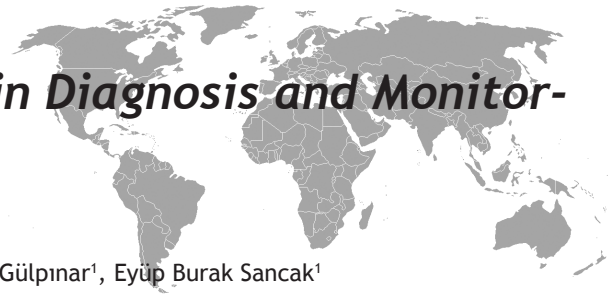
Eur J Gen Med 2015; 12(2):187-193
DOI : 10.15197/sabad.1.12.40

Review Article

Is PSA Still the Best Marker in Diagnosis and Monitoring of Prostate Cancer?



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ABSTRACT

Prostate cancer is the second most common cancer in males. At an early stage, prostate cancer barely causes any symptoms. The presence of symptoms upon presentation usually implies the presence of locally-advanced or metastatic disease. Therefore, early detection of prostate cancer is a necessity. Serum Prostate-Specific Antigen (PSA) test and Digital Rectal Examination (DRE) are used for early detection by the urologist. However serum PSA level is not only affected by the tumours but also other factors. The limitations of serum PSA test led to the introduction and application of various PSA derivatives to improve test sensitivity and specificity. In this review article, we provide a literature review and analysis of the currently available PSA test and its derivatives compared to new and developing potential tumour markers for detection and monitoring of prostate cancer.

Key words: *PSA derivates, prostate cancer, tumour marker*

Prostat Kanseri Tanısı ve Görüntülemesinde PSA Hala En İyi Belirteç midir?

ÖZET

Erkeklerde 2. en sık görülen kanser tipi prostat kanserleridir. Erken evrede herhangi bir semptom vermez. Local ileri evre ve metastatik durumlarda semptomlar ortaya çıkar. Bu nedenle prostat kanserinin erken tesbiti zorunludur. Ürologlar tarafından serum prostat spesifik antijen (PSA) testi ve parmakla rektal muayene kanserin erken tesbitinde kullanılır. Bununla birlikte serum PSA seviyesi sadece tümörlerden değil başka faktörlerden de etkilenir. Serum PSA testinin kısıtlamaları, özgüllük ve duyarlılığın artırılması amacıyla çeşitli PSA türevlerinin ortaya çıkmasına yol açtı. Şu an uygulanan PSA testi ve türevlerinin analizi ile prostat kanserinin tesbiti ve izlenmesi için yeni ve gelişen potansiyel tümör belirteçlerinin karşılaştırılması literatür değerlendirmesi olarak bu derleme yazısında sunulmuştur.

Anahtar kelimeler: *PSA türevleri, prostat kanseri, tümör belirteci*

INTRODUCTION

Prostate cancer is the fifth most common world malignancy and the second most common cancer in males (1). It also constitutes more than 10 percent of newly diagnosed cancers, more in developed than in developing countries (19 and 5.3 percent, respectively) and, hence, representing a worldwide challenge for clinicians (2). At an early stage, prostate cancer barely causes any symptoms. The presence of symptoms upon presentation usually implies the presence of locally – advanced or metastatic disease. Therefore, early detection of prostate cancer is a necessity (3). Before the use of serum Prostate-Specific Antigen (PSA) test, early diagnosis of prostate cancer largely relied on Digital Rectal Examination (DRE).(4) However, DRE alone could potentially overlook a significant number of early cancers(5) as reproducibility of DRE for detecting prostate cancer is only fair even in the experienced hands

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Received: 08.03.2014, Accepted: 03.06.2014

(6). In current practice, most urologists use a combination of DRE and PSA to detect prostate cancer and decide upon the need for prostatic biopsies (7). PSA can also be implemented to identify the extent of the disease (staging), provide an idea about the post – radiotherapy or surgery disease control (prognosis) and determine patient response to local or systemic therapy (monitoring) (8, 9). Moreover, although screening protocols for prostate cancer are still under debate, PSA has evolved to become the main tool used in screening for prostate cancer (10, 11). Nevertheless, serum PSA has its own limitations. PSA expression is influenced by age, race and prostate volume (12, 13). PSA level is also strongly affected by androgens. For instance, in men with hypogonadism and low testosterone levels, serum PSA may be low in spite of the presence of prostate cancer (14). Conversely, an elevated PSA indicating the presence of prostate disease might not necessarily be related to cancer (3). The limitations of serum PSA test led to the introduction and application of various PSA derivatives to improve test sensitivity however with impaired specificity. More recent innovations in the field of oncology highlighted the urgent need for novel prostate tumour markers that will eventually increase early cancer detection, provide accurate diagnosis, demonstrate the aggressiveness of disease and effectively monitor the response to initial treatment (15). In this review article, we provide a literature review and analysis of the currently available PSA test and its derivatives compared to new and developing potential tumour markers for detection and monitoring of prostate cancer.

Main body

What is Prostate – Specific Antigen?

Prostate specific antigen, also known as human Kallikrein 3 (hk3), is an androgen-regulated serine protease that is produced almost exclusively by prostatic ductal and acinal epithelium (16). The gene responsible for PSA production resides within chromosome 19q133-4.(17) In a normal prostate, PSA is mainly excreted into prostatic ducts, with only a small proportion escaping into the main circulation and, hence, the detectable serum PSA. PSA was first isolated in seminal fluid analysis in the 1960s.(18) In 1979, for the first time, PSA was isolated from normal, benign hyperplastic and malignant prostate tissue specimens (4) and, therefore, suggesting its use as a tumour marker for prostate cancer. However, the use of PSA reliably in clinical practice did not take place till mid 1980s (19).

Factors affecting PSA level and its diagnostic role

It is noteworthy that high PSA level in men with prostate cancer is the result of disrupted basement membrane and ductal lumen architecture rather than an actual increase in PSA production (20). Therefore, prostatic pathology (prostatitis, benign prostatic hyperplasia – BPH or prostate cancer) is a crucial factor in determining PSA level (21). To a lesser extent, prostatic manipulation by DRE, biopsy or transurethral resection (TUR) might result in a slightly higher serum PSA (22). However, it has been shown that DRE – related PSA rise is rarely clinically significant (23). Age, race, androgens and prostate volume are known PSA-determining factors, with higher PSA expression in older, black men and in those with higher androgen levels and larger prostates (11, 12). Also, significant decline in PSA level can be observed by using 5α-Reductase inhibitors (type 2 isoenzyme inhibitors and dual type 1 and 2 isoenzyme inhibitors) for BPH treatment (24). Lastly, there is some evidence that other factors such as ejaculation, body weight, carbohydrate intake, and insulin resistance could influence serum PSA levels (25).

The role of PSA in detection of prostate cancer

In 1994, serum PSA test was officially approved for detection of early prostate cancer (26) and implementation of PSA test led to an increase in detection of organ-confined prostate cancer (27). The probability of diagnosing prostate cancer on biopsy specimen increases significantly with higher PSA levels (28) and it has been documented that at serum PSA level above 4 nanograms per millilitre (ng/ml), PSA test has an approximate sensitivity of 20% and specificity of 60% to 70% (29). An attempt to increase PSA sensitivity by lowering threshold levels for biopsy will potentially help detecting more cancers, however, it will also risks identifying clinically insignificant tumours. As a compromise, suggestion is made to reduce threshold PSA level for younger population (i.e. age – adjusted PSA) (12).

Role of PSA in monitoring response to prostate cancer treatment

A detectable PSA following radical treatment could be a sign of tumour recurrence or presence of residual benign prostate tissue. It has been agreed that biochemical recurrence following radical prostatectomy is defined as PSA value ≥0.2 ng/ml followed by a repeat PSA value ≥0.2 ng/ml.(30) Recurrence after radiotherapy or brachytherapy for prostate cancer is concluded to represent a PSA

***Table 1**. Novel tumour markers for prostate cancer (15).*

Potential marker	Description	Method of detection	Potential type of marker
Circulating tumour cells (CTC)	Circulating prostate cancer cells	Serum marker	Diagnostic and prognostic
Early prostate cancer antigen (EPCA)	Nuclear matrix protein	Serum marker	Diagnostic
Prostate-specific membrane antigen (PSMA)	Type II membrane glycoprotein	Serum marker	Diagnostic
Human glandular kallikrein 2 (hK2)	Prostatic secretary protein	Serum marker	Diagnostic and prognostic
m/z 7771	Unknown protein	Serum marker	Diagnostic
Transforming growth factor-B1 (TGF-B1)	Multifunctional cytokine	Serum marker	Diagnostic
Interleukin-6 (IL-6) and IL-6 receptors (IL-6R)	Multifunctional cytokine	Serum marker	Diagnostic and prognostic
Vascular cell adhesion molecule (VCAM)	Cell adhesion molecule	Serum marker	Prognostic
Matrix metalloproteinase-2 (MMP-2)	Cell adhesion molecule	Serum marker	Prognostic
Bone-specific alkaline phosphatase (bALP)	Marker of bone turnover	Serum marker	Prognostic
Total alkaline phosphatase (tALP)	Marker of bone turnover	Serum marker	Prognostic
Cross-linked C-terminal of type 1 collagen (CTx)	Marker of bone turnover	Serum marker	Prognostic
C-terminal telopeptides of type 1 collagen (ICTP)	Marker of bone turnover	Serum marker	Prognostic
Amino-terminal procollagen propeptides of type 1 collagen (PINP)	Marker of bone turnover	Serum marker	Prognostic
Soluble ErbB3 (sErbB3)	Marker of bone turnover	Serum marker	Prognostic
a-methylacyl coenzyme A racemaster (AMACR)	Fat metabolism enzyme	Tissue marker	Diagnostic and prognostic
MDM2 gene	Negative regulator of p53 tumour suppressor	Tissue marker	Prognostic
Ki-67	Marker of cellular proliferation	Tissue marker	Prognostic
Prostate cancer antigen 3 (PCA3)	Genetic marker	Urine markers	Diagnostic
Sarcosine	N-methyl derivative of glycine	Urine markers	Diagnostic
Calgranulin B	S-100 calcium binding protein	Urine markers	Diagnostic
TMPRSS2:ER gene fusions	Genetic marker	Urine markers	Diagnostic

rise of ≥2 ng/ml above the nadir (31). The role of PSA in monitoring prostate cancer can be divided according to tumour stage and aggressiveness:

• Early stage prostate cancer. Regular serum PSA level check following radical treatment can identify early recurrence before the tumour would be detectable by any other method (32). However, the nature of the radical treatment selected could potentially affect PSA monitoring. For instance, an initial transient PSA rise is often noticed following radio- and brachytherapy, which can interfere with disease monitoring. This transient PSA rise can be explained by the release of PSA due to cell death and radiation-related increased vascular permeability (33).

• Advanced and metastatic prostate cancer. The value and utility of PSA monitoring declines as prostate cancer becomes more aggressive, either as a result of less PSA production (undifferentiated cancer) or due to suppressed PSA production caused by antiandrogen therapy. Also, prostate cancer progression results in a more heterogeneous disease with variable PSA expression giving falsely high or low PSA level (34).

What are the in-use PSA derivatives?

Numerous modifications on PSA test have been introduced with a view to improvise test reliability. These include:

• Volume – based PSA measurements. This category includes PSA Density-PSAD (PSA divided by prostate volume), complexed PSAD (complexed PSA divided by prostate volume), and PSA transition zone density (PSA divided by transition zone volume). In all above, volume measurements are ultrasound-based. Three studies illustrated a relationship between PSAD and prostate cancer,(35, 36) two of them suggested the use of PSAD of ≥0.15 as a cut-off point to perform prostate biopsies in patients with PSA levels between 4 and 10 ng/ml and non-suspicious DRE (36, 37). Among all volume – based PSA tests, PSA transition zone volume carries the highest overall sensitivity and specificity for prostate cancer detection in patient with PSA levels between 4 to 10 ng/ml (38).

• Prostate-Specific Antigen Velocity (PSAV). The rate of PSA change is linked to the risk of prostate cancer (39) as in prostate cancer, PSA rises quicker than those without the disease (28). Nevertheless, conflicting results from different studies regarding the relevance of PSAV in diagnosis of prostate cancer are noticed (9) and a recent meta analysis claimed no prognostic benefit of PSAV prior to prostate cancer treatment compared to PSA alone (39).

• Free versus complexed Prostate-Specific Antigen (fPSA vs cPSA). PSA is generally measured in two forms; free and complexed-bound to protein. It is established that patients with prostate cancer have higher complexed and lower free PSA levels (40) and, therefore, the measurement of the percentage of fPSA (%fPSA) has superior diagnostic value over total PSA alone (41), especially when total PSA levels are between 4 and 10 ng/ml detecting 95% of cancers and avoiding 20% of negative prostate biopsies (42). This information can be implemented to

advise patients with PSA levels between 4 and 10 ng/ml on their risk of having prostate cancer. cPSA, on the other hand, has been studied and shown to have higher specificity compared to total PSA and comparable specificity to %fPSA in diagnosis of prostate cancer (43).

• PSA Isoforms. PSA precursor (proPSA or pPSA) is analysed to identify its significance in detection of prostate cancer. ProPSA has been linked to prostate cancer (44) and many studies illustrated the benefit of proPSA in diagnosis of prostate cancer in patients with PSA levels between 2 and 4 ng/ml(45) and between 4 and 10 ng/ml (46).

• Human kallikrein 2 (hK2). hk2 is a closely related protease in the kallikrein gene family. It has been shown that hk2 could predict cancer grade and volume and, hence, it can potentially be used in prostate cancer monitoring (47). The limitations of PSA discussed earlier clearly determine the necessity for new more sensitive and specific 'ideal' tumour markers for prostate cancer diagnosis and monitoring and, therefore, a number of novel biomarkers are currently being tested for these purposes (Table 1).
• Alpha-methylacyl-CoA racemase (AMACR). AMACR, an enzyme involved in fat metabolism, is heavily expressed in prostate cancer. Detection of AMACR in prostate biopsy samples showed sensitivity and specificity for prostate cancer of 97% and 100%, respectively (48) and, in a recent quantitative study, polymerase chain reaction (PCR) was implemented to detect urinary AMACR in a total of 92 patients revealing lower sensitivity (70%) and specificity (71%) for prostate cancer but, surprisingly, urinary AMACR PCR test was significantly superior to traditional serum PSA test (49).

• Early prostate cancer antigen (EPCA). EPCA are proteins that are almost exclusively present in prostate cancer(50) and promising tumour marker for prostate cancer detection with a reported sensitivity and specificity of 84% and 85%, respectively (51). In another study, serum EPCA analysis of 385 men showed as high as 94% sensitivity and 92% specificity compared to 65% specificity for serum PSA test (52).

• Circulating tumour cells (CTC). These are tumour cells accessing the main circulation and carrying prognostic significance, mainly in castrate-resistant prostate cancer (53, 54). Currently, CTC role in monitoring and predicting survival in prostate cancer is being investigated as an exploratory endpoint in CYP17 enzyme inhibitor trial (55).

• Prostate cancer gene 3 (PCA3). PCA3 is a segment of mRNA on chromosome 9 which can be overexpressed in prostate cancer. The role of Urinary PCA3 in diagnosis of prostate cancer is compared to PSA in 122 men demonstrating a sensitivity of 69% for both but superior specificity for PCA3 (79%) compared to PSA (60%) alone (56). A year after, a comparative multi-centric study of 586 men revealed improved specificity for PCA3 test in detection of prostate cancer (57).

• Insulin-like growth factors high affinity binding protein – 2 (IGFBP2). A recently published study using data from Prostate Cancer Prevention Trial (PCPT) revealed 50% increased risk of prostate cancer in the presence of higher serum IGFBP2 levels (58). Further clarification before justifying the role of IGFBP2 in prostate cancer is needed.

CONCLUSIONS

• Prostate cancer is a common disease and the application of PSA as a diagnostic tool revolutionised tumour detection and management.

• Although not disease-specific, the use of serum PSA in combination of DRE is still the widely accepted primary tool in the diagnosis of prostate cancer. The role of PSA in prostate cancer monitoring is less prominent in advanced or metastatic than early stage disease.

• Despite improved sensitivity, the application of various PSA derivatives risks impairing specificity for prostate cancer detection and, therefore, numerous novel biomarkers for prostate cancer are identified with promising results however their exact role in prostate cancer diagnosis, monitoring and prognosis is still debatable and require further investigation.

• Future research should be directed to identify an ideal and single biomarker that is capable of definitely distinguishing between 'clinically – significant' and insignificant prostate cancer.

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