

Prostate specific antigen: a useful but limited marker for prostate cancer

Prostate specific antigen is widely used as a tumour marker for prostate cancer.

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Prostate cancer (Pca) is the second most common cause of cancer worldwide. The incidence rates vary geographically, with the highest rates observed in highly resourced countries. Although lower rates are observed in developing countries, sub-Saharan Africa included, the mortality rate is reported to be higher. This is partly attributable to lack of screening programmes and presentation in advanced stages of the disease in the majority of cases.¹ Like other cancers, the target in the management of Pca is early detection when cure is more likely. Prostate specific antigen (PSA) is widely used as a tumour marker for Pca, both for the detection and staging of the disease, as well as in determining prognosis and monitoring treatment response.^{2,3} Notably, benign conditions of the prostate, some pre-analytical and analytical factors may also affect PSA levels, resulting in false positive (over-diagnosis) or false negative results (under-diagnosis), with subsequent inappropriate patient management.^{2,4} Several measures are reported to be useful in improving the value of PSA in Pca.^{2,3,5} Consideration of these factors may improve the validity of PSA results interpretation and subsequently appropriate steps in patient management.

What is PSA?

PSA, also called kallikrein 3, is a glycoprotein encoded by the KK-3 gene located on chromosome 19. It is an androgen-regulated serine protease secreted almost exclusively by the epithelial cells of the prostate gland into the seminal fluid. The production of PSA by non-prostatic tissues and tumours has been reported. The main function of PSA is to liquefy semen and to dissolve the cervical mucus, thus facilitating sperm motility. A small amount of PSA normally enters the bloodstream and exists in serum

in different molecular forms at varying proportions.^{2,3,5} The identification of these different forms of PSA has led to improved use of PSA in prostate cancer detection.

Molecular forms of PSA in blood

There are two main forms:

- complexed/bound form (cPSA) – major form
- complexed with α_1 -antichymotrypsin (ACT) – major subform (70 - 90%)
- complexed to other protease inhibitors; α_2 -macroglobulin (AMG), inter- α trypsin inhibitor and α -antitrypsin (minor amounts)
- uncomplexed/unbound/free (fPSA) – minor form (10 - 30%).

Total PSA (tPSA) = cPSA + fPSA

Isoforms of fPSA:^{5,6}

- pPSA (pro-PSA)
- bPSA (BPH-PSA)
- iPSA (inactive-PSA).

The main site of clearance of serum PSA is the liver (cPSA and fPSA) and the kidney (fPSA). The half-life of PSA in serum is $\pm 2-3$ days.⁷

Prostate cancer and PSA

PSA is widely used as a tumour marker in Pca. Typically, PSA levels are elevated in Pca mainly due to disruption of the normal glandular architecture, resulting in more PSA being released into the circulation; hence its use as a marker of Pca.⁵ PSA has been shown to be useful in the screening, diagnosis and staging of Pca as well as in monitoring response to therapy. Screening of asymptomatic men, although not recommended by other organisations,

should take into consideration the risk factors for Pca, which include increasing age, race and heredity.^{2,3,8}

The PSA test is not a definitive test for detecting prostate cancer; it only predicts the need for biopsy, which is a definitive test.

Determination of PSA in blood

Pre-analytical factors

Several pre-analytical factors may influence the serum level of PSA. Awareness of these factors should help improve the quality of the sample and subsequently the validity of the results.

Timing of sample collection

Serum PSA may be elevated post digital rectal examination (DRE), ejaculation, needle biopsy and transurethral resection of the prostate (TURP), prostate massage, transrectal ultrasound, and rigid cystoscopy, as well as bicycle riding. Drugs like finasteride cause about 50% reduction in PSA levels.^{2,3,6,9} These factors should be taken into consideration when collecting blood samples for PSA determination. In order to eliminate their effect, it is recommended that blood for PSA determination should be:³

- drawn before a DRE or 3 days thereafter
- delayed for 48 hours after ejaculation
- delayed for at least 6 weeks after needle biopsy of the prostate

PSA

- delayed for at least 6 weeks after TURP
- delayed for 1 week after prostate massage
- taken before or be delayed for 1 week after ultrasound and a rigid cystoscopy procedure
- taken prior to any period of sustained bicycle riding or
- taken before finasteride therapy.

Sample type and stability

In principle, either serum or plasma is suitable for the determination of different molecular forms of PSA. After collection, blood should be separated preferably, within 3 hours. However, up to 16 hours is allowed.³ A sample intended to be used for measurement of tPSA, when stored at 20 - 25°C, will see a 25% reduction in 1 week; it will however remain stable for 5 days when stored at 4 - 8°C. fPSA remains accurate for 1 day when a sample is stored at 4°C. fPSA is reported to be more stable in plasma than in serum, hence plasma (with heparin or EDTA anticoagulant) is recommended.⁸

Analytical factors

Different immunoassays are currently available for the determination of the majority of the molecular forms of PSA. AMG-PSA is reported to be immunologically unreactive. Different assays or even the same assay with different lots of reagent may produce different results. This variation may be due to changes in calibration, production lot variation, assay reaction time, reagent matrices, assay sensitivity and imprecision.^{2,4,10} Because of this, a threshold quoted for one assay cannot necessarily be transferred to another as this may influence the interpretation of results. Efforts are being made to standardise PSA assays so as to improve harmonisation of results for patient serum samples.

Laboratory results and interpretation

Because different assays may report different reference ranges for serum PSA, it is essential that the reporting of results should include the assay method used and the reference ranges thereof. The interpretation of the results should be based on the indication for the test.

Table 1. Interpretation of PSA results

PSA level (ng/ml)	Interpretation	Probability that a carcinoma is present ⁸
0 - 4	'Normal'	17%
4 - 10	Borderline ↑ (grey zone)	30%
>10	Significant ↑	>49%

PSA levels in prostate cancer detection

The PSA test is not a definitive test for detecting prostate cancer; it only predicts the need for biopsy, which is a definitive test. The interpretation of PSA levels (Table 1) is based on the cut-off of <4 ng/ml as originally determined using the Hybritech assay.¹⁰

It is important to note that:

- 'normal' PSA level does not rule out the presence of cancer
- elevated PSA level does not indicate the presence of Pca
- the greatest overlap between Pca and benign prostatic hyperplasia (BPH) occurs in the grey zone.

This limited sensitivity (false negative) and specificity (false positive) of PSA suggests that the use of PSA alone may not be sufficiently reliable to determine the need for biopsy and therefore cancer detection. While biopsy is recommended for PSA levels >10 ng/ml, further tests are needed to improve the sensitivity and specificity of PSA at levels below 10 ng/ml region.¹¹

What measures can be used to improve the value of PSA in predicting the need for biopsy?

• PSA in conjunction with DRE

PSA and DRE together perform better than when each is used individually in the screening of prostate cancer. The addition of transrectal ultrasonography has shown added benefit in the diagnosis and is therefore recommended as an additional tool.^{2,8,10}

• Age- and race-specific reference ranges

Because of the physiological increase in prostate volume with age, the level of PSA tends to increase with age and using standard

Table 2. Recommended age- and race-specific reference ranges²

Age (yrs)	PSA (ng/ml)	
	White	Black
40 - 49	0 - 2.5	0 - 2.0
50 - 59	0 - 3.5	0 - 4.0
60 - 69	0 - 4.5	0 - 4.5
70 - 79	0 - 6.5	0 - 5.5

reference range of <4 ng/ml for all men may not be appropriate (Table 2). The use of age-adjusted reference ranges improves the sensitivity of PSA testing in younger men.^{2,4,12} While the specificity is improved in older men, this occurs at the cost of lowered sensitivity. The use of race-adjusted reference ranges has also improved the detection of curable cancer in black patients.

• Molecular forms of PSA and their derived ratios

Both Pca and benign prostatic disorders typically cause an elevation in tPSA. Notably, the proportionality of serum PSA forms and their derived ratios vary between benign conditions and Pca. Therefore, determination of these individual forms and/or their ratios may improve the diagnostic specificity for cancer detection. These measures have been reported to be useful, especially in cases of borderline increases in PSA, where there is the greatest overlap between benign causes and Pca. Pca is associated with elevated levels of cPSA, PSA-ACT, PSA-ACT:tPSA ratio and pPSA, and decreased fPSA, while benign conditions are associated with elevated levels of fPSA, bPSA and iPSA.^{3,5,6,8,11} These findings led to the recommendation that these markers could be used to improve the specificity of PSA in Pca detection. Most of these markers were found to be more useful for PSA levels within the 'grey' zone, especially when DRE is negative.

%fPSA: This is the ratio of fPSA/tPSA. Lower ratios suggest increased probability for cancer and the need for a biopsy. A

cut-off of 25% has been recommended by some.^{3,6,11}

%pPSA: This is the ratio of pPSA/fPSA. An increased % pPSA suggests a high probability for Pca and the need for a biopsy.^{5,6} This tool is reported to be more useful for PSA in the range of 2 - 10 ng/ml.

• PSA density

This is a comparison of the tPSA level and the volume of the prostate (measured using transrectal ultrasound). Men with larger prostates tend to produce more PSA, so this factor is an adjustment to compensate for the size. Elevated levels (>0.15) suggest an increased risk for Pca and therefore the need to perform a biopsy.^{3,6,8}

• PSA velocity

This is a change in PSA levels over time and its determination requires ≥ 3 PSA values taken over ≥ 18 months. Values $>0.75 \mu\text{g/l/}$ year indicates a high risk of Pca and the need for a biopsy to be performed.^{3,6,8} In order to improve the reliability of the results, the same sample type and comparable test methods should be used.

PSA as a tool for the staging of Pca

tPSA correlates with both clinical and pathological stages of Pca. Higher levels are associated with advanced stages of the disease. Patients with organ-confined disease seldom have levels >50 ng/ml, suggesting that those with these elevated levels most likely have extracapsular tumour extension.²

PSA as a tool in monitoring treatment response

During treatment for Pca, PSA levels should fall to very low or undetectable levels at the end of treatment. Due to the 2 - 3-day half-life of PSA, this may take 2 - 3 weeks after surgery to occur.² If the rate of fall of PSA is slower than depicted by the half-life, or the levels do not fall to very low levels, residual cancer should be suspected. An increase in PSA after normalisation suggests recurrence

of cancer and this usually precedes clinical recurrence by months to years.⁵

PSA doubling time (PSADT) measures how rapidly the PSA level doubles. It is useful in the detection of recurrence after cancer treatment. PSADT <10 months is associated with metastatic disease.^{5,6}

Three consecutive PSA rises above the nadir (the lowest post-treatment value) is recommended as evidence of treatment failure after radiation therapy.³ Ultrasensitive PSA (USPSA) test which detects PSA at much lower levels than the traditional test is recommended as a monitoring tool for detecting residual or recurrent cancer.³ The benefit of doing this test is that residual or recurrent disease will be detected much earlier. It is important that PSA determinations during follow-up should be done by the same laboratory to avoid inter-laboratory variation of results.

Interpretive comments on results

As part of diagnostic service provision, it is appropriate that laboratories, through expert committees, should provide interpretive comments on results so as to guide clinicians in terms of further management of the patient. Feedback from clinicians would be beneficial, especially if there is a need to modify the comments based on local evidence.

References available at www.cmej.org.za

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- Mortality rate from Pca is high in sub-Saharan countries.
- PSA remains a useful tumour marker in Pca.
- Measures to improve the value of PSA in detecting Pca have been reported.
- Improved relationship between the laboratory and clinicians may enhance patient management.