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Association of the extent of therapy with prostate cancer in those receiving testosterone therapy in a US commercial insurance claims database

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Abstract

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AUTHOR CONTRIBUTION

The authors' responsibilities were as follows: LDS, HD, FA and KT designed the study; FA and KT contributed equally to this work; HD performed the statistical analysis; LDS wrote the manuscript; all authors participated in data interpretation; all authors provided critical revision of the manuscript for important intellectual content.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding and senior author (KT) upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

SUPPORTING INFORMATION

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

Background: Conflicting evidence remains in the association of testosterone therapy (TTh) with prostate cancer (PCa). This inconsistency maybe due, in part, to the small sample sizes from previous studies and an incomplete assessment of comorbidities, particularly diabetes.

Objective: We investigated the association of PCa with TTh (injection or gel) and different TTh doses and determined whether this association varies by the presence of diabetes at baseline in a large, nationally representative, commercially insured cohort.

Design: We conducted a retrospective cohort study of 189 491 men aged 40–60 years old in the IBM MarketScan® Commercial Database, which included 1424 PCa cases diagnosed from 2011 to 2014. TTh was defined using CPT codes from inpatient and out-patient, and NDC codes from pharmacy claims. Multivariable adjusted Cox proportional hazards models were used to compute hazard ratios for patients with incident PCa.

Results: We found a 33% reduced association of PCa after comparing the highest category (>12) of TTh injections with the lowest (1–2 injections) category (HR = 0.67, 95% CI: 0.54–0.82). Similar statistical significant inverse association for PCa was observed for men who received TTh topical gels (>330 vs 1- to 60-days supply). Among nondiabetics, we found significant inverse association between TTh (injection and gel) and PCa, but a weak interaction between TTh injections and diabetes ($P = .05$).

Conclusion: Overall, increased use of TTh is inversely associated with PCa and this remained significant only among nondiabetics. These findings warrant further investigation in large randomized placebo-controlled trials to infer any health benefit by TTh.

Keywords

health claims data and diabetes; prostate cancer; testosterone therapy

1 | INTRODUCTION

The relationship between high levels of serum testosterone and use of testosterone therapy (TTh) with prostate cancer (PCa) remains one of the long-standing controversies in urological research in the past 70 years.^{1–3} In recent years, there has been an increasing interest in studying the effects of low levels of testosterone on the incidence of PCa, which remains the second most commonly diagnosed cancer and the sixth most common cause of cancer-related mortality among men worldwide.^{4,5} Studies have shown that one-third of men over 45 years old demonstrate low levels of testosterone.^{6–8} In the United States (US), it has been reported that there are approximately 2.4 million men, aged 40–69, with testosterone deficiency,^{9,10} and by 2025, approximately 6.5 million American men, aged 30–80, are projected to suffer from testosterone deficiency.⁸ An increase in the prevalence of testosterone deficiency is partly due to the increasing older adult population and to rising rates of obesity and metabolic syndrome in the last two decades. These factors likely contributed to the increased use of TTh in the United States from 0.81% in 2001 to 2.9% in 2011.^{11,12} However, between 2013 and 2014 the US Food and Drug Administration issued a safety bulletin due to findings from two studies reporting an increased association of myocardial infarction and stroke associated with TTh.^{13,14} Furthermore, recently

Baillargeon et al reported that the percentage of US men receiving testosterone prescriptions decreased from 2013 through 2016 coinciding with the FDA communication.¹⁵

A meta-analysis of eight randomized controlled trials (RCTs) reported that TTh did not increase the incidence of PCa.¹⁶ Subsequently, a larger meta-analysis of 11 RCTs reported similar findings.¹⁷ Although RCTs represent the most rigorous study design in terms of reducing confounding and selection bias, they often lack generalizability and a large sample size. Both of these limitations maybe addressed by using a large administrative claims database.

Modifiable causes of PCa are poorly understood, in part because PCa is a heterogenous diseases in which modifiable factors for indolent vs fatal PCa differ.¹⁸ Diabetes is associated with a reduced incidence of PCa,^{19,20} but a recent meta-analysis showed that diabetes may result in a worse prognosis of PCa.²¹ A link between prevalent diabetes and low levels of testosterone has also been reported.²² Yet, there is a research gap in our understanding on whether history of diabetes influences the role of TTh in PCa. Therefore, the objectives of this study are to investigate the association of PCa with TTh (injection or gel) and different TTh doses and to determine whether this association varies by history of diabetes at baseline in a large administrative database.

2 | MATERIALS AND METHODS

2.1 | Data source

We used data from the IBM MarketScan® Commercial Database, which includes longitudinal inpatient, outpatient and prescription claims data from a nationwide, employer-based, commercially insured population in the United States. Data were available from 1 January 2011 to 31 December 2014. Previous meta-analysis considered 36 months a long-term exposure to TTh.¹⁶ IBM MarketScan® database holds medical and pharmacy claims for nearly 80% of the commercially insured population, covering nearly 45 000 000 unique individuals per year. The database captured person-specific healthcare utilization, expenditures and enrolment across the inpatient and outpatient settings as well as drug prescription. Data were de-identified in accordance with the Health Insurance Portability and Accountability Act requirements. This study was approved by the University of Texas Health Science Center-Houston IRB.

2.2 | Sample selection

We identified men between the ages of 40 and 64 who received at least one testosterone injection or prescription for testosterone gel in the inpatient or outpatient setting. TTh use was identified in two ways: (a) the national drug code (NDC) from the pharmacy claims; (b) current Procedural Terminology Coding System, 4th edition (CPT-4) for inpatient and outpatient claims. From this cohort, a minimum of 6 months of continuous enrolment before the first TTh claim (index claim) was required to ensure there was no prior TTh claim in inpatient, outpatient or pharmacy records and to exclude men who had been diagnosed with PCa prior to the index claim.

2.3 | TTh treatment definitions

Eligible subjects were categorized based on the formulation of their TTh use (index date): gels, injections or combination of both injections and gels. These two formulations were considered because they were the most commonly used TTh in-office and pharmacy-dispensed TTh in the United States among a privately insured population.²³ The gel or the injection groups included men who used only TTh gels or injections, respectively, while individuals in the combination group had both TTh gel prescription and TTh injection. To assess the independent dose-response effect of TTh gels and injections on the incidence of PCa, we categorized gel and injection groups into quartiles according to cohort distribution of TTh use. The measure of dosage for TTh gel and injection was days' of supply and number of injections, respectively. The cumulative dose of TTh was assessed by summing the total service dates of testosterone injections or the supply days' of gels from the time of TTh initiation to either the date of PCa diagnosis, until the patient was no longer enrolled in the health plan, or until the end of the study follow-up period (31 December 2014).

2.4 | Covariates

Patient' age was examined at the index date. The patient's comorbidity status was defined using the Charlson Comorbidity Index (CCI)²⁴ using information from the diagnosis codes in inpatient and outpatient claims corresponding to a date of service 6 months prior to the index claim (baseline period). Use of insulin medications, statins and prostate specific-antigen examinations during the baseline period were also included (binary and categorical variables). Additional indications for TTh were identified using International Classification of Diseases 9th Revision, Clinical Modification code (ICD-9-CM) codes: hypogonadism, hypertension, diabetes, muscular wasting and disuse atrophy, malaise and fatigue, chronic fatigue syndrome, functional quadriplegia, malaise and fatigue, osteoporosis, testicular dysfunction, erectile dysfunction, depressive disorder, benign neoplasm, anterior pituitary disorder and decreased libido.²⁵ No data were available on race, laboratory findings, occupational, environmental and or lifestyle factors.

2.5 | Outcome measure

Prostate cancer diagnosis was defined based on either one or more inpatient facility claims with a primary discharge of PCa (ICD-9-CM = 185.0) or two or more outpatient claims on different days not more than 6 months apart with a diagnosis of PCa.

2.6 | Statistical analysis

Patients' characteristics were compared between PCa cases and non-PCa patients using *chi-square* tests for categorical variables and t test for continuous variables. We conducted multivariable Cox proportional hazards models using days since TTh initiation until PCa diagnosis, loss to follow-up, or the end of study as the event time variable. Scaled Schoenfeld residuals were used to test the proportional hazards assumption. Multivariable models were adjusted using a priori knowledge to identify confounders (age, CCI Comorbidity, hypogonadism, hypertension, diabetes, malaise and fatigue, malaise and fatigue, osteoporosis, testicular dysfunction, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, use of insulin, use of statin and prostate-specific

antigen [PSA]) to assess the incidence of PCa following use of TTh.²⁶ Participants were censored if they were not enrolled in the IBM MarketScan® Commercial Database for two continuous months or until the end of study period. Two separate analyses were conducted for only TTh injection, and only gel groups to examine the incidence of PCa related to different levels of TTh use dosage. For TTh injections, we compared > 12 injections vs 1–2 injections (reference group); and for TTh gels, we compared >330 days of gel supply vs 1–60 days of gel supply (reference group). Muscular wasting and disuse atrophy, chronic fatigue syndrome, functional quadriplegia and benign neoplasms were excluded from the primary and secondary models because of small sample sizes. Further stratified analyses were conducted to determine whether a history of diabetes at baseline modified the association between TTh gels and injections and PCa. Multiplicative interaction terms were incorporated into the models, and likelihood ratio tests were used to test for interaction. All analyses were conducted with SAS software, version 9.4 (SAS Institute, Inc). All *P* values were two-sided at the type I error $\alpha = .05$ level.

3 | RESULTS

A total of 189 491 TTh initiators met the study eligibility criteria. The median follow-up time for study participants was 26 months. Table 1 showed patients characteristics by PCa status. Among TTh initiators, there were 1424 (0.8%) PCa cases during the follow-up period. Compared with men who did not develop PCa, PCa cases were older (69.8% vs 41.8%) with higher comorbidity scores over 2 (21.5% vs 11.2%). Furthermore, PCa cases had more clinical conditions such as hypertension (28.0% vs 25%), osteoporosis (2.5% vs 2.4%), erectile dysfunction (14.0% vs 11.8%), use of statin (40.8% vs 34.6%) and PSA more than once (62.8% vs 51.9%).

Table S1 reports patients' baseline characteristics presented in quartiles of TTh injection and days of gel supply dosage. The days of supply of gels prescribed ranged from 1 to >330 days, and the mean and SD are 240 and 251 days, respectively. The number of injections in our sample ranged from 1 to >12, and the mean and SD were 11 and 17, respectively. A greater proportion of gel users compared with injection users had diabetes (28.1% vs 23.2%), were older than 56 years (44.9% vs 39.7%), had statin use (40.3% vs 27.2%), had one or more PSA tests (59.4% vs 43.6%) and had two or more comorbidities (11.6% vs 10.9%). However, gel users had less hypogonadism (29.3% vs 41.3%) and relatively slightly less hypertension (24.2% vs 25.9%).

Table 2 shows the multivariable associations of TTh use (injection and gel dosage) with time to PCa. Men who took >12 TTh injections had a lower probability of PCa compared with men with 1–2 injections (HR = 0.67, 95% CI: 0.53–0.83) after adjusting for age, CCI Comorbidity, hypogonadism, hypertension, diabetes, malaise and fatigue, malaise and fatigue, osteoporosis, testicular dysfunction, erectile dysfunction, depressive disorder, anterior pituitary disorder, decreased libido, use of insulin, use of statin and PSA. The trend of this association remained statistically significant (*P* for trend < .0001). Similarly, men with >330 days of TTh gel supply had a decreased association of PCa compared with men with 1–60 days of gel supply (HR = 0.58, 95% CI: 0.48–0.72). The trend of this relationship was also statistically significant (*P* for trend < .0001). In the total population, history of

diabetes at baseline was negatively associated with PCa (HR = 0.63, 95% CI: 0.53–0.76, $P < .001$). In sensitivity analysis, we excluded PCa cases the first 24 months to reduce probability of reverse causality; however, the results remained very similar (data not shown).

In stratified and multivariable analyses, we examined the association between TTh use injection and gel dosage and PCa by history of diabetes at baseline (Table 3). Only among nondiabetic men, we observed the same inverse associations between TTh injection and gel and PCa after comparing highest vs lowest category, HR = 0.63, 95% CI: 0.49 – 0.81, P for trend $< .0001$; and HR = 0.55, 95% CI: 0.43 – 0.69, P for trend $< .0001$, respectively. The interaction between TTh injection and diabetes was weakly associated with PCa (P for interaction = .05), but not significant at all for TTh gel (P for interaction = 0.20).

4 | DISCUSSION

In this large US administrative healthcare claims database that investigated prospectively the association of TTh use with PCa, we observed a reduced probability of PCa in men with a higher use of TTh injections compared with men with a lower number of TTh injections. The trend of this association was also significant. A similar decreased association of PCa was found after comparing the highest with the lowest category of topical gel days' supply, including a significant trend of the association. In stratified analysis, there were significant inverse associations between TTh injections (high vs low) and topical gels (high vs low) and PCa among nondiabetic men. No significant associations were identified among diabetic men.

A number of studies and reviews have previously addressed the association between TTh use and PCa.^{27,28} Therefore, several aspects of the findings of our investigation merit further discussion. First, our study included a large sample size of 189 491 men followed for three years with a total of 1424 incident PCa cases (median follow-up time is 26 months). More specifically, there were 608 PCa cases in the TTh injection group and 733 PCa cases in the TTh topical gel use group. These groups have a large sample size to conduct these associations. The issue of a small sample size of PCa cases with TTh use has been one of the most common limitations from previous studies, including meta-analysis.^{16,17} For instance, Cui *et al* meta-analysis consisted of eight randomized trials with a total of 10 PCa cases in the TTh injection group ($n = 969$) and eight PCa cases in the control group ($n = 578$). Boyle *et al* meta-analysis consisted of 11 randomized trials and included a total of 20 PCa cases.

Second, the measures of association of our study showed a reduced probability for PCa among men who used TTh (highest vs lowest category of TTh injections and highest to lowest category of TTh gel supply). The direction of these associations seems to concur with the two meta-analyses of RCTs. Cui *et al* showed a summary OR of 0.74,¹⁶ while Boyle *et al* showed a summary OR of 0.87,¹⁷ albeit both were not statistically significant. Yet, the direction and strength of these measures of association from the previous meta-analyses should be highlighted independently of the dichotomized statistical significance of P values ($P_{\text{value}} < .05$). Similarly, a more recent study reported a small effect on the overall of PCa among TTh users ($n = 284$), but this effect was not statistically significant (OR = 1.03, 95% CI: 0.90, 1.17).

Third, although our study did not investigate PCa disease progression, which is the clinically relevant outcome, it is noteworthy to mention that even more recent studies on disease progression have not found a higher probability of PCa among TTh users either. In fact, the direction of the measures of association is in the opposite direction. For instance, two recent nested case-control studies (American²⁹ and European³⁰) that used well-characterized cancer registries did not report a higher probability of disease progression among TTh users. The European study (50 PCa cases among 284 TTh users) reported an inverse association with aggressive PCa, which was defined by T1 to T2, Gleason score of 8–10, 20 > PSA <50 ng/mL, not N1, not M1, locally advanced, regional and distant metastatic PCa among TTh users (OR = 0.50, 95% CI: 0.37, 0.67).³⁰ The American study (115 PCa cases among 564 TTh users) focused on high-grade PCa and found a reduced association of it among men who used TTh (OR = 0.84, 95% CI: 0.67, 1.05), but this was not statistically significant.²⁹ Further, dose-response analysis by this latter study showed that the higher probability of high tumour grade did not increase with an increasing number of testosterone injections (OR = 1.00, 95% CI: 0.98, 1.01).

Fourth, the stratified analyses conducted in this study showed a significant inverse association with PCa among men who used TTh and topical gels only in the nondiabetic group, but a lack of significance in the diabetic group. This observation warrants further scrutiny. There is solid evidence from a previous meta-analysis of 19 observational studies that showed an inverse relationship between history of diabetes and incident total PCa.³¹ These studies argued that the inverse relationship between diabetes and PCa is found only when men have been diagnosed with diabetes for more than 1, 3 or 6 years.^{19,32} In contrast, a recent meta-analysis of 17 cohort studies found that pre-existing diabetes was associated with a 29% increase probability of PCa-specific mortality.²¹ Our stratified findings seem to concur, in part, with this latter meta-analysis. Since our results showed a significant inverse relationship between TTh and PCa only among nondiabetic, we could hypothesize that diabetes has a stronger effect on increasing probability of PCa than the beneficial effects of TTh. Therefore, diabetes overwhelmed the beneficial effects provided by TTh use on reducing the association with PCa among diabetics, and thus, no statistical association was found in this group. Yet, this latter statement is only hypothetical.

Our study has a number of strengths. This study included a large sample size, number of patients with incident PCa, long follow-up data, detailed information on patient's exposure to TTh use on the basis of filled prescriptions and inclusion of clinically relevant comorbidities. These strengths increased our statistical power for the categorical comparisons groups and generalizability for studies with similar study populations and also reduced residual confounding because of our well-characterized modifiable factors.

Yet, the present study has limitations as well. First, general limitations of retrospective cohort studies based on healthcare claims data, such as possible coding errors or omissions of claims. For instance, comorbidities were identified using ICD-9-CM codes, which it is possible that resulted in incorrect capture of medical conditions due to undercoding, upcoding or miscoding, leading to classification bias in those comorbidities at baseline. However, this inaccurate capture of information will be considered nondifferential misclassification because they were collected before the disease developed, which in general

influence associations to the null (1.0). Also, this study lacks the comparison group of no TTh use. Second, limiting the pre-index period to six months did not allow to capture full medical history (patients may have had the comorbidity of interest before the start of the pre-index period). Third, evidence of a filled prescription with pharmaceutical data did not confirm actual use of a medication and over-the-counter medications could not be identified. Fourth, our database did not include important confounders such as race/ethnicity and body mass index that have been shown to be strongly associated with PCa and testosterone (endogenous and exogenous). Small percentage differences may be due to the large sample size and not necessarily clinically relevant differences. Also, although we adjusted for hypogonadism and age in the multivariable analysis, we cannot rule out potential residual confounding by these factors. Fifth, this same database did not include information on the serologic or diagnostic indications for treatment. Further, our study population only included patients with employer-based commercially insured population; therefore, our results may not be generalizable to patients with PCa using other types of insurance or no insurance at all. Finally, due to the nature of this retrospective cohort study, we cannot infer causality; therefore, these findings should be interpreted with caution as we only identified an inverse association between TTh and PCa.

5 | CONCLUSION

In summary, this large US administrative healthcare claims database found an inverse association between use of TTh prescription (high vs low) and PCa. Stratified analysis showed there were significant inverse associations between TTh injections (high vs low) and topical gels (high vs low) and PCa among nondiabetic men. No significant associations were identified among diabetic men. Yet, these findings warrant further investigation in large placebo-controlled trials to be able to reduce potential inherent observational study bias and to be able to infer a health benefit by TTh.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Baseline characteristics by PCa status, IBM MarketScan® Commercial Database, 2011–2014

	No-prostate cancer 188 067	Prostate cancer 1424	P-value
TTh form, %			
Injection	42.6	42.7	.38
Gel	50.7	51.5	
Combination	6.7	5.8	
Age, %			
40–45	14.5	2.2	<.0001
46–50	19.8	6.9	
51–55	23.9	21.1	
56–60	24.3	39.8	
61–65	17.5	30	
CCI comorbidity, %			
0	64.3	57.4	<.0001
1	24.5	21.1	
2	5.3	10.9	
3 or more	5.9	10.6	
Hypogonadism, %	34.9	36.2	.33
Hypertension, %	25	28	.01
Diabetes, %	25.9	26	.88
Muscular wasting and disuse atrophy, %	0.1	0.3	.05
Malaise and fatigue, %	23.7	20.3	.00
Chronic fatigue syndrome, %	0.8	0.6	.31
Functional quadriplegia, %	0	0	.77
Other malaise and fatigue, %	23.1	19.8	.00
Osteoporosis, %	2.4	2.5	<.0001
Testicular dysfunction, %	1.4	1.3	.67
Erectile dysfunction, %	11.8	14	.01
Depressive disorder, %	5.3	5.6	.65
Benign neoplasm, %	0.6	0.3	.13
Anterior pituitary disorder, %	1.5	0.8	.05
Decreased libido, %	2.6	3	.29
Use of Insulin, %	6.4	6	.51
Use of Statin, %	34.6	40.8	<.0001
# of PSA tests, %			
0	48.1	37.2	<.0001
1	47	49.9	
2	4.9	12.9	

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen.

Multivariable^a associations of TTh use (injection and gel dosage) with PCa, IBM MarketScan® Commercial Database, 2011–2014

TABLE 2

Characteristics TTh injections N = 80 259			Characteristics TTh gels N = 95 664		
HR	95% CI	P-value	HR	95% CI	P-value
1–2	1	Ref.	1	Ref.	<.0001
3–4	0.98	0.77, 1.24	1.02	0.83, 1.24	.86
5–12	0.78	0.63, 0.97	0.79	0.65, 0.98	.03
>12	0.67	0.54, 0.83	0.58	0.48, 0.72	<.0001

Abbreviations: PCa, prostate cancer; TTh, testosterone therapy.

^a Adjusted for age, CCI Comorbidity, hypogonadism, hypertension, muscular wasting and disuse atrophy, malaise and fatigue, chronic fatigue syndrome, other malaise and fatigue, osteoporosis, erectile dysfunction organic, depressive disorder, anterior pituitary disorder, decreased libido, use of insulin, use of statin and number of PSA tests were controlled in the model.

Multivariable^a association of TTh use (injection and gel) with prostate cancer stratified by diabetes status (at baseline), IBM MarketScan® Commercial Database, 2011–2014

TABLE 3

Diabetic patients N = 19 844					Diabetic patients N = 27 309				
Characteristics TTh injections					Characteristics TTh gels				
	HR	95% CI	P-value	P-trend		HR	95% CI	P-value	P-trend
1–2	1.0	Ref.		.37	1–60	1.0	Ref.		.89
3–4	1.04	0.64, 1.67	.89		61–150	1.29	0.88, 1.90	.20	
5–12	1.08	0.72, 1.62	.70		151–330	1.02	0.68, 1.52	.93	
>12	0.79	0.51, 1.23	.30		>330	0.69	0.45, 1.07	.10	
Nondiabetic patients N = 60 785					Nondiabetic patients N = 68 791				
Characteristics TTh injections					Characteristics TTh gels				
	HR	95% CI	P-value	P-trend		HR	95% CI	P-value	P-trend
1–2	1.0	Ref.		<.0001	1–60	1.0	Ref.		<.0001
3–4	0.96	0.73, 1.26	.75		61–150	0.93	0.73, 1.17	.51	
5–12	0.69	0.53, 0.88	.00		151–330	0.72	0.57, 0.92	.01	
>12	0.63	0.49, 0.81	.00		>330	0.55	0.43, 0.69	<.0001	

^a Adjusted for age, CCI Comorbidity, hypogonadism, hypertension, muscular wasting and disuse atrophy, malaise and fatigue, chronic fatigue syndrome, other malaise and fatigue, osteoporosis, erectile dysfunction organic, depressive disorder, anterior pituitary disorder, decreased libido, use of insulin, use of statin and number of PSA tests were controlled in the model.