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Prostate cancer biomarkers: An update

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Abstract

Many aspects of prostate cancer diagnosis and treatment could be greatly advanced with new, effective biomarkers. Prostate-specific antigen (PSA) has multiple weaknesses as a biomarker, such as not distinguishing well between cancer and benign prostatic hyperplasia or between indolent and aggressive cancers, thus leading to overtreatment, especially unnecessary biopsies. PSA also often fails to indicate accurately which patients are responding to a given treatment. Yet PSA is the only prostate cancer biomarker routinely used by urologists. Here, we provide updated information on the most relevant of the other biomarkers currently in use or in development for prostate cancer.

Recent research shows improvement over using PSA alone by comparing total PSA (tPSA) or free PSA (fPSA) with new, related markers, such as prostate cancer antigen (PCA) 3, the individual molecular forms of PSA (proPSA, benign PSA, and intact PSA), and kallikreins other than PSA. Promising results have also been seen with the use of the fusion gene TMPRSS2:ERG and with various forms of the urokinase plasminogen activation receptor. Initially, there were high hopes for early PCA, but those data were not reproducible and thus research on early PCA has been abandoned.

Much work remains to be done before any of these biomarkers are fully validated and accepted. Currently, the only markers discussed in this paper with Food and Drug Administration-approved tests are PCA 3 and an isoform of proPSA, [-2]proPSA. Assays are in development for most of the other biomarkers described in this paper. While the biomarker validation process can be long and filled with obstacles, the rewards will be great—in terms of both patient care and costs to the health care system.

Keywords: Prostate cancer; Biomarkers; Prostate-specific antigen; Prostate cancer antigen 3

Introduction

In Europe and the United States, prostate cancer is the most common solid neoplasm and the second leading cause of deaths due to cancer in men [1,2]. The use of prostate-specific antigen (PSA) as a prostate cancer screening tool has led to a downstaging and downgrading of the disease at the time of diagnosis and a reduction in prostate cancer mortality. However, PSA-based screening is also associated with overdiagnosis and overtreatment. The fact that PSA is synthesized by all prostate epithelial cells, whether normal, hyperplastic, or cancerous, weakens the specificity of PSA as a cancer biomarker. Elevated serum PSA levels may reflect the presence of cancer or may be caused by benign prostatic hyperplasia (BPH), infection, and chronic inflammation. PSA requires interpretation within the context of the given clinical scenario. Additional variation in PSA levels is introduced by the different analytical methodologies. Consequently, despite its tremendous value in clinical practice, PSA is not the ideal biomarker for prostate cancer detection and management. For this reason, countless efforts have been made to develop prostate cancer biomarkers.

The National Institutes of Health define "biomarker" as a trait that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmaceutical response to a therapeutic intervention [3]. Cancer biomarkers are produced either by the tumor or by the body in response to the tumor. Various types of biomarkers can be used in the detection of prostate cancer depending on the clinical circumstances: early detection/screening, diagnosis, prognosis, prediction, therapeutic target, and evaluating a surrogate end point [4].

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In recent years, the medical literature has displayed a rapidly increasing interest in biomarkers. A number of biomarkers have subsequently been discovered and studied, but to date, only 1 biomarker is routinely used by urologists—PSA. This reflects the complex analytical and regulatory challenges for applying biomarkers in prostate cancer care. These challenges include the status of intellectual property protection, availability of standard reference materials for assays, complexity of assay formats, implementation of quality control to assure reproducibility and accuracy, sufficient market testing size to assess commercialization methods, lack of clear guidelines for good manufacturing/laboratory practice, lack of quality control requirements for all phases of biomarker development, and cost and effort required to accumulate clinical data under appropriately designed, prospective trials. The interval required for resolution of patent issues and assay standardization and for validation, testing, and regulatory approval is also an inhibiting factor [5].

Biomarker research is generally done within the context of standard clinical care, not clinical trials, and has largely been guided by intuition and experience rather than well-structured analyses. Thus, most biomarker findings are not reproducible. Indeed, most biomarkers that have appeared to be biomedically and statistically significant at a center are not confirmed by others [6]. In 2002, the National Cancer Institute's Early Detection Research Network developed a highly regulated process based on a 5-phase approach to systematic discovery and evaluation of biomarkers mimicking drug development, which is a highly regulated process [7].

With this rigorous framework in mind, this review describes the status of prostate cancer biomarkers currently in use or under development. A PubMed/Medline search was conducted to identify original articles from January 2000 to March 2003. The searches were limited to articles in English. The keywords included prostate cancer and biomarkers or markers. The articles with highest level of evidence or at the validation stage were selected and reviewed with the consensus of the authors of this article.

Prostate cancer antigen 3

In 1999, Bussemakers et al. [8] were the first to publish their findings regarding a new prostate cancer–related gene, DD3. Using the polymerase chain reaction (PCR) method, they saw this gene was overexpressed in prostate tumor tissue, it had low rates of expression in hyperplastic prostate tissue, and it could not be quantified in the normal tissue of many organs, including the prostate, testicles, bladder, kidney, seminal vesicles, brain, and lungs. It was named prostate cancer antigen 3 (PCA3) and corresponds to a noncoding region of the 9q21-22 chromosome, the function of which is unknown. de Kok et al. [9] confirmed Bussemakers' findings, observing that the PCA3 messenger RNA (mRNA) was expressed 6 to 34 times more in the tumor tissue than in healthy tissue.

Initial development phase for PCA3 assays

With these findings, Hessels et al. [10] applied the notion that following transrectal massage, prostate cells could be found in urine so as to quantify urinary PCA3 mRNA. As PSA is only slightly overexpressed in tumor cells in comparison with healthy cells, they introduced the concept of the PCA3 score, obtained by dividing PCA3 mRNA by PSA mRNA. The authors found that, for any given cutoff, the PCA3 score exhibited sensitivity and specificity rates of 67% and 83%, respectively, based on a study of 108 patients undergoing biopsy for serum PSA levels >3 ng/ml. Its superiority was confirmed in other studies using a new evolution of the test that compared urinary PCA3 with PSA in patients preselected for a prostate biopsy owing to elevated serum PSA levels [11].

In 2006, Groskopf et al. [12] demonstrated the greater stability of PCA3 at room temperature and redesigned the test using samples that were collected in a single test tube following prostate massage and later analyzed. Numerous trials were subsequently conducted based on this PCA3 test, with discrimination rates varying from 94% to 100% [13,14], superior to those reported for earlier versions of the test.

Clinical application of PCA3

The studies mentioned thus far were investigating the value of this marker to reduce unnecessary biopsies. Marks et al. [15] were the first to study the value of PCA3 in 226 patients who underwent a subsequent biopsy, demonstrating its superiority to PSA. Nevertheless, the mean PCA3 values did not discriminate between high-grade (Gleason score ≥ 7) or low-grade (Gleason score <7) tumors.

Therefore, 2 multicenter prospective trials (1 European and 1 US trial) were carried out in patients undergoing a first or second biopsy. Both studies reported a comparable area under the curve (AUC) (0.65 vs. 0.68). The European study observed a slightly greater predictive value in the second biopsy than in the first, which contrasted with the results of the American trial. Both studies concluded that by combining PCA3 with other established risk factors such as age, rectal examination, prostate volume, and percentage of fPSA, diagnostic accuracy was enhanced in multivariate regression models [14,16]. In line with these results, Ankerst et al. [17] revealed that incorporating PCA3 into the risk calculator of the Prostate Cancer Prevention Trial improved diagnostic accuracy compared with previously established risk factors. Chun et al. [18], in a sample of 809 patients, showed that adding PCA3 to the established risk factors improved the predictive values of the nomograms by 2% to 5%. In fact, these new nomograms have been externally validated and represent another tool in clinical decision making in urology. Using Chun's nomogram, a recent study avoided 21% of unnecessary biopsies at the expense of losing 6.8% of tumors [19]. Even further,