EDITOR’S AND PUBLISHER’S NOTE

This issue marks one or two ‘behind the scenes’ changes to Disease Markers.

Firstly, the journal is now published by ASFRA BV. ASFRA is a small specialist publisher concentrating upon computing and biotechnology orientated projects. The company is based in Edam, The Netherlands, and has an experienced staff of qualified scientists and publishers.

Our change of publisher has been brought about after amicable discussions with our founding partners—John Wiley and Sons, Ltd. UK. In today’s increasingly large world, all concerned felt that a (small), specialist, journal like ours could perhaps flourish better as part of a smaller programme and so ASFRA, who work closely with Wiley on a number of projects, agreed to take on the publishing responsibilities.

We do not plan many changes. The format will remain the same, although 1993 may well see a 4-issue schedule rather than the 6 announced by Wiley. Both editors and publisher will strive to get the journal back on schedule and, as an aid to publishing time, ASFRA will be delighted to receive future articles on floppy diskettes. The text should be sent on a hard floppy (3.5") with a note of the operating system (APPLE or MS DOS) and the word processing system used. This must be in addition to the manuscript which will be used for refereeing and other administrative activities.

The editors have also decided that we should try to change, slightly, the direction of the journal—emphasizing more the biotechnology aspects of our field. We are therefore moving towards emphasizing some of the increasingly important technical advances in disease marker research and coming issues will feature reviews on this area as an introduction and incentive to attract more research papers. Papers on such topics as ‘comparative genomic hybridization’ and ‘molecular techniques in HLA typing’ will be welcome in the effort to move forward. The growing place of the computer in the diagnostic and research laboratory must also be acknowledged and the journal could become a useful forum for the exchange of ideas on new programmes and opportunities. We are soliciting material in this area and will be glad to consider any proffered manuscripts.

Finally, our American Editor, Dr R. A. Gatti has chosen this moment to step down from that post. We are very grateful for his support during the past few years and will be seeking a replacement as soon as we have got through this change-over period. Dr Gatti has kindly agreed to join the journal’s Advisory Board.

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REVIEW ARTICLE

PROSTATE SPECIFIC ANTIGEN (PSA)

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KEY WORDS Prostate specific antigen (PSA) Prostate cancer Prostate disease Acid phosphatase

INTRODUCTION

Prostate specific antigen (PSA) is a serine protease produced by epithelial cells of both benign and malignant prostate tissue. PSA is present in the sera of healthy males and increases with benign prostate diseases, including benign prostatic hypertrophy (BPH), trauma, and prostatitis. Generally, serum PSA results also are increased in patients with prostate cancer, however, up to 40 per cent or more of patients with localized disease have levels within the reference range. The major use of PSA is following the course of individuals with known prostate cancer. In these patients, PSA levels reflect cancer status following a variety of therapeutic modalities. As a rule, PSA is superior to prostatic acid phosphatase (PAP) in following patients with known prostate cancer. PSA shows less diurnal variability and is more stable than PAP. Additionally, PSA rises faster than PAP and is elevated in a higher percentage of patients at each clinical stage of prostate cancer. PSA is useful in predicting tumor recurrence months before it can be detected by other methods.

BACKGROUND

PSA, which was discovered in the 1970s, is a serine protease composed of a single chain glycoprotein with 240 amino acids. The 34 kDa protein has various isometric forms with isoelectric points between 6.8 and 7.2 (Osterling, 1991). PSA is present in normal, hyperplastic, and malignant prostate tissue and occurs in serum of healthy men as well as those with prostatic disease. Normally, PSA is secreted into the prostatic ducts. In seminal fluid, PSA’s function appears to involve dissolution of seminal coagulum. In most patients, over 80 per cent PSA circulates as an 80–90 kDa complex between PSA and α-1-antichymotrypsin. A 25–40 kDa compound is a minor immunoreactive component. It is unknown whether this noncomplexed fraction is a precursor, active, or inactivated form of PSA (Lilja et al., 1991).

Increases in serum PSA occur in prostate cancer as well as in a number of benign prostate diseases such as benign prostatic hypertrophy (BPH), prostatitis, prostatic infarcts, trauma, and urinary retention. Prostate cancer tissue generally contributes about 10 times more to serum PSA levels as compared to an equal amount of normal prostate tissue. Digital rectal examination (DRE) usually does not have a clinically
significant effect on PSA results (Thomson and Clejan, 1992; Brawer et al., 1988; Osterling, 1992). However, significant increases in serum PSA levels occur after prostatic massage, needle biopsy, or prostate surgery. For example, transurethral resection for BPH causes over a 50-fold increase in PSA results (Osterling, 1991). The half-life of PSA in serum is about 2–3 days. Thus, it may take 2–3 weeks for PSA results to return to baseline following situations or procedures which cause elevations. For as long as a month following needle biopsy of the prostate, falsely elevated PSA results can occur owing to persistent leakage of PSA into serum. Although PSA levels fluctuate unpredictably during the day, the magnitude of the variation is considerably less than for prostatic acid phosphatase (PAP) (Schifman et al., 1987; Chodak et al., 1990). On the average, variation of PSA levels throughout the day is in range of 10–15 per cent. The day-to-day variation is small even in patients with advanced prostate cancer (Maatman, 1989). Stamey et al. (1987) report decreases in PSA following hospitalization, although the exact mechanism for this change is unclear. In serum specimens, PSA is more stable than PAP when stored at room temperature. Even at room temperature, PSA decreases only about 3 per cent over a 24-h period (Schifman et al., 1987). At −20°C, PSA appears to be stable for at least several weeks (Simms and Gleeson 1991).

**ASSAY**

Immunoassay is used to measure PSA in serum specimens. The serum can be refrigerated at 4°C, but freezing at −20°C is recommended for prolonged storage before assay. As of mid-1992, Hybritech and Abbott offer assays that are FDA approved, but applications are pending from several other companies. A number of other assays including Pros-Check are used throughout the world. Problems including the high dose hook effect or interference from antibody to reagents have been reported only rarely (Osterling, 1991; Vessella et al., 1992). A larger problem is differences among assays and thus as with other tumor markers, care must be taken in interpreting results from different assays. Differences in PSA assay results have been attributed to standardization, but other factors also must be involved. For example, Turkes showed the Pros-Check assay compared to the Hybritech R assay yields higher results up to about 300 μg l⁻¹, but lower results above this level (Turkes et al., 1991). Rank order differences among assays could be caused by PSA complexes or variation in glycosylation of PSA (Stenman et al., 1991). In serum, PSA is bound to α-amtichymotrysin and at high PSA levels a complex with α₁-protease inhibitor can occur (Stenman et al., 1991). Assay antibodies can react differently with the various PSA forms. Effects are complicated because different amounts of the various PSA forms can occur in the assay standard or label as well as in the patient specimen. Considerable differences in control results also occur among assays (Table 1), but these differences are not necessarily the same as those that occur with patient specimens. Controls are made by adding seminal plasma to a human serum pool; one factor may be the complex formed with α₂ macroglobulin when PSA is added to serum in vitro (Lilja et al., 1991).

For both the Hybritech and Abbott assays, the reference interval is <4 μg l⁻¹. Another method described in the literature, the Pros-Check assay, has a reference
Table 1. Prostate specific antigen: median results (µg l\(^{-1}\))

<table>
<thead>
<tr>
<th>Assay kit manufacturer</th>
<th>K-06</th>
<th>K-07</th>
<th>K-08</th>
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<tr>
<td>Abbott</td>
<td>16·3</td>
<td>17·2</td>
<td>16·4</td>
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<tr>
<td>Diagnostic Products</td>
<td>7·3</td>
<td>7·8</td>
<td>7·0</td>
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<tr>
<td>Hybritech Tandem-E</td>
<td>9·9</td>
<td>10·3</td>
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†The author gratefully acknowledges the assistance of the College of American Pathologists in providing the Survey Data that were presented in their 1992 Ligand Assay Set K-B Participant Summary Report.

range up to 2·5 µg l\(^{-1}\). Despite the lower reference range, the Pros-Check method yields patient results 1·4 to 1·8 times higher than the Hybritech Tandum R assay (Brawer, 1991). PSA results do not appear to increase with age in men without prostatic disease (Carter et al., 1992).

Because PSA measurements are used to assess the completeness of tissue removal following radical prostatectomy, analytical sensitivity of PSA assays is important. What represents a zero or nondetectable PSA result, however, is a complex question. Some investigators believe that results following radial prostatectomy values should be ‘in the female range’. In women, PSA results are in the range of 0·1 to 0·2 µg l\(^{-1}\), but higher results are seen occasionally. Several explanations for the high results in women have been proposed including anti-PSA antibodies or other interfering antibodies. Investigators have shown periurethral glands in females stain positively for PSA (Pollen and Dreilinger, 1984) and thus it has been postulated that there may be a molecule similar to PSA circulating in females. For these reasons, some investigators recommend a different criteria for specimens lacking PSA; they suggest serum specimens from men following cystoprostatectomy where the absence of prostate cancer has been established (Brawer and Lange, 1989). With an ultrasensitive PSA assay, Graves et al., determined the upper PSA limit as 0·10µg l\(^{-1}\) in such patient specimens (Graves et al., 1992).

SCREENING

The goal of screening patients for prostate cancer is to detect the disease while it remains confined to the prostate in the hope that this represents a curable stage of the disease. The value of screening for prostate cancer, however, is controversial. The role of PSA in screening for prostate cancer has been studied by several different groups. Catalonia et al., conclude PSA is not sufficiently sensitive to be used alone as a screening test, but PSA is a useful adjunct to digital rectal examination (DRE) and ultrasonography in detecting prostate cancer (Catalonia et al., 1991). Using PSA, approximately twice as many prostate cancers can be detected as with DRE, but some prostate cancers will be missed by relying on PSA results alone (Osterling, 1992).
A major problem with using PSA for screening is most PSA elevations are caused by BPH (Drago, 1989). Although reports vary widely, the percentage of men with BPH who have PSA results above the reference range is up to 80 per cent or more (Brawer and Lange, 1989; Graves et al., 1992). Most patients with BPH and increased PSA have results between 4 and 10 μg l⁻¹, but about 3 per cent of patients have results over 10 μg l⁻¹ (Hudson et al., 1989, Ercole et al., 1987). By comparison, prostate cancer is present in about 75 per cent of patients with PSA results over 10 μg l⁻¹ and in roughly half with those with results greater than 4 μg l⁻¹. The probability of prostate cancer is proportional to PSA level. Higher PSA levels tend to occur in patients with metastatic prostate cancer (Figure 1), but there is tremendous overlap in results seen in various stages of prostate cancer. Up to 40 per cent or more of patients with prostate cancer have PSA results within the reference range, but most of these patients have only localized disease (Osterling, 1992).

Investigators generally recommend patients with PSA of 10 μg l⁻¹ or more should undergo transrectal ultrasound and biopsy. For example, Stamey recommends men with abnormal DRE or with PSA results greater than 10 μg l⁻¹ should undergo biopsy to exclude prostate cancer. If biopsies are negative and the PSA is greater than 30 μg l⁻¹, he suggests additional biopsies in an effort to detect transitional zone cancer (Stamey, 1992). Controversy surrounds the proper approach to patients with a normal DRE and a PSA of 4 to 10 μg l⁻¹. Some investigators recommend ultrasound and biopsy of suspicious lesions for this patient group (Osterling, 1992).
Several approaches have been used to increase the specificity of PSA in screening for prostate cancer. One approach is to correlate PSA results with prostate volume as determined by ultrasound. This technique has been useful in distinguishing patients with BPH from prostate cancer, especially when PSA is minimally elevated. Patients with PSA between 4 and 10 µg l\(^{-1}\) in association with a small prostate gland are more likely to have prostate cancer (Benson et al., 1992). Another approach is to determine the rate of change of PSA over time. Carter et al., (1992) using stored serum specimens, found serial increases in PSA improved the specificity of serum PSA for prostate cancer.

**DIAGNOSIS**

PSA is elevated in a variety of prostatic diseases and therefore is not diagnostic of prostate cancer. Very high PSA levels, however, especially in the absence of history of trauma or acute infection, are suspicious of prostate cancer. Of note, there is at least one report of a patient with a persistent elevation of serum PSA (95–99 µg l\(^{-1}\)), but no identifiable prostate malignancy (Glenski et al., 1992). Diagnostic problems arise in biopsy specimens of metastatic tumors of uncertain origin. In these cases, immunohistochemical testing of the biopsy material for PSA and prostatic acid phosphatase (PAP) is performed. PSA staining is specific for prostate cancer with about 98 per cent of such tumors showing positive PSA immunoreactivity.

**PROGNOSIS**

A critical need is to identify those prostate carcinoma patients who will go on to have widespread disease. Histologic tumor grade is an excellent predictor of disease progression. DNA analysis and staging are used as well. Serum PSA results correlate with both the stage and grade of prostate cancer (Babaian et al., 1991). In an individual patient, however, PSA results are not reliable in predicting pathological stage. The reasons are that most men with prostatic cancer have coexisting BPH which increases PSA to a variable extent plus PSA production by the prostate cancer can vary depending on differentiation of the tumor (Partin et al., 1990). Thus considerable overlap of PSA results occurs in any given stage of prostatic carcinoma. Organ-confined prostate cancer, however, is only rarely associated with PSA results greater than 50 µg l\(^{-1}\) (Osterling, 1991).

**FOLLOW-UP**

The main value of PSA measurements is following patients with metastatic prostate cancer. As compared with prostatic acid phosphatase (PAP), PSA is superior for monitoring patients because it is elevated in a larger percentage of patients at each stage of the disease (Stamey and Kabalin, 1985; Figure 2). In patients with active stage D\(_2\) prostate cancer, PSA is increased in up to 98 per cent of patients, including the 22 per cent who have PAP results within the reference range. About 1 per cent of patients, however, have elevated PAP in the absence of an increased PSA (Ercole et al., 1987).
Serum PSA is valuable as a tumor marker in patients who have undergone radical prostatectomy, irradiation, or hormonal therapy. Additionally, PSA is helpful in determining the need for follow-up bone scans and in interpreting abnormal bone scan findings (Freitas et al., 1991). Following radical prostatectomy, PSA results should yield results in the nondetectable range (less than 0·1 to 0·2 μg l⁻¹ as determined by the commonly used assays). Even low serum PSA levels following radical prostatectomy are associated with poor prognosis. For example, results over 0·4 μg l⁻¹ 3–6 months after radical prostatectomy are associated with disease reoccurrences (Lightner et al., 1990).

Data suggest serum PSA results may be useful in assessing response of prostate cancer to radiation therapy (Chodak et al., 1990; Zagars et al., 1991). With external beam radiation, PSA results tend to be mildly and transiently elevated. By 3 months following irradiation, PSA results decrease in almost all patients. PSA continues to fall for up to 12 months in most patients, but usually remains detectable in serum (Zagars et al., 1991). Following hormone therapy, PSA results are commonly within the reference range even in the presence of significant metastatic prostate cancer. There appears to be a direct influence of androgen deprivation on PSA expression, independent of effects on anti-tumor activity (Leo et al., 1991). Response of PSA to endocrine therapy, however, predicts the patient’s response. Patients have a more favorable prognosis when PSA rapidly decreases following endocrine therapy (Arai et al., 1990).
CONCLUSION

PSA has replaced PAP as the mainstay in monitoring prostate cancer patients. Following treatment, PSA accurately reflects patient status and prognosis. PSA can predict tumor recurrence months before it can be detected by other methods (Osterling, 1991).

REFERENCES


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