Biochimica et Biophysica Acta 1846 (2014) 99–112

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbacan

Review

Prostate-specific antigen and other serum and urine markers in prostate cancer

Carsten Stephan [a,b,*], Bernhard Ralla [a], Klaus Jung [a,b]

[a] Department of Urology, Charité – Universitätsmedizin Berlin, Berlin, Germany
[b] Berlin Institute for Urologic Research, Berlin, Germany

ARTICLE INFO

Article history:
Received 15 December 2013
Received in revised form 24 March 2014
Accepted 1 April 2014
Available online 13 April 2014

Keywords:
PSA
Prostate cancer
Prostate health index
PCA3
TMPRSS2
Biomarkers

ABSTRACT

Prostate-specific antigen (PSA) is one of the most widely used tumor markers, and strongly correlates with the risk of harboring from prostate cancer (PCa). This risk is visible already several years in advance but PSA has severe limitations for PCa detection with its low specificity and low negative predictive value. There is an urgent need for new biomarkers especially to detect clinically significant and aggressive PCa. From all PSA-based markers, the FDA-approved Prostate Health Index (phi) shows improved specificity over percent free and total PSA. Other serum kallikreins or sarcosine in serum or urine show more diverging data. In urine, the FDA-approved prostate cancer gene 3 (PCA3) has also proven its utility in the detection and management of early PCa. However, some aspects on its correlation with aggressiveness and the low sensitivity at very high values have to be re-examined. The detection of a fusion of the androgen regulated TMPRSS2 gene with the ERG oncogene (from the ETS family), which acts as transcription factor gene, in tissue of ~50% of all PCa patients was one milestone in PCa research. When combining the urinary assays for TMPRSS2:ERG and PCA3, an improved accuracy for PCa detection is visible. PCA3 and phi as the best available PCa biomarkers show an equal performance in direct comparisons.

Contents

Abbreviations: %fPSA, ratio of fPSA to tPSA (in percent) also known as f/tPSA ratio or percent free PSA; %[−2]proPSA, percentage of [-2]proPSA to fPSA; A2M, alpha2-macroglobulin; ACT, alpha-1-antichymotrypsin; ANN, artificial neural network; API, alpha1-protease inhibitor; AUC, area under the receiver-operating characteristic curve; BPH, benign prostate hyperplasia; bPSA, "benign"PSA a clipped subform of free PSA; cPSA, sum of the complexed PSA with ACT and API; DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; fPSA: free, unbound PSA to other proteins; iPSA, "intact" or unclipped free PSA form; KLK1, pancreatic/renal kallikrein; KLK2, human glandular kallikrein 2; KLK3, identical with PSA; KLK4 to KLK15, all other kallikreins 4 to 15; LR, logistic regression; MIC-1, macrophage inhibitory cytokine 1; MIF, cytokine macrophage migration inhibitory factor; OR, odds ratio; PCa, prostate cancer; PCA3 prostate cancer gene 3, noncoding messenger RNA; phi, prostate health index; proPSA, a free PSA subform containing a seven amino acid N-terminal pro-leader peptide in its native form that is termed [−7]proPSA which is rapidly truncated by proteolytic cleavage to other proPSA subforms [−4]proPSA, [−5]proPSA or [−2]proPSA; PSA: prostate-specific antigen, a widely used serum marker for prostate cancer management; PSA-A2M, PSA complexed with A2M; PSA-ACT, PSA bound to ACT; PSA-API, PSA bound to alpha1-protease inhibitor; ROC, receiver-operating characteristic; tPSA, total PSA; TMPRSS2, androgen regulated gene that is fused with the ERG transcription factor gene

* Corresponding author at: Department of Urology, Charité – Universitätsmedizin Berlin, CCM, Charitéplatz 1, D-10117 Berlin, Germany. Tel.: +49 30 450 515052; fax: +49 30 450 515904.
E-mail address: carsten.stephan@charite.de (C. Stephan).

http://dx.doi.org/10.1016/j.bbcan.2014.04.001
0304-419X/

1. PSA and prostate cancer

1.1. Prostate cancer incidence and mortality

The increasing use of serum prostate-specific antigen (PSA) within the last 25 years lifted prostate cancer (PCa) to the most frequent neoplasia in men in the Western world [1,2]. In Europe, an incidence of 416 700 new cases and a mortality of 92 200 cancer deaths per year was reported for 2012 [3]. There have been an estimated 233 000 new cases and 29 480 cancer deaths in the USA for 2014 [1]. Worldwide approximately 900 000 new cases and 258 000 PCa related deaths have been reported for 2008 [4]. For the year 2030, an incidence of 1.7 million PCa and an annual mortality rate of 0.5 million men have been proposed [4].

1.2. Biology of PSA and its correlation with PCa

PSA is one of the most widely used biomarkers. The serine protease PSA was detected in serum in 1980 [5]. Since then it has revolutionized the management of PCa [6]. Biologically, PSA is responsible for semen liquefaction and secreted into the seminal plasma [7]. Usually, the retrograde release of PSA into the bloodstream is a rare event in healthy men. It occurs with a frequency of less than one PSA molecule per million secreted PSA molecules, leading to a concentration of <4 ng/ml in serum, which is a million-fold lower than the PSA concentration in seminal plasma (0.5–5 mg/ml). Only a destruction of the basement membrane of prostate epithelial cells may result in excessive escape of PSA into the blood circulation [8].

However, besides PCa, also benign prostate diseases, as well as physical trauma of the prostate can result in significant increases of serum PSA. Thus, elevated serum PSA levels only indicate pathologies of the prostate gland, including PCa, but PSA is not cancer-specific. In the USA, almost 55% of all men aged 40 years or older were estimated to have a PSA test during the preceding 2 years [9]. There is a strong correlation between the serum PSA concentration and the risk of PCa [10–12]. In 2950 American men undergoing prostate biopsy and showing PSA values <4 ng/ml and a 7 year follow-up the prevalence of PCa increased from 6.6% among men with a PSA of 0–0.5 ng/ml to 10.1% and 17% for PSA values of 0.6–1.0 and 1.1–2 ng/ml and finally to 23.9% and 26.9% among those with PSA values of 2.1–3 and 3.1–4 ng/ml [11]. In the way of this landmark trial, clinicians began to consider PSA as a continuum, with increasing levels reflecting greater risk. The concept of a low PSA limit where below PCa could not be detected was largely abandoned. Further large studies show similar results. In 5855 screened Swedish men, the PCa detection rates during a 7.6 year follow-up were for the following PSA ranges: 0–0.49 ng/ml, 0% (0 from 958); 0.5–0.99 ng/ml, 0.9% (17/1992); 1–1.49 ng/ml, 4.7% (54/1138); 1.5–1.99 ng/ml, 12.3% (70/571); 2–2.49 ng/ml, 21.4% (67/313); 2.5–2.99 ng/ml, 25.2% (56/222); 3–3.99 ng/ml, 33.3% (89/267); 4–6.99 ng/ml, 38.9% (103/265); 7–9.99 ng/ml, 50% (30/60); >10 ng/ml, 76.8% (53/69) [10]. However, regular biopsy was only offered at PSA levels >3 ng/ml [10]. Noteworthy, within 3 years there was no single case of a detected PCa in those men with an initial PSA level of <1 ng/ml [10]. Comparable PCa detection rates were obtained from 10 523 screened Dutch men [12], where biopsy was performed at PSA concentrations >4 ng/ml or if digital rectal examination (DRE) and/or transrectal ultrasound were suspicious for cancer. Here, the PCa detection rates for the respective PSA ranges were as follows: PSA 0–0.9 ng/ml, 0.2% (9/3858); 1–1.9 ng/ml, 1.3% (43/3305); 2–2.9 ng/ml, 2.2% (29/1314); 3–3.9 ng/ml, 6.3% (46/734); 4–9.9 ng/ml, 21.7% (238/1095) and >10 ng/ml, 52.1% with 113 PCa from 217 screened men [12]. Another study in 26 111 screened men with 2122 detected PCa had increasing PCa detection rates as follows: PSA 0–1 ng/ml, 1%, PSA 1.1–2.5 ng/ml: 8%; PSA 2.6–4 ng/ml: 20%; PSA 4.1–10: 31% and PSA >10 ng/ml: 56% [13]. Furthermore, in those 1356 men who underwent radical prostatectomy, the organ confined tumors decreased in the 5 PSA-ranges from 82% and 78% over 77% to 67% and 44% showing also a relationship between PSA and aggressiveness and tumor stage [13]. Those large studies clearly prove the relationship between increasing PSA values and an increasing risk of harboring a PCa, as reviewed [14–16]. There is strong evidence that PSA can be used to predict the PCa risk many years in advance [14].

Another important point is the risk of metastatic PCa and its relationship with PSA measurement. Data from 76 813 men from 4 centers of the European Randomized Study of Screening for Prostate Cancer (ERSPC) were evaluated for the presence of metastatic disease by imaging or by PSA values >100 ng/ml at diagnosis or during 12 years of follow-up. Overall, 666 men with metastatic PCa were detected, 256 in the screening arm and 410 in the control arm. The cumulative incidence of metastatic PCa was significantly reduced with PSA screening ($p < 0.001$) and the relative reduction was 30% ($p = 0.001$) in the intention-to-screen analysis or already 42% ($p = 0.0001$) for those men who were actually screened [17].

Furthermore, recent long-term follow-up data for 25–30 years show that also the risk to die from metastatic PCa with 44% is strongly increased for men aged 45 to 55 years when their PSA is within the 10th percentile (≥1.6 or ≥2.4 ng/ml) [18]. Those men with PSA values below the respective medians (<0.68 or <0.85 ng/ml) only have a risk to die of metastatic PCa of lower than 0.3% [18].

So far, it seems unlikely that PSA can be replaced as first line screening parameter within the next years. PSA is also the key parameter for prediction [17], staging and monitoring of PCa [15]. PSA improves treatment selection and patient care, and predicts the risk of complications and disease recurrence [14].

1.3. PSA limitations

However, for PCa detection but not for monitoring or prediction, PSA has incisive limitations. As already mentioned, benign prostate diseases such as benign prostate hyperplasia (BPH) or prostatitis as well as manipulations (bicycling, digital rectal examination, catheterization) of the prostate can also cause elevated PSA serum concentrations [6,19]. This leads to a low specificity and low positive predictive value if a single PSA measurement is used to predict PCa, especially in the