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 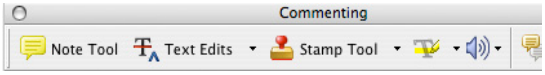

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 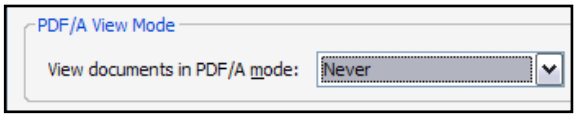

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 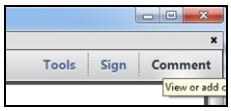

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 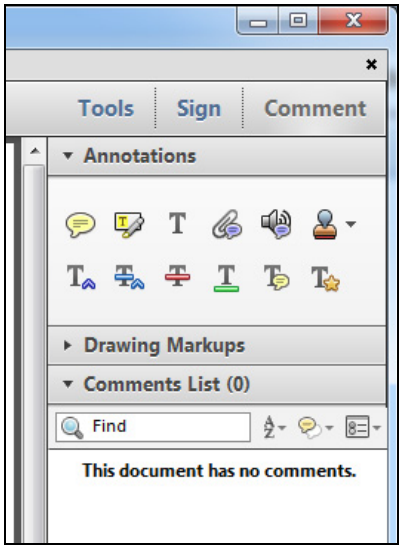
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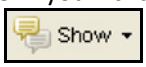
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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Health Outcomes Research

Use of Testosterone Replacement Therapy in the United States and Its Effect on Subsequent Prostate Cancer Outcomes

Alan L. Kaplan and Jim C. Hu

OBJECTIVE To assess utilization trends and determine the effect of testosterone replacement therapy on outcomes in men who subsequently developed prostate cancer.

METHODS We used linked Surveillance, Epidemiology, and End Results—Medicare data to identify 149,354 men diagnosed with prostate cancer from 1992 to 2007. Of those, 2,237 men (1.5%) underwent testosterone replacement therapy before their prostate cancer diagnosis. Propensity scoring methods were used to assess cancer-specific outcomes of testosterone replacement vs no replacement therapy.

RESULTS Testosterone replacement was associated with older age at cancer diagnosis, nonwhite race, and higher comorbidity ($P < .001$). No testosterone vs testosterone before the prostate cancer diagnosis was associated with higher grade (34% vs 30%, $P < .0001$) and more T4 (6.5% vs 4.3%, $P < .0001$) tumors. Mortality was decreased in men with ≥2 prostate-specific antigen (PSA) tests in the year before their cancer diagnosis. No significant difference was found between groups in overall survival, cancer-specific survival, or use of salvage androgen-deprivation therapy after initial treatment.

CONCLUSION Through our observational study design, we show that testosterone use was low throughout the study period. Testosterone use was not associated with aggressive prostate cancer and did not affect overall or disease-specific mortality. Although our findings support growing evidence that testosterone replacement is safe with respect to prostate cancer, confirmatory prospective studies are needed. UROLOGY ■: ■—■, 2013. © 2013 Elsevier Inc.

Up to 25% of older men experience hypogonadism. Prevalence is higher in men with comorbid disease and increases with age starting in the fourth decade.[1-3] Hypogonadal men have lower muscle mass, bone mineral density, and hemoglobin, and are in poorer general health.[4] During the past decade, there has been increasing awareness of the health benefits conferred by testosterone replacement therapy (TRT).[5] TRT for hypogonadism increases muscle mass and bone mineral density, decreases fat mass, and improves mood, libido, and sexual performance.[4-6]

Despite these benefits, there is an historical fear that administration of exogenous testosterone may increase the risk of developing prostate cancer or an aggressive form of the disease.[5,7] The seminal report by Huggins et al[8] in 1941 demonstrated that prostate cancer is androgen-dependent, in that testosterone "enhanced the rate of growth" of prostate cancer. Forty years later, Fowler et al[9] found that 87% of men with metastatic prostate cancer who received exogenous testosterone suffered exacerbation, leading to the oft-repeated suggestion that TRT in men with prostate cancer was akin to "pouring gasoline on a fire."

This historical concern that has led to hesitation in TRT administration for men without prostate cancer appears unfounded. Several longitudinal studies have shown no influence of serum testosterone levels on the risk of developing prostate cancer.[6,10] Although many small trials and 1 large specialty-center study demonstrate prostate safety with TRT, population-based data are limited, and practice patterns and outcomes in the community remain unclear.[10,11] Therefore, the objectives of our study were to characterize the use of TRT and its effect on outcomes in men that subsequently developed prostate cancer.

METHODS

Our study was approved by the University of California Los Angeles Institutional Review Board. Patient-specific data were de-identified, and requirement for consent was waived.

Financial Disclosure: *The authors declare that they have no relevant financial interests.*
Funding Support: *J.C.H. receives salary support from Department of Defense Physician Training Award W81XWH-08-1-0283.*

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Submitted: January 15, 2013, accepted (with revisions): March 22, 2013

0090-4295/13/$36.00
http://dx.doi.org/10.1016/j.urology.2013.03.049

Table 1. Characteristics of the study population

Variable	Categories	Before Propensity Weighting			After Propensity Weighting		
		No TRT No. (%)	TRT No. (%)	*P* Value	No TRT No. (%)	TRT No. (%)	*P* Value
Age, y	65-69	37,584 (25.5)	413 (18.5)	<.0001	37,422 (25.4)	591 (26.0)	.1755
	70-74	47,350 (32.2)	762 (34.0)		47,384 (32.3)	773 (34.0)	
	≥75	62,183 (42.3)	1062 (47.5)		62,287 (42.3)	896 (40.0)	
Race	White/non-Hispanic	11,8504 (80.6)	1743 (77.9)	<.0001	118,428 (80.5)	1835 (81.1)	.9430
	Black/non-Hispanic	14,482 (9.8)	294 (13.1)		14,552 (9.9)	211 (9.4)	
	Hispanic	8039 (5.5)	165 (7.4)		8080 (5.5)	125 (5.5)	
	Asian/non-Hispanic	6092 (4.1)	35 (1.6)		6034 (4.1)	90 (4.0)	
Charlson Comorbidity Index score	0	100,758 (68.4)	1352 (60.5)	<.0001	100,565 (68.4)	1551 (68.6)	.7444
	1	30,536 (20.8)	582 (26.0)		30,647 (20.8)	479 (21.2)	
	≥2	15,823 (10.8)	303 (13.5)		15,881 (10.8)	230 (10.2)	
Median household income in census tract of residence, $	<35,000	51,097 (34.7)	829 (37.1)	.048	51,140 (34.8)	759 (33.6)	.3624
	35,000-44,999	34,568 (23.5)	495 (22.1)		34,532 (23.5)	503 (22.3)	
	45,000-59,999	32,438 (22.1)	459 (20.5)		32,399 (22.0)	510 (22.5)	
	≥60,000	29,014 (19.7)	454 (20.3)		29,022 (19.7)	488 (21.6)	
At least a high school education in census tract of residence, %	<75	31,326 (21.3)	507 (22.7)	<.0001	31,351 (21.3)	481 (21.3)	.3186
	75-84.9	34,446 (23.4)	461 (20.6)		34,397 (23.3)	493 (21.8)	
	85-89.9	29,397 (20.0)	404 (18.1)		29,350 (20.0)	432 (19.1)	
	≥90	51,948 (35.3)	865 (38.6)		52,014 (35.4)	854 (37.8)	
Population density	Metropolitan	132,344 (90.0)	2051 (91.7)	.007	13,2361 (90.0)	2025 (89.6)	.6164
	Nonmetropolitan	14,773 (10.0)	186 (8.3)		14,733 (10.0)	236 (10.4)	
PSA tests 1-y before to diagnosis, No.	0	26,477 (18.0)	256 (11.4)	<.0001	26,329 (17.9)	410 (18.1)	.3873
	1	49,353 (33.5)	684 (30.6)		49,279 (33.5)	705 (31.2)	
	2	39,509 (26.9)	671 (30.0)		39,572 (26.9)	622 (27.5)	
	3+	31,778 (21.6)	626 (28.0)		31,914 (21.7)	524 (23.2)	
Preventive tests 1-y before diagnosis, No.	0	31,406 (21.4)	325 (14.5)	<.0001	31,251 (21.2)	478 (21.1)	.6717
	1	52,398 (35.6)	757 (33.9)		52,350 (35.6)	770 (34.1)	
	2	46,667 (31.7)	812 (36.3)		46,761 (31.8)	741 (32.8)	
	3+	16,646 (11.3)	343 (15.3)		16,732 (11.4)	272 (12.0)	

PSA, prostate-specific antigen; TRT, testosterone replacement therapy.

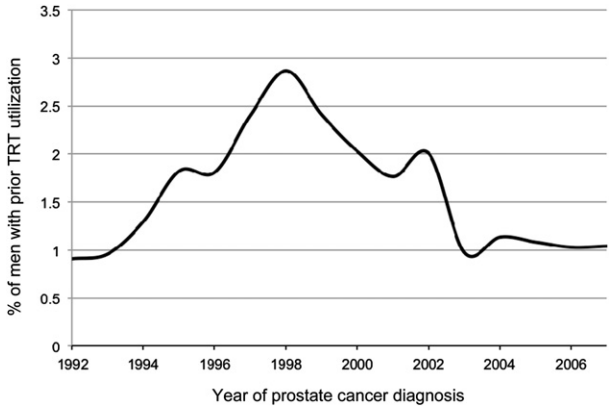

Figure 1. Use of testosterone replacement therapy (TRT) in men diagnosed with prostate cancer in a given year.

Data Source

We analyzed Surveillance, Epidemiology, and End Results (SEER)—Medicare data, which consisted of a linkage of population-based cancer registries from 20 SEER regions covering approximately 28% of the United States (U.S.) population with Medicare administrative data.[12] Medicare provides health care benefits to most elderly Americans. SEER-Medicare linked data captures approximately 97% of incident cancer cases and collects data on patient demographics, tumor characteristics, and initial treatment course.[13]

Study Cohort

We identified 348,372 men aged 65 years or older with a pathologic diagnosis of prostate cancer from 1991 to 2007. We excluded 113,844 men who were enrolled in a health maintenance organization or who were not enrolled in both Medicare Part A and B throughout the study period to avoid unreliable claims submissions. Complete information, including race, marital status, and clinical stages, was available for 169,414 men. An additional 20,060 men without 1 year of available data before their cancer diagnosis to assess comorbidity were excluded. After complete exclusion criteria were applied, our remaining cohort consisted of 149,354 men with prostate cancer. We divided this cohort into those who received TRT (n = 2237) before their prostate cancer diagnosis and those who did not (n = 147,117). TRT usage was identified by the presence of Physicians Current Procedural Terminology Coding System, 4th edition (CPT-4), for injection-based (J0900, J1060, J1070, J1080, J2320, J3120, J3130, J3140, J3150) and subcutaneous pellet (S0189) testosterone formulations.

Control Variables

Information on patient age (65-69, 70-74, ≥75 years) was obtained from the Medicare denominator file, whereas race (white/non-Hispanic, black/non-Hispanic, Hispanic, Asian/non-Hispanic), SEER region, education level, household income, population density (urban vs rural), and tumor characteristics were obtained from SEER registry data. Because of small numbers, we combined the Hawaii and rural Georgia SEER registries.

Comorbidity was assessed using the Klabunde modification of the Charlson Comorbidity Index based on inpatient, outpatient, and physician services the year before the prostate cancer diagnosis.[14] In addition, access to medical care, particularly Medicare-covered preventative testing (cholesterol screening, influenza vaccination, colonoscopy) and the frequency of prostate-specific antigen (PSA) screening before the prostate cancer diagnosis, may influence tumor stage and grade and survival outcomes, and we captured the use of these services through Medicare. Treatment type was also captured by the associated CPT-4 procedure code.

Outcomes

On the basis of receipt of TRT, we examined prostate cancer–specific outcomes, including tumor grade on biopsy specimen, clinical stage, initial treatment modality, and need for salvage androgen-deprivation therapy (ADT), and disease-specific and overall survival. Use of ADT was identified using techniques previously described.[15]

Statistical Analysis

We used weighted propensity score methods to adjust for differences in demographic and tumor characteristics.[16,17] Propensity score methods permit control for observed confounding factors that may influence group assignment and outcomes by using a single composite measure, attempting to balance patient characteristics between groups as would cohort randomization. Because length of follow-up varied, we compared rates (events per 100 person-years) of overall survival, disease-specific survival, and need for salvage ADT by TRT vs no TRT before the prostate cancer diagnosis. All tests were considered statistically significant at $\alpha = 0.05$. Statistical analyses were performed with SAS 9.1.3 software (SAS Institute Inc, Cary, NC).

RESULTS

Median age of our study sample was 73 years (interquartile range [IQR], 69-78 years). Of the 149,354 men in our cohort, 2,237 (1.50%) used TRT before their prostate cancer diagnosis. Use increased with age: 47.5% on TRT were aged 75 years or older (Table 1). TRT use was greater between 1997 and 2002 (Fig. 1), peaking in 1998, with 2.8% of those diagnosed with prostate cancer using TRT. Median length of TRT use was 93 days (IQR, 30-449 days).

We observed minimal sociodemographic differences between groups. Propensity weighted analysis found no significant demographic factors associated with TRT usage. However, TRT was associated with PSA testing and preventive tests performed in the year before diagnosis ($P < .0001$), although this pattern lost significance with propensity analysis.

Median follow-up after the prostate cancer diagnosis was 5.0 years (IQR, 2.9-7.6 years). In adjusted analyses (Table 2), TRT vs no TRT men were more likely to be diagnosed with moderately differentiated disease (63.5% vs 59.2%, $P < .001$) and less likely to have poorly differentiated disease (29.7% vs 34.2%, $P < .001$). In addition, TRT vs no TRT men were more likely to be diagnosed with clinical stage T3 (4.0% vs 3.1%, $P < .001$) and less likely to have T4 disease (4.3% vs 6.5%, $P < .001$). TRT vs no TRT men were more likely to

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Table 2. Unadjusted and adjusted prostate cancer-specific outcomes for testosterone replacement therapy before prostate cancer diagnosis vs no testosterone replacement therapy

Variable	Categories	No TRT No. (%)	TRT No. (%)	*P* Value	No-TRT No. (%)	TRT No. (%)	*P* Value
Grade	Well	9722 (6.6)	160 (7.2)	<.0001	6.6	6.8	<.0001
	Moderately	87,084 (59.2)	1444 (64.6)		59.2	63.5	
	Poorly	50,311 (34.2)	633 (28.3)		34.2	29.7	
Clinical stage	T1	58,807 (40.0)	932 (41.7)	<.0001	40.0	41.6	<.0001
	T2	74,210 (50.4)	1152 (51.5)		50.5	50.1	
	T3	4580 (3.1)	73 (3.3)		3.1	4.0	
	T4	9520 (6.5)	80 (3.6)		6.5	4.3	
Initial treatment	ADT	24,878 (16.9)	321 (14.4)	.006	16.9	12.3	<.0001
	RP	27,034 (18.4)	401 (17.9)		18.4	20.0	
	RT	74,391 (50.6)	1181 (52.8)		50.6	53.1	
	WWAS	20,814 (14.2)	334 (14.9)		14.1	14.7	

Q4 ADT, androgen-deprivation therapy; RP, radical prostatectomy; RT, radiotherapy; WWAS, watchful waiting with active surveillance.

Table 3. Adjusted survival and disease severity outcomes in men who did and did not use testosterone replacement therapy

Per 100 person-years	No TRT	TRT	*P* Value
Overall survival	6.87	6.56	.2882
Disease-specific survival	1.56	1.34	.2586
Use of salvage ADT	1.32	1.21	.5250

undergo radical prostatectomy (20.0% vs 18.4%), radiotherapy (53.1% vs. 50.6%), and active surveillance (14.7% vs 14.1%; all P <.001). No TRT was associated with greater use of ADT (16.9% vs 12.3%, P <.0001). Finally, use of TRT was not associated with differences in overall survival (P = .288), disease-specific survival (P = .259), or need for salvage ADT (P = .525; Table 3).

COMMENT

Men who experience hypogonadism are in poorer general health than eugonadal men.[4] Hypogonadism is associated with the development of the metabolic syndrome,[18] type 2 diabetes mellitus,[19] and cardiovascular disease.[20] Hypogonadal men incur higher medical costs compared with controls.[21,22] Men treated with TRT demonstrate improved sexual function, mood, and experience improved overall health.[4,6,7,23,24] Prevalence of hypogonadism, as determined by longitudinal and cross-sectional studies, ranges from 2.1%-25%, depending on the strictness of criteria.[1-3,25] Average ages in these cohorts ranged between 47 and 59 years. These studies uniformly show that the prevalence of hypogonadism increases with age, starting in the fourth decade, and increases with medical comorbidity such as the metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease.[1] Men in the Massachusetts Male Aging Study (MMAS) demonstrated a 10% decrease in total testosterone per decade and a 24% decrease in free testosterone per decade.[25]

Our study has many important findings. First, overall use of TRT was low throughout the study period, peaking at 2.8% in 1998. Given the median age in our cohort was Q2 73 years, we expected the prevalence of hypogonadism would be higher than in the aforementioned studies. Despite abundant contrary evidence and expert reviews attempting to dispel the fallacy that TRT increases prostate cancer risk, the myth persists.[6,8] In an international survey study, more than 50% of physicians cited prostate cancer risk as their rationale for withholding TRT in hypogonadal men.[26]

Second, a use of TRT was not associated with more aggressive prostate cancer at diagnosis. Men in the TRT group were no more likely to be diagnosed with poorly differentiated tumors or T4 disease, even after adjusting for the number of preventive and PSA tests before diagnosis. A recently published prospective, observational cohort of 1365 hypogonadal men in the United Kingdom treated with TRT found no significant increase in prostate cancer incidence.[12] Of the 14 incident cancers in that cohort, all tumors were clinically localized and curable. Prostate cancer detection in several TRT trials of approximately 1% is similar to age-matched populations.[6,27,28] Our findings corroborate those of previous studies.

Third, TRT use did not worsen overall or cancer-specific survival. Median follow-up in our study was 5.0 years (IQR, 2.9-7.6 years). Even in high-risk prostate cancer, the likelihood of death in this timeframe is low. However, we also found no significant difference between groups for rates of skeletal-related events or the need for Q3 salvage ADT.

Finally, increased frequency of PSA testing in our cohort predicted improved overall and cancer-specific survival. We hypothesized that men treated with TRT would seek more medical care and undergo more preventive testing and cancer screening than controls. In adjusting for this potential confounder, we examined the number of PSA tests in the year before the prostate cancer diagnosis and the number of preventive tests before diagnosis. The improved cancer-specific and overall survival was an important finding in light of the recent U.S. Preventive Services Task Force recommendations

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against prostate cancer screening.[29] Our findings agree with those of the European Randomized Study of Screening for Prostate Cancer trial, which showed a statistically significant absolute risk reduction in prostate cancer-specific mortality (relative risk, 0.80; 95% confidence interval, 0.65-0.98).[30]

Our findings must be interpreted in the context of the study design. First, claims-based data are designed to provide billing rather than clinical information. More comprehensive clinical data regarding TRT administration, diagnoses of hypogonadism, and prostate cancer outcomes might have influenced the associations we identified. We were not unable to identify users of TRT before age 65 years nor do we have information on serum testosterone levels that prompted therapy. Our study primarily captures TRT encounters in the era before aggressive pharmaceutical company marketing and did not capture testosterone gel or oral formulations. Gel formulations were not approved by the U.S. Food and Drug Administration until the end of our study period, and oral testosterone is rarely used in the U.S.

Second, our analysis only captures TRT usage during Medicare coverage. Limited data exist regarding TRT use in men aged younger than 65 years. Although the prevalence of hypogonadism increases as men age, we were only able to capture those with Medicare eligibility.

Third, 5-year survival after prostate cancer diagnosis is high, and longer follow-up might impact the effect of TRT on cancer-specific outcomes. However, patients in the TRT group were no more likely to have poor tumor grade or stage characteristics nor did they require salvage ADT more frequently, both of which are surrogate markers of poor prostate cancer prognosis.

CONCLUSION

Despite the high prevalence of hypogonadism in older men and well-established health benefits of TRT, use of TRT is markedly low. The concern of increasing prostate cancer risk or cancer severity by administering TRT has been widely disproved. Using SEER-Medicare linked data, we found no change in prostate cancer-specific outcomes, cancer-specific survival, or overall survival in men treated with TRT before their prostate cancer diagnosis. Our population-based study adds to the growing body of evidence that TRT does not confer worse prostate cancer outcomes.

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