

REVIEW

Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review

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This paper provides a systematic review of the literature about prostate cancer risk associated with testosterone therapy for hypogonadism. A comprehensive search of MEDLINE, EMBASE and other resources was conducted to identify articles that highlight occurrences of prostate cancer in men receiving testosterone therapy for hypogonadism treatment. Articles that met study inclusion criteria were assessed for causality between testosterone treatment and prostate cancer, increased prostate-specific antigen or abnormal digital rectal examination findings. Of 197 articles relating to testosterone therapy, 44 met inclusion criteria: 11 placebo-controlled, randomized studies; 29 non-placebo-controlled studies of men with no prostate cancer history; and 4 studies of hypogonadal men with history of prostate cancer. Of studies that met inclusion criteria, none demonstrated that testosterone therapy for hypogonadism increased prostate cancer risk or increased Gleason grade of cancer detected in treated vs untreated men. Testosterone therapy did not have a consistent effect on prostate-specific antigen levels.

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Introduction

Testosterone therapy has been administered for male hypogonadism for decades^{1–4} and has seen increasing use in part because of the availability of well-tolerated testosterone formulations.^{5–10} When administered cautiously, testosterone therapy is safe and effective in mitigating the signs and symptoms of hypogonadism,¹¹ which include lower libido; erectile dysfunction; fatigue; decreased muscle strength, bone mineral density and body hair; increased body fat; anemia; hot flushes; and mood changes.^{10,12,13} Testosterone therapy may also have beneficial effects on the lipid profile and cardiovascular system.¹⁴

Testosterone therapy for male hypogonadism is generally safe, with possible adverse effects of benign prostatic hyperplasia, erythrocytosis, sleep apnea, gynecomastia, testicular atrophy, fluid retention and local reactions at sites of buccal, topical, subcutaneous and intramuscular administration.¹⁵ There is, however, an important and unresolved question of whether testosterone therapy increases the risk of new prostate cancer or the recurrence or progression of prostate cancer.

Long-standing concerns about testosterone treatment for hypogonadism are derived from Huggins and Hodges' landmark observation in 1941 stating that testosterone reduction causes regression of metastatic prostate cancer and testosterone administration causes prostate cancer growth.¹⁶ Huggins and Hodges' conclusion about exogenous testosterone and cancer growth was drawn from observation of just one patient without prior castration. The precise relationship of endogenous testosterone and exogenous testosterone therapy and the risk of prostate cancer, as well as prostate cancer progression, has not yet been made clear.^{15,17,18}

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Recently published opinions regarding this question have stated that an association cannot be confirmed.^{13,17,19–24} The Institute of Medicine Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy in 2004 advised against starting a long-term study of the risks associated with testosterone therapy in older men unless short-term studies conclusively demonstrated the benefit of such therapy.²⁵ It has been estimated that a long-term, randomized, placebo-controlled study would involve following 6000 elderly hypogonadal men for 6 years to determine whether treatment increases the risk of prostate cancer.¹⁹ In the absence of such a study, it is worthwhile to address the unresolved question regarding the potential association of testosterone therapy and the risk of developing or promoting the recurrence or progression of prostate cancer.

This article distills findings from the literature in an effort to provide as authoritative an answer as possible to the question of whether the risk of prostate cancer is higher in hypogonadal men treated with testosterone than in hypogonadal men who have not received testosterone treatment.

Materials and methods

Search strategy

The electronic databases MEDLINE and EMBASE were searched for studies published in the English language from 1970 through 2008, using as keywords and key phrases testosterone combined with cypionate, enanthate, proprionate, gel, patch, oral, therapy, prostate cancer risk and prostate-specific antigen (PSA). A supplemental search was conducted of references cited in journal articles, conference proceedings and books. Study investigators were queried for additional references.

Selection of studies for systematic review

As indicated in Figure 1, titles and abstracts of the studies retrieved by the literature search were reviewed by medical staff. For studies that appeared relevant and for which full text reports were available, a decision was made whether to analyze them further, based on their clinical features and quality of study methods.

To maximize data, many types of reports were accepted, from single and multiple case reports to studies that were randomized or nonrandomized; open- or closed-label; placebo-, active- or noncontrolled; prospective or retrospective; sequential, parallel, or crossover; blinded or not blinded; conducted in one or more clinics or private practices; and pharmacokinetic or pharmacodynamic. Also, studies of men with or without a history of prostate cancer were accepted.

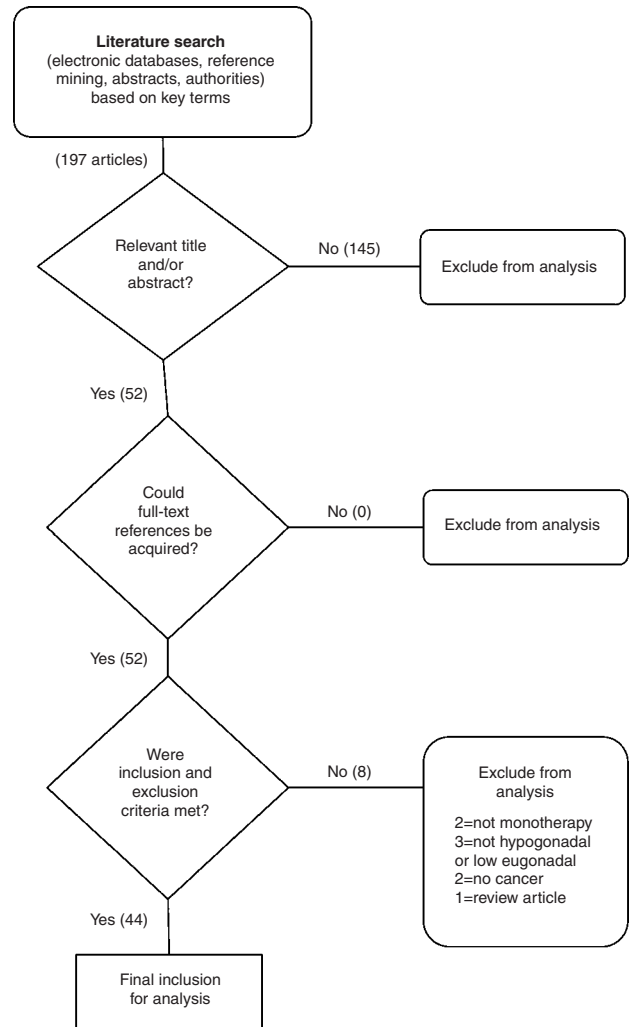


Figure 1 Process to select studies for systematic review.

Inclusion and exclusion criteria

Inclusion required that each study involve adult men who received testosterone therapy for signs and symptoms of hypogonadism or had abnormally low or low-normal testosterone levels of any etiology. Included studies had defined criteria of hypogonadism and required histologic confirmation of prostate cancer. Excluded from this investigation were review articles, meta-analyses, and reports of studies in which testosterone therapy was not administered as monotherapy or outcomes had no apparent relevance to the association between the risk of prostate cancer and testosterone therapy in hypogonadal men. Meta-analyses and review articles were referred to as a source of data to identify individual articles that met the scope and methodology of this systematic review.

Review and data extraction methods

For each study uncovered by the broad search, details concerning the study's objectives, design,

subjects, testosterone and other therapy, testosterone levels, hypogonadism symptoms, digital rectal examination (DRE) and PSA findings, cancers detected, and conclusions were entered into a Microsoft Excel workbook for subsequent data extraction and analysis.

Results

The literature search uncovered 197 articles, of which 52 had possible relevance to this systematic review as indicated by their title or abstract. Upon review of the full text of these 52 articles, 8 were excluded from analysis because they did not involve testosterone administered as monotherapy ($n=2$), involved subjects who were neither hypogonadal nor in the low-eugonadal range ($n=3$), provided no data relevant to prostate cancer risk ($n=2$), or were found to be review articles ($n=1$). The remaining 44 studies of testosterone supplementation are included in this analysis.

Of the 44 studies of men who had not had prostate cancer, 11 are placebo-controlled and randomized (Table 1) and 29 are not placebo-controlled (Table 2). Among the 29 not placebo-controlled, 15 are prospective and 14 are retrospective studies, including a case series of 20 men in whom prostate cancer developed during testosterone therapy and 8 reports of 1 or 2 cases. Also included are four non-placebo-controlled reports of testosterone therapy in hypogonadal men who had previously been treated for prostate cancer (Table 3).

Placebo-controlled studies

In the 11 placebo-controlled, randomized studies, prostate cancer was detected in 7 of the 542 men treated with testosterone as monotherapy (1.3%) and 5 of the 333 men who received placebo (1.5%; Table 1). Prostate cancer incidences across studies varied from 0% for both the testosterone and the placebo groups in seven studies^{14,27,28,30,31,34,35} to 9.5% for the testosterone group and 21% for the placebo group in the study by Marks *et al.*²⁹ Prostate cancer in testosterone-treated men was detected at as early as 3 months³³ and in placebo-treated men at as early as 6 months.²⁹ Gleason grades were reported for four testosterone-treated patients (two of grade 5, one of grade 6 and one of grade 7) and four placebo-treated subjects (all grade 6).^{26,29}

The Amory *et al.*²⁶ study included prostate ultrasound examination of all men entering and completing the study. Prostate volume increased significantly in all groups over the 3-year study period, with the increase in the testosterone-only group similar to that seen in the placebo group ($P=0.35$).²⁶

In the Marks *et al.* study, there were no remarkable changes in prostate tissue (for example, histologic changes, tissue biomarkers for cell proliferation and angiogenesis) in men receiving testosterone therapy compared to men receiving placebo, or in individuals' baseline levels compared to 6-month levels. These results indicate that exogenous testosterone does not accumulate in the prostate or provoke major biological change in the prostate gland.²⁹

Non-placebo-controlled studies of men with no history of prostate cancer

Of the 21 non-placebo-controlled studies, 1 was a retrospective study of 20 cases of prostate cancer diagnosed in men receiving testosterone therapy for hypogonadism in six private practices³⁶ (Table 2). Eleven of these cancers were detected during the first 2 years of testosterone therapy, and 9 were detected 28 months to 8 years after the start of therapy.³⁶ Gleason scores were 6 in nine cancers, 7 in six cancers, 8 in three cancers and 9 in two cancers.³⁶

Among the other 20 non-placebo-controlled studies, 6 prostate cancers were detected in 4 retrospective studies (Table 2),^{52,54–56} and 6 prostate cancers were detected in 3 prospective studies.^{39,50,51} In these seven studies, prostate cancer incidences ranged from 1.2 to 4.5%. One cancer developed within 3 months of the start of testosterone therapy⁵² (Table 2). In Rhoden and Morgentaler's 2003 1-year retrospective study, prostate cancer (Gleason score 7) developed in 1 of 20 men (5%) at high risk for prostate cancer because of prostate intraepithelial neoplasia (PIN) detected at baseline prostate biopsy. No cancers developed among 55 men in whom PIN was not found on baseline biopsy (Table 2).⁵⁴

Among the eight case reports of prostate cancer detected in hypogonadal men, one is of a man who received testosterone therapy for pituitary insufficiency for 15 years before prostate cancer was detected. Another describes two men with Klinefelter syndrome in whom the cancer was detected after 7 and 35 years of testosterone therapy, respectively.

Studies of testosterone therapy in men with a history of prostate cancer

One prospective and three retrospective case series examined 53 men who received testosterone therapy for hypogonadism and had been treated for prostate cancer (Table 3).^{65–68} There was no evidence of prostate cancer recurrence in these men over periods of 0.5–12 years. The prospective case series included five men who had subcapsular orchiectomy to treat advanced prostatic carcinoma; these men had PSA increases while undergoing testosterone therapy for up to 2.5 years.⁶⁵ One retrospective

Table 1 Placebo-controlled, randomized studies of testosterone supplementation in hypogonadal men

Study	Patients (N) Age range (years)	T therapy and outcome ^a	PSA (ng per 100 ml)	Prostate cancer cases (n)
Amory <i>et al.</i> ²⁶ 3-year study of TIM alone or with finasteride on BMD	70 65–83	TIM-only (TE, <i>n</i> = 24), 200 mg every 2 weeks; TIM + finasteride (<i>n</i> = 22), TIM 200 mg every 2 weeks + finasteride 5 mg daily; PBO (<i>n</i> = 24) From baseline of 9.9–10.5 nmol l ⁻¹ , TT increased significantly in TIM-only and TIM + finasteride groups; no change in PBO group	PSA normal at baseline and increased by 1.0–1.4 (<i>P</i> < 0.001) in TIM-only group; no significant change in other groups	3 TIM-only group 2 (Gleason grade 5); PBO group 1 (elevated PSA; Gleason grade not supplied)
Bhasin <i>et al.</i> ²⁷ 3-month study of TTD in HIV-infected men	41 18–60	TTD (Androderm, <i>n</i> = 20) 5 mg daily From baseline of 8.9 ± 0.4 nmol l ⁻¹ , TT increased to 12.7 ± 1.2 in TTD group and increased from 7.3 ± 0.6 to 7.7 ± 0.8 in PBO group	No significant change from baseline	0
Kenny <i>et al.</i> ²⁸ 1-year study of TTD effects on bone and muscle	67 70–80	TTD (Androderm, <i>n</i> = 34) 5 mg daily From baseline of 13.5 ± 6.0 nmol l ⁻¹ , T increased to 22.2 ± 10.9 in TTD group (<i>P</i> = 0.001) and increased from 13.5 ± 3.7 to 16.1 ± 5.7 in PBO group (<i>P</i> = 0.005)	PSA increased from baseline of 2.0 ± 1.4 to 2.6 ± 1.8 (<i>P</i> = 0.04) in TTD group and from 1.9 ± 1.0 to 2.2 ± 1.5 (<i>P</i> = 0.09) in PBO group	0
Marks <i>et al.</i> ²⁹ 6-month study of TIM effects on prostate tissue; prostate biopsy at start and end of study	40 44–78	TIM (TE, Delatestryl, <i>n</i> = 21) 150 mg every 2 weeks Median T increased in TIM group from baseline 9.8 (range, 6.3–15.4 nmol l ⁻¹) to 22.2 (range, 9.4–41.3; <i>P</i> < 0.001) and decreased in PBO group from 9.8 (range, 4.7–13.6) to 9.5 (range, 3.1–24.8) (<i>P</i> = 0.11)	PSA increased from baseline of 1.55–2.29 (<i>P</i> < 0.001) in TIM group and from 0.97 to 1.10 (<i>P</i> < 0.006) in PBO group	6 TIM group 2 (Gleason grades 7 and 6); PBO group 4 (1 of Gleason grade 7, 3 of Gleason grade 6)
Okun <i>et al.</i> ³⁰ 2-month study of TIM in men with Parkinson disease and probable T deficiency	30 60–79	TIM (TE, <i>n</i> = 15) 200 mg every 2 weeks From baseline of 13.0 ± 3.6 nmol l ⁻¹ , mean TT increased to 35.7 ± 14.3 in TIM group and increased from 9.5 ± 4.6 to 11.5 ± 5.6 in PBO group	PSA remained < 4.0 except for unsustained increase to 5.5 in a PBO patient and to 4.6 in a TIM patient	0
Sih <i>et al.</i> ³¹ 1-year study of TIM	32 TIM group mean, 65; PBO group mean, 68	TIM (TC, <i>n</i> = 17) 200 mg every 2 weeks From baseline of 10.2 ± 0.9 nmol l ⁻¹ , mean TT increased to 12.8 ± 3.2 in TIM group and increased from 8.1 ± 0.7 to 9.6 ± 0.8 in PBO group	Mean PSA increased from 1.0 ± 0.2 at baseline to 1.9 ± 0.3 in TIM group and from 1.5 ± 0.3 to 2.0 ± 0.4 in PBO group	0
Snyder <i>et al.</i> (1999) ³² 3-year study of TTD effects on BMD in men with an overall relatively mild hypogonadism	108 67–79	Scrotal TTD (Testoderm, <i>n</i> = 54) 6 mg daily From baseline of 12.7 ± 2.7 nmol l ⁻¹ , mean TT increased to 21.7 ± 8.6 at 6 months and stayed at that level until 3 years in TTD group and did not change from baseline of 12.8 in PBO group	Mean PSA increased from 1.6 ± 1.0 at baseline to 2.2 ± 1.8 (<i>P</i> < 0.001) in TTD group and from 1.7 ± 1.1 to 1.9 ± 1.4 in PBO group	1 TTD group 1 (details not supplied)

Table 1 (Continued)

Study	Patients (N) Age range (years)	T therapy and outcome ^a	PSA (ng per 100 ml)	Prostate cancer cases (n)
Steidle <i>et al.</i> ³³ 3-month study of TG effects on androgen levels, body composition and sexual function	406 20–80	TG (Testim) 50 mg daily (<i>n</i> = 99) or 100 mg daily (<i>n</i> = 106) or TTD (Androderm, <i>n</i> = 102) 5 mg daily Mean T in nmol l ⁻¹ at baseline and 3 months for 50 mg TG, 100 mg TG, TTD and PBO groups was 9.2 ± 3.4 and 13.8 ± 8.1, 7.7 ± 2.4 and 17.1 ± 8.2, 8.3 ± 2.8 and 11.9 ± 4.6, and 7.6 ± 2.8 and 7.3 ± 2.7, respectively	Baseline PSA and increase at 3 months were 1.2 ± 1.0 and 0.3 ± 1.8 (<i>P</i> < 0.01 vs PBO) for 50 mg TG; 1.2 ± 0.9 and 0.1 ± 0.4 for 100 mg TG; 1.4 ± 1.1 and 0.2 ± 0.6 for TTD; and 1.1 ± 1.0 and -0.1 ± 0.4 for PBO	2 TTD group 2 (details not supplied)
Tan and Pu ³⁴ 1-year study of effects of TIM in hypogonadal men with Alzheimer disease	10 68–80	TIM (TE, <i>n</i> = 5) 200 mg every 2 weeks From baseline of 4.4 nmol l ⁻¹ , mean TT increased to 11.8 in TIM group	PSA increased from 0.98 to 1.37 (<i>P</i> = 0.07) in TIM group	0
Tenover ¹⁴ 3-month crossover study of effects of TIM; not all subjects were hypogonadal	13 57–76	TIM (TE, <i>n</i> = 6) 100 mg every week From baseline of 11.6 ± 0.4 nmol l ⁻¹ , mean TT increased to 19.7 ± 0.7 in TIM group and to 11.7 ± 0.6 in PBO group	PSA increased from 2.1 ± 0.4 to 2.7 ± 0.5 (<i>P</i> < 0.01) in TIM group; no significant change from baseline in PBO group	0
Wittert <i>et al.</i> ³⁵ 1-year study of effects of TO on muscle and fat mass in men with low-normal gonadal status (FT in normal range and TT > 8 nmol l ⁻¹)	76 60–86	TO (TU, <i>n</i> = 39) 80 mg BID From baseline of 17.0 ± 4.4 nmol l ⁻¹ , mean TT declined by 1.7 ± 1.2 in TO group; and from baseline of 15.6 ± 4.5 declined by 0.7 ± 0.11 in PBO group	PSA ≤ 5 at baseline increased by 0.1 ± 0.8 in TO group and 0.4 ± 1.2 (<i>P</i> = 0.47) in PBO group	0

Abbreviations: BMD, bone mineral density; FT, free testosterone; HIV, human immunodeficiency virus; PBO, placebo; PSA, prostate-specific antigen; T, testosterone; TC, testosterone cypionate; TE, testosterone enanthate; TG, testosterone gel; TIM, intramuscular testosterone; TO, oral testosterone; TT, total testosterone; TTD, transdermal testosterone undecanoate patch.

^aT in reported conventional units converted to SI units using T in ng per 100 ml × 0.03467 = nmol l⁻¹.

series followed 31 men who had brachytherapy for early prostate cancer and were treated with testosterone for up to 8.5 years. PSA values were <1 ng ml⁻¹ following treatment; no baseline PSA levels were available.⁶⁶ The other two retrospective studies included a total of 17 men who had radical prostatectomy. PSA levels remained undetectable for up to 12 years, including 1 man whose prostate showed a positive surgical margin.^{67,68}

Discussion

The 11 placebo-controlled, randomized studies included in this review provide direct comparisons of the incidence of new prostate cancer in hypogonadal men receiving testosterone therapy and hypogonadal men not receiving testosterone. The prostate cancer incidence was similar in groups receiving testosterone therapy and those receiving placebo, 1.3 and 1.5%, respectively, which is similar to detection rates in screening programs.²⁴

Of the placebo-controlled studies, the Marks *et al.*²⁹ study had the highest prostate cancer incidences, 9.5% in the testosterone group and 21% in the placebo group. This was the only placebo-controlled study in which end-of-study prostate biopsies were performed routinely, optimizing the chance of detecting cancers. Because only one of the study's subjects had a PSA level >4.0 ng ml⁻¹, the six cancers might not have been detected had the biopsies not been performed.²⁹ Marks *et al.*²⁹ believe that the prostate cancers detected at the end of the study were present at the study's start, even though all subjects randomized into the study had a negative enrollment biopsy, and concluded that testosterone therapy cannot be implicated as a prostate cancer stimulus. The prostate cancer incidence rates in the Marks *et al.* study agree with those in another 2006 study. Morgentaler and Rhoden⁶⁹ included routine prostate biopsy and found prostate cancer in 15.1% of 345 men with a PSA level of ≤4.0 ng ml⁻¹.

Amory *et al.*²⁶ found lower prostate cancer incidences than Marks *et al.*: 6.2% in men who

Table 2 Non-placebo-controlled studies of men with no history of prostate cancer

Study	Patients (N) Age Range (years)	T therapy and outcome ^a	PSA (ng ml ⁻¹)	Prostate cancer cases (n)
<i>Case study</i>				
Gaylis <i>et al.</i> ³⁶ 2-month to 8-year retrospective case study of prostate cancer occurring in men receiving T therapy in six private practices	20 49–85	TIM (<i>n</i> = 13); TG or T cream (<i>n</i> = 3); TTD (<i>n</i> = 3); TG + TIM (<i>n</i> = 1); doses varied or unspecified Variable monitoring, especially by nonurologists; mean pretreatment T 6.2 nmol l ⁻¹ (15.5 in 1 patient) increased (for a minority of patients) to 28.7 (range, 26.7–32.5)	Baseline PSA 0.9–15 in 16 men; at cancer detection, PSA 1.1–329 (median, 5.1)	20 11 detected within 2 years of T therapy initiation and 9 within 28 months to 8 years; Gleason score 6 in 9 men, 7 in 6 men, 8 in 3 men, and 9 in 2 men
<i>Prospective studies</i>				
Arver <i>et al.</i> ³⁷ 16-month prospective, open-label, nonrandomized study of TTD in men receiving T therapy	37 21–65	Before study, subjects were taking TIM (TE) with mean dose 229 mg; after 8-week washout, T therapy with TTD (Androderm) 5 mg daily titratable within first 3 months Baseline TT < 8.7 nmol l ⁻¹ (or < 10.3 for Klinefelter syndrome) was normalized in 93% of men after 1 year Single injection of TIM (TB) 200 or 600 mg From baseline below-normal levels of androgens (T + DHT), group 1 (200 mg TIM) androgen levels did not rise to normal; group 2 (600 mg TIM) androgen levels increased significantly (<i>P</i> < 0.01) and were maintained in normal range	Lower PSA during TTD than during TIM: decreased from baseline 1.00 ± 0.16 to 0.51 ± 0.10 after washout of TIM, then increased to 0.66 ± 0.12 during TTD	0
Behre and Nieschlag ³⁸ 4-month prospective, randomized phase I PK/PD study of a single TIM injection in men previously treated with another TIM	8 28–48	TTD (Androderm, <i>n</i> = 26) 5 mg daily or TIM (TE, <i>n</i> = 32) 200 mg every 2 weeks From baseline TT ≤ 300 ng per 100 ml (≤ 350 for Klinefelter syndrome), normal circadian levels were achieved with TTD, and supraphysiologic T levels existed for several days after each TIM administration	No significant PSA change; individual values never > ULN	0
Dobs <i>et al.</i> ³⁹ 2-year prospective, multicenter, parallel-group, randomized study comparing TTD and TIM in men previously treated with TIM	66 22–65	TTD (Androderm, <i>n</i> = 26) 5 mg daily or TIM (TE, <i>n</i> = 32) 200 mg every 2 weeks From baseline TT ≤ 300 ng per 100 ml (≤ 350 for Klinefelter syndrome), normal circadian levels were achieved with TTD, and supraphysiologic T levels existed for several days after each TIM administration	No clinically relevant changes from baseline PSA levels of ≤ 4 with TTD or TIM	3 TIM group, 1 case, 54-year-old man, PSA increased from 5.0 to 12.6 between weeks 12 and 24; biopsy performed despite 2 normal results on ultrasonography TTD group, 2 cases, detected in men with normal PSA but abnormal ultrasonography results at study end
Douglas <i>et al.</i> ⁴⁰ 4-month (range, 2.25–5) prospective, nonrandomized study of the effect of T therapy on PSA and PSMA levels	10 40–76	TIM (TE) 200 mg every 2 weeks or TTD (Testoderm) 6 mg daily T rose from baseline average of 11.0 nmol l ⁻¹ to 23.9	Mean PSA 1.32 over entire study with no appreciable change during T therapy	0
El-Sakka <i>et al.</i> ⁴¹ 1-year prospective, nonrandomized study of the effect of T therapy on PSA in men with ED	187 ≥ 45 (mean, 62.8) (17 of 204 enrolled patients discontinued therapy during first 6 mo and were not included in results)	Parenteral T every 2–4 weeks; details not supplied Baseline T of 6.2 ± 3.1 nmol l ⁻¹ (range, 3.1–9.4) increased to 27.4 ± 14.6 (<i>P</i> < 0.05)	Mean pretreatment PSA 1.8 ± 1.4 increased to 2.7 ± 2.3 (<i>P</i> > 0.05)	0

Table 2 (Continued)

Study	Patients (N) Age Range (years)	T therapy and outcome ^a	PSA (ng ml ⁻¹)	Prostate cancer cases (n)
Gooren ⁴² 10-year prospective, nonrandomized study of TO safety in hypogonadal men	35 15–62	TO (TU) 80–200 mg daily Mean T increased from 5.4 ± 1.9 to 6.5 ± 1.9 nmol l ⁻¹ over periods of 1–10 years; 28 subjects had previously been treated with TIM	PSA measured only during the last 2 years of study; all values <4	0
Katznelson <i>et al.</i> ⁴³ 1.5-year prospective, nonrandomized study of effect of TIM on BMD and lean body mass in men with acquired hypogonadism	29 22–69	TIM (TE) 100 mg every week Longitudinal T level data not provided	No PSA increase over unspecified baseline levels	0
McNicholas <i>et al.</i> ⁴⁴ 3-month prospective, active-controlled, randomized study of TG	208 31–80	TG (Testim) 50 mg daily (<i>n</i> = 68) or 100 mg daily (<i>n</i> = 72) or TTD (Andropatch, <i>n</i> = 68) 5 mg per day From baseline levels of 7.92 ± 2.45, 7.95 ± 2.17 and 7.90 ± 2.23 nmol l ⁻¹ , mean T increases were 12.41 ± 12.56, 6.54 ± 8.62 and 3.82 ± 4.39 for TG 100, TG 50 mg, and TTD, respectively	Mean baseline PSA group values 1.17–1.40 with relatively small changes from baseline: most increases <1, with PSA staying <4.0	0
Meikle <i>et al.</i> ⁴⁵ 1-year prospective, open-label, multicenter study of prostate size in men treated with TTD after ≥3 months of previous therapy with TIM or TTD	29 21–65	TTD (Androderm) 5 mg daily TT remained in normal range during T therapy (mean, 20.8 ± 6.9 nmol l ⁻¹); all men had been treated with TIM before study	Mean PSA 1.0 at baseline, 0.51 after 8-week androgen withdrawal, then 0.66 during T therapy	0
Pechersky <i>et al.</i> ⁴⁶ 6-month prospective, nonrandomized, open-label study of the effect of TO on DHT, estradiol, and prostate volume	207 40–83	Group 1 (<i>n</i> = 92, plasma T > 13 nmol l ⁻¹) TO (TU) 80 mg daily; group 2 (plasma T < 13) TO (TU) 60 mg BID; group 2a (<i>n</i> = 95; LH suppressed by T); group 2b (<i>n</i> = 20, LH not suppressed by T) Group 1 T increased from baseline of 13.9 ± 1.0 to 24.6 ± 1.7 nmol l ⁻¹ ; group 2a T increased from 4.9 ± 1.0 to 16.7 ± 0.3; group 2b T increased from 9.7 ± 0.7 to 10.1 ± 1.0; plasma LH (elevated >9.8 IU l ⁻¹ at baseline in all groups) decreased significantly in all groups	PSA after 6 months of treatment decreased by 45% in group 1, 38% in group 2a, and 7% in group 2b	0
Snyder <i>et al.</i> ⁴⁷ 3-year prospective, nonrandomized study of the effects of TTD	18 22–78	Scrotal TTD (Testoderm) 6 mg daily Mean baseline TT 2.7 ± 2.7 nmol l ⁻¹ was titrated to 14.1 ± 5.6 at 6 months and remained at about this level for remainder of study	Mean PSA 2.0 ± 0.6 at baseline and 2.0 ± 0.2 at 3 years (<i>P</i> = 0.6)	0
Von Eckardstein and Nieschlag ⁴⁸ 3.2-year open-label, prospective, nonrandomized phase II study of TIM	7 19–57	TIM (TU) 1000 mg at intervals increasing from every 6 weeks to every 12 weeks Mean baseline TT of 5.2 ± 3.1 nmol l ⁻¹ increased to 12.6 ± 3.7	Mean baseline PSA 0.6 ± 1.3 increased to 0.8 ± 0.4 at end of trial	0

Table 2 (Continued)

Study	Patients (N) Age Range (years)	T therapy and outcome ^a	PSA (ng ml ⁻¹)	Prostate cancer cases (n)
Wang <i>et al.</i> ⁴⁹ 6-month prospective, randomized, multicenter study of the effect of TG on sexual function, mood, muscle strength and body composition	227 19–68	TG (AndroGel) 5 or 10 g daily (adjustable to 75 mg daily at day 90 if T outside normal range) or TTD (Androderm) 5 mg daily Mean T values at days 0 and 180 were 8.22 ± 0.55 and 14.14 ± 0.88 nmol l ⁻¹ for TTD group; 8.22 ± 0.53 and 19.24 ± 1.18 (dose stayed at 50 mg TG) or 15.60 ± 3.68 (dose titrated from 50 to 75 mg TG at day 90); and 8.60 ± 0.55 and either 25.79 ± 2.55 (dose stayed at 100 mg TG) or 24.72 ± 1.05 (dose titrated from 100 mg TG to 75 mg)	Baseline and 90-day PSA values were 0.89 ± 0.08 and 1.19 ± 0.12 (<i>P</i> = 0.008), 0.88 ± 0.08 and 1.105 ± 0.14 (<i>P</i> = 0.05), and 0.89 ± 0.10 and 0.88 ± 0.09 for the TG 100 mg daily, TG 50 mg daily, and TTD groups, respectively	0
Wang <i>et al.</i> ⁵⁰ 3.5-year prospective, open-label study of long-term TG treatment on sexual function, mood, lean and fat mass and BMD; continuation of a 6-month study (Wang <i>et al.</i> ⁴⁹); study was not powered to determine effects of T therapy on prostate cancer risk	123 19–68	TG (AndroGel) 5, 7.5 or 10 g daily Mean baseline T < 10.4 nmol l ⁻¹ was raised to normal levels	Mean PSA 0.85 at baseline and 1.11 at 6 months, with no further significant increases	3 63-year-old man taking 10 mg TG in whom PSA increased from 3.6 at baseline to 5.7 ng ml ⁻¹ at 12 months 62-year-old man taking 10 mg TG in whom PSA increased from 3.2 to 6.2 at 12 months 65-year-old man taking 7.5 mg TG in whom PSA increased from 2.6 at baseline to 5.8 at 18 months (biopsy, negative) to 6.6 at 24 months when repeat biopsy was positive for prostate cancer
Swerdloff and Wang ⁵¹ 3-year prospective, open label, nonrandomized (after first 6 months) study of TG	163 19–67	TG (AndroGel or Testogel) 5, 7.5 or 10 g daily Baseline T < 10.4 nmol l ⁻¹ was raised to normal levels	Baseline PSA < 4 in all patients; mean levels in general remained in normal range while increasing by 0.37	2 1 after 12 months in man with PSA 5.7, and 1 after 18 months in man with PSA 6.2 (these prostate cancers appear to be 2 of the 3 reported by Wang <i>et al.</i> ⁵⁰)
<i>Retrospective studies</i> Guay <i>et al.</i> ⁵² 2- to 3-month retrospective study of PSA level and risk of prostate cancer during T therapy or clomiphene	90 40–80	TIM (TE, <i>n</i> = 25) 200 mg every 2 weeks or 300 mg every 3 weeks, nonscrotal TTD (<i>n</i> = 16) 5 mg daily or clomiphene (<i>n</i> = 49) 50 mg orally TID for 2–3 months In the clomiphene group, mean FT level increased from baseline of 3.4 ± 1.0 nmol l ⁻¹ to 6.6 ± 2.6 (<i>P</i> < 0.001) in the 40–60-year age group and from 2.8 ± 0.6 to 5.8 ± 1.8 (<i>P</i> < 0.001) in the 61–80-year age group	Mean baseline PSA increased significantly for 61- to 80-year group but not for 40- to 60-year group treated with TIM or TTD Mean baseline and post-T therapy PSA values for 40- to 60- and 61- to 80-year age groups were, respectively, for TIM 0.69 ± 0.19 and 1.01 ± 0.25 (<i>P</i> = 0.055) and 1.70 ± 0.35 and 2.64 ± 0.65 (<i>P</i> = 0.018); for TTD 0.78 ± 0.10 and 0.98 ± 0.18 (<i>P</i> = 0.214) and 1.70 ± 0.35	3 9 men had biopsies because of suspicious PSA levels and 1 because of an abnormal DRE result; 2 cancers were found on initial biopsy and a third on rebiopsy (the report does not indicate whether cancers were detected in men treated with T or clomiphene)

Table 2 (Continued)

Study	Patients (N) Age Range (years)	T therapy and outcome ^a	PSA (ng ml ⁻¹)	Prostate cancer cases (n)
Hajjar <i>et al.</i> ⁵³ 2-year retrospective study of long-term T therapy vs no T therapy	72 Mean, 71.8 in T therapy group, 69.9 in control group	TIM (TE or TC, n = 45) 200 mg every 2 weeks Mean baseline T 10.8 ± 0.7 nmol l ⁻¹ in the TIM group and 9.6 ± 0.7 in the control group; T levels under treatment not reported	and 0.64 ± 0.65 (P = 0.018); and, for clomiphene 2.0 ± 1.8 and 2.8 ± 3.1 (P = 0.068) and 2.0 ± 2.2 and 3.2 ± 4.8 (P = 0.063) Mean PSA increased by 0.25 ± 0.40 from baseline 1.4 ± 0.3 in the control group TC group and from baseline 1.3 ± 0.2 in TIM group	It is presumed there was no case of prostate cancer because there is no mention in the report of prostate cancer as a distinct entity, although benign prostatic hyperplasia/prostate cancer is listed as occurring in six control subjects and two study patients
Rhoden and Morgentaler ⁵⁴ 1-year retrospective study of T therapy in men at high risk for prostate cancer because of high-grade PIN compared to men without high-grade PIN	75 42–77	TIM (TE, n = 32) or TG (n = 23) in PIN-negative group; TIM (n = 11) or TG (n = 9) in PIN-positive group; doses not specified Mean baseline TT 10.2 ± 4.4 and 10.3 ± 3.2 nmol l ⁻¹ (P = 0.88) increased to 22.2 ± 11.2 and 21.4 ± 9.4 at 1 year in PIN-negative and PIN-positive groups, respectively	In PIN-positive and PIN-negative groups, respectively, mean levels similar at baseline (1.49 ± 1.1 and 1.53 ± 1.6) and 1 year (1.82 ± 1.1 and 1.78 ± 1.6), with mean increases of 0.33 ± 0.6 and 0.25 ± 0.6 (all, P > 0.05) Mean baseline 1.83 ± 1.9 (range, 0.3–9.4) increased by 0.31 ± 0.76 to 2.14 ± 2.0 (17% increase)	1 57-year-old man, PIN positive at 1 year, PSA increased from 1.7 to 2.6, Gleason grade 7 (4 + 3)
Rhoden and Morgentaler ⁵⁵ 1-year retrospective study of the influence of demographic and biochemical characteristics on PSA response to T therapy in men with normal prostate biopsy	58 42–77	TIM (n = 33) or TG (AndroGel or Testim, n = 25); doses not specified Mean baseline TT of 10.3 ± 5.4 and 10.1 ± 3.1 nmol l ⁻¹ increased to 21.2 ± 12.4 and 22.2 ± 8.4 in TIM and TTD groups, respectively	Mean baseline 1.83 ± 1.9 (range, 0.3–9.4) increased by 0.31 ± 0.76 to 2.14 ± 2.0 (17% increase)	1 55-year-old man, PSA rose from 5 at baseline to 8.2 after 12 months; biopsy, positive
Gerstenbluth <i>et al.</i> ⁵⁶ 2- to 82-month (mean, 30) retrospective study of PSA changes during T therapy in men with ED	54 42–76	TIM (TC) 200–300 mg every 2–4 weeks Mean baseline TT of 6.6 nmol l ⁻¹ (range, 0.7–1.0) increased to 33.8 (range, 5.2–91.2)	Mean, 1.86 (range, 0.0–15.80) before T therapy; 2.82 (range, 0.0–32.36) after T therapy; mean change, 0.96 (P < 0.01)	1 60-year-old man, pretreatment PSA 3.70 rose to 5.90 after 15 months of T therapy; six biopsies were done because of PSA rise, and one was positive for cancer
<i>Studies of 1 or 2 cases</i> Bydder <i>et al.</i> ⁵⁷ Man with Klinefelter syndrome	Age (years) 55	TIM for 1 month, then TIM 600 mg every 6 months for 7 years T increased from low-normal to 17 nmol l ⁻¹	PSA went from normal to 27.5	1 Gleason 7
Hwang <i>et al.</i> ⁵⁸ Man with Klinefelter syndrome	49	TIM TE for 35 years TT levels were kept normal	After 35 years, PSA increased from 3.6 to 12.2	1 Gleason 4
Curran and Bihrlé ⁵⁹ ED led to diagnosis of hypogonadism	85 67	TIM for 6 months TT 1.4 nmol l ⁻¹ before TIM was started	PSA 2.7 increased to 55.2 (with nodule palpated on DRE)	1 Gleason 6–8

Table 2 (Continued)

Study	Patients (N) Age Range (years)	T therapy and outcome ^a	PSA (ng ml ⁻¹)	Prostate cancer cases (n)
Ferri and Norman ⁶⁰ Man with hypogonadism		TIM 200 mg every 3 weeks for 8 years T 8.7 nmol l ⁻¹ before TIM was started	PSA 15.8 after 8 years (at time of biopsy) with decline to 0.6 at 3 months after stopping TIM	1 Gleason 6
Halland <i>et al.</i> ⁶¹ Man with pituitary insufficiency	45	TIM 250 mg every 3 weeks for 15 years, after 2 months of mesterolone therapy No T levels were reported	PSA 22 (first ever determined)	1 Gleason 5
Jackson <i>et al.</i> ⁶² Prostatic disease related to T therapy	Patient 1, 62; patient 2, 74	TIM TC 200 mg every 3 weeks for 10 weeks (patient 1); TIM TC was started only after biopsy showed benign transitional metaplasia of the prostate in patient 2 T 5.9 and 0.7 nmol l ⁻¹ before TIM was started in patients 1 and 2, respectively	PSA 14.2 and 0.1 in patients 1 and 2, respectively	2 Gleason 8 (patient 1; report does not indicate score for patient 2)
Loughlin and Richie ⁶³ Man with decreased libido	58	TIM 180 mg every 2 weeks T 1.4 nmol l ⁻¹ before TIM was started	Baseline PSA of 3.5 rose to 4.4 at 6 months and 5.1 at 8 months	1 Gleason 5
Sandeman ⁶⁴ Man treated with T for impotence after radiotherapy for prostate cancer ≥5 years ago	≥70	TIM, dose and duration unknown (patient had been under treatment elsewhere, where history of previous prostate cancer was probably not known) No T levels reported	Unknown	1 Metastatic disease in nodes, chest and bones

Abbreviations: BMD, bone mineral density; DHT, dihydrotestosterone; DRE, digital rectal examination; ED, erectile dysfunction; FT, free testosterone; LH, luteinizing hormone; PIN, prostate intraepithelial neoplasia; PK/PD, pharmacokinetic/pharmacodynamic; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; T, testosterone; TB, testosterone buccal; TC, testosterone cypionate; TE, testosterone enanthate; TG, testosterone gel; TIM, intramuscular testosterone; TO, oral testosterone; TT, total testosterone; TTD, transdermal testosterone undecanoate patch; TU, testosterone undecanoate; ULN, upper limit of normal.

^aT in reported conventional units converted to SI units using T in ng per 100 ml × 0.03467 = nmol l⁻¹.

Table 3 Non-placebo-controlled case studies of testosterone use in hypogonadal men who have had prostate cancer

Study	Patients (N) Age range (years)	T therapy and outcome	PSA (ng ml ⁻¹)	Prostate cancer status
Ferreira <i>et al.</i> ⁶⁵ 1.5- to 2.5-year prospective study of men with subcapsular orchiectomy for advanced prostatic carcinoma >3 years earlier, with PSA stable and bone scans negative for metastases	5 71–77	TIM (TE) 250 mg every 3 weeks Baseline TT 12–32 ng per 100 ml with increase to 280–352	Baseline range 2.0–7.4; final range 4.5–8.4; only 1 patient had a significant (>10) PSA rise, to 12, after 14 months (this decreased to 7.2)	No evidence of local recurrence or distant disease
Sarosdy ⁶⁶ 0.5- to 8.5-year retrospective study of men with T therapy started 0.5–4.5 years after brachytherapy for early prostate cancer	31 51–79	T therapy of patient's preference, mostly TIM (TC); various doses Baseline TT 30–255 ng per 100 ml with increase to 365–1373	No baseline levels were obtained; most recent value <1 in all patients	No confirmed recurrence or progression
Agarwal and Oefelein ⁶⁷ 9- to 29-month retrospective study of T therapy in men who had radical retropubic prostatectomy	10 59–69	1% TG (AndroGel or Testim, <i>n</i> = 7), TTD (Androderm, <i>n</i> = 1), or TIM (TC, <i>n</i> = 2); doses not specified Baseline TT 197 ng per 100 ml increased to 591 (<i>P</i> = 0.0002)	PSA remained undetectable (<0.1)	No PSA recurrence
Kaufman and Graydon ⁶⁸ 1- to 12-year retrospective study of T therapy in men who had curative radical prostatectomy, one with positive surgical margin	7 50–79 (age at prostatectomy)	TTD (<i>n</i> = 3), various and titrated doses; TG (<i>n</i> = 2) 5 g daily, TIM (<i>n</i> = 2); doses not specified In 1 case, baseline T 269 ng per 100 ml decreased to 214–260; in 4 cases, T increased from 51 to 214, 50 to 307, 353 to 563, and 19 to 545; other changes not recorded	PSA remained undetectable (<0.1)	No biochemical or clinical evidence of recurrence

Abbreviations: PSA, prostate-specific antigen; T, testosterone; TC, testosterone cypionate; TE, testosterone enanthate; TG, testosterone gel; TIM, intramuscular testosterone; TT, total testosterone; TTD, transdermal testosterone undecanoate patch.

received testosterone as monotherapy and 5.5% in men who received placebo. The combination therapy arm of this study was not evaluated; however, it should be noted that no incidences of prostate cancer were reported in men who received testosterone with finasteride. Routine end-of-study biopsy was not performed. In only one subject, prostate cancer was suspected because of an elevated PSA level. A second case was detected because of an abnormal DRE, and a third, though seemingly untraditional signs and symptoms suggestive of prostate cancer, because of asthenia and fever. In the Marks *et al.*²⁹ study, all the cancers, regardless of testosterone or placebo grouping, were detected at 6 months in men who had a negative DRE result at 3 months and a negative start-of-study biopsy. Reports of other placebo-controlled studies did not disclose why prostate cancers were suspected.

This review's 21 non-placebo-controlled studies provide information about the effect of testosterone

therapy on PSA level and its relation to prostate cancer, though not about the relative risk of prostate cancer developing or progressing in testosterone-treated vs nontreated men. In Guay *et al.*'s⁵² transdermal testosterone undecanoate patch and intramuscular testosterone groups, PSA levels increased in men aged 61–80 years (*P* = 0.018 and 0.005, respectively) but not to the same degree in men aged 40–60 years (*P* = 0.055 and 0.214, respectively). Biopsies were triggered by suspicious PSA levels in nine cases and a nodule detected by DRE in one case, resulting in three cancers detected (3% of 90 men).⁵²

In the Gerstenbluth *et al.*⁵⁶ study, a rise in PSA level above 4.0 ng ml⁻¹ led to biopsy in 6 of the 54 men (11.1%) and to 1 prostate cancer (1.9%). All of the men met inclusion criteria, with a PSA level <4.0 ng ml⁻¹ before treatment, normal results on DRE, or a pretreatment prostate biopsy negative for cancer for men with an abnormal DRE or an elevated PSA level. PSA levels increased, but no cancers

were detected in the El-Sakka *et al.*⁴¹ 1-year study of patients with hypogonadism associated with erectile dysfunction. Douglas *et al.*⁴⁰ found a rise in PSA level of about 40% and a doubling of average serum testosterone level for 10 men receiving therapy with testosterone patch, but no cancer cases; neither PSA nor prostate-specific membrane antigen were testosterone dependent. In this study, PSA was found to be less sensitive than DRE in detecting prostate cancer in the series of 20 cases collected retrospectively by Gaylis *et al.*³⁶ In the Rhoden and Morgentaler⁵⁵ study, testosterone therapy caused only a mild increase in PSA levels in most men and did not appear to be influenced by age or baseline PSA or serum testosterone levels.

High-grade PIN is associated with a higher risk of developing prostate cancer⁷⁰; prostate cancer develops in 25.8% of men with high-grade PIN within 3 years of the PIN finding.⁷¹ Upon biopsy before testosterone therapy in the Rhoden and Morgentaler⁵⁴ study, 20 prostates were positive for high-grade PIN and 55 were negative. The PIN-positive and PIN-negative groups had similar mean levels of testosterone ($P=0.88$) and PSA ($P>0.05$) at baseline and at the end of the 1-year study. The single prostate cancer detected in the study group was in a man whose prostate was PIN positive (5%). The prostate cancer incidence rate was 1.3% for the entire group.⁵⁴ In a subsequent report, Morgentaler²⁴ concluded that testosterone therapy did not cause precipitous progression of prostate cancer in these men.

Data in the studies covered by this review are insufficient to determine whether more severe grades of prostate cancer are found with testosterone treatment vs without, but they seem to indicate the cancer grades are not necessarily more severe with treatment. The Gleason grades of 6 and 7 in the cancers detected by Marks *et al.*²⁹; the scores of 6, 7 and 8–10 in the Gaylis *et al.*³⁶ study; and the score of 7 in the Rhoden and Morgentaler⁵⁴ study suggest that these cancers are all of clinical significance, regardless whether in testosterone-treated or nontreated subjects. Further, data from the four studies of men who received testosterone therapy over periods of up to 12 years after treatment for prostate cancer provide no evidence that testosterone therapy increased the risk of cancer recurrence or metastasis.^{65–68}

This review was designed to provide information to help answer the specific question about whether prostate cancer risks are increased by testosterone therapy for hypogonadism. The review included studies of adult men of any age with hypogonadism of any etiology, regardless whether the studies were placebo-controlled and randomized or involved men with previous prostate cancer.

The extensive variation of the 44 study designs and objectives, inclusion and exclusion criteria, patient populations, testosterone formulations and dosages, baseline testosterone levels, and other

features, however, limit the conclusions that can be drawn relating testosterone therapy to the risk of new prostate cancer or recurrence of prostate cancer. The small number of placebo-controlled studies, intrinsic weaknesses of noncontrolled or retrospective trials, short duration and small numbers of subjects in some studies, and varied response of serum testosterone levels to testosterone administration are among other limitations of this review. Further, none of the studies was planned or powered to answer this review's single, salient question of whether testosterone therapy increases the risk of prostate cancer. Despite these limitations, this review discloses data that permit relevant observations.

First, there is no evidence that US Food and Drug Administration (FDA)-approved formulations of testosterone therapy increase the risk of prostate cancer in hypogonadal men. As shown by the overall similar incidence of prostate cancer in testosterone- and placebo-treated subjects in the 11 placebo-controlled studies, a higher incidence of prostate cancer was detectable within 6 months in placebo-treated subjects.^{14,26–35} In addition, the higher number of prostate cancers detected at 6 months in the placebo group than in the testosterone group may indicate that testosterone plays a protective role in hypogonadism.

There were no cancer recurrences or metastases in patients treated with FDA-approved testosterone formulations who had a history of prostate cancer.^{65–68} Further, men with high-grade PIN treated with testosterone did not have a greater increase in PSA or a significantly elevated risk of prostate cancer than testosterone-treated men without PIN.⁵⁴ Testosterone therapy did not cause a sudden progression to prostate cancer in men with PIN.⁵⁴ There are no data suggesting that testosterone therapy favors the development of more severe grades of prostate cancer compared to placebo or no treatment with testosterone, as evidenced by Gleason scores.

The value of PSA level as an indicator of possible prostate cancer makes its relationship to FDA-approved testosterone therapy a matter of some importance. In the studies covered in this review, there was no consistent effect of testosterone therapy on PSA level; PSA levels were increased in men aged 61–80 years but not in younger men,⁵² or increased in the first 6 months of testosterone therapy but not during the next 3 years.⁵⁰ However, other PSA isoforms that impact the risk of a positive biopsy, such as a low or falling percent free PSA, have not been adequately studied in this population of men. Gore *et al.* demonstrated that optimizing the distribution and number of cores sampled during prostate biopsy increases the prostate cancer detection rate. An improved sampling regimen detected a ~25% risk of cancer developing in men with PSA between 2.5 and 4.0 ng ml⁻¹ and a ~50% risk of cancer developing in men with PSA between 4.0 and 10 ng ml⁻¹.⁷² It remains prudent to perform a

biopsy before the initiation of testosterone therapy for men with higher PSA levels.

Although non-FDA-approved testosterone supplementation was not the focus of this review, a study by Shariat *et al.*⁷³ reported two highly unusual cases of aggressive prostate cancer after initiation of a non-FDA-approved oral supplement that contained a proprietary combination of substances that included testosterone, estradiol, chrysin and elk velvet antler. Furthermore, androgen-independent disease developed quickly in these patients within months of beginning combined androgen blockade. Laboratory analysis of the product demonstrated that it was a more potent stimulator of prostate cancer cell growth compared to testosterone alone in both hormone-refractory (DU-145) and hormone-sensitive (LNCaP) human prostate cancer cell lines. These cases suggest that standard formulations of testosterone therapy, tested in FDA trials before approval, can be used safely, but there may be a significant risk when combining androgens and estrogens with other bioactive substances. This merits further study and caution.⁷³

Because of its restricted focus on the risk of prostate cancer, this review has not considered to any great extent other negative and positive effects of testosterone therapy, including effects on prostate size, symptoms of prostatism, signs and symptoms of hypogonadism, lipids and the cardiovascular system, hematocrit increase, sleep apnea and fluid retention. The review published recently by Seftel⁴ covers pharmacologic and clinical profiles of available and potential testosterone preparations and monitoring and safety issues associated with testosterone therapy.

In addition, an important study from the Endogenous Hormones and Prostate Cancer Collaborative Group was recently published. This study investigated 18 prospective longitudinal studies that analyzed whether differences in circulating levels of sex hormones were related to risk of prostate cancer. This collaborative analysis definitively found no association between serum testosterone concentrations and the risk of prostate cancer.⁷⁴

The studies in this review demonstrate that FDA-approved testosterone therapy is well tolerated, safe and efficacious in the treatment of hypogonadal men.

Conclusion

There is no evidence that testosterone therapy increases the risk of prostate cancer in hypogonadal men. Selected studies in this systematic review demonstrated that the incidence rates for developing prostate cancer did not increase and did not cause high-grade PIN to progress to frank prostate cancer in hypogonadal men treated with testosterone therapy. Further, endogenous concentrations of serum testosterone have not been directly linked to

abnormal changes in PSA, and testosterone therapy appears to be safe in men treated with curative therapy for prostate cancer. FDA-approved formulations of testosterone therapy may be administered to symptomatic hypogonadal men who have either normal PSA and DRE results or higher/rising PSA levels or abnormal DRE results but a prostate biopsy that is negative for cancer. Testosterone therapy requires regular monitoring of PSA and DRE. Urologic referral is recommended for prostate biopsy if there is a rise in PSA levels or an abnormality detected by DRE. An important finding demonstrates that testosterone therapy can be safely administered with monitoring to men who have had curative therapy for prostate cancer and have symptoms of hypogonadism.

Author contributions

Dr Shabsigh, Dr Crawford, Dr Nehra and Dr Slawin had full access to all of the data in the review and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Dr Shabsigh was a consultant for American Medical Systems, Auxilium, Bayer Schering Pharma, Boehringer Ingelheim, Indevus Pharmaceuticals, Johnson & Johnson, Lilly, and Pfizer. He was a lecturer for American Medical Systems, Bayer Schering Pharma, Lilly, and Pfizer. Dr Crawford was a lecturer for Auxilium, Endocare, GlaxoSmithKline, Oncura and Sanofi-Aventis. He was on a scientific trial for Oncura. He was a consultant for the National Institutes of Health and the University of Colorado Cancer Center. Dr Nehra was a consultant for GlaxoSmithKline, Indevus and Pfizer. Dr Slawin was a board member and consultant for Bellicum Pharmaceuticals, Inc. He was an investor, owner of Indevus Pharmaceuticals. He was a meeting participant for Boehringer Ingelheim. He was on a scientific trial and a meeting participant for Novacea.

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