Prostate cancer and testosterone replacement therapy: what is the risk?

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The use of testosterone replacement therapy is increasing in men with hypogonadal symptoms. In this article the authors discuss the evidence that supports the careful use of testosterone replacement in men with successfully treated prostate cancer.

The last decade has seen a rise in testosterone replacement therapy (TRT) internationally. Controversy continues, however, on the impact of TRT and its effect on the prostate. While the effects of TRT on benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) are as yet unsettled, the role of TRT in prostate cancer appears to be clearer.

The effects of testosterone and castration on the prostate and prostate cancer have a long history, with the sentinel publication of Charles Huggins and Clarence V. Hodges in 1941 as the first clear demonstration of the effects of withdrawing testosterone by castration or oestrogen on the progression of prostate cancer. In that publication, the authors also showed that, in a single patient, withdrawal of testosterone by castration and subsequent replacement of testosterone had the deleterious effect of causing the prostate cancer to first involute then regrow.

This publication and subsequent reviews and presentations led to the conventional wisdom that testosterone could cause prostate cancer, and that TRT could either induce de novo prostate cancer or unearth an occult prostate malignancy. Indeed, an international survey published in 2007 showed that as many as 70% of healthcare providers were concerned about the association of TRT and prostate cancer.

WISDOM CHALLENGED

This conventional wisdom is gradually being challenged by newer studies. The Endogenous Hormones and Prostate Cancer Collaborative Group reviewed 18 prospective studies and reported that there was no signal that endogenous testosterone levels correlated to prostate cancer, and that TRT did not increase the risk of prostate cancer.

Figure 1. Conventional wisdom was that prostate cancer growth increased in a linear way in response to serum testosterone (line A). In the saturation model, prostate growth is sensitive to testosterone at near-castration levels, but reaches a plateau as testosterone concentrations rise (line B)
Similarly, many studies have shown that TRT does little to change PSA when hypogonadal men are treated to normalise testosterone levels. Morgentaler has proposed the ‘saturation model’ theory for testosterone and the prostate, stating that while prostate cancer is exquisitely testosterone-sensitive at very low testosterone levels, once the androgen receptors are fully occupied, further testosterone levels do little to change prostate or prostate cancer dynamics. This concept is supported by PSA studies in men taking TRT showing only modest PSA rises, usually in those men with the lowest initial testosterone.

It has been suggested that high-grade prostate cancer is associated with lower levels of endogenous testosterone. In a recent study of 681 men undergoing a 12-core prostate biopsy, low testosterone level was found to be an independent risk factor for high-grade prostate cancer. Similarly, Garcia-Cruz et al found that low pre-treatment testosterone levels were significantly related to poor prognostic factors. While the aetiology of low testosterone in high-grade prostate cancer patients remains uncertain, the body of evidence for this relationship continues to grow, leading some to suggest that monitoring testosterone levels prior to biopsy may provide prognostic information.

TRT AND PROSTATE CANCER HISTORY
Currently, there is rising interest in the treatment of men with a history of prostate cancer, both treated and under active surveillance, with TRT. The first studies documented the safety of TRT in men who had undergone radical prostatectomy with favourable pathology and undetectable PSA. More than 250 men treated with TRT that were reported in the literature show no evidence of recurrence or progression of prostate cancer.

More recent studies have reviewed men treated with external beam radiation therapy or brachytherapy and TRT. These studies in highly selected patients have also shown safety and no signal to recurrence, progression or significant PSA rise. In another multicentre study of a small number of highly selected patients with active surveillance, hypogonadism and TRT, the safety of TRT was again suggested. These studies are of small numbers and limited follow-up, and need confirmation by larger numbers and longer observation. The message, however, is clear: TRT appears to help men with hypogonadism, and is safe if vigilant follow-up is maintained.

The SEER study by Baillargeon et al and a very recent meta-analysis by Boyle et al add further data to the safety discussion of TRT in men with or at risk for prostate cancer. The SEER study has shown there is no clear signal in this large population that TRT had any negative effect on the frequency of high-grade prostate cancer. While more data are needed, healthcare providers can begin to consider treating their hypogonadal prostate cancer patients with TRT if they are symptomatic, have documented low testosterone levels and are properly counselled and informed.

REFERENCES

KEY POINTS
- Testosterone is important in the development of the prostate
- No data support testosterone replacement as a cause of prostate cancer
- Men with successfully treated prostate cancer can be safely treated with testosterone replacement
- Men on testosterone replacement should have their prostate monitored with PSA and DRE