Will Emerging Prostate Cancer Markers Redeem Themselves?

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During the last several decades, the incidence of prostate cancer has increased dramatically, largely because of the widespread use of prostate-specific antigen (PSA)2 for diagnostic screening. Serum PSA is undoubtedly one of the most clinically useful cancer markers. Early detection of clinically relevant cancers is possible with PSA-based screening, but the overall benefit of screening is debatable. The benefits and harms of PSA-based screening have recently been assessed in 2 randomized studies. In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial from the US, no benefit could be demonstrated for PSA screening in men between 55 and 74 years of age. In the European study, however, a 20% reduction in mortality was observed after a mean follow-up time of 8.8 years in men between 55 and 69 years of age who were screened for PSA (1). Thus, the results from screening studies are conflicting. PSA is not a cancer specific. The serum PSA concentration also reflects prostate volume, and thus it increases in benign prostatic hyperplasia and in various other benign conditions. Therefore, many men will be subjected to unnecessary repeat biopsies, causing a major amount of concern and discomfort. Another problem with PSA-based screening is the high rate of overdiagnosis, i.e., finding clinically insignificant cancers that would not surface during the patient’s remaining life. The rate of overdiagnosis has been estimated at up to 50%. Many men with such tumors will receive unnecessary treatment, with the associated harmful effects. To reduce treatment of patients who do not benefit from it, clinicians are increasingly using active surveillance. Patients judged to have a good prognosis, based on a biopsy Gleason score of ≤6, a PSA density <0.15, and no more than 2 biopsy cores with cancer, are monitored according to a strict scheme comprising PSA measurement, clinical examination, and annual repeat biopsies. Active treatment is offered if the tumor shows signs of progression. Active surveillance is underused, however, because of a lack of reliable criteria to trigger intervention (i.e., it is not possible to reliably differentiate innocuous tumors from those that need curative therapy). A promising new prostate cancer marker, PCA3 (prostate cancer antigen 3), has recently become available, and its utility for predicting short-term biopsy progression has been studied in an active surveillance program (2).

PCA3 is a noncoding mRNA encoded by the PCA3 [prostate cancer antigen 3 (non-protein coding); also called DD3] gene. PCA3 is highly prostate specific and is overproduced 66-fold on average in prostate cancer tissue, compared with benign prostate tissue. Various assays for PCA3 detection based on reverse-transcription PCR have been developed, and an automated method (3) is commercially available (Progensa®; Gen-Probe). In this assay, PCA3 and PSA mRNAs are amplified from urinary cells in the voided urine collected immediately after a standardized rectal palpation. The PSA mRNA value reflects the amount of prostatic cells, whereas the ratio of PCA3 to PSA mRNA reflects the proportion of tumor cells in the sample. This ratio is multiplied by a factor of 1000 to produce the PCA3 score. Despite the rather demanding sampling procedure, which is crucial for a reliable result, the reproducibility of the assay has been found to be good.

The probability of prostate cancer increases with an increasing PCA3 score. A score of 35 corresponds to a 30%–47% probability of cancer in a biopsy, but the optimal cutoff is a matter of discussion. With the automated probe transcription-mediated amplification method [Progensa (3)] and a PCA3 score cutoff of 35, prostate cancer was detected with a diagnostic sensitivity of 47%–58% and a diagnostic specificity of >70% for the detection of cancer in biopsy. Some studies have shown that PCA3 gives larger values for the area under the ROC curve (AUC) (0.66–0.76) than PSA (0.52–0.73). Furthermore, the PCA3 score has been reported to correlate with tumor volume, but not with prostate volume or the total PSA concentration in serum. The PCA3 score has also been associated with extracapsular extension (4). In other studies, however, the correlation between PCA3 and classic prognostic parameters has not been confirmed. The effect of α-reductase inhibitors, hormonal treatments, and other therapies on

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2 Nonstandard abbreviations: PSA, prostate-specific antigen; PCA3, prostate cancer antigen 3; AUC, area under the ROC curve; %fPSA, proportion of free PSA.
PCA3 production is not known, but repeat biopsies do not seem to affect the result.

The high cancer specificity of PCA3 and its suggested potential in assessing tumor aggressiveness have led to great expectations for the use of PCA3, both to reduce the need to perform biopsy and to aid in guiding therapy, as, for example, in stratifying patients to either surveillance or prompt treatment. These aspects were recently evaluated by Tosoian et al. (2). They studied 294 men in the Johns Hopkins surveillance program beginning in 2007 and compared PCA3 scores in men with progression in follow-up biopsy with those in men without progression. They found no difference between the 2 groups in mean PCA3 score (P = 0.13), and ROC curve analysis revealed that PCA3 was not useful for identifying men with progression in biopsy (AUC = 0.589; P = 0.076). Men with progression, however, had a significantly lower proportion of free PSA (%fPSA) (P = 0.013) compared with those without progression. The fairly short follow-up time is a potential limitation of the study, and the patients represented a subset with a favorable prognosis, as evidenced by a fairly low total PSA concentration and a high %fPSA at enrollment, combined with an excellent adherence to the surveillance program. Another study has reported more-promising results regarding the utility of PCA3 for predicting outcomes. Remzi et al. (5) found higher PCA3 scores in men with positive biopsies (median PCA3 score, 50.4) that were preceded by ≥2 negative biopsies, compared with men with subsequent negative surveillance biopsies (median PCA3 score, 28.2; P < 0.001). The investigators also concluded that an increased score combined with high-grade prostatic intraepithelial neoplasia might predict cancer at follow-up biopsy. Thus, the results regarding the benefits of PCA3 are conflicting, and the utility of PCA3 for guiding prostate cancer treatment needs further studies.

Although the validity of the use of PCA3 alone as a prognostic marker is controversial, it is worth using multivariable methods to evaluate its utility in combination with other markers. Tosoian et al. found a low %fPSA to be significantly associated with a positive biopsy (2), and other studies have shown that %fPSA predicts tumor aggressiveness and upgrading of the Gleason score in biopsy after radical prostatectomy. In an earlier study, a model based on a multivariable analysis of PCA3, total PSA, and biopsy Gleason score was found to improve the prediction of extracapsular extension (4). It would be interesting to see whether inclusion of %fPSA would further improve the prognostic value of various mathematical models.

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References


3 Other relevant references are listed in the Data Supplement that accompanies the online version of this perspective at http://www.clinchem.org/content/vol56/issue8.