Prostate-Specific Antigen Comes of Age in Diagnosis and Management of Prostate Cancer

In the 6 years since the introduction of the first commercial immunoassays for prostate-specific antigen (PSA), this unique tissue-specific antigen has become established as the most useful serological marker for monitoring patients with prostate cancer. The antigen was originally isolated from semen by three independent laboratories searching for semen-specific antigens (1–3). Later, at Roswell Park Institute, the antigen was purified from normal prostate tissue, its natural source (4). This research group pioneered the use of PSA as a tumor marker to monitor patients with prostate cancer (5).

Subsequent experience has shown that PSA is considerably more useful than prostatic acid phosphatase to monitor prostate cancer (6, 7). Serum concentrations of PSA correlate strongly with the volume and clinical stage of prostate cancer. After radical prostatectomy for localized cancer (stages A and B), serum PSA falls to amounts that are undetectable by the current generation of immunoassays for PSA (7). Serially increasing concentrations of PSA above the limits of detection of current tests appear to be the earliest sign of residual cancer (7–11). Many physicians no longer use prostatic acid phosphatase to routinely monitor their cancer patients, although rare cases of patients with metastatic prostate cancer and normal PSA concentrations have been published (12).

More recently, PSA has been recommended as an important adjunct to a careful digital rectal examination to screen men over age 50 years for prostate cancer (13–15). In these studies, approximately one-third of the men (range 30–35%) with increased PSA values (>4 μg/L by Tandem-R PSA) had prostate cancer on rectal biopsy. In contrast, in patients with abnormal prostates by rectal examination and positive biopsies for prostate cancer, between 17% and 23% had PSA values in the normal range (<4 μg/L) (13–15). Because of this overlap, PSA should never be used as the sole screening test for cancer. Other common prostate conditions such as benign prostatic hypertrophy (BPH) and prostatitis can produce increases in serum PSA similar to those seen in cancer patients. In patients with increased PSA concentrations on screening, only a careful digital rectal examination coupled with a rectal ultrasound evaluation, with systematic as well as directed biopsy of suspicious hypoechoic areas, can distinguish BPH from cancer (16).

A recent retrospective serological study showed that the rate of increase in PSA in serial determinations was useful for distinguishing early prostate cancer from BPH (17). Patients with prostate cancer showed a more rapid increase in their PSA (>0.75 μg/L per year) than did patients with BPH, at a specificity of 90%. These serological changes occurred ~5 years before clinical diagnosis. That study greatly strengthens the argument for periodic screening of men older than age 50 years with a digital rectal examination and a determination of serum PSA, to detect prostate cancer at a stage when it is still potentially curable (18, 19). The use of PSA as a screening test to detect early prostate cancer will substantially increase the demand for this test.

In the current issue of Clinical Chemistry, Vessella et al. (20) and DNistrian et al. (21) describe clinical testing of a second-generation test for PSA, the Abbott IMx PSA test. This test offers the advantages of an automated microprocessor-controlled analyzer, which also provides various other clinically important immunoassays, e.g., serum β-fraction of human chorionic gonadotropin, α-fetoprotein, and carcinoembryonic antigen. In addition, the IMx PSA offers the convenience of a short assay time, calibration curve storage, and an enzyme label with a fluorescent substrate, thereby avoiding radioactive reagents.

In their extensive comparative studies of samples from normal patients and patients with prostate cancer and benign prostatic hypertrophy, Vessella et al. demonstrated that the IMx PSA yielded results essentially identical to the Hybridtech Tandem-R test, a widely used immunoradiometric test for PSA licensed by the US Food and Drug Administration. In a smaller study of serum samples from patients not selected for prostate pathology, DNistrian et al. (21) similarly found that the IMx PSA values were essentially identical to Hybridtech’s immunoenzymometric assay for PSA, the Tandem-E PSA assay. This is not surprising, because the manufacturer calibrated the IMx assay against the Tandem-R PSA calibrators. From the practical point of view, laboratories assaying many PSA samples may find the 23-tube limit per run (plus one calibrator) of the IMx PSA inconvenient, particularly in view of the projected large volume of PSA testing that will be required if PSA is widely accepted as a cancer screening test in the coming years. Nonetheless, as an automated PSA immunoassay that yields PSA values highly comparable with those of the Tandem-R and Tandem-E PSA tests, the IMx PSA is likely to find widespread acceptance in clinical laboratories.

Vessella et al. (20) make an additional claim for the IMx PSA that is less well documented, i.e., that it has a significantly lower biological detection limit than the Tandem-R test and therefore can detect residual cancer.
at an earlier stage after radical prostatectomy. In contrast, the Dnistran group found that the IMx PSA and the Tandem-E PSA tests had similar lower limits of detection (21). The concept of the biological detection limit introduced by Vessella et al. (20) is an appealing one, because this measure of assay sensitivity takes into account both the analytical sensitivity (lower limit of detection) of an assay as well as the additional variability caused by the biological matrix (e.g., serum) in which the analyte (PSA) is found. Nevertheless, the evidence presented here is contradictory as to whether the Abbott IMx PSA offers any significant advantage in sensitivity over the Hybritech Tandem-R and Tandem-E tests.

The potential usefulness of an ultrasensitive PSA test to detect residual cancer at a very early stage after radical prostatectomy was recently reported by our Stanford research group (22). That study describes development of a dedicated well-controlled ultrasensitive PSA radioimmunoassay capable of detecting residual cancer on an average of 10 months earlier than the current generation of tests (22).1 Earlier detection of residual cancer was possible because of the observation that patients after prostatectomy with no evidence of cancer always had PSA concentrations <0.1 μg/L by this ultrasensitive test. Patients with residual cancer showed progressive increases in PSA >0.1 μg/L (22). Vessella et al. (20) confirmed these findings here. We call the PSA value of 0.1 μg/L the residual cancer detection limit1, similar to the term clinical threshold used by Vessella et al. (20).

However, the current IMx PSA test lacks the necessary calibrators and serum PSA controls to ensure reliable results in the ultrasensitive range. Vessella et al. suggest that the manufacturer provide at least two external PSA curve controls in the ultrasensitive range (i.e., PSA <0.5 μg/L). In addition, the IMx PSA should also include several PSA calibrators in the ultra-low-concentration range to qualify as an ultrasensitive test. As a rule of thumb, assays should have at least one calibrator per log10 unit interval over the working assay range. Currently, the IMx PSA has no PSA calibrators between 0.03 (the lower limit of detection of the test) and 2.0 μg/L, a concentration difference of almost 70-fold. The sole purpose of an ultrasensitive PSA assay is to diagnose residual cancer at the earliest possible stage after prostatectomy (22).1 Thus, extra quality-control samples should be included in this assay.

There is currently no proven effective adjuvant therapy for treating prostate cancer at very early stages. Care must be used, therefore, in making the diagnosis of residual cancer based solely on PSA concentrations. In postprostatectomy patients with PSA values increasing to >0.1 μg/L (the residual cancer detection limit or clinical threshold), serial PSA values should be monitored until a progressive linear increase in PSA concentrations above this value is clearly established by an ultrasensitive PSA assay.1 A single PSA >0.1 μg/L indicates a high probability of residual cancer, but does not prove that cancer is invariably present. Once a diagnosis of residual cancer has been established, the availability of well-controlled ultrasensitive PSA tests in the near future will allow experimental clinical trials to proceed to test the effectiveness of various adjuvant regimens for treating very early residual disease.1

Clinical chemists should look for the following critical control features in future ultrasensitive PSA assays: (a) several PSA calibrators in the ultrasensitive range (<0.5 μg/L), ideally with at least one calibrator near 0.1 μg/L; and (b) multiple PSA controls (ideally, human serum samples) in the low-concentration range to control for interassay variation (e.g., two samples <0.3 μg/L, with one sample close to the 0.1 μg/L detection limit for residual cancer (22). As an extra precaution, samples with PSA values at or near 0.1 μg/L should probably be analyzed in duplicate by the ultrasensitive tests. These assay features are necessary to meet the need for adequate control at diagnostically critical concentrations, a principle accepted by clinical biochemists and regulatory agencies. Because of these special requirements, it may be best for manufacturers to offer two PSA assays, i.e., a standard one for screening purposes and for monitoring prostate cancer patients with established disease (working range >0.3 μg/L), and a separate well-controlled ultrasensitive assay to monitor patients after radical prostatectomy for detecting early evidence of residual disease (working range >0.05 μg/L).

With the rapidly expanding clinical usefulness of PSA, laboratory clinicians can expect to see a variety of new PSA tests in the coming years. However, issues of major importance remain to be resolved in this rapidly evolving field. First, there is a need for an international antigen standard (23). Several of the current generation of immunosensors of PSA differ considerably in their values when used to test the same patients' samples (23–25). Much of this difference appears to be due to differences in the assigned protein values of the PSA used to calibrate the tests (23, 25); adoption of an international antigen standard would help resolve this issue. Second, PSA is a chymotrypsin-like serine protease with sequence relatedness to the kallikrein family (26). Most PSA in serum is bound to serum proteinase inhibitors, especially α1-antichymotrypsin and α1-macroglobulin (27, 28). The binding of PSA to these macromolecules in serum may interfere with antibody binding, especially in solid-phase assays utilizing monoclonal antibodies. Use of a defined matrix diluent containing these natural proteinase inhibitors may be necessary for standardizing different assays based on different monoclonal and polyclonal antibodies. In view of the evidence that monitoring serial PSA values over time may have clinical usefulness for early detection of prostate cancer (17), the need to calibrate the different commercial PSA tests to the same antigen standards

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and diluent matrices is critical. Values obtained by different PSA assay methodologies cannot be used interchangeably at the current time.

Early resolution of these assay standardization issues coupled with the increased availability of a new generation of rapid, automated, nonisotopic PSA assays such as the IMx PSA described in this issue of Clinical Chemistry, both in the standard and the ultrasensitive formats, will provide a powerful and convenient tool for clinicians in diagnosing and managing patients with prostate cancer.

I thank T. A. Stamey for helpful discussions and review of this work.

References

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