proportion of patients covered.

indications and automatic renewal of prescriptions without re-evaluation of patients' symptoms, is a looming concern.[25,39] Such concerns were reinforced by Reimer and Bytzer's findings, which showed that only 27% of people receiving long-term treatment had a verified diagnosis justifying the need for long-term treatment.[40] The NICE clinical guidelines recommend long-term PPI therapy for rare conditions like Zollinger–Ellison syndrome or Barrett's esophagus as well as for patients with severe esophagitis, who have not responded to an initial high-dose 8-week treatment, and for patients who have experienced a dilation of an esophageal stricture.[12] In general, the recommended duration of PPI treatment in clinical guidelines rarely exceeds 12 weeks. We found that 22% remained on treatment 1 year after treatment initiation. The proportion was highest among the oldest age group (36%) and lowest among the youngest (13%). Extended treatment durations among older adults are concerning in light of widespread polypharmacy and increased risk of adverse events with PPI use.[41] In fact, we observed that nearly half of older adults in our data used PPIs concurrently with NSAIDs, acetylsalicylic acid, oral anticoagulants, or platelet inhibitors, reflecting the level of polypharmacy among older adults using PPIs. Given the recent evidence of PPIs potentially facilitating injurious effects of NSAIDs in the small intestines, especially in older people and other high-risk patients,[20] this pattern of high concurrent drug use might be

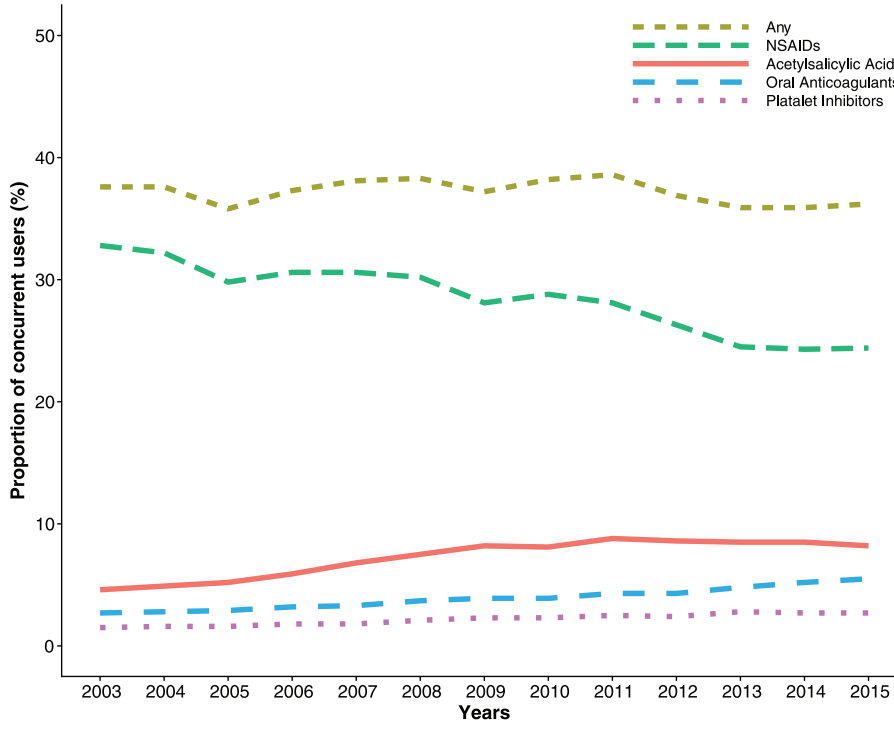


Figure 5. Concurrent use of proton-pump inhibitors with drugs that are ulcerogenic or increase the risk of upper gastrointestinal bleeding. NSAIDs, nonsteroidal anti-inflammatory drugs.

concerning. However, as we were unable to link prescription data with clinical information, we cannot rule out that these patients were appropriately prescribed PPIs as bleeding prophylaxis.

The vast majority of PPI users in our population initiated treatment with higher-dose PPIs and after 1 year 21% remained on that treatment, for example, had not switched to lower-dose PPIs or discontinued treatment. This might indicate that their underlying symptoms are more severe than among those initiating treatment on lower doses and reflect the level of difficulty some users experience when discontinuing treatment due to resurfacing symptoms.[42]

Recently, Helgadottir and colleagues demonstrated that among confirmed GORD patients on long-term PPI treatment, women were more likely than men to be able to lower their dose by half, while still achieving symptom relief.[43] In our study we found no observable difference in treatment durations by patient sex, nor did women seem more likely to initiate or maintain treatment on lower-dose PPIs. Thus, it is conceivable that women might be able to tolerate lower PPI doses than is mostly used nowadays.

The present study has several limitations. First, as with all register-based drug studies, it is not certain that individuals who filled the PPI prescriptions actually consumed the drugs. To address this, we performed a sensitivity analysis (Supplementary Figure S1) requiring at least two PPI prescription fills within a year to count as a prevalent PPI user, which resulted in lowered prevalence estimates. Actual consumption might thus in reality lie between these two measures of prevalence. Second, the study data did not contain information on clinical characteristics such as indications underlying the PPI prescriptions and/or the severity of symptoms, which prevented us from drawing sound conclusions on the appropriateness of PPI prescribing in our population. Third, information on PPI use within nursing homes was not included in the IMR until 2010,

which presumably resulted in an underestimation of the prevalence of PPI use among the elderly in the first half of the study period. Fourth, information on exact dosing for each prescription was not available in our data preventing us from accurately assessing prescribed doses. Our assessments of PPI doses were based on dispensed tablet strengths and therefore only an approximation of actual doses. Finally, PPIs became available OTC on 1 February 2009. However, the proportion of PPIs sold OTC was relatively low, ranging from 1% to 10% of the total number of DDDs sold annually from 2009 to 2015, and may therefore only have led to a slight underestimation of overall PPI use.

In conclusion, over a 13-year follow-up period we observed a considerable increase of real-world PPI use in a nationwide population setting, particularly among older adults. We found that a number of patients stayed on PPI treatment for longer periods than is recommended by clinical guidelines, mainly on higher doses. In view of these results, further initiatives towards appropriate prescribing of PPIs, especially in terms of the adoption of de-prescribing strategies, are warranted.

Acknowledgements

We thank Guðrún Kristín Guðfinnsdóttir and Kristinn Jónsson at the Directorate of Health in Iceland for extracting the data for this study. HZ is the guarantor of the article. ÓÖH and HZ designed the study. ÓÖH, HZ, AP, and SHL contributed to the data analysis and all authors contributed to the interpretation of the data. ÓÖH drafted the manuscript and all authors participated in the interpretation of the data and revision of the content of the manuscript. The final version of the manuscript was revised and approved by all authors.

Funding

This study was funded by the University of Iceland Research Fund, grant number HI16090004, and by the Icelandic Research Fund, grant number 152715-053.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

ORCID iD

ÓskarÖrnHálfdánarson https://orcid.org/0000-0002-4564-6126

References

1. Raghunath AS, Hungin AP, Mason J, *et al.* Symptoms in patients on long-term proton pump inhibitors: prevalence and predictors. *Aliment Pharmacol Ther* 2009; 29: 431–439.
2. Dent J, El-Serag HB, Wallander MA, *et al.* Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005; 54: 710–717.
3. Lundell L, Miettinen P, Myrvold HE, *et al.* Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis. *Clin Gastroenterol Hepatol* 2009; 7: 1292–1298.
4. Mahon D, Rhodes M, Decadt B, *et al.* Randomized clinical trial of laparoscopic Nissen fundoplication compared with proton-pump inhibitors for treatment of chronic gastro-oesophageal reflux. *Br J Surg* 2005; 92: 695–699.
5. Mehta S, Bennett J, Mahon D, *et al.* Prospective trial of laparoscopic nissen fundoplication versus proton pump inhibitor therapy for gastroesophageal reflux disease: seven-year follow-up. *J Gastrointest Surg* 2006; 10: 1312–1316.
6. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther* 2013; 15: S5.
7. Bhatt DL, Scheiman J, Abraham NS, *et al.* ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents. *J Am Coll Cardiol* 2008; 52: 1502–1517.
8. Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G, *et al.* Dabigatran, rivaroxaban, or apixaban versus warfarin in patients with nonvalvular atrial fibrillation: a systematic review and meta-analysis of subgroups. *Thrombosis* 2013; 2013: 640723.
9. Hreinsson JP, Kalaitzakis E, Gudmundsson S, *et al.* Upper gastrointestinal bleeding: incidence, etiology and outcomes in a population-based setting. *Scand J Gastroenterol* 2013; 48: 439–447.
10. Hreinsson JP, Palsdóttir S and Bjornsson ES. The association of drugs with severity and specific causes of acute lower gastrointestinal bleeding: a prospective study. *J Clin Gastroenterol* 2016; 50: 408–413.
11. Katz PO, Gerson LB and Vela MF. Guidelines for the diagnosis and management

of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308–328.

12. NICE. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management, guidance and guidelines, https://www.nice.org.uk/guidance/cg184 (accessed 22 November 2017).
13. McCarthy DM. Adverse effects of proton pump inhibitor drugs: clues and conclusions. *Curr Opin Gastroenterol* 2010; 26: 624–631.
14. Zhou B, Huang Y, Li H, *et al*. Proton-pump inhibitors and risk of fractures: an update meta-analysis. *Osteoporos Int* 2016; 27: 339–347.
15. Lazarus B, Chen Y, Wilson FP, *et al*. Proton pump inhibitor use and the risk of chronic kidney disease. *JAMA Intern Med* 2016; 176: 238–246.
16. Law EH, Badowski M, Hung YT, *et al*. Association between proton pump inhibitors and microscopic colitis. *Ann Pharmacother* 2017; 51: 253–263.
17. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, *et al*. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. *Ren Fail* 2015; 37: 1237–1241.
18. Naito Y, Kashiwagi K, Takagi T, *et al*. Intestinal dysbiosis secondary to proton-pump inhibitor use. *Digestion* 2018; 97: 195–204.
19. Llorente C, Jepsen P, Inamine T, *et al*. Gastric acid suppression promotes alcoholic liver disease by inducing overgrowth of intestinal Enterococcus. *Nat Commun* 2017; 8: 837.
20. Marlicz W, Łoniewski I, Grimes DS, *et al*. Nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and gastrointestinal injury: contrasting interactions in the stomach and small intestine. *Mayo Clin Proc* 2014; 89: 1699–1709.
21. Waldum HL, Qvigstad G, Fossmark R, *et al*. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. *Scand J Gastroenterol* 2010; 45: 389–394.
22. Niklasson A, Lindström L, Simrén M, *et al*. Dyspeptic symptom development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial. *Am J Gastroenterol* 2010; 105: 1531–1537.
23. Naunton M, Peterson GM and Bleasel MD. Overuse of proton pump inhibitors. *J Clin Pharm Ther* 2000; 25: 333–340.
24. Grant K, Al-Adhami N, Tordoff J, *et al*. Continuation of proton pump inhibitors from hospital to community. *Pharm World Sci* 2006; 28: 189–193.
25. Batuwitage BT, Kingham JG, Morgan NE, *et al*. Inappropriate prescribing of proton pump inhibitors in primary care. *Postgrad Med J* 2007; 83: 66–68.
26. Ladd AM, Panagopoulos G, Cohen J, *et al*. Potential costs of inappropriate use of proton pump inhibitors. *Am J Med Sci* 2014; 347: 446–451.
27. Wallerstedt SM, Fastbom J, Linke J, *et al*. Long-term use of proton pump inhibitors and prevalence of disease- and drug-related reasons for gastroprotection – a cross-sectional population-based study. *Pharmacoepidemiol Drug Saf* 2017; 26: 9–16.
28. Moriarty F, Bennett K, Cahir C, *et al*. Characterizing potentially inappropriate prescribing of proton pump inhibitors in older people in primary care in Ireland from 1997 to 2012. *J Am Geriatr Soc* 2016; 64: e291–e296.
29. Pottegård A, Broe A, Hallas J, *et al*. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. *Ther Adv Gastroenterol* 2016; 9: 671–678.
30. Cahir C, Fahey T, Teeling M, *et al*. Potentially inappropriate prescribing and cost outcomes for older people: a national population study. *Br J Clin Pharmacol* 2010; 69: 543–552.
31. Furu K, Wettermark B, Andersen M, *et al*. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010; 106: 86–94.
32. Embætti Landlæknis. Lyfjagagnagrunnur landlaeknis Hlutverk-og-rekstur, https://www.landlaeknir.is/servlet/file/store93/item27765/Lyfjagagnagrunnur_landlaeknis_Hlutverk-og-rekstur_loka_14.10.15.pdf (accessed 22 November 2017).
33. Lyfjastofnun. Icelandic Medicines Agency, https://www.ima.is (accessed 13 April 2018).
34. WHOCC. ATC/DDD Index, https://www.whocc.no/atc_ddd_index/ (accessed 6 November 2017).
35. The R Foundation. The R project for statistical computing, https://www.r-project.org/ (accessed 6 November 2017).

36. RStudio. Open source and enterprise-ready professional software for R, https://www.rstudio.com/ (accessed 6 November 2017).

37. Ksiądzyna D, Szeląg A and Paradowski L. Overuse of proton pump inhibitors. *Pol Arch Intern Med* 2015; 125: 289–298.

38. El-Serag HB, Sweet S, Winchester CC, *et al*. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871–880.

39. Heidelbaugh JJ, Kim AH, Chang R, *et al*. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Ther Adv Gastroenterol* 2012; 5: 219–232.

40. Reimer C and Bytzer P. Clinical trial: long-term use of proton pump inhibitors in primary care patients – a cross sectional analysis of 901 patients. *Aliment Pharmacol Ther* 2009; 30: 725–732.

41. Maes ML, Fixen DR and Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Ther Adv Drug Saf* 2017; 8: 273–297.

42. Björnsson E, Abrahamsson H, Simrén M, *et al*. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. *Aliment Pharmacol Ther* 2006; 24: 945–954.

43. Helgadóttir H, Metz DC, Lund SH, *et al*. Study of gender differences in proton pump inhibitor dose requirements for GERD: a double-blind randomized trial. *J Clin Gastroenterol* 2017; 51: 486–493.

Paper II

Received: 18 July 2018 | Revised: 21 October 2018 | Accepted: 24 October 2018

DOI: 10.1002/pds.4702

WILEY

ORIGINAL REPORT

Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control study

Óskar Ö. Hálfdánarson[1] | Katja Fall[2,3] | Margret H. Ogmundsdottir[4] | Sigrún H. Lund[1] | Eiríkur Steingrímsson[4] | Helga M. Ogmundsdottir[5] | Helga Zoega[1,6]

[1] Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

[2] Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden

[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[4] Department of Biochemistry and Molecular Biology, BioMedical Center, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[5] Cancer Research Laboratory, BioMedical Center, Faculty of Medicine, University of Iceland, Reykjavik, Iceland

[6] Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales, Sydney, Australia

Correspondence
Ó. Ö. Hálfdánarson, Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Sturlugata 8, 101 Reykjavík, Iceland.
Email: ooh@hi.is

Funding information
Icelandic Research Fund, Grant/Award Number: 152715-053

Abstract

Purpose: Increased expression of Vacuolar-type H^+ ATPases (V-ATPases), in the plasma membrane of cancer cells has been suggested to contribute to the development of aggressive cancer phenotypes by promoting acidic tumor microenvironments. Accumulating data suggest that proton pump inhibitors (PPIs) may elicit a chemopreventive effect via V-ATPase inhibition in some cancers, but evidence is still limited. Therefore, we aimed to explore a potential preventive role of PPIs in this study.

Methods: In this population-based case-control study, we identified incident cases of breast cancer (n = 1739), prostate cancer (n = 1897), and malignant melanoma (n = 385) in Iceland between 2005 and 2014 from the Icelandic Cancer Registry. We assessed varying levels of PPI use through record linkages to the Icelandic Medicines Registry. For each case, we selected up to 10 age-matched, sex-matched, and calendar-matched population controls using risk-set sampling. Using conditional logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) controlling for NSAID use.

Results: Adjusted ORs associated with ever use of PPIs were 1.03 (95% CI: 0.92-1.16) for breast cancer, 1.12 (95% CI: 1.00-1.25) for prostate cancer, and 0.84 (95% CI: 0.69-1.12) for malignant melanoma. Analyses of high use of PPIs (≥1000 DDDs) yielded ORs of 0.97 (95% CI: 0.78-1.19), 1.20 (0.99-1.47), and 0.59 (0.40-1.13) for breast cancer, prostate cancer, and malignant melanoma, respectively. Analyses of cumulative exposure to PPIs did not support a dose-response relationship for any of the three cancer types.

Conclusions: Our findings do not support a chemopreventive effect of PPI use on breast cancer, prostate cancer, or malignant melanoma.

KEYWORDS

breast cancer, melanoma, pharmacoepidemiology, prostate cancer, proton pump inhibitors, V-ATPase

1 | INTRODUCTION

Altered energy metabolism of cancer cells, characterized by high-glycolytic rate, has been proposed as one of the hallmarks of cancers.[1] This high rate of glycolysis generates an excess amount of protons within the intracellular environment of cancer cells.[2] A slightly alkaline intracellular pH is preserved by facilitating the transport of metabolic products out of cancer cells and into the extracellular environment,

via membrane-bound transporters and channels, thus promoting an acidic extracellular environment.[3] Among these, membrane-bound proteins are the vacuolar type H^+ ATPases (V-ATPases), which are complex multisubunit proteins that can be found in a variety of cellular membranes where they facilitate the transport of protons and regulate intracellular and extracellular pH.[4-6] Plasmalemmal expression of V-ATPases has been associated with increased cancer cell survival, enhanced metastatic potential and the development of multidrug resistance through the acidification of the tumor microenvironment.[7-13] Furthermore, inhibition of V-ATPase function, via either V-ATPase specific inhibitors or proton pump inhibitors (PPIs), has been shown to have anticarcinogenic effects in a variety of cell-based and animal-based models, including breast cancer,[14,15] prostate cancer,[16] and melanoma.[17,18]

PPIs are commonly used drugs that are generally well tolerated and routinely prescribed for acid-related disorders of the gastrointestinal tract.[19] They are prodrugs that accumulate and become active in acidic environments where they inhibit acid secretion.[20] Originally developed to inhibit the extrusion of protons through H^+/K^+ ATPases in the parietal cells of the stomach,[21] PPIs have also been shown to reduce V-ATPase activity.[22,23] Previous observational studies on PPI use and cancer risk have primarily focused on cancers of the digestive organs (ICD-10: C15-C26) and have reported conflicting results. Several studies found that PPI use is not associated with colorectal cancer risk.[24-27] Three studies concluded that PPI use was not associated with increased risk of pancreatic cancer,[28-30] while others have reported the opposite.[31,32] Furthermore, some studies have reported an increased risk of oesophageal and/or gastric cancer associated with PPI use,[33-37] although some of them are likely subject to reverse causality,[31] confounding by indication,[34-36] or time-related biases such as immortal time bias and latency bias.[37,38]

In Iceland, the most commonly diagnosed cancers are prostate cancer among men and breast cancer among women.[39] Both have been studied in relation with the effect of V-ATPase inhibition, yielding promising anticancer effects in vitro and in vivo.[14-16] Melanoma is less common, but acidic pH has been shown to enhance the invasive potential of melanoma cells,[40,41] suggesting that inhibiting V-ATPase function may have antineoplastic effects.[17,18] Therefore, we aimed to explore a potential preventive role of PPIs by conducting a population-based case-control study using risk-set sampling. Cancer development typically occurs over long periods of time,[42] and it is not inconceivable that an imminent disease may affect intake of medications. Thus, we implemented a lag-time period in our analyses to minimize the risk of reverse causation. To our knowledge, this is the first population-based study to test if PPI use is associated with the risk of breast cancer, prostate cancer, or malignant melanoma.

KEY POINTS

- Previous studies in vivo/in vitro have reported that proton pump inhibitors (PPIs) may have antineoplastic effects
- This is the first epidemiological study to test if PPI use affects the risk of malignant melanoma, breast or prostate cancer
- Our results do not support a clear association between PPI use and malignant melanoma, breast or prostate cancer
- Future well-controlled epidemiological studies should take clinical staging into account, given the available evidence that Vacuolar-type H^+ ATPase (V-ATPase) is highly expressed in the plasma membrane of metastatic cancer cells.

2 | METHODS

2.1 | Setting

We conducted a population-based–nested case-control study in Iceland, to assess the association between proton pump inhibitor use and the risk of a first-time diagnosis of breast cancer, prostate cancer, or malignant melanoma among adults (18 years and older). Our study base consisted of all adult residents of Iceland on January 1, 2003, including both prevalent and incident users of PPIs. Using personal identification numbers, unique to every individual residing in Iceland, we linked nationwide data from the Cancer Registry, Medicines Registry, and Population Register.

The Icelandic Cancer Registry contains nationwide information on every cancer diagnosis in Iceland since 1955, categorized according to the 10th revision of the International Statistical Classification of Diseases (ICD-10).[43] The Icelandic Medicines Registry contains individual information on all dispensed prescription drugs in outpatient care in Iceland since January 1, 2003. The drugs of interest were classified according to the World Health Organization (WHO) Anatomical Therapeutic Chemical/defined daily doses (ATC/DDD) classification.[44] As of 2010, the Icelandic Medicines Registry also holds information on dispensed prescription drugs within nursing homes in Iceland.[45,46] The completeness of the Icelandic Medicines Registry is high, ranging from 91% to 98% of all dispensed prescription drugs for the study years.

From the Icelandic Population Register, we obtained information about all citizens, Icelandic, and foreign, residing in Iceland during the study period, including data on: month and year of birth, sex, residency on January 1, 2003, migration status, and date of death (if appropriate).

2.2 | Cases

From the Icelandic Cancer Registry, we identified 1739 individuals with a first-time diagnosis of breast cancer (ICD10: C50), 1897 individuals with a first-time diagnosis of prostate cancer (ICD-10: C61), and 385 individuals with a first-time diagnosis of malignant melanoma (ICD-10: C43) between January 1, 2005 and December 31, 2014. The date of diagnosis for each cancer was defined as the index date. We excluded individuals who had previously been diagnosed with any cancer prior to the start of the study period.

2.3 | Population controls

We selected controls from the total underlying adult population in Iceland (N = 220 512). Using risk-set sampling, we matched up to 10 controls to each case on birth year, sex, and calendar time. The controls had to be alive and cancer free at the index date. Each case was eligible for sampling as a control before the time of disease onset, and each sampled control was eligible to later become a case. The resulting odds ratios (ORs) should therefore provide estimates of the incidence rates comparable with those expected from a cohort study in the source population.[47] To ensure comparable exposure opportunity time within each risk set between cases and controls (ie, the amount of time prior the index date available for exposure ascertainment), all individuals had to have resided in Iceland from January 1, 2003 to the index date.

2.4 | Drug exposure

From the Icelandic Medicine Registry, we obtained information on all dispensed PPIs from 2003 to 2014. Four PPIs were prescribed to patients within the study population during this period: omeprazole (A02BC01), lansoprazole (A02BC03), rabeprazole (A02BC04), and esomeprazole (A02BC05). We defined the exposure as PPI use before the index date for both cases and controls. Individuals with one or more PPI dispensing prior to the assigned index date were considered as "ever-users" of PPIs, while those without any PPI dispensing were classified as "never-users."

Cumulative dose, measured as the total amount of dispensed "defined daily doses" (DDDs) prior to index date, was also estimated for each patient (<365 DDDs, 365-730 DDDs, 731-1096 DDDs, >1096 DDDs). We defined high-level PPI use as dispensed prescriptions for greater than or equal to 1000 DDDs prior to index date. Furthermore, based on a daily intake of one tablet, we estimated the duration of each PPI prescription among ever users, and subsequent dispensings were then added together to estimate the cumulative duration of PPI use prior to the index date (0-1 years, 1-5 years, >5 years).

To minimize the risk of reverse causality biasing our effect estimates, we introduced a lag period where the exposed person time within 24 months leading up to the index date was disregarded.

Since use of nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with both PPI use[48,49] and cancer,[50-52] we further obtained prescription data for the use of prescription NSAIDs, both aspirin and nonaspirin (ATC codes: M01A [excluding M01AX], B01AC06, N02BA01). To approximate longer-term use of NSAIDs, individuals with at least two NSAID dispensings prior to the index date were considered as NSAID users in our analysis.

2.5 | Statistical analysis

We used conditional logistic regression to calculate ORs and 95% confidence intervals (CIs) for the association between PPI use and a first-time diagnosis of the cancers of interest, based on a prevalent user design, analyzing each cancer separately. Analyses were adjusted for NSAID use prior to index date. We did not add patient sex or birth to the multivariate regression models, as the matching of cases and controls on these variables was successful; only one prostate case could not be matched to any controls and was therefore excluded.

We performed subgroup analyses, assessing the effect of high-PPI use, cumulative dose, cumulative duration of PPI use, and calendar period (2005-2008, 2009-2011, and 2012-2014) on the hypothesized associations. Additionally, we performed several sensitivity analyses by implementing various lag times between 0 and 2 years with 6-month intervals. Furthermore, we repeated the main analysis employing a new-user study design, where we excluded all patients who dispensed a prescription for a PPI drug during 2003 or 2004, the first 2 years of the Icelandic Medicine Registry. Finally, we performed a post hoc supplementary analysis by clinical stage, ie, whether the disease was localized or nonlocalized, among patients diagnosed with prostate cancer between 2005 and 2012. Unfortunately, we did not have information on clinical staging for the years 2013 and 2014 and were thus unable to include them in the analysis. Also, we were unable to perform a similar analysis for breast cancer and malignant melanoma because of large amounts of missing information on clinical stage for these cancers in the years prior to 2012.

All analyses were performed using R[53] and R Studio.[54] The study was approved by the National Bioethics Committee in Iceland (study reference number: VSNb2015080004/03.03). As the study was based on national registry data, we did not obtain informed consent from individuals in the study population. All personal information was encrypted and de-identified prior to analysis.

3 | RESULTS

3.1 | Baseline characteristics

We identified 1739 cases of breast cancer, 1897 cases of prostate cancer, and 385 cases of malignant melanoma and matched these, respectively, with 17 390, 18 968, and 3850 population controls. The median age at index date was 62 years (Interquartile range [IQR]: 52-72 years) among breast cancer cases, 70 years (IQR: 63-77 years) among prostate cancer cases, and 55 years (IQR: 42-68 years) among melanoma cases (Table 1). Exposure opportunity time was comparable between cases and control for all three cancer types (Table 1).

3.2 | Association between PPI use and breast cancer, prostate cancer, or malignant melanoma

We first estimated the ORs for breast cancer, prostate cancer, and malignant melanoma associated with ever use and high use of PPIs, accounting for patient age, sex, calendar time, and NSAID use. These analyses yielded neutral adjusted ORs (Table 2).

We then conducted stratified analyses by cumulative duration of PPI use (0-1, 1-5, >5 years), cumulative dose (<365 DDDs, 365-730 DDDs, 731-1096 DDDs, >1096 DDDs). For breast and prostate cancer, these analyses mainly yielded ORs that were close to unity and similar to those observed for high use (Table 2). For prostate cancer,

TABLE 1 Baseline characteristics of breast cancer, prostate cancer, and malignant melanoma cases and matched controls

	Breast Cancer		Prostate Cancer*		Melanoma	
	Cases (%) (n = 1739)	Controls (%) (n = 17 390)	Cases (%) (n = 1897)	Controls (%) (n = 18 968)	Cases (%) (n = 385)	Controls (%) (n = 3850)
Sex						
Female	1739 (100.0)	17 390 (100.0)	-	-	231 (60.0)	2310 (60.0)
Male	-	-	1897 (100.0)	18 968 (100.0)	154 (40.0)	1540 (40.0)
Age at index date						
18-29 years	7 (0.4)	70 (0.4)	0 (0.0)	0 (0.0)	34 (8.8)	340 (8.8)
30-39 years	57 (3.3)	570 (3.3)	0 (0.0)	0 (0.0)	46 (12.0)	460 (12.0)
40-49 years	286 (16.5)	2860 (16.5)	28 (1.5)	280 (1.5)	74 (19.2)	740 (19.2)
50-59 years	421 (24.2)	4210 (24.2)	232 (12.2)	2320 (12.2)	79 (20.5)	790 (20.5)
60-69 years	468 (26.9)	4680 (26.9)	655 (34.5)	6550 (34.5)	61 (15.8)	610 (15.8)
70-79 years	292 (16.8)	4680 (16.8)	669 (35.3)	6690 (35.3)	54 (14.1)	540 (14.1)
80+ years	208 (12.0)	2080 (12.0)	313 (16.5)	3128 (16.5)	37 (9.6)	370 (9.6)
Calendar period (year of index date)						
2005-2008	661 (38.0)	6610 (38.0)	807 (42.5)	8068 (42.5)	158 (41.1)	1580 (41.1)
2009-2011	558 (32.1)	5580 (32.1)	523 (27.6)	5230 (27.6)	126 (32.7)	1260 (32.7)
2012-2014	520 (29.9)	5200 (29.9)	567 (29.9)	5670 (29.9)	101 (26.2)	1010 (26.2)
Ever use of NSAIDs before index date						
No	796 (45.8)	8008 (46.0)	836 (44.1)	8943 (47.1)	196 (50.9)	2105 (54.7)
Yes	943 (54.2)	9382 (54.0)	1061 (55.9)	10 025 (52.9)	189 (49.1)	1745 (45.3)
Exposure opportunity time (days)						
Overall—mean	1848		1797		1763	
By case-control status—mean	1848	1848	1797	1797	1763	1763

†One prostate case could only be matched to nine controls but was included in all analyses.

we observed a slightly elevated adjusted OR of 1.26 (95% CI: 1.02-1.55) for cumulative dose of over 1096 DDDs and 1.22 (95% CI: 1.04-1.42) for cumulative use for 1 to 5 years. For malignant melanoma, the effect estimates decreased with increased PPI use but did not indicate a dose-response relationship.

Removing or changing the lag period did not significantly affect the observed associations between PPI use and first-time diagnosis for any of the three cancers of interest (Table S1), suggesting that reverse causality did not have a major impact on the main results. Also, employing a new-user design, rather than a prevalent-user design, did not change the results from the main analysis in any significant way (Table S2). In a supplementary analysis based on clinical stage, we observed similar risk estimates between subgroups (Table S3).

4 | DISCUSSION

In this population-based–nested case-control study, we found no clear evidence of a link between PPI use and reduced risks of breast cancer, prostate cancer, or malignant melanoma.

To our knowledge, this is the first epidemiological study to explore the possibility of a chemopreventive effect of PPI use on breast cancer, prostate cancer, and malignant melanoma risk. PPIs are prodrugs that selectively accumulate in acidic spaces where pH is below 4 and become functionally active through protonation.[55] Previous studies indicating an antitumor effect of PPIs have mainly been conducted using cell-based and animal-based models. Those studies suggest that PPI treatment may inhibit proliferation of cancer cells, induce cytotoxicity, and reduce tumor growth.[17,56,57] The proposed underlying mechanism is that PPIs inhibit V-ATPases residing in the plasma membrane, inducing intracellular acidification and alkalization of the tumor microenvironment, which should hypothetically, have a chemopreventive effect. Although we observed a pattern of reduced risk of malignant melanoma with increased PPI use, the observed ORs did not indicate a dose-response relationship. For prostate cancer, we observed a marginally elevated ORs, but these results are likely a result of unmeasured confounding.

If PPIs do indeed possess a chemopreventive effect for these cancer types, our null findings could be explained by a number of factors. For PPIs to have a chemopreventive effect, they would first of all have to be distributed to tumor sites with low pH. Once there, the tumor microenvironment would have to be acidic enough for the PPIs to become functionally active and inhibit the flow of protons through the V-ATPase, from the intracellular environment and into the extracellular environment. And even if this occurs, it might still not be enough to alkalize the tumor microenvironment. Although V-ATPase expression in the plasma membrane of cancer cells has been associated with the acidification of the tumor microenvironment, there are also other pH-regulating proteins, such as Na^+/H^+ exhangers (NHE), carbonic anhydrases, HCO_3-transporters, and monocarboxylate

TABLE 2 Proton pump inhibitor (PPI) use among breast cancer, prostate cancer, and malignant melanoma cases and matched controls in 2005 to 2014

	Breast Cancer				Prostate Cancer				Malignant Melanoma			
Subgroups	Cases (%)	Controls (%)	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Cases (%)	Controls (%)	OR (95% CI)[a]	Adjusted OR (95% CI)[b]	Cases (%)	Controls (%)	OR (95% CI)[a]	Adjusted OR (95% CI)[b]
Never use	1208 (69.5)	12 189 (70.1)	1.00 (ref)	1.00 (ref)	1342 (70.7)	13 899 (73.3)	1.00 (ref)	1.00 (ref)	301 (78.2)	2925 (76.0)	1.00 (ref)	1.00 (ref)
Ever use	531 (30.5)	5201 (29.9)	1.03 (0.92-1.15)	1.03 (0.92-1.16)	555 (29.3)	5069 (26.7)	1.14 (1.03-1.27)	1.12 (1.00-1.25)	84 (21.8)	925 (24.0)	0.87 (0.67-1.13)	0.84 (0.69-1.12)
High use (≥ 1000 DDDs)	108 (6.2)	1110 (6.4)	0.97 (0.79-1.19)	0.97 (0.78-1.19)	124 (6.5)	1028 (5.4)	1.23 (1.01-1.49)	1.20 (0.99-1.47)	10 (2.6)	159 (4.1)	0.61 (0.32-1.18)	0.59 (0.40-1.13)
Cumulative dose (DDDs)												
<365	320 (18.4)	3209 (18.4)	1.01 (0.88-1.15)	1.01 (0.88-1.15)	338 (17.8)	3160 (16.7)	1.12 (0.98-1.27)	1.10 (0.96-1.25)	66 (17.1)	597 (15.5)	1.06 (0.80-1.41)	1.02 (0.76-1.36)
365-730	77 (4.4)	608 (3.5)	1.28 (1.00-1.63)	1.28 (1.00-1.64)	73 (3.9)	603 (3.2)	1.26 (0.98-1.62)	1.24 (0.96-1.59)	5 (1.3)	121 (3.1)	0.39 (0.16-0.97)	0.37 (0.15-0.93)
731-1096	34 (2.0)	374 (2.2)	0.92 (0.64-1.32)	0.92 (0.64-1.32)	29 (1.5)	368 (1.9)	0.82 (0.56-1.20)	0.80 (0.54-1.18)	4 (1.0)	68 (1.8)	0.56 (0.20-1.54)	0.53 (0.19-1.46)
>1096	100 (5.7)	1010 (5.8)	1.00 (0.81-1.25)	1.00 (0.80-1.25)	115 (6.1)	938 (4.9)	1.29 (1.05-1.59)	1.26 (1.02-1.55)	9 (2.4)	139 (3.6)	0.61 (0.31-1.22)	0.58 (0.29-1.16)
Cumulative duration of use (years)												
0-1	264 (15.2)	2554 (14.7)	1.04 (0.91-1.20)	1.04 (0.90-1.20)	258 (13.6)	2525 (13.3)	1.06 (0.92-1.23)	1.05 (0.91-1.21)	55 (14.3)	468 (12.1)	1.13 (0.83-1.54)	1.09 (0.79-1.49)
1-5	184 (10.6)	1811 (10.4)	1.03 (0.87-1.21)	1.03 (0.87-1.21)	210 (11.1)	1752 (9.2)	1.24 (1.07-1.45)	1.22 (1.04-1.42)	21 (5.4)	335 (8.7)	0.60 (0.38-0.96)	0.57 (0.36-0.91)
>5	83 (4.8)	836 (4.8)	1.00 (0.79-1.28)	1.00 (0.79-1.28)	87 (4.6)	792 (4.2)	1.15 (0.91-1.45)	1.12 (0.89-1.42)	8 (2.1)	122 (3.2)	0.62 (0.30-1.30)	0.59 (0.28-1.24)
Calendar period[c]												
2005-2008	117 (17.7)	1285 (19.4)	0.89 (0.72-1.10)	0.88 (0.71-1.09)	165 (20.4)	1426 (17.7)	1.20 (1.00-1.45)	1.19 (0.99-1.43)	25 (15.8)	242 (15.3)	1.04 (0.66-1.64)	1.00 (0.63-1.58)
2009-2011	202 (36.2)	1820 (32.6)	1.18 (0.98-1.42)	1.16 (0.96-1.40)	164 (31.4)	1519 (29.0)	1.12 (0.92-1.36)	1.11 (0.91-1.35)	28 (22.2)	314 (24.9)	0.85 (0.54-1.34)	0.85 (0.53-1.35)
2012-2014	212 (40.8)	2096 (40.3)	1.02 (0.85-1.23)	1.05 (0.87-1.27)	226 (39.9)	2124 (37.5)	1.11 (0.93-1.32)	1.06 (0.88-1.27)	31 (30.7)	370 (36.6)	0.76 (0.49-1.19)	0.71 (0.45-1.12)

Abbreviation: CI: confidence interval; OR: odd ratio.

[a]Matched on birth year, sex, and calendar time.

[b]Matched on birth year, sex, calendar time and controlled for NSAID use.

[c]Year of index date.

transporters (MCTs)[3,58] that participate in the extrusion of protons out into the extracellular environment. Therefore, these membrane-bound transporters might maintain an acidic extracellular pH, lessening the impact of PPI-inhibited V-ATPase function.

V-ATPase expression has been shown to be increased in highly metastatic cancer cells compared with poorly metastatic cells,[59,60] implicating a potentially more important role of V-ATPase in tumor progression and invasiveness rather than cancer initiation. These reports make it plausible that the acidity of the tumor microenvironment during initial tumourigenesis might not be sufficient for the PPIs to accumulate at the primary tumor site. As an attempt to explore this issue, we performed a post hoc analysis among patients diagnosed with prostate cancer, which did not yield conclusive results. Therefore, a systematic analysis taking clinical stage into account for all three cancer types would provide further insight into this matter.

The main strength of our study was that it is nested within a clearly defined population-based cohort and is based on high quality, nationwide data sources. Furthermore, underlying data on exposure and outcome were collected prospectively and independently from each other for the entire Icelandic population, therefore eliminating any potential recall bias. The sampling method, where controls were randomly selected from the underlying population, minimized the risk of selection bias. Additionally, the inherent time varying nature of our study design allowed us to avoid common time related biases, such as immortal time bias and latency bias that have been shown to be an issue in studies of drug-cancer associations.[38,42] Furthermore, the study design ensured the same exposure opportunity time among cases and controls.

Our study has several limitations. First, it lacked important individual level information on common risk factors for PPI use and cancer, such as BMI, smoking, socioeconomic status (SES), and comorbidities. Therefore, residual confounding might explain the slightly elevated risk estimates observed for prostate cancer, eg, among ever users of PPIs and those with 1 to 5 years of cumulative duration of PPI use. Second, individuals already in contact with the healthcare system through prescription use of PPIs may be more likely than those without such prescriptions to receive a cancer diagnosis, yielding elevated risk estimates (detection bias). However, our sensitivity analyses allowing different lag periods to be tested suggest that such mechanisms had limited influence on our findings. Third, in 2009 low-dose PPIs became available over-the-counter (OTC) in Iceland, and OTC use is not recorded in the Medicine Registry. This may have led to some misclassification of PPI use in our study but is unlikely to have impacted the results much as the amount of OTC use was relatively low during the study period, ranging from 1% to 10% of total PPI volume sold annually in 2009 to 2014.[61] Another misclassification of PPI exposure might has modestly biased the study results since we did not have information on PPI use prior to 2003, causing some potential PPI users before 2003 to be considered as never users. Furthermore, we attempted to control for longer-term NSAID therapy prior to index date, but since these drugs are commonly used OTC, misclassification of NSAID exposure is likely to have occurred.

In conclusion, our findings did not support a chemopreventive effect of PPI use against breast cancer, prostate cancer, or malignant melanoma. Future well-controlled epidemiological studies need to take clinical staging into account, given the available evidence that V-ATPase is highly expressed in the plasma membrane of metastatic cancer cells.

ETHICS STATEMENT

The study was approved by the National Bioethics Committee in Iceland (study reference number: VSNb2015080004/03.03).

ACKNOWLEDGEMENTS

We thank Guðrún Kristín Guðfinnsdóttir and Kristinn Jónsson at the Directorate of Health in Iceland and Laufey Tryggvadóttir, Helgi Birgisson, and Guðríður Helga Ólafsdóttir at the Icelandic Cancer Registry, for extracting the data for this study. All authors approved the final version of the article, including the authorship list.

This study was funded by the Icelandic Research Fund, grant number 152715-053. Dr Zoega was also supported by a Scientia Fellowship from the University of New South Wales. The funding sources had no influence on the design or conduct of this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

Helga Zoega is the guarantor of the article. Helga Ogmundsdóttir, Margret H. Ogmundsdottir, Eiríkur Steingrímsson, and Helga Zoega conceived the study, and Óskar Ö. Hálfdánarson and Helga Zoega designed it. Óskar Ö. Hálfdánarson, Helga Zoega, Katja Fall, and Sigrún Helga Lund contributed to the data analysis, and all authors contributed to the interpretation of the data. Óskar Ö. Hálfdánarson drafted the manuscript, and all authors participated in the interpretation of the data and revising the content of the manuscript. The final version of the manuscript was revised and approved by all authors.

ORCID

Óskar Ö. Hálfdánarson https://orcid.org/0000-0002-4564-6126

REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646-674.
2. Pavlova NN, Thompson CB. The emerging hallmarks of cancer metabolism. *Cell Metab*. 2016;23(1):27-47.
3. Parks SK, Chiche J, Pouysségur J. Disrupting proton dynamics and energy metabolism for cancer therapy. *Nat Rev Cancer*. 2013;13(9):611-623.
4. Forgac M. Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology. *Nat Rev Mol Cell Biol*. 2007;8(11):917-929.
5. Beyenbach KW. The V-type H+ ATPase: molecular structure and function, physiological roles and regulation. *J Exp Biol*. 2006; 209(4):577-589.
6. Wagner CA, Finberg KE, Breton S, Marshansky V, Brown D, Geibel JP. Renal Vacuolar H^+-ATPase. *Physiol Rev*. 2004;84(4):1263-1314.
7. Capecci J, Forgac M. The function of vacuolar ATPase (V-ATPase) a subunit isoforms in invasiveness of MCF10a and MCF10CA1a human breast Cancer cells. *J Biol Chem*. 2013;288(45):32731-32741.
8. Feng S, Cai M, Liu P, et al. Atp6v1c1 may regulate filament actin arrangement in breast cancer cells. Rameshwar P, ed. *PLoS ONE*. 2014;9(1):e84833.

9. Martínez-Zaguilán R, Raghunand N, Lynch RM, et al. pH and drug resistance. I. Functional expression of plasmalemmal V-type H+-ATPase in drug-resistant human breast carcinoma cell lines. *Biochem Pharmacol*. 1999;57(9):1037-1046.
10. Xu X, You J, Pei F. Silencing of a novel tumor metastasis suppressor gene LASS2/TMSG1 promotes invasion of prostate cancer cell in vitro through increase of vacuolar ATPase activity. *J Cell Biochem*. 2012;113(7):2356-2363.
11. Licon-Munoz Y, Michel V, Fordyce CA, Parra KJ. F-actin reorganization by V-ATPase inhibition in prostate cancer. *Biol Open*. 2017; 6(11):1734-1744.
12. Nishisho T, Hata K, Nakanishi M, et al. The a3 isoform vacuolar type H +-ATPase promotes distant metastasis in the mouse B16 melanoma cells. *Mol Cancer Res*. 2011;9(7):845-855.
13. Fais S. Evidence-based support for the use of proton pump inhibitors in cancer therapy. *J Transl Med*. 2015;13(1). Retrieved April 18, 2018, from http://www.translational-medicine.com/content/13/1/368
14. Katara GK, Kulshrestha A, Jaiswal MK, Pamarthy S, Gilman-Sachs A, Beaman KD. Inhibition of vacuolar ATPase subunit in tumor cells delays tumor growth by decreasing the essential macrophage population in the tumor microenvironment. *Oncogene*. 2016;35(8): 1058-1065.
15. Schneider LS, von Schwarzenberg K, Lehr T, et al. Vacuolar-ATPase inhibition blocks iron metabolism to mediate therapeutic effects in breast cancer. *Cancer Res*. 2015;75(14):2863-2874.
16. Michel V, Licon-Munoz Y, Trujillo K, Bisoffi M, Parra KJ. Inhibitors of vacuolar ATPase proton pumps inhibit human prostate cancer cell invasion and prostate-specific antigen expression and secretion. *Int J Cancer*. 2013;132(2):E1-E10.
17. Marino ML, Fais S, Djavaheri-Mergny M, et al. Proton pump inhibition induces autophagy as a survival mechanism following oxidative stress in human melanoma cells. *Cell Death Dis*. 2010;1(10):e87-e87.
18. De Milito A, Canese R, Marino ML, et al. pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. *Int J Cancer*. 2010;127(1):207-219.
19. Raghunath AS, Hungin APS, Mason J, Jackson W. Symptoms in patients on long-term proton pump inhibitors: prevalence and predictors. *Aliment Pharmacol Ther*. 2009;29(4):431-439.
20. Sachs G, Shin JM, Howden CW. Review article: the clinical pharmacology of proton pump inhibitors. *Aliment Pharmacol Ther*. 2006; 23(s2):2-8.
21. Strand DS, Kim D, Peura DA. 25 years of proton pump inhibitors: a comprehensive review. *Gut Liver*. 2017;11(1):27-37.
22. Moriyama Y, Patel V, Ueda I, Futai M. Evidence for a common binding-site for omeprazole and N-Ethylmaleimide in subunit a of chromaffin granule vacuolar-type H+-ATPase. *Biochem Biophys Res Commun*. 1993;196(2):699-706.
23. Sabolic I, Brown D, Verbavatz JM, Kleinman J. H(+)-ATPases of renal cortical and medullary endosomes are differentially sensitive to Sch-28080 and omeprazole. *Am J Physiol-Ren Physiol*. 1994;266(6): F868-F877.
24. Chubak J, Boudreau DM, Rulyak SJ, Mandelson MT. Colorectal cancer risk in relation to use of acid suppressive medications. *Pharmacoepidemiol Drug Saf*. 2009;18(7):540-544.
25. van Soest EM, van Rossum LGM, Dieleman JP, et al. Proton pump inhibitors and the risk of colorectal cancer. *Am J Gastroenterol*. 2008;103(4):966-973.
26. Robertson DJ, Larsson H, Friis S, Pedersen L, Baron JA, Sørensen HT. Proton pump inhibitor use and risk of colorectal cancer: a population-based, Case–Control Study. *Gastroenterology*. 2007;133(3):755-760.
27. Yang Y, Hennessy S, Propert K, Hwang W, Sedarat A, Lewis JD. Chronic proton pump inhibitor therapy and the risk of colorectal cancer. *Gastroenterology*. 2007;133(3):748-754.
28. Hicks B, Friis S, Pottegård A. Use of proton pump inhibitors and risk of pancreatic cancer. *Pharmacoepidemiol Drug Saf*. 2018;27(8):926-930.
29. Chien L-N, Huang Y-J, Shao Y-HJ, et al. Proton pump inhibitors and risk of periampullary cancers-a nested case-control study: PPI and the risk of periampullary cancers. *Int J Cancer*. 2016;138(6):1401-1409.
30. Bradley MC, Murray LJ, Cantwell MM, Hughes CM. Proton pump inhibitors and histamine-2-receptor antagonists and pancreatic cancer risk: a nested case–control study. *Br J Cancer*. 2012;106(1):233-239.
31. Kearns MD, Boursi B, Yang Y-X. Proton pump inhibitors on pancreatic cancer risk and survival. *Cancer Epidemiol*. 2017;46:80-84.
32. Peng Y-C, Lin C-L, Hsu W-Y, et al. Proton pump inhibitor use is associated with risk of pancreatic cancer: a nested case–control study. *Dose-Response*. 2018;16(4). 155932581880328
33. 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(10):e017739.
34. Rodriguez LAG, Lagergren J, Lindblad M. Gastric acid suppression and risk of oesophageal and gastric adenocarcinoma: a nested case control study in the UK. *Gut*. 2006;55(11):1538-1544.
35. Tamim H, Duranceau A, Chen L-Q, Lelorier J. Association between use of acid-suppressive drugs and risk of gastric cancer. A nested case-control study. *Drug Saf*. 2008;31(8):675-684.
36. Poulsen AH, Christensen S, McLaughlin JK, et al. Proton pump inhibitors and risk of gastric cancer: a population-based cohort study. *Br J Cancer*. 2009;100(9):1503-1507.
37. 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*. 2017;67(1):28-35.
38. Suissa S, Suissa A. Proton-pump inhibitors and increased gastric cancer risk: time-related biases. *Gut*. 2018. gutjnl-2017-315729
39. Cancer summary < Icelandic Cancer Registry. Retrieved March 9, 2018, from http://www.krabbameinsskra.is/indexen.jsp.
40. Rofstad EK, Mathiesen B, Kindem K, Galappathi K. Acidic extracellular pH promotes experimental metastasis of human melanoma cells in Athymic nude mice. *Cancer Res*. 2006;66(13):6699-6707.
41. Martínez-Zaguilán R, Seftor EA, Seftor RE, Chu YW, Gillies RJ, Hendrix MJ. Acidic pH enhances the invasive behavior of human melanoma cells. *Clin Exp Metastasis*. 1996;14(2):176-186.
42. Pottegård A, Friis S, Stürmer T, Hallas J, Bahmanyar S. Considerations for Pharmacoepidemiological studies of drug-cancer associations. *Basic Clin Pharmacol Toxicol*. 2017. Retrieved January 5, 2018. https://doi.org/10.1111/bcpt.12946
43. Sigurdardottir LG, Jonasson JG, Stefansdottir S, et al. Data quality at the Icelandic cancer registry: comparability, validity, timeliness and completeness. *Acta Oncol Stockh Swed*. 2012;51(7):880-889.
44. WHOCC - ATC/DDD Index. Retrieved May 21, 2018, from https://www.whocc.no/atc_ddd_index/.
45. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB. SÃ¸rensen HT. The Nordic countries as a cohort for Pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol*. 2010;106(2):86-94.
46. Lyfjagagnagrunnur_landlaeknis_Hlutverk-og-rekstur_loka_14.10.15.pdf. Retrieved November 22, 2017, from https://www.landlaeknir.is/servlet/file/store93/item27765/Lyfjagagnagrunnur_landlaeknis_Hlutverk-og-rekstur_loka_14.10.15.pdf.
47. Rothman KJ. *Epidemiology: An Introduction*. 2nd ed. New York, NY: Oxford University Press; 2012.
48. Marlicz W, Łoniewski I, Grimes DS, Quigley EM. Nonsteroidal anti-inflammatory drugs, proton pump inhibitors, and gastrointestinal injury: contrasting interactions in the stomach and small intestine. *Mayo Clin Proc*. 2014;89(12):1699-1709.
49. Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. *Arthritis Res Ther*. 2013; 15(Suppl 3):S5.

50. Doat S, Cénée S, Trétarre B, et al. Nonsteroidal anti-inflammatory drugs (NSAIDs) and prostate cancer risk: results from the EPICAP study. *Cancer Med*. 2017;6(10):2461-2470.
51. de Pedro M, Baeza S, Escudero M-T, et al. Effect of COX-2 inhibitors and other non-steroidal inflammatory drugs on breast cancer risk: a meta-analysis. *Breast Cancer Res Treat*. 2015;149(2):525-536.
52. Ulrich CM, Bigler J, Potter JD. Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics. *Nat Rev Cancer*. 2006;6(2):130-140.
53. R: The R Project for Statistical Computing. Retrieved November 6, 2017, from https://www.r-project.org/.
54. RStudio—open source and enterprise-ready professional software for R. Retrieved November 6, 2017, from https://www.rstudio.com/.
55. Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. *J Neurogastroenterol Motil*. 2013;19(1):25-35.
56. De Milito A, Canese R, Marino ML, et al. pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. *Int J Cancer J Int Cancer*. 2010;127(1):207-219.
57. Zhang S, Wang Y, Li SJ. Lansoprazole induces apoptosis of breast cancer cells through inhibition of intracellular proton extrusion. *Biochem Biophys Res Commun*. 2014;448(4):424-429.
58. Iessi E, Logozzi M, Mizzoni D, Di Raimo R, Supuran C, Fais S. Rethinking the combination of proton exchanger inhibitors in cancer therapy. *Metabolites*. 2017;8(1):2.
59. Sennoune SR, Bakunts K, Martínez GM, et al. Vacuolar H+-ATPase in human breast cancer cells with distinct metastatic potential: distribution and functional activity. *Am J Physiol Cell Physiol*. 2004;286(6):C1443-C1452.
60. Nishisho T, Hata K, Nakanishi M, et al. The a3 isoform vacuolar type H^+-ATPase promotes distant metastasis in the mouse B16 melanoma cells. *Mol Cancer Res MCR*. 2011;9(7):845-855.
61. Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. *Ther Adv Gastroenterol*. 2018;11. 175628481877794

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Hálfdánarson ÓÖ, Fall K, Ogmundsdottir MH, et al. Proton pump inhibitor use and risk of breast cancer, prostate cancer, and malignant melanoma: An Icelandic population-based case-control study. *Pharmacoepidemiol Drug Saf*. 2018;1–8. https://doi.org/10.1002/pds.4702

Paper III

Use of proton pump inhibitors and mortality among Icelandic patients with prostate cancer

Running title: PPIs and mortality in prostate cancer patients

Óskar Ö. Hálfdánarson[1], Anton Pottegård[2], Sigrún H. Lund[3], Margret H. Ogmundsdottir[4], Helga M. Ogmundsdottir[5], Helga Zoëga[1,6]

[1] Centre of Public Health Sciences, Faculty of Medicine, University of Iceland, Reykjavík, Iceland

[2] Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense, Denmark.

[3] deCODE genetics, Reykjavik, Iceland.

[4] Department of Biochemistry and Molecular Biology, BioMedical Center, Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

[5] Cancer Research Laboratory, BioMedical Center, Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

[6] Medicines Policy Research Unit, Centre for Big Data Research in Health, University of New South Wales, Sydney, New South Wales, Australia

Keywords: Proton pump inhibitors, prostate cancer, mortality, pharmacoepidemiology

Total word count: 2610 (excluding abstract, references, legends to tables, and legends to figures)

Number of figures: 1

Number of tables: 3

Corresponding author:
Óskar Örn Hálfdánarson
Centre of Public Health Sciences
Faculty of Medicine
University of Iceland
Sturlugata 8, 101 Reykjavík, ICELAND
ooh@hi.is

AUTHORSHIP STATEMENT

Helga Zoëga is the guarantor of the article. Helga M. Ogmundsdottir, Margret H Ogmundsdottir and Helga Zoëga conceived the study; and Óskar Ö. Hálfdánarson and Helga Zoëga designed it. Óskar Ö. Hálfdánarson, Helga Zoëga, Anton Pottegard and Sigrún Helga Lund contributed to the data analysis and all authors contributed to the interpretation of the data. Óskar Ö. Hálfdánarson drafted the manuscript and all authors participated in the interpretation of the data and revising the content of the manuscript. The final version of the manuscript was revised and approved by all authors.

There are no competing interests to declare.

ABSTRACT

Aims: Proton pump inhibitors (PPIs) have both been reported to enhance chemosensitivity and contribute to increased mortality among cancer patients. Due to conflicting reports, we aimed to determine whether PPI use is associated with mortality among prostate cancer patients.

Methods: In this population-based cohort study, we identified all eligible patients with an incident diagnosis of prostate cancer in Iceland between 2007-2012 (n = 1058). We used time-dependent Cox proportional hazard regression models to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific and all-cause mortality associated with post-diagnosis use of PPIs, defined as at least ≥2 filled prescriptions after diagnosis and lagged by 12 months.

Results: Among the study cohort, we identified 347 (32.8%) post-diagnosis PPI users and 711 (67.2%) non-users. Out of the 347 patients using PPIs after diagnosis, 59 patients (17.0%) died due to any cause and 22 patients (6.3%) due to prostate cancer, compared with 144 (20.3%) and 76 (10.7%) among non-users, respectively. Post-diagnosis PPI use was not statistically significantly associated with prostate cancer-specific mortality (HR 0.88; 95% CI: 0.52-1.48) or all-cause mortality (HR 1.02; 95% CI: 0.73-1.43). Stratification by timing of use and clinical stage did not reveal any statistically significant associations to the mortality outcomes of interest. Furthermore, we did not find any evidence of a significant dose-response relationship.

Conclusions: Our findings did not indicate an association between post-diagnosis PPI use and mortality among prostate cancer patients.

STATEMENT 1

What is already known about this subject?

- An acidic tumor microenvironment has been associated with a malignant cancer phenotype.
- Although *in vitro* and *in vivo* studies have suggested that proton pump inhibitors have antineoplastic properties and increase chemosensitivity a recent observational study reported that PPI use was associated with increased prostate cancer-specific and overall cancer mortality.

STATEMENT 2

What this study adds:

- Contrary to a previous report, post-diagnosis PPI use was not associated with increased mortality among prostate cancer patients.
- We found no evidence of decreased mortality risk among post-diagnosis PPI users.
- Timing of use was not statistically significantly associated with the outcome and we did not observe a dose-response association.

INTRODUCTION

Proton pump inhibitors (PPIs) are commonly used drugs and their use has been increasing quite rapidly over the last decade.[1] As potent inhibitors of acid secretion, PPIs were originally developed to inhibit the activity of the H+/K+ ATPase, a type of proton pump that secretes gastric acid from parietal cells of the stomach.[2] However, they have also been shown to have an affinity for another proton pump, i.e. the vacuolar H+-ATPase (V-ATPase).[3, 4] The V-ATPase is frequently seen overexpressed in the plasma membrane of cancer cells where they are believed to promote alkalization of the cytoplasm and acidification of the tumor microenvironment.[5–10] Increased tumor acidity has been associated with a malignant cancer phenotype characterized by increased invasiveness, metastatic potential, and drug resistance.[11–13] Thus, due to the ability of PPIs to inhibit V-ATPase function their repositioning as potential antineoplastic agents has been suggested.[14] Studies, *in vitro* and *in vivo*, have reported a potential anticancer activity of PPIs[15–17] and a phase II trial among breast cancer patients with a metastatic disease reported increased efficacy of chemotherapy in patients pre-treated with PPIs.[18] Furthermore, a clinical study among osteosarcoma patients found that pre-treatment with PPIs improved the effectiveness of chemotherapy.[19] These results highlight a potential avenue for studying whether PPI use increases the effectiveness of cancer therapy in various cancer types.

The potential association between PPI use and cancer mortality has not been evaluated conclusively in epidemiological studies. A study among pancreatic cancer patients found no association between PPI use and survival.[20] Another study found that PPI use, and use of histamine receptor-2 antagonist (H2RA), was associated with improved overall survival among patients with head and neck squamous cell cancer.[21] A recent Danish study

reported that PPI use was associated with increased cancer-specific mortality for a number of cancer types, including prostate cancer.[22]

Prostate cancer is the second most commonly diagnosed cancer among men and the fifth most frequent cause of cancer-specific death.[23] Given the conflicting results of the few epidemiological studies conducted so far, the increasing overall use of PPIs, and the high incidence of prostate cancer, we aimed to utilize the high-quality nationwide registry data available in Iceland to examine the association between post-diagnosis PPI use and mortality among prostate cancer patients.

METHODS

Data sources

This was a population-based cohort study where we used unique personal identification numbers to link together data from the Icelandic Cancer Registry,[24] the Icelandic Medicines Registry, the Icelandic Population Register, the Cause of Death Register, and from electronic health records of Landspitali – The National University Hospital of Iceland.

Study population

Eligible patients, identified using the Icelandic Cancer Registry, were all adult Icelandic residents between 40 – 85 years of age with a verified first-time diagnosis of prostate cancer (ICD-10: C61) between January 1, 2007 and December 31, 2012.

Follow-up and mortality outcomes

The primary outcome in all analyses was prostate cancer-specific mortality. The secondary outcome was all-cause mortality. Prostate cancer-specific mortality was defined by the relevant ICD-10 code (C61) as the underlying cause of death. Eligible patients were followed from 12 months after prostate cancer diagnosis until their death, emigration, or end of the study period (December 31, 2015). We excluded those patients who died or emigrated from Iceland within 12 months after diagnosis.

Exposure assessment

We obtained information on PPI use from the Icelandic Medicine Registry; a nationwide prescription registry with a completeness ranging from 91% to 99%. Although PPIs became available over-the-counter (OTC) in 2009 the majority (>90%) of PPIs between 2009 and 2015 were obtained by prescription.[1] We considered the Anatomical Therapeutic

Chemical (ATC)[25] code group A02BC as a PPI dispensing. Four PPI substances were prescribed within our cohort during the period under study: omeprazole (A02BC01), lansoprazole (A02BC03), rabeprazole (A02BC04), and esomeprazole (A02BC05). The information we received for every PPI prescription between 1 January 2003 and 31 December 2015, including date of dispensing, ATC code, and number of dispensed 'defined daily doses' (DDDs).

The primary exposure was post-diagnosis PPI use, defined as at least two or more filled PPI prescriptions after prostate cancer diagnosis. In all analyses, we considered the exposed person-time of post-diagnosis PPI users in a time-dependent manner to avoid time-related biases such as immortal time bias.[26] In the main analysis, patients were thus initially considered unexposed until they received a second PPI prescription, after which they were considered exposed for the remainder of follow-up. Furthermore, the exposed person-time was lagged by 12 months to account for the possibility of reverse causation and to allow for a biologically meaningful latency period, since it is unlikely that a short duration of drug use would influence mortality outcomes in a significant way. Patients that did not receive at least two PPI dispensing after diagnosis were thus considered as non-users.

For the purposes of secondary analyses, we explored the timing of PPI use by assessing pre-diagnosis PPI use. Patients were considered pre-diagnosis users if they received at least two PPI prescriptions in the 3 years prior to diagnosis. Pre-diagnosis use was modelled as a time-fixed covariate, i.e. a dichotomous yes/no variable. Thus, patients exposed to PPIs were either considered to be 'new PPI users' or 'continued PPI users' based on their exposure status before and after diagnosis. We defined new users as those patients that only used PPIs after diagnosis while those who used PPIs prior to and after diagnosis were considered as

continuing PPI users. Additionally, we estimated the cumulative dose for each patient based on the total number of dispensed DDDs during exposed person-time (0 DDDs, 1-365 DDDs, >365 DDDs).

Covariates

We considered a range of demographic and clinical factors for multivariable adjustments. Patient age at diagnosis and year of diagnosis were modelled as continuous variables. A medication-based comorbidity score was derived by identifying the number of different prescription drug groups that were dispensed in the 12 months prior to a cancer diagnosis[27]. To be categorized in the same group the drugs had to share the same initial four characters of the ATC classification system. The medication-based comorbidity score was then modelled as a continuous variable. Clinical stage according to the tumor-node-metastasis (TNM) system was classified into three categories if information on M was available: localized (M0), non-localized (M1), and unknown (Mx or information missing). We adjusted for the following clinical variables: Gleason score was grouped into five distinct categories (2-5, 6, 7, ≥8, unknown). Cancer treatment in the 12 months following diagnosis was accounted for in the following way: cancer surgery was categorized into three categories (total excision of prostate, partial excision of prostate, no surgery), cancer drug treatment was grouped into four categories (chemotherapy, endocrine therapy, combination of chemotherapy and endocrine therapy, no therapy), and radiotherapy was modelled as a dichotomous variable (radiotherapy, no radiotherapy).

Data analysis

We used a time-dependent Cox proportional hazard regression models, with time since diagnosis as the underlying time-scale, to estimate crude and multivariable adjusted hazard

ratios (HRs) and 95% confidence intervals (CIs) for prostate cancer-specific mortality and all-cause mortality associated with post-diagnosis PPI use modelled as a time-dependent covariate where patients were considered unexposed until they had met the exposure criteria, and then remained exposed throughout follow-up. In multivariable adjusted analyses we adjusted for the aforementioned covariates, also listed in Table 1.

In the main analysis, we assessed PPI use following prostate cancer diagnosis; modelled as a time-dependent covariate as described above. Exposed person-time was then lagged by 12 months following a second dispensing of a post-diagnosis PPI prescription. Furthermore, we performed three secondary analyses. First, PPI use was stratified by continuing users versus new users. Second, we stratified by clinical stage (localized versus non-localized). Third, we stratified PPI use by cumulative dose (0 DDDs, 1-365 DDDs, >365 DDDs).

We performed three sensitivity analyses to assess the definition of PPI use. In the first one, post-diagnosis PPI use was defined as at least one filled PPI prescriptions following diagnosis and the exposure was modelled as a time-dependent covariate as in the main analysis. In the second sensitivity analysis, we defined post-diagnosis PPI use as at least two filled prescriptions within 12 months following the diagnosis of prostate cancer. In a third sensitivity analysis, we defined post-diagnosis PPI use as at least two filled prescriptions and assessed the exposure continuously throughout follow-up as a time-dependent covariate. Thus, by assuming a daily intake of one DDD and estimating the duration of each prescription as the number of dispensed DDDs we allowed patients to move back and forth between periods of non-use and periods of use.

All analyses were performed using the survival package[28] in R.[29] This study was approved by the National Bioethics Committee in Iceland (study reference number: VSNb2015080004/03.03).

RESULTS

We initially identified 1138 prostate cancer patients, but after implementing the exclusion criteria 1058 were eligible for inclusion in the study (Figure 1). During 4810 person-years of follow-up, we identified a total of 203 patients (19.2%) that died, thereof 98 patients (9.3%) that died due to prostate cancer. The median follow-up time was 4.6 years. Among eligible patients, 347 (32.8%) were identified as post-diagnosis PPI users; thereof 182 (52.4%) were continuous users and 165 (47.6%) new users. Among the 347 post-diagnosis PPI users we identified 59 patients (17.0%) that died from any cause and 22 patients (6.3%) that died from prostate cancer, compared with 144 patients (20.3%) and 76 patients (10.7%) among non-users, respectively. The median age among post-diagnosis PPI users was 69 years (interquartile range: 63 – 76) while it was 69 years (interquartile range: 62 – 75) among non-users. The majority of all patients were diagnosed with a localized disease; 81.6% among post-diagnosis PPI users and 77.2% among non-users. Compared with non-users, post-diagnosis PPI users had a higher median of medication-based comorbidity score (Table 1).

In the main analysis, we observed adjusted HRs of 0.88 (95% CI: 0.52 – 1.48) for prostate cancer-specific mortality and 1.02 (95% CI: 0.73 – 1.43) for all-cause mortality among post-diagnosis PPI users as compared with non-users (Tables 2 and 3). In secondary analyses for prostate cancer-specific mortality (Table 2), we observed adjusted HRs of 0.45 (95% CI: 0.21 – 0.98) among continuous PPI users and 1.12 (95% CI: 0.61 – 2.08) among new PPI users, when we stratified by timing of PPI use. Stratifying by clinical stage yielded adjusted HRs of 0.50 (95% CI: 0.22 – 1.16) and 1.00 (95% CI: 0.44 – 2.27) among patients with localized and non-localized disease, respectively. For cumulative dose, we observed an adjusted HR for cumulative use of 1-365 DDDs of 0.91 (95% CI: 0.43 – 1.90) and 0.86 (95% CI: 0.45 – 1.61) for >365 DDDs. For all-cause mortality (Table 3), the adjusted HRs were 0.67 (95% CI:

0.43 – 1.04) and 1.25 (0.82 – 1.92) among continuous and new PPI users, respectively. Analyses stratified by clinical stage yielded an adjusted HR of 0.74 (95% CI: 0.47 – 1.15) among patients with localized disease and 1.18 (95% CI: 0.58 – 2.34) among patients with non-localized disease. For cumulative PPI use, we observed adjusted HRs of 1.19 (95% CI: 0.76 – 1.87) and 0.91 (95% CI: 0.61 – 1.37) for patients using 1-365 DDDs and >365 DDDs, respectively.

Redefining post-diagnosis use as at least one filled prescription for a PPI drug yielded similar result as in the main analysis (Table S1). When we redefined the exposure opportunity window by assessing PPI use only in the 12 months following prostate cancer diagnosis, we observed HRs that were slightly lower, but mostly in line with those observed in the main analysis (Table S2). When post-diagnosis PPI use was assessed continuously throughout follow-up, we observed higher HRs than in the main analysis, but the estimates were not statistically significant (Table S3).

DISCUSSION

In this population-based cohort study among Icelandic prostate cancer patients, we did not observe a clear association between post-diagnosis PPI use and mortality among prostate cancer patients.

To our knowledge, this is only the second observational study to explore the association between PPI use and mortality among prostate cancer patients. Recently, post-diagnosis use of PPIs was reported to have led to increased mortality among cancer patients; both among cancer patients overall and among patients with certain site-specific cancers, including prostate cancer.[22] PPIs are commonly used among cancer patients,[30] often as a preventive measure against the risk of gastric damage following chemotherapy, radiotherapy, and steroid use.[31] Furthermore, PPI use has been shown to be associated with indicators of worse overall health[32] and among prostate cancer patients PPIs have been suggested to be related to decreased overall health.[33] However, our results were not consistent with the findings of Tvingsholm et al., in that we did not observe an increase in mortality among post-diagnosis PPI users.

Although the study by Tvingsholm et al., suggests that PPI use is associated with excess mortality among cancer patients, and that the association might be substance specific, previous clinical studies have reported that PPIs might enhance the effectiveness of chemotherapy.[18, 19] However, there have also been reports of unwanted drug interactions between PPIs and oral anticancer agents suggesting a negative impact of PPIs on chemotherapeutic efficacy.[31, 34] Unfortunately, we were unable to perform stratified analyses by chemotherapy or PPI substance in our study due to the small sample size leading to low numbers in stratified subgroups.

The study has several limitations that might have influenced our observations. First, clinical data on the underlying indications for PPI use was not available, leaving us unable to adjust for the potential of confounding by indication. Second, we did not have information on concomitant use of other drugs that might influence our estimates, e.g. statins which have been reported to be associated with decreased mortality among prostate cancer patients.[35, 36] Third, we lacked information on clinical diagnoses to be able to adjust for disease-based comorbidities, although we made an attempt to counteract this limitation by using a medication-based comorbidity score as a proxy for the Charlson comorbidity index. Fourth, misclassification of PPI use might have resulted from OTC use and from use within the hospital setting, since we only had information on dispensed PPI drugs to the outpatient population. Fifth, we were unable to obtain information on the measured level of prostate specific antigen (PSA) at diagnosis; a variable that is used in clinical staging and could influence prognosis. Finally, as in all studies of this nature, our assessment of PPI use is based on dispensed drugs, which we cannot be sure are necessarily consumed. However, we tried to minimize the influence of this potential bias by the requirement of PPI users having received at least two filled prescriptions, in the main analysis. The primary strength of our study was the clearly defined population-based cohort and our utilization of high-quality nationwide registry data. Furthermore, utilization of registry data removed the risk of recall-bias.

In summary, our findings do not indicate that post-diagnosis PPI use influences mortality risk among prostate cancer patients. However, due to the small size of our cohort and short follow-up time, the resulting estimates had quite wide CIs, which limits our ability to draw any definitive conclusions. Future studies should use a larger cohort, longer follow-up time, and aim to minimize the potential impact of confounding by indication to further elucidate whether PPI use influences mortality among prostate cancer patients.

ACKNOWLEDGEMENTS

We thank Guðrún Kristín Guðfinnsdóttir & Kristinn Jónsson at the Directorate of Health in Iceland, Laufey Tryggvadóttir, Helgi Birgisson, and Guðríður Helga Ólafsdóttir at the Icelandic Cancer Registry, and Sif Sumarliðadóttir, Erna Karlsdóttir, and Jakob Jóhannsson at Landspítali – the National University Hospital of Iceland for extracting the data for this study.

This study was funded by the Icelandic Research Fund, grant number 152715-053. Dr Zoëga was also supported by a Scientia Fellowship from the University of New South Wales. The funding sources had no influence on the design or conduct of this study.

REFERENCES

[1] Hálfdánarson ÓÖ, Pottegård A, Björnsson ES, et al. Proton-pump inhibitors among adults: a nationwide drug-utilization study. *Ther Adv Gastroenterol* 2018; 11: 175628481877794.

[2] Sachs G, Shin JM, Briving C, et al. The Pharmacology of the Gastric Acid Pump: The H+,K+ ATPase. *Annu Rev Pharmacol Toxicol* 1995; 35: 277–305.

[3] Moriyama Y, Patel V, Ueda I, et al. Evidence for a Common Binding-Site for Omeprazole and N-Ethylmaleimide in Subunit A of Chromaffin Granule Vacuolar-Type H+-ATPase. *Biochem Biophys Res Commun* 1993; 196: 699–706.

[4] Sabolic I, Brown D, Verbavatz JM, et al. H(+)-ATPases of renal cortical and medullary endosomes are differentially sensitive to Sch-28080 and omeprazole. *Am J Physiol-Ren Physiol* 1994; 266: F868–F877.

[5] Capecci J, Forgac M. The Function of Vacuolar ATPase (V-ATPase) a Subunit Isoforms in Invasiveness of MCF10a and MCF10CA1a Human Breast Cancer Cells. *J Biol Chem* 2013; 288: 32731–32741.

[6] Cotter K, Capecci J, Sennoune S, et al. Activity of Plasma Membrane V-ATPases Is Critical for the Invasion of MDA-MB231 Breast Cancer Cells. *J Biol Chem* 2015; 290: 3680–3692.

[7] Hinton A, Sennoune SR, Bond S, et al. Function of a subunit isoforms of the V-ATPase in pH homeostasis and in vitro invasion of MDA-MB231 human breast cancer cells. *J Biol Chem* 2009; 284: 16400–16408.

[8] Michel V, Licon-Munoz Y, Trujillo K, et al. Inhibitors of vacuolar ATPase proton pumps inhibit human prostate cancer cell invasion and prostate-specific antigen expression and secretion. *Int J Cancer* 2013; 132: E1–E10.

[9] Riemann A, Schneider B, Gündel D, et al. Acidosis Promotes Metastasis Formation by Enhancing Tumor Cell Motility. In: Elwell CE, Leung TS, Harrison DK (eds) *Oxygen Transport to Tissue XXXVII*. New York, NY: Springer New York, pp. 215–220.

[10] Nishisho T, Hata K, Nakanishi M, et al. The a3 isoform vacuolar type H^+-ATPase promotes distant metastasis in the mouse B16 melanoma cells. *Mol Cancer Res MCR* 2011; 9: 845–855.

[11] Martinez-Zaguilan R, Lynch RM, Martinez GM, et al. Vacuolar-type H(+)-ATPases are functionally expressed in plasma membranes of human tumor cells. *Am J Physiol-Cell Physiol* 1993; 265: C1015–C1029.

[12] Rofstad EK, Mathiesen B, Kindem K, et al. Acidic Extracellular pH Promotes Experimental Metastasis of Human Melanoma Cells in Athymic Nude Mice. *Cancer Res* 2006; 66: 6699–6707.

[13] Spugnini EP, Sonveaux P, Stock C, et al. Proton channels and exchangers in cancer. *Biochim Biophys Acta BBA - Biomembr* 2015; 1848: 2715–2726.

[14] Ikemura K, Hiramatsu S, Okuda M. Drug Repositioning of Proton Pump Inhibitors for Enhanced Efficacy and Safety of Cancer Chemotherapy. *Front Pharmacol*; 8. Epub ahead of print 12 December 2017. DOI: 10.3389/fphar.2017.00911.

[15] Luciani F, Spada M, De Milito A, et al. Effect of Proton Pump Inhibitor Pretreatment on Resistance of Solid Tumors to Cytotoxic Drugs. *JNCI J Natl Cancer Inst* 2004; 96: 1702–1713.

[16] De Milito A, Canese R, Marino ML, et al. pH-dependent antitumor activity of proton pump inhibitors against human melanoma is mediated by inhibition of tumor acidity. *Int J Cancer J Int Cancer* 2010; 127: 207–219.

[17] Azzarito T, Venturi G, Cesolini A, et al. Lansoprazole induces sensitivity to suboptimal doses of paclitaxel in human melanoma. *Cancer Lett* 2015; 356: 697–703.

[18] Wang B-Y, Zhang J, Wang J-L, et al. Intermittent high dose proton pump inhibitor enhances the antitumor effects of chemotherapy in metastatic breast cancer. *J Exp Clin Cancer Res*; 34. Epub ahead of print December 2015. DOI: 10.1186/s13046-015-0194-x.

[19] Ferrari S, Perut F, Fagioli F, et al. Proton pump inhibitor chemosensitization in human osteosarcoma: from the bench to the patients' bed. *J Transl Med* 2013; 11: 268.

[20] Kearns MD, Boursi B, Yang Y-X. Proton pump inhibitors on pancreatic cancer risk and survival. *Cancer Epidemiol* 2017; 46: 80–84.

[21] Papagerakis S, Bellile E, Peterson LA, et al. Proton Pump Inhibitors and Histamine 2 Blockers Are Associated with Improved Overall Survival in Patients with Head and Neck Squamous Carcinoma. *Cancer Prev Res (Phila Pa)* 2014; 7: 1258–1269.

[22] Tvingsholm SA, Dehlendorff C, Østerlind K, et al. Proton pump inhibitor use and cancer mortality: Proton pump inhibitors and cancer. *Int J Cancer* 2018; 143: 1315–1326.

[23] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries: Global Cancer Statistics 2018. *CA Cancer J Clin*. Epub ahead of print 12 September 2018. DOI: 10.3322/caac.21492.

[24] Sigurdardottir LG, Jonasson JG, Stefansdottir S, et al. Data quality at the Icelandic Cancer Registry: comparability, validity, timeliness and completeness. *Acta Oncol Stockh Swed* 2012; 51: 880–889.

[25] WHO. WHOCC - ATC/DDD Index, https://www.whocc.no/atc_ddd_index/ (accessed 28 May 2018).

[26] Weberpals J, Jansen L, Carr PR, et al. Beta blockers and cancer prognosis – The role of immortal time bias: A systematic review and meta-analysis. *Cancer Treat Rev* 2016; 47: 1–11.

[27] Lix L, Smith M, Pitz M, Ahmed R, Quon H, Griffith J, Turner D, Hong S, Prior H, Banerjee A, Koseva I, Kulbaba C. *Cancer data linkage in Manitoba: expanding the infrastructure for research*. Winnipeg, MB: Manitoba Centre for Health Policy, 2016.

[28] Therneau TM. *A Package for Survival Analysis in S*, https://CRAN.R-project.org/package=survival (accessed 14 November 2018).

[29] R: The R Project for Statistical Computing, https://www.r-project.org/ (accessed 6 November 2017).

[30] Smelick GS, Heffron TP, Chu L, et al. Prevalence of Acid-Reducing Agents (ARA) in Cancer Populations and ARA Drug–Drug Interaction Potential for Molecular Targeted Agents in Clinical Development. *Mol Pharm* 2013; 10: 4055–4062.

[31] Numico G, Fusco V, Franco P, et al. Proton Pump Inhibitors in cancer patients: How useful they are? A review of the most common indications for their use. *Crit Rev Oncol Hematol* 2017; 111: 144–151.

[32] Hvid-Jensen F, Nielsen RB, Pedersen L, et al. Lifestyle factors among proton pump inhibitor users and nonusers: a cross-sectional study in a population-based setting. *Clin Epidemiol* 2013; 5: 493–499.

[33] Westerman ME, Sharma V, Karnes RJ. MP69-20 THE IMPACT OF PROTON-PUMP INHIBITORS ON OUTCOMES FOLLOWING RADICAL PROSTATECTOMY. *J Urol* 2016; 195: e905.

[34] Sun J, Ilich AI, Kim CA, et al. Concomitant Administration of Proton Pump Inhibitors and Capecitabine is Associated With Increased Recurrence Risk in Early Stage Colorectal Cancer Patients. *Clin Colorectal Cancer* 2016; 15: 257–263.

[35] Larsen SB, Dehlendorff C, Skriver C, et al. Postdiagnosis Statin Use and Mortality in Danish Patients With Prostate Cancer. *J Clin Oncol* 2017; 35: 3290–3297.

[36] Yu O, Eberg M, Benayoun S, et al. Use of Statins and the Risk of Death in Patients With Prostate Cancer. *J Clin Oncol* 2014; 32: 5–11.

TABLES

Table 1. Descriptive characteristics of a cohort of Icelandic prostate cancer patients diagnosed between 1 January 2007 and 31 December 2012 by post-diagnosis PPI user status.

		Prostate Cancer	
		Proton pump inhibitor use	
		Non-users	Post-diagnosis users
		N = 711	N = 347
Pre-diagnosis use (%)	Yes	59 (8.3)	182 (52.4)
	No	652 (91.7)	165 (47.6)
Age at diagnosis - years	Median (IQR)	69 (62 - 75)	69 (63 - 76)
Age groups (%)	40-54	47 (6.6)	14 (4.0)
	55-69	338 (47.5)	169 (48.7)
	70-85	326 (45.9)	164 (47.3)
Year of diagnosis (%)	2007-2009	349 (49.1)	208 (59.9)
	2010-2012	362 (50.9)	139 (40.1)
Clinical stage	Localized	549 (77.2)	283 (81.6)
	Non-localized	59 (8.3)	22 (6.3)
	Unknown	103 (14.5)	42 (12.1)
Gleason score	<7	371 (52.2)	177 (51.0)
	7	195 (27.4)	103 (29.7)
	≥8	134 (18.8)	60 (17.3)
	Unknown	11 (1.6)	7 (2.0)
Radiotherapy (%)[a]	Yes	196 (27.6)	92 (26.5)
	No	515 (72.4)	255 (73.5)
Cancer surgery (%)[a]	Total excision of prostate	173 (24.3)	86 (24.8)
	Partial excision of prostate	63 (8.9)	44 (12.7)
	No surgery	475 (66.8)	217 (62.5)
Cancer drug treatment (%)[a]	Yes	62 (8.7)	31 (8.9)
Chemotherapy (%)[a]	Yes	8 (1.1)	1 (0.3)
Endocrine therapy (%)[a]	Yes	43 (6.0)	24 (6.9)
Chemotherapy & endocrine therapy[a]	Yes	11 (1.5)	6 (1.7)
Medication-based comorbidity	Median (IQR)	5 (3 - 8)	8 (5 - 10)

[a]Treatment in first year after diagnosis

Table 2. Cox proportional hazard regression models for associations between post-diagnosis PPI use and prostate cancer-specific among patients diagnosed with prostate cancer in Iceland between 2007 and 2012

	Prostate cancer-specific mortality			
PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Non-use	76	3640	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	22	1171	0.85 (0.52 - 1.38)	0.88 (0.52 - 1.48)
Timing of use				
Continuous PPI use	8	734	0.45 (0.22 - 0.93)	0.45 (0.21 - 0.98)
New PPI use	14	437	1.39 (0.77 - 2.53)	1.12 (0.61 - 2.08)
Clinical stage				
Localized	8	1006	0.55 (0.25 - 1.23)	0.50 (0.22 - 1.16)
Non-localized	9	39	0.92 (0.43 - 1.96)	1.00 (0.44 - 2.27)
Cumulative dose				
1-365 DDDs	9	390	1.04 (0.52 - 2.09)	0.91 (0.43 - 1.90)
>365 DDDs	13	780	0.75 (0.41 - 1.37)	0.86 (0.45 - 1.61)

Abbreviations: DDD, defined daily doses; HR, hazard ratio; CI, confidence interval

[b]Adjusted for age at diagnosis
[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

Table 3. Cox proportional hazard regression models for associations between post-diagnosis PPI use and all-cause mortality among patients diagnosed with prostate cancer in Iceland between 2007 and 2012

	All-cause mortality			
PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Non-use	144	3640	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	59	1171	1.16 (0.85 - 1.59)	1.02 (0.73 - 1.43)
Timing of use				
Continuous PPI use	28	734	0.81 (0.54 - 1.22)	0.67 (0.43 - 1.04)
New PPI use	31	437	1.57 (1.04 - 2.36)	1.25 (0.82 - 1.92)
Clinical stage				
Localized	33	1006	0.99 (0.65 - 1.50)	0.74 (0.47 - 1.15)
Non-localized	13	39	1.08 (0.57 - 2.06)	1.18 (0.58 - 2.34)
Cumulative dose				
1-365 DDDs	27	390	1.61 (1.06 - 2.44)	1.19 (0.76 - 1.87)
>365 DDDs	32	780	0.93 (0.63 - 1.38)	0.91 (0.61 - 1.37)

Abbreviations: DDD, defined daily doses; HR, hazard ratio; CI, confidence interval

[b]Adjusted for age at diagnosis
[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

FIGURES

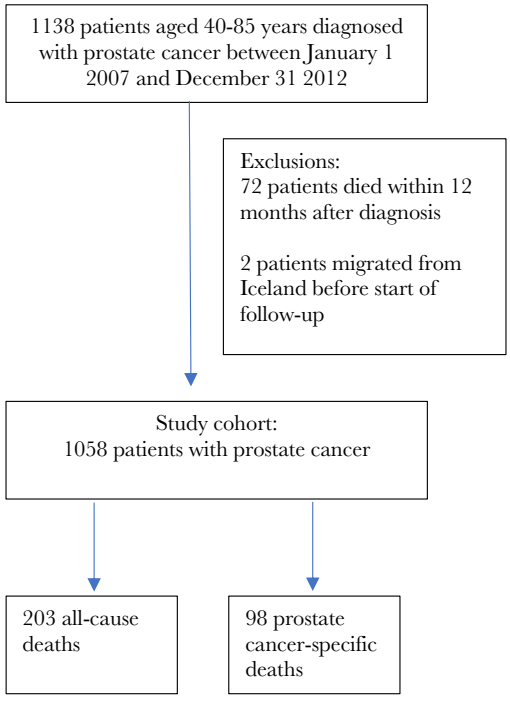


Figure 1. Study flow chart of cohort identification

SUPPLEMENTARY TABLES

Table S1. Sensitivity analysis of the association between time-varying post-diagnosis PPI use, prostate cancer-specific mortality, and all-cause mortality among prostate cancer patients in Iceland, where post-diagnosis use was defined as at least one dispensed PPI prescription after diagnosis and post-diagnosis users were considered unexposed up until the received their first PPI dispensing and then exposed thereafter

PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Prostate cancer-specific mortality				
Non-use	65	3203	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	33	1608	0.97 (0.63 - 1.50)	1.04 (0.66 - 1.65)
All-cause mortality				
Non-use	129	3203	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	74	1608	1.07 (0.79 - 1.43)	0.98 (0.71 - 1.34)

Abbreviations: HR, hazard ratio; CI, confidence interval

[b]Adjusted for age at diagnosis

[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

Table S2. Sensitivity analysis of the association between post-diagnosis PPI use, prostate cancer-specific mortality, and all-cause mortality among prostate cancer patients in Iceland, where post-diagnosis use of PPIs was assessed in the first 12 months following prostate cancer diagnosis.

PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Prostate cancer-specific mortality				
Non-use	85	3930	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	13	881	0.64 (0.36 - 1.15)	0.63 (0.34 - 1.18)
All-cause mortality				
Non-use	163	3930	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	40	881	1.03 (0.73 - 1.46)	0.84 (0.58 - 1.23)

Abbreviations: HR, hazard ratio; CI, confidence interval

[b]Adjusted for age at diagnosis
[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

Table S3. Sensitivity analysis of the association between time-varying post-diagnosis PPI use, prostate cancer-specific mortality, and all-cause mortality among prostate cancer patients in Iceland, where post-diagnosis use was assessed continuously throughout follow-up.

PPI exposure	No of deaths	No of person years	Age adjusted HR (95% CI)[b]	Adjusted HR (95% CI)[c]
Prostate cancer-specific mortality				
Non-use	77	4012	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	21	798	1.33 (0.82 - 2.19)	1.48 (0.88 - 2.47)
All-cause mortality				
Non-use	158	4012	1.00 (Reference)	1.00 (Reference)
Post-diagnosis PPI use	45	798	1.33 (0.95 - 1.87)	1.30 (0.92 - 1.85)

Abbreviations: HR, hazard ratio; CI, confidence interval

[b]Adjusted for age at diagnosis

[c]Adjusted for age at diagnosis, calendar period, clinical stage, Gleason score, medication-based comorbidity, surgery, endocrine and/or chemotherapy, radiotherapy

Appendix

A.

VÍSINDASIÐANEFND

Hafnarhúsið, Tryggvagata 17
101 Reykjavík,

Sími: 551 7100, Bréfsími: 551 1444
netfang: vsn@vsn.is www.vsn.is

Háskóli Íslands, Læknadeild, lýðheilsuvísindi
Helga Zoega, dósent í lýðheilsuvísindum
Vatnsmýrarvegur 16
101 Reykjavík

Reykjavík 27. október 2015
Tilv.: VSNb2015080004/03.03

Efni: Varðar: 15-115-afg -Faraldsfræðileg rannsókn á áhrifum lyfja úr flokki prótonpumpuhemla (PPI) á krabbamein í mönnum.

Umsókn þinni til Vísindasiðanefndar hefur verið gefið númerið **VSN-15-115**. Við förum vinsamlegast fram á að það númer verði notað í samskiptum vegna þessarar umsóknar.

Á fundi sínum 27.10.2015 fjallaði Vísindasiðanefnd um umsókn þína vegna ofangreindrar rannsóknaráætlunar. Meðrannsakendur þínir eru: Eiríkur Steingrímsson, Óskar Örn Hálfdánarson, Helga M. Ögmundsdóttir og Margrét Helga Ögmundsdóttir.

Eftir að hafa farið vandlega yfir umsókn þína og innsend gögn gerir Vísindasiðanefnd ekki athugasemdir við framkvæmd rannsóknarinnar. Með vísan til 1. mgr. 27. gr. laga nr. 44/2014, heimilar Vísindasiðanefnd aðgang að þeim upplýsingum sem fram koma í kafla B-2 í umsókn til nefndarinnar úr Lyfjagagnagrunni landlæknis, Krabbameinsskrá og Þjóðskrá. Með vísan til laga nr. 44/2014, um vísindarannsóknir á heilbrigðissviði, er rannsóknaráætlunin endanlega samþykkt með þeim almenna fyrirvara að lögbundið samþykki skráarhaldara skv. 2. mgr. 27. gr. laga nr. 44/2014 verður að liggja fyrir áður en vinna með heilbrigðisgögn viðkomandi stofnunar/skráarhaldara hefst.

Vísindasiðanefnd áréttar að ábyrgðarmaður rannsóknarinnar ber ábyrgð á að sótt sé um viðeigandi leyfi fyrir rannsókninni hjá þeim stofnunum sem við á. Óheimilt er að hefja framkvæmd rannsóknarinnar fyrr en þau liggja fyrir. Afrit leyfa/samstarfsyfirlýsinga þurfa að berast nefndinni. Áréttað er að allar fyrirhugaðar breytingar á þegar samþykktri rannsóknaráætlun þurfa að koma inn til nefndarinnar til umfjöllunar. Jafnframt ber ábyrgðarmanni að sækja um breytingar til þeirra stofnanna, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna, um framangreint, ef við á.

Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Minnt er á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju og ósk um gott rannsóknargengi,
f.h. Vísindasiðanefndar,

Kristján Erlendsson, læknir, formaður

B.

VÍSINDASIÐANEFND
Borgartúni 21 - 4. hæð
105 Reykjavík.

Sími: 551 7100, Bréfsími: 551 1444

netfang: vsn@vsn.is www.vsn.is

Helga Zoëga, prófessor
Háskóli Íslands
101 Reykjavík

Reykjavík 6. september 2016
Tilv.: VSNb2016080001/03.01

Efni: Varðar: 16-124 - Prótonpumpuhemlar og möguleg áhrif þeirra á framþróun krabbameina og lifun krabbameinssjúklinga

Umsókn þinni til Vísindasiðanefndar hefur verið gefið númerið **VSN-16-124.** Við förum vinsamlegast fram á að það númer verði notað í samskiptum vegna þessarar umsóknar.

Á fundi sínum 06.09.2016 fjallaði Vísindasiðanefnd um umsókn þína vegna ofangreindrar rannsóknaráætlunar. Meðrannsakendur þínir eru: Óskar Örn Hálfdánarson, doktorsnemi, Eiríkur Steingrímsson, prófessor, Helga M. Ögmundsdóttir, prófessor og Sigrún Helga Lund, dósent.

Samkvæmt lið B-1 í umsókn þinni inniheldur rannsóknarúrtakið alla einstaklinga á Íslandi sem greinast með krabbamein á tímabilinu frá 1. janúar 2003 til og með 31. desember 2012.

Þá kemur fram í fylgiskjali 1 í lið B-2 í umsókn að:

„Unnið verður með fyrirliggjandi upplýsingar úr Krabbameinsskrá, Lyfjagagnagrunni Embættis landlæknis, Dánarmeinaskrá og frá Landspítala - Háskólasjúkrahúsi (LSH).
Krabbameinsskrá
Krabbameinsgreiningar frá og með 1. janúar 2003 til 31. desember 2012. Þær breytur sem sótt verður um að fá aðgang að úr skránni eru eftirfarandi: aldur, kyn, dagsetning greiningar, greiningarár, aldur við greiningu, númer æxlis, meingerð æxlis ***(vefjagerð og tegund æxlis)****, dánardagur og ICD-10 kóði meins. Með því að byggja á ICD-10 kóðum World Health Organization (WHO) munum við flokka tegundir krabbameins á eftirfarandi hátt: Öll krabbamein (C00-C96), sortuæxli (C43), brjóstakrabbamein (C50) og blöðruhálskirtilskrabbamein (C61).*
Lyfjagagnagrunnur
Útleystar lyfjaávísanir fyrir prótonpumpuhemlum (PPI) frá 1. janúar 2003 til og með 31. desember 2015. Unnið verður með upplýsingar um aldur (fæðingarár og fæðingarmánuður), kyn, útleystar lyfjaávísanir fyrir PPI lyf, heiti lyfs, fjöldi útleystra DDD á lyfjaávísu, ATC-kóði lyfs, dagsetning lyfjaúttektar, afgreiðslustaður, sérgrein læknis sem skrifar upp á lyfið og skráð lögheimili þann 1. janúar 2003 (flokkað eftir landshlutaskiptingu Hagstofunnar).
Óskað er eftir því að Embætti landlæknis bæti einnig við upplýsingum um brottflutning frá Íslandi (dagsetning) og innflutning til Íslands (dagsetning) úr Þjóðskrá Íslands við rannsóknargagnagrunninn.
Dánarmeinaskrá
Upplýsingar um dánardag og dánarmein einstaklinga í rannsóknarhóp sem láta lífið á rannsóknartímabilinu verða sóttar í Dánarmeinaskrá. Flokkun dánarmeina verður byggð á alþjóðlegri tölfræðiflokkun sjúkdóma og skyldra heilbrigðisvandamála (ICD-10).
Landspítali - Háskólasjúkrahús

Við munum nálgast upplýsingar frá Landspítala-Háskólasjúkrahúsi (LSH) um framþróun meinanna hjá einstaklingum í rannsóknarhóp. Þær breytur sem sóttar verða til LSH eru eftirfarandi:
Skurðaðgerð vegna krabbameins (Vöruhús gagna):
- ICD-10 kóði meins (tegund meins)
- NCSP-IS kóði aðgerðar (tegund aðgerðar)
- Dagsetning aðgerðar.
Geislameðferð vegna krabbameins (Geisladeild LSH):
- ICD-10 kóði meins (tegund meins)
- Heildargeislaskammtur
- Daglegur geislaskammtur
- Meðferð hafin, dags.
- Meðferð hætt, dags.
Prótonpumpuhemlar og möguleg áhrif þeirra á framþróun krabbameina og lífun krabbameinssjúklinga.
Lyfjameðferð vegna krabbameins (Vöruhús gagna & Aria MedOnc lyfjaskráningarkerfið):
- ICD-10 kóði meins (tegund meins)
- Heiti lyfs
- Lyfjaskammtur
- Meðferð hafin, dags.
- Meðferð hætt, dags.
Svörun meðferða vegna krabbameins (Uppfletting í sjúkraskýrslum):
- No response, partial response eða full response."
Samkvæmt umsókn er ætlað að sækja gögn úr Krabbameinsskrá, Lyfjagagnagrunni Embættis landlæknis, Dánameinaskrá, Vöruhúsi gagna LSH, Geisladeild LSH, Aria MedOnc lyfjskráningarkerfi LSH og úr sjúkraskýrslum.

Áætluð rannsóknarlok eru í september 2018. Samkvæmt umsókn er frambúðarvarðveisla skv. 7. gr. laga nr. 44/2014 ekki fyrirhuguð. Að því virtu ber að eyða gögnum sem aflað er til rannsóknarinnar eða verða til við framkvæmd hennar fyrir árslok 2023.

Með vísan til 1. mgr. 27. gr. laga nr. 44/2014 heimilar Vísindasiðanefnd aðgang að framangreindum upplýsingum úr ofangreindum skrám. Með vísan til 1. mgr. 12. gr. laga nr. 44/2014 er rannsóknaráætlun endanlega samþykkt með þeim almenna fyrirvara að lögbundið samþykki skráarhaldara skv. 2. mgr. 27. gr. laganna verður að liggja fyrir áður en vinna með heilbrigðisgögn viðkomandi stofnunar/skráarhaldara hefst.

Vísindasiðanefnd áréttar að ábyrgðarmaður rannsóknarinnar ber ábyrgð á að sótt sé um viðeigandi leyfi fyrir rannsókninni hjá þeim stofnunum sem við á. Óheimilt er að hefja framkvæmd rannsóknarinnar fyrr en þau liggja fyrir. Afrit leyfa/samstarfsyfirlýsinga þurfa að berast nefndinni. Áréttað er að allar fyrirhugaðar breytingar á þegar samþykktri rannsóknaráætlun þurfa að koma inn til nefndarinnar til umfjöllunar. Jafnframt ber ábyrgðarmanni að sækja um breytingar til þeirra stofnanna, sem veitt hafa leyfi vegna framkvæmdar rannsóknarinnar eða öflunar gagna, um framangreint, ef við á.

Vísindasiðanefnd bendir rannsakendum vinsamlegast á að birta VSN tilvísunarnúmer rannsóknarinnar þar sem vitnað er í leyfi nefndarinnar í birtum greinum um rannsóknina. Minnt er á að tilkynna rannsóknarlok til nefndarinnar.

Með kveðju og ósk um gott rannsóknargengi,
f.h. Vísindasiðanefndar,

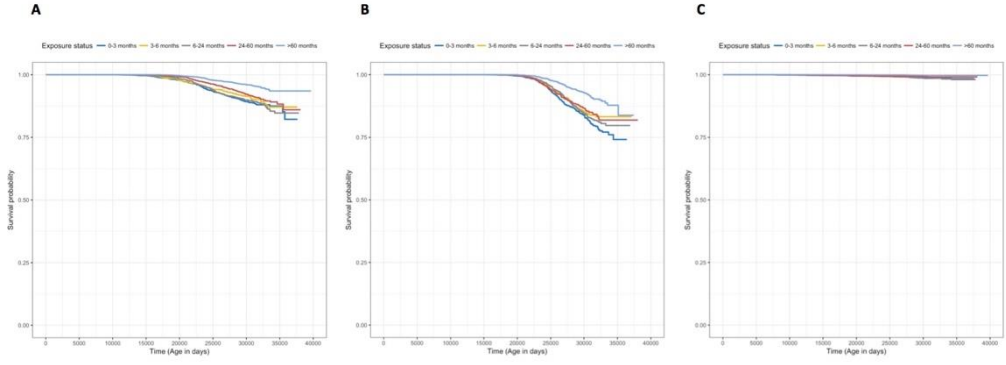
Kristján Erlendsson, læknir, formaður

C.

Using a cohort study design, we conducted analyses on proton pump inhibitor use among patients diagnosed with breast cancer, prostate cancer, and malignant melanoma between 2003 and 2014. We assessed various levels of PPI exposure, i.e. ever use (defined as one filled PPI prescription during follow-up) and cumulative use (in months, assuming the intake of one DDD per day). The exposure was not assessed in a time-dependent manner. We used Cox proportional hazard regression models, with age as the underlying time-scale, to estimate HRs and 95% CIs. The results displayed in the table and the figure are influenced by immortal time bias.

	Breast Cancer			Prostate Cancer			Malignant melanoma		
Subgroups	**Events**	**Adjusted HR†**	**95% CI**	**Events**	**Adjusted HR†**	**95% CI**	**Events**	**Adjusted HR†**	**95% CI**
Never use of PPI	832	1.00 (ref)	1.00 (ref)	984	1.00 (ref)	1.00 (ref)	272	1.00 (ref)	1.00 (ref)
Ever use of PPI	720	0.83	0.75 - 0.92	779	0.85	0.77 - 0.93	127	0.65	0.52 - 0.80
Cumulative dose (DDDs)									
0 - 3 months	219	1.05	0.90 - 1.22	252	1.11	0.96 - 1.27	52	0.88	0.65 - 1.18
3 - 6 months	91	0.92	0.74 - 1.14	96	0.89	0.73 - 1.10	14	0.55	0.32 - 0.95
6 - 24 months	184	1.00	0.86 - 1.18	180	0.94	0.80 - 1.10	36	0.87	0.61 - 1.24
24 - 60 months	128	0.80	0.67 - 0.97	144	0.86	0.73 - 1.03	17	0.53	0.32 - 0.87
>60 months	98	0.44	0.35 - 0.54	107	0.47	0.39 - 0.58	8	0.20	0.10 - 0.40

†Adjusted for age, sex, and prior NSAID use



A, breast cancer; B, prostate cancer; C, malignant melanoma