

# Testosterone and Prostate Cancer

Does testosterone cause prostate CA?

Does testosterone protect against prostate CA?

Can testosterone be used in men with a history of prostate CA?

Can testosterone be used in men with active prostate CA?

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# Prostate Cancer Risk in Testosterone-Treated Men

\*Data from all published prospective studies on circulating levels of total and free testosterone do not support the hypothesis that high levels of circulating androgens are associated with an increased risk of prostate cancer.

\*The long standing “androgen hypothesis” of increasing risk with increasing androgen levels can be rejected.

\*Instead, high levels within the reference range of androgens, estrogens and adrenal androgens decrease aggressive prostate cancer risk. (Note: high level of estrogen!)

\*High-grade prostate cancer has been associated with a low plasma level of testosterone.

Raynaud JP. Prostate cancer risk in testosterone-treated men. J Steroid Biochem Mol Biol. 2006 Dec; 103(1-5): 261-266

# Testosterone Replacement Therapy and Prostate Cancer

\*If Testosterone truly caused significant PCA growth, however, there should be observable evidence for it, such as increased PCA rates in men receiving TRT or among men with high endogenous T.

\*Yet, multiple reviews have failed to identify any such supporting evidence.

Morgantaler, A. Testosterone replacement therapy and prostate cancer. *Unroll Clin N Am.* 2007; 34: 555-563

\*The issue at hand, however, is whether T administration causes increased PCA growth in a previously untreated man.

\*It is simply astounding to discover that the origin of this long-standing near - universal belief was based on a single patient.

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## Saturation Model

\*There is strong evidence that a saturation level exists for prostate tissue with regard to T, with T levels greater than this saturation point not associated with additional growth. (due to maximum saturation of receptor sites).

\*The saturation for T in prostate tissue likely occurs at relatively low serum concentrations (<200 pg/ml). because TRT in hypogonadal men causes only a minor increase in PSA and prostate volume.

\*These results suggest that maximal or near-maximal prostate growth occurs at low circulating levels of T.

## Saturation Model

\*If TRT truly increased PCA rates in the short term, there should be an observable increased rate of PCA in men receiving TRT, an effect that has not been demonstrated.

\*There is no dispute that the presence of androgen is important for PCA growth or that severe reduction of androgens cause PCA regression. The question at hand is whether higher concentrations of T cause increasingly greater PCA growth, especially beyond the near-castrate range.

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\*Not one study has shown a direct correlation between total T levels and PCA.

\*The largest study of this type actually noted reduced PCA risk in men with higher T levels.

\*These prospective longitudinal studies proved two uniform and convincing points:

\*1) that men who develop PCA do not have higher baseline T levels and

\*2) that men with higher T levels are at no greater risk for developing OPCA than men with lower T concentrations.

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\*Other work has shown that low T is associated with high-grade Gleason scores, advanced stage at presentation, and worse survival.

\*Clinical PCA almost never occurs when men are in their 20's, when T levels are at their lifetime peak. Conversely, it becomes highly prevalent when men are older and T levels have declined.

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\*One should expect to see a substantial number of PCA cases in extremely young men, but we don't.

\*Because castration causes PCA to regress, how is it possible that T administration would fail to cause PCA to grow?

\*This suggests a model of saturation in which existing PCA tumors have access to all the androgens they can use at fairly low serum concentrations, with higher amounts representing a surfeit without impact on further growth.

\*These results indicate that changes in serum androgen levels in hypogonadal men are not reflected with the prostate itself.

\*Yet, all available evidence fails to demonstrate any significant relationship between T and PCA beyond the castrate or near-castrate range.

\*There is a powerful effect of T concentration on prostate cancer growth. However, this effect clearly plateaus at some low concentration of T.

\*Our old analogy of T being like food for a hungry tumor is false and misleading... "T is like water for a thirsty tumor." Once the thirst has been quenched by adequate (and relatively low) T concentrations, additional amounts were as nothing more than an excess.

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\*There are now several publications reporting no ill effects from administration of TRT in hypogonadal men previously treated for PCA.

\*The theory that higher T leads to enhanced PCA growth has been widely held for more than two thirds of a century.

\*Arguments offered over the years to support this theory lack substance, scientific rigor, or relevance.

\*Evidence for a lack of a growth-enhancing effect of T beyond the near-castrate level includes the following:

\*1) longitudinal studies show no correlation of PCA risk with serum T levels.

\*2) no precipitous increase in PCA is seen in high-risk men receiving TRT

\*3) PCA risk does not seem to be reduced in men with low T.

\*4) Clinical disease is almost nonexistent when T levels are at their lifetime peak.

\*5) PCA only becomes highly prevalent when T levels have declined.

\*Studies have failed to show any correlation between higher T levels and tumor grade, stage of presentation, or survival.

\*Available evidence now supports a different model in which PCA growth is stimulated at near-castrate serum T concentrations but then soon reaches a saturation point greater than which higher T concentrations provide no increased stimulus to growth= maximum saturation.

\*Withholding of TRT in men because of the fear of PCA risk or progression is no longer tenable in an age of evidence-based medicine, because neither evidence nor theory supports this position.

\*Physicians should be freed of antiquated and unscientific restrictions that inhibit optimal treatment of their patients.

Morgantaler A. Testosterone replacement therapy and prostate cancer. Unroll Clin N Am. 2007; 34: 555-563

\*The long-standing belief that higher T leads to greater PCA growth in noncastrated men is contrary to all accumulated evidence and should be discarded.

\*The relation of T and PCA seems most consistent with a saturation model in which there is a powerful impact of serum T on PCA growth at castrate or near-castrate concentrations but little or no effect at higher t concentrations.

\*A wealth of evidence suggests that TRT does not increase PCA risk.

## Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

\*The prohibition against the use of testosterone therapy in men with a history of prostate cancer is based on a model that assumes the androgen sensitivity of prostate cancer extends throughout the range of testosterone concentrations.

Morgantaler A. Testosterone therapy for men with prostate cancer: Scientific and ethical considerations. J of Urology. 2009 Mar; 181: 972-978



\*The impetus for reconsidering T therapy in men with PCA stems from several factors, one of which is the increasing recognition of the health benefits of T improvements in energy, vitality, sexual desire, erectile function, body composition and bone mineral density.

\*Another impetus is failure to observe a significant increase in PCA associated with T therapy in the general population, as would be predicted by traditional androgen dependent model of PCA.

\*Finally, there has been pressure from the substantial number of PCA survivors who desire an improved quality of life resulting from testosterone administration.

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\*A key observation is that AR has a definite binding capacity for androgen. Maximal binding (saturation) has been demonstrated to occur at low androgen concentrations.

\*Once AR is saturated with androgen, higher androgen concentrations do not result in greater androgen -AR binding and therefore no greater stimulation.

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\*A meta-analysis of 19, controlled T therapy studies revealed no greater proportion of adverse prostate outcomes, such as increased PSA or PCA development in men treated with T vs. placebo.

\*At least 21 longitudinal studies have examined the relationship of serum sex hormones to PCA development, and a majority revealed no significant relationship between androgens and PCA.

\*In 2008 a global collaborative study was performed to investigate this issue with greater statistical power obtained by pooling original data from 18 individual studies.

\*The results revealed no association between any serum androgen measurement and PCA, including total and free T.

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\*Overall the evidence fails to support the long-standing assumption that higher T leads to greater PCA growth throughout the entire range of T concentrations.

\*There is a limit to the ability of androgens to stimulate prostate growth. Once maximal growth has been achieved, even log increases in androgen concentration produce no additional growth.

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\*Increasing T well into the supraphysiological range causes no increase in PSA or prostate volume.

\*There appears to be no association between high serum T and risk of clinical PCA.

\*Worrisome prognostic features have been associated with low rather than high T.  
PCA risk is associated with the severity of T deficiency.

\*The evidence indicates that PCA growth behaves in an androgen depended manner at low T concentrations and becomes androgen indifferent at higher concentrations = the saturation model.

\*It seems logical to surmise that many men with untreated, albeit undiagnosed PCA must already be receiving T therapy since 1 in 7 (15%) hypogonadal men with PSA less than 4 ng/ml has biopsy detectable PCA.

\*If increasing T in hypogonadal men causes more rapid PCA growth, one would predict a substantial rate of new PCA cases detected in T trials. However, a meta-analysis revealed that T treated men were at no greater risk for negative prostate outcomes than placebo treated men.

\*Traditional assumption of more rapid PCA growth with higher T has failed to find compelling scientific support, except for the special case of pharmacological or surgical androgen deprivation.

\*No increases in intraprostatic concentrations of T, or changes in cellular markers of proliferation, were seen after 6 months of T therapy in men despite large increases in serum T.

\*The prostate is somehow protected from large changes in serum T.

Testosterone therapy may not present undue risk even when men have prostate CA in situ.

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## Testosterone Therapy in Men with Untreated Prostate Cancer on Active Surveillance

\*T therapy in 13 hypogonadal men with untreated PCA for a mean of 12 months was not associated with an increase in PSA or substantial rate of grade progression on repeat biopsy

\*These pilot results suggest that T therapy may be cautiously considered in men with low-risk untreated PCA.

Morgentaler A. Testosterone therapy in men with untreated prostate cancer. J Urol. 2011 Apr; 185(4): 1256-60.



## Analysis of the PSA Response After Initiating Testosterone Supplementation in Patients Who Have Previously Received Management for Their Localized Prostate Cancer

\*T therapy by injection or transdermal gel is effecting in improving T level following RP and EBRT.

\*No significant differences were noted between these groups with regard to PSA levels after T.

\*This pilot study confirmed consistent efficacy and safety concerning the use of T after PCA therapy, regardless of the type of cancer treatment.

Davila H et al. Analysis of the PSA response after initiating testosterone supplementation in patients who have previously received management for their localized prostate cancer. University of South Florida, Tampa, FL.

## Testosterone Replacement Therapy May be Viable Treatment in Men with Prostate Cancer

\*USF urologists start testosterone supplementation after 1 year of successful therapy for patients who have undergone surgery for prostate CA.

Gagnon, L. Testosterone replacement therapy may be viable treatment in men with prostate cancer. Urology Times, 2009, Feb.1

## Testosterone Therapy May Benefit Prostate Cancer Treatment

\*"For many decades it had been believed that a history of prostate cancer, even if treated and cured, was an absolute contraindication to testosterone therapy, due to the belief that testosterone activated prostate cancer growth, and could potentially cause dormant cancer cells to grow rapidly."

\*This study looked at men who had been diagnosed with low to moderately aggressive prostate cancer based on the Gleason score. Their prostate cancer had not been treated previously, and during the study they were given testosterone therapy for between one and eight years. (They still had untreated PCA.)

\*Their PSA levels did not change and there was no progression of the men's prostate cancer in the short to medium term.

Stacy G. Testosterone therapy may benefit prostate cancer treatment. Health, 2011, Apr. 25

\*It has been known that testosterone therapy can have various beneficial effects, including improvement in fatigue, libido, and sexual function. It may also improve mood, blood sugar control, metabolic syndrome, muscle mass, and bone density.

\*An increasing number of newly diagnosed men with prostate cancer opting for active surveillance, and with many of them also desiring treatment for their signs and symptoms of testosterone deficiency, the results suggest a reevaluation of the long standing prohibition against offering testosterone therapy to men with prostate cancer.”

## Testosterone and Prostate Cancer: An historical Perspective on a Modern Myth

\*This historical perspective reveals that there is not now—nor has there ever been a scientific basis for the belief that T causes prostate CA to grow.

\*The original assertion that higher T cause enhanced PCA growth has persisted as a medical myth since 1941 despite all evidence to the contrary.

\*The true nature of this myth is revealed best by its historical origin—an equivocal blood test result in a single patient. Other investigators failed to note worrisome PCA progression with T administration and even reported beneficial subjective response.

\*Longitudinal studies have repeatedly and consistently rejected this hypothesis. And if T is “food for hungry tumor”, then why is the cancer rate only 1% for men receiving testosterone when 1 out of 7 men has biopsy detectable PCA?

Morgantaler A. Testosterone and prostate cancer: An historical perspective on a modern myth. *European Urology*: 2006; 50; 935-939

## Testosterone Replacement For Hypogonadism After Treatment of Early Prostate Cancer with Brachytherapy

\*PSA levels were <1 ng/ml in 31 patients (100%) after brachytherapy.

\*No patients stopped TRT because of cancer recurrence or documented cancer progression.

\*In patients with low serum testosterone levels and symptoms of hypogonadism, TRT may be used with caution and close follow-up after prostate brachytherapy.

Sarosdy MF; Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. Cancer. 2007 Feb.1; 109 (3): 536-541

\*The danger of belief trumping evidence is that it impairs our ability to behave logically and consistently, and can cause us to disregard awkward data that may ultimately provide promising avenues for research.

\*Can we continue to justify denying TRT to symptomatic men after definitive treatment for PCA when history teaches us that T administration failed to cause disease progression even in men with untreated, widely metastatic PCA?

Might it even be possible that androgen administration could prevent PCA?

After 65 years it is time to discard the myth and to entertain new ideas regarding the relationship of testosterone and PCA.

