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The role of 5 α -reductase inhibitors in gastro-oesophageal cancer risk: a nested case-control study

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Title: The role of 5 α -reductase inhibitors in gastro-oesophageal cancer risk: a nested case-control study.

Short title: 5AR inhibitors and gastro-oesophageal cancer

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Abbreviations: 5AR: 5 α -reductase; BMI: body mass index; CI: confidence interval; OR: Odds ratio; PCCIUR: Primary Care Clinical Information Unit Research

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Abstract

Background and aims: The strong male predominance of gastro-oesophageal cancer suggests sex hormones play an important role. 5 α -reductase (5AR) inhibitors have antiandrogen effects, and have been shown to decrease proliferation and metastasis in gastric and oesophageal cancer cell lines. Consequently, we conducted the first epidemiologic investigation into the association between 5AR inhibitor use and gastro-oesophageal cancer risk.

Methods: We conducted a nested case-control study within the Scottish Primary Care Clinical Information Unit Research database. Male cases diagnosed with oesophageal or gastric cancer between 1999 and 2011 were matched to up to five male controls based on birth year, diagnosis year and general practice. We used electronic prescribing records to ascertain medication use. We used conditional logistic regression to calculate odds ratios (ORs) for the association between 5AR inhibitor use and cancer risk, after adjusting for comorbidities and aspirin, statin or proton pump inhibitor use.

Results: The study included 2,003 gastro-oesophageal cancer cases and 9,650 controls. There was some evidence of reduced gastro-oesophageal cancer risk among 5AR inhibitor users (adjusted OR= 0.75; 95% CI: 0.56, 1.02), particularly for finasteride (adjusted OR=0.68; 95% CI 0.50, 0.94). These associations appeared to follow a dose-response pattern, with more marked decreases among those who received at least twelve 5AR inhibitor (adjusted OR= 0.62; 95% CI: 0.40, 0.98; p-value for trend = 0.036) or finasteride (adjusted OR= 0.58; 95% CI 0.36, 0.93; p-value for trend = 0.013) prescriptions.

Conclusions: We found evidence of reduced gastro-oesophageal cancer risk among users of 5AR inhibitors, particularly finasteride. However, larger epidemiological studies are required before randomised controlled trials are considered.

Keywords: Gastric cancer; Oesophageal cancer; Androgen; 5 α -reductase inhibitors

Introduction

Oesophageal and gastric cancer are among the most common cancers in the world, with around 456,000 and 952,000 new cases diagnosed annually.¹ Prognosis is extremely poor, even in high-income countries such as the UK, where nearly 55% of patients die within one year of diagnosis.² The strong male predominance of gastro-oesophageal cancer³⁻⁵ has prompted much interest in the role of sex hormones.^{6, 7} This hormonal hypothesis is supported by findings of reduced gastric cancer incidence among hormone replacement therapy users, and women with a longer time between menarche and menopause.⁸

5 α -reductase (5AR) inhibitors (including finasteride and dutasteride) are widely used⁹ medications for the treatment of benign prostatic hyperplasia¹⁰, the most common urologic disease among elderly males.¹¹ They reduce prostate size, and relieve urinary symptoms, by inhibiting the androgen receptor thus preventing the conversion of testosterone to the more biologically active dihydrotestosterone.^{12, 13} 5AR inhibitors have been shown to increase the ratio of oestrogen to testosterone¹⁴, and have been linked with some hormonal side effects such as gynaecomastia.¹⁵ Preclinical evidence that androgen receptors are present within oesophageal¹⁶⁻¹⁸ and gastric cancer tumours¹⁹⁻²¹, and that their inhibition reduces cell proliferation and migration^{22, 23}, suggests that medications with hormonal effects could influence gastro-oesophageal cancer risk. Surprisingly, clinical studies have yet to assess the impact of 5AR inhibitor use on gastro-oesophageal cancer.

Consequently, in a population-based primary care cohort from Scotland, we conducted the first study to investigate whether 5AR inhibitor use was associated with a reduced risk of gastro-oesophageal cancer.

Methods

Data

We conducted a nested case-control study within the Primary Care Clinical Information Unit Research (PCCIUR) database.²⁴ Between 1993 and 2011, the PCCIUR collected computerised medical records from approximately 15% of the Scottish general practice population, and includes details on patient demographics (e.g. age, gender), primary care encounters, clinical diagnoses and prescriptions. Access to the PCCIUR data was approved by the Research Applications and Data Management Team, University of Aberdeen. Ethical approval for this study was supplied by the Queen's University Belfast, School of Medicine Ethics Committee (reference number: 15.43).

Cases and controls

Our primary outcome was gastro-oesophageal cancer since classifying tumours arising close to the oesophagogastric junction is difficult.^{25, 26} Cases and controls were restricted to males as 5AR inhibitors are not used in females. Cases were defined as patients with a primary oesophageal (Read code: B10..) or gastric (Read code: B11..) cancer diagnosis between 1st January 1999 and 30th April 2011. Up to five controls were randomly selected for each case matched on year of birth, year of diagnosis and general practice. The index date was defined as the diagnosis date of the case in each matched group. The start of the exposure period was the latest of 1st January 1996 (as prescriptions before this were less likely to be generated electronically) or the date of general practice registration. Additionally, the exposure period was truncated to ensure it was identical across the matched groups.²⁷ Cases and controls with an earlier cancer diagnosis (other than non-melanoma skin cancer), and those with less than a three year exposure window, were excluded from the study.

50

51 Definition of exposure

52 We identified 5AR inhibitor use from electronic prescription records. We used the British
53 National Formulary to compile a list of proprietary and generic names for 5AR inhibitor
54 medications (Appendix 1). We excluded prescriptions before 1st January 1996 and those in
55 the year prior to the index date (to prevent reverse causation). We defined patients as users
56 if they had at least one prescription during the exposure period. To enable the testing of dose-
57 response relationships, we calculated the total number of prescriptions received during the
58 exposure period and split patients into lower (less than 12 prescriptions) and higher (at least
59 12 prescriptions) users.

60 Confounding factors

61 We identified eleven comorbidities (myocardial infarction, heart failure, peripheral vascular
62 disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive
63 pulmonary disease, rheumatoid arthritis, diabetes, renal disease, liver disease) using Read
64 codes recorded by the GP during the exposure period.²⁸ Use of aspirin, statins, and proton
65 pump inhibitors within the exposure period was identified from prescription records
66 (Appendix 1), as associations with oesophageal and/or gastric cancer have been identified
67 previously.²⁹⁻³² Lifestyle data including obesity (body mass index, BMI>30), smoking status
68 (never, ex, current) and alcohol use (none, low [e.g. moderate or light drinker], high [e.g.
69 above recommended limits, chronic alcoholism]) were also recorded in the PCCIUR data using
70 Read codes.

71

Statistical analysis

We calculated descriptive statistics, and compared the demographics and clinical characteristics of the cases and controls. We used conditional logistic regression to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for the association between 5AR inhibitor use and gastro-oesophageal cancer risk. The matched design accounted for the effect of age, general practice and year of diagnosis with additional adjustments made for statin use (yes/no), aspirin use (yes/no), proton pump inhibitor use (yes/no), and the presence of each comorbidity (yes/no) using regression. We conducted separate site-specific analysis for oesophageal and gastric cancer, and used an interaction test to formally test for differences across sites. Similarly, we conducted separate gastro-oesophageal analyses for finasteride and dutasteride, as they use different mechanisms to inhibit testosterone metabolism.³³

Sensitivity and subgroup analyses

We investigated the impact of additionally adjusting for lifestyle factors (smoking, alcohol consumption and obesity) using complete case and multiple imputation with chained equations methods. The imputation used ordered logit models with age and deprivation, separately for cases and controls. Briefly, this is a simulation-based approach for handling missing data which leads to valid statistical inferences.³⁴ Sensitivity analyses were also conducted investigating the impact of excluding prescriptions in the two years prior to the index date (as opposed to one in the main analysis), and defining medication users as patients with at least three 5AR inhibitor prescriptions (as opposed to one in the main analysis).

Finally, to investigate confounding, we conducted separate negative control analyses³⁵ for liver (Read code: B15..) and pancreatic (Read code: B17..) cancer, as there is little evidence of androgen receptor expression in these sites^{36, 37}, but they should be subject to many of the same potential biases as gastro-oesophageal cancer. Therefore, if confounding was driving our gastro-oesophageal cancer results we would expect to see similar associations for liver and pancreatic cancer. Conversely, findings of meaningful associations for gastro-oesophageal cancer, which are not replicated among the negative controls, would support a causal interpretation. Analyses were conducted using Stata version 13.³⁸

Results

Descriptive statistics

We identified 2,003 cases of gastro-oesophageal cancer (1,364 oesophageal and 639 gastric cancer) (Table 1). An average of 4.8 controls were matched for each case, with a median exposure period of 5.4 years (min 3.0, max 15.1). A larger proportion of cases than controls had a history of COPD (12.3 vs. 8.6%), and were more likely to be current or ex-smokers (70.8 vs. 61.0%), drink high levels of alcohol (9.7 vs. 7.3%) and have a BMI under thirty (85.7 vs. 80.1%).

Association between 5AR inhibitor use and gastro-oesophageal cancer

Overall, 2.7% of cases and 3.2% of controls used 5AR inhibitors. Finasteride (2.9% of study population) was more commonly used than dutasteride (0.3%). There was some evidence of a reduction in gastro-oesophageal cancer risk among 5AR inhibitor users ($OR_{adj} = 0.75$; 95% CI: 0.56, 1.02; Table 2), particularly those using finasteride ($OR_{adj} = 0.68$; 95% CI: 0.50, 0.94). In contrast, there was no significant association between dutasteride use and gastro-oesophageal cancer risk ($OR_{adj} = 1.53$; 95% CI 0.67, 3.50). There were signs of a dose-response relationship, with more marked associations among patients who received at least twelve 5AR inhibitor ($OR_{adj} = 0.62$; 95% CI: 0.40, 0.98; p-value for trend = 0.036) or finasteride ($OR_{adj} = 0.58$; 95% CI: 0.36, 0.93; p-value for trend = 0.013) prescriptions. There was no evidence of a difference in associations between gastric ($OR_{adj} = 0.68$; 95% CI: 0.39, 1.17) or oesophageal ($OR_{adj} = 0.78$; 95% CI: 0.55, 1.13) cancer (p-value for interaction=0.633).

Sensitivity and subgroup analysis

In general, our results were little altered in sensitivity analyses (Table 3). Similar findings were observed when excluding prescriptions in the two years prior to diagnosis, or when the exposure definition of 'ever use' was based upon three or more prescriptions. Additionally adjusting for lifestyle factors (smoking, alcohol consumption, and obesity) using multiple imputation methods resulted in similar findings to the main analysis. Our estimates were slightly attenuated when adjusting for lifestyle factors using complete-case methods, although our conclusions were unaltered. Finally, in negative control analyses, there was no evidence of a protective association between 5AR inhibitor use and liver ($OR_{adj} = 1.03$; 95% CI: 0.50, 2.11) or pancreatic ($OR_{adj} = 0.91$; 95% CI: 0.50, 1.69) cancer risk.

Discussion

Summary of main findings

In this novel population-based study of gastro-oesophageal cancer cases and controls, there was evidence that users of 5AR inhibitors, and particularly finasteride, had lower cancer risk than non-users. These associations appeared to follow a dose-response relationship, and were not replicated in negative control analyses for liver or pancreatic cancer.

Strengths and limitations

Our study is the first to investigate the effect of 5AR inhibitor use on gastro-oesophageal cancer risk. It is based on high-quality and nationally representative data.³⁹ We used prescribing information collected as part of routine clinical care, in many cases, several years before the onset of oesophageal or gastric cancer, which accurately reflects GP prescribing practices and negates the risk of recall bias. Although a weakness of this approach is that we do not know if patients used their medications, the main conclusions were similar when restricting our analysis to those who received multiple repeat 5AR inhibitor prescriptions (>12), where non-compliance is likely to be less of a concern.

Our study is observational and hence open to confounding. Although we have controlled for several of the key determinants of cancer risk through the matched design and analysis (e.g. age, comorbidities), some other risk factors, including ethnicity and nutrition, were not available. However, the lack of a protective association for pancreatic and liver cancer, which should share many of the same potential biases as gastro-oesophageal cancer, suggests that residual confounding is not solely driving our results. The statistical power of our analysis is

limited by our sample size and the relatively low use of 5AR inhibitors within our study population.

Our analysis is based on cancer diagnoses recorded in GP electronic records. Although a recent Clinical Practice Research Datalink study found that over 95% of gastro-oesophageal cancers are captured within GP records⁴⁰, a higher proportion of oesophageal cancers were recorded in the PCCIUR data than in the Scottish Cancer Registry, which could suggest some misclassification of cancer site in our study.⁴¹ This potential issue would not affect our primary analysis which combined oesophageal and gastric cancers. Finally, histological data were not available to allow a separate analysis of squamous cell carcinoma and adenocarcinoma, the two most common forms of gastro-oesophageal cancer. One preclinical study has demonstrated a higher concentration of androgen receptors in adenocarcinoma compared to squamous cell carcinoma, suggesting that 5AR inhibitors may have stronger effects in adenocarcinoma tumours.⁴²

Comparisons with other research

To our knowledge, this is the first study to investigate the association between 5AR inhibitors and gastro-oesophageal cancer risk. Several studies have previously demonstrated lower prostate cancer risk among 5AR inhibitor users.⁴³⁻⁴⁷ For example, one randomised controlled trial reported that patients treated with finasteride had a 30% (95% CI: 24, 35) lower risk of prostate cancer than those assigned to a placebo.⁴⁵ Epidemiological studies have also reported a reduced risk of bladder cancer, but not breast cancer, among 5AR inhibitor users.⁴⁸⁻⁵⁰

Implications for clinicians, policymakers and researchers

Our results suggest that the use of 5AR inhibitors may be associated with reduced gastro-oesophageal cancer risk. These results are compatible with preclinical evidence from oesophageal and gastric cancer cell lines demonstrating that androgen receptor inhibition leads to decreased proliferation and metastasis^{22, 23}, and are consistent with ecological findings of lower gastro-oesophageal cancer incidence among females³ and prostate cancer survivors (who would have typically been treated with anti-androgen therapy).⁵¹ Our finding of a weaker association for dutasteride is difficult to explain as it is a stronger androgen receptor inhibitor, and has a longer half-life than finasteride.³³ However, it is possible that our inconsistent findings reflect the very low use of dutasteride within our study population (<0.3%), which hindered our statistical power. Differences in gastro-oesophageal cancer risk by 5AR inhibitor type should be explored further in larger studies and/or in settings where dutasteride is more commonly prescribed.

The role of 5AR inhibitors as a chemopreventive agent should be explored further, particularly as they are inexpensive (finasteride costs £1.73 [\$2.24] per 28-tablet pack)⁵², have no major safety concerns, and are well tolerated by patients.^{53, 54} These medications may have greatest utility among patients at high risk of gastro-oesophageal cancer, such as those with Barrett's oesophagus or advanced gastric premalignant lesions.^{55, 56} In this paper we have demonstrated that the association with gastro-oesophageal cancer adheres to several of Hill's criteria for causation including biological plausibility, experimental evidence, strength of association, temporality, biological gradient, and specificity.⁵⁷ However, our findings should be replicated in larger epidemiological studies, with detailed information on tumour

206 morphology and/or androgen receptor status, before randomised controlled trials can be
207 considered.

208

209 Conclusions

210 In this novel population-based study, we found a 25% lower gastro-oesophageal cancer risk
211 among 5AR inhibitor users. This association should be replicated in larger epidemiological
212 studies before randomised controlled trials are considered.

References

1. GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012 [03/11/2016]; Available from: <http://globocan.iarc.fr/Default.aspx>.
2. Office for National Statistics. Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015. 2016 [cited 2016 07/10/2016]; Available from: <http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinenglandadultsdiagnosed/2010and2014andfollowedupto2015#5-year-survival>.
3. Coupland VH, Allum W, Blazeby JM, et al. Incidence and survival of oesophageal and gastric cancer in England between 1998 and 2007, a population-based study. *BMC Cancer*. 2012;12:11. Epub 2012/01/14.
4. Sipponen P, Correa P. Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis. *Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association*. 2002;5(4):213-9. Epub 2002/12/20.
5. Rutegard M, Shore R, Lu Y, et al. Sex differences in the incidence of gastrointestinal adenocarcinoma in Sweden 1970-2006. *European journal of cancer (Oxford, England : 1990)*. 2010;46(6):1093-100. Epub 2010/03/02.
6. Tian Y, Wan H, Lin Y, et al. Androgen receptor may be responsible for gender disparity in gastric cancer. *Medical Hypotheses*. 2013;80(5):672-4.
7. Sukocheva OA, Li B, Due SL, et al. Androgens and esophageal cancer: What do we know? *World Journal of Gastroenterology : WJG*. 2015;21(20):6146-56.
8. Camargo MC, Goto Y, Zabaleta J, et al. Sex Hormones, Hormonal Interventions and Gastric Cancer Risk: A Meta-Analysis. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2012;21(1):20-38.
9. Powell-Smith A, Goldacre B. *OpenPrescribing.net*. 2016.
10. Roehrborn CG. Benign Prostatic Hyperplasia: An Overview. *Reviews in Urology*. 2005;7(Suppl 9):S3-S14.
11. Robert G, Descaseaud A, Allory Y, et al. Should We Investigate Prostatic Inflammation for the Management of Benign Prostatic Hyperplasia? *European Urology Supplements*. 2009;8(13):879-86.
12. McConnell JD, Roehrborn CG, Bautista OM, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. *New England Journal of Medicine*. 2003;349(25):2387-98.
13. McConnell JD, Bruskewitz R, Walsh P, et al. The Effect of Finasteride on the Risk of Acute Urinary Retention and the Need for Surgical Treatment among Men with Benign Prostatic Hyperplasia. *New England Journal of Medicine*. 1998;338(9):557-63.
14. Yao S, Till C, Kristal AR, et al. Serum estrogen levels and prostate cancer risk in the prostate cancer prevention trial: a nested case-control study. *Cancer Causes & Control*. 2011;22(8):1121-31.
15. Ramot Y, Czarnowicki T, Zlotogorski A. Finasteride induced Gynecomastia: Case report and Review of the Literature. *International Journal of Trichology*. 2009;1(1):27-9.
16. Awan AK, Iftikhar SY, Morris TM, et al. Androgen receptors may act in a paracrine manner to regulate oesophageal adenocarcinoma growth. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology*. 2007;33(5):561-8. Epub 2007/01/27.
17. Nordenstedt H, Younes M, El-Serag HB. Expression of Androgen Receptors in Barrett Esophagus. *Journal of clinical gastroenterology*. 2012;46(3):251-2.
18. Yamashita Y, Hirai T, Mukaida H, et al. Detection of androgen receptors in human esophageal cancer. *The Japanese journal of surgery*. 1989;19(2):195-202. Epub 1989/03/01.

19. Kominea A, Konstantinopoulos PA, Kapranos N, et al. Androgen receptor (AR) expression is an independent unfavorable prognostic factor in gastric cancer. *Journal of cancer research and clinical oncology*. 2004;130(5):253-8. Epub 2004/02/14.
20. Matsui M, Kojima O, Kawakami S, et al. The prognosis of patients with gastric cancer possessing sex hormone receptors. *Surgery today*. 1992;22(5):421-5. Epub 1992/01/01.
21. Wu CW, Chi CW, Chang TJ, et al. Sex hormone receptors in gastric cancer. *Cancer*. 1990;65(6):1396-400. Epub 1990/03/15.
22. Zhang B-g, Du T, Zang M-d, et al. Androgen receptor promotes gastric cancer cell migration and invasion via AKT-phosphorylation dependent upregulation of matrix metalloproteinase 9. *Oncotarget*. 2014;5(21):10584-95.
23. Zhang Y, Pan T, Zhong X, et al. Androgen receptor promotes esophageal cancer cell migration and proliferation via matrix metalloproteinase 2. *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*. 2015;36(8):5859-64. Epub 2015/03/01.
24. The Institute of Applied Health Sciences. PCCIU Background. 2016; Available from: <http://www.abdn.ac.uk/iahs/research/primary-care/pcciur/background.php>.
25. Chandrasoma P, Wickramasinghe K, Ma Y, et al. Adenocarcinomas of the distal esophagus and "gastric cardia" are predominantly esophageal carcinomas. *The American journal of surgical pathology*. 2007;31(4):569-75. Epub 2007/04/07.
26. Rüdiger Siewert J, Feith M, Werner M, et al. Adenocarcinoma of the Esophagogastric Junction: Results of Surgical Therapy Based on Anatomical/Topographic Classification in 1,002 Consecutive Patients. *Annals of Surgery*. 2000;232(3):353-61.
27. Suissa S, Dell'aniello S, Vahey S, et al. Time-window bias in case-control studies: statins and lung cancer. *Epidemiology (Cambridge, Mass)*. 2011;22(2):228-31. Epub 2011/01/14.
28. Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Family Practice*. 2010;11:1-.
29. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *Br Med J*. 2010;340:12.
30. Rothwell PM, Fowkes FGR, Belch JFF, et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet*. 2011;377(9759):31-41.
31. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. *Gut*. 2014;63(8):1229-37. Epub 2013/11/14.
32. Ahn JS, Eom C-S, Jeon CY, et al. Acid suppressive drugs and gastric cancer: A meta-analysis of observational studies. *World Journal of Gastroenterology : WJG*. 2013;19(16):2560-8.
33. Nickel JC. Comparison of Clinical Trials With Finasteride and Dutasteride. *Reviews in Urology*. 2004;6(Suppl 9):S31-S9.
34. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30(4):377-99. Epub 2011/01/13.
35. Lipsitch M, Tchetgen ET, Cohen T. Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. *Epidemiology (Cambridge, Mass)*. 2010;21(3):383-8.
36. Munoz J, Wheler JJ, Kurzrock R. Androgen receptors beyond prostate cancer: an old marker as a new target. *Oncotarget*. 2015;6(2):592-603.
37. Targarona EM, Pons MD, Gonzalez G, et al. Is exocrine pancreatic cancer a hormone-dependent tumor? A study of the existence of sex hormone receptors in normal and neoplastic pancreas. *Hepato-gastroenterology*. 1991;38(2):165-9. Epub 1991/04/01.
38. StataCorp. *Stata Statistical Software: Release 13*. College Station, TX: StataCorp LP 2013.
39. Elder R, Kirkpatrick M, Ramsay W, et al. Measuring quality in primary medical services using data from SPICE. 2007.

40. Boggon R, van Staa TP, Chapman M, et al. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiology and drug safety*. 2013;22(2):168-75. Epub 2012/12/15.
41. Information Services Division (Scotland). Cancer Statistics. [cited 2016 04/11/2016]; Available from: <http://www.isdscotland.org/Health-Topics/Cancer/Cancer-Statistics/>.
42. Tihan T, Harmon JW, Wan X, et al. Evidence of androgen receptor expression in squamous and adenocarcinoma of the esophagus. *Anticancer research*. 2001;21(4b):3107-14. Epub 2001/11/20.
43. Roehrborn CG, Andriole GL, Wilson TH, et al. Effect of dutasteride on prostate biopsy rates and the diagnosis of prostate cancer in men with lower urinary tract symptoms and enlarged prostates in the Combination of Avodart and Tamsulosin trial. *European urology*. 2011;59(2):244-9. Epub 2010/11/26.
44. Andriole GL, Bostwick DG, Brawley OW, et al. Effect of Dutasteride on the Risk of Prostate Cancer. *New England Journal of Medicine*. 2010;362(13):1192-202.
45. Thompson IMJ, Goodman PJ, Tangen CM, et al. Long-Term Survival of Participants in the Prostate Cancer Prevention Trial. *New England Journal of Medicine*. 2013;369(7):603-10.
46. Murtola TJ, Tammela TL, Maattanen L, et al. Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial. *British journal of cancer*. 2009;101(5):843-8. Epub 2009/08/06.
47. Robinson D, Garmo H, Bill-Axelsson A, et al. Use of 5 α -reductase inhibitors for lower urinary tract symptoms and risk of prostate cancer in Swedish men: nationwide, population based case-control study. *BMJ : British Medical Journal*. 2013;346.
48. Morales EE, Grill S, Svatek RS, et al. Finasteride Reduces Risk of Bladder Cancer in a Large Prospective Screening Study. *European urology*. 2016;69(3):407-10. Epub 2015/09/01.
49. Duijnhoven RG, Straus S, Souverein PC, et al. Long-term use of 5 alpha-reductase inhibitors and the risk of male breast cancer. *Cancer Causes & Control*. 2014;25(11):1577-82.
50. Robinson D, Garmo H, Holmberg L, et al. 5-alpha reductase inhibitors, benign prostatic hyperplasia, and risk of male breast cancer. *Cancer Causes & Control*. 2015;26(9):1289-97.
51. Cooper SC, Croft S, Day R, et al. Patients with prostate cancer are less likely to develop oesophageal adenocarcinoma: could androgens have a role in the aetiology of oesophageal adenocarcinoma? *Cancer causes & control : CCC*. 2009;20(8):1363-8. Epub 2009/05/21.
52. Joint Formulary Committee. Losartan. In: Joint Formulary Committee. *British National Formulary*. [BNF online]. 2016 [cited 2017 13/04/17]; Available from: <https://www.medicinescomplete.com/mc/bnflegacy/current/PHP1219-losartan-potassium.htm>.
53. Yuan JQ, Mao C, Wong SYS, et al. Comparative Effectiveness and Safety of Monodrug Therapies for Lower Urinary Tract Symptoms Associated With Benign Prostatic Hyperplasia A Network Meta-analysis. *Medicine (Baltimore)*. 2015;94(27):7.
54. Naslund MJ, Miner M. A review of the clinical efficacy and safety of 5 alpha-reductase inhibitors for the enlarged prostate. *Clin Ther*. 2007;29(1):17-25.
55. de Jonge PJ, van Blankenstein M, Looman CW, et al. Risk of malignant progression in patients with Barrett's oesophagus: a Dutch nationwide cohort study. *Gut*. 2010;59(8):1030-6. Epub 2010/07/20.
56. Solaymani-Dodaran M, Logan RFA, West J, et al. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Gut*. 2004;53(8):1070-4.
57. Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58(5):295-300.

Tables and Figures

Table 1: Characteristics of controls and cases with gastro-oesophageal cancer

	Cases (%)	Controls (%)
Count	2,003	9,650
Median Exposure Years (IQR)	5.4 (4.0,7.6)	5.4 (4.0,7.6)
Year of Diagnosis		
1999-2003	670 (33.4)	3,238 (33.6)
2004-2007	921 (46.0)	4,416 (45.8)
2008-2011	412 (20.6)	1,996 (20.7)
Mean Age (SD)	68.2 (11.0)	67.7 (10.8)
<39	18 (0.9)	89 (0.9)
40-59	421 (21.0)	2,093 (21.7)
60-79	1,264 (63.1)	6,193 (64.2)
80+	300 (15.0)	1,275 (13.2)
Smoking status		
Non-smoker	498 (29.2)	2,871 (39.0)
Ex-smoker	649 (38.0)	2,655 (36.1)
Current smoker	561 (32.8)	1,835 (24.9)
Missing	295	2,289
Alcohol Consumption		
No	259 (17.6)	1,123 (17.4)
Low	1,071 (72.7)	4,857 (75.3)
High	143 (9.7)	474 (7.3)
Missing	530	3,196
Obesity		
Not Obese	1,716 (85.7)	7,725 (80.1)
Obese	287 (14.3)	1,925 (19.9)
Deprivation Quintile		
1 (Least Deprived)	235 (11.9)	1,113 (11.7)
2	358 (18.1)	1,713 (18.0)
3	431 (21.8)	2,092 (22.0)
4	476 (24.1)	2,319 (24.4)
5 (Most Deprived)	473 (24.0)	2,271 (23.9)
Missing	30	142
Common Comorbidities^a		
Connective Tissue Disease	853 (42.6)	4,145 (43.0)
Diabetes	229 (11.4)	1,019 (10.6)
MI	216 (10.8)	936 (9.7)
COPD	246 (12.3)	830 (8.6)
CVD	199 (9.9)	785 (8.1)
Other Medication Use		
Aspirin	611 (30.5)	2,802 (29.0)
Statin	507 (25.3)	2,316 (24.0)
Proton pump inhibitors	521 (26.0)	1,910 (19.8)

^a For brevity, only the 5 most common comorbidities are listed. The full analysis included myocardial infarction (MI), heart failure, peripheral vascular disease, cerebrovascular disease (CVD), connective tissue disease, dementia, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, diabetes, renal disease and liver disease

Table 2: 5AR inhibitor use and upper gastrointestinal cancer risk^b

Medication	Cases n,(%)	Controls n,(%)	Unadjusted OR (95% CI) ^c	Adjusted OR (95% CI) ^d	P-value trend
Gastro-oesophageal					
Any 5AR inhibitor					
Never use	1,949 (97.3)	9,343 (96.8)	Ref	Ref	0.036
Ever use	54 (2.7)	307 (3.2)	0.80 (0.59,1.08)	0.75 (0.56,1.02)	
0-11 prescriptions	31 (1.5)	150 (1.6)	0.94 (0.63,1.40)	0.89 (0.60,1.32)	
12+ prescriptions	23 (1.1)	157 (1.6)	0.66 (0.42,1.04)	0.62 (0.40,0.98)	
Finasteride					
Never use	1,956 (97.7)	9,357 (97.0)	Ref	Ref	0.013
Ever use	47 (2.3)	293 (3.0)	0.73 (0.53,1.00)	0.68 (0.50,0.94)	
0-11 prescriptions	26 (1.3)	140 (1.5)	0.86 (0.56,1.31)	0.80 (0.52,1.23)	
12+ prescriptions	21 (1.0)	153 (1.6)	0.62 (0.39,0.98)	0.58 (0.36,0.93)	
Dutasteride					
Never use	1,995 (99.6)	9,627 (99.8)	Ref	Ref	0.225
Ever use	8 (0.4)	23 (0.2)	1.53 (0.67,3.48)	1.53 (0.67,3.50)	
0-11 prescriptions	6 (0.3)	20 (0.2)	1.27 (0.50,3.25)	1.32 (0.51,3.37)	
12+ prescriptions	2 (0.1)	3 (0.0)	3.33 (0.56,19.95)	2.88 (0.48,17.47)	
Oesophageal					
Any 5AR inhibitor					
Never use	1,326 (97.2)	6,366 (96.9)	Ref	Ref	0.125
Ever use	38 (2.8)	202 (3.1)	0.85 (0.59,1.21)	0.78 (0.55,1.13)	
0-11 prescriptions	21 (1.5)	94 (1.4)	1.00 (0.62,1.63)	0.93 (0.57,1.52)	
12+ prescriptions	17 (1.2)	108 (1.6)	0.71 (0.42,1.19)	0.65 (0.38,1.11)	
Gastric					
Any 5AR inhibitor					
Never use	623 (97.5)	2,977 (96.6)	Ref	Ref	0.136
Ever use	16 (2.5)	105 (3.4)	0.71 (0.42,1.21)	0.68 (0.39,1.17)	
0-11 prescriptions	10 (1.6)	56 (1.8)	0.83 (0.42,1.66)	0.79 (0.39,1.58)	
12+ prescriptions	6 (0.9)	49 (1.6)	0.57 (0.24,1.34)	0.56 (0.24,1.32)	

^b OR: odds ratio; CI: confidence interval

^c Conditioned on year of birth, general practice and year of diagnosis

^d Additionally adjusted for use of aspirin, statins and proton pump inhibitors, and the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease and liver disease.

Table 3: Sensitivity and negative control analyses for 5AR inhibitor use^e

	Cases n,(%)	Controls n,(%)	Unadjusted OR (95% CI) ^f	Adjusted OR (95% CI) ^g
Gastro-oesophageal				
2- year exposure lag				
Never use	1,964 (98.1)	9,404 (97.5)	Ref	Ref
Ever use	39 (1.9)	246 (2.5)	0.73 (0.52,1.04)	0.68 (0.48,0.97)
Ever use ≥3 prescriptions				
Never use	1,955 (97.6)	9,384 (97.2)	Ref	Ref
Ever use	48 (2.4)	266 (2.8)	0.82 (0.59,1.12)	0.77 (0.56,1.07)
MI lifestyle adjusted^h				
Never use	1,949 (97.3)	9,343 (96.8)	Ref	Ref
Ever use	54 (2.7)	307 (3.2)	0.80 (0.59,1.08)	0.78 (0.58,1.06)
Lifestyle complete caseⁱ				
Never use	1,396 (96.8)	5,927 (96.2)	Ref	Ref
Ever use	46 (3.2)	234 (3.8)	0.85 (0.61,1.19)	0.86 (0.61,1.21)
Liver				
Any 5AR inhibitor				
Never use	289 (96.0)	1,410 (96.5)	Ref	Ref
Ever use	12 (4.0)	51 (3.5)	1.17 (0.60,2.26)	1.03 (0.50,2.11)
Pancreatic				
Any 5AR inhibitor				
Never use	396 (96.4)	1,914 (96.4)	Ref	Ref
Ever use	15 (3.6)	72 (3.6)	0.97 (0.54,1.74)	0.91 (0.50,1.69)

^e OR: odds ratio; CI: confidence interval

^f Conditioned on year of birth, general practice and year of diagnosis

^g Additionally adjusted for use of aspirin, statins and proton pump inhibitors, and the presence of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease and liver disease.

^h Additionally adjusted for smoking, alcohol consumption and obesity using multiple imputation with chained equations with age, gender and deprivation used in the imputation, separately for cases and controls, using chained ordered logit models

ⁱ Additionally adjusted for smoking, alcohol consumption and obesity

Appendices

Appendix 1: List of generic and proprietary drug names for each exposure and confounder medication

Substance Name	Drug Name
5AR Inhibitor	Avodart, Dutasteride, Finasteride, Proscar
Aspirin	Asasantin, Aspirin, Caprin, Co-codaprin, Micropirin, Migramax, Nu-Seals
Dutasteride	Dutasteride, Avodart
Finasteride	Finasteride, Proscar
Proton pump inhibitor	Esomeprazole, Heliclear, Helimet, Lansoprazole, Losec, Nexium, Omeprazole, Pantoprazole, Pariet, Protium, Rabeprazole Sodium, Zoton
Statin	Atorvastatin, Cholib, Crestor, Dorisin, Fluvastatin, Inegy, Lescol, Lipitor, Lipostat, Luvinsta, Pinmactil, Pravastatin, Rosuvastatin, Simvador, Simvastatin, Stefluvlin, Zocor