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Conventional and Promising Biomarkers for Prostate Cancer their Clinical Implication and Prospective Role

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Abstract

Prostate cancer (PCa) is one of the most common cancer in men and most common causes of male cancer-related deaths. Over many years, biomarkers have been extensively studied for screening, diagnosis, prediction of (PCa) behavior and outcome and for assigning the patients during treatments. Molecular biomarkers could also help scientists to attain better understanding for the molecular basis of the disease and prediction of the patient response to therapies. Early detection of PCa was made possible about 30 years ago by the introduction of prostate specific antigen (PSA) in the clinical practice. However, PCa screening remains controversial, because of the risk of over diagnosis and/or over treatment and the inability to detect a significant proportion of advanced tumors. Several novel biomarkers have shown promises in preliminary studies. This review will focus on traditional biomarkers approved by FDA as PSA, PSA isoforms, Prostate health index (phi) and prostate cancer antigen 3 (PCA3), also novel and promising PCa biomarkers as Prostate stem cell antigen (PSCA) and Urokinase plasminogen activator (uPA), emphasizing on their molecular and biochemical basis, clinical implication and prospective role.

Keywords: Prostate cancer; Genetic susceptibility; Biomarkers

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men, with 1.1 million new cases estimated to have occurred in 2012 worldwide [1]. Incidence rates vary by more than 25-fold worldwide [2,3]. Most of the variations reflect differences in the use of prostate-specific antigen (PSA) testing [4]. (PCa) is the fifth leading cause of cancer death worldwide, with the highest mortality rates found in the Caribbean and Southern and Middle Africa. The reason for the high prostate cancer risk among some populations of African descent is still poorly understood, although it may in part reflect differences in genetic susceptibility [5]. During the 1930s, Gutmans' and his colleagues discovered increased acid phosphatase activity in the serum of 11/15 men with metastatic PCa, and only in 1/88 men with other non-cancerous conditions [6]. Few years later Huggins showed that castration in men with advanced PCa resulted in clinical relief, which was accompanied by a decline in serum acid phosphatase [7] Thus, acid phosphatase fulfilled the definition of biomarker more than 80 years ago and became the first PCa biomarker known.

PCa Biomarkers

Biomarkers may be defined in several ways. A simple definition proposed by the US Food and Drugs Administration (FDA) is 'Any measurable diagnostic indicator that is used to assess the risk or presence of disease'. However according to the US National Institutes of Health (NIH) a more comprehensive definition of a biomarker has been suggested as - 'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to therapeutic intervention' [8].

Cancer biomarkers are produced either by the tumor cells or by the body in response to the tumor. In this review we will focus on the following categories of clinical utility and uses of PCa biomarkers (illustrated in Table 1), however some biomarkers could be used for more than one of the following categories and tools: a)Screening/Early detection : the biomarker is used for evaluating patients with either risk factors or suggestive symptoms of PCa. b) Diagnostic: this biomarker can help classical histopathological characteristics in assessing, staging or confirming PCa. c) Prognostic: this biomarker is used to predict the overall outcome of a patient, regardless of therapy, regards to risk of recurrence, relapse or progression. d) Predictive: this biomarker is used to predict or monitor the effectiveness of the treatment, beside this biomarkers may identify subpopulations of patients who are most likely to respond to a given therapy. A predictive biomarker can be a

Phases	Type of studies	Outcome
Phase I	**Preclinical exploration**	Promising directions are explored and potential biomarkers identified
Phase II	**Clinical assay and validation**	Determination of the potential capacity of the biomarker to established disease
Phase III	**Retrospective longitudinal**	Determine how well biomarkers detect pre-clinical disease through retrospectively testing
Phase IV	**Prospective screening**	Identify the characteristics of the disease detected by the biomarker and determine the false positive rate
Phase V	**Cancer control**	Quantification of the role of the biomarkers in the reduction of disease burden through Phase 5 population screening

Table 1: Structured phased -model for development evaluation, and validation of biomarkers modified from Pepe et al., and Paradiso et al. [11,13].

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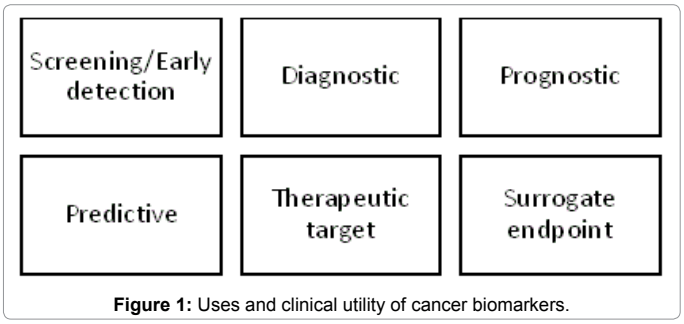

Figure 1: Uses and clinical utility of cancer biomarkers.

target for therapy. e) Therapeutic target: this biomarker can potentially identify the molecular targets of novel therapies therefore identify the patients who will benefit from such particular therapeutic regimen. f) Surrogate endpoint: this biomarker is used to substitute for a clinical endpoint and/or to measure clinical benefit, harm or lack of benefit or harm (Figure 1) [9]. Ideal biomarker must be strictly able to differentiate between cancerous tissue from benign tissue, aggressive tumors from insignificant one; it should be of high specificity and sensitivity. Furthermore, it should be a non-invasive test and inexpensive [10]. Structured phased -model for development evaluation, and validation of biomarkers has been proposed by Pepe et al. [11], and has been adopted and modified by others [12,13]. This model was comparable with that commonly used in drug development; phase 1 preclinical exploratory studies, phase 2 clinical assay and validation, phase 3 retrospective longitudinal repository studies, phase 4 prospective screening studies and phase 5 cancer control studies, as shown in Table 1. Only PSA has been categorized as phase 4, prospective screening trials [11].

PSA and PSA kinetics

PSA is a glycoprotein, encoded by the KLK3 gene, which belongs to the family of human kallikerin proteins and is a neutral serine protease, it has several isoforms [14]. PSA testing was first approved by the U.S. Food and Drug Administration (FDA) in 1986. It was indicated firstly as prognostic marker for PCa, its value in that manner has never been challenged. PSA test revolutionized the PCa screening and diagnosis landscape, the introduction of PSA as a screening test has led to a sharp increase in the incidence of PCa because there has been a shift to diagnosis at earlier stages, consequently reducing mortality from PCa [15]. PSA is one of the few molecular markers routinely used for detection, risk stratification, and monitoring clinical response to treatments [16]. Although PSA is organ specific, it not cancer-specific, some non-malignant diseases can cause rise in PSA levels, e.g. benign prostatic hyperplasia (BPH) and prostatitis. In men with serum level of PSA between 4-10 ng/ml (the so-called gray zone) it is very difficult to discriminate between patients with PCa and those with BPH or others suffering from prostatitis or even as a result of prostate manipulation, which can also increase PSA levels [17]. In spite of low specificity, PSA is still, in combination with a digital rectal examination (DRE) the most commonly used diagnostic method for PCa. [18]. For many years, widespread use of PSA has led to an increase in diagnostic prostate biopsies, some of these screen-detected tumors might not have become clinically significant during lifetime with over diagnosis of those patients, some times over treatment and bringing psychological burden to the patient [19]. Even though, PCa screening based on PSA levels still a matter of contraverse, it will be extensively studied because of many of its characteristics [20]. Another tool concerning PSA kinetics has been investigated in order to improve its diagnostic accuracy or to be used as prognostic marker during follow up as PSA density, velocity and doubling time. Vickers and his colleagues has reported that PSA velocity and PSA doubling time are correlated with PCa diagnosis at biopsy, however, they found little evidence that both provide additional value to absolute total PSA level alone [21]. However PSA doubling time has been deducted to be of high sensitivity for prediction of recurrence after radical prostatectomy and radiotherapy [22].

PSA Derivatives, Isoforms and Prostate Health Index (phi)

PSA exists in two forms: free (fPSA) and bound or complexed. About 75% of serum PSA is bound to alfa-1-antichymotrypsin, 1–2% forms a complex with alfa-1-proteinase inhibitor and 5–10% occurs in complex with alfa-2-macroglobulin. The FDA has approved the use of percent fPSA testing (%fPSA) [i.e., (fPSA/tPSA) × 100] as an adjunct to tPSA in men with a tserum tPSA concentration between 4 and 10 ng/mL which could improve the diagnostic accuracy of the PSA test alone [23]. (%fPSA) tends to increase in BPH compared with PCa [24], and low %fPSA is associated with more aggressive PCa [25].

PSA have 3 distinct cleavage isoforms: pro-PSA, BPH associated PSA (BPSA), and intact free PSA [26]. PSA is synthesized from the inactive pro-PSA form which is activated through removal of a short peptide by human glandular kallikrein 2. Truncated forms of pro-PSA [−2] (proPSA) is pro form with remaining un-cleaved amino acids. Cancerous prostate cells contain higher levels of [−2] (proPSA) [26]. Moreover, [−2] (proPSA) reported to be of the highest specificity for PCa screening and was the most efficient predictor of PCa aggressiveness [27].

Numerous studies demonstrated significant improvement in PCa detection using a PSA isoform [−2] (proPSA) and its percentage derivative %proPSA [proPSA/ (fPSA X 1000) X100], especially with multivariate regression analysis [28,29]. Recently further improvement in PCa diagnosis was developed by the formula of prostate health index (Phi), that combines three forms of PSA ie: tPSA, fPSA and [−2] (proPSA) (Phi = [-2]proPSA/free PSA) × √PSA), Phi is a single score that can be used as an aid in clinical decision-making [30], in screening [31] and in prediction of aggressive PCa [32]. Eventually %p2PSA (based on 2 markers) and even more Phi (based on 3 markers) demonstrated better diagnostic performance than tPSA and %fPSA for PCa detection as was indicated by better specificities at high sensitivities, results that indicate a potential reduction of unnecessary biopsies. Additionally, correlations between %p2PSA or Phi with Gleason score suggested that these biomarkers may more accurately detect aggressive PCa [31,33]. Two biomarkers have been approved recently by the FDA. These include proPSA as part of the Phi and Prostae cancer antigen 3 (PCA3) [34].

PCA3 as Urine Biomarker

PCA3 was first described as the Differential Display clone 3 (DD3) gene in 1999 [35], it is noncoding messenger RNA (mRNA) ; overexpressed in 95% of prostate cancers with a median 66-fold upregulation and no expression in cell lines of non-prostatic cancers and benign non-prostate tissue [35,36]. It is a prostate-specific and highly over expressed in primary PCa specimens and PCa metastases therefore it has been proposed as a promising diagnostic tool for PCa in urine [36] and in tissue [37]. Urinary assay, transcription-mediated amplification (TMA) method (PCA3, Gen-Probe Incorporated) for PCA3 assessment was developed in the last decade by Groskopf et al. [38], it measures both PCA3 mRNA and PSA mRNA in first-

catch urine samples collected after DRE (three strokes per lobe) This method of urine collection provides higher informative rates compared to samples obtained without performing a DRE [39]. As prostate is anatomically in direct relation to the urethra, so just after performance of pressure within the prostate by DRE there will be shed and release of prostate cells within the prostate duct system into the urinary tract and thus into the urine. Quantitative PCA3 score is calculated as a ratio between PCA3 and PSA mRNA ([PCA3 mRNA / PSA mRNA] × 1000). PSA mRNA concentrations are used in this calculation to normalize for the quantity of PSA mRNA, since KLK3, the gene encoding for PSA, is not up-regulated in PCa [38].

PCA3 urine assay has promising role in improving the accuracy of PCa detection in the PSA gray zone [40,41]. It was postulated that PCA3 score may be a novel molecular marker for classification of patients diagnosed with PCa due to the significant PCA3 score association with tumor volume and Gleason score in prostatectomy specimens [42]. Furthermore, PCA3 could improve the specificity to diagnose PCa and prevent many unnecessary prostate biopsies [43]. As a prognostic marker, the quantitative urinary PCA3 score was reported to be directly related to the probability of positive biopsy [44]. The results were promising, however the diagnostic value needs to be further validated in a multicenter setting and followed closely to show if indeed the PCA3 urine test is able to "predict" the presence of PCa.

uPA and uPA Receptors as Prognostic Biomarkers

The Uokinase plasminogen activation system is involved in the process of extracellular matrix degradation, thereby represents a potential target for PCa biomarkers through its involvement in various phases of tumor development, progression and metastases. uPA is an inactive precursor of serine protease, is secreted as a zymogen (pro-uPA), and activation of pro-uPA is accelerated by its binding to its specific soluble cell-surface uPA receptor (uPAR), promoting the transformation of plasminogen into plasmin [45]. Plasmin subsequently activates a cascade of proteases involved in wide degradation process of various forms of extracellular matrix proteins because of its broad spectrum of substrate specificities. In addition to the proteolytic degradation activity of uPA, the binding of uPA to uPAR also results in signaling cascade of events leading to cell migration, tissue remodeling, atherogenesis, angiogenesis [46] and cell proliferation [45]. Increased serum levels of different forms of uPAR have been associated with distant metastases and poor prognosis in various cancers [47,48]. Multiple studies reported that higher plasma or serum levels of uPA correlate with the tumor progression, suggesting uPA as a poor prognostic marker in PCa [49-51]. uPA and uPAR expression are up regulated in aggressive PCa cells and in stromal cells surrounding the tumor so they correlate with the metastatic potential of prostate cancer cells [52]. Overexpression of both uPA and its inhibitor (PAI-1), in PCa specimen after radical prostatectomy in men with PCa, was associated with aggressive PCa and recurrence [53]. Steuber et al. demonstrated that uPAR were significant predictors of PCa biopsy specimens of patients with an elevated PSA and serum levels of soluble uPAR and fPSA before prostate biopsy improved the regression model accuracy for prediction of PCa [54]. Numerous studies reported the potential prognostic value of uPA and uPAR, moreover levels of uPA and uPAR have been associated with advancing stage of PCa and bone metastases [47,55,56]. Meanwhile preoperative plasma uPA was a strong predictor of biochemical recurrence and associated with aggressive recurrence and distant metastasis with fast PSA doubling time [53]. However, Milanese and his colleagues found no significant prediction of uPAR for PCa, so far uPAR was helpful in predicting the presence of poor pathologic characteristics [57].

Prostate Stem Cell Antigen (PSCA)

Reiter and his colleges reported the identification of a predominantly cell surface antigen; PSCA. It has been identified at first through an analysis of genes up regulated in the LAPC-4 prostate xenograft model of human PCa [58]. It is located on chromosome 8q24.2 and PSCA encodes a 123 amino acid glycoprotein, a glycosyl phosphatidylinositol- anchored cell surface protein related to the Ly-6/Thy-1 family of cell surface antigens, that bears 30% homology to stem cell antigen type 2 (SCA-2). This homology PSCA was a misnomer since it is neither a marker for a stem cell nor an exclusive protein of prostate cells [59]. The possible mechanism of PSCA overexpression in PCa may be gene amplification, as PSCA is located on chromosome 8q24.2 [58] which is often amplified in metastatic and recurrent PCa and considered to indicate a poor prognosis [60]. Furthermore, PSCA is in close proximity to the c-myc oncogene, which is usually amplified in recurrent and metastatic PCa [61].

Within the prostate, PSCA is expressed in basal and secretory epithelial cells as well as neuroendocrine cells [62]. Immunohistochemical studies of PCSA showed that, It was not only detected in more than 80% of primary PCa tissues but also in metastatic lesions [62,63]. Additional reports have demonstrated a significant relationship between PSCA expression and seminal vesicle and capsular invasion [64], Other researchers reported that increased PSCA expression in PCa were significantly associated with higher Gleason score, advanced stage, extra-prostatic extension, distant metastases and increased risk of biochemical recurrence or progression to androgen-independent disease [62,64,65]. Follow up of patients with advanced PCa noted that patients who expressed PSCA had worse disease-free survival than negative PSCA' PCa patients [66,67].

Reverse transcription polymerase chain reaction (RT-PCR) analysis for PSCA revealed recently that greater levels of PSCA mRNA was correlated with metastatic PCa [63,68] Furthermore, PSCA has been considered to be an indicator of poor prognosis [58,69]. All these characteristics make PSCA a potentially useful predictor for high-risk and metastatic PCa and suggesting that PSCA may be promising for the molecular staging of PCa [70].

Recently, In a study published this year, PSCA was found to be an important biomarker for predicting BPH patients who are at high risk for PCa development [71].

Conclusion

Introduction of PSA in clinical practice and its approval by FDA as a screening biomarker has resulted in revolution in early detection, diagnosis and reduced mortality from PCa, however there was consequently overdiagnosis of prostate biopsies with increase in insignificant PCa incidence worldwide, resulting in potential overtreatment but sometimes inability to detect a significant proportion of PCa cases. Lately great effort and numerous studies have been introduced to improve diagnosis, monitoring, assessment of therapeutic response and to guide molecular targeted therapy of PCa patients. An integrated approach with measurement of different isoforms of PSA, kinetic tools of PSA and calculation ratios or scores as phi in combination with new genetic and urine biomarkers hold the promise of improving screening for and diagnosis of PCa. Urine can serve as an ideal, non-invasive tool, easy to obtain sample and to get the biochemical and molecular information about the released prostate cells in urine. PCA3 as a PCa specific and non-invasive urine biomarker

Biomarker	Biochemical characteristic	Type	Sample	Reference
PSA*	Kallikrein-related peptidase 3 Secreted serine protease	Screening/ Diagnostic	Blood	[14,72]
PSA density, Velocity, doubling time	Kinetic characterization of PSA	Diagnostic/prognostic/predictor of recurrence?	Blood	[21,22]
fPSA*, tPSA ,-2pro-PSA*	Isoforms and cleavage forms of PSA	Diagnostic with better diagnostic performance	Blood	[29,30]
Phi*	Score formula = [-2]proPSA/free PSA) × √PSA	Diagnostic	Blood	[33,34]
PCA3*	Non coding mRNA, highly up-regulated in PCa	Diagnostic (indicator for repeat biopsy)	Urine /tissue	[41,73]
uPA, uPAR	Precursor for serine protease and its receptor for degradation of extra cellular matrix	Prognostic (increased uPA and uPAR in PCa patients with bone metastasis)	Tissue/blood	[47,57]
PSCA	Membrane glycoprotein. Specific production in the prostate and possible target for therapy Prognostic	Prognostic (correlated with higher Gleason score, higher stage, and the presence of metastasis)	Tissue / blood	[62,74]

*FDA approved

Table 2: Some conventional and promising PCa biomarkers.

has obtained FDA approval to be a clinical aid tool regarding decision making regarding the repeat biopsy setting. It showed higher specificity and diagnostic accuracy for PCa outcome compared to serum PSA.

The tremendous progress that has been made in last decade within the field of molecular profiling have led to the discovery of novel, promising biomarkers as uPA, uPAR and recently PSCA which may be one of most promising biomarkers for molecular staging of prostate cancer especially after standardization of its RT-PCR methodology. However, multiple studies aiming to detect PCa specific biomarkers within peripheral blood mononuclear cells are also ongoing and some promising results in this field are to be expected, Some of the extensively studied, some of the conventional and promising PCa biomarkers are shown in Table 2. In conclusion, the gain of technical improvements in the field of molecular biology during last decades led to new breakthroughs in PCa biomarkers and although results already seem promising so far, there are still major steps to be made. Finally, it is becoming clear that panels of biomarkers, or molecular signatures are far more powerful than single or small combinations of biomarkers.

Conflict of Interest Statement

Both authors declare that they have no conflicting interests in relation to this manuscript.

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