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Review

New biomarkers for diagnosis and prognosis of localized prostate cancer

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ABSTRACT

The diagnostics and management of localized prostate cancer is complicated because of cancer heterogeneity and differentiated progression in various subgroups of patients. As a prostate cancer biomarker, FDA-approved detection assay for serum prostate specific antigen (PSA) and its derivatives are not potent enough to diagnose prostate cancer, especially high-grade disease (Gleason ≥7). To date, a collection of new biomarkers was developed. Some of these markers are superior for primary screening while others are particularly helpful for cancer risk stratification, detection of high-grade cancer, and prediction of adverse events. Two of those markers such as proPSA (a part of the Prostate Health Index (PHI)) and prostate specific antigen 3 (PCA3) (a part of the PCA3 Progensa test) were recently approved by FDA for clinical use. Other markers are not PDA-approved yet but are available from Clinical Laboratory Improvement Amendment (CLIA)-certified clinical laboratories. In this review, we characterize diagnostic performance of these markers and their diagnostic and prognostic utility for prostate cancer.

1. Introduction

Localized prostate cancer is one of the most common cancer types in men in industrialized countries, and its incidence continues to increase [1]. In most cases, prostate cancer develops slowly, although aggressive, rapidly growing forms also occur. Development of potent prostate cancer-specific biomarkers is essential for appropriate population screening, identification of high-risk patients and ensuring early diagnosis of the malignancy.

There are several types of molecular markers that could be useful for risk evaluation, diagnosis, and prognosis of prostate cancer. Predictive markers can be helpful for estimation of clinical outcomes of a treatment. Prognostic markers have a clinical value for evaluating the risk of adverse events, including death, tumor relapse, or metastases [2].

To date, prostate specific antigen (PSA) is the only biomarker approved by the US Food and Drug Administration (FDA) for prostate cancer detection and prognosis [3]. PSA is a kallikrein is a serine protease secreted by prostate epithelial cells. It is primarily involved in liquefying human sperm through a proteolytic mechanism [4]. Initially, implementation of PSA in clinical practice led to increased detection of men with early-stage prostate cancer [5]. Moreover, efforts were made to develop a prostate cancer staging method based on PSA detection and to use this marker for prognostic purposes [6].

However, PSA showed serious limitations and inconsistency as a diagnostic and prognostic marker for prostate cancer. In fact, PSA is not a cancer-specific but an organ-specific marker. This protease is produced by prostatic epithelium at low levels in normal conditions, with a dramatic increase during progression from benign prostatic hyperplasia to prostate cancer and further cancer advancing [7]. In men aged over 60 years, PSA production is increased, which reduces the sensitivity of PSA detection test for prostate cancer diagnosis [8]. In addition, elevated PSA levels can be observed in non-cancer prostate pathology such as acute prostatitis [9]. By contrast, PSA levels can be decreased in men who are treated with specific therapeutic agents with anti-androgenic effects, such as 5-α reductase inhibitors [10]. Additionally, the correlation of PSA level with prostate cancer severity is rather weak, which undermines its use for disease grading [11]. Taken together, these drawbacks reduce the clinical utility of serum PSA for prostate cancer screening and prognosis.

Therefore, the search for novel markers of prostate cancer

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continues. Newly detected markers should not only be diagnostically useful, but, ideally, should help for both prostate cancer risk assessment and disease progression monitoring. In this review, we will consider a number of novel molecular markers that could potentially improve the effectiveness of prostate cancer screening and diagnostics and be useful for cancer treatment and monitoring.

2. Assessment of the clinical value of cancer biomarkers

Development of novel cancer biomarkers requires its identification, ideally, obtaining knowledge about its role and significance in prostate carcinogenesis. Next come testing of the potential biomarker's clinical utility and its validation in patients, assessing its sensitivity, specificity, area under the receiver operator characteristic curve (AUC), predictive value (positive and negative) and other parameters [12]. There are many potential cancer biomarkers but only few of them are robust enough to show a true analytical and clinical value and to fulfill FDA selection criteria for clinical use. Moreover, FDA approval is not a guarantee of successful clinical application of a biomarker, as it was the case with PSA, which, however is still broadly used in routine screening for prostate cancer [13].

A positive validation of a potential biomarker is an essential prerequisite for its introduction into clinical practice. However, there are many obstacles that can reduce significance of a biomarker in a real-life clinical use after validation. For instance, a biomarker can be useful for prostate cancer diagnosis but fail to be a good indicator of cancer treatment or predictor of adverse cancer-induced Such biomarker would be characterized by high performance combined with a limited clinical value [14]. Therefore, implementation of a biomarker in broad clinical practice should be preceded by follow-up studies evaluating these aspects. During the recent years, new methods for theoretical estimation of potential biomarkers' clinical utility were developed. For instance, computer simulation can take into account different factors that affect the marker's efficiency in real practice. Decision curve analysis (DCA) can help predicting beneficial effects of a biomarker or diagnostic assay on clinical decisions *via* a spectrum of theoretical threshold probabilities for intervention [15].

3. Novel diagnostic biomarkers for prostate cancer

3.1. ProPSA & prostate health index

ProPSA represents the inactive precursor of PSA, which has a leader sequence of seven amino acids called (−7)proPSA. In humans, kallikreins 2 and 4 are involved in the activation of PSA through cleavage of the proleader sequence [16]. Partial cleavage of the proleader sequence results in generation of several proPSA isoforms, of which (−2)proPSA was shown to be predominant in prostate cancer samples [17]. Prostate health index (PHI) is one of the tools that allowed improving prostate cancer diagnosis. It can be calculated as a function of relationship of (−2)proPSA, free PSA and total PSA. Another PSA form is inactive since the protease is bound to a protease inhibitor such as α_1-antitrypsin, α_1-antichymotrypsin, or α_2-macroglobulin [18]. The PHI test involves measuring the three PSA forms (total PSA, free PSA, and the [−2]proPSA) in the blood serum. This formula is also helpful to discriminate between the benign prostate hyperplasia and prostate cancer in subjects with suspected cancer. The PHI score was developed by the US company Beckman Coulter Inc. (Brea, CA), validated by Catalona et al. [19], and the validity was then replicated by numerous multicenter follow-up clinical trials in various countries [20–24]. A summary of clinical validation studies for the PHI test is presented in Table 1.

In the initial study, Catalona et al. [19] showed the validity of the PHI score to identify prostate cancer with Gleason grade of 3 + 4 and higher with AUC of 0.703 in biopsies of non-prostate cancer men with total PSA of 2–10 ng/ml. In biopsies from men with total PSA of 4–10 ng/ml, similar AUC value (i.e. 0.707) were obtained by Loeb et al. [25] thereby replicating significance of the PHI score for discrimination of Gleason disease of grade 3 + 4 and greater. In this clinical study, there was AUC 0.707 to discriminate Gleason disease of grade 3 + 4 and higher. De la Calle et al. [23] obtained AUC 0.815 to detect high-grade prostate cancer (grade 3 + 4 and greater) therefore confirming results of Loeb et al. [25].

A recent meta-analysis of 24 clinical studies reported diagnostic characteristics of the PHI score as follows: pooled specificity 0.34, sensitivity 0.89, AUC 0.76 to detect prostate cancer [26]. For high-grade disease, the PHI test had pooled specificity 0.34, sensitivity 0.93, AUC 0.82. These findings showed high discrimination power of the PHI to identify aggressive prostate cancer: a recent meta-analysis reported overall specificity of 0.17 and sensitivity of 0.90 to detect Gleason disease of grade 3 + 4 and greater [27]. In patients after radical prostatectomy, PHI was found to be associated with adverse characteristics of prostate cancer [17]. Furthermore, ProPSA & PHI was recently approved by FDA as a diagnostic marker for clinical use [28].

3.2. Prostate cancer antigen 3 (PCA3)

Prostate cancer antigen 3 (PCA3) is the second FDA-approved molecular marker for detection of prostate cancer [29]. PCA3 is a prostate-specific non-coding RNA, which is highly expressed in prostate cancer cells [30]. It was found that PCA3 regulates cell survival through controlling androgen receptor (AR)-dependent signaling and expression of AR cofactors and genes involved in procarcinogenic epithelial-mesenchymal transition [31,32]. Interestingly, PCA3 expression is absent in non-cancer prostate pathologies, such as benign prostatic hyperplasia, atypical small acinar proliferation, prostatitis, and prostatic intraepithelial neoplasia [33]. These features make PCA3 promising for clinical use.

PCA3-based test developed by Progensa (Marlborough, MA, USA) represents quantitative detection of urinary PCA3 and PSA RNAs in men with increased serum PSA and initial negative prostate biopsy. The quantification is performed with help of RT-PCR that in turn allows calculating PCA3 score (the ratio of PCA3 transcripts to PSA transcripts). That score can help clinicians to decide whether or not to repeat biopsy in men aged over 50 years who has already underwent one or more biopsies [34]. A PCA3 score < 25 indicates a low risk for induction of prostate cancer, while a greater score indicates increased probability to identify prostate cancer in a biopsy [35]. In practice, many investigators use a PCA3 score threshold of 35 [36–38]. A choice of the cut-off value significantly influences specificity, sensitivity and predictive value of the PCA3 score: a cut-off at 20 was shown to significantly improve the diagnostic accuracy of this marker, while a cut-off at 35 reduced the number of needless samples recommended for the repeat biopsy [37,39,40]. A recent meta-analysis using cut-off 20 versus 35 showed global sensitivity 0.93 vs. 0.80, specificity 0.65 vs. 0.44, AUC 0.85 vs. 0.72, positive predictive value (PPV) 1.86 vs. 1.58, negative predictive value (NPV) 0.81 vs. 0.43, and diagnostic odds ratio (DOR) 5.73 vs. 3.45 [40]. Therefore, the cut-off at 20 appears to have a greater diagnostic value compared with the cut-off at 35.

For the urine PCA3 test, Cui et al. [41] summarized the results of 46 clinical studies involving a total of 12,295 patients. The diagnostic value of the PCA3 test was superior to that of the total PSA test and its derivatives such as free PSA, %free PSA, PSA velocity (reflects rate of changes in PSA levels), and free PSA/total PSA [42–44]. Combination of PCA3 with PHI improved the selection of patients for the initial biopsy with an overall diagnostic accuracy of 0.77 [43,45]. Taken together, these findings show that PCA3 has a high diagnostic performance and utility for selecting high-risk patients. Furthermore, urinary sample for PCA3 detection can be easily obtained after digital rectal examination (DRE). However, there was an observation that this test can be effective only for prediction of the first repeat biopsy, but not the following biopsies [42].