Incidence of Prostate Cancer in Hypogonadal Men Receiving Testosterone Therapy: Observations from 5-Year Median Followup of 3 Registries

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Abbreviations and Acronyms

DRE = digital rectal examination

EAU = European Association of Urology

ERSPC = European Randomized Study of Screening for Prostate Cancer

LUTS = lower urinary tract symptoms

PCa = prostate cancer

PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

PSA = prostate specific antigen

T = testosterone

TRUS = transrectal ultrasound

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Purpose: Although there is no evidence that testosterone therapy increases the risk of prostate cancer, there is a paucity of long-term data. We determined whether the incidence of prostate cancer is increased in hypogonadal men receiving long-term testosterone therapy.

Materials and Methods: In 3 parallel, prospective, ongoing, cumulative registry studies 1,023 hypogonadal men received testosterone therapy. Two study cohorts were treated by urologists (since 2004) and 1 was treated at an academic andrology center (since 1996). Patients were treated when total testosterone was 12.1 nmol/l or less (350 ng/dl) and symptoms of hypogonadism were present. Maximum followup was 17 years (1996 to 2013) and median followup was 5 years. Mean baseline patient age in the urological settings was 58 years and in the andrology setting it was 41 years. Patients received testosterone undecanoate injections in 12-week intervals. Pretreatment examination of the prostate and monitoring during treatment were performed. Prostate biopsies were performed according to EAU guidelines.

Results: Numbers of positive and negative biopsies were assessed. The incidence of prostate cancer and post-prostatectomy outcomes was studied. A total of 11 patients were diagnosed with prostate cancer in the 2 urology settings at proportions of 2.3% and 1.5%, respectively. The incidence per 10,000 patient-years was 54.4 and 30.7, respectively. No prostate cancer was reported by the andrology center. Limitations are inherent in the registry design without a control group.

Conclusions: Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer. If guidelines for testosterone therapy are properly applied, testosterone treatment is safe in hypogonadal men.

Key Words: testosterone, prostatic neoplasms, incidence, testosterone undecanoate, hypogonadism

Clinical evidence suggests that T therapy improves symptoms of hypogonadism.[1–4] One of the major concerns of T therapy is PCa growth.[5] The biochemical response of prostate cells is regulated mainly by the density and activity of the intracellular androgen receptor and not by total

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plasma circulating T.[6] However, the concept that T or 5α-dihydrotestosterone induces initiation, promotion and/or development of PCa is as yet an unproven premise since no data are available to our knowledge to demonstrate that androgens are direct chemical carcinogens and cause direct transformation of normal prostate epithelial cells into neoplastic cells.

Considerable skepticism exists concerning the newly advanced hypothesis that "T therapy does not pose a greater risk for development of PCa."[6] However, no compelling evidence is available to discredit or dismiss this newly advanced hypothesis.[7,8] Longitudinal studies of endogenous androgens failed to demonstrate any increased PCa risk with higher levels.[9] Also, the placebo arm of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial involving prostate biopsies at years 2 and 4 did not demonstrate an increased PCa risk.[10] To date, little or no biochemical recurrence has been reported in men with PCa treated with T after radical prostatectomy.[11,12] Since there are no large, long-term prospective studies, the impact of T therapy on PCa risk has not been adequately evaluated. We present data on the incidence of PCa from 3 independent observational studies in which more than 1,000 hypogonadal men were treated with T therapy for up to 17 years.

METHODS

Patients and Data Collection

Three parallel, ongoing, prospective, cumulative registry studies were performed. Because the centers operate independently, we describe patient cohorts and methods separately.

Cohort 1. At an Institute of Urology and Andrology, 261 men with a mean age of 59.53±8.35 years (range 32 to 84) were included in the registry. All subjects had presented with erectile dysfunction, which routinely leads to the measurement of T as recommended in the EAU guidelines on erectile dysfunction.[13] If T was 12 nmol/l or less (350 ng/dl), symptoms of hypogonadism were present and contraindications absent, T therapy was recommended. Mean followup was 4.6±1.4 years (range 1 to 7) and median followup was 5 years.

Cohort 2. In a private urological practice 340 men with a mean age of 57.37±7.03 years (range 32 to 69) were included in the registry. All subjects had sought urological consultation for various medical conditions, eg erectile dysfunction, questions about T status or a variety of urological complaints. Approximately 40% of patients had been referred by other specialists with a suspicion of T deficiency. If T was 12.1 nmol/l or less (350 ng/dl), symptoms of hypogonadism were present and contraindications absent, T therapy was recommended. Mean followup was 5.1 ± 2.1 years (range 1 to 8) and median followup was 6 years.

Cohort 3. At the Centre for Reproductive Medicine and Andrology/Clinical Andrology, University of Muenster, 422 men with a mean age of 41±12 years (range 15 to 72) were included in the registry. Overall 188 subjects had primary hypogonadism (including 56 patients with Klinefelter syndrome), 125 had secondary hypogonadism and 109 had late onset hypogonadism. The cohort consisted of relatively young men presenting with symptoms of hypogonadism such as fatigue, depression, loss of libido and decreased sexual function, as well as unfavorable changes in body composition (gaining of fat mass and waist circumference despite physical activity). If T was 12 nmol/l or less (350 ng/dl), symptoms of hypogonadism were present and contraindications absent, T therapy was initiated. Mean followup was 5.9±3.6 years (range 2 to 17) and median followup was 5 years.

Primary Exposure

In all 3 cohorts baseline PSA levels were less than 4 ng/ml. All patients received injections of T undecanoate (1,000 mg Nebido®) in intervals of 12 weeks after an initial interval of 6 weeks for up to 75 months (cohort 1), 87 months (cohort 2) or 17 years (cohort 3). Pretreatment examination of the prostate and monitoring during treatment were performed as shown in table 1. Biopsies were performed if PSA increased to more than 4 ng/ml or by more than 0.75 ng/ml within 12 months, or if there were suspicious findings on DRE or TRUS. Twelve-core biopsies (2 cores each from apex, middle and base of left and right anatomical zones) were performed according to German Society of Urology guidelines, which are in accordance with those of the EAU.[14]

Outcome Measures

Numbers of positive and negative biopsies were assessed. Prostate cancer incidence and outcomes of PCa biopsy or post-prostatectomy outcomes were also studied.

Statistical Analysis

For continuous variables mean, median, SD, range, minimum, maximum and sample size for the overall sample and various groups were reported at each point. For categorical variables the frequency distribution was reported. We tested the hypotheses regarding change in outcome scores across the study period by fitting a linear mixed effects model to the data. Time (to indicate followup interviews) was included as a fixed effect in the model. A random effect was included in the model for the intercept. Estimation and test of change in scores were determined by computing the differences in least square means at baseline vs the score at each followup interview. For the correlation study the Pearson correlation was calculated between baseline changes in outcomes at various points. The significance of each correlation was tested using Fisher's test.

PCa incidence was calculated as the number of cancers divided by the total number of person-years of followup expressed in 10,000 years units. The estimate along with a confidence interval was calculated using Poisson regression. Statistical analyses were generated using SAS® for Windows® version 9.3.

Table 1. *Clinical practice routine for prostate examination before initiation of testosterone replacement therapy and monitoring during treatment*

	Cohort 1	Cohort 2	Cohort 3
Screening:			
PSA	At screening + 2–7 days before first injection	At screening + 1–3 wks before first injection	At screening + 2–7 days before first injection
DRE	At screening + 2–7 days before first injection	At screening	At screening + 2–7 days before first injection
TRUS	At screening + 2–7 days before first injection	At screening	At screening + 2–7 days before first injection
Monitoring:			
PSA	Every 3 mos in first yr then twice/yr	On day of first injection then at every other visit (twice/yr)	Every 3 mos in first yr then once/yr (if younger than age 40) or twice/yr (age 40 or older)
DRE	Every 3 mos in first yr then twice/yr	At each visit	Every 3 mos in first yr then once/yr (if younger than age 40) or twice/yr (age 40 or older)
TRUS	At every other visit (twice/yr)	On day of first injection then at every other visit (twice/yr)	At every other visit (twice/yr)
Mean ± SD yrs followup	4.6 ± 1.4	5.1 ± 2.1	5.9 ± 3.6
Median yrs followup	5	6	5

RESULTS

A total of 1,023 patients were on T therapy and followed for up to 17 years with a median followup of approximately 5 years. As shown in table 2, at baseline the patients exhibited many comorbidities. In the combined study population there were 11 cases of PCa which translated into a proportion of 1.08%. This figure is lower than that reported by the PLCO (7.35%) and ERSPC (9.6%) trials, respectively.[15,16] Furthermore, the incidence per 10,000 person-years was lower in this study (54.4 and 30.7 in cohorts 1 and 2, respectively) compared with PLCO and ERSPC (116 and 96.6), respectively.[15,16]

In cohort 1 PSA increased from 0.86±0.57 ng/ml (range 0.01 to 2.88) at baseline to 1.41±0.62 ng/ml (range 0.00 to 2.98) ($p < 0.0001$) and prostate volume increased from 27.9±8.15 ml (range 10 to 56) to 34.79±8.69 ml (range 15 to 57.5) at the end of the observation period ($p < 0.0001$). A total of 26 prostate biopsies were performed, of which 20 were negative and 6 positive. The individual patient data from men diagnosed with PCa are shown in table 3. The diagnoses were made after a minimum of 6 injections (approximately 15 treatment months) and a maximum of 18 injections (approximately 51 treatment months). Tumor stage in all patients ranged from cT2a to cT2c. Gleason score was 5 in 2 patients, 6 in 3 and 7 in 1 patient. Lymph nodes and surgical margins were negative in 5 patients who underwent radical prostatectomy and were not available in 1 patient who underwent external beam radiation therapy. One of the patients had Klinefelter syndrome. The incidence of PCa was 2.3% (6 of 261 men, 95% CI 0.24–3.4) and the estimated incidence per 10,000 patient-years was 54.4 (95% CI 9.783–94.052). After a minimum of 1 year after cancer treatment and PSA remaining below the detection limit, 5 of the 6 patients who were hypogonadal and had symptoms of hypogonadism decided to resume T therapy after consulting with the urologist and giving informed consent.

In cohort 2 PSA increased from 1.74±0.94 ng/ml (range 0.10 to 3.90) at baseline to 1.96±1.03 ng/ml (range 0.27 to 3.24) ($p < 0.0001$) and prostate volume increased from 28.96±10.41 ml (range 7 to 56) to 29.88±13.85 ml (range 11 to 59) at the end of the observation period ($p < 0.0001$). A total of 53 prostate biopsies were performed, of which 48 were negative and 5 were positive. All 5 patients had chronic prostatitis and LUTS at baseline. The individual patient data from men diagnosed with PCa are shown in table 3. The diagnoses were made after a minimum of 3 injections (approximately 10 treatment months) and a maximum of 7 injections (approximately 19 treatment months). Tumor stage in all patients was pT2a. Gleason score was 5 in 1 man and 6 in the other 4. All men underwent radical prostatectomy, and had negative lymph nodes and surgical margins. The incidence of PCa was 1.5% (5 of 340 men, 95% CI 0.24–3.4) and the estimated incidence per 10,000 patient-years was 30.698 (95% CI 12.778–73.754).

In cohort 3 the results at the median of the observation period are reported to facilitate comparability with the other 2 cohorts. As previously stated median followup was 5 years. PSA increased from 1.5±0.4 ng/ml (range 0.2 to 3.4) at baseline to 1.8±0.4 ng/ml (range 0.2 to 4.3) after 5 years ($p < 0.001$ for overall change from baseline) and prostate volume increased from 16.8±5.0 ml (range 6 to 37) to 20.9±5.3 ml (range 11 to 47) after 5 years ($p < 0.001$). A total of 13 prostate biopsies were performed, of which all were negative.

DISCUSSION

The findings from these 3 independent registries with more than 1,000 patients treated for a median followup of 5 years with testosterone revealed an incidence of PCa less than that detected in general screening trials (table 4). In the combined cohorts the incidence of PCa was 1.08%, which is lower

Table 2. *Baseline patient characteristics and comorbidities according to medical history and investigator assessment*

	Cohort 1	Cohort 2	Cohort 3
Mean ± SD age	59.53 ± 8.35	57.37 ± 7.03	41 ± 12
Mean ± SD yrs followup	4.6 ± 1.4	5.1 ± 2.1	5.9 ± 3.6
Median yrs followup	5	6	5
Mean ± SD kg wt	100.13 ± 14	104.04 ± 16.39	100.8 ± 11.8
Mean ± SD kg/m^2 body mass index	31.73 ± 4.42	33.26 ± 5.35	31.1 ± 5.1
No. normal wt (%)	11 (4)	25 (7)	58 (14)
No. overweight (%)	88 (34)	78 (23)	155 (37)
No. obese (%)	162 (62)	237 (70)	209 (50)
Mean ± SD cm waist circumference	107.66 ± 10.03	105.88 ± 8.61	113.3 ± 11.2
No. normal (less than 94 cm) waist circumference (%)	8 (3)	12 (4)	51 (12)
No. increased (94–101.9 cm) waist circumference (%)	74 (28)	107 (31)	89 (21)
No. substantially increased (102 cm or greater) waist circumference (%)	179 (69)	221 (65)	281 (67)
Mean ± SD nmol testosterone/ng/dl	7.72 ± 2.07/222.6 ± 59.7	9.87 ± 1.34/284.7 ± 38.6	5.2 ± 2.2/150 ± 63.4
Mean ± SD ml prostate vol	27.9 ± 8.15	28.96 ± 10.41	16.8 ± 5.0
Mean ± SD ng/ml PSA	0.86 ± 0.57	1.74 ± 0.94	1.5 ± 0.4
No. comorbidities according to medical history at baseline (%):			
Hypertension (said to have hypertension or on antihypertensive drug)	118 (45)	161 (47)	222 (53)
Type 2 diabetes	60 (23)	113 (33)	71 (17)
Dyslipidemia (said to have high cholesterol or on lipid lowering drug)	87 (33)	89 (26)	191 (45)
Coronary artery disease	32 (12)	40 (13)	26 (6)
Myocardial infarction	2 (1)	40 (13)	15 (4)
Stroke	2 (1)	6 (2)	2 (0)
Erectile dysfunction	261 (100)	174 (51)	174 (41)
BPH/LUTS	158 (61)	130 (38)	61 (14)
Prostatitis	30 (11)	141 (41)	52 (12)
Osteoporosis	14 (5)	59 (17)	65 (15)
Klinefelter syndrome	5 (2)	34 (10)	56 (13)
History of orchiectomy and/or cryptorchidism (primary hypogonadism)	7 (3)	23 (8)	51 (12)
No. comorbidities according to investigator assessment (%):			
Hypertension (medical history and/or systolic blood pressure 130 mm Hg or greater and/or diastolic blood pressure 85 mm Hg or greater and/or antihypertensive drugs)	227 (87)	314 (92)	341 (81)
Type 2 diabetes (medical history and/or hemoglobin A1c 6.5% or greater and/or fasting glucose 126 mg/dl or greater)	80 (31)	113 (33)	132 (31)
Prediabetes (fasting glucose 100 mg/dl or greater but no known diabetes)	60 (23)	53 (16)	208 (54)
Dyslipidemia (medical history and/or triglycerides 150 mg/dl or greater and/or high-density lipoprotein 40 mg/dl or less)	245 (94)	340 (100)	304 (72)
Erectile dysfunction (medical history and/or International Index of Erectile Function-Erectile Function domain score 21 or less)	261 (100)	231 (68)	Not applicable
BPH/LUTS (medical history and/or International Prostate Symptom Score 8 or greater and/or LUTS drugs)	199 (76)	161 (47)	Not applicable

than that reported by PLCO (7.35%) and ERSPC (9.6%), respectively.[15,16] In addition, the incidence per 10,000 person-years was lower in cohort 1 (54.4) and cohort 2 (30.7) compared with 116 and 96.6 in the PLCO and ERSPC, respectively.[15,16] These data suggest that treatment with testosterone does not increase the risk of PCa, and support previous arguments that place the fear of T therapy and PCa in a more rational perspective.[6,9]

To put these data in context and to provide a frame of reference, in table 4 we included data from the PLCO in the U.S., in which 38,345 men age 55 to 74 years in the control arm were followed for 7 years. Of those men 2,820 were diagnosed with PCa (7.35%), representing an incidence of 116 per 10,000 person-years.[15] Similarly, data from ERSPC (72,891 patients, mean age 50 to 74 years and a followup of 11 years) showed that 6,963 patients were diagnosed with PCa (9.6%), with an incidence of 96.6 per 10,000 person-years.[16] Our findings showed that the incidence per 10,000 patient-years was approximately 54.4 in the first registry, 30.7 in the second registry and none in the third registry. In contrast, the incidence per 10,000 person-years was 116 and 96.6 in PLCO[15] and ERSPC,[16] respectively. These observations suggest that the incidence of PCa in patients on T therapy was not greater than in the general population. These data lend credence to previous reports which demonstrated no association of circulating androgens with PCa.[9,10]

We must point out that the data from our registries cannot be directly compared with the 2 large scale screening studies due to the inherent limitations of observational studies.[15,16] Furthermore, we note that the mean age of men in PLCO and ERSPC was 55 to 74 years, whereas our cohorts included men 15 to 84 years old. Thus, it is likely that the

Table 3. *Individual data of patients diagnosed with prostate cancer*

Pt No.	Family History of PCa	Age at Treatment Initiation	Prostate Vol at Treatment Initiation (ml)	PSA at Treatment Initiation (ng/ml)	Mo of Diagnosis after Treatment Initiation	PSA at Diagnosis (ng/ml)	Tumor Stage	Gleason Score*	Body Mass Index (kg/m^2)	Comorbidities	Metabolic Syndrome (No. factors)	T at Baseline	T:PSA Ratio	C-Reactive Protein	Back on T Replacement Therapy†
Cohort 1:															
73	PCa uncle (father's brother)	52	21	2.1	18	3.2	pT2a	2+3=5	40.12	Prostatitis, LUTS, type 2 diabetes	Yes (5)	7.3	3.5	1.8	No
129	PCa father	67	36	0.81	48	1.69	pT2c	3+2=5	39.07	Benign prostatic hyperplasia, type 1 diabetes, cardiovascular disease, osteoporosis	Yes (4)	6.9	8.5	1	Yes (for 37 mos)
166	No PCa history	73	29	0.47	51	2.23	pT2c	3+3=6	38.44	Prostatitis, LUTS, type 2 diabetes	Yes (5)	4.9	10.4	2.2	Yes (for 15 mos)
223	No PCa history	51	17	0.29	33	1.21	pT2b	3+3=6	26.87	Klinefelter, osteoporosis	Yes (4)	3.8	13.1	1	Yes (for 15 mos)
260	No PCa history	64	33	1.75	15	5.71	pT2c	3+4=7	29.41	Type 2 diabetes, renal cysts bilat	Yes (4)	5.6	3.2	Less than 1	Yes (for 16 mos)
261	No PCa history	65	31	0.84	15	2.46	pT2c	3+3=6	29.05	Peyronie disease	Yes (3)	8.9	10.6	Less than 1	Yes (for 20 mos)
Cohort 2:															
231	No PCa history	65	44	3.1	10	5.8	pT2a	3+3=6	37.03	Chronic prostatitis, LUTS	Yes (3)	10.1	3.3	5.2	No
232	PCa brother	63	46	3.1	10	6.3	pT2a	3+2=5	29.96	Chronic prostatitis, LUTS	Yes (3)	10.1	3.3	6.3	No
233	PCa brother	67	46	2.85	11	4.97	pT2a	3+3=6	29.70	Chronic prostatitis, LUTS	Yes (4)	9.7	3.4	3.7	No
257	No PCa history	61	40	2.92	17	4.89	pT2a	3+3=6	32.56	Chronic prostatitis, LUTS, type 2 diabetes	Yes (4)	7.3	2.5	2.8	No
258	PCa father, breast Ca mother	66	38	2.81	19	5.19	pT2a	3+3=6	34.02	Chronic prostatitis, LUTS, type 2 diabetes	Yes (4)	8.0	2.8	2.1	No

*All Gleason scores from radical prostatectomy specimens except for patient 166 with Gleason score from biopsy specimens.
†There was no biochemical recurrence in any of the patients back on testosterone replacement therapy.

Table 4. *Summary of prostate cancer incidence in all 3 registries compared to 2 large scale screening projects*

	Cohort 1	Cohort 2	Cohort 3	PLCO[15]	ERSPC[16]
No. pts	261	340	422	38,343	72,891
Age (range)	59.5	57.4	41	55–74	50–74
Max yrs followup	6	7	17	7	11
PCa cases	6	5	0	2,820	6,963
Proportion	2.3	1.5	0	7.35	9.6
Incidence/10,000 pt-yrs	54.4	30.7	0	116	96.6

inclusion of younger patients may have contributed to the lower incidence of PCa in these cohorts, and caution should be exercised in interpreting these data due to such limitations. However, the incidence of PCa was lower than expected in the 3 cohorts described here.

No correlation or association between T therapy and increased PCa risk or increased aggressiveness of PCa at diagnosis have been reported,[17] and the detection of PCa was approximately 1% in previously reported clinical trials.[18,19] In uncontrolled studies of men with PCa, T therapy after radical prostatectomy resulted in few cases of biochemical recurrence.[11] Data from meta-analyses have suggested that there is no clinically significant adverse impact on PCa incidence in the T therapy studies that were analyzed.[20,21]

Despite the widespread belief regarding the contraindication of T therapy in hypogonadal men with known or suspected PCa, there is no convincing evidence that the normalization of T levels presents a greater risk for the progression of PCa. T therapy may be considered in selected hypogonadal men who were treated for PCa and without evidence of active disease.[11] To date, there is no convincing evidence that T therapy is a risk factor for PCa.[6,9] Guidelines for monitoring have been developed, which, if properly followed, would render T therapy safe and effective in hypogonadal men without fear and suspicion of PCa. Thus, fear that T therapy causes PCa may not be justified in light of the aforementioned arguments.[9,11,22]

The EAU guidelines on male hypogonadism suggest that men who are treated surgically for localized prostate cancer, and who are currently without any evidence of active disease and meet the diagnosis of hypogonadism can be cautiously considered candidates for T therapy, not before 1 year of followup after surgery and if there is no PSA recurrence.[22] Similar recommendations were noted in the International Society for the Study of the Aging Male,[23] International Society for Sexual Medicine[24] and Endocrine Society[25] guidelines.

Although considerable evidence exists indicating no relationship between T and increased risk of PCa,[26] decades of physician training with the notion that T is fuel for PCa made it difficult to dispel such a fallacy and the myth persisted.[11] In the absence of long-term followup data demonstrating a reduced risk of PCa in hypogonadal men receiving T therapy, considerable skepticism remains throughout the medical community, and this is an expected natural and acceptable path of medical and scientific discourse.[27–29] In view of the current evidence, clinicians will be compelled to think this over, and cannot justify withholding T therapy from hypogonadal men and men who have been successfully treated for PCa.[30] It should be emphasized that as with any therapy for any pathological condition, a balance between the anticipated risks and benefits of therapy needs to be achieved, and proper evaluation of the therapy for each individual is recommended.

We must note that in the 2 registries from urological settings, in which patients had a mean age of approximately 60 years, adherence to the EAU guidelines on male hypogonadism was excellent,[22] and screening and monitoring were performed accurately and meticulously, even going beyond the recommended intervals.

Limitations of the study include the registry design and the lack of a control group. The combined data from 3 independent observational registries were not from a randomized controlled study designed to assess the incidence of PCa.

CONCLUSIONS

The incidence of PCa in these registry studies of 1,023 men followed prospectively while receiving T therapy for a median of 5 years was 1.08%. This value is smaller than PCa rates reported in long-term screening trials, which ranged from 7.35% to 9.6%. Although definitive safety data regarding T therapy must await large, long-term, controlled trials, these data suggest that testosterone therapy does not increase the risk of PCa.

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