Future Directions in Prostate Cancer Diagnosis

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Abstract

In our aging society, the incidence of prostate cancer will continue to increase, and improvements in detection and treatment of this prevalent yet extremely treatable and curable disease are needed. Research into new molecular markers described in this chapter is especially promising. These markers will improve specificity and sensitivity of screening and will serve to supplement or supplant current prostate-specific antigen screening. Targeted biopsy utilizing new radiographic techniques such as Doppler ultrasound, magnetic resonance imaging, and magnetic resonance spectroscopy can reduce the number of needle cores and improve pathologic specimen quality. Improvements in anesthetic agents and techniques decrease discomfort and improve patient readiness to undergo prostate biopsy. As emerging research continues to elucidate the pathology of prostate cancer, diagnostic screening expands into genetic and even viral etiologies that may offer the possibility of a vaccine against prostate cancer.

Keywords: prostate cancer, screening, PSA, biopsy, ultrasound, bioimaging, biomarker

New Diagnostic Screening Tools

Complementary to the development of novel techniques in performing the procedure of prostate gland biopsy, the discovery of clinically-significant biomarkers for the early and accurate detection of prostate cancer has been the focus of research for a majority of institutions seeking to redefine current standards of care which hope to decrease worldwide mortality from prostate cancer as well as morbidity from prostate biopsy. Current data...
from recently concluded chemoprevention trials\(^1\) underscore the less-than-optimal nature of the current molecular marker of choice, serum prostate-specific antigen (PSA), for identifying men with prostate cancer. Poor specificity and positive predictive value (25%-30\%) observed for this test are further aggravated by findings from the Prostate Cancer Prevention Trial demonstrating that 15\% of men with a negative PSA test (<4 ng/mL) and normal digital rectal examination (DRE) have prostate cancer and 15\% of these undiagnosed prostate cancer cases have potentially lethal high-grade tumors.\(^2\) Although PSA is prostate disease-specific, it is not prostate cancer-specific, and for this reason, a vacuum remains for other molecular markers that may serve to supplement or supplant the serum PSA test leading not only to increased detection of clinically significant disease, but reduced number of unnecessary prostate biopsies.

Among the score of biomarkers being studied, several markers and techniques deserve attention because of the published data showing promise that better prostate cancer screening methods will be available in the near future that will maintain noninvasiveness and acceptability for both patients and urologists in clinical practice.

**uPM3/DD3**

A notable shift from the traditional blood-based human biologic specimens such as serum and plasma has characterized the noteworthy advances in prostate screening tools currently being developed around the world. A prototypical and very promising biomolecular test for prostate cancer, the uPM3 (DiagnoCure, Quebec, Canada), is conducted on urine specimens from men after they have undergone a vigorous prostate examination or an **attentive DRE.**\(^3\) This particular method of extracting a test specimen for laboratory examination takes advantage of expulsion of prostate epithelial cellular material expressed in the urine after manipulation of the prostate gland. The molecular basis for the test lies in assaying for *DD3*, a prostate cancer-specific gene that was shown to be strongly overexpressed in more than 95\% of primary prostate cancer specimens and in metastatic prostate cancer.\(^4,5\) Compared with benign prostate tissue, *DD3* was noted to be up-regulated 66-fold in malignant prostate tissue that hinted to a diagnostic potential for this non-protein coding gene.\(^6\)

In an initial study, it was found that mRNA transcripts of the *DD3* gene could be detected in cell lysates from urinary sediments of men after attentive DRE using a time-resolved florescence-based quantitative reverse transcription-polymerase chain reaction (RT-PCR) assay.\(^8\) Using measured PSA transcripts to correct for the number of prostate cells in the urinary specimen, an optimal cut-off value for this *DD3*-based RT-PCR assay garnered a specificity of 83\% and a negative predictive value of 90\%. To further refine the technique, the uPM3 test was developed utilizing a nucleic acid sequence-based amplification assay that simultaneously quantifies