Hypothesis/Commentary

Androgen and Prostate Cancer: Is the Hypothesis Dead?

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Abstract

Data from animal, clinical, and prevention studies support the role of androgen in prostate cancer growth, proliferation, and progression. However, results serum-based epidemiologic studies in humans have been inconclusive. Part of the inconsistency in these findings stems from differences in study population, assay accuracy, intraperson variation, and limited sample size. Recently, data from a large pooled analysis of 18 prospective studies (3,886 cases and 6,438 healthy controls) showed no association between serum androgen and prostate cancer risk. It is not surprising that the pooled analysis did not find a positive link between circulating levels of total testosterone and prostate cancer risk because, individually, few of the 18 studies included in the pooled analysis reported a substantial positive association. The null result, however, does not pronounce a death sentence for the androgen hypothesis; rather, it underscores the importance of a better understanding of androgen action within the prostate, including the relationship between tissue and serum levels of androgen. In this commentary, we explain why circulating levels of testosterone may not reflect androgen action in the prostate and why tissue levels of androgen, in particular dihydrotestosterone, and the androgen receptor and its coregulators are critical to androgen action in the prostate and should be incorporated in future studies. It is timely to integrate system thinking into our research and use an interdisciplinary approach that involves different disciplines, including epidemiology, endocrinology, pathology, and molecular biology, to help dissect the complex interplay between sex steroids and genetic and lifestyle factors in prostate cancer etiology. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2525–30)

Introduction

In a recent article, Roddam et al. and the Endogenous Hormone and Prostate Cancer Collaborative Group (1) reported no association between blood levels of total testosterone and prostate cancer risk based on pooled analysis of 18 prospective studies. The pooled analysis included 3,886 men with prostate cancer and 6,438 controls. It is the largest serum-based study with the most elegant and comprehensive analysis to date to test a central hypothesis in prostate cancer etiology. It is not surprising that the pooled analysis did not find a positive link between circulating levels of total testosterone and prostate cancer risk because, individually, few of the 18 studies included in the pooled analysis reported a substantial positive association.

How do we interpret this null result? Does this mean that, as suggested by the accompanying editorial (2), the androgen hypothesis, the most biologically plausible and widely tested hypothesis for prostate cancer, is dead? Is it time to abandon the androgen hypothesis and channel our energy and resources in research on nonandrogen risk factors? Definitely not! In our view, the null finding on total serum testosterone from the pooled analysis underscores the importance of a better understanding of the relationship between tissue and serum levels of androgens to clarify the role of androgens in prostate cancer etiology.

The Origin of the Androgen Hypothesis

To appreciate fully the importance of tissue levels of androgen and the possibility that serum testosterone may not reflect androgen action within the prostate, we need to understand the biosynthesis and metabolism of androgens, androgen signaling within the prostate, and the origin of the testosterone hypothesis in prostate cancer. In 1941, Huggins and Hodges (3) showed that marked reductions in serum testosterone levels by castration or high-dose estrogen therapy resulted in the regression of metastatic prostate cancer. This seminal work (which won them a Nobel prize in 1966) and subsequent studies led to the hypothesis that higher testosterone levels cause enhanced growth of prostate cancer and resulted in the use of androgen ablation therapy for the management of prostate cancer (4). The androgen hypothesis was further supported by the fact that the introduction of supplementary testosterone can induce prostate cancer in rat models (5).

Androgen Metabolism in the Prostate

In men, testosterone is synthesized primarily in the testes and, to some extent, in the adrenal glands. In the circulation, about 45% of the total testosterone binds to sex hormone–binding globulin (SHBG), about 50% binds loosely to albumin, and <4% is unbound (free testosterone; refs. 6-8). Within the prostate, testosterone is converted irreversibly to 5α-dihydrotestosterone by the enzyme 5α-reductase type II, encoded by the *SRD5A2* gene (Fig. 1; refs. 6–8). Although testosterone and 5α-dihydrotestosterone can bind the androgen receptor (Fig. 1), androgen receptor has a higher affinity for 5α-dihydrotestosterone than for testosterone, and androgen receptor is more transcriptionally active when bound to 5α-dihydrotestosterone. The activity of the 5α-dihydrotestosterone–androgen receptor transcription factor complex is modulated by translocation to the cell nucleus and the binding of various androgen receptor coregulators, including coactivators and corepressors (Fig. 1; refs. 9-11). The 5α-dihydrotestosterone–androgen receptor–coregulator complex can translocate to the cell nucleus, where it activates transcription of genes with hormone-responsive elements in their promoters to induce androgen signaling (12). Thus, androgenic action in the prostate is determined by a multitude of factors, including concentration of androgen receptor and its coregulators as well as tissue levels of 5α-dihydrotestosterone. 5α-dihydrotestosterone levels in the prostate are determined by (*a*) testosterone metabolism, (*b*) metabolism of androstenedione via 5α-androstanedione, and (*c*) 5α-dihydrotestosterone inactivation by its reduction to 3α- or 3β-androstanediol (Fig. 1), a process that is reversible. Both 5α-dihydrotestosterone metabolites can be conjugated into 3α- or 3β-androstanediol glucuronide, an irreversible process.

Despite the critical role of tissue 5α-dihydrotestosterone in prostate growth and proliferation, data on the relationship between tissue androgens and prostate cancer are limited. In addition, little is known about the correlation between serum and tissue levels of androgens in healthy men, partly because of the difficulty in obtaining fresh normal prostate tissue, the complexity related to tissue processing for hormone assays, and tissue heterogeneity (13). Our group is currently developing assays to overcome some of these limitations as well as assessing androgen profiles in normal, hyperplastic, and tumor tissue. In most epidemiologic studies, the serum level of 3α-androstanediol glucuronide, a terminal metabolite of testosterone, is used as a surrogate marker for tissue androgen levels. It should be noted that circulating levels of 3α-androstanediol glucuronide reflect activities of both 5α-reductase types I and II, with type I expressed more abundantly in extraprostatic tissues such as the skin and type II in the prostate (14). The concentration of 3α-androstanediol glucuronide in serum correlates well with 5α-reductase activity in genital skin (6, 7, 15, 16); recent data from studies of finasteride, a 5α-reductase type II inhibitor, show that serum levels of 5α-dihydrotestosterone and 3α-androstanediol glucuronide decrease concomitantly in treated men, suggesting that serum levels of 3α-androstanediol glucuronide may reflect predominantly the activity of the steroid 5α-reductase type II (6, 17).

Several lines of evidence also support the importance of tissue androgens. For example, data from the Prostate Cancer Prevention Trial showed that the use of finasteride reduces the risk for prostate cancer by 25% (18), suggesting that 5α-reductase type II activity (and therefore testosterone metabolism within the prostate) plays a role in prostate cancer, which in turn supports the important role of tissue 5α-dihydrotestosterone in pros-
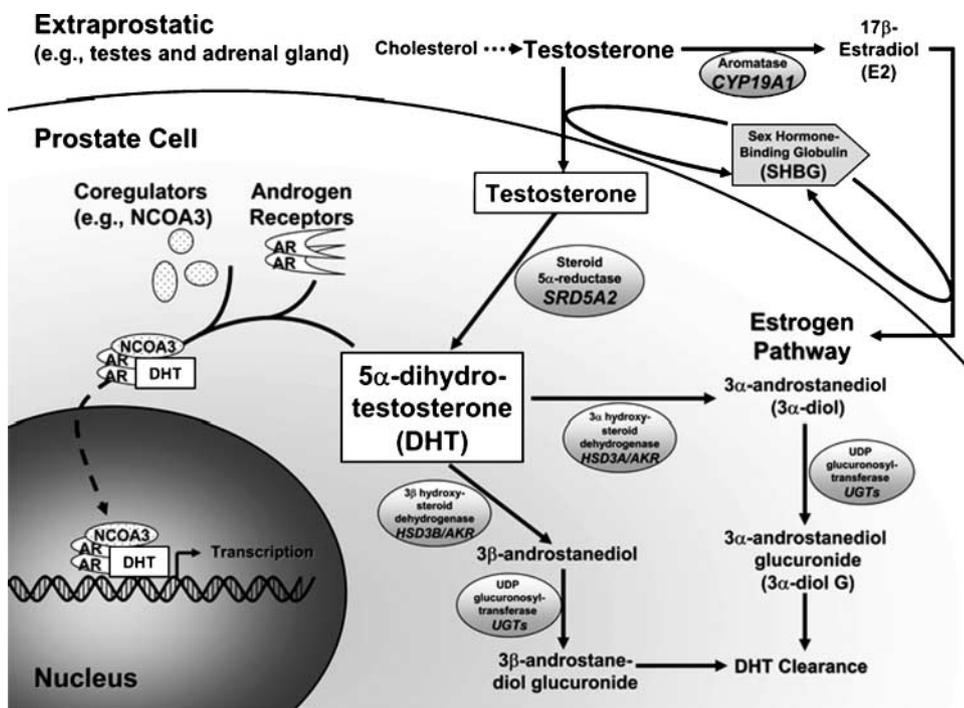

Figure 1. Androgen metabolism in the prostate.

tate carcinogenesis. Previous studies have shown that men treated with finasteride had elevated levels of serum testosterone (19). The fact that prostate cancer risk was reduced among those with elevated serum testosterone further supports the important role of tissue androgen in prostate cancer. In addition, testosterone replacement therapy for late-onset hypogonadal men increased serum testosterone levels to the reference range but did not change prostate tissue levels of testosterone and dihydrotestosterone or any biomarkers related to prostate cancer (including androgen receptor, Ki-67, CD34, PSA, PAP2A, VEGF, NXK3, Clusterin), further supporting the idea that serum androgen levels may not reflect intraprostatic levels (20); these men also had similar cancer incidence or severity to the control group. Furthermore, it is noteworthy that in the pooled analysis of Roddam et al., the association with total serum testosterone levels was null but the results for free testosterone and 3α-androstanediol glucuronide were weakly positive, although they did not reach statistical significance.

Androgenic Action in the Prostate

It is important to distinguish between serum androgen levels and androgenic action. Androgenic action in the prostate is related to tissue 5α-dihydrotestosterone levels and concentrations of androgen receptor and its coregulators. The importance of androgen receptor and its coregulators (both coactivators such as AIB1/SRC3 and corepressors such as DAX1 and SHP) in androgen signaling and action is well-established but rarely incorporated in epidemiologic investigations, partly because of the fact that prostate tissue is needed to quantify the levels of androgen receptor and its coregulators and because of the lack of highly specific antibodies for the coregulators for expression studies. Two epidemiologic studies examined polymorphic variants of the *AR* gene and its coactivator *AIB1* in cases and controls, with mixed results (11, 21). Studies on androgen receptor coactivators in prostate cancer showed that androgen receptor coactivators are associated with disease aggressiveness and poor prognosis (22), with androgen receptor activation related to androgen-refractory disease (23), and with resistance to antiandrogen (24, 25). The role of androgen receptor corepressors in prostate cancer is not yet well-defined.

Although data on prostate tissue hormones are limited, it has been shown that the concentration of 5α-dihydrotestosterone in serum is a fraction of that of testosterone (on average, 50 versus 500-1,000 ng/dL), whereas the concentration of 5α-dihydrotestosterone in prostatic tissue is several times higher than that of testosterone (6, 26). These observations are consistent with the hypothesis that most tissue 5α-dihydrotestosterone is derived through testosterone metabolism within the prostate and that serum testosterone levels may not reflect tissue levels of 5α-dihydrotestosterone and androgenic action in the prostate. If this working hypothesis is valid, then it is important to investigate tissue levels of 5α-dihydrotestosterone in conjunction with androgen receptor and its coregulators to understand better the role of androgen in prostate cancer. Conceptually, it is possible that a subset of men with relatively normal levels of serum testosterone could be at risk for developing prostate cancer if their tissue 5α-dihydrotestosterone levels are high as a result of active 5α-reductase activity and/or slow 5α-dihydrotestosterone catabolism. Alternatively, these men could have more active 5α-dihydrotestosterone–androgen receptor–coregulator complexes resulting from, for example, shorter *AR* CAG repeats of the *AR* gene (27), which has been associated with increased prostate cancer risk (see review ref. 28). Currently, it is unclear what concentration of tissue 5α-dihydrotestosterone is needed to elicit androgen receptor activation and which cofactors or their concentration are necessary for androgen-dependent activation of the various androgen-responsive genes. It may be that it is not necessary to have very high levels of 5α-dihydrotestosterone (or serum total testosterone) to initiate androgen signaling in the prostate. A good example is that androgen receptor activity could be achieved through the presence of adrenal androgen, even after androgen ablation therapy (29, 30). If this is the case, it would be difficult to detect a substantial difference in circulating levels of total testosterone in serum-based epidemiologic studies.

Related to androgen action but too broad of a topic to be adequately discussed in this commentary are the genes that are transcribed by the androgen receptor transcription factor complex. For example, recent reports showed that the androgen-regulated and prostate tissue–specific transmembrane protease serine 2 (*TMPRSS2*) gene is frequently fused to members of the oncogenic erythroblastosis virus E26 transforming sequence family of transcription factors in PSA-screened prostate cancers as well as about 20% of prostatic intraepithelial neoplasia (see review ref. 31). It is not clear how interactions between androgens and the genes that are transcribed due to androgenic action influence prostate cancer risk.

The Complex Relationship of Serum Testosterone with Age, Tumor Grade, and Obesity

Aside from how well intraprostatic hormone levels are represented in the serum, there are other unresolved issues with serum androgens, including their relationship to age, tumor grade, and obesity. First, it is well known that serum androgen levels decline with increasing age (32), whereas increasing age is one of the only established risk factors for prostate cancer (along with race and family history; refs. 6, 7). Roddam et al. (1) did not find statistically significant association between risk for prostate cancer and sex hormone concentrations according to age at diagnosis (categorized as <60, 60-69, and ≥70 years old). A recent prospective study, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which was not available in time for the Roddam et al. (1) pooled analysis and the largest single study to date with 727 incident Caucasian prostate cancer cases and 889 matched controls, reported that a higher testosterone-to-SHBG ratio was related to an increased risk primarily in men 65 years of age or older (33); testosterone-to-SHBG ratios were not assessed in the study of Roddam et al.. Studies on androgen refractory prostate cancers show that adaptive changes could occur within the prostate that increase sensitivity to adrenal androgens, which might explain this seeming paradox

(29, 30). Second, there is some evidence to suggest that high serum levels of testosterone are associated with an increased risk for low-grade prostate tumors but a decreased risk for high-grade prostate cancer (34, 35). In the pooled analysis, there is no evidence that total testosterone was linked to a reduced risk for high-grade tumors, but there was a suggestive association between free testosterone and an increased risk for low-grade tumors. The relationship between androgens and tumor grade is further complicated by the effects of obesity. There is some evidence that obese men have decreased risk for low-grade prostate cancer and increased risk for high-grade disease (see review ref. 34), which is consistent with findings that these men also tend to have lower serum levels of testosterone (36, 37); together, these findings also corroborate findings that higher serum testosterone concentrations are associated with an increased risk for low-grade prostate cancer but with a reduced risk for high-grade prostate cancer (38). However, obesity is also related to increased levels of inflammatory markers, which are also putative risk factors for prostate cancer (Fig. 2; ref. 6). The biological significance of these observations is not clear. Obviously, the relationship between serum testosterone and prostate cancer may be modified by these and other modifiers of disease risk and needs to be dissected further.

SHBG—Not Just a Carrier Protein

Of great interest from the pooled analysis is the finding that serum SHBG was modestly and inversely associated with prostate cancer risk (14% reduction; 95% confidence interval, 2-25%; comparing the highest to the lowest quintile), which indirectly supports the importance of bioavailable testosterone and intraprostatic 5α-dihydrotestosterone. SHBG has long been regarded as carrier protein for sex steroids and a regulator of free testoster-

one in the circulation but recent data suggest that SHBG may have an effect on carcinogenesis that is independent of its function as a regulator of the free fraction of androgens and estrogens. For example, signal transduction at the plasma membrane allows certain steroid hormones to act without entering the cell by interacting with SHBG membrane receptors (see review in ref. 39). In addition, estradiol can activate the androgen receptor (independent of 5α-dihydrotestosterone) by using SHBG as an intermediate (see review in ref. 39), although this pathway is complex and not well-understood, and the potential independent effects of SHBG have not been investigated fully. Most recently, mouse models show that SHBG mediates an endocytic pathway for steroid hormone uptake, which is crucial in the development of reproductive organs (40).

8q24—a Promising Region

The most promising finding in prostate cancer research is genetic susceptibility at several loci on chromosome 8q24 about 300 kb from the *MYC* gene that was identified first in 2006 and subsequently in 2007 by several studies with different populations, including genomewide association studies in Caucasian and African-American populations (32-41). In contrast to the inconsistent and null findings related to serum androgens in the last few decades, it is remarkable that the observation that 8 variants in the 8q24 region contribute substantially to prostate cancer risk is highly reproducible across populations (41-50). Although these variants are outside of known coding regions and the functional significance of these variants is unclear, along with twin and family studies, the 8q24 finding underscores the importance of genetic susceptibility in prostate cancer. The mechanism by which the risk variants on 8q24 contribute to an increased risk for prostate cancer remains unknown. The probability that
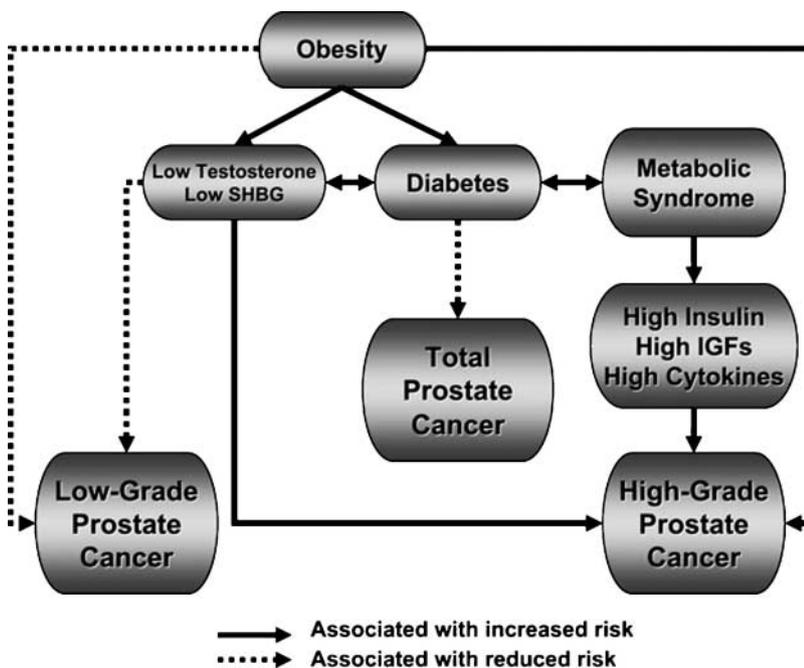

Figure 2. Putative relationships among obesity, metabolic syndrome, serum testosterone, and risk for prostate cancer. *Solid arrow,* associated with increased risk; *dashed arrow,* associated with reduced risk.

these variants have an impact on androgen biosynthesis and metabolism is remote but should not be dismissed entirely because the *MYC* oncogene, which resides about 250 to 340 kb away from the 8q24 susceptibility locus, has been shown to partner with androgen receptor for *in vivo* cross-talk between androgen receptor– and c-Met-mediated signaling pathways (51). Fine-mapping of this region and functional studies are underway to help clarify the role of these variants in prostate cancer.

What's Next?

The report by Roddam et al. provided evidence that total circulating testosterone is not associated with prostate cancer. However, this null finding does not alter our knowledge about the importance of androgen in prostate cancer because bioavailable testosterone may be more important than total testosterone, especially from the perspectives of treatment (such as in androgen deprivation therapy) and prevention (such as using chemopreventive agents to inhibit the intraprostatic metabolism of testosterone to 5α-dihydrotestosterone). In addition, limitations of current epidemiologic methods for detecting small-to-moderate associations are such that finding evidence of no association needs to be interpreted cautiously. Rather, this study raises several unanswered questions, including the role of androgen in tissues and androgen action in the prostate, and it highlights the fact that more work is required to clarify the complex relationship between androgens and prostate cancer. Clearly, it is essential to understand better, at the epidemiologic, biochemical, and molecular level, those factors that may affect tissue levels of androgen. For example, it is critical to examine the joint effects of androgen receptor and serum and tissue levels of androgen on prostate cancer risk because androgen action is exerted through the androgen receptor and its coregulators. In addition, a better understanding of the relationships between tissue and serum androgen is crucial. It is difficult to measure tissue levels of androgen in healthy subjects for epidemiologic studies; thus, it would be useful to know which serum markers will best reflect tissue androgen levels. With the improvement of technology, we now have the opportunity to produce a more complete androgen profile (>10 metabolites in one run) with gas chromatography–mass spectrometry or liquid chromatography–mass spectrometry to help reveal new metabolites that may be more closely correlated with tissue levels of 5α-dihydrotestosterone. As it was suggested in the accompanying editorial, it is time to develop new study designs and involve investigators from various disciplines, including epidemiology, endocrinology, pathology, and molecular biology, to resolve these issues, so we can to move the field forward. In our view, the pooled analysis has succeeded in shifting our focus from serum androgens to other aspects of research related to androgen activities, including tissue levels of hormones and the relationships among androgens, androgen receptor, and androgen receptor cofactors. Such a shift in focus is timely and a much needed new way of thinking to dissect the complex interplay between sex steroids and genetic and lifestyle factors, a crucial step to a better understanding of prostate cancer etiology.

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