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

Running Title: 5α-reductase inhibitors and gastro-oesophageal cancer risk

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Key points:

- 5α-reductase (5AR) inhibitors have antiandrogen effects, and have been shown to decrease cancer cell proliferation and metastasis.
- We conducted a nested case-control study within the Scottish Primary Care Clinical Information Unit Research database to assess the association between 5AR inhibitor use and gastro-oesophageal cancer.
- There was some evidence of reduced gastro-oesophageal cancer risk among 5AR inhibitor users, particularly for finasteride.
- Larger epidemiological studies are required before randomised controlled trials are considered.

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Abstract

Purpose: The strong male predominance of gastro-oesophageal cancer suggests sex hormones play an important role. 5α-reductase (5AR) inhibitors have antiandrogen effects, and have been shown to decrease cancer cell proliferation and metastasis. 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 decreases were more marked among those who received at least 3 years of 5AR inhibitors (adjusted OR= 0.54; 95% CI: 0.27, 1.05; p-value=0.071) or finasteride (adjusted OR=0.49; 95% CI 0.24, 0.99; p-value=0.046).

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.

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 cancer(3-5) 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)

5α-reductase (5AR) inhibitors (including finasteride and dutasteride) are widely used(9) medications for the treatment of benign prostatic hyperplasia(10), the most common urologic disease among elderly males causing symptoms including nocturia urinary urgency.(11) Once prescribed, they are used indefinitely to reduce prostate size 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 testosterone(14), and have been linked with some hormonal side effects such as gynaecomastia.(15) Preclinical evidence that androgen receptors are present within oesophageal (16-18) and gastric cancer tumours (19-21), 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 and general practice (equivalent to US family practice centres). Controls were chosen to ensure they were registered with the general practice during the year of the cases cancer diagnosis to prevent confounding due to secular time effects or changes in coding practices. The index date was defined as the diagnosis date of the case in each matched group.

Definition of exposure

We identified 5AR inhibitor use from electronic prescription records. We used the British National Formulary to compile a list of proprietary and generic names for 5AR inhibitor medications (Appendix 1). The start of the exposure assessment window 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. The exposure assessment window ended one year before cancer diagnosis to prevent reverse causation. Additionally, the exposure assessment window 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 assessment window, were excluded from the study. We defined patients as users if they had at least one prescription during the exposure assessment window.

To enable the testing of dose-response relationships, we extracted data on the medication prescribed, number of packs/tablets and medication strength, and calculated defined daily doses (DDDs). The DDD system is a validated measure of drug consumption maintained by the World Health Organization.(28) A single DDD is the average maintenance dose per day of a drug used for its main indication in adults (e.g. BPH for finasteride). We calculated the total number of DDDs received during the exposure window and categorized patients into those receiving 0 (never users), between 1 and 365 DDDs (less than 1 years usage), between 366 and 1095 DDDs (between 1 and 3 years usage), and more than 1095 (more than 3 years usage).

Confounding factors

We identified eleven comorbidities (myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, connective tissue disease, dementia, chronic obstructive pulmonary disease, rheumatoid arthritis, diabetes, renal disease, liver disease) using Read codes recorded by the GP during the exposure assessment window.(29) This list was based on the comorbidities comprising the Charlson comorbidity index after removing rare diseases within the UK (e.g. AIDS), cancer (as those with previous cancer are excluded from the study), and those which may lie on the causal pathway between 5ARI use and gastro-oesophageal cancer (e.g. peptic ulcer). Read codes are a thesaurus of clinical terms broadly based on ICD codes and have been widely used within UK general practice since 1985.(30)

Use of aspirin, statins, and proton pump inhibitors within the exposure assessment window was identified from prescription records (Appendix 1), as associations with oesophageal and/or gastric cancer have been identified previously.(31-34) Lifestyle data including obesity (body mass index, BMI>30), smoking status (never, ex, current) and alcohol use (none, low [e.g. moderate or light drinker], high [e.g. above recommended limits, chronic alcoholism]) were also recorded in the PCCIUR data using Read codes. Lifestyle factors were assessed using the record closest to the date of cases cancer diagnosis within the exposure assessment window.

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.(35)

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 (Scottish Index of Multiple Deprivation quintile based on the postcode of the GP practice), separately for cases and controls. Briefly, this is a simulation-based approach for handling missing data which leads to valid statistical inferences.(36) 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 analyses(37) for liver (Read code: B15..) and pancreatic (Read code: B17..) cancer, as there is little evidence of androgen receptor expression in these sites(38, 39), 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.(40)

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 assessment window 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 more marked associations among patients who received at least 3 years of 5AR inhibitors (adjusted OR= 0.54; 95% CI: 0.27, 1.05; p-value=0.071) or finasteride (adjusted OR=0.49; 95% CI 0.24, 0.99; p-value=0.046). 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 were most marked in those receiving at least 3 years of 5AR inhibitors, 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.(41) 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. As almost all patients received 5ARI inhibitors for BPH we were unable to adjust for this factor in our analysis. Although this could have introduced confounding by indication in our analysis, we think this is unlikely given the lack of any evidence of an association between BPH and gastro-oesophageal cancer risk. 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 records(42), a higher proportion of oesophageal cancers were recorded the PCCIUR data than in the Scottish Cancer Registry, which could suggest some misclassification of cancer site in our study.(43) 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.(44) Our exposure data is based on prescription data so we can not be sure that patients consumed their medications. We would expect the magnitude of this potential misclassification to be small and to result in slightly attenuated estimates (as it is unlikely to act non-differentially between study arms).

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.(45-49) 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.(47) Epidemiological studies have also reported a reduced risk of bladder cancer, but not breast cancer, among 5AR inhibitor users.(50-52)

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 females(3) and prostate cancer survivors (who would have typically been treated with anti-androgen therapy).(53) 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.(35) 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)(54), have no major safety concerns, and are well tolerated by patients.(55, 56) 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.(57, 58) 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.(59) However, our findings should be replicated in larger epidemiological studies, with detailed information on tumour morphology and/or androgen receptor status, before randomised controlled trials can be considered.

Conclusions

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

Disclosures

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Conflict of Interest: he authors declare that they have no conflict of interest

Authors' contributions: All authors conceived the study. JB conducted the analysis and drafted the initial manuscript. All authors critically revised the article for intellectual content and approved the final manuscript.

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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 gastro-oesophageal cancer risk[b]

Medication	Cases n,(%)	Controls n,(%)	Unadjusted OR (95% CI)[c]	Adjusted OR (95% CI)[d]	P-value
		Gastro-oesophageal			
Any 5AR inhibitor					
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)	0.75 (0.56,1.02)	0.065
<365 DDDs	22 (1.1%)	127 (1.3%)	0.77 (0.49,1.22)	0.74 (0.47,1.17)	0.201
366 - 1095 DDDs	22 (1.1%)	100 (1.0%)	1.03 (0.64,1.65)	0.94 (0.58,1.53)	0.813
>1095 DDDs	10 (0.5%)	80 (0.8%)	0.57 (0.29,1.10)	0.54 (0.27,1.05)	0.071
Finasteride					
Never use	1,956 (97.7)	9,357 (97.0)	Ref	Ref	
Ever use	47 (2.3)	293 (3.0)	0.73 (0.53,1.00)	0.68 (0.50,0.94)	0.020
<365 DDDs	18 (0.9%)	119 (1.2%)	0.69 (0.42,1.13)	0.65 (0.39,1.07)	0.090
366 - 1095 DDDs	20 (1.0%)	95 (1.0%)	0.98 (0.60,1.61)	0.90 (0.54,1.48)	0.667
>1095 DDDs	9 (0.4%)	79 (0.8%)	0.51 (0.25,1.03)	0.49 (0.24,0.99)	0.046
Dutasteride					
Never use	1,995 (99.6)	9,627 (99.8)	Ref	Ref	
Ever use	8 (0.4)	23 (0.2)	1.53 (0.67,3.48)	1.53 (0.67,3.50)	0.312
<365 DDDs	6 (0.3%)	18 (0.2%)	1.41 (0.55,3.61)	1.45 (0.56,3.73)	0.439
366 - 1095 DDDs	1 (0.0%)	4 (0.0%)	1.21 (0.12,12.06)	1.16 (0.12,11.65)	0.899
>1095 DDDs	1 (0.0%)	1 (0.0%)	5.00 (0.31,79.94)	4.03 (0.25,65.80)	0.328
		Oesophageal			
Any 5AR inhibitor					
Never use	1,326 (97.2)	6,366 (96.9)	Ref	Ref	
Ever use	38 (2.8)	202 (3.1)	0.85 (0.59,1.21)	0.78 (0.55,1.13)	0.191
<365 DDDs	14 (1.0%)	86 (1.3%)	0.71 (0.40,1.26)	0.67 (0.38,1.20)	0.178
366 - 1095 DDDs	15 (1.1%)	64 (1.0%)	1.09 (0.61,1.95)	1.00 (0.55,1.80)	0.990
>1095 DDDs	9 (0.7%)	52 (0.8%)	0.79 (0.38,1.63)	0.72 (0.35,1.51)	0.387
		Gastric			
Any 5AR inhibitor					
Never use	623 (97.5)	2,977 (96.6)	Ref	Ref	
Ever use	16 (2.5)	105 (3.4)	0.71 (0.42,1.21)	0.68 (0.39,1.17)	0.162
<365 DDDs	8 (1.3%)	41 (1.3%)	0.91 (0.43,1.95)	0.86 (0.40,1.86)	0.701
366 - 1095 DDDs	7 (1.1%)	36 (1.2%)	0.93 (0.41,2.11)	0.87 (0.38,2.00)	0.745
>1095 DDDs	1 (0.2%)	28 (0.9%)	0.16 (0.02,1.18)	0.16 (0.02,1.20)	0.075

[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 case[i]				
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, Stefluvin, Zocor