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Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth

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Abstract

Objectives: To review the historical origins and current evidence for the belief that testosterone (T) causes prostate cancer (pCA) growth.

Methods: Review of the historical literature regarding T administration and pCA, as well as more recent studies investigating the relationship of T and pCA.

Results: In 1941 Huggins and Hodges reported that marked reductions in T by castration or estrogen treatment caused metastatic pCA to regress, and administration of exogenous T caused pCA to grow. Remarkably, this latter conclusion was based on results from only one patient. Multiple subsequent reports revealed no pCA progression with T administration, and some men even experienced subjective improvement, such as resolution of bone pain. More recent data have shown no apparent increase in pCA rates in clinical trials of T supplementation in normal men or men at increased risk for pCA, no relationship of pCA risk with serum T levels in multiple longitudinal studies, and no reduced risk of pCA in men with low T. The apparent paradox in which castration causes pCA to regress yet higher T fails to cause pCA to grow is resolved by a saturation model, in which maximal stimulation of pCA is reached at relatively low levels of T.

Conclusions: This historical perspective reveals that there is not now—nor has there ever been—a scientific basis for the belief that T causes pCA to grow. Discarding this modern myth will allow exploration of alternative hypotheses regarding the relationship of T and pCA that may be clinically and scientifically rewarding.

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*The great enemy of the truth is very often not the lie . . .
but the myth—persistent, persuasive, and unrealistic.*

—John F. Kennedy
1962 Yale Commencement speech

1. Introduction

One of the principles of evidence-based medicine is that concepts that fail to withstand scientific

scrutiny are to be discarded. Such a time has come for the belief that testosterone (T) causes enhanced growth of prostate cancer (pCA). This change in perspective is prompted not only by current evidence, but also by critical examination of the historical origins of the belief.

In 1941 Huggins and Hodges [1] established the hormonal responsiveness of pCA by reporting that marked reductions in T by castration or estrogen treatment caused metastatic pCA to regress, and also that administration of exogenous T caused pCA to grow. Many of us learned from our professors to describe the relationship of T to pCA as “fuel for a fire” and “food for a hungry tumor.” To this day, androgen ablation remains a mainstay of treatment for advanced pCA, and the concern regarding T and the risk of pCA has reached to the highest levels of medicine.

In 2001 the then-director of the National Cancer Institute in the United States explained his reluctance to fund a large testosterone replacement therapy (TRT) trial by stating that he was “concerned that testosterone could spur the growth of prostate cancer among some men in the study” [2]. TRT has long been considered taboo among men with a prior history of pCA regardless of disease status, and product information mandated by the US Food and Drug Administration states that “known or suspected carcinoma of the prostate” is a contraindication for T products [3]. Three years ago the US National Institutes of Health temporarily halted all T-related research, in part on the basis of safety concerns related to T and pCA, until the Institute of Medicine pondered how to best perform research in this area.

This relationship of T to pCA has come under greater scrutiny over the last decade with the increased interest in the treatment of hypogonadism with TRT, and the growing number of pCA survivors who are symptomatically hypogonadal and requesting treatment. While there is no dispute that castration causes pCA to regress, proof for the second part of Huggins’ assertion, that T causes pCA to grow, has been elusive.

Recent reviews [4–6] have failed to find any compelling evidence to support this contention. The report by the Institute of Medicine concluded, “In summary, the influence of testosterone on prostate carcinogenesis and other prostate outcomes remains poorly defined...” [7]. The lack of evidence for what has been assumed for decades to be a solid relationship between T and pCA has been confusing for clinicians and the public. As a student once asked innocently, “If testosterone is so bad for prostate cancer, why is it so hard to prove?”

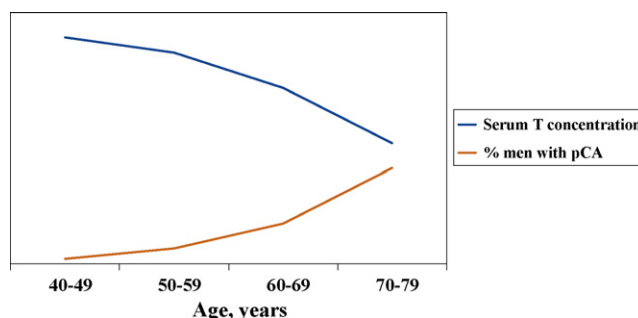


Fig. 1 – Prostate cancer prevalence and testosterone levels with ageing. pCA: prostate cancer, T: testosterone.

The underlying logic has always been strained and inconsistent. The disease is almost never seen during the peak T years of the late teens and early 20s, and only becomes prevalent when men are older and T levels have declined (Fig. 1). If T were really “fuel for a fire,” then why would the microfoci of pCA noted in young men from autopsy studies [8] not develop into frank cancer at early ages? If the answer is that it may take 30 or 40 yr for T to stimulate pCA to grow into a clinical tumor, then why do we have any hesitation in offering TRT to men in their 60s and 70s?

In the absence of current supporting evidence for the concept that T causes enhanced pCA growth, an investigation was performed of the early literature on this topic to examine the historical origins of this belief.

2. Huggins’ experiment with T injections and pCA

In a 1967 review, Huggins [9] provided this perspective on his landmark 1941 work: “Orchiectomy or the administration of phenolic estrogens resulted in regression of cancer of the human prostate whereas, in untreated cases, testosterone enhanced the rate of growth of the neoplasm.” What does the paper actually show?

In addition to showing that castration and estrogen treatment caused acid phosphatase levels to decline in men with metastatic pCA, Huggins and Hodges [1] reported that daily injection of testosterone propionate caused acid phosphatase levels to increase. Although three men were injected with testosterone propionate, results were only provided for two. One of these two had already been castrated. In the remaining individual, acid phosphatase levels rose during 18 d of T injection, but fluctuated widely before and afterwards,

reaching the same peak levels 3 wk after discontinuation of T. No other clinical information was offered.

The original assertion that T caused pCA growth in untreated individuals was thus based on equivocal acid phosphatase results in a single individual.

3. Additional experience with exogenous T in men with metastatic pCA

The largest series of exogenous T in men with metastatic pCA was reported by Fowler and Whitmore [10], who reviewed the experience at Memorial Sloan Kettering Cancer Center in New York from 1949 to 1967. Sixty-seven men, all with a history of bone metastases, received T injections under various protocols, and unfavorable responses were noted, which included subjective symptoms, such as increased bone pain, or objective progression, including a rise in acid phosphatase. Of 52 men with evaluable responses, 45 had unfavorable responses. However, only four of these men had not previously undergone orchiectomy or estrogen treatment. Within this untreated group one man had an early “unfavorable response” (within 30 d of beginning T injections), another had a subjective “beneficial response,” and the remaining two eventually developed unfavorable responses at 56 and 310 d of daily T administration, respectively. Given the advanced stage of pCA in these men and the lack of a control group, we must consider that the “unfavorable responses” seen in this population may have been due to the natural history of their disease.

Largely overlooked by history is the experience of other investigators of that era, who failed to note progression of pCA with exogenous T and even noted beneficial effects in some [11,12]. For example, Prout and Brewer [12] reported results of daily T injections for a median of 13 d in 26 men with stage C and D disease, of whom 20 had not undergone castration or other hormonal treatment. “Most of these individuals experienced an increase in sense of well being and some noticed vague diminution in pain.” In addition, they reported that the acid phosphatase response to T injection was “extremely variable.”

Pearson [13] reported on a previously untreated patient with advanced prostatic cancer with severe bone pain from osseous metastases, who was treated with daily injections of testosterone propionate. “There was prompt relief of pain, and within a few weeks he was asymptomatic.” The patient remained asymptomatic for 9 mo, during which time he received daily T injections.

These various historical reports lack modern standards for determining true progression of pCA, such as a reliable marker (i.e., prostate-specific antigen [PSA]) or control groups. However, no studies within the last 25 yr have replicated these early experiences with T administration in men with pCA. Despite their limitations, these reports thus provide a valuable perspective on the effect of T on pCA progression. The failure to observe rapid clinical progression with T administration even in men with advanced disease argues strongly against the contention that T causes enhanced growth of pCA.

4. T and pCA in the modern era

4.1. Testosterone flare

With the introduction in the 1980s of luteinising hormone-releasing hormone agonists that reduced T to castrate levels, it was noted that a transient rise in T occurred over the first 8–10 d. Reports of adverse events occurring during this period of time, such as increased bone pain, urinary retention, and vertebral collapse with paraplegia, have been attributed to pCA growth attributable to this “testosterone flare” [14].

However, in the few studies that measured PSA in men with advanced pCA during the period of elevated testosterone, PSA values never rose above baseline [15,16]. Since PSA correlates well with pCA progression [17], the flat PSA curve noted during the interval of T flare suggests that increased T did not cause pCA to progress in these patients. Is it possible that the adverse events noted during the flare interval may have been due to the natural history of metastatic pCA or to the direct effects of T on bone metabolism?

4.2. Clinical trials of TRT

No large, long-term studies of TRT have been performed. However, the pCA rate in published TRT trials is approximately 1% [4]. This rate is similar to the cancer detection rate in prostate cancer-screening trials. Nevertheless, it must also be recognized that the number of men included in studies of ≥ 1 yr is quite small.

4.3. Longitudinal studies

The relationship of T and other hormones to subsequent development of pCA has been studied in at least 16 population-based longitudinal studies [18–22]. Not one has shown a direct correlation

between total T levels and pCA. Isolated associations with minor androgens [23], calculated free T [19], or quartile analysis of hormone ratios [24] have not been confirmed by subsequent studies [18,20–22]. Surprisingly, the largest study [20] of this type noted an increased pCA risk with low T levels.

4.4. pCA rates in men with low T

If high T is believed to be associated with an increased risk of pCA, it follows that low T should be associated with reduced risk. However, prostate biopsy in 77 hypogonadal men with normal digital rectal examination and PSA of ≤ 4.0 ng/ml revealed cancer in 11 men [25]. This 14.3% cancer rate is similar to the 15.2% pCA rate noted by Thompson et al. [26] in the placebo arm of the Prostate Cancer Prevention Trial.

4.5. TRT in a high-risk population

Frank pCA has been reported to develop over 3 years in $\geq 25\%$ of men with high-grade prostatic intra-epithelial neoplasia (PIN) [27]. In one study [28], TRT was provided to 20 hypogonadal men with PIN and 55 hypogonadal men with benign biopsies. At the end of 12 mo, pCA was identified in one man in the PIN group and none in the benign group, which represents a 5% cancer rate in the PIN group and a 1.3% risk overall. These results do not suggest a precipitous increase of pCA growth or development in this high-risk group.

5. Resolving the paradox

The paradox of these data can be summarized as follows: Since lowering T causes pCA to regress, why is it that raising T fails to cause pCA to grow? The solution lies in the concept of saturation, in which maximal stimulation of pCA growth is achieved at some relatively low concentration of T. This model for T and pCA was suggested by Fowler and Whitmore [10], who concluded a quarter century ago that “normal endogenous testosterone levels may be sufficient to cause near maximal stimulation of prostatic tumors.”

At T levels below the saturation point, pCA growth would be expected to vary with T concentration, which is consistent with the observation of pCA regrowth with T normalization after androgen ablation. This model is also supported by the observation that exogenous T administered to normal men fails to cause any increase in PSA or prostate volume [29,30]. In hypogonadal men, TRT results in only modest increases in prostate size, approximately 15% for PSA

and prostate volume [4], with volume increasing to match eugonadal men, but rising no higher [31].

6. Conclusions

The original assertion that higher T causes enhanced pCA growth has persisted as a medical myth since 1941 despite all evidence to the contrary. Longitudinal studies have repeatedly and consistently rejected this hypothesis. And if T is “food for a hungry tumor,” then why is the cancer rate only 1% for men receiving TRT when one of seven hypogonadal men has biopsy-detectable pCA?

Yet 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 responses. Reviewing the relatively benign clinical course of their previously untreated patients, Fowler and Whitmore [10] postulated that near-maximal stimulation of pCA occurs at T concentrations found in normal men. This saturation model is consistent with current data regarding T and pCA. In summary, there is not today—nor has there ever been—a scientific basis for the contention that a higher T concentration causes pCA growth, acutely or long-term.

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 hypogonadal men after definitive treatment for localized pCA when history teaches us that T administration failed to cause disease progression even in men with untreated, widely metastatic pCA? Might there also be clues regarding the biology of pCA in the accumulating evidence linking low T with pCA, including associations with high-grade disease [32], higher stage at presentation [33], and worse prognosis [34]? Might it even be possible that androgen administration could prevent pCA [35,36]? After 65 yr it is time to discard the myth and to entertain new ideas regarding the relationship of T and pCA.

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