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# Incidence of prostate cancer in men with testosterone deficiency and a family history of prostate cancer receiving testosterone therapy: a comparative study

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## ABSTRACT

**Objective** To investigate the incidence of any PCa diagnosis in men with testosterone deficiency (TD) who have a family history of PCa and were prescribed TTh compared with a control cohort of men with TD with a family history of PCa but who were not prescribed TTh, over a period of 10 years.

**Methods and analysis** Retrospective cohort study using data from 1 January 2012 to 7 March 2024 (TriNetX database). After meeting the inclusion criteria, 3041 men were analysed: 628 with family history of PCa and TD who received TTh, and 2413 who did not. We used propensity score matching to balance baseline characteristics between cohorts. The main outcomes were the risk of any PCa diagnosis and any active treatment (including radical prostatectomy, androgen deprivation therapy, brachytherapy, radiation and cryoablation) among men with TD who received TTh versus a matched cohort who did not.

**Results** Over 10 years, the risk of PCa diagnosis did not significantly differ between men who received TTh (6.26%) and those who did not (5.46%), HR 0.81, 95% CI 0.51 to 1.28. Similarly, no significant difference was found in the risk of receiving any active treatment for PCa between those who received TTh (2.73%) and those who did not (3.69%), HR 0.55, 95% CI 0.29 to 1.03.

**Conclusions** Men with TD and a family history of PCa who were prescribed TTh showed comparable risks of being diagnosed with PCa or receiving any active treatment for PCa, relative to men with analogous TD and family history, but who did not receive TTh.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous research has demonstrated that testosterone therapy (TTh) is safe and does not increase the risk of prostate cancer (PCa) in men with testosterone deficiency (TD) who are considered low risk of developing the disease. However, the specific relationship between TTh and PCa incidence in men with TD who are considered high risk for prostate cancer (eg, family history) has never been investigated yet.

### WHAT THIS STUDY ADDS

⇒ The present study shows that over a 10-year period, men with TD and a family history of PCa who were prescribed TTh did not have a significantly higher risk of being diagnosed with PCa or receiving any active treatment for PCa, compared with a matched cohort of men with TD and family history of PCa who never received TTh.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings from the present study may stimulate researchers to investigate the role of TTh in TD men considered high risk for PCa through clinical trials. Moreover, this study may influence clinical practice by reassuring physicians about prescribing TTh in this specific population.

## INTRODUCTION

In a recent randomised clinical trial (RCT) of hypogonadal men, the incidence of prostate cancer (PCa) was similar among those receiving testosterone therapy (TTh) compared with those receiving placebo.[1] Of note, the analysed population did not include men considered at high risk for PCa.[1] These results validate previous findings from a meta-analysis of both observational studies and RCTs, reporting no increased risk of PCa incidence or alterations in prostate-specific antigen (PSA) levels in hypogonadal men receiving TTh.[2] Nevertheless, testosterone and its more potent metabolite dihydrotestosterone are known regulators of prostate growth and concerns persist regarding TTh prescription in men at high risk for PCa, as these have an elevated risk of developing the disease compared with the general population.[3–6] As such, in these subsets of men, TTh could potentially accelerate the growth

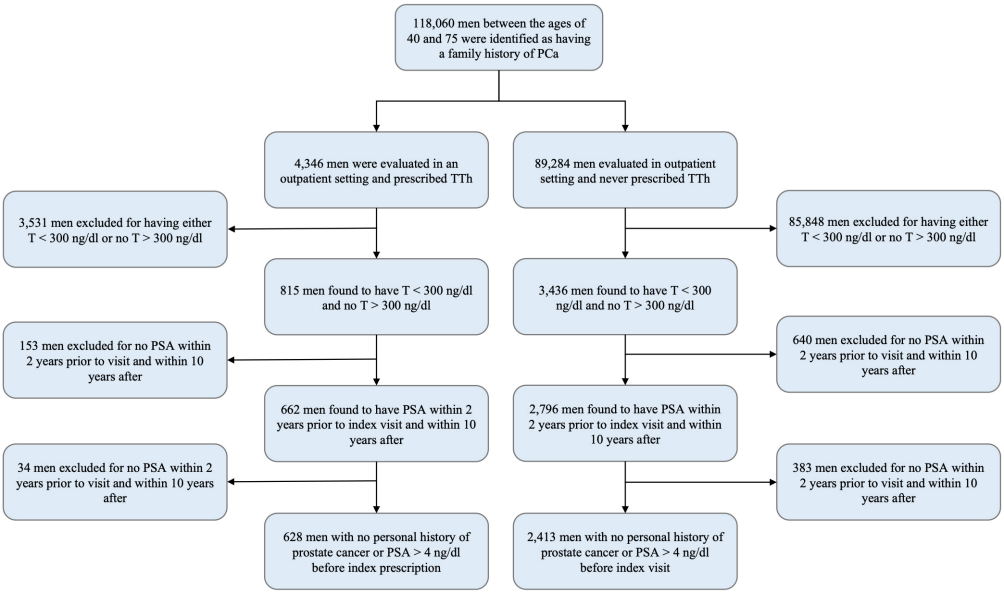


**Figure 1** Flow chart of cohort construction. PCa, prostate cancer; PSA, prostate-specific antigen; TTh, testosterone therapy.

of undetected tumours or trigger the onset of PCa. Currently, there is a lack of data concerning the risk of PCa among men receiving TTh who are considered at high risk for the disease (ie, family history of PCa). In this regard, the European Association of Urology (EAU) and the American Urological Association (AUA) guidelines have not issued specific recommendations on TTh prescribing for high-risk men due to a known family history of PCa.[7 8] The only existing recommendations focus on TTh in hypogonadal men with a personal history of PCa, highlighting the lack of sufficient evidence to accurately assess the risk–benefit ratio of TTh in these men.[7–10] Given the lack of data, the present study aimed to compare the incidence of PCa diagnosis and the likelihood of receiving active treatment for PCa in men with testosterone deficiency (TD) and a family history of PCa prescribed with TTh as compared with a control group who did not receive TTh within 6 months to 10 years after the index prescription.

## MATERIALS AND METHODS

### Patient and public involvement

The TriNetX Research Network, a database that connects insurance claims to individual electronic medical records from 85 healthcare organisations and 120 million patients, was used to generate the subject pool. The data were retrieved as of March 2024 and include record from January 2012 to March 2024. The current study was conducted in adherence to the principles outlined in the Declaration of Helsinki.[11] The Strengthening the Reporting of Observational Studies in Epidemiology checklist was followed to ensure high-quality presentation of the study.[12]

The research question and outcomes were developed based on the clinical importance of understanding the relationship between TTh and PCa risk in TD men considered high risk for the disease (with a family history of PCa). To the best of our current knowledge, this outcome has never been investigated. Patients were not involved in choosing what information to share or in what format. For future studies on this topic, particularly prospective trials, researchers should consider involving patients in the design process, outcome selection and dissemination planning to ensure the research addresses patient priorities and concerns.

### Data source and study protocol

The dataset was constructed using patient demographics, diagnoses (using International Classification of Diseases, 10th Revision, Clinical Modification (ICD10 CM) codes), procedures (using Current Procedural Terminology (CPT) codes), medications (using standardised RxNorm codes for clinical drugs) and laboratory values (using TriNet Curated codes (TNX Curated) and Logical Observation Identifiers Names and Codes) from 85 healthcare organisations and insurance claims from Medicare, Medicaid, Veterans Administration and commercial companies. We constructed our cohort with 3044 men with TD and a family history of PCa who were evaluated in the outpatient setting from the period of 1 January 2012 to 10 March 2024. Details on ICD19 CMN codes, CPT codes.

### Prespecified outcome

The primary outcome was to compare the incidence of any PCa diagnosis in men with TD and family history of PCa receiving TTh versus a matched cohort of men with TD and family history of PCa who were never prescribed TTh. The secondary outcome was to compare the incidence of active treatment for PCa between the two aforementioned cohorts, including radical prostatectomy (CPT 55866), androgen deprivation therapy (leuprolide—RxNorm 42375, enzalutamide (RxNorm 1307298,

**Table 1** Comparative analysis of demographic characteristics, comorbidities and laboratory measurements of men with a family history of PCa receiving TTh and the control group, before and after propensity score matching

| | Before PSM | | | | After PSM | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient group** | **+TTh*** | **–TTh†** | **P value** | **SD** | **+TTh*** | **–TTh†** | **P value** | **SD** |
| Variables considered for PSM | | | | | | | | |
| Number of patients | 628 | 2413 | | | 623 | 623 | | |
| Age, mean (SD), years | 55.1 (8.05) | 57.8 (8.36) | **<0.0001** | 0.3 | 55.2 (8.02) | 55.2 (8.13) | 0.91 | 0.01 |
| Ethnicity/race, No (%) | | | | | | | | |
| Not Hispanic or Latino | 541 (86.15) | 2164 (89.68) | **0.01** | 0.11 | 541 (86.84) | 547 (87.8) | 0.61 | 0.03 |
| Hispanic or Latino | 32 (5.09) | 152 (6.3) | 0.26 | 0.05 | 32 (5.14) | 31 (4.96) | 0.9 | 0.01 |
| Black/Afro-American | 73 (11.62) | 404 (16.74) | **0.002** | 0.15 | 72 (11.56) | 61 (9.79) | 0.31 | 0.06 |
| White | 485 (77.23) | 1781 (73.8) | 0.08 | 0.08 | 482 (77.39) | 499 (80.96) | 0.24 | 0.07 |
| Tobacco use, No. (%) | 33 (5.26) | 165 (6.84) | 0.15 | 0.07 | 33 (5.30) | 26 (4.17) | 0.35 | 0.05 |
| Obesity, No. (%) | 181 (28.82) | 647 (26.81) | 0.31 | 0.05 | 178 (28.57) | 190 (30.5) | 0.46 | 0.04 |
| PSA within 2 years Prior to Index, mean (SD), ng/mL | 1.1 (0.92) | 1.3 (1.2) | 0.22 | 0.05 | 1.3 (0.77) | 0.97 (0.74) | 0.29 | 0.05 |
| Testosterone, mean (SD), ng/dL | 203 (121) | 205 (91.2) | 0.41 | 0.05 | 204 (87.3) | 211 (84.9) | 0.24 | 0.07 |
| Variables not considered for PSM | | | | | | | | |
| Haematocrit, mean (SD), % | 44 (4.8) | 42.1 (5.06) | **<0.0001** | 0.39 | 44 (4.79) | 42.9 (4.62) | **<0.0001** | 0.24 |
| Oestradiol, mean (SD), ng/dL | 25.9 (14.1) | 24.9 (9.91) | 0.62 | 0.08 | 25.9 (14.2) | 25.7 (12) | 0.94 | 0.02 |
| SHBG (SD), ng/dL | 27.5 (15.6) | 30.5 (15.1) | 0.06 | 0.19 | 27.6 (15.7) | 29.2 (15) | 0.42 | 0.11 |
| HbA1c, mean (SD), mmol/mol | 6.13 (1.2) | 6.31 (1.48) | **0.03** | 0.14 | 6.11 (1.18) | 6.24 (1.14) | 0.17 | 0.1 |
| Alcohol use, No. (%) | 30 (4.78) | 123 (5.1) | 0.74 | 0.02 | 30 (4.82) | 31 (4.98) | 0.89 | 0.01 |
| Obstructive sleep apnoea, No. (%) | 188 (29.94) | 513 (21.26) | **<0.0001** | 0.2 | 185 (29.7) | 134 (21.51) | **<0.0001** | 0.19 |

Five patients were excluded during propensity score matching due to insufficient overlap in baseline characteristics with the control group.
*Men with testosterone deficiency and family history of prostate cancer receiving TT.
†Men with testosterone deficiency and with family history of prostate cancer not receiving TT.
HbA1c, glycated haemoglobin; PCa, prostate cancer; PSA, prostate-specific antigen; PSM, Propensity Score Matching; PSM, Propensity Score Matching; SD, standard deviation; SHBG, sex hormone-binding globulin; TT, total testosterone; -TTh, men who never recieved testosterone therapy; TTh, testosterone therapy; +TTh, men recieving testosterone therapy.

Table 2 Type of TTh administered men who received TT

| Route of TTh administration* | TTh† (n=628) |
|---|---|
| Topical TTh | 287 (45.7) |
| Injectable TTh | 309 (49.2) |
| Nasal TTh | 29 (4.62) |
| Oral TTh | 24 (3.82) |
| Implant TTh | 44 (7) |

*This table represents the number of patients who were prescribed the method of TTh at least once. The sum of the percentages may exceed 100% as some men may have been prescribed more than one type of TTh (due to discontinuation, ineffectiveness, etc), resulting in some patients being counted more than once.
†Men with testosterone deficiency and family history of prostate cancer receiving TTh.
TT, total testosterone; TTh, testosterone therapy.

bicalutamide—RxNorm 83008, abiraterone—RxNorm 1100072), radiation of the prostate (ICD-10 D7Y7), brachytherapy (CPT 55876) or cryoablation (CPT 55873).

### Hypothesis

We hypothesised that men with TD and a family history of PCa who received TTh would have similar rates of (1) PCa diagnosis and (2) active treatment for PCa as compared with a matched control cohort of men with TD and a family history of PCa who did not receive TTh. We aimed to compare these rates between the two groups over a period ranging from 6 months to 10 years from the index prescription or equivalent time point.

### Cohort identification and generation

We identified men aged 40–75 years old with a family history of PCa (ICD10 Z80.42). TD was defined according to the criteria set by the AUA, which included having at least one total testosterone (tT) level below 300 ng/dL with no level greater than 350 ng/dL prior to the index prescription.[7] Two cohorts were generated: (1) men with TD and family history of PCa who were prescribed TTh (RxNorm 10739) in the outpatient setting (CPT 1013626) and (2) men with TD with family history of PCa who were evaluated in the outpatient settings (CPT 1013626) but were never prescribed TTh. Men were excluded if they had any of the following before or at the time of the index prescription or outpatient visit: finasteride (RxNorm 25025) or dutasteride (RxNorm 228790) prescription, PCa diagnosis (ICD10 C61) or any PCa treatment, including radical prostatectomy (CPT 55866), androgen deprivation therapy (leuprolide—RxNorm 42375, enzalutamide—RxNorm 1307298, bicalutamide—RxNorm 83008, abiraterone—RxNorm 1100072), radiation therapy (ICD-10 D7Y7), brachytherapy (CPT 55876) or cryoablation (CPT 55873).

All subjects included were required to have at least one PSA within 2 years prior to initiating TTh. Men with a PSA above 4 ng/mL prior to the index prescription or outpatient visit were excluded to reduce the number of men with undiagnosed PCa at the time of the index prescription. A follow-up PSA within 10 years of index TTh prescription was required for all subjects included. Individuals who died during the follow-up period without completing required PSA testing were excluded from the analysis. PCa diagnoses were captured through standardised codes at time of occurrence, with patients retained in the analysis even if they subsequently died. A flow diagram was built to illustrate the process through which the final cohorts were generated (figure 1).

### Covariates

To balance for impactful baseline characteristics, we used the TriNetX database to propensity score match and create insignificant differences between the two cohorts at the time of the index TTh prescription. The TriNetX database uses greedy nearest neighbour matching to perform 1:1 matching with a calliper width of 0.1 times pooled SD. The order of rows is randomised by the TriNetX algorithm to eliminate bias. The following variables were accounted for and subsequently matched for age at index prescription, ethnicity (Hispanic/Latino, not Hispanic Latino), race (black, white), tobacco use, obesity, and PSA in serum or plasma and tT. Baseline characteristics such as haematocrit, oestradiol, sex hormone-binding globulin and haemoglobin A1c, alcohol consumption and obstructive sleep apnoea are reported but not matched for.

### Statistical analysis

The statistical analysis consisted of several steps. First, mean SD or frequencies and proportions were reported

Table 3 Cox proportional HR predicting the risk of any PCa diagnosis and the risk of receiving any active treatment among +TTh cohort versus −TTh (matched control cohort)

| | Patients with outcome, No./Total No., (%) | | | |
|---|---|---|---|---|
| Outcome | +TTh* | −TTh† | HR (95% CI)‡ | P value |
| Diagnosis of any PCa | 39/623 (6.26%) | 34/623 (5.46%) | 0.81 (0.51 to 1.28) | 0.36 |
| Any active treatment for PCa§ | 17/623 (2.73%) | 23/623 (3.69%) | 0.55 (0.29 to 1.03) | 0.10 |

*Men with testosterone deficiency and family history of prostate cancer receiving TTh.
†Men with testosterone deficiency and with family history of prostate cancer not receiving TTh.
‡Adjusted HR.
§Active treatment includes any of the following: radical prostatectomy, androgen deprivation therapy, cryoablation or brachytherapy.
PCa, prostate cancer; TTh, testosterone therapy.

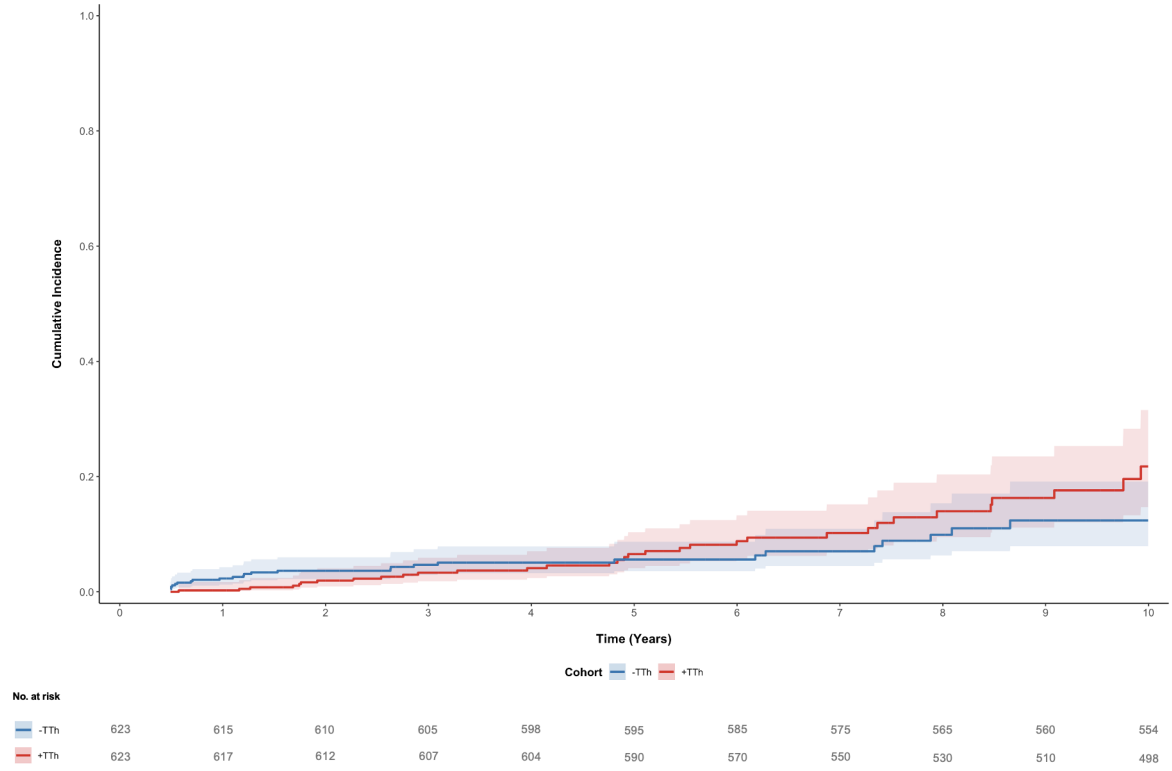


**Figure 2** Kaplan-Meier curve displaying the cumulative incidence of any PCa diagnosis among men with a family history of PCa receiving TTh (+TTh) and a matched control group of men with testosterone deficiency and family history of PCa who did not receive any TTh (–TTh). PCa, prostate cancer; TTh, testosterone therapy.

for continuous or categorical variables, respectively. Second, propensity score matching was applied. SD was used to evaluate the balance of baseline characteristics in the propensity score matching populations. Third, we used $\chi^2$ tests and t-tests to identify differences between the two cohorts for categorical and continuous variables, respectively. We reviewed the distribution of our continuous variables and confirmed that they met the assumptions for parametric testing. For any variables that did not meet these assumptions, we used the Wilcoxon Mann-Whitney test instead of the t-test. Fourth, the associations between the primary and secondary outcomes were evaluated using the Cox proportional hazards regression model, from which adjusted HRs were calculated. In order to account for the violation of proportional hazards assumption in our Cox regression analysis, we additionally performed restricted mean survival time (RMST) analysis using numerical integration of our Kaplan-Meier curves to provide the average time patients remained outcome-free during the 10-year follow-up period. The follow-up period started 6 months after the index date (to reduce the number of men with unidentified PCa), with a maximum duration of 10 years. Fifth, the cumulative incidences for both primary and secondary endpoints were calculated using Kaplan-Meier survival analysis. Differences were deemed statistically significant using a two-sided p<0.05. The Kaplan-Meier estimates of patients at risk of any PCa diagnosis were calculated at 1 year, 5 years and 10 years for both cohorts. All analyses were performed using the TriNetX database, which uses the R's Survival package, V.3.2–3 (R Group for Statistical Computing).

## RESULTS

A flow chart of the cohort construction from 118 060 participants is provided in figure 1. Our final sample size was determined by the total number of patients in the TriNetX database meeting our inclusion and exclusion criteria.

### Baseline characteristics of the study subjects

The demographic characteristics, comorbidities and laboratory measurements of men who received TTh and men who did not receive TTh before and after propensity score matching are detailed in table 1. A total of 628 men who received TTh and 2413 who did not receive TTh cohorts were identified. Subsequent propensity score matching was performed to ensure comparability between the two cohorts, resulting in equivalent data for 623 men in both cohorts. After matching, the disparities in demographic characteristics, comorbidities and laboratory findings between the cohorts were minimal and effectively balanced, p>0.05 (table 1). Both cohorts of men who were prescribed TTh and the men who were not prescribed TTh were white (77.39 vs 80.96, p=0.24) and non-Hispanic or Latino (86.84% vs 87.8%, p=0.61). There was no statistically significant difference in baseline

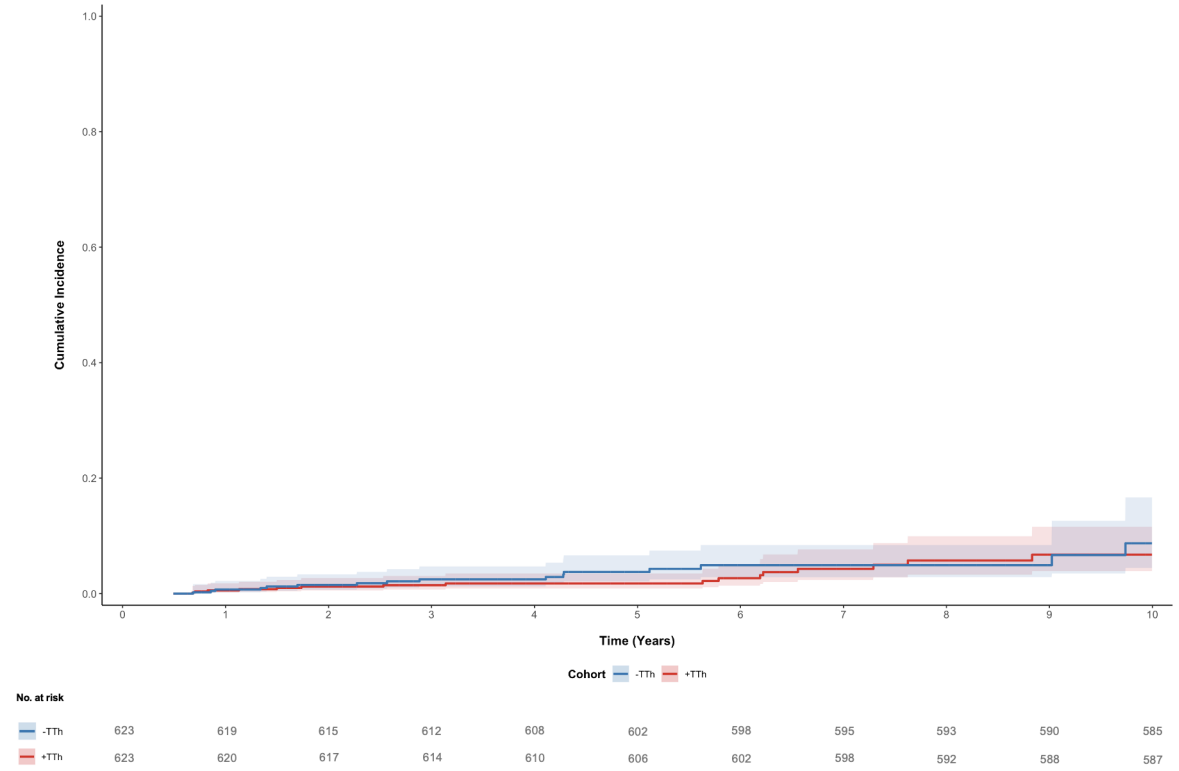


**Figure 3** Kaplan-Meier curve displaying the cumulative incidence of any active PCa treatment among men with a family history of PCa receiving TTh (+TTh) and a matched control group of men with testosterone deficiency and family history of PCa who did not receive any TTh (–TTh). PCa, prostate cancer; TTh, testosterone therapy.

PSA (1.3±0.77 ng/mL, 0.97±0.74 ng/mL) or tT levels (204±87.3 ng/dL, 211±84.9 ng/dL). The methods of TTh administration are highlighted in table 2. Injectable TTh was the most administered method (49.2%), followed by topical (45.7%) along with subcutaneous implants (7%), nasal (4.62%) and oral (3.82%) methods, respectively. It is noteworthy to mention that the collective percentages surpass 100%, which can be attributed to a subset of participants being prescribed multiple TTh modalities over time.

### Risk of prostate cancer diagnosis and active treatment in men with TD and a family history of prostate cancer

Table 3 presents the Cox proportional hazard ratios predicting the risk of any PCa diagnosis and any active treatment for PCa in men who received TTh compared with the men who did not receive TTh. There was no significant increased risk of any PCa diagnosis within 10 years between men who received (6.26%) and those who did not receive TTh (5.46%), HR 0.81, 95% CI 0.51 to 1.28, p=0.36 (table 3 and figure 2). Similarly, there was no increased risk of receiving any active PCa treatment within 10 years between men who received (2.73%) vs those who did not receive TTh (3.69%), HR 0.55, 95% CI 0.29 to 1.03, p=0.10 (table 3 and figure 3). For any PCa diagnosis, the Kaplan-Meier risk estimates for men who received TTh were 0.2% (95% CI 0% to 1.7%), 6.5% (95% CI 4.1% to 10.3%) and 21.7% (95% CI 14.7% to 31.5%) at 1, 5 and 10 years, respectively. For those who did not receive TTh, the corresponding risk estimates were 2.3% (95% CI 1.3% to 4.3%), 5.6% (95% CI 3.6% to 8.7%) and 12.4% (95% CI 7.9% to 19.1%), respectively. For any active PCa treatment, the risk estimates for men who received TTh were 0.6% (95% CI 0.2% to 1.8%), 1.7% (95% CI 0.9% to 3.5%) and 6.7% (95% CI 3.9% to 11.6%) at 1, 5 and 10 years, respectively, while for those who did not receive TTh, the risk estimates were 0.7% (95% CI 0.2% to 2.2%), 3.8% (95% CI 2.1% to 6.6%) and 8.7% (95% CI 4.5% to 16.7%), respectively, at the same time points (table 4). Lastly, in order to address the violation of proportional hazards assumption observed over the Kaplan-Meier curves (figures 2 and 3), where risk patterns changed over time, and considering that the HRs (0.81) 95% CI 0.51 to 1.28) for PCa diagnosis and 0.55 (95% CI 0.29 to 1.03) for active treatment) did not fully capture these time-varying relationships, we performed RMST analysis for both outcomes (measurement of the area under the Kaplan-Meier curves over the 10-year period). For PCa diagnosis, this revealed that over 10 years, TTh+patients remained PCa-free for an average of 8.74 (95% CI 8.66 to 8.82) years, compared with 8.85 (95% CI 8.77 to 8.93) years in the TTh– group (difference: −0.11 years or approximately −40 days). These findings reflect the overall pattern seen in the Kaplan-Meier estimates, where the initial lower risk in the TTh+ group (0.2% vs 2.3% at 1 year) shifted to higher risk by 10 years (21.7% vs 12.4%). Similarly, for active treatment, TTh+

Table 4 Kaplan-Meier risk estimates of any PCa diagnosis and of receiving any active treatment among +TTh versus −TTh (matched control cohort)

| Kaplan-Meier risk estimates of any PCa diagnosis (%, 95% CI) | | |
|---|---|---|
| Time point (years) | +TTh* | −TTh† |
| 1 | 0.2% (0% to 1.7%) | 2.3% (1.3% to 4.3%) |
| 5 | 6.5% (4.1% to 10.3%) | 5.6% (3.6% to 8.7%) |
| 10 | 21.7% (14.7% to 31.5%) | 12.4% (7.9% to 19.1%) |
| Kaplan-Meier risk estimates of any active PCa treatment‡ (%, 95% CI) | | |
| 1 | 0.6% (0.2% to 1.8%) | 0.7% (0.2% to 2.2%) |
| 5 | 1.7% (0.9% to 3.5%) | 3.8% (2.1% to 6.6%) |
| 10 | 6.7% (3.9% to 11.6%) | 8.7% (4.5% to 16.7%) |

*Men with testosterone deficiency and family history of prostate cancer receiving TTh.
†Men with testosterone deficiency and with family history of prostate cancer not receiving.
‡Active treatment includes any of the following: radical prostatectomy, androgen deprivation therapy, cryoablation or brachytherapy.
PCa, prostate cancer; TTh, testosterone therapy.

patients remained treatment-free for an average of 9.15 (95% CI 9.07 to 9.23) years, compared with 9.09 (95% CI 9.01 to 9.17) years in the TTh− group (difference: 0.06 years (−0.02, 0.14) or approximately 22 days), consistent with both the HR and the Kaplan-Meier estimates at 10 years (6.7% vs 8.7%).

## DISCUSSION

In the present study, we investigated the rates of PCa diagnosis and active PCa treatment in two matched groups, each consisting of 623 men with TD and a family history of PCa. One cohort received TTh, while the other never received TTh. According to current results, we found no significant difference in the incidence of any PCa diagnosis or active treatment for PCa between the two cohorts over a 10-year time frame. To our knowledge, this is the first study to evaluate the risk of PCa diagnosis in testosterone-deficient men who are considered high risk for PCa (family history) and treated with TTh. In this regard, all published studies investigating the relationship between TTh and risk of PCa have primarily focused on men with low to intermediate risk of PCa. As such, the latest evidence comes from the study conducted by Bhasin *et al* in which the risk of PCa and other adverse prostate events in a cohort of men from the TRAVERSE trial was investigated.[1] More in detail, the authors analysed these outcomes in 2601 men treated with TTh and 2603 in the placebo group. With a mean follow-up of 33 months, the authors did not find any significant difference in terms of incidence of high grade or any PCa in TTh group respect to placebo.[1] Of note, the population that was analysed was created by excluding men at high risk for PCa (eg, history of PCa, PSA concentrations greater than 3.0 ng/mL or a prostate nodule or induration at baseline). Likewise, the other two RCTs found similar results. Wittert *et al* in their T4DM randomised, double-blind, placebo-controlled trial, investigated the effects of TTh on type 2 diabetes mellitus and the mean change from baseline in 2-hour OGTT glucose at 2 years from therapy initiation.[13] In parallel, they also conducted a masked monitoring of PSA changes in both the treatment and placebo groups. From a safety perspective, TTh was not found to be associated with an increased risk of PCa compared with placebo. However, the study did reveal that TTh was linked to elevated haematocrit and PSA levels.[13] It is important to underline that we are not fully aware if patients included in this RCT were at high risk (ie, family history) for PCa.[13] Additionally, Snyder *et al* conducted another RCT involving 790 men aged 65 or older with TD. The participants were randomly assigned to receive either TTh (gel formulation) or a placebo gel for a period of 1 year.[14] The authors excluded men at high risk for PCa. They observed four PCa cases, three of which were in the TTh group. Despite these low rates, the authors concluded that the generalisability of their findings is limited.[14] In this regard, the available evidence coming from these RCTs, despite being conducted in men not considered high risk for PCa, supports the conclusion that TTh is safe with regard to any PCa diagnosis. Notably, even meta-analytical data by Zheng *et al*, which included 35 studies (30 RCT and 5 cohort studies) with a total of 7740 men, further supports that TTh does not increase the risk of PCa.[15] Certainly, it is important to consider that not all patients in these RCTs and cohort studies included in the cited meta-analysis underwent a prostate biopsy, and as a major limitation, it is possible that some PCa diagnoses were missed because they may not have presented with high PSA levels that would have led to a prostate biopsy. Furthermore, evidence regarding TTh is available in the context of active surveillance for PCa or in men who have already been treated for PCa. In this respect, based on small studies, it appears that TTh may even have a protective effect against PCa progression in men on active surveillance.[16 17] As such, a detailed analysis of our Kaplan-Meier curves reveals a complex temporal relationship between TTh and PCa risk. Hence, TTh showed

a potentially protective effect in the early years, but the curves diverged in later follow-up, with the TTh+ group showing higher cumulative incidence by the 10-year mark (21.7% vs 12.4%). Although not statistically significant, this difference of approximately 10% at 10 years deserves careful consideration from a clinical perspective as it may show a possible influence of TTh towards PCa development. Although this holds true, definitive and clinically meaningful conclusions are too precocious to be made in the absence of prospective randomised studies. To what concerns men who had active treatment (ie, radical prostatectomy), the most-updated AUA and EAU guidelines emphasise the lack of sufficient evidence to quantify the risk–benefit ratio of TTh in these men.[7 8] The same holds even more true for men considered at high risk for PCa due to lack of studies in these specific settings.

Lastly, the biological rationale behind studies supporting the safety of TTh in terms of PCa development requires further exploration. One speculation relates to the androgen saturation theory, which proposes that prostate tissue becomes less responsive to androgens beyond a certain threshold of circulating testosterone.[18] This theory potentially explains why TTh may not increase PCa risk, even in men considered high risk. Additionally, TTh may also potentially be involved in reducing inflammation and oxidative stress in the prostate, factors that could be implicated in carcinogenesis.[19] As such, the time-dependent pattern observed in our study could reflect these competing mechanisms, with initial protective effects potentially giving way to growth stimulation in susceptible individuals over time. To our knowledge, this is the first study addressing this clinical question, and our findings underscore the need for further investigation, particularly through prospective studies, to better understand the relationship between TTh and PCa in men considered at high risk for PCa. Despite this, it is important to highlight the study's limitations. First, the analysed data come from a TriNetX which relies on electronic health records from participating healthcare organisations. As such, incomplete, inaccurate or inconsistently recorded data could have affected the reliability of our study results. Moreover, we may have not captured all relevant confounding factors (ie, treatment compliance). For instance, the TriNetX system used in our study does not provide specific data on prostate nodules, further limiting the ability to exclude all men with undiagnosed PCa based on this clinical feature. In this regard, our approach to handling mortality differed from traditional competing risk analyses. We excluded patients who died without PSA testing rather than treating deaths as competing events, while patients who developed PCa were counted in the outcome regardless of subsequent death. This could affect risk estimates if excluded patients had different characteristics. Additionally, the healthcare organisations contributing data to TriNetX may not be representative of the entire population, potentially leading to selection bias. Moreover, the use of 1:1 propensity score matching is mandated by the TriNetX database software. As such, 2:1 or 5:1 matching could have potentially increased the statistical power of the present study; however, this is not possible to perform with TriNetX due to the database's intrinsic capabilities. Similarly, the platform's aggregate data structure prevents additional propensity score adjustments beyond the matching process already implemented. These limitations may have restricted our ability to detect smaller differences between groups. Second, the retrospective nature of the study raises concerns about potential confounding factors. For example, patients in the TTh group could have been followed up more closely, increasing the likelihood of detecting PCa in respect to those who never received TTh. Third, the study focused on the diagnosis of PCa rather than its incidence, as determining incidence would have required to prostate biopsy of all men. Fourth, there is a lack of data on clinically significant PCa in the TriNetX database (ie, Gleason Score). As a proxy, we used active treatment to approximate the definitions, but this should be referred to as 'active treatment for PCa' rather than 'clinically significant PCa'. It is also possible that some patients with a diagnosis of clinically insignificant PCa (ie, Gleason score 3+3) might have chosen to undergo active treatment, although the paradigm for treating low-grade group PCa has evolved over the analysed time period, making it challenging to entirely account for this factor.

Fifth, our analysis revealed a violation of the proportional hazards assumption, as it has been evidenced by crossing Kaplan-Meier curves. In this regard, the calculated HRs represented average effects that gave more statistical weight to earlier time points where more patients were under observation, potentially masking important temporal relationships. As such, we addressed this limitation by performing RMST analysis, which provided further data towards the time-varying relationship between TTh and the two outcomes of interest. Lastly, we lack information on the duration of TTh use and whether any patients switched between different TTh regimens. Despite these limitations, this study is the first to investigate the association between TTh and PCa incidence in men with TD and a family history of PCa. The large cohort size is a notable strength, and the findings should stimulate the scientific community to conduct RCTs in this field, which are crucial for further understanding the relationship between TTh and PCa in this population.

## CONCLUSIONS

Findings from this population-based study revealed that men with TD, who are considered high risk for PCa due to a positive family history and who received TTh, did not show a higher risk of being diagnosed with any PCa or of receiving any active treatment, compared with a matched cohort of men with TD and a family history of PCa who never received TTh over a 10-year period. Prospective RCTs are needed to confirm these findings and to assess their reproducibility over extended follow-up periods.

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**Patient consent for publication** Not applicable.

**Ethics approval** This study used deidentified patient data from the TriNetX Research Network, which connects insurance claims to individual electronic medical records from 85 healthcare organisations. TriNetX assumes responsibility for deidentification of the data in a process that adheres to Section x164.514(b)(1) of the Health Insurance Portability and Accountability Act Privacy Rule. As this study used only deidentified patient records and did not involve collection, use or transmittal of individually identifiable data, it was exempt from Institutional Review Board review.

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**Data availability statement** Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party and are not publicly available (TriNetX).



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## REFERENCES

1 Bhasin S, Travison TG, Pencina KM, *et al*. Prostate Safety Events During Testosterone Replacement Therapy in Men With Hypogonadism: A Randomized Clinical Trial. *JAMA Netw Open* 2023;6:e2348692.
2 Boyle P, Koechlin A, Bota M, *et al*. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. *BJU Int* 2016;118:731–41.
3 Xia B-W, Zhao S-C, Chen Z-P, *et al*. Relationship between serum total testosterone and prostate volume in aging men. *Sci Rep* 2021;11:14122.
4 Bartsch G, Rittmaster RS, Klocker H. Dihydrotestosterone and the concept of 5alpha-reductase inhibition in human benign prostatic hyperplasia. *Eur Urol* 2000;37:367–80.
5 Carson C, Rittmaster R. The role of dihydrotestosterone in benign prostatic hyperplasia. *Urology* 2003;61:2–7.
6 Swerdloff RS, Dudley RE, Page ST, *et al*. Dihydrotestosterone: Biochemistry, Physiology, and Clinical Implications of Elevated Blood Levels. *Endocr Rev* 2017;38:220–54.
7 Mulhall JP, Trost LW, Brannigan RE, *et al*. Evaluation and Management of Testosterone Deficiency: AUA Guideline. *J Urol* 2018;200:423–32.
8 Salonia A, Bettocchi C, Capogrosso P, *et al*. EAU guidelines on sexual and reproductive health. Arnhem, The Netherlands EAU Guidelines Office; 2023. Available: https://uroweb.org/guidelines/sexual-and-reproductive-health
9 Teeling F, Raison N, Shabbir M, *et al*. Testosterone Therapy for High-risk Prostate Cancer Survivors: A Systematic Review and Meta-analysis. *Urology* 2019;126:16–23.
10 Kardoust Parizi M, Abufaraj M, Fajkovic H, *et al*. Oncological safety of testosterone replacement therapy in prostate cancer survivors after definitive local therapy: A systematic literature review and meta-analysis. *Urol Oncol* 2019;37:637–46.
11 World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA* 2013;310:2191–4.
12 Elm E von, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
13 Wittert G, Bracken K, Robledo KP, *et al*. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol* 2021;9:32–45.
14 Snyder PJ, Bhasin S, Cunningham GR, *et al*. Effects of Testosterone Treatment in Older Men. *N Engl J Med* 2016;374:611–24.
15 Zeng B, Qiu S, Xiong X, *et al*. The effect of different administrations of testosterone therapy on adverse prostate events: A Bayesian network meta-analysis. *Front Endocrinol (Lausanne)* 2022;13:1009900.
16 Morgentaler A, Lipshultz LI, Bennett R, *et al*. Testosterone therapy in men with untreated prostate cancer. *J Urol* 2011;185:1256–60.
17 Kacker R, Hult M, San Francisco IF, *et al*. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. *Asian J Androl* 2016;18:16–20.
18 Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol* 2009;55:310–20.
19 Lee JH, Lee SW. Testosterone and Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Propensity Score-Matched Analysis. *J Sex Med* 2016;13:1047–55.