Commentary

Regarding prostate-specific antigen: let’s not shoot the messenger

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Introduction

It is well known that androgens drive prostate cancer and the inhibition of 5α-reductase results in an inhibition of the conversion of testosterone to dihydrotestosterone, the active androgen in the prostate. Recently, two large prospective randomized trials have tested the 5α-reductase inhibitors, finasteride1 and dutasteride2 compared to placebo for the chemoprevention of prostate cancer in middle aged and elderly men. Both trials demonstrated that 5α-reductase inhibitor therapy significantly decreased subsequent low-grade (Gleason score ≤ 6) prostate cancers, however, high-grade (Gleason score 8–10) prostate cancers were significantly increased by nearly 2-fold.3 Stated otherwise, therapy with a 5α-reductase inhibitor to prevent prostate cancer resulted in one additional high-grade cancer as a trade-off to avoid four low-grade cancers.3 Although these findings have been vigorously debated, there has been no definitive explanation why they should be discounted, and they have come under intense scrutiny by the US Food and Drug Administration.3 Additionally, these findings should not be surprising since it was previously shown that the treatment of men with finasteride who have high-grade prostatic intraepithelial neoplasia (PIN), a common precursor lesion of prostate cancer, results in a significant increase in prostate cancer by 1 year.4

5α-reductase inhibitors significantly reduce the synthesis of prostate-specific antigen (PSA), a protein made by the epithelial cells of the prostate. We propose that the actual reduction in prostate tissue PSA concentration over time might result in the promotion of high-grade prostate cancer. Furthermore, we feel this needs serious attention by the medical community given the widespread use of these drugs to treat both benign prostatic hyperplasia (BPH) and male pattern baldness.5

Histologic prostate cancer is exceedingly common in the USA; autopsy data reveal that latent prostate cancer is present in 30% of men in their 30s, 50% of men in their 50s and more than 75% of men in their 80s.6 In contrast, the lifetime risk of invasive prostate cancer in the USA is 16%.7 Therefore, most prostate cancers in the population are indolent and of no threat to health or life. But, how might chemoprevention with 5α-reductase inhibitors promote histologic indolent prostate cancers to become high-grade invasive cancers?

The physiological role of PSA

PSA is a serine protease made primarily by normal prostate tissue, benign hyperplastic prostate tissue and all grades of prostate cancer; its primary function is to liquefy semen by proteolysing the gel proteins of the seminal fluid.8 The transcription of this protease is activated by dihydrotestosterone8 and that is why 5α-reductase inhibitor therapy, which inhibits the conversion of testosterone to dihydrotestosterone, results in a decrease in local PSA.
synthesis and subsequent decrease in blood PSA concentration. Structurally, the prostate compartmentalizes PSA so that only a small amount enters the general circulation, resulting in the concentration of prostate tissue PSA (0.5–2.0 mg/ml) being a million-fold greater than that of PSA in the blood (0.5–2.0 ng/ml). Blood levels of PSA correlate directly with the size of the prostate, and prostate cancer results in proportionally more PSA being released into the circulation than does BPH, since prostate cancer results in disruption of basal cells and basement membrane which surround the secretary epithelium. The active PSA that diffuses into the blood is rapidly bound to the protease inhibitor α1-antichymotrypsin and the remaining free PSA that diffuses into the blood is inactive since it underwent proteolysis in the prostate prior to entering the circulation; therefore, PSA in the blood has no enzymatic activity. It is extensively known that blood PSA testing has become a very popular tool for prostate cancer screening and the monitoring of its treatment.

The antiangiogenic property of PSA

Intriguingly, PSA has been shown to have significant antiangiogenic activity and this property of PSA might in part explain the indolence and slow growth of most prostate cancers. In vitro, PSA inhibits endothelial cell proliferation, migration and invasion. Moreover, it inhibits endothelial response to the proangiogenic proteins fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF); additionally, in a murine model of metastatic melanoma, purified human PSA significantly reduced the mean number of lung nodules, presumably by its antiangiogenic properties. Other in vitro data demonstrate that PSA can convert plasminogen to biologically active angiostatin-like fragments; the antiangiogenic properties of PSA are most likely related to its enzymatic activity. Notably, angiogenesis is crucial in the development and progression of prostate cancer from high-grade PIN to focal cancer and onward to invasive cancer and metastatic cancer. Microvessel density is a histologic marker of the neo-angiogenic process and is an indicator of tumor aggressiveness and metastatic potential of many tumors including prostate cancer. Importantly, microvessel density in prostate cancer tissue correlates directly with the Gleason score and long-term risk of death from advanced prostate cancer in most, but not all studies. Furthermore, the Gleason score of early non-palpable prostate cancer can indeed increase over time with microvessel density.

PSA, angiogenesis and curiosities

The antiangiogenic property of PSA might explain many curiosities reported in the medical literature. Among men with endocrine-treated prostate cancer and no metastasis, the level of prostate tissue PSA obtained by fine-needle aspiration correlated inversely with progressive disease and was far superior to blood free and total PSA in predicting progressive disease. When the men were divided into tertiles based on the prostate tissue PSA level and followed for at least 6 years, 93% (56 out of 60) of the patients in the lowest tissue PSA tertile developed progressive disease compared to 15% (9 out of 60) in the middle tissue PSA tertile and none of the 59 patients in the highest tissue PSA tertile. It appears that a high prostate tissue PSA concentration provided a local antiangiogenic environment that inhibited the progression of prostate cancer.

The progression of prostate cancer to metastatic disease has occurred in patients with undetectable or low-blood PSA concentrations; in contrast, patients undergoing radical prostatectomy with preoperative blood PSA concentration >20 ng/ml exhibited varying degrees of disease progression. Likewise, the antiangiogenic properties of PSA might explain some of these inconsistencies.

Statin therapy used for cholesterol lowering has been found to significantly lower blood PSA concentration. The decline in PSA is dose-dependent and more pronounced in subjects with the greatest decreases in low-density lipoprotein (LDL) cholesterol levels and also the highest PSA concentration at baseline. This is of some concern as statins are increasingly used for aggressive LDL cholesterol lowering in wide segments of the population for long time periods. In fact, some observational data suggest statins increase the risk of prostate cancer showing a significant trend of increasing risk with increasing cumulative dose of statins. Plausibly, beyond the hypcholesterolemic action of statins, this might occur due to a chronically decreased prostate tissue PSA concentration favoring angiogenesis.

It is noteworthy that blood PSA concentration is significantly increased immediately after ejaculation and remains elevated for 24 h. Remarkably, observational studies have demonstrated that men who had high ejaculation frequencies sustained over long time periods exhibited a decreased risk of organ-confined prostate cancer. Therefore, it is possible that those men had a chronically higher prostatic PSA concentration due to the ejaculatory frequency and this resulted in a relative resistance to local angiogenesis.
PSA is not truly prostate specific and is found in women, notably in breast tissue, and its biological function is not known. The blood PSA level varies cyclically with the menstrual cycle and peaks 10 days after the progesterone spike, presumably progesterone activates the transcription of PSA. It is of considerable interest that some breast cancers express PSA and the presence of PSA in breast cancer tissue is associated with smaller tumors with lower cellularity and a significantly lower risk of subsequent relapse and death. One might speculate that the PSA in breast cancer tissue maintains a relative antiangiogenic environment resulting in less tumor growth.

**Conclusion**

Therefore, PSA in the blood represents a messenger informing the physician of potential prostate cancer and a useful biomarker to gauge the success of prostate cancer treatment. At the tissue level, in addition to liquefying semen, it appears that the high concentrations of PSA maintain a relative antiangiogenic state, which plays a role in keeping high-grade PIN from progressing to prostate cancer and keeping indolent prostate cancer from becoming more aggressive and metastasizing. The local tissue concentration of prostatic PSA and its angiogenic function should not be minimized given the high prevalence of high-grade PIN and histologic prostate cancer in men of all ages. The medical community needs to be aware that therapeutic agents that potentially decrease local tissue PSA concentration resulting in a locally more antiangiogenic environment might spur the growth of high-grade prostate cancer. This concept is particularly cogent when therapeutic agents are used for prolonged periods of time in broad segments of the population, such as the 5α-reductase inhibitors for the treatment of BPH and male pattern baldness. There now have been two large prospective trials showing a possible cancer signal with the 5α-reductase inhibitors. Is it worth the risk of using these drugs to treat BPH if they avoid four low-grade indolent cancers in exchange of causing one high-grade cancer? Are more hairs on the scalp worth the risk of high-grade prostate cancer? If statins and 5α-reductase inhibitors both lower PSA concentration, is there a particularly increased risk of high-grade prostate cancer when used together? At a minimum, physicians need to maintain a heightened level of vigilance regarding the potential of prostate cancer promotion when using these drugs.

Finally, nutrition and lifestyle changes, without changing PSA concentration, have been shown to favorably modulate prostatic gene expression having critical roles in tumorigenesis in patients with low-risk prostate cancer. Similarly, green tea catechins have been shown to be safe and effective in preventing subsequent prostate cancer in patients with high-grade PIN without changing PSA concentration. Perhaps, nature is telling us that the chemoprevention of prostate cancer should not include shooting the messenger.

**Conflict of interest:** None declared.

**References**


