Do We Need PSA and Early Detection of Prostate Cancer?

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1. Introduction

PSA measurement is the most important tool for early detection of prostate cancer and is still considered the best marker in the entire field of cancer. However, PSA testing has its limitations. One of these limitations is that PSA is not cancer-specific but rather tissue-specific. The test has relatively poor specificity (resulting in many unnecessary prostate biopsies), furthermore high rates of over-detection and overtreatment affect patients’ quality of life. New assays measuring different molecular forms of PSA have resulted only in a moderate improvement of specificity especially beyond the PSA range of 2 to 10 ng/ml. Novel biomarkers for prostate cancer detection are emerging and they might enable clinicians to differentiate indolent from aggressive cancers in order to minimize overtreatment in future.

2. PSA test and prostate cancer risk

A key question is whether plasma PSA levels can predict long-term risk for prostate cancer. Lilja and colleagues recently assessed whether various PSA forms and human kallikrein 2 (hK2) measured at age 44 to 50 years could predict an individual’s long-term risk of incident prostate cancer [2]. The investigators found that PSA was an excellent predictor of prostate cancer incidence. Each 1 ng/ml increase in total PSA was associated with a 3.69 odds ratio of cancer (95% confidence interval, 2.99–4.69). However, including other PSA forms or hK2 as part of the assessment process did not add to the predictive value of total PSA.

Similarly, Aus and colleagues found that biennial PSA screening reduced the risk of being diagnosed with metastatic prostate cancer by 48.9%, although screening increased the risk of diagnosing prostate cancer 1.8-fold [3]. The researchers also found that there was a 20% chance of being diagnosed with cancer if the baseline PSA was ≥ 2 ng/ml. Thus, PSA level is a powerful tool for stratifying patients into low- versus high-risk groups.
3. **PSA test and detection of clinically significant tumors**

Results from baseline PSA and digital rectal examination screening, as well as diagnostic follow-up results in the first year following enrollment were recently reported from the prospective randomized Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening trial [4]. The investigators indicated that most prostate cancer cases detected through PSA testing are less aggressive and may not become symptomatic during a patient’s lifetime. Similarly, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported that the ratio between incidence and mortality was 14.8 versus 2.25, further highlighting the problem of overdetection [5].

Furthermore Thompson and colleagues also found that the prevalence of prostate cancer increased with PSA level [6]. Although the rate of cancer detection in men with PSA < 3 ng/ml was quite high, PSA was not very effective at detecting clinically significant tumors. Interestingly, patients with a PSA of 4 ng/ml had a false positive rate of at least 20%. There is also a likelihood that false-positive cases identified through routine screening may be due to benign prostatic hyperplasia (BPH) and other disorders affecting the prostate.

4. **PSA kinetics and PSA isoforms**

PSA kinetics like PSA velocity (PSA-V) and PSA doubling time (PSADT) are important indicators of risk, as are percentage of free PSA versus percentage of complexed PSA and pro-PSA.

D’Amico and colleagues analyzed data of 1095 men with localized prostate cancer who underwent radical prostatectomy. They found that a PSA increase of >2 ng/ml during the year prior to diagnosis was significantly associated with a shorter time to biochemical recurrence, death from prostate cancer and death from any cause [7]. PSADT was also implemented as a useful tool to select patients suitable for active surveillance as was recently shown by Khatami and coworkers [8].

Since the early 1990s, PSA interaction with antiproteinases has been extensively studied [9]. Active PSA forms stable complexes with both alpha-macroglobulin and alpha-1-antichymotrypsin, and the extent of such complex formation may indicate the turnover rate of active PSA in intercellular fluid or blood plasma in vivo [10].

It was anticipated that assessing these different molecular forms of PSA would improve the specificity of PSA testing, but the results did not support this conclusion beyond the PSA range of 2 to 10 ng/ml.

Complexed PSA may be as accurate as the ratio of free-to-total PSA and superior to total PSA in the PSA range 2–10 ng/ml. In a meta-analysis Roddan and colleagues reported that the use of complexed PSA or free-to-total PSA when the total PSA ranged from 2 to 10 ng/ml might reduce the number of unnecessary biopsies while maintaining a high detection rate [11]. The potential utility of more recently identified forms of free PSA, including pro-PSA, intact free PSA, and BPH-related PSA (BPSA), has yet to be realized and could further improve the specificity of PSA testing in prostate cancer [12,13].

5. **New biomarkers on the horizon—is the PSA era really over?**

Due to the low specificity of PSA significant efforts have been initiated to find new biomarkers aiming to avoid unnecessary biopsies. As prostate cancer cells shed into urine it is an attractive target to detect RNA, DNA and proteins with modern molecular technologies.

The DD3PCA3 gene is located on chromosome 9q21-22 and is the most prostate cancer-specific gene that has been described to date. Investigators have found that the prostate cancer antigen 3 (PCA3) is overexpressed in more than 95% of primary prostate cancers [14]. Urinary specimens are obtained from patients after digital rectal palpation and analyzed by quantitative RT-PCR to detect PCA3 mRNA. This promising test is now being developed and commercially available. The PCA3 test combines a high specificity and sensitivity but sampling is sensitive and reference centres with suitable laboratory equipment still are sparse [15,16].

The glutathione-S-transferase P1 gene (GSTP1) hypermethylation in urine was evaluated recently by Woodsen and collegues. In 100 analysed urinary specimens they could show a 98% specificity and 75% sensitiviy of GSTP1 methylation. Large prospective screening trials are needed to further explore the utility of this prostate cancer marker [17].

However, a variety of promising urinary markers for prostate cancer are currently under investigation but are not within the scope of this article [18].

Autoantibody signatures have also been identified in prostate cancer but these markers still need to be validated in healthy versus diseased prostate tissue [19]. If validated, however, a test matching these autoantibodies against peptides derived from prostate-cancer tissue could ultimately be used as screening test for prostate cancer.
6. Summary

PSA remains a significant predictor of prostate cancer and will continue to function as an important marker for prostate cancer in the near future [20–23]. Integration of new biomarkers in addition to refining PSA kinetics may help to avoid overtreatment and serve as a guide to initiate treatment allowing clinicians and patients to decide whether further evaluation is appropriate.

Conflicts of interest

The authors have nothing to disclose.

References