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Testosterone therapy in relation to prostate cancer in a US commercial insurance claims database

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Abstract

Background—We conducted a study assess whether testosterone therapy (TT) alters prostate cancer risk using a large US commercial insurance research database.

Methods—From the HealthCore Integrated Research Database (HIRD^{SM}), we selected men aged 30 years or greater who were new users of TT during 2007–2015. We selected two comparison groups: 1) unexposed (matched 10:1); 2) new users of phosphodiesterase type 5 inhibitor (PDE5i). Incident prostate cancer was defined as diagnosis of prostate cancer within four-weeks following prostate biopsy. Propensity scores and inverse probability of treatment weights were used in Poisson regression models to estimate adjusted incidence rates, incidence rate ratios (IRRs) and 95% confidence intervals (CI). Subgroup analyses included stratification by prostate cancer screening, hypogonadism, and follow-up time.

Results—The adjusted prostate cancer IRR was 0.77 (95%CI: 0.68, 0.86) when comparing TT with the unexposed group and 0.85 (95%CI: 0.79, 0.91) in comparison with the PDE5i group. Inverse associations between TT and prostate cancer were observed in a majority of subgroup analyses, although in both comparisons estimates generally attenuated with increasing time following initial exposure. Amongst TT users, duration of exposure was not associated with prostate cancer.

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FINANCIAL DISCLOSURES

DCB, LEP, and SL are employees of HealthCore, Inc. a subsidiary of Anthem Inc. PTC is a former employee of HealthCore, Inc. a subsidiary of Anthem Inc. and holds stock in Anthem Inc.

DATA ANALYSIS INTEGRITY

DCB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conclusions—Men who received TT did not have a higher rate of prostate cancer compared with the unexposed or PDE5i comparison groups. The inverse association between TT and prostate cancer could be the result of residual confounding, contraindication bias, or undefined biologic effect.

Impact—This study suggests that limited TT exposure does not increase risk of prostate cancer in the short-term.

Keywords

Androgens; Epidemiology; Incidence; Prostatic Neoplasms; Risk; Testosterone

Introduction

In recent decades, testosterone therapy (TT) has dramatically increased in the United States[1], though trends have recently plateaued and slightly decreased.[2] TT is approved by the United States Food and Drug Administration for men with hypogonadism—confirmed morning serum testosterone of <300 ng/dL—due to disorders of the testicles, pituitary gland, or brain. There are few specific signs or symptoms of hypogonadism (incomplete/delayed sexual development, body hair loss, very small testes) and the majority of TT is prescribed for non-specific signs or symptoms (e.g., fatigue, reduced muscle bulk, increased body fat) that are age-related.[3] Although testosterone trials have provided some evidence that TT in men older than 65 years may aid some of the maladies associated with hypogonadism (sexual function, physical function, mood, and depressive symptoms),[4] no trial was designed to evaluate risk of prostate cancer, and most observational studies of this relation have been underpowered.

In 1941, Huggins and Hodges showed that prostate cancer was androgen-dependent[5] and this led to the development of androgen deprivation therapy as well as a plethora of basic, animal and epidemiologic studies of sex steroid hormones and prostate cancer. These studies have clearly demonstrated the importance of the androgen pathway in prostate cancer *progression*, and the largest epidemiologic study to date of prediagnostic circulating hormones has recently found that men with very low endogenous testosterone may have a reduced risk of developing prostate cancer.[6] Whether exogeneous testosterone alters risk of prostate cancer is largely unknown. Exogeneous supplementation of a single metabolite within a complex biochemical pathway with a multitude of phenotypic effects deserves careful scientific study that cannot be substituted with studies focused on endogenous androgens.[7,8] Therefore, we conducted a study using a large U.S. commercial insurance research database to assess whether TT was associated with risk of prostate cancer.

Material and Methods

The HealthCore Integrated Research Database (HIRD^{SM}) is a repository of administrative claims beginning in 2006 with linked medical, pharmacy and eligibility data for approximately 59 million researchable covered lives (at the time of this study) with a median continuous membership of 3 years enrolled in 14 commercial health plans across the US.[9,10] From the HIRD, we selected men aged 30 years or greater with medical and pharmacy

coverage who were newly dispensed a TT prescription (see Supplemental Table 1 for codes) during 1/1/ 2007–7/31/2015. We selected two control groups to which we compared the TT exposed group: 1) unexposed men; and 2) men dispensed one or more phosphodiesterase type 5 inhibitor (PDE5i) prescriptions. Our study design included the PDE5i group as to provide a comparison with a group of men who were willing, able, and motivated to seek medical care when symptomatic and fill prescriptions. In addition, PDE5i medications are not associated with risk of prostate cancer.[11] The unexposed comparison group was matched with a target ratio of 10:1 using date of birth (+/− 183 days), outpatient physician visit (+/− 60 days of TT subject's dispensed prescription date), and US region of residence. For the PDE5i comparison group, we selected all men newly dispensed a PDE5i during the study period. Men of comparison groups who were dispensed TT during follow-up were right-censored and entered, at that time, into the TT exposed group. Once exposed to TT, men remained in the TT group until event date or right-censoring. Male sex was determined by both self-report and a lack of ICD-9 codes indicating transgenderism or GID.

Index dates were: date of first dispensing of TT for exposed subjects; date of the matched outpatient physician visit for unexposed comparison group subjects; and date of first dispensing of PDE5i for the PDE5i comparison group subjects. We required a *minimum* 12-month continuous enrollment prior to index date. Men were excluded if, in the pre-index period, there was evidence suggesting they may have had prevalent prostate cancer. Thus we excluding men that had any code indicating prostate cancer, prostate cancer-specific treatment, elevated PSA (or lab test showing >4ng/ml), prostate ultrasound guidance, prostate biopsy, medications containing estrogen, transgenderism or GID (any timepoint), prostatectomy, congenital absence of prostate, TT dispensing, or PDE5i dispensing or erectile dysfunction (TT vs. unexposed comparison only) (see Supplemental Tables 1 and 2 for codes). Matching of unexposed men occurred after exclusions had been applied to maximize algorithm efficiency. All subjects were followed from index date until the earliest of: end of study (7/31/2015), health plan disenrollment, estrogen use, or prostate cancer (outcome).

TT exposure durations were calculated as days supplied plus a bridge rule to account for non-adherence and differences in dispensing and use. Based on exploratory analysis of missing days' supply (for oral, topical, patch, implant) and recommended usage (for injection), the bridge rule for all TT formulations was 30 days, except for mail-order TT formulations with a bridge rule of 90 days.

Incident prostate cancer was defined as diagnosis of prostate cancer (ICD-9: 185.xx) within four-weeks following a prostate biopsy (see Supplemental Table 3 for codes) using biopsy date as date of diagnosis. To assess the validity of this definition, study eligible men who had ever lived in Georgia were submitted to the Georgia Comprehensive Cancer Registry (GCCR) for probabilistic linkage.[9] We also assessed metastatic prostate cancer, using the Dolan algorithm.[12] This study was approved by the New England IRB and the Georgia Department of Public Health IRB. HIRD^{SM} data are accessible under contract with HealthCore Inc.

Statistical analysis

We first calculated unadjusted matched/crude prostate cancer incidence rates and 95% confidence intervals (CI) for each of the exposure groups. We then used logistic regression to compute propensity scores[13] and estimated standardized differences to assess covariate balance.[14] Propensity score models included age, region, index date, pre-index time, and the following pre-index period covariates: Deyo-Charlson co-morbidity index, obesity, benign prostatic hyperplasia, family history of prostate cancer, inflammatory diseases of the prostate, other prostate disorders, urinary symptoms, osteoarthritis, biologic treatment, antineoplastics treatment, anti-TNF treatment, alpha-reductase treatments, HIV therapy, presence of any oncologist visit, prostate cancer screening, annual examinations, ER utilization during the past year, and inpatient hospitalization utilization during the past year. Inverse probability of treatment weights were used in Poisson regression models to estimate adjusted prostate cancer incidence rates, incidence rate ratios (IRRs), and their respective 95% CIs using doubly robust estimation.[15]

We conducted subgroup analyses by pre-index prostate cancer screening, hypogonadism, and or benign prostatic hyperplasia. We assessed associations by amount of pre-index enrollment time, calendar year of index date and follow-up time since index date.

Amongst the TT group, we estimated IRRs by time on TT, number of TT refills, route of administration, and change in circulating testosterone concentration during TT.

Using the cancer registry data from GCCR as a gold standard, we estimated the positive predictive value (PPV) and sensitivity of the prostate cancer case definition in each group, and corrected effect estimates for outcome misclassification.[16]

Results

Cohort characteristics

There were 76,159 men in the TT group who were matched with 721,326 unexposed men (Table 1, Supplemental Table 4). For the PDE5i comparison, there were 113,041 TT men available for comparison with 147,620 PDE5i users. Median TT exposure time was 65 days. The TT vs unexposed groups were closely matched on age and region (Table 1). Propensity score weighting achieved good comparability ($d < |0.20|$) for both comparison groups (Table 1). Fatigue, hypogonadism, and psychosexual dysfunction were not included in the PS due to convergence issues. We conducted sensitivity analyses in which we additionally controlled for these factors. Our prostate cancer case definition had high sensitivity (91.2%, 95%CI: 87.7, 94.0%) and PPV (81.7%, 95%CI: 77.9, 85.0%) that did not differ substantially by analytic group.[9]

Comparison of TT with unexposed group

We identified 335 prostate cancers in 178,704 person-years in the TT group and 4,133 cases in 1.6 million person-years in the unexposed group (Table 2). Unadjusted age- and region-matched prostate cancer incidence rates were 187.5 per 100,000 person-years in the TT group and 245.5 in the unexposed group, resulting in an IRR of 0.76 (95%CI: 0.68, 0.85,

Figure 1). This estimate was similar to the propensity score adjusted IRR of 0.77 (95%CI: 0.68, 0.86). An unmeasured confounder would have to have an IRR of 1.92 with both TT and prostate cancer to explain away this observed association.[17,18] In analyses further adjusted for fatigue, hypogonadism, and psychosexual dysfunction, results were slightly attenuated with an adjusted IRR of 0.86 (95%CI: 0.74, 1.00), while results were similar when further adjusting for outcome misclassification (adjusted IRR=0.75, 95%CI: 0.67, 0.84). Inverse associations between TT and prostate cancer were also observed when stratified by prostate cancer screening, hypogonadism, or benign prostatic hyperplasia in the pre-index period (Table 2). Effect estimates did not differ appreciably by duration of pre-index time, although incidence rates did decrease in both TT and unexposed groups which appeared to be related to decreasing prostate cancer incidence by calendar year. Effect estimates attenuated with time from index date, from stronger estimates of 0.51 (<6 months), to 0.72 (6–12 months), to 1.03 (12–24 months). The last period analyzed, of 24 months and greater post index, had an IRR of 0.74.

Comparison of TT with PDE5i group

Similar results were observed when comparing TT with PDE5i users (Table 3). The crude IRR was 0.71 (95%CI: 0.64, 0.76, Figure 2) and the propensity score adjusted IRR was 0.85 (95%CI: 0.79, 0.91). Results were similar to the overall analyses, when further adjusting for unbalanced factors not included in the propensity score (adjusted IRR=0.87, 95%CI: 0.80, 0.94), and when adjusting for outcome misclassification (adjusted IRR=0.91, 95%CI: 0.85, 0.98). Subgroup analyses using the PDE5i comparison group were mostly similar to those using the unexposed comparison group, including attenuation to the null with increased time since index date with sequential 6-month period IRRs of 0.53, 0.83, 0.88 and 0.96. One difference in the PDE5i analyses, to that of the unexposed group analyses, was an attenuated association with increased pre-index time, with an adjusted IRR of 1.06 (95%CI=0.85, 1.33) among individuals with at least 5 years.

Assessments within TT users

Among men who received TT, duration of therapy, number of prescription fills, and route of administration were not associated with prostate cancer (Table 4). Within the TT group, men who experienced more extreme changes in circulating testosterone levels (increased or decreased) had inverse associations with prostate cancer, relative to men closer to the average change.

Associations with metastatic prostate cancer

There were 17 prostate cancer cases with metastatic disease at diagnoses during 178,704 person-years in the TT group and 195 cases during 1.7 million person-years in the unexposed group providing an adjusted IRR of 0.77 (95%CI:0.46, 1.29). For the PDE5i comparison, the TT group had 28 metastatic prostate cancer cases diagnosed during 267,795 person-years and the PDE5i group had 50 cases during 370,507 person-years providing an adjusted IRR of 1.07 (95%CI:0.77, 1.49).

Analyses of testosterone and prostate-specific antigen

In men who received TT for whom we had testosterone laboratory data, circulating testosterone concentrations increased from a pre-index median of 237 ng/dL to 351 ng/dL (Supplemental Table 5). This increase didn't vary by age but did vary by pre-index circulating testosterone concentration, with greater increases observed for men with lower pre-index concentrations. Circulating prostate-specific antigen (PSA) concentrations, in the subset of men we had such data for, were not largely different between TT and comparison groups (Supplemental Tables 6 and 7). PSA concentrations in TT men increased by a median change of 0.1 ng/mL when comparing pre-index with post-index periods, while the median changes were zero in the comparison groups.

Discussion

In this study of a large healthcare claims database, men who received TT had a lower rate of prostate cancer compared with unexposed men or men receiving a PDE5i. The inverse association between TT and risk of prostate cancer was observed for a majority of subgroup analyses—including stratifications by prostate cancer screening, hypogonadism, and benign prostatic hyperplasia in the pre-index period—yet the association between TT and reduced prostate cancer risk generally attenuated with increased time following initial exposure.

The majority of prior studies to have assessed TT in relation to prostate cancer have had small populations with imprecise effect estimates.[19–25] There has been only two previous studies that have had large numbers of topical TT users and that have had sufficient prostate cancer cases to provide precise estimates of association. The first was a study of cases from the National Prostate Cancer Register of Sweden compared with matched controls.[26] This study included 284 prostate cancer cases who had previously received a TT prescription and found no association between TT and prostate cancer (odds ratio (OR)=1.03, 95% CI:0.90, 1.17). The second study was a retrospective cohort of 147,593 U.S. male Veterans that had one or more laboratory test-based flags for hypogonadism.[27] Within this cohort, 58,617 received TT, and a total of 1,439 prostate cancers were diagnosed. The adjusted hazard ratio (HR) for the association between TT and prostate cancer was 0.90 (95% CI:0.81, 1.01). Associations in these two studies did not vary by route of TT administration, time between therapy and risk period, or duration of treatment.

The Swedish study[26], discussed above, also observed that TT was positively-associated with more favorable-risk prostate cancer (OR=1.35, 95%CI:1.16, 1.56) and negatively-associated with aggressive cancer (OR=0.50, 95%CI:0.37, 0.67). The positive association with favorable-risk prostate cancer was already apparent and strongest within the first year of TT, leading the authors to suggest detection bias. The negative association with aggressive cancer only became apparent after the first year of TT, which the authors speculated may be the result of hypogonadal-genesis of poorly differentiated prostate cancer that is reversible with short-term TT. However, the study of U.S. Veterans found no association between TT use and aggressive prostate cancer (HR=0.89; 95% CI:0.70, 1.13). Although we could not assess prostate cancer stage and grade in this study, our findings of inverse associations between TT and the outcomes of metastatic prostate cancer and overall prostate cancer incidence contrast with the Swedish study and are more in line with the U.S. Veterans study.

There have been two prior studies of intravenous TT in older men of the SEER-Medicare database. The first found evidence for an inverse association with high grade prostate cancer (OR=0.84, 95%CI:0.67, 1.05) and no association with the high-risk disease proxy of receipt of primary androgen deprivation therapy (OR=0.97, 95% CI:0.74, 1.30)[28]. The second study found no increased risk of higher grade or higher stage prostate cancer.[29] In fact, this latter SEER-Medicare study—which assessed TT exposure retrospectively amongst a cohort of confirmed prostate cancer cases—found that men who were TT-exposed were more likely to be diagnosed with moderately-differentiated than less-differentiated prostate cancer, and were more likely to be diagnosed with clinical stage T3 over T4 prostate cancer, each relative to prostate cancer cases who had not previously received TT. Combined with our findings herein, the results of these four large observational studies support a hypothesis of no increased risk of prostate cancer amongst men who receive TT and acknowledge the possibility that an inverse association may exist.[26]

An inverse association between TT and prostate cancer could be attributable to residual confounding. For example, very low endogenous free testosterone levels could decrease the risk of prostate cancer[6] and increase the likelihood of receiving TT; although it is important to note that, amongst those diagnosed with hypogonadism, ~80% of TT prescriptions are based on tests of testosterone and ~15% are based on tests of free testosterone.[27] Another example is diabetes has been inversely associated with prostate cancer[30] and correlates with hypogonadism, increasing the likelihood of TT.[31] Residual confounding would have to be strong, given our estimate that an unmeasured confounder would have to have an IRR of 1.92 with both TT and with prostate cancer to account for the TT-prostate cancer association. However, residual confounding is supported by attenuation to the null with increased pre-index time in the PDE5i comparison, which increases the likelihood of ascertaining confounding factors. Contraindication bias could also explain the observed association, whereby factors and symptoms perceived by the physician to be related with a higher risk of prostate cancer (e.g., family history, borderline PSA, urogenital symptoms) may reduce the likelihood of the physician prescribing TT,[32] which would have the effect of causing a decreased prostate cancer incidence rate in the TT group and increased rate in the unexposed group. Lastly, the inverse association between TT and prostate cancer could be the result of a biological effect, such as causing an increase in pro-apoptotic signaling during early prostate carcinogenesis.[33] Any biological effect would have to be able to explain the immediacy of the observed association and the general attenuation of effect over the 2-year period following initial exposure. It is true that the estimate with the unexposed comparison was similar in the last time period (adjusted $IRR_{\geq 24\ months}$=0.74, 95%CI:0.62, 0.88) as the overall association, but the equivalent estimate with the PDE5i comparison group was null (adjusted $IRR_{\geq 24\ months}$=0.96, 95%CI:0.87, 1.07), a pattern which mirrors the results of another recent study.[25] Lastly, there was no evidence that length of time of TT exposure altered the rate of prostate cancer within the TT group.

Strengths of our study include use of a large database that enabled assessment of a younger population (unlike SEER-Medicare), and use of a validated prostate cancer definition with high sensitivity (91.2%) and positive predictive value (81.7%) that were similar between comparison groups, thus mitigating outcome misclassification bias.[9] Limitations include lack of cancer stage and grade, lack of an ability to offer a precise estimate of TT in relation

to metastatic or aggressive prostate cancer, reliance on claims/payer data to infer clinical variables, availability of PSA and testosterone concentrations for only a subset of subjects, data are not informative about long latency between exposure and outcome, and limited ability or inability to assess differences by age at initial TT exposure, race, specific forms/regimens of TT, or hypogonadal subtype.

This study provides evidence that men who receive TT do not have a higher rate of prostate cancer than unexposed men or men receiving PDE5i. The inverse association between TT and prostate cancer could be the result of residual confounding, contraindication bias, or undefined biologic effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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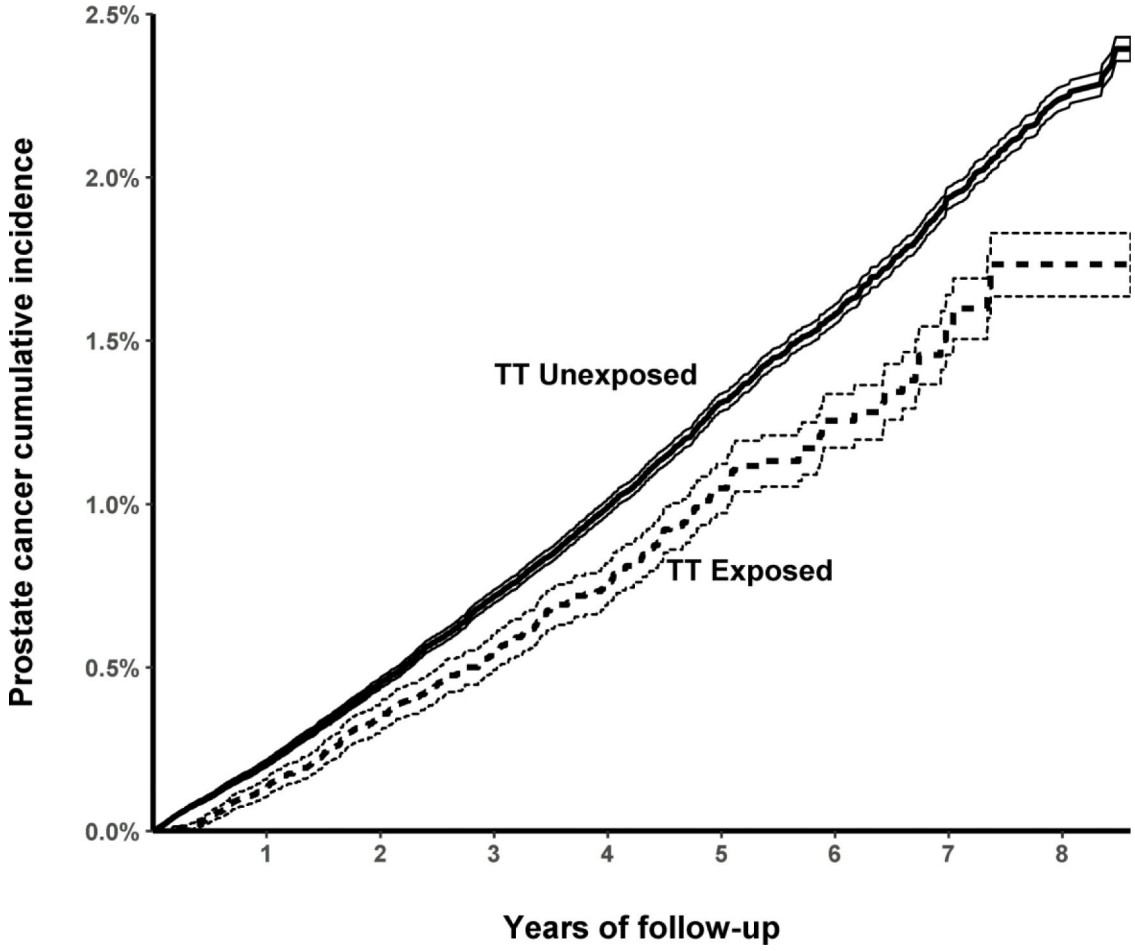

Figure 1: Crude cumulative incidence of prostate cancer comparing TT exposed group with unexposed group

The x-axis shows the years of follow-up and the y-axis shows the crude cumulative incidence of prostate cancer as a percentage of the denominator. The crude cumulative incidence for the TT exposed group is shown as a dashed line, with adjacent smaller-width, dashed lines representing 95 percent confidence intervals. The crude cumulative incidence for the unexposed group is shown as a solid line, with adjacent smaller-width, solid lines representing 95 percent confidence intervals.

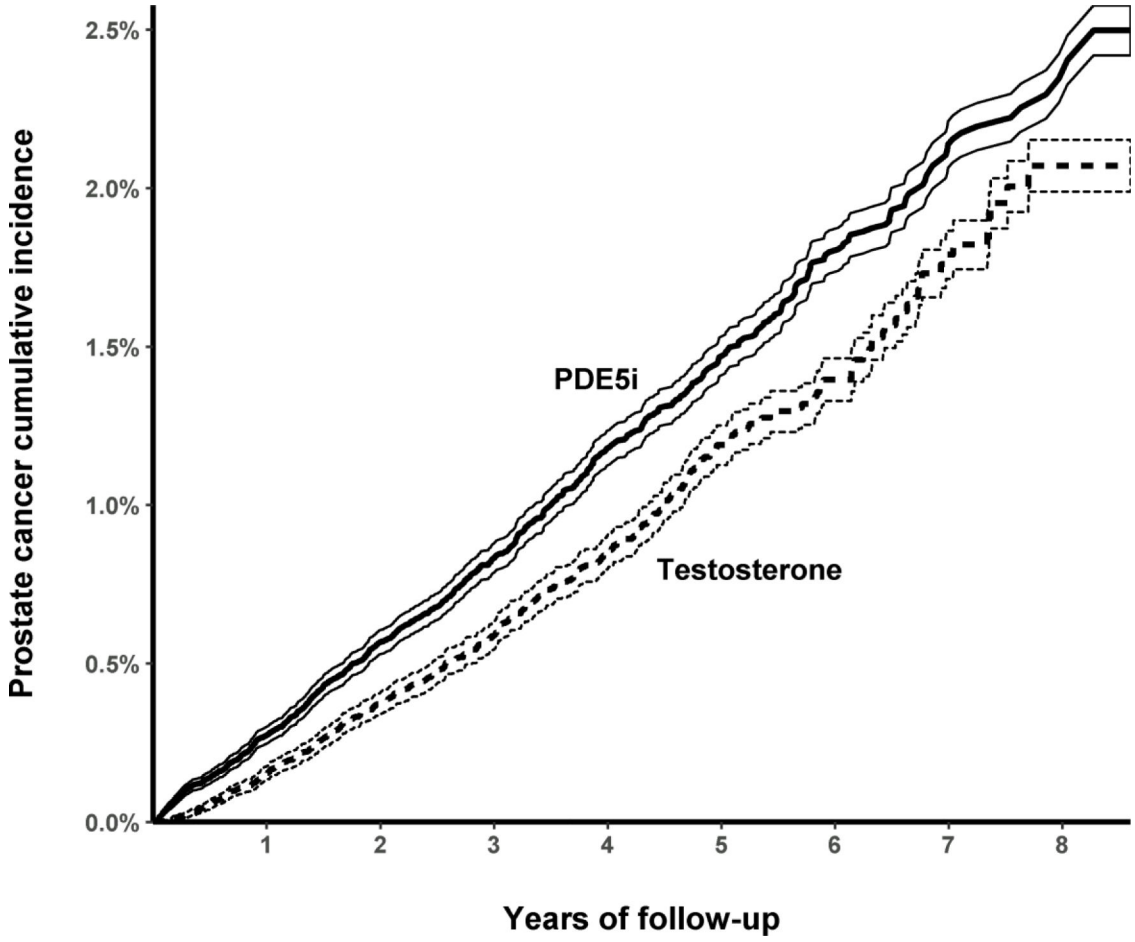

Figure 2: Crude cumulative incidence of prostate cancer comparing TT exposed group with PDE5i comparison group

The x-axis shows the years of follow-up and the y-axis shows the crude cumulative incidence of prostate cancer as a percentage of the denominator. The crude cumulative incidence for the TT exposed group is shown as a dashed line, with adjacent smaller-width, dashed lines representing 95 percent confidence intervals. The crude cumulative incidence for the PDE5i comparison group is shown as a solid line, with adjacent smaller-width, solid lines representing 95 percent confidence intervals.

Table 1.

Characteristics of members in each treatment group before propensity score weighting

Characteristic	TT	Unexposed	Standardized Difference	Standardized Difference after PS	TT	PDE5i	Standardized Difference	Standardized Difference after PS
	n (%) / *median (IQR)*	n (%) / *median (IQR)*			n (%) / *median (IQR)*	n (%) / *median (IQR)*		
Number of men	76,159 (100.0)	721,326 (100.0)	–	–	113,041 (100.0)	147,620 (100.0)	–	–
Age at index date	*50.0 (15.0)*	*50.0 (15.0)*	*−0.005*	*0.004*	*51.0 (14.0)*	*53.0 (13.0)*	*−0.096*	*0.005*
30–44	22,751 (29.9)	214,074 (29.7)	0.004	−0.014	30,354 (26.9)	30,753 (20.8)	0.142	0.055
45–64	46,550 (61.1)	442,171 (61.3)	−0.004	0.013	71,752 (63.5)	105,509 (71.5)	−0.171	−0.122
65+	6,858 (9.0)	65,081 (9.0)	−0.001	−0.001	10,935 (9.7)	11,358 (7.7)	0.070	0.117
Region								
MidWest	20,263 (26.6)	191,169 (26.5)	0.002	0.002	29,103 (25.7)	20,649 (14.0)	0.298	0.001
Northeast	6,204 (8.1)	59,619 (8.3)	−0.004	−0.008	10,382 (9.2)	34,967 (23.7)	−0.399	0.004
South	31,166 (40.9)	292,337 (40.5)	0.008	−0.001	46,577 (41.2)	49,856 (33.8)	0.154	−0.007
West	17,246 (22.6)	166,035 (23.0)	−0.009	0.005	24,743 (21.9)	35,068 (23.8)	−0.044	0.008
Other	1,280 (1.7)	12,166 (1.7)	−0.000	−0.001	2,236 (2.0)	7,080 (4.8)	−0.156	−0.011
Calendar year of index date								
2007 – 2009	21,625 (28.4)	215,048 (29.8)	−0.031	−0.003	33,080 (29.3)	68,183 (46.2)	−0.355	0.014
2010 – 2012	33,662 (44.2)	318,694 (44.2)	0.000	0.002	49,842 (44.1)	54,855 (37.2)	0.142	−0.005
2013 – 2015	20,872 (27.4)	187,584 (26.0)	0.032	0.001	30,119 (26.6)	24,582 (16.7)	0.244	−0.010
Duration of pre-index period								
5 or more years	18,885 (24.8)	209,139 (29.0)	−0.095	0.041	28,870 (25.5)	26,077 (17.7)	0.192	−0.018
4–4.99 years	9,323 (12.2)	91,690 (12.7)	−0.014	0.002	14,170 (12.5)	15,816 (10.7)	0.057	0.011
3–3.99 years	11,966 (15.7)	115,617 (16.0)	−0.009	−0.024	18,004 (15.9)	22,193 (15.0)	0.025	0.004
2–2.99 years	17,510 (23.0)	150,982 (20.9)	0.050	−0.018	25,658 (22.7)	37,559 (25.4)	−0.064	0.004
1–1.99 years	18,475 (24.3)	153,898 (21.3)	0.070	−0.009	26,339 (23.3)	45,975 (31.1)	−0.177	0.002
In the year prior to index date								
History of medical diagnoses								

Characteristic	TT	Unexposed	Standardized Difference	Standardized Difference after PS	TT	PDE5i	Standardized Difference	Standardized Difference after PS
	n (%) / *median (IQR)*	n (%) / *median (IQR)*			n (%) / *median (IQR)*	n (%) / *median (IQR)*		
Family history of prostate cancer	462 (0.6)	4,300 (0.6)	0.001	0.001	797 (0.7)	870 (0.6)	0.014	−0.003
Fatigue	42,639 (56.0)	172,488 (23.9)	0.693	0.669	59,380 (52.5)	31,501 (21.3)	0.683	0.517
Hyperplasia of prostate	10,126 (13.3)	78,307 (10.9)	0.075	0.013	17,596 (15.6)	19,340 (13.1)	0.070	−0.005
Hypogonadism	32,246 (42.3)	32,928 (4.6)	0.996	0.948	49,047 (43.4)	8,318 (5.6)	0.977	0.890
Inflammatory disease of prostate	3,519 (4.6)	26,187 (3.6)	0.050	0.012	5,831 (5.2)	5,832 (4.0)	0.058	−0.003
Obesity	15,670 (20.6)	88,245 (12.2)	0.227	0.014	23,427 (20.7)	16,305 (11.0)	0.267	−0.007
Osteoporosis	1,770 (2.3)	8,892 (1.2)	0.083	0.009	2,553 (2.3)	1,434 (1.0)	0.102	−0.019
Other diseases of prostate	1,528 (2.0)	12,162 (1.7)	0.024	0.006	2,505 (2.2)	2,765 (1.9)	0.024	−0.001
Psychosexual dysfunction	5,394 (7.1)	13,104 (1.8)	0.257	0.258	10,012 (8.9)	12,525 (8.5)	0.013	−0.003
Pulmonary hypertension	483 (0.6)	3,903 (0.5)	0.012	0.001	731 (0.6)	598 (0.4)	0.033	0.017
Urinary symptoms	10,078 (13.2)	77,553 (10.8)	0.076	0.015	16,351 (14.5)	16,191 (11.0)	0.105	−0.006
Prescription medications								
5–alpha reductase inhibitors	4,980 (6.5)	35,075 (4.9)	0.072	0.013	8,040 (7.1)	8,343 (5.7)	0.060	−0.003
Antineoplastics and adjunctive therapies	610 (0.8)	5,663 (0.8)	0.002	0.002	893 (0.8)	881 (0.6)	0.023	−0.003
AntiTNFs and adjunctive therapies	594 (0.8)	5,649 (0.8)	−0.000	0.002	896 (0.8)	876 (0.6)	0.024	−0.001
Biologics	917 (1.2)	8,224 (1.1)	0.006	0.007	1,347 (1.2)	1,536 (1.0)	0.014	−0.006
HIV antiretroviral therapy	1,052 (1.4)	3,588 (0.5)	0.092	0.001	1,385 (1.2)	912 (0.6)	0.064	−0.013
Statins	27,933 (36.7)	217,569 (30.2)	0.138	0.016	43,525 (38.5)	51,344 (34.8)	0.077	−0.000
Comorbidity measures								
Deyo Charlson comorbidity index	*0.0 (1.0)*	*0.0 (1.0)*	*0.130*	*0.009*	*0.0 (1.0)*	*0.0 (1.0)*	*0.182*	*−0.014*
0	41,673 (54.7)	446,069 (61.8)	−0.145	−0.065	59,775 (52.9)	89,517 (60.6)	−0.157	−0.018
1	18,483 (24.3)	154,736 (21.5)	0.067	0.057	28,148 (24.9)	34,072 (23.1)	0.043	0.028

Characteristic	TT	Unexposed	Standardized Difference	Standardized Difference after PS	TT	PDE5i	Standardized Difference	Standardized Difference after PS
	n (%) / *median (IQR)*	n (%) / *median (IQR)*			n (%) / *median (IQR)*	n (%) / *median (IQR)*		
2+	16,003 (21.0)	120,521 (16.7)	0.110	0.020	25,118 (22.2)	24,031 (16.3)	0.151	−0.008
Enhanced Elixhauser index	*2.0 (2.0)*	*1.0 (3.0)*	*0.250*	*0.055*	*2.0 (3.0)*	*1.0 (3.0)*	*0.307*	*0.038*
0	13,717 (18.0)	211,929 (29.4)	−0.270	−0.199	18,994 (16.8)	37,788 (25.6)	−0.216	−0.097
1	18,289 (24.0)	185,671 (25.7)	−0.040	0.007	26,015 (23.0)	40,004 (27.1)	−0.094	−0.010
2+	44,153 (58.0)	323,726 (44.9)	0.264	0.166	68,032 (60.2)	69,828 (47.3)	0.261	0.088
Enhanced Charlson comorbidity index	*0.0 (1.0)*	*0.0 (1.0)*	*0.134*	*0.011*	*1.0 (2.0)*	*0.0 (1.0)*	*0.191*	*−0.011*
0	38,953 (51.1)	422,280 (58.5)	−0.149	−0.071	55,809 (49.4)	84,852 (57.5)	−0.163	−0.025
1	18,733 (24.6)	158,990 (22.0)	0.060	0.057	28,292 (25.0)	34,732 (23.5)	0.035	0.030
2+	18,473 (24.3)	140,056 (19.4)	0.117	0.028	28,940 (25.6)	28,036 (19.0)	0.159	−0.001
Service utilization								
Had a specialist visit (urologist, oncologist, pathologist)	13,989 (18.4)	97,261 (13.5)	0.134	0.051	24,401 (21.6)	24,080 (16.3)	0.135	0.040
Had an annual wellness visit	10,083 (13.2)	78,909 (10.9)	0.071	0.045	11,466 (10.1)	17,807 (12.1)	−0.061	−0.055
Had a prostate cancer screen	5,625 (7.4)	40,197 (5.6)	0.074	0.046	6,660 (5.9)	8,663 (5.9)	0.001	−0.039
Outpatient visits	6.0 (12.0)	3.0 (7.0)	0.349	0.093	5.0 (9.0)	3.0 (7.0)	0.161	0.002
0	10,661 (14.0)	147,900 (20.5)	−0.173	−0.105	18,565 (16.4)	31,101 (21.1)	−0.119	−0.037
1	5,610 (7.4)	83,078 (11.5)	−0.142	−0.107	10,590 (9.4)	15,924 (10.8)	−0.047	−0.012
2+	59,888 (78.6)	490,348 (68.0)	0.243	0.161	83,886 (74.2)	100,595 (68.1)	0.134	0.040
ER visits	*0.0 (0.0)*	*0.0 (0.0)*	*0.133*	*0.039*	*0.0 (0.0)*	*0.0 (0.0)*	*0.055*	*0.002*
0	68,116 (89.4)	673,332 (93.3)	−0.140	−0.107	104,044 (92.0)	137,897 (93.4)	−0.053	−0.005
1	6,654 (8.7)	41,657 (5.8)	0.114	0.089	7,729 (6.8)	8,529 (5.8)	0.044	0.006
2+	1,389 (1.8)	6,337 (0.9)	0.082	0.060	1,268 (1.1)	1,194 (0.8)	0.032	−0.003
Inpatient visits	*0.0 (0.0)*	*0.0 (0.0)*	*0.102*	*0.030*	*0.0 (0.0)*	*0.0 (0.0)*	*0.049*	*0.005*
0	71,734 (94.2)	696,286 (96.5)	−0.111	−0.081	108,037 (95.6)	142,556 (96.6)	−0.051	−0.006
1	3,554 (4.7)	20,812 (2.9)	0.094	0.066	4,156 (3.7)	4,329 (2.9)	0.042	0.004

Characteristic	TT	Unexposed	Standardized Difference	Standardized Difference after PS	TT	PDE5i	Standardized Difference	Standardized Difference after PS
	n (%) / *median (IQR)*	**n (%) / *median (IQR)***			**n (%) / *median (IQR)***	**n (%) / *median (IQR)***		
2+	871 (1.1)	4,228 (0.6)	0.060	0.049	848 (0.8)	735 (0.5)	0.032	0.006
Office visits	*3.0 (5.0)*	*1.0 (3.0)*	*0.431*	*0.114*	*2.0 (3.0)*	*2.0 (3.0)*	*0.196*	*−0.003*
0	13,959 (18.3)	195,665 (27.1)	−0.211	−0.133	24,617 (21.8)	40,126 (27.2)	−0.126	−0.026
1	11,643 (15.3)	165,353 (22.9)	−0.195	−0.154	22,226 (19.7)	32,492 (22.0)	−0.058	−0.020
2+	50,557 (66.4)	360,308 (50.0)	0.338	0.239	66,198 (58.6)	75,002 (50.8)	0.156	0.038

Abbreviations: ER, emergency room; HIV, human immunodeficiency virus; IQR, inter-quartile range; PDE5i, phosphodiesterase type 5 inhibitor; PS, propensity score; PSA, prostate-specific antogen; TNF, tumor necrosis factor; TT, testosterone therapy.

Table 2.

Incidence rates and incidence rate ratios for prostate cancer for TT and unexposed groups and by pre-index characteristics

Category	TT				Unexposed				Age- and region-matched Incidence Rate Ratio (95%CI)	PS Adjusted Incidence Rate Ratio (95%CI)
	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)		
Overall	76,159	335	178,704	187.5 (168.4, 208.6)	721,326	4,133	1,683,470	245.5 (238.1, 253.1)	0.76 (0.68, 0.85)	0.77 (0.68, 0.86)
Subgroups										
PSA test in pre-index period										
Yes	14,546	55	32,875	167.3 (128.4, 217.9)	59,069	407	130,239	312.5 (283.6, 344.4)	0.54 (0.41, 0.71)	0.54 (0.40, 0.72)
No	61,613	280	145,829	192.0 (170.8, 215.9)	662,257	3,726	1,553,231	239.9 (232.3, 247.7)	0.80 (0.70, 0.90)	0.80 (0.70, 0.91)
Prostate cancer screen in the pre-index period										
Yes	20,713	100	47,903	208.8 (171.6, 254.0)	162,966	1,222	350,320	348.8 (329.8, 368.9)	0.60 (0.49, 0.73)	0.60 (0.48, 0.74)
No	55,446	235	130,801	179.7 (158.1, 204.2)	558,360	2,911	1,333,150	218.4 (210.6, 226.4)	0.82 (0.72, 0.94)	0.82 (0.71, 0.95)
No PSA test and no PCa screen in the pre-index period	45,541	197	107,982	182.4 (158.7, 209.8)	521,186	2,655	1,248,121	212.7 (204.8, 221.0)	0.85 (0.74, 0.99)	0.86 (0.73, 1.01)
Hypogonadism diagnosis in the pre-index period										
Yes	32,246	123	72,994	168.5 (141.2, 201.1)	32,928	124	45,322	273.6 (229.4, 326.3)	0.62 (0.48, 0.79)	0.63 (0.49, 0.82)
No	43,913	212	105,710	200.5 (175.3, 229.4)	688,398	4,009	1,638,148	244.7 (237.3, 252.4)	0.81 (0.71, 0.94)	0.84 (0.73, 0.98)
Benign prostatic hyperplasia in the pre-index period										
Yes	10,126	74	25,676	288.2 (229.5, 362.0)	78,307	891	185,506	480.3 (449.8, 512.9)	0.60 (0.47, 0.76)	0.55 (0.43, 0.71)
No	66,033	261	153,028	170.6 (151.1, 192.6)	643,019	3,242	1,497,965	216.4 (209.1, 224.0)	0.79 (0.69, 0.89)	0.82 (0.71, 0.94)
Pre-index enrollment time										
≥2 years	51,876	212	121,050	175.1 (153.1, 200.4)	525,550	2,702	1,129,304	239.3 (230.4, 248.5)	0.73 (0.63, 0.84)	0.72 (0.62, 0.84)
≥3 years	36,818	146	83,444	175.0 (148.8, 205.8)	386,530	1,771	772,056	229.4 (218.9, 240.3)	0.76 (0.64, 0.90)	0.74 (0.62, 0.89)

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Category	TT				Unexposed				Age- and region-matched Incidence Rate Ratio (95%CI)	PS Adjusted Incidence Rate Ratio (95%CI)
	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)		
≥4 years	25,934	87	55,541	156.6 (127.0, 193.3)	279,871	1,145	516,564	221.7 (209.2, 234.9)	0.70 (0.56, 0.88)	0.68 (0.54, 0.86)
≥5 years	17,418	47	34,197	137.4 (103.3, 182.9)	194,522	608	326,212	186.4 (172.1, 201.8)	0.74 (0.54, 1.00)	0.71 (0.51, 0.97)
Calandar year of index date										
2007–2009	21,625	173	72,756	237.8 (204.9, 276.0)	215,048	2,229	778,501	286.3 (274.7, 298.5)	0.83 (0.70, 0.97)	0.84 (0.71, 1.00)
2010–2012	33,662	143	80,793	177.0 (150.2, 208.5)	318,694	1,642	684,425	239.9 (228.6, 251.8)	0.73 (0.62, 0.88)	0.72 (0.60, 0.87)
2013–2015	20,872	19	25,155	75.5 (48.2, 118.4)	187,584	262	220,545	118.8 (105.2, 134.1)	0.64 (0.40, 1.01)	0.59 (0.35, 0.99)
Follow-up period relative to index date										
<6 months	76,159	27	35,069	77.0 (52.8, 112.3)	721,326	528	323,782	163.1 (149.7, 177.6)	0.47 (0.32, 0.70)	0.51 (0.34, 0.77)
≥6 & <12 months	64,164	45	29,479	152.7 (114.0, 204.5)	589,975	487	270,125	180.3 (165.0, 197.0)	0.82 (0.60, 1.13)	0.72 (0.51, 1.01)
≥12 & <24 months	53,878	93	45,116	206.1 (168.2, 252.6)	492,355	936	411,903	227.2 (213.1, 242.3)	0.95 (0.77, 1.18)	1.03 (0.82, 1.30)
≥24 months	36,539	170	69,041	246.2 (211.9, 286.2)	334,378	2,182	677,660	322.0 (308.8, 335.8)	0.78 (0.66, 0.92)	0.74 (0.62, 0.88)

*per 100,000 person-years

Abbreviations: CI, confidence interval; PCa, prostate cancer; PS, propensity score; PSA, prostate-specific antogen; TT, testosterone therapy.

Table 3.

Incidence rates and incidence rate ratios for prostate cancer for TT and PDE5i analytic groups and by pre-index characteristics

Category	TT				PDE5i				Unadjusted Incidence Rate Ratio (95%CI)	PS Adjusted Incidence Rate Ratio (95%CI)
	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)		
Overall	113,041	563	267,795	210.2 (193.6, 228.3)	147,620	1,091	370,507	294.5 (277.5, 312.5)	0.71 (0.64, 0.79)	0.85 (0.79, 0.91)
Subgroups										
PSA test in pre-index period										
Yes	22,022	95	49,665	191.3 (156.4, 233.9)	18,328	135	43,989	306.9 (259.3, 363.3)	0.62 (0.48, 0.81)	0.73 (0.60, 0.87)
No	91,019	468	218,130	214.6 (196.0, 234.9)	129,292	956	326,518	292.8 (274.8, 312.0)	0.73 (0.66, 0.82)	0.87 (0.81, 0.94)
Prostate cancer screen in the pre-index period										
Yes	33,083	181	77,206	234.4 (202.7, 271.2)	35,143	293	87,886	333.4 (297.3, 373.8)	0.70 (0.58, 0.85)	0.85 (0.74, 0.97)
No	79,958	382	190,589	200.4 (181.3, 221.6)	112,477	798	282,622	282.4 (263.4, 302.6)	0.71 (0.63, 0.80)	0.85 (0.78, 0.92)
No PSA test and no PCa screen in the pre-index period	65,288	323	156,778	206.0 (184.7, 229.8)	99,367	703	250,853	280.2 (260.3, 301.8)	0.74 (0.64, 0.84)	0.89 (0.81, 0.97)
Hypogonadism diagnosis in the pre-index period										
Yes	49,047	223	111,853	199.4 (174.9, 227.3)	8,318	46	16,034	286.9 (214.9, 383.0)	0.70 (0.51, 0.95)	0.72 (0.57, 0.91)
No	63,994	340	155,942	218.0 (196.0, 242.5)	139,302	1,045	354,473	294.8 (277.5, 313.2)	0.74 (0.65, 0.84)	0.87 (0.80, 0.94)
Benign prostatic hyperplasia in the pre-index period										
Yes	17,596	148	44,547	332.2 (282.8, 390.3)	19,340	195	47,111	413.9 (359.7, 476.3)	0.80 (0.65, 0.99)	0.86 (0.74, 1.00)
No	95,445	415	223,249	185.9 (168.8, 204.7)	128,280	896	323,396	277.1 (259.5, 295.8)	0.67 (0.60, 0.75)	0.83 (0.77, 0.90)
Pre-index enrollment time										
≥2 years	78,598	372	184,835	201.3 (181.8, 222.8)	91,827	625	224,866	277.9 (257.0, 300.6)	0.72 (0.64, 0.82)	0.85 (0.78, 0.93)
≥3 years	56,239	249	128,035	194.5 (171.8, 220.2)	59,092	340	138,275	245.9 (221.1, 273.5)	0.79 (0.67, 0.93)	0.91 (0.81, 1.02)

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Category	TT				PDE5i				Unadjusted Incidence Rate Ratio (95%CI)	PS Adjusted Incidence Rate Ratio (95%CI)
	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)	N	# PCa Cases	Person-years	Incidence Rate* (95%CI)		
≥4 years	39,785	154	85,328	180.5 (154.1, 211.4)	39,125	185	84,928	217.8 (188.6, 251.6)	0.83 (0.67, 1.03)	0.95 (0.81, 1.10)
≥5 years	26,704	83	52,415	158.4 (127.7, 196.4)	24,432	80	47,526	168.3 (135.2, 209.6)	0.94 (0.69, 1.28)	1.06 (0.85, 1.33)
Calendar year of index date										
2007–2009	33,080	290	111,245	260.7 (232.3, 292.5)	68,183	744	216,131	334.2 (320.4, 369.9)	0.76 (0.66, 0.87)	0.83 (0.70, 0.97)
2010–2012	49,842	242	120,078	201.5 (177.7, 228.6)	54,855	318	129,315	245.9 (220.3, 274.5)	0.82 (0.69, 0.97)	0.73 (0.62, 0.88)
2013–2015	30,119	31	36,472	85.0 (59.8, 120.9)	24,582	29	25,061	115.8 (80.4, 166.5)	0.73 (0.44, 1.22)	0.64 (0.40, 1.01)
Follow-up period relative to index date										
<6 months	113,041	47	52,104	90.2 (67.8, 120.1)	147,620	153	67,150	227.8 (194.5, 267.0)	0.40 (0.29, 0.55)	0.53 (0.43, 0.65)
≥6 & <12 months	95,454	81	43,860	184.7 (148.5, 229.6)	122,605	132	56,164	235.0 (198.2, 278.7)	0.76 (0.58, 1.01)	0.83 (0.68, 1.01)
≥12 & <24 months	80,191	139	67,363	206.3 (174.7, 243.7)	102,326	233	86,795	268.4 (236.1, 305.2)	0.80 (0.65, 0.99)	0.88 (0.75, 1.02)
≥24 months	54,774	296	104,468	283.3 (252.8, 317.5)	72,432	573	160,398	357.2 (329.2, 387.7)	0.81 (0.70, 0.94)	0.96 (0.87, 1.07)

* per 100,000 person-years

Abbreviations: CI, confidence interval; PCa, prostate cancer; PDE5i, phosphodiesterase type 5 inhibitor; PS, propensity score; PSA, prostate-specific antogen; TT, testosterone therapy.

Table 4.

Among TT exposed group, adjusted incidence rate ratio of prostate cancer by TT therapy characteristics.

Characteristic	Cases	N	Person-Years	Unadjusted IRR (95%CI)	Adjusted IRR (95%CI)
Time on testosterone - all medications[1]					
<3 months	172	39,184	88,374	Referent	Referent
3–6 months	67	16,529	36,970	0.93 (0.70, 1.23)	0.97 (0.73, 1.29)
6 or more months	91	19,080	51,571	0.91 (0.70, 1.17)	0.97 (0.75, 1.26)
Number of testosterone fills of first medication[2]					
1 to 2	211	46,602	106,212	Referent	Referent
3 to 7	79	18,321	42,918	1.17 (0.90, 1.52)	1.14 (0.69, 1.49)
8 or more	46	9,869	27,784	1.20 (0.87, 1.65)	1.14 (0.83, 1.56)
Route of Administration[3]					
Patch	205	41,037	102,531	0.85 (0.68 – 1.06)	0.86 (0.69 – 1.08)
Injection	125	33,400	73,408	Referent	Referent
Change in testosterone level on therapy[4]					
Decrease	6	2,268	6,417	Referent	Referent
Increase	27	6,480	18,877	1.53 (0.63, 3.71)	1.40 (0.56, 3.49)
Change in testosterone level on therapy (based on quartiles)[5]					
Decrease	6	2,268	6,417	0.60 (0.22, 1.66)	0.64 (0.23, 1.80)
0 – 91	12	2,101	6,131	1.26 (0.55, 2.92)	1.13 (0.48, 2.68)
92–286	10	2,192	6,446	Referent	Referent
287 +	5	2,187	6,300	0.51 (0.17, 1.50)	0.50 (0.17, 1.49)

[1]Adjusted for: age, pre-index time, DCI, pre-index annual flag, pre-index T test, pre-index PSA test, index date year.

[2]Adjusted for: age, route of administration, prindex time, DCI, pre-index annual flag, pre-index T test, pre-index PSA test, index date year.

[3]Other administrations excluded (N=356); Adjusted for: time on T, age, pre-index time, DCI, pre-index annual flag (1yr), pre-index PSA test, pre-index T test, index date year

[4]Adjusted for: pre-index T result, age, time between tests, DCI, pre-index PSA test, index date year, urinary symptoms, other prostate disease, inflammatory prostate, BPH, hypogonadism, osteoporosis, diabetes (complicated and uncomplicated), liver failure.

[5]Adjusted for: pre-index T result, age, time between tests, pre-index annual flag (1yr), DCI, pre-index PSA test, index date year, pre-index specialist flag, urinary symptoms, other prostate disease, inflammatory prostate, BPH, hypogonadism, family history of prostate cancer, psychosexual dysfunction, osteoporosis, diabetes (complicated and uncomplicated), liver failure.