Prostate Cancer and Prostate-Specific Antigen: The More We Know, the Less We Understand

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Since its discovery in 1979, prostate-specific antigen (PSA) has revolutionized the way we manage prostate cancer (1). Prior to the discovery of PSA, prostate cancer was detected either by digital rectal examination (although only one-third of cases are typically organ-confined) or when a patient presented with inanition, pain, or a pathologic fracture (2). Physicians of the pre-PSA era had no way to reliably detect the disease early. The discovery of PSA changed all of that. Results of initial studies of PSA in patients with prostate cancer suggested that PSA was best used to monitor treatment efficacy because patients whose PSA levels decreased after treatment had superior outcomes compared with those whose levels did not. Subsequent studies found that when PSA levels were used to evaluate asymptomatic individuals, those individuals had cancers that were early-stage and, after the first round of screenings, subsequent tumors were almost always organ-confined (3–5). An increase in the rate of prostate cancer detection, a shift to lower clinical stages, a decrease in the rate of metastatic disease, and a decrease in prostate cancer mortality have all been variously attributed to PSA screening (6).

In reviewing the saga of PSA from a marker of treatment outcome to a diagnostic tool, many wish that a more rigorous evaluation had been conducted ab initio. For example, the authors of the initial publication on PSA (1) suggested that it may be a useful marker for disease monitoring and diagnosis, but reflected on its lack of tumor specificity. The subsequent struggle to determine the upper-limit-of-normal (ULN) or cutoff point that separates “normal” PSA values from “abnormal” ones illustrates this problem. One initially suggested ULN was 2.6 ng/mL (7). A reasonable PSA level for the clinical diagnosis of prostate cancer was initially thought to be greater than or equal to 10.0 ng/mL (8). This level decreased to 4.0 ng/mL (9) and more recently to 3.0 ng/mL and then to 2.5 ng/mL (10,11). Each time a lower ULN is used in diagnostic testing, the types of tumors detected (i.e., tumor volume, grade, and pathologic stage) are considered biologically significant. With the use of current diagnostic methods (i.e., obtaining 10–12 biopsy core samples, sampling the peripheral zone of the prostate gland, and using ultrasound guidance), we do not know the prevalence of prostate cancer in men with PSA values in the 0–2.5 ng/mL range. We anticipate that these data will be available from the Prostate Cancer Prevention Trial, in which all men undergo an end-of-study biopsy, regardless of their PSA level (12). It will be of interest to examine the hypothesis of Stamey (13)—that the likelihood of a positive biopsy is similar at all values of PSA less than 10 ng/mL—in this cohort. This uncertainty about the ULN for PSA screening and the poor specificity of the test contribute to two current clinical challenges: 1) Only one man in four with a PSA level greater than 4.0 ng/mL is found to have prostate cancer on biopsy, and 2) about one-third of prostate cancers are detected in men with a normal PSA level.

Added now to our PSA tribulations is the observation by Cramer et al. (14) in this issue of the Journal that PSA values may be related to polymorphisms in the PSA gene promoter. The authors had previously identified a single nucleotide polymorphism (SNP) in an androgen-responsive element located in the PSA gene promoter that was variably related to PSA levels. To explore the range of possible polymorphisms that might be associated with PSA levels, the authors measured PSA values in a cohort of 518 men at risk of lung disease. After excluding all African Americans and men with a history of prostate cancer or a PSA level less than 0.1 ng/mL, the authors sequenced regions of the PSA genes of the remaining men and identified several SNPs in the 5′ upstream region. Three of the SNPs had population frequencies in the 20% range and were statistically significantly associated with increased serum PSA levels. Results of in vitro studies demonstrated that these same three variants had increased promoter activity. The authors correctly suggest that these findings should be incorporated in the definition of an individual’s normal PSA level. Nevertheless, we cannot be certain whether these polymorphisms directly affect PSA levels in men or whether they increase the risk of prostate cancer and thereby (indirectly) increase PSA levels. Clearly, the role of PSA in prostate cancer detection needs further exploration. Further confounding this issue are the high rate of undetected, microscopic disease and our inability to distinguish between prevalent prostate cancers that will lead to morbidity or death and indolent tumors that are of little biologic consequence to the patient.

The Cramer et al. study (14) is important on several levels. First, it sends a strong message that these PSA polymorphisms should be examined prospectively with respect to their impact on PSA as a predictive biomarker, perhaps in one of several ongoing large-scale prostate-related trials. If the entire breadth of the PSA screening issue is to be examined, serious consideration should be given to the conduct of a trial that examines constitutional and lifestyle factors along with potential biomarkers and links these results not with the detection of prostate...
cancer but with disease that proves to be biologically consequential. Second, although PSA has had a profound effect on the identification of prostate cancer, this study demonstrates the need to constantly refine and improve this important diagnostic tool and to explore other diagnostic modalities.

REFERENCES