



# Testosterone Replacement Therapy and Prostate Cancer Incidence

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While early studies demonstrated a positive association between testosterone and prostate cancer, evidence on the nature of the relationship has evolved with time and newer data. Studies examining links between baseline testosterone levels as well as testosterone therapy and incident prostate cancer, reveal a more complex relationship. Moreover, investigators have reported their initial experiences with supplementing testosterone in men with a history of both treated and untreated prostate cancer.

**Key Words:** Androgens; Hypogonadism; Prostatic neoplasms; Testosterone

## INTRODUCTION

The recognition by Huggins and Hodges [1] that castration leads to prostate cancer regression both earned the Nobel Prize in Medicine and drew a link between prostate cancer and testosterone levels. However, recent re-analyses of the original data has brought into question the simple linear relationship between testosterone levels and prostate carcinogenesis [2]. Despite the USA Food and Drug Administration keeping warnings regarding prostate cancer in place on testosterone products, the data surrounding the relationship between prostate cancer and testosterone remains mixed.

Prostate cancer remains the most commonly diagnosed male cancer in the USA, with an estimated 220,000 cases in 2015 leading to 27,000 deaths [3]. While screening practices have been questioned, given the prevalence of the disease, at the same time, investigators have been

searching for risk factors that would inform interventions to lessen the disease burden [4]. Moreover, given the high long-term survival rates with prostate cancer, investigators have also attempted to determine the safety of therapies in men with prostate cancer that has been identified or is under treatment.

As the population ages, the number of hypogonadal men is increasing. Treatment of hypogonadism with testosterone therapy (TT) has been shown to improve muscle mass and strength, sexual function and desire, mood, and bone mineral density [5-9]. However, concerns remain about possible negative implications of TT for cancer risk. Studies have explored how a male's baseline testosterone levels may relate to his risk of prostate cancer. In addition, investigators have studied whether testosterone supplementation is associated with risk of prostate cancer incidence, progression, or recurrence.

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## TESTOSTERONE LEVELS AND PROSTATE CANCER RISK

In 2008, the Endogenous Hormones and Prostate Cancer Collaborative Group [10] published an analysis of the 18 prospective studies from populations around the world examining the association between males' baseline testosterone levels and prostate cancer incidence. In all, data from 3,886 men with incident prostate cancer and 6,438 control subjects were analyzed. Among the control subjects, the mean age at recruitment ranged from 46 to 72 years, and the date of study recruitment ranged from 1961 through 2001. Time to prostate cancer diagnosis varied between individual studies, with relatively short periods in some (e.g., <3 years) and longer ones in others (e.g., >7 years). The authors did not identify a relationship between any sex hormone level (e.g., total testosterone, free testosterone, estradiol, dihydrotestosterone) and prostate cancer. For example, the relative risk for testosterone was 0.94 (95% confidence interval [CI], 0.82 to 1.07). Importantly, no heterogeneity was identified between any studies, suggesting this was a uniform finding regardless of the time period or geography of the included study.

The group next performed several subgroup analyses based on grade or stage of tumor and again found no association between testosterone level and prostate cancer risk. Moreover, adjustment for potential confounders including body mass index, marital status, educational attainment, smoking, and alcohol consumption did not alter the conclusions. Additional subgroup analyses based on year of diagnosis (to attempt to account for prostate-specific antigen [PSA] screening practices), age at prostate cancer diagnosis, and time between blood collection and prostate cancer diagnosis did not show any significantly different results.

However, some groups have reported an inverse relationship between baseline testosterone levels and prostate cancer risk. A prospective study of 206 patients found the incidence of prostate cancer to be higher in men with low compared to high testosterone levels (38.9% vs. 29.5%) [11]. Another study of 345 hypogonadal men also found that men with the lowest T levels had the highest risk of prostate cancer [12].

In contrast, other groups have identified a positive rela-

tionship between testosterone levels and prostate cancer risk. The placebo arm of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial found that men with the highest baseline testosterone level had a higher risk of prostate cancer [13]. In addition, in a study of 420 men with a PSA <10 ng/mL who underwent a prostate biopsy, a higher baseline testosterone level was associated with a higher risk of prostate cancer [14].

In addition to prostate cancer incidence, groups have also explored tumor characteristics in relation to baseline testosterone levels. Studies in the United States, Europe, and Asia have all identified an association between high grade prostate cancer and low testosterone levels. In one of the larger studies, Lane et al [15] reported that among 455 men who underwent radical prostatectomy, those with a testosterone level <250 ng/dL had 2.4 times higher odds for a Gleason pattern  $\geq 4$  on pathology compared to men with normal testosterone. In contrast, Porcaro et al [16] reported 5 fold higher odds of high-grade disease after radical prostatectomy in men in the highest testosterone group. Still other groups have found no relationship between testosterone level and cancer grade [17].

Tumor stage has also been studied in relation to testosterone in radical prostatectomy patients. Low testosterone levels have been associated with higher rates of seminal vesical invasion or non-organ-confined disease. For example, in a series of 107 patients, men with low testosterone had a higher prevalence of >T2 disease (43% vs. 25%) [18]. Still other groups have found no relationship between testosterone level and cancer stage [19,20].

The risk of disease recurrence after radical prostatectomy has also been studied. The definition of biochemical recurrence can vary between studies, which may limit comparisons. Nevertheless, in a prospective study of 60 men after radical prostatectomy, Kim et al [21] found a higher risk of biochemical recurrence (PSA  $\geq 0.2$  ng/mL) in men with lower testosterone. In contrast, Salonia et al [22] found that a higher testosterone level increased the risk of biochemical failure (PSA  $\geq 0.1$  ng/mL) in an Italian cohort of radical prostatectomy patients. Further demonstrating the heterogeneity in the literature, other groups have reported no relationship between testosterone levels and PSA recurrence [15,23].

## TESTOSTERONE THERAPY AND INCIDENT PROSTATE CANCER

Several trials on men on TT found no higher risk of prostate cancer than the general population [24,25]. Among 163 hypogonadal men followed for up to 42 months, 3 received a prostate biopsy due to PSA elevation which produced a prostate cancer diagnosis [24]. A meta-analysis of 19 placebo-controlled trials also failed to demonstrate a higher risk of prostate cancer in men on TT [26]. In that study, there were a total of 651 men on testosterone supplementation and 433 on placebo. Follow-up ranged from 3 months to 3 years. The mean age of testosterone patients was 63 years, with an average baseline testosterone level of 320 ng/dL, which rose to 536 ng/dL while on treatment. Among the men on testosterone, the rate of prostate cancer was 9.2 cases per 1,000 person years compared to 8.3 per 1,000 person years for men not on supplementation, which was not significantly different (odds ratio, 1.09; 95% CI, 0.48 to 2.49). While reassuring, poor follow-up makes definitive conclusions difficult, as the trials included in the meta-analysis may have precluded adequate detection of risk if exposure to exogenous testosterone supplementation alters the prostate's chemical milieu to favor cancer development, which may take several years to manifest. A recent retrospective study from the UK with up to 20 years of follow-up suggested no increased risk of prostate cancer in men on testosterone treatment [27]. In this study, the authors identified 1,365 men on testosterone supplementation with a mean age at evaluation of 54.2 years (range, 24 to 88 years) who were followed for up to 20 years (total follow-up for 2,966 person-years). The authors reported 14 cases of incident prostate cancer (1 case per 212 person-years of follow-up). They also noted that all diagnosed tumors were clinically localized. Recently, a study by our group examined 247 hypogonadal men on testosterone and compared the group to 211 men not placed on supplementation [28]. Of the men on testosterone, 70 were on injectable and 177 men were on transdermal therapy. Cancer outcomes were determined by linkage to the Texas Cancer Registry to remove the requirement for continuous patient follow-up. In total, 28 men developed cancer—17 of the men (8.1%) not on TT and 11 (4.4%) of the men on TT. Thus, no significant differ-

ence in prostate cancer risk based on TT status was found (hazard ratio, 1.2; 95% CI, 0.54 to 2.5). Importantly, prostate biopsy rates were similar between the groups, with 64 of 247 (25.9%) men on TT and 67 of 211 (31.8%) not on TT receiving a prostate biopsy during follow-up ( $p=0.17$ ).

Another group of men that may be at higher risk for prostate carcinogenesis are men with prostatic intraepithelial neoplasia (PIN) on prior prostate biopsy. Rhoden and Morgentaler [29] reported outcomes in 20 men with PIN on testosterone supplementation. After one year of therapy, they reported no change in PSA. However, for an abnormal digital rectal examination, one man underwent a prostate biopsy, which revealed cancer.

## TESTOSTERONE THERAPY IN MEN WITH PROSTATE CANCER

Recently, several groups have reported the use of testosterone replacement therapy in men after a diagnosis of prostate cancer. Investigators have reported favorable outcomes with testosterone supplementation after radical prostatectomy. In the largest study to date, Pastuszak et al [30] report the outcome of 103 men treated with testosterone after radical prostatectomy including 26 patients with high risk disease. With an average follow-up of 27.5 months, the authors noted 4 recurrences, which was similar to their comparison (non-supplementation) group. Sarosdy [31] reported the treatment of 31 men with testosterone supplementation after brachytherapy. After a median follow-up of 5 years, no prostate cancer recurrences were reported. Favorable outcomes have also been reported after external beam radiotherapy [32-34].

In contrast, Leibowitz et al [35] reported data on 96 men after prostate cancer treatment (e.g., radical prostatectomy, brachytherapy, external beam radiotherapy, and androgen deprivation) who were on testosterone supplementation. They reported 41 men who had biochemical progression.

Limited data also exist surrounding testosterone supplementation in males with untreated prostate cancer on active surveillance. Morgentaler et al [36] reported the outcomes of a retrospective analysis of 13 men on active surveillance seen at two institutions. Twelve men had Gleason 6 disease and one man had low volume Gleason 7 disease.

No change in PSA or prostate volume was reported. Surveillance biopsies raised concerns about progression in 2 men. One remained under surveillance with reassuring findings on subsequent biopsy. The other underwent radical prostatectomy.

## CONCLUSIONS

The relationship between testosterone and prostate cancer remains complex. While most studies suggest no relationship between testosterone supplementation and prostate cancer incidence and progression, findings in the literature are heterogeneous. Theories have been proposed to attempt to explain this discrepancy. The 'saturation theory' posits that the prostate is most sensitive to androgens at lower testosterone levels when androgen receptors are receptive [37]. At higher levels, when all androgen receptors are bound, higher testosterone levels will not further stimulate prostate cells. Such a theory is supported by the observation that men with a testosterone level  $>250$  ng/dL will not see a change in PSA when placed on testosterone supplementation [8]. In contrast, men with a baseline testosterone level  $<250$  ng/dL will experience a rise in PSA with testosterone treatment.

Another hypothesis to explain the relationship between testosterone and prostate cancer is the time dependence theory. Based on the observations that 1) men with the lowest and highest testosterone levels develop high risk disease and 2) men with prostate cancer appear to have a stable testosterone level over time (as opposed to an age-related decline), Salonia et al [38,39] posited that duration of prostate exposure to androgen levels is the primary driver for risk.

As large, randomized placebo-controlled trials are lacking, the uncertainty surrounding the safety of TT and prostate cancer will remain. Nevertheless, most published studies are reassuring, with most of the discrepancy likely due to methodologic and patient heterogeneity. Current professional society guidelines for testosterone supplementation provide appropriate recommendations for proper patient treatment and monitoring [40].

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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