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# Trends in Testosterone Therapy use in Prostate Cancer Survivors in the United States

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# Keywords

Prostate Cancer; Testosterone; Hypogonadism; Survivorship

# Introduction

Testosterone deficiency (TD), or hypogonadism, is defined by the combination of a low serum testosterone laboratory value and associated symptoms such as decreased libido, fatigue, depression, and lean body mass, erectile dysfunction<sup>1</sup>. The prevalence of TD in the United States ranges from 6 to 39% depending on definitions used and populations studied<sup>2</sup>. TD is readily treatable with testosterone therapy (TTh) and its use has increased more than six-fold between 2002 and 2013, from 0.52% of men to 3.2% in the United States<sup>3</sup>. Despites its popularity and efficacy<sup>4,5</sup>, a concern surrounding the link between testosterone and prostate cancer gives some clinicians pause in prescribing TTh to patients with a history of prostate cancer (CaP). Indeed, the FDA requires labels on testosterone products warning of "a potential risk of prostate cancer and increase in prostatic specific antigen (PSA)<sup>6</sup>." This may lead to some men failing to receive treatment that could otherwise benefit them.

In 1941, Drs. Huggins and Hodges established the androgen-dependent model of CaP by demonstrating regression of metastatic CaP in men who had been castrated<sup>7</sup>. The corollary to this model led to a fear that administering testosterone to men will likewise fuel CaP growth. However, evidence has emerged in the interim that have provided a more contemporary understanding of the relationship between androgen receptor function, prostate specific antigen (PSA) levels, and CaP growth which suggest TTh does not increase the risk of CaP recurrence. Indeed, groups have reported treating men with testosterone after the diagnosis and treatment of prostate cancer<sup>8,9</sup>. The American Urological Association guidelines as well as numerous reviews and meta-analyses have reinforced the safety of TTh in men with TD and treated prostate cancer<sup>10–13</sup>. Given the contradictions in product warning labels and current clinical evidence, we sought to characterize the demographics and usage patterns of TTh in men with a history of prostate cancer in the U.S.

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## Materials and Methods

The present study utilized the Optum's De-identified Clinformatics® Data Mart database, which is a commercial and Medicare Advantage claims database that includes patient enrollment, physician, facility data, laboratory results and pharmacy claims for 77 million individuals in the United States. To assess TTh prescribing patterns, associated diagnoses and laboratory values, we examined the cohort from 2003 to 2018.

International Classification of Diseases 9th revision and 10th revision, Clinical Modification (ICD-9-CM, ICD-10-CM) codes, Current Procedural Terminology (CPT) codes were used to identify men 40 years and over who had a diagnosis of CaP and who had undergone subsequent treatment with either surgery or radiation (See Supplementary Table 1). Logical Observation Identifiers Names and Codes (LOINC®) were used to query testosterone and PSA laboratory test values which were available for a subset of individuals before and after TTh initiation. Pharmacy and procedural claims data using prescription names, Healthcare Common Procedure Coding System (HCPCS), and CPT codes were used to identify specific testosterone formulations administered. If testosterone or PSA laboratory values were available, they must have occurred within 1 year before initiation of TTh after prostate cancer treatment. PSA and testosterone laboratory values were converted to pg/mL and ng/mL respectively. We excluded men who had less than 6 months of enrollment time before or after CaP treatment. This study was deemed exempt by the Institutional Review Board of Stanford University. Mean and standard deviation of age was reported and compared by Student's t-test between men with TTh after CaP and those without. Frequencies and percentages were reported for categorical variables and compared by Chisquare tests. Medians and interquartile ranges were reported for PSA, testosterone lab tests due to non-normal data distribution. Due to data-use agreements regarding minimum cell size numbers, we can only provide approximation when any individual cell would be <11. Rather than exclude all numbers, we provide approximations when necessary. All analyses were performed by SAS (version 9.4; SAS Institute Inc., Cary, NC).

# Results

Over the duration of the study period, a total of 126,374 men completed treatment for CaP (42,515 surgery, 75,186 radiation, 8,673 both). Of these, 3,074 men (2.4%) received testosterone after CaP treatment. Compared to those who did not receive TTh after Cap treatment, most men who went on to receive testosterone were younger (63.8 vs 67.3), white, college educated, and higher earning, and living in the South. They were also more likely to have erectile dysfunction and depressive disorder, and less likely to have a pre-treatment PSA of >10 (Table 1). Asians were the least likely ethnic group to undergo TTh.

Temporally, we observed a rise in the use of testosterone after CaP from the beginning of the study period until it peaked in 2013, going from 0.21% of men to 4.9% of men representing a more than 20-fold increase over 10 years. This trend was seen after separating men by prostate cancer treatment modality (radiation versus surgery versus combination).

After 2013, rates decreased annually until a plateau of approximately 1.79% of men (Figure 1A).

There were differences in the cohorts of men receiving testosterone depending on whether their prostate cancer treatment was surgery or radiation. The median (interquartile range) pre-treatment PSA in the post-surgery group was 0 (0 –0), 0.2 (0 –0.8) in the post-radiation group, and 0 (0 –0.5) in those that received both radiation and surgery for prostate cancer treatment. Median (Interquartile Range) of Testosterone levels before initiation of T therapy was 254 (188 – 343), 214 (98 – 303), and 172 (14 – 335) ng/dL respectively in those groups. The median time to initiation of TTh from prostate cancer treatment was 78.4 weeks in the post-surgical cohort and 100.4 weeks in the post-radiation cohort and 137.4 weeks in the combination cohort, and the median duration of TTh in years was 1.37, 0.83, and 0.94 in those cohorts respectively (Table 2). The cohort receiving testosterone after surgery was comprised of men who were younger, more likely to be White, more likely to have a Bachelor Degree or higher, and more likely to earn 100k+ per year when compared to the radiation cohort (Table 3). 34.0 to 37.4% of men did not have a testosterone lab value checked before initiation of TTh and the most popular route of TTh was through injection, and secondarily, topical.

# Discussion

During the study period, we observed an annual increase in men receiving testosterone after prostate cancer treatment until a peak is seen in 2013 followed by subsequent year-over-year declines (Figure 1A and 1B). A higher proportion of men who end up receiving testosterone have pre-treatment PSAs in the 0-4 pg/dL range suggesting men with lower risk disease are more likely to be prescribed testosterone than those higher risk patients with a pre-treatment PSA greater than 10. Demographic differences in race, education and income between those receiving TTh after prostate cancer treatment and those not suggest that socioeconomic factors may play a role in who ends up needing and receiving testosterone. 144 of the 3,074 men (4.7%) had a combination of surgical and radiation treatment of prostate cancer diagnoses and still went on to receive TTh. In addition, among subjects with laboratory data available, TTh was started on men with low or unmeasurable PSA values duration consistent with treated prostate cancer, and with testosterone levels consistent with AUA guideline suggested thresholds of 300 ng/dL. Significantly higher rates of diagnoses of erectile dysfunction and depression in the group receiving testosterone suggest that men are being treated for symptoms in addition to low laboratory levels. Over one third of men did not have a testosterone level obtained before initiation of TTh, slightly higher than the approximate 25% reported in previous series on the general U.S. population<sup>14</sup>. TTh was started sooner and was sustained for longer durations after those completing surgical therapy compared to those completing radiation therapy. Starting TTh sooner after surgery may be potentially explained by differences in post-treatment PSA kinetics amongst the two cohorts, with PSAs reaching stable nadirs more expediently after surgery than radiation. Unique post-radiotherapy effects such as PSA bounce, which can occur in approximately a third of patients<sup>15</sup>, may lead to cessation of testosterone therapy that would otherwise not occur in the surveillance of patients post-surgery.

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The current analysis demonstrates that the trends in testosterone prescriptions in patients that had CaP treated mirrored general national trends overall. Indeed, a report by Baillargeon et. al reviewed testosterone prescriptions in commercially insured men from 2002–2016 and demonstrated the same peak and decline seen in the current report. Their hypothesis suggests that publications in the years 2013 and 2014 regarding cardiovascular risks associated with TTh may have contributed to hesitation among providers in starting patients on testosterone in general<sup>3</sup>. The work of Huggins and Hodges established the testosteronedependent nature of prostate cancer and postulated a directional association between the two. However, more modern data suggest that the association is complex and likely not simply linear in nature. Studies have shown increases in PSA in hypogonadal men treated with exogenous testosterone, but not in eugonadal subjects<sup>16–18</sup> Morgentaler and Traish sought to resolve this paradox when they proposed the saturation theory of prostate cancer in 2009<sup>19</sup> which holds that prostate tissue, while responsive to changes in serum androgens at low concentrations, are no longer sensitive to them once a saturation point is reached, at approximately the 250ng/dL range<sup>20</sup>. Numerous studies have demonstrated a lack of increased risk of either biochemical or clinical evidence of prostate cancer recurrence in men receiving clinically-indicated TTh after surgery $^{21-23}$  or radiation $^{24-27}$ . There is even evidence supporting the safety of TTh in men on active surveillance<sup>28</sup>.

Despite the growing body of knowledge supporting the safety of TTh in men with treated prostate cancer, the Endocrine Society guidelines recommend against starting TTh in men with a history of prostate cancer. In contrast, the AUA guidelines note an absence of evidence linking TTh to the development of prostate cancer<sup>1,29</sup>. In 2016, Kaplan et. al published independent recommendations<sup>30</sup> after reviewing the literature. In it, they recommend PSA levels be undetectable following radical prostatectomy or stable for a 6-month period after radiation treatment. They also caution starting TTh in men at high risk for recurrence or progression. Several limitations warrant mention. As an analysis of population-based administrative claims database, the validity of the results rely on valid and proper diagnosis and procedural coding. Some men may obtain testosterone that is not reimbursed by insurance, and therefore are not captured in the database. Testosterone prescriptions may have been filled but not actually taken. This methodology of this study allows it to evaluate clinical trends and patterns over time, but it does not reveal causality or etiology of observations. Importantly, relevant clinicopathoogical CaP data such as Gleason Score or cancer stage were unfortunately not available for analysis, and precludes the study's ability to comment on safety or oncologic outcomes of TTh in treated CaP.

Nevertheless, the current report demonstrates that many men are treated with TTh after prostate cancer therapy with pre-TTh PSA levels attributable to no active disease. The data on testosterone prescriptions are consistent with trends seen in the general population. TTh initiation often occurs in the presence of evidence of clinical and laboratory-confirmed TD. However, the findings that only roughly two-thirds of patients have testosterone levels checked before initiation of TTh suggests room for improvement for guideline-adherent treatment of TD.

Increased provider vigilance in obtaining appropriate laboratory workup in symptomatic patients before TTh is encouraged.

# Conclusions

National trends in testosterone prescriptions for men with treated prostate cancer demonstrates that many men are treated with TTh after prostate cancer therapy. TTh is being initiated post-treatment with patterns of indications and monitoring consistent with the general population. More data are necessary and continued monitoring of testosterone prescribing trends will be important as more data become available.

# Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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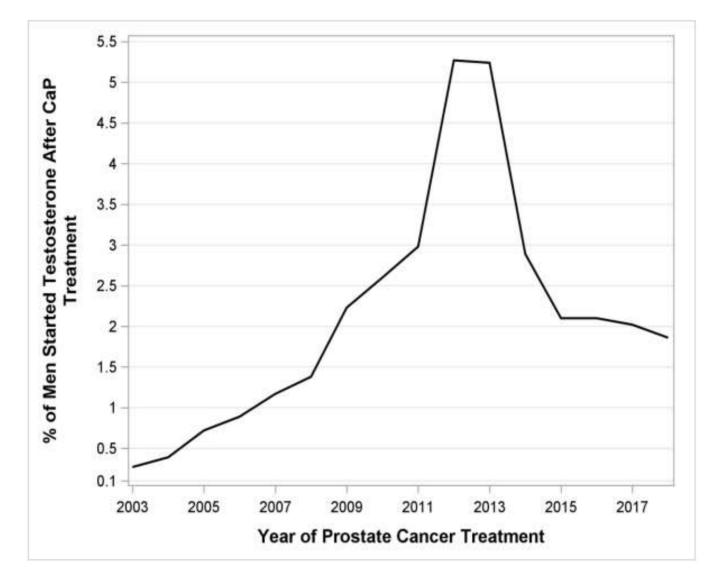
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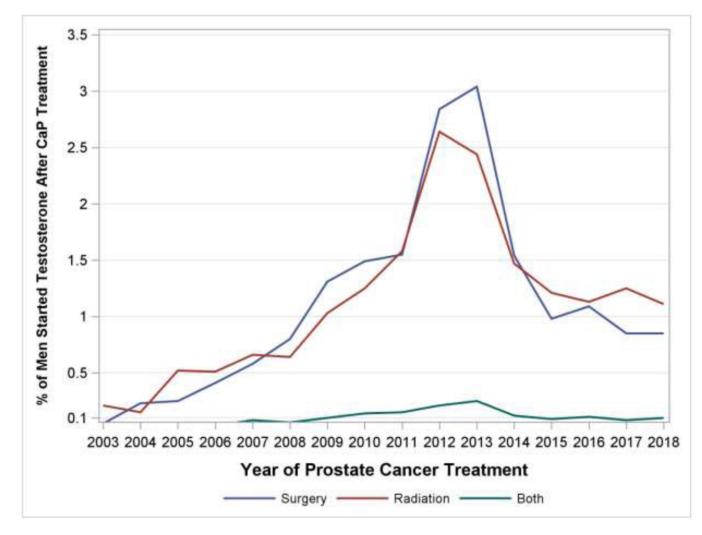
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#### Figure 1A:

Percentage of men started on Testosterone after prostate cancer treatment. B: Percentage of men started on Testosterone after prostate cancer treatment, separated by treatment modality

#### Table 1:

Demographics of men receiving and not receiving testosterone therapy (TTh)after prostate cancer treatment. "Other" testosterone routes include subcutaneous pellets, buccal, and intranasal formulations.

		Men without TTh after CaP treatment Mean (STD)	Men with TTh after CaP treatment Mean (STD)	p-value
	n=	123,300	3,074	
	Mean Age (STD), years	67.3 (8.9)	63.8 (9.3)	<.0001
Age	<55	10332 (8.38)	524 (17.05)	<.0001
	55–65	39023 (31.65)	1198 (38.97)	
	65+	73945 (59.97)	1352 (43.98)	
Follow-Up	<1 year	19189 (15.56)	149 (4.85)	<.0001
	1–2	27032 (21.92)	355 (11.55)	
	2+	77079 (62.51)	2570 (83.6)	
Year	2003–6	15830 (12.84)	429 (13.96)	<.0001
	2007–10	32411 (26.29)	1186 (38.58)	
	2011–2014	32222 (26.13)	912 (29.67)	
	2015+	42837 (34.74)	547 (17.79)	
Race	Asian	2458 (1.99)	27 (0.88)	<.0001
	Black	14107 (11.44)	269 (8.75)	
	Hispanic	9282 (7.53)	209 (6.8)	
	White	86517 (70.17)	2335 (75.96)	
	Unknown	10936 (8.87)	234 (7.61)	
Education	Less than 12th grade	602 (0.49)	<11	<.0001
	High School Diploma	30342 (24.61)	632 (20.56)	
	Less than Bachelor degree	63352 (51.38)	1602 (52.11)	
	Bachelor Degree or plus	20910 (16.96)	684 (22.25)	
	Unknown	8094 (6.56)	140+	
Annual Household	2017	2/7// (21.71)	520 (17 52)	
Income	<50K	26766 (21.71)	539 (17.53)	<.0001
	50–100K 100K+	38606 (31.31)	949 (30.87)	
	Unknown	33354 (27.05) 24574 (19.93)	1111 (36.14) 475 (15.45)	_
Decise		× ,	370+	< 0001
Region	Midwest	29279 (23.75)		<.0001
	Northeast	13282 (10.77)	190 (6.18)	
	South	53346 (43.27)	1781 (57.94)	
	West	27225 (22.08)	725 (23.58)	
	Unknown	168 (0.14)	<11	_

		Men without TTh after CaP treatment Mean (STD)	Men with TTh after CaP treatment Mean (STD)	p-value
	n=	123,300	3,074	
Testosterone Therapy Route:	Injection		1412 (46.60)	
	Topical		1029 (33.96)	
	Other		589 (19.44)	
Comorbidities:	% With Diabetes	30330 (24.60)	760 (24.72)	0.8738
	% with Erectile Dysfunction	20801 (16.87)	863 (28.07)	<.0001
	% with Depressive Disorder	4593 (3.73)	184 (5.99)	<.0001
	% with Hypertension	78550 (63.71)	1994 (64.87)	0.1863
Pretreatment PSA (pg/dL)	0-4	10863 (26.88)	386 (36.18)	<.0001
	4–10	21316 (52.75)	560 (52.48)	
	10+	8232 (20.37)	121 (11.34)	

#### Table 2:

Characteristics of Men Receiving Testosterone Therapy after Prostate Cancer Treatment by Prostate Cancer Treatment Modality.

	T after Surgery	T after Radiation	T after Radiation and Surgery
n=	1587	1631	144
Median (IQR) Testosterone Level before starting testosterone therapy (ng/dL)	254 (188 - 343)	214 (98 - 303)	172 (14 – 335)
Percent of Men without a testosterone lab level before starting testosterone therapy	37.4%	35.7%	34.0%
Median (IQR) Time between prostate cancer treatment and starting testosterone (Weeks)	78.4 (33.3 – 171.4)	100.4 (41.4 - 189.9)	137.4 (62.5 - 261.4)
Median (IQR) Post-Treatment PSA before starting testosterone therapy (ng/mL)	0 (0 – 0)	0.2 (0 – 0.8)	0 (0 – 0.5)
Duration of TTh (years), median (IQR)	1.37 (0.27 – 4.82)	0.83 (0.18 - 3.45)	0.94 (0.17 – 3.41)

### Table 3:

Demographic Differences in Men Receiving Testosterone Therapy (TTh) after Prostate Cancer Treatment by Prostate Cancer Treatment Modality. "Other" testosterone routes include subcutaneous pellets, buccal, and intranasal formulations.

		TTh after Surgery	TTh after Radiation	TTh after Radiation and Surgery
		n (%)	n (%)	n (%)
	n=	1587	1631	144
	Mean Age (STD), years	59.8 (7.8)	67.5 (9.0)	61.7 (7.9)
Age	<55	410 (25.83)	145 (8.89)	31 (21.53)
	55–65	775 (48.83)	493 (30.23)	70 (48.61)
	65+	402 (25.33)	993 (60.88)	43 (29.86)
Education	Less than 12th Grade	<11	<11	0 (0)
	High School Diploma	309 (19.47)	352 (21.58)	20+
	Less than Bachelor Degree	810 (51.04)	861 (52.79)	69 (47.92)
	Bachelor Degree Plus	395 (24.89)	328 (20.11)	39 (27.08)
	Unknown	70+	80+	<11
Race	Asian	14 (0.88)	13 (0.8)	0 (0)
	Black	120 (7.56)	164 (10.06)	11+
	Hispanic	91 (5.73)	124 (7.6)	<11
	White	1247 (78.58)	1200 (73.57)	112 (77.78)
	Unknown	115 (7.25)	130 (7.97)	11 (7.64)
Region	Midwest	221 (13.93)	171 (10.48)	11+
	Northeast	80+	100+	<11
	South	945 (59.55)	922 (56.53)	86 (59.72)
	West	332 (20.92)	427 (26.18)	34 (23.61)
	Unknown	<11	<11	0
Income	<50K	218 (13.74)	345 (21.15)	24 (16.67)
	50-100K	481 (30.31)	513 (31.45)	45 (31.25)
	100K+	664 (41.84)	508 (31.15)	61 (42.36)
	Unknown	224 (14.11)	265 (16.25)	14 (9.72)
Comorbidities	% With Diabetes	338 (21.30)	459 (28.14)	37 (25.69)
	% with Erectile Dysfunction	495 (31.19)	404 (24.77)	36 (25.00)
	% with Depressive Disorder	107 (6.74)	84 (5.15)	<11
	% with Hypertension	981 (61.81)	1106 (67.81)	93 (64.58)
Testosterone Therapy Route:	Injection	746 (47.76)	718 (44.57)	52 (36.36)
	Topical	605 (38.73)	463 (28.74)	39 (27.27)

		TTh after Surgery	TTh after Radiation	TTh after Radiation and Surgery
		n (%)	n (%)	n (%)
	n=	1587	1631	144
	Other	211 (13.51)	430 (26.69)	52 (36.36)