Long-term Exposure to Testosterone Therapy and the Risk of High Grade Prostate Cancer

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

PSA = prostate specific antigen

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Purpose: To our knowledge no population based studies have been done to examine whether long-term exposure to testosterone therapy is associated with an increased risk of high grade prostate cancer. We examined whether exposure to testosterone during a 5-year period was associated with an increased risk of high grade prostate cancer and whether this risk increased in a dose-response fashion with the cumulative number of testosterone injections.

Materials and Methods: Using SEER (Surveillance, Epidemiology and End Results)-Medicare linked data we identified 52,579 men diagnosed with incident prostate cancer between January 1, 2001 and December 31, 2006 who had a minimum of 5 years continuous enrollment in Medicare before the cancer diagnosis. We excluded patients diagnosed at death or after autopsy, those enrolled in a health maintenance organization in the 60 months before diagnosis and those with unknown tumor grade or tumor stage. In the 5 years before diagnosis 574 men had a history of testosterone use and 51,945 did not.

Results: On logistic regression adjusting for demographic and clinical characteristics exposure to testosterone therapy was not associated with an increased risk of high grade prostate cancer (OR 0.84, 95% CI 0.67−1.05) or receipt of primary androgen deprivation therapy following diagnosis (OR 0.97, 95% CI 0.74−1.30). In addition the risk of high grade disease did not increase according to the total number of testosterone injections (OR 1.00, 95% CI 0.98−1.01).

Conclusions: Our finding that testosterone therapy was not associated with an increased risk of high grade prostate cancer may provide important information regarding the risk-benefit assessment for men with testosterone deficiency considering treatment.

Key Words: prostatic neoplasms, testosterone, androgens, neoplasm grade, SEER program

TESTOSTERONE prescriptions for older men in the United States have increased more than threefold in the last decade.[1] Despite this rapid growth to our knowledge there have been no large, long-term, randomized, controlled trials of testosterone therapy to establish its safety. Currently there is considerable debate about the association between testosterone therapy and prostate cancer.[2−16] Research dating back to the 1940s established the testosterone dependence of prostate cancer and led to widespread concern that testosterone therapy may increase the risk of prostate cancer or an aggressive form of the disease.[6,17] Although several

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longitudinal studies subsequently showed no increased risk of prostate cancer incidence associated with testosterone use,[3,5,7,18–20] no population based studies been done to examine the association of high grade prostate cancer with testosterone exposure beyond 1 year. Given the slow course of prostate cancer development and the unknown latency period associated with testosterone exposure, examining this risk during a sufficient period is critically important from a clinical and a public health perspective.

Therefore, we examined whether exposure to testosterone in a 5-year period was associated with an increased risk of high grade prostate cancer at diagnosis and whether this risk increased in dose-response fashion with the total number of testosterone injections. As an additional marker of high risk disease we examined the receipt of primary ADT.

MATERIALS AND METHODS

Data Source

We analyzed data from SEER-Medicare, a linkage of population based cancer registries from 20 SEER regions, which cover approximately 28% of the population of the United States, with Medicare administrative data.[21] Approximately 94% of patients recorded in the SEER registry have been linked to their Medicare claims for covered health related services.

Study Cohort

Using SEER-Medicare linked data we identified 52,579 men diagnosed with incident prostate cancer between January 1, 2001 and December 31, 2006 who had a minimum of 5 years of available records. We excluded from study patients diagnosed at death or after autopsy, those enrolled in a health maintenance organization in the 60 months before diagnosis with incident prostate cancer and those with unknown tumor grade or stage. Among the cohort 574 men had a history of testosterone use before the prostate cancer diagnosis and 51,945 did not.

Testosterone Therapy

Testosterone therapy was defined using HCPCS (Health Care Procedure Coding System) drug administration codes, including J0900—testosterone enanthate, up to 1 cc; J1060—testosterone cypionate, up to 1 ml; J1070—testosterone cypionate, up to 100 mg; J1080—testosterone cypionate, up to 200 mg; J3120—testosterone enanthate, up to 100 mg; J3130—testosterone enanthate, up to 200 mg; J3140—testosterone suspension, up to 50 mg; J3150—testosterone propionate, up to 100 mg; and S0189—testosterone pellet, 75 mg (table 1). The cumulative dose of testosterone was assessed by summing the total number of testosterone injections for the 5-year period.

Risk Factors

Sociodemographic characteristics examined included age at diagnosis, marital status (currently married or currently not married), race/ethnicity (nonHispanic white, black, Hispanic American or other) and the percentage of those living below the poverty line in the census tract. Race/ethnicity was self-reported during the initial enrollment with the Social Security Administration. We included this variable in our analyses because cancer treatment and outcomes may vary by race/ethnicity. Clinical factors assessed included receipt of PSA tests and number of visits with a primary care physician. Comorbidity was measured with an adaptation of the Charlson comorbidity index[22] using information from the diagnosis codes in hospital and physician claims (inpatient and outpatient) corresponding to a date of service in the year before the cancer diagnosis.

Table 1. *Intramuscular testosterone*

Drug Name (dose)	HCPCS Code
Testosterone cypionate:	J1070
Up to 100 mg	
1 cc, 200 mg	J1080
Up to 50 mg	J1090
Testosterone enanthate:	
Up to 100 mg	J3120
Up to 200 mg	J3130
Testosterone suspension (up to 50 mg)	J3140
Testosterone propionate (up to 100 mg)	J3150

Outcomes

The primary outcome of this study was high tumor grade on biopsy specimen at diagnosis. As an additional marker of high risk disease we also examined primary ADT, defined as receiving at least 6 months of exclusive ADT in the first 12 months after the prostate cancer diagnosis.

Tumor Grade Classification

Before 2003 cancer grade was captured in the SEER database using certain categories, including low—Gleason 2-4, moderate—Gleason 5-7 or high—Gleason 8-10. In 2003 Gleason grade 7 was switched to the high grade category. From 2004 and thereafter the SEER database has captured specific Gleason score, allowing classification into similar groupings for data prior to 2003. Therefore, the high grade category was different in 2003 compared with the other study years. To examine the potential impact of this classification system we performed an analysis in which we removed all patients who were diagnosed with prostate cancer in 2003.

Statistical Analysis

Differences in the proportion of study characteristics among testosterone users and nonusers were assessed using Pearson chi-square analysis. Logistic regression models were then used to evaluate whether the likelihood of being diagnosed with high grade disease varied as a function of the cumulative testosterone dose. All analyses were performed with SAS®, version 9.1. This study was reviewed and approved by the University of Texas Medical Branch institutional review board.

RESULTS

The supplementary table (http://jurology.com/) lists demographic and clinical characteristics of testosterone therapy users and nonusers. The distribution