

CLINICAL REVIEW

Prostate Specific Antigen and Its Latest Challenger

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ABSTRACT

Currently, screening for prostate specific antigen (PSA) is regarded as the standard of early testing for prostate cancer, and has been used in clinical settings for over a decade. However, due to inherent problems in specificity and accuracy of the PSA test, much research worldwide has been directed towards identifying specific features of PSA or other serum-based biomarkers to test for early signs of prostate cancer. Recently, a new biomarker, early prostate cancer antigen (EPCA)-2 has been identified. Preliminary investigations have led to suggestions that it possesses the specificity to potentially replace PSA as the standard of prostate cancer screening. The purpose of this article is to provide a review of prostate cancer detection via prostate specific antigen (PSA), to consider the findings surrounding EPCA-2, and offer expert commentary on the prospects of this new biomarker. PSA appears to be the most useful marker that we have today. Although the EPCA-2 has displayed some very promising results, further investigation into this and other biomarkers are required.

INTRODUCTION

Prostate cancer is the most commonly diagnosed malignancy, and second most common cause of cancer-related death in American men. Worldwide, prostate cancer ranks fourth amongst the most common male malignancies.¹ The annual incidence of this disease has been accelerating since 1975, with the rates peaking during the years between 1989 and 1992. This coincided with the introduction of the prostate-specific antigen (PSA) test and was a time that saw the annual incidence of prostate cancer in men ages 50-59 rise to 105 per 100,000.¹

Since its implementation, PSA screening has brought with it early intervention using effective treatments, and a consequent decrease in morbidity. It has also been suggested that the increasing incidence prior to 1989 was attributable to an increasing interest surrounding early detection which preceded the arrival of PSA screening.² Despite its success over the past decade, shortcomings inherent to this test have driven researchers to attempt to discover a more sensitive and more precise tumor marker that identifies prostate cancer. Increasingly, aging populations and the apparent significance of the disease add to the urgency in refining the diagnosis of prostate cancer.

Considerable media attention was given to a recent study by researchers at the Johns Hopkins University School of Medicine which announced the identification of early prostate cancer antigen-2 (EPCA-2), a new serum-based biomarker of prostate cancer. Its founders have claimed it to have a very high sensitivity and specificity for prostate cancer and the media have suggested that it could potentially revolutionize clinical diagnosis.

This paper will attempt to review PSA testing, its advantages and shortcomings, as well as the recent study which identified EPCA-2, and what its prospects are as a revolutionary biomarker in prostate cancer.

PROSTATE SPECIFIC ANTIGEN (PSA)

PSA is a glycoprotein which acts as a serine protease enzyme. It is secreted from the prostate gland in high concentrations into the seminal fluid and functions to liquefy the seminal coagulum.³ More specifically, PSA is produced by the epithelium of the prostate and periurethral glands. Relative to its concentration in seminal fluid, PSA is found at much lower levels in the serum. Although the mechanism by which PSA gains access into the systemic circulation is unknown, the discovery of its presence in male serum in the 1980's completely

transformed the clinical detection and management of prostate cancer.

Currently, PSA in conjunction with the digital rectal examination, and transrectal ultrasound guided biopsy of the prostate comprise the most valuable means of assessing the possibility of prostate cancer in a given patient. These additional investigative modalities are necessary because PSA in and of itself is not a very specific test for cancer of the prostate. Elevated levels of PSA are also found in entities such as benign prostatic hyperplasia, prostatitis, and even after urethral instrumentation.

As such, researchers have continually worked to refine PSA screening by investigating various characteristics of PSA that would assist in more accurately detecting prostate cancer.

One such feature of PSA is its rate of change, otherwise known as PSA velocity. A 1992 study by Carter et al. established the now widely accepted PSA velocity cut off of 0.75 ng/mL as being highly suspicious of the presence of prostate cancer. It was shown that this particular value offered 90% specificity and 72% sensitivity in cancer detection for PSA values between 4 and 10 ng/mL.

A second characteristic of PSA that is used to maximize its efficacy in cancer detection is known as PSA density. This particular construct is a quantification of PSA as a function of prostate gland volume. In 1992, Benson et al. were the first to propose that PSA density could help in deciphering whether elevations in PSA were malignant in nature, however, the usefulness of PSA density since then has come into question. Initial studies in the area of PSA density showed that a cutoff of 0.15 as a threshold for biopsy was useful, but several studies have challenged this notion. One particular investigation, among others, by Catalona et. al showed that half of the cancers detected in men with a PSA between 4 and 10 ng/mL would have been missed using a PSA density cutoff of 0.15. The questionable efficacy of PSA density in cancer screening is attributable to the fact that PSA is produced only in the epithelium of the prostate, and epithelial to stromal ratios differ in every individual prostate gland. Furthermore, variation and error in the ultrasound based calculation of prostatic volume may lead to conflicting results. Although PSA density is not widely accepted as a means of more accurate cancer screening, some clinicians employ it as an additional method in assessing for the risk of prostate cancer in concert with other screening tools.

Thirdly and most recently, PSA screening was further refined through the investigation of the various forms of PSA – namely its free and complexed molecular states. Complexed PSA exists in two ways. The serum PSA is either irreversibly bound to a serine protease inhibitor known as α 1-antichymotrypsin (ACT), or it is bound to a large plasma protein known as α 2-macroglobulin (A2M). Both complexed forms are enzymatically inactive and only the former is immunoreactive. Free PSA on the other hand, is found in

much lower concentrations relative to the complexed PSA-ACT and is enzymatically inactive as well as immunoreactive.

It is now well established that individuals with prostate cancer have a greater proportion of complexed serum PSA, and conversely, a lower percentage of free PSA than compared to other men without prostate cancer and/or other benign diseases of the prostate.² The reason for this variation is hypothesized to be a result of differences in expression of PSA isoforms by the transitional zone of the prostate where benign prostatic hyperplasia originates, compared with that of the peripheral zone where most prostate cancer arises.² Many studies have attempted to precisely define the parameters of free PSA in prostate cancer. The widely accepted cutoff was established by Catalona et al. in a 1998 study which showed that a free PSA cutoff of 25% relative to total PSA, detected 95% of prostate cancers and avoided 20% of unnecessary biopsies in men with PSA levels between 4 and 10 ng/mL.²

EARLY PROSTATE CANCER ANTIGEN-2 (EPCA-2)

Getzenberg et al. of the Johns Hopkins University School of Medicine have claimed the discovery of two unrelated prostate cancer biomarkers known as early prostate cancer antigen (EPCA) and early prostate cancer antigen-2 (EPCA-2). The most recent of these discoveries, EPCA-2, has been trumpeted by the media as a potential revolution in the screening and diagnosis of prostate cancer.

The molecular basis for this discovery is the nuclear matrix. Both ECPA and ECPA-2 were discovered using a proteomic approach to examine nuclear structural elements found within prostate cancer cells. Composed of various proteins, nucleoli, and nuclear pore complexes, the nuclear matrix is the scaffolding framework of the nucleus, and by some, has been characterized as analogous to the cellular cytoskeleton.⁴ Some nuclear matrix proteins can be common to all cell types, while others are specific to particular cell types and/or to the state of differentiation.⁴ EPCA-2 is one such nuclear matrix protein which Getzenberg et al. have described as being associated very closely with prostate cancer.⁶

In the Getzenberg study, EPCA-2 levels were assessed in 330 individuals that were categorized into six groups: 1) men with normal PSA and no evidence of disease; 2) men with elevated PSA and negative biopsies; 3) men with benign prostatic hyperplasia; 4) men with organ-confined prostate cancer (i.e. cancerous cells have not breached the prostatic capsule); 5) men with non-organ-confined prostate cancer (i.e. cancerous cells have spread beyond the prostatic capsule); and 6) men with prostate cancer but normal PSA. An additional sample set composed of men and women with other benign diseases and non-metastatic cancer were analyzed as a control group to assess the specificity of EPCA-2. Prior to this investigation, a pilot study was performed using enzyme linked immunosorbent assay (ELISA) technology to establish an appropriate EPCA-2 cutoff.

Both sensitivity and specificity comparisons were then made between PSA and EPCA-2 based on these categories.

The researchers' analysis demonstrated that within the 98 men who comprised the first 3 groups, a PSA cutoff of 2.5ng/mL had a specificity of 65% compared with a specificity of 92% using EPCA-2 and its established cutoff. Within the 80 men who comprised groups 4 and 5, a PSA cutoff of 2.5ng/mL offered a 90% sensitivity compared with a 94% sensitivity using EPCA-2. However, the study's investigators did comment that "The PSA values were indicative of the populations that were deliberately selected to show individuals in whom PSA was and was not a good indicator, and as such, do not indicate the expected performance in a true screening setting."⁶

Another finding of this investigation was that the EPCA-2 test was capable of better differentiating between men with organ-confined prostate cancer and non-organ-confined prostate cancer as compared to PSA. Although they report these findings as statistically significant, they do acknowledge that the study was not specifically designed to assess the biomarkers capabilities in this area. They have indicated that the data highlights the potential for EPCA-2 to do this and that specifically designed investigations are required.⁶

EXPERT OPINION

Dr. Edward Matsumoto, Assistant Professor and Assistant Program Director at the Institute of Urology of McMaster University offered some critical insight to the new EPCA-2 biomarker: "The results of the Getzenberg study are really quite promising, but it is too early on to say anything definitive." He went on to highlight the study's nonrandomized design in which patients were retrospectively assigned to either the organ-confined prostate cancer group or non-organ-confined prostate cancer group prior to having EPCA-2 levels analyzed. He cautioned that, "Without a large, well-designed RCT, we cannot put much weight to claims as the ones made in the media about EPCA-2". Dr. Matsumoto mentioned that several other prostate cancer biomarkers with similar preliminary results have been discovered and was uncertain as to why this particular amount of media attention was placed on EPCA-2. As far as PSA is concerned, Dr. Matsumoto provided a bottom-line analysis: "The skepticism surrounding PSA is that, despite much literature on the efficacy of PSA testing, there is no level I evidence that PSA screening saves lives." He mentions that two large randomized-control studies currently underway in the urological communities of the United States and Europe which promise to provide much needed clarity on the issue of PSA testing.

CONCLUSION

Currently the clinical use of PSA screening has proven itself to be successful in detecting early stages of prostate cancer among the general population. However, because PSA screening is beset, among other limitations, with problems of low specificity, the search for a better biomarker has yielded some promising candidates, one of them being EPCA-2.

Although promising in its initial results on a screened sample of men, the specificity EPCA-2 has demonstrated has yet to be reproduced conclusively in an unselected clinical population. Furthermore, its use as a clinical diagnostic tool can only come about after refining the testing process for greater sensitivity. Whether EPCA-2 will eventually replace PSA as the diagnostic tool of choice for prostate cancer remains to be seen only after EPCA-2 has proven its utility beyond controlled investigative studies and to the general population.

In the meantime, as EPCA-2 is further investigated, several other biomarkers of prostate cancer have been identified, including human glandular kallikrein-2, prostate specific membrane antigen and p27. As with EPCA-2, the clinical effectiveness of screening for these compounds will be an interesting area of upcoming research, as potentially one, or a combination of these may replace PSA as the screening tool of choice. †

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