Clinical Use of Prostate Specific Antigen (PSA)

JMAJ 47(12): 549–554, 2004

Koichiro AKAKURA
Head, Department of Urology, Tokyo Kosei Nenkin Hospital

Abstract: Like other countries, Japan is recording a rapid increase in the incidence of prostate cancer. The use of serum PSA (prostate specific antigen) measurement as a blood marker for prostate cancer has become widespread. Higher levels of PSA are associated with a higher probability of a diagnosis of prostate cancer. Needle biopsies detect prostate cancer in 20–30% of cases with PSA levels of 4.1–10 ng/ml, and 30–50% or more of cases higher than 10 ng/ml. All cases showing PSA levels of 4.1 ng/ml or more should be referred to specialist urologists, as well as those showing PSA levels of 4.0 ng/ml or less and positive findings on digital rectal examination. However, PSA also increases in other conditions such as benign prostatic hyperplasia, prostatitis, and urinary retention, and this fact needs careful attention. In addition, there is a risk that administration of antiandrogen may lower PSA levels and mask the presence of prostate cancer. So-called gray-zone cases with PSA levels of 4–10 ng/ml present a problem of differentiation from benign prostatic hyperplasia. Improvement in accuracy has been attempted with various approaches, such as PSA density, PSA free/total ratio, PSA velocity, and age-specific PSA reference ranges. In observation after the treatment of prostate cancer, PSA is useful for the early diagnosis of recurrence and relapse.

Key words: Prostate cancer; Prostate specific antigen (PSA); Blood marker; Screening

Introduction

In the past, Japan had a lower incidence of prostate cancer than European countries and the U.S. However, Japan is also recording a rapid increase in the incidence of prostate cancer, reflecting the aging of society and changes in lifestyle. The use of the measurement of prostate specific antigen (PSA) as a blood marker for...
prostate cancer has become widespread. As a result, physicians other than specialist urologists are now required to measure serum PSA and appropriately manage patients showing high PSA values.

This article outlines the characteristics and significance of PSA, as well as key points in measurement and clinical action.

**Characteristics of PSA**

1. **Characteristics of PSA protein**

   PSA is a glycoprotein occurring abundantly in seminal fluid. It has a molecular weight of about 34,000, and consists of 240 amino acid residues and 4 sugar chains. PSA belongs to the kallikrein family and exerts serine protease activity. Although its physiological actions are unknown, it is considered to play a role in the liquefaction of coagulated seminal fluid.

   PSA protein is produced in prostatic epithelial cells in an androgen-dependent manner. Mediated by androgen receptors, androgen binds to the androgen response element located upstream of the PSA gene, and stimulates the production of the PSA messenger RNA and protein.

2. **Prostate cancer and PSA**

   The expression of PSA protein is not specific to prostate cancer. It is specific to prostatic epithelial cells in various conditions including normal and hyperplastic conditions. However, while almost all PSA protein is secreted into seminal fluid in normal conditions, PSA protein leaks into blood in prostate cancer. Serum PSA measurement is, therefore, useful for the diagnosis and observation of prostate cancer. It is widely used as a blood marker for prostate cancer for the purposes of screening and detection of recurrence after treatment.

   Higher levels of serum PSA are associated with a higher probability of diagnosing prostate cancer. Prostate cancer is detected in 20–30% of cases showing PSA levels of 4.1–10 ng/ml, and 30–50% or more of cases showing PSA levels of 10 ng/ml or more. However, it should be noted that cancer is found in about 15% of patients showing normal PSA and induration of the prostate detected by digital rectal examination (DRE). Serum PSA increases with the progression of prostate cancer. Almost all cases of progressive prostate cancer with bone metastasis present abnormally elevated serum PSA.

3. **Molecular forms of blood PSA and differences between assay kits**

   PSA in blood occurs in the form of free PSA and in forms bound to α1-antichymotrypsin and α2-macroglobulin (Fig. 1). Most PSA assay kits detect free PSA and α1-antichymotrypsin-bound PSA. It is desirable that a kit is capable of the simultaneous equimolar detection of both forms. However, different kits show different ability of equimolar detection.

   Formerly, because of the differences in sensitivity and other properties of commercially available assay kits, there were wide variations in the results of PSA measurement depending on the type of kit used. Accordingly, the data were usually converted to results obtained with the Tandem-R kit, which was commonly used in Europe and the U.S. However, this conversion was not always reliable because of the problem of equimolarity. Recent efforts toward standardization have greatly improved equimolarity among different kits, and interkit differences are diminishing.

---

**Fig. 1 Molecular forms of PSA in blood**

Free PSA
PSA-ACT: α1-antichymotrypsin-bound PSA
PSA-MG: α2-macroglobulin-bound PSA
\(\square\)\(\triangle\): Epitopes
PROSTATE SPECIFIC ANTIGEN (PSA)

Protected by needle biopsy that was conducted because of elevated serum PSA despite the lack of abnormal findings on DRE, transrectal ultrasound, and MRI. The occurrence of T1c cancer is increasing rapidly with the widespread use of serum PSA measurement. In Japan, too, many cases of prostate cancer detected recently have been classified as T1c.

In T1c cancer, cancer is present despite the absence of clear induration or imaging abnormalities. In the diagnosis of such cancer, it is important to obtain biopsy specimens evenly from all parts of the prostate. For this reason, it has become common practice to diagnose T1c prostate cancer using random systematic prostate biopsies under transrectal ultrasound guidance.7)

Factors Affecting Serum PSA

Diseases other than prostate cancer may cause elevation of serum PSA, and this fact needs attention in interpreting measurement data (Table 1).

1. Factors that can increase serum PSA

Slight increases in serum PSA may be observed in benign prostatic hyperplasia. Abnormally elevated levels of serum PSA may persist for a long time in acute prostatitis. Therefore, if prostatitis is suspected and elevated serum PSA is observed, remeasurement of serum PSA should be conducted after administering antibacterial drugs, and then the necessary action should be reconsidered. It should also be noted that a temporary increase in serum PSA may be caused by urinary retention, ejaculation, prostate palpation, urethral catheterization, prostate biopsy, and other kinds of stimulation.12)

2. Factors that can decrease serum PSA

It is important to consider the possibility that administering antiandrogen may reduce serum PSA8) and mask the presence of prostate cancer. When antiandrogen is prescribed as a
hormone therapy for benign prostatic hyperplasia, it must be preceded by serum PSA measurement and DRE to disprove the existence of cancer.

3. Variations in serum PSA

While serum PSA shows diurnal variations associated with variations in serum testosterone, the range of PSA variation is small. PSA is not excreted from the kidneys, and its half-life in blood is relatively long (2.2–3.2 days). Therefore, serum PSA in patients with renal insufficiency does not differ from that in healthy individuals, and no significant changes in serum PSA are observed between before and after hemodialysis.

Attempts to Improve Specificity

Cases showing serum PSA levels of 4.1–10 ng/ml are regarded as gray-zone cases, in which differentiation between prostate cancer and benign prostatic hyperplasia is an important clinical problem. Various attempts have been made to improve the accuracy of differential diagnosis of these diseases.

1. PSA density

The value obtained by dividing serum PSA level by prostate volume is called PSA density (PSAD; the ratio of PSA level to prostate volume). Taking advantage of the correlation between serum PSA and the size of adenoma in benign prostatic hyperplasia, this method intends to minimize the contribution of hyperplasia to PSA levels. Several cut-off values have been proposed, e.g., 0.15 ng/ml/cc. This method is used as an aid in determining the necessity for prostate biopsy in gray-zone cases.

2. PSA free/total ratio

When we examine the percentages of different molecular forms of PSA in blood, it was found that the percentage of free PSA remains low in prostate cancer, as compared with that of \( \alpha_1 \)-chymotrypsin-bound PSA. Based on this fact, attempts have been made to discriminate prostate cancer using the ratio of free PSA to total PSA measured in blood. The cut-off level is usually set at 15–25%.

\( \gamma \)-seminoprotein (\( \gamma \)-Sm) is a blood marker for prostate cancer used in Japan. While \( \gamma \)-Sm has been identified to be the same substance as PSA, the measurement of \( \gamma \)-Sm mainly reflects the amount of free PSA. Based on this fact, the usefulness of the \( \gamma \)-Sm/PSA ratio has been reported.

3. PSA-ACT

As mentioned above, patients with prostate cancer show an elevated percentage of \( \alpha_1 \)-antichymotrypsin-bound PSA (PSA-ACT). Attempts have been made to improve the accuracy of diagnosis by directly measuring PSA-ACT.
4. PSA velocity

Compared with non-cancer diseases, prostate cancer shows steady year-by-year increases in serum PSA. Based on this fact, it has been proposed that PSA velocity (PSAV; rate of change in PSA over time) calculated from successive measurements of serum PSA may be useful in discriminating cancer. The cut-off level is set at about 0.75 ng/ml/year.

5. Age-specific PSA reference ranges

Serum PSA increases gradually as the patient ages. Because of this fact, some researchers have recommended that the cut-off level for normal serum PSA should be defined according to age. An example of these age-specific reference ranges is: 2.5 ng/ml for the 40–49 age range, 3.5 ng/ml for the 50–59 age range, 4.5 ng/ml for the 60–69 age range, and 6.5 ng/ml for the 70–79 age range. However, in using this approach, attention must be paid to the existence of large ethnic differences.

As outlined above, a number of attempts have been made to improve the efficiency of diagnosis in gray-zone cases. However, no consensus has been reached as to the usefulness of these approaches and the appropriate cut-off levels.

Significance of Serum PSA Measurement in the Followup of Prostate Cancer

1. Serum PSA after radical prostatectomy

Because radical prostatectomy for prostate cancer removes all prostatic tissue including the normal parts, postoperative serum PSA levels are either zero or negligibly low. Almost all recurrent cases show increases in serum PSA some years before a clear manifestation of clinical recurrence. The elevation in serum PSA above the limit of measurement sensitivity is called “biochemical recurrence” or “PSA recurrence.” Even earlier detection of the signs of recurrence has been attempted by measuring low levels of PSA with high-sensitivity PSA assay kits.

2. Serum PSA after radiotherapy for prostate cancer

Serum PSA also decreases in response to radiotherapy for prostate cancer. However, the decrease is slow and sometimes takes over one year to nadir. The PSA nadir level is not zero, but is usually in the range of 0.2–0.6 ng/ml. For this reason, determining “PSA recurrence” is based on the observation of three consecutive increases, rather than the absolute value of serum PSA.

3. Serum PSA after hormone therapy for prostate cancer

Serum PSA measurement is also useful in the followup after hormone therapy for prostate cancer. The PSA reactivity measured three or six months after treatment initiation is a significant predictor of long-term prognosis. Relapse of disease can be detected early based on “PSA relapse,” which is defined as three consecutive increases in serum PSA.

Conclusion

Serum PSA measurement is an essential test in the diagnosis and treatment of prostate cancer. Because this test facilitates the simple screening for prostate cancer, its use is expected to become increasingly widespread in the future. It is hoped that physicians other than urologists also understand the characteristics and key points of this method, and use it actively in their practice.

REFERENCES


2) Rittenhouse, H.G., Finlay, J.A., Mikolajczyk, S.D. et al.: Human kallikrein 2 (hK2) and prostate-specific antigen (PSA): tow closely related, but distinct, kallikreins in the pros-