Testosterone Therapy Among Prostate Cancer Survivors

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ABSTRACT

Introduction: The use of testosterone in men with a history of prostate cancer remains controversial in light of established findings linking androgens to prostate cancer growth. However, hypogonadism significantly affects quality of life and has negative sequelae, and the risks and benefits of testosterone therapy might be worthwhile to consider in all men, even those with a history of high-risk prostate cancer.

Aim: To discuss the effects of testosterone on the prostate and the use of testosterone therapy in hypogonadal men with a history of prostate cancer.

Methods: Review of the literature examining the effects of testosterone on the prostate and the efficacy and safety of exogenous testosterone in men with a history of prostate cancer.

Main Outcome Measures: Summary of effects of exogenous and endogenous testosterone on prostate tissue in vitro and in vivo, with a focus on effects in men with a history of prostate cancer.

Results: Testosterone therapy ameliorates the symptoms of hypogonadism, decreases the risk for its negative sequelae, and can significantly improve quality of life. Recent studies do not support an increased risk for de novo prostate cancer, progression of the disease, or biochemical recurrence in hypogonadal men with a history of non–high-risk prostate cancer treated with testosterone therapy. Evidence supporting the use of testosterone in the setting of high-risk prostate cancer is less clear.

Conclusion: Despite the historical reluctance toward the use of testosterone therapy in men with a history of prostate cancer, modern evidence suggests that testosterone replacement is a safe and effective treatment option for hypogonadal men with non–high-risk prostate cancer. Additional work to definitively demonstrate the efficacy and safety of testosterone therapy in men with prostate cancer is needed, and persistent vigilance and surveillance of treated men remains necessary.

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Key Words: Hypogonadism; Testosterone; Hormone Replacement; Prostate Cancer; Prostatectomy; Radiation Therapy

INTRODUCTION

Hypogonadism is newly diagnosed in approximately 500,000 men annually and is characterized by decreased serum testosterone levels. Hypogonadal men can experience signs and symptoms such as impaired sexual function, decreased muscle mass and strength, decreased bone mineral density, decreased cognition, and depressive symptoms.[1,2] Hypogonadism affects 5.6% of men 30 to 79 years old and 18.4% of men older than 70 years and increases in incidence with age; no difference in prevalence by race or ethnic group has been observed.[3–5] This older population also is frequently affected by prostate cancer, which accounts for one in five new cancer diagnoses.[6] However, prostate cancer mortality has decreased 50% during the past two decades as a result of improvements in early detection and treatment. As a result, more patients are living with a history of prostate cancer. The aging of the U.S. male population and the growing population of prostate cancer survivors have resulted in a significant increase in the number of men reaching older age, thus increasing the likelihood of hypogonadism in these men.

From 2001 to 2011, androgen use in men older than 40 years increased more than threefold with its ability to treat the symptoms of hypogonadism (50.6%), fatigue (34.5%), erectile dysfunction (31.9%), and psychosexual dysfunction (11.8%).[7] Long-term testosterone therapy also has been found to

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significantly increase trabecular and cortical bone mineral density, which is significant in light of the high frequency (20−50%) of hypogonadal testosterone levels in men with symptomatic vertebral fractures and hip fractures.[8,9] Current evidence also supports the notion that testosterone acts as an immunomodulatory and atheroprotective hormone.[10] As such, testosterone therapy has been associated with decreased mortality and improvement of cardiovascular risk factors, including fat mass and glycemic control.[11] However, controversy regarding the use of exogenous testosterone and associated cardiovascular risk remains, with numerous studies during the past decade supporting and refuting an association between testosterone use and increased cardiovascular risk.[12] Additional concerns initially arose after reports of increased cardiovascular risks associated with testosterone prescriptions.[13,14] These claims are based largely on two flawed studies but have raised the profile of these concerns. In contrast, several dozen articles have suggested that testosterone deficiency actually decreases cardiovascular risk (reviewed by Morgentaler et al[11]).

In the setting of prostate cancer, testosterone therapy use has been historically controversial owing to concerns raised by a landmark study that linked administration of exogenous testosterone to stimulation of prostate cancer growth.[15] In 1941, Huggins and Hodges[15] established a direct relation between prostate cancer and androgens. Their androgen-dependent model of prostate cancer growth was based on the observation that bilateral orchiectomy of eight men in their cohort and estrogen injections in another five men resulted in a marked decrease in serum acid phosphatase, a serum marker for prostate cancer that has since been replaced by prostate-specific antigen (PSA). In addition, they found that testosterone injections in three men resulted in marked increases in serum acid phosphatase and concluded that androgen injections stimulated prostate cancer growth. However, recent evidence does not support these early findings and in fact argues against them. The first study to observe a link between an increased risk of prostate cancer and low serum testosterone levels was published by Morgentaler et al[16] in 1996 and identified prostate cancer in 14% of 77 men with low serum testosterone levels (Table 1). The significant impact that hypogonadism has on quality of life and the need to treat a growing population of men, many of whom will have prostate cancer during their lives, demonstrate a need for higher-quality evidence evaluating the safety and efficacy of testosterone therapy in these men. In this review, we examine the evidence for testosterone's effect on the prostate, focusing on endogenous and exogenous testosterone and normal and malignant prostate tissue.

METHODS

A review of literature was performed using the PubMed database to identify English-language studies and review articles related to data on testosterone replacement therapy and prostate cancer. An analysis of the historical perspective was conducted, and study findings from 1994 to the present were considered. The seminal 1941 study by Huggins and Hodgins[15] was included.

MAIN OUTCOME MEASURES

Based on the literature, the effects of exogenous and endogenous testosterone on prostate tissue in vitro and in vivo were summarized, with a focus on effects in men with a history of prostate cancer.

RELATION BETWEEN ENDOGENOUS TESTOSTERONE LEVELS AND PROSTATE CANCER

Low Serum Testosterone

Available evidence supports an increased risk of prostate cancer in men with low serum testosterone levels, with studies observing higher rates of prostate cancer incidence, higher-grade disease, and higher likelihood of extraprostatic extension, biochemical recurrence (BCR), and positive surgical margins.[17] Morgentaler et al[16] suggested a possible relation between low testosterone and increased risk of prostate cancer in their study of 77 men with low total or free testosterone levels, normal digital rectal examination results, and PSA levels no higher than 4.0 ng/mL. They identified a high prevalence of biopsy-detectable prostate cancer in these men (11 men, 14%), despite their normal PSA levels. A prospective study of 206 men (103 with benign prostatic hyperplasia [BPH] and 103 with prostate cancer) found that lower testosterone levels correlated with a higher probability of finding advanced prostate cancer.[18] A study of 568 patients who underwent prostate biopsy examination found that men with low testosterone levels (<3.85 ng/mL) had a significantly higher incidence of prostate cancer than men in the high testosterone group (≥3.85 ng/mL; 38.0% vs 29.5%, $P = .018$).[19] A prostate cancer screening program used in 718 men investigated whether serum testosterone could serve as an adjunct test to validate PSA-weighted risk of prostate cancer in the "gray" diagnostic area (PSA = 3.0−<10.0 ng/mL).[20] The investigators found that men with modestly increased PSA level (<10.0 ng/mL) and low total testosterone level (mean = 3.6 ng/mL) were at increased risk for prostate cancer. A retrospective analysis of 345 hypogonadal men with a PSA level no higher than 4.0 ng/mL observed that prostate cancer was detected in more men with a testosterone level lower than 250 ng/dL compared with those with a testosterone level higher than 250 ng/dL (21% vs 12%, respectively).[21]

Low serum testosterone levels also correlate with more aggressive prostate cancer. Hoffman et al[22] examined 117 men and observed that those with low free testosterone levels (≤1.5 ng/dL) had more extensive prostate cancer, based on a higher frequency of positive biopsy results (43% vs 22%, $P = .013$) and more high-grade tumors with a Gleason sum of at least 8 (7 of 64 vs 0 of 48, $P = .025$) than men with normal free testosterone levels (>1.5 ng/dL). García-Cruz et al[23] found

Table 1. Studies on the relation between low endogenous testosterone levels and prostate cancer

References	Patients, n	Study type	Endogenous TTh level	CaP outcomes
Morgantaler et al[16]	77	Retrospective	T < 300 ng/dL or free T < 1.6 ng/dL	CaP incidence of 14% (11/77)
Mearini et al[18]	206	Prospective	≤2.4 ng/mL	14.2% of patients had clinically locally advanced or metastatic CaP and 57.1% have pathologically locally advanced CaP
			≤0.5 ng/mL	40% of patients had clinically locally advanced or metastatic CaP and 60% has a pathologically locally advanced CaP
Shin et al[19]	568	Prospective	<3.85 ng/mL	CaP incidence 38.0% (vs 29.5% high T group)
Karamanolakis et al[20]	718	Prospective	<3.0 ng/mL	CaP incidence 30% (29/97)
Morgantaler and Rhoden[21]	345	Retrospective	<250 ng/dL	CaP incidence 21% (vs 12% in men with T > 250 ng/dL)
Hoffman et al[22]	117	Retrospective	T < 300 ng/dL or free T < 1.5 ng/dL	CaP incidence 43% (vs 22%)
García-Cruz et al[23]	137	Prospective	<346 ng/dL	Tumor burden 53% (vs 32% in men with T > 346 ng/dL); tumor bilaterality 50% (vs 25.5% in men with T > 346 ng/dL)
Isom-Batz et al[24]	326	Retrospective	<385 ng/dL	Associated with advanced pathologic stage (OR = 2.3, 95% CI = 1.1–5.0, $P = .03$)
Lane et al[25]	455	Prospective	<220 ng/dL	Higher frequency of Gleason score 4–5 disease (OR = 2.4, 95% = CI 1.01–5.7, $P = .48$)
Botto et al[26]	431	Prospective	<3 ng/mL	Higher frequency of Gleason score 4 disease (47% vs 28%)
Dai et al[27]	110	Prospective	<250 ng/dL	Pathologic Gleason score ≥ 8 in 44.4% of hypogonadal patients (8/18) vs 15.2% of eugonadal patients (14/92)
Xylinas et al[28]	107	Prospective	<3 ng/mL	Gleason score ≥ 7 83% vs 69%; locally advanced pathologic stage pT3–pT4: 43% vs 25%
Kim et al[29]	60	Retrospective	<3 ng/mL	Higher incidence of extraprostatic invasions (61.9% vs 28.2%) and biochemical recurrence (23.8% vs 5.1%)
Salonia et al[30]	673	Prospective	Total T < 1 ng/mL	Higher incidence of seminal vesicle invasion (OR = 3.11, $P = .006$)
Teloken et al[31]	64	Retrospective	<2.7 ng/mL	Increased positive surgical margins ($P = .026$)

CaP = prostate cancer; OR = odds ratio; T = testosterone; TTh = testosterone therapy.

in a prospective study of 137 men that testosterone levels were inversely related to prostate cancer bilaterality and percentage of tumor in the biopsy specimen ($P < .01$). A multivariate analysis of 326 men showed that lower testosterone levels correlated with adverse pathologic stage, clinical stage, biopsy grade, and PSA.[24] A prospective study including 455 patients associated low pretreatment total testosterone with Gleason pattern 4 and 5 cancers at prostatectomy.[25] In a prospective study observing 431 men, patients with testosterone levels lower than 3 ng/mL had a higher frequency of Gleason 4 disease than patients with higher total testosterone levels (47% vs 28%, $P = .002$).[26] Similarly, data from ethnic Chinese patients with localized prostate cancer treated with radical prostatectomy showed that compared with those with low-grade disease (15.2%), patients with high-grade disease (44.4%), or a Gleason score of at least 8, had significantly lower preoperative total testosterone levels.[27]

Results from a study of 107 men with localized prostate cancer treated with radical prostatectomy concluded that low preoperative serum testosterone was a predictor of aggressive disease (Gleason score > 7) and extraprostatic disease (pathologic stage > pT2).[28] Comparably, a study of clinical data from 60 men associated a low serum testosterone level (<3 ng/mL) with an increased risk of extraprostatic cancer extension and an increased risk of BCR.[29] A cohort of 673 consecutive European Caucasian patients showed that only a circulating total testosterone level lower than 1 ng/mL was an independent predictor of seminal vesicle invasion.[30] In contrast with previous data, this study did not associate preoperative circulating total testosterone levels with a higher risk of prostate cancer. A retrospective study evaluating 64 patients with localized prostate cancer treated with radical retropubic prostatectomy found that patients with low total testosterone levels had an increased risk of positive surgical margins ($P = .026$).[31]

Table 2. Studies on the relation between normal and high endogenous testosterone levels and prostate cancer

References	Patients, n	Study type	Endogenous TTh level	CaP outcomes
Shaneyfelt et al[32]	2,310	Cohort/nested case-control	—	Highest quartile 2.34 times more likely to develop CaP than those in lowest quartile (95% CI = 1.30–4.20)
Gann et al[33]	612	Retrospective	Highest vs lowest quartiles	OR = 2.60, 95% CI = 1.34–5.0, $P = 0.004$
Yano et al[34]	420	Retrospective	4.2 ± 2.6 ng/mL	Pretreatment T higher in patients diagnosed with CaP than in patients diagnosed with BPH (3.6 ± 1.4 ng/mL, $P = 0.007$)
Salonia et al[35]	724	Cohort	Lowest and highest circulating T	Both associated with high-risk CaP (non-linear U-shape behavior)
Porcaro et al[36]	220	Retrospective	TT > 15.5 nmol/L	Higher risk for tumors Gleason sum ≥ 8 (OR = 1.31 vs TT < 15.5 nmol/L)
Salonia et al[37]	605	Prospective	Continuous variable	Early BCR in 5.6% (PSA ≥ 0.1 ng/mL) within 24 mo after RP
Roddam et al[38]	3,886	Prospective, pooled 18-study analysis	Quartiles	Not significant
Muller et al[39]	3,255	REDUCE trial	<2.88 ng/mL	Not significant
Platz et al[40]	460	Prospective, nested case-control	Highest vs lowest quartiles	Not significant
Stattin et al[41]	708	Retrospective	Highest TT quintile = 0.80	Small decrease in CaP risk (95% CI = 0.59–1.06, $P = .05$)
Mearini et al[42]	65	Prospective	>2.4 ng/mL	OR = 0.15, 95% CI = 0.03–0.68, $P = .014$
Ahmadi et al[43]	194/317	Prospective, matched controls	High TT, FT controls	$P < .001$; protective against CaP, enhanced by each decade of increasing age
Røder et al[44]	227	Prospective	>11 ng/mL	Lower risk of biochemical failure (HR = 0.53, 95% CI = 0.31–0.90, $P = 0.02$)
Imamato et al[45]	222	Retrospective	>4.9 ng/mL	Positive prognostic value
Yamamoto et al[46]	272	Retrospective	>300 ng/dL	84.9% 5-y PSA failure-free survival rate (vs 67.8% of patients with serum T < 300 ng/dL)

BCR = biochemical recurrence; BPH = benign prostatic hyperplasia; CaP = prostate cancer; FT = free testosterone; HR = hazard ratio; OR = odds ratio; PSA = prostate-specific antigen; REDUCE = Reduction by Dutasteride of Prostate Cancer Events; RP = radical prostatectomy; T = testosterone; TT = total testosterone; TTh = testosterone therapy.

Normal and High Serum Testosterone

Overall, data from studies examining the effects of normal to high endogenous serum testosterone levels on prostate cancer are inconsistent, although these studies do not exhibit any obvious methodologic inconsistencies to explain the discrepancies in findings between them. A meta-analysis restricted to two studies that adjusted for serum hormone levels in the highest quartile found that these men were 2.34 times more likely to develop prostate cancer (Table 2).[32] A prospective, nested case-control study of 612 cases associated high-normal serum testosterone levels with an increased risk of prostate cancer.[33] A study examining 420 men who underwent prostate biopsy examination and had testosterone levels determined found that in patients with PSA levels lower than 10 ng/mL, pretreatment testosterone levels were significantly higher in those with prostate cancer than those with benign biopsy findings ($P = .007$).[34] In another significant study, Salonia et al[35] examined a cohort of 724 men with low-risk (34.7%), intermediate-risk (43.9%), or high-risk (21.4%) prostate cancer and observed that men with the lowest and highest serum testosterone levels were at increased risk for prostate cancer recurrence after radical prostatectomy ($P = .03$). Porcaro et al[36] found that increased pretreatment testosterone levels were associated with Gleason sums of at least 8. Salonia et al[37] subsequently found that in a cohort of 605 European Caucasian men with prostate cancer who underwent radical prostatectomy, pretreatment total testosterone level was an independent predictor of early BCR (PSA ≥ 0.1 ng/mL) at median follow-up of 24 months. Patients with early BCR (5.6%) did not differ in predictors such as age, body mass, serum PSA, preoperative serum total testosterone, 17β-estradiol, SHBG, rate of

hypogonadism, and clinical stage from those without BCR ($P \geq .05$ for all comparisons) but did show a greater prevalence of biopsy Gleason scores of at least 4 plus 3 ($P \leq .001$).

In contrast, pooled data from 18 prospective studies encompassing 3,886 men with a history of prostate cancer and 6,438 controls found no associations between risk of prostate cancer and serum testosterone levels.[38] A study examining the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial showed that men with the lowest baseline testosterone levels had the lowest prostate cancer risk, whereas men with normal baseline testosterone levels showed no association between testosterone and prostate cancer risk.[39] Platz et al[40] followed 460 prostate cancer cases and found no association between total testosterone levels and prostate cancer. However, they did report that higher total testosterone level was positively associated with disease with a Gleason sum lower than 7 and inversely associated with disease with a Gleason sum of at least 7.

In further juxtaposition with the previous studies, Stattin et al[41] analyzed data from three cohorts encompassing 708 patients and observed a small but significant decrease in prostate cancer risk in men with high total testosterone levels. These findings were supported by two subsequent prospective studies of 65 and 194 men that demonstrated a protective effect of higher total testosterone levels against prostate cancer.[42,43] A prospective cohort study of 227 patients with median follow-up of 7.7 years showed that increased pretreatment serum testosterone (>11 nmol/L) correlated with a decreased risk of BCR after radical prostatectomy.[44] Two studies, by Imamoto et al[45] and Yamamoto et al,[46] observed that higher pretreatment testosterone levels predicted a positive prognosis in patients with metastatic and localized prostate cancer.

PSA and Serum Testosterone

The introduction of PSA to the prostate cancer detection armamentarium substantially increased the detection rate of organ-confined tumors. Mearini et al[18] investigated whether serum testosterone levels could further distinguish prostate cancer from BPH, with testosterone emerging as an independent predictor of prostate cancer as a continuous and binary variable. The sensitivity and specificity of testosterone as a diagnostic marker varied according to threshold values (32% and 91%, respectively, at a PSA threshold of 2.4 ng/mL, and 19% and 99%, respectively, at a PSA threshold of 0.50 ng/mL). Further, Mearini et al found that prostate cancer was associated with lower testosterone levels than BPH, the increasing the predictive accuracy of PSA in distinguishing the two conditions.

PSA secretion is under androgenic control. Androgen deprivation results in a significant decrease in PSA levels and remains a mainstay of treatment for advanced prostate cancer.[47] Conversely, an increase in serum testosterone results in an increase in PSA in men with castrate-level testosterone concentrations, but only until a plateau level is reached at relatively low serum testosterone concentrations. Studies on the administration of supraphysiologic doses of testosterone in healthy volunteers have not demonstrated an increase in PSA or prostate volume for up to 9 months, supporting the central hypothesis of the prostate saturation model (discussed below) that testosterone stimulates prostate tissue, but only up to the point of androgen receptor (AR) saturation.[48] Further, studies on androgen-sensitive prostate cancer cell lines have shown that androgens affect the proliferation of prostate cancer cells in a biphasic pattern of promoting optimal cell growth at low concentrations and then inhibiting proliferation at higher concentrations.[49]

Although evidence suggests that high PSA and low serum testosterone levels are predictive of prostate cancer, attempts to associate androgen levels with serum PSA have been largely unsuccessful. Monath et al[50] found no correlation between total serum testosterone levels and PSA, even when corrected for age and weight, suggesting that the determination of total serum testosterone level does not improve the sensitivity or specificity of PSA as a tumor marker.

PSA AND TESTOSTERONE—THEORIES TO EXPLAIN THE ASSOCIATIONS

Prostate Saturation and Time-Dependence Theories

The findings of Huggins and Hodges[15] were widely accepted for decades, resulting in a marked reluctance to use exogenous testosterone to treat hypogonadal men with any history of prostate cancer, for fear that high testosterone levels would increase prostate cancer risk and growth. During the past two decades, this concept has been refuted by in vitro and clinical studies. The recent body of evidence examining the relation between androgens and prostate cancer has demonstrated several potential mechanisms by which androgens interact with prostate tissue and has refuted the simple notion that androgens serve solely to stimulate prostate tissue and cancer cell growth. One of the theories proposed to explain the association between prostate tissue growth and androgen stimulation, particularly at lower serum testosterone levels, is the prostate saturation model. An alternative model, the time-dependence model, proposes an increased risk of prostate cancer at low and high serum testosterone levels, demonstrating a U-shaped risk relation.[35]

The prostate saturation model, proposed by Morgentaler[51] posits that prostate ARs are sensitive to androgen stimulation up to their saturation point, after which no additional response to increasing levels of androgen results. Clinical evidence in support of the prostate saturation theory comes in the form of small increases in PSA levels in the setting of low serum testosterone levels, which subsequently plateau. Studies for an established clinical threshold of these receptors have exhibited varied results, so a precise AR saturation point in vivo remains to be established and might in fact vary among individuals, particularly in the setting of prostate cancer. However, evidence supports that an overall low serum testosterone level, likely below levels that typically define

hypogonadism, is required to reach AR saturation.[52] In an investigation of 31 young men who received weekly intramuscular testosterone injections that raised testosterone to supraphysiologic levels, none of the 31 healthy volunteers had significant changes in prostate volume or in semen or serum PSA levels.[48] Two clinical studies separated men into groups with baseline serum testosterone levels lower than vs higher than 250 ng/dL and observed a significant PSA increase in men in with levels lower than 250 ng/dL, with no significant increase in PSA in men with baseline testosterone level higher than 250 ng/dL.[53,54] Moreover, a randomized, double-blinded, placebo-controlled trial showed that testosterone therapy failed to cause a significant increase in prostate tissue androgen levels and cellular functions.[55] A 2013 study by Rastrelli et al[56] supported a potential prostate AR saturation point of approximately 8 nmol/L (~238 ng/dL). Further controlled studies examining the merits of the saturation model at the tissue and systemic levels would significantly affect the approach to hypogonadal men with prostate cancer, because such studies could more definitively assess the risks of offering testosterone therapy to men with a history of prostate cancer by merging molecular data on AR saturation in the prostate with serum hormone data. In vitro support for the prostate saturation model comes from the observation that androgen-sensitive prostate cancer cell lines demonstrate cell growth at low concentrations, a brief period of growth stabilization, and then growth inhibition at ever increasing androgen levels.[49]

The time-dependency theory, proposed by Salonia et al,[35] was put forth as an alternative hypothesis to the association between androgens and prostate cancer. This theory is based in the observation that the lowest and highest levels of total serum testosterone were significantly associated with high-risk prostate cancer, thus exhibiting non-linear U-shaped behavior. Salonia et al suggested that total testosterone levels could stabilize with time in patients with prostate cancer, depending on the fluctuation of the levels of circulating sex steroids during an individual's lifespan. This hypothesis is not currently supported by other findings.

TESTOSTERONE THERAPY IN MEN WITH HISTORY OF PROSTATE CANCER

Radical Prostatectomy

Testosterone therapy is withheld from many patients with a history of treated prostate cancer for fear that exogenous testosterone will stimulate latent prostate cancer growth. However, several recent studies support the safe use of testosterone therapy in men with a history of prostate cancer treated using radical prostatectomy.

A retrospective review of seven hypogonadal men treated with testosterone after curative radical prostatectomy found no evidence of local recurrence or distant spread of prostate cancer in any of the patients after a follow-up of 1 to 12 years.[57] Similarly, a series of 10 men treated with radical prostatectomy and subsequent topical, transdermal, or intramuscular testosterone supplementation found that no patient had detectable (>0.01 ng/mL) PSA at a median follow-up of 19 months (Table 3).[58] Mean total serum testosterone levels increased from 197 to 591 ng/dL ($P = .0002$), and patients showed statistically significant improvements in quality-of-life scores evaluated using the Hormone Domain of the EPIC Health Related Quality of Life questionnaire ($P = .0001$). Khera et al[59] performed a retrospective 7-year chart review of records of hypogonadal men after radical prostatectomy that displayed undetectable PSA values and negative surgical margins on pathologic specimens after treatment with testosterone therapy. After mean treatment period of 36 months and 13-month follow-up, testosterone levels increased from 255 to 459 ng/dL, and no patients showed an increase in PSA. More recently, 103 hypogonadal men treated with transdermal testosterone were compared with 49 non-hypogonadal men with low-, intermediate-, and high-risk prostate cancer; all men were treated with prostatectomy. After a median follow-up of 27.5 months, testosterone levels significantly increased in the treatment group.[60] A statistically, albeit not clinically, significant increase in PSA was observed in the high-risk and non–high-risk subgroups. PSA velocity was calculated to better understand whether the observed PSA increases in men on testosterone were indicative of prostate cancer recurrence. Despite the small PSA increases in men on testosterone, PSA velocities were not supportive of prostate cancer growth or recurrence in these men. Notably, in the high-risk subgroup of men on testosterone, four patients were observed to have prostate cancer recurrence, whereas eight men in the high-risk reference subgroup developed recurrence, with no recurrence observed in the low- or intermediate-risk subgroups.[60] Although these findings do not prove that testosterone therapy is protective in patients with a history of prostate cancer, it is potentially significant. Other small studies have examined patients with high- and non–high-risk prostate cancer receiving testosterone therapy after radical prostatectomy, with similar findings on the impact on PSA and prostate cancer recurrence and progression.[61–64]

Radiation Therapy

Although several recent clinical studies have suggested that testosterone therapy in men after radical prostatectomy is safer than previously thought, similar results have been observed in small studies of men with prostate cancer treated with radiation therapy. However, high-level evidence in this subset of men with a history of prostate cancer remains lacking. Nevertheless, existing data examining testosterone therapy in patients with prostate cancer after radiotherapy have shown increases in PSA, largely in the absence of prostate cancer progression or recurrence.

An observational study followed 31 hypogonadal men for 1.5 to 9 years after radiation therapy and found a significant increase in testosterone levels from 188 to 498 ng/dL, with a transient increase in PSA in only one patient, and no evidence of prostate

Table 3. Studies on testosterone therapy in men with history of prostate cancer

References	Patients, n	Study type	Treatment	Pretreatment characteristics	CaP recurrence
Agarwal and Oefelein[58]	10	Prospective	Radical prostatectomy	PSA < 0.001 ng/mL	No PSA recurrence
Khera et al[59]	57	Retrospective	Radical prostatectomy	PSA < 0.001 ng/mL; negative surgical margins, negative lymph node involvement, T2 disease or less	No PSA recurrence
Pastuszak et al[60]	103	Retrospective	Radical prostatectomy	Median PSA = 0.004 ng/ml	BCR in high-risk patients: 4 in treatment group (15%) and 8 in reference group (53%)
Sathyamoorthy et al[61]			Radical prostatectomy		
Matsushita et al[62]			Radical prostatectomy		
Davila et al[63]			Radical prostatectomy		
Nabulsi et al[64]			Radical prostatectomy		
Sarosdy et al[65]	31	Retrospective	Brachytherapy (20), external-beam radiotherapy (11)	Median PSA = 5.3 ng/mL, most common Gleason score = 6 (61.3%), more frequent clinical stage = T1c (64.5%)	Transient PSA increase in 1 patient, no CaP recurrence
Morales et al[66]	5	Prospective	External-beam radiotherapy	Mean T = 1.5 ng/mL	Transient PSA increase < 1.5 ng/mL, no CaP recurrence
Pastuszak et al[67]	13	Retrospective	Radiation therapy	Median PSA = 0.3 ng/mL	Transient PSA increase in 1 patient, no BCR or CaP recurrence
Balbontin et al[68]	20	Prospective	Brachytherapy	Mean PSA = 6.2 ng/mL	Baseline decrease in PSA from 0.7 to 0.1 ng/mL, no CaP progression or recurrence
Pastuszak et al[69]	98	Retrospective	Radiation therapy	Median PSA = 0.08 ng/mL	No PSA change in low- or intermediate-risk group; PSA increase from 0.10 to 0.36 ng/mL in high-risk patients; 6 men (6.1%) with BCR
Rhoden and Morgentaler[70]	75	Prospective	Active surveillance	20 with high-grade PIN vs 55 without	CaP in 1 patient (1.6%)
Marks et al[55]	41	Prospective	—	Mean T = 282 ng/dL	CaP incidence 4/19 (placebo group) and 2/21 (TRT group); 1 patient with PSA > 4.0 ng/mL
Morgentaler et al[71]	13	Prospective	Active surveillance	Mean PSA = 5.5 ± 6.4 ng/mL	No change in PSA (3.6 ± 2.6 ng/mL, $P = .29$), no prostate volume change, no local CaP progression or distant disease
Morales[72]	7	Prospective	Active surveillance	Baseline PSA 1.7–13.4 μg/L; CaP ≤ T2c	Variable PSA response; modest increase in 1 patient, rapid increase with positive biopsy in 1 patient
Kacker et al[73]	28	Retrospective	Active surveillance	Baseline PSA = 3.29 ± 2.50 ng/mL	No significant PSA increase; biopsy progression similar for T treatment and control groups (32.1% vs 44.7%)
Ferreira et al[74]	5	Prospective	Surgical castration	Stable baseline PSA < 10 ng/mL	PSA increase to 12 ng/mL in 1 patient (20%) after 14 mo

BCR = biochemical recurrence; CaP = prostate cancer; PIN = prostatic intraepithelial neoplasia; PSA = prostate-specific antigen; T = testosterone; TRT = testosterone replacement therapy.

cancer progression.[65] Furthermore, 86.1% of patients who received any testosterone therapy continued receiving treatment for 4.5 to 8.5 years. A prospective study following five men with prostate cancer treated using external-beam radiotherapy and presenting with testosterone deficiency showed that each patient reported a marked symptomatic response to testosterone therapy.[66] These included decreased hot flushes, decreased fatigue and improved libido, and improved erectile function. Only one man had a transient increase in PSA during the median 2.5 years of study, but none of the men had cancer recurrence. A retrospective review of 13 hypogonadal patients with a history of prostate cancer treated with testosterone therapy after radiation treatment observed only one patient with a transient PSA increase during a follow-up period of up to 67.3 months, and no men were found to have BCR or cancer progression.[67] Pastuszak et al[67] also assessed change in hypogonadal symptoms after treatment by direct patient questioning and reported subjective improvement in energy, libido, and erections by 85%, 85%, and 54% of these men, respectively. A prospective study examining 20 hypogonadal men with prostate cancer treated using brachytherapy and subsequently treated with long-acting testosterone undecanoate injections and followed for a median longer than 2.5 years primarily showed an improvement in erectile function in the absence of advanced or metastatic disease.[68] Interestingly, PSA levels in this cohort decreased from a baseline of 0.7 ng/mL before testosterone therapy to 0.1 ng/mL at last follow-up ($P < .001$). In a retrospective multi-institutional review of 98 hypogonadal men with a history of low-, medium-, and high-risk prostate cancer treated with radiation therapy and testosterone, serum testosterone levels increased from a median of 209 to 420 ng/dL during follow-up ($P < .001$).[69] No increase in PSA was noted in men with low- or medium-risk disease, but a small, statistically significant, increase in PSA was observed in the high-risk subgroup. This observed increase is consistent with prior studies of hypogonadal men treated with testosterone showing small increases in PSA levels in the treatment and placebo groups.[55,70]

Overall, testosterone therapy in men with prostate cancer treated using radiation appears to result in small increases in PSA levels and low rates of BCR in line with or below published rates. Although these results are reassuring, the limited amount of long-term data available and the absence of prospective controlled trials make it difficult to draw definitive conclusions regarding the benefits and safety of testosterone therapy in these patients. Patient selection for treatment should consider men whose quality-of-life impairment puts them at further risk for sequelae of untreated hypogonadism, and these men should be carefully monitored during treatment.

Men on Active Surveillance

Active surveillance is used in patients at low risk for prostate cancer progression for which the benefits of foregoing definitive treatment outweigh the risks. Only three small series to date have examined the effects of testosterone therapy in men with untreated prostate cancer.[71,72] Morgentaler et al[71] followed 13 symptomatic, testosterone-deficient men on active surveillance for prostate cancer and found no changes in PSA level or prostate volume. Furthermore, no local prostate cancer progression or distant disease was observed in the short to medium term (median treatment = 2.5 years). In a second study, Morales[72] studied seven patients with prostate cancer and low serum testosterone and reported variable responses to testosterone therapy. Owing to the unpredictable and limited nature of these results, Morales proposed establishing an international registry as a way to establish basic parameters for consideration of testosterone therapy in men with prostate cancer on active surveillance. In the largest series to date, Kacker et al[73] identified 28 testosterone-deficient men on testosterone therapy for at least 6 months while on active surveillance and compared them with 96 untreated testosterone-deficient men on active surveillance. No significant increases in serum PSA were observed in men on testosterone therapy, and the overall rate of prostate cancer progression at biopsy examination was no greater in the treatment group than in the comparison group (32.1% vs 44.7%, respectively).

Importantly, all these studies examined small cohorts and were not randomized or controlled. Although further studies are needed to draw reliable conclusions on testosterone therapy for men on active surveillance, the growing body of evidence in hypogonadal, testosterone-treated men with treated and untreated prostate cancer that supports the safety of testosterone therapy is reassuring.

Men at Risk for Prostate Cancer and With Locally Advanced Prostate Cancer

Studies also have examined the impact of testosterone therapy in men at risk for prostate cancer. Rhoden and Morgentaler[70] studied 75 hypogonadal men with and without high-grade prostatic intraepithelial neoplasia (PIN^+ and PIN^-, respectively). Fifty five men in the PIN^- group and 20 men in the PIN^+ group completed 12 months of testosterone therapy, after which only one man in the PIN^+ group was found to have cancer, with a cancer rate of only 1.3% for the entire study population after 1 year of testosterone therapy.

Even in men with a history of advanced prostate cancer with hypogonadal symptoms, testosterone therapy might be feasible without significantly increasing the risk of cancer progression. In a small 2006 study by Ferreira et al[74] of five men with advanced prostate cancer who had undergone surgical castration, testosterone therapy resulted in symptomatic improvement, without evidence of local recurrence or distant metastasis after 18 months of follow up.

RELATION BETWEEN TESTOSTERONE AND PROSTATE CANCER

In vitro studies on androgen-sensitive prostate cancer cell lines support a biphasic effect of androgens on prostate cancer cells. At

extremely low physiologic androgen levels, prostate cancer cells will survive, but with their growth halted.[49] However, at low physiologic testosterone levels (<2.4 ng/mL), prostate cancer cell proliferation is androgen dependent. For example, androgen levels of 0.23 ng/mL and 1 to 2 ng/mL for cell lines LnCaP and MDA PCa 2b, respectively, promote optimal cell growth.[49] These growth-enhancing androgen levels are within a man's physiologic low range of serum testosterone. These data might explain prostate cancer recurrence in men treated with androgen-deprivation therapy. Immediately after treatment, the extremely low androgen levels stifle prostate cancer growth, but after 12 to 33 months, levels increase from castrate to low.[75] Prevention of recurrence in these patients involves maintaining extremely low levels of serum androgen, despite side effects that include impotence, hot flashes, fatigue, and decreased functional activity.[76]

However, all men eventually develop castration-resistant prostate cancer (CRPC) from prolonged androgen-deprivation therapy and adapt to long-term exposure to androgen-deprivation therapies, presumably owing to sustained AR signaling by different mechanisms that include increased expression of wild-type and ligand-independent AR variants, AR gene amplification, and AR mutations.[77–84] Despite the many methods CRPC cells use to exhibit resistance, AR-positive human CRPC cell lines can be inhibited by supraphysiologic androgen levels.[85,86] Supraphysiologic testosterone levels allow the stabilization of ligand-bound AR in the nucleus, which inhibits relicensing, or the multiple use of a single origin of DNA replication, and thus facilitates apoptosis.[87,88] Supraphysiologic testosterone also can induce lethal double-stranded DNA breaks in CRPC cells, which can be potentiated by single-agent oral etoposide through its ability to inhibit topoisomerase IIβ and DNA repair.[89] Based on these preclinical findings, Schweizer et al[90] recently examined the effects of treatment with "bipolar androgen therapy" in 14 men with a history of prostate cancer to assess the effect of supraphysiologic serum testosterone levels and near-castrate testosterone levels on CRPC cells. Men were rapidly cycled between low and high testosterone levels over three 28-day cycles during which they injected testosterone followed by return to near-castrate testosterone levels. Subjects received simultaneous androgen-deprivation therapy and oral etoposide. The investigators believed that CRPC cells highly expressing AR would be vulnerable to apoptosis when exposed to supraphysiologic testosterone levels, whereas CRPC cells that survived owing to low AR levels or through adaptive downregulation of AR would die at sudden re-exposure to low testosterone over the course of the 28-day treatment cycles.[90] Remarkably, 12 of 13 subjects had a decrease in PSA after bipolar androgen therapy and were allowed to return to castrate-range testosterone levels after completion of study. Within 1 month of PSA progression, 10 patients were placed on second-line AR-directed therapy and all 10 were resensitized and showed PSA decreases (range = 30.8–99.5%).[90] These results demonstrate prostate cancer cell adaptation to low testosterone concentrations and their vulnerability to death at high testosterone concentrations, suggesting that prostate cancer response might be affected by the quantity and timing of circulating androgens.

Song and Khera[49] also demonstrated a dose-dependent inhibition of prostate cancer cell proliferation in vitro as physiologic androgen levels increased from the normal range, starting at a testosterone level of 4 ng/mL. Hatzoglou et al[91] also found that testosterone induced a dose-dependent inhibition of cell growth, increased apoptosis, and decreased prostate cell migration, adhesion, and invasiveness in human LNCaP cells. Taken together, these data offer cellular-level evidence for the clinical observation that exogenous testosterone in men with prostate cancer have low rates of cancer progression or recurrence.

Limitations to the study of the relation between testosterone and prostate cancer include issues of intraindividual variation in testosterone measurements (not considering diurnal variations in testosterone levels) and issues of reproducibility of testosterone measurements among patients of different ages, health, and biological patterns, among other factors. Further, different testosterone assay methods could further confound current and future findings.

SUMMARY AND CONCLUSIONS

A significant number of recent studies with methodologic differences and small samples have made it challenging to provide clear answers to questions regarding the safety and efficacy of testosterone therapy in patients with a history of prostate cancer. However, the preponderance of modern evidence supports the conclusion that treatment of men with a history of prostate cancer with testosterone therapy is safe, with low risk of cancer progression or recurrence, particularly in men with non–high-risk disease. Few data in men with high-risk disease are available, although current data show comparable cancer risk in men with high-risk cancer treated with testosterone as in those who are untreated and suggest a potential protective response in some studies.

We recommend consideration of testosterone therapy in all hypogonadal men with a history of prostate cancer and an individualized discussion with interested patients regarding the risks and benefits of therapy. In men for whom the benefits of testosterone therapy clearly outweigh the risks, specifically those with significant health and vitality impairment in the absence of treatment who have a history of non–high-risk prostate cancer, we recommend treatment. Consideration of testosterone therapy in men with a history of high-risk disease remains controversial in the absence of larger studies examining risk specifically in this group of men, although with appropriate monitoring, therapy also should be considered in these men. Nonetheless, in the absence of definitive data showing that testosterone therapy does not increase risk of prostate cancer progression or recurrence in these men, regardless of prostate cancer severity, men undergoing

testosterone therapy should continue to be closely and regularly monitored by their clinicians.

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