Prostate specific antigen

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Summary

The concentration of prostate specific antigen in the blood can help in the assessment and management of early prostate cancer. However, it is important to understand the biology underlying the test. Recent refinements have addressed some of the weaknesses of the test. These include age-related prostate specific antigen reference limits, the free to total prostate specific antigen ratio and prostate specific antigen rates of change including velocity or doubling time. Measuring prostate specific antigen without understanding the underlying biology or without applying these refinements may result in more harm than good.

Key words: prostate cancer.

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Introduction

Prostate specific antigen (PSA) is the name commonly used for a protein that is normally secreted by the healthy prostate gland into semen. PSA is a kallikrein protease whose biological role in semen is to hydrolyse the high molecular weight proteins secreted by the seminal vesicles. This converts the seminal gel to its fluid form to enable spermatozoa to swim free. PSA occurs naturally in semen, but the occasional molecule escapes into the interstitium of the prostate gland and then via the lymphatics to the blood. The PSA concentration in blood is a million times lower than in semen.

The test

A sample of venous blood is needed to measure the concentration of PSA. The result may be affected by mechanical disturbance of the gland such as digital rectal examination, exercise or ejaculation which ideally should be avoided for a day or two before the test. Samples should also be analysed within 24 hours as PSA (especially free PSA) decays *in vitro*. Although PSA concentrations measured by different laboratory methods are far more comparable today than even five years ago, it is unwise to compare results between laboratories as important differences may still exist.

Age-related PSA reference limits

As the prostate gland typically enlarges with ageing, the larger gland will expectedly release more PSA. This leads to a normal age-related rise in serum PSA concentrations.

There is an age-related rise in the upper reference limit from 2 microgram/L in young men to up to 9 microgram/L in the very old (Fig. 1). The age-related upper reference limit of PSA maintains a 95% specificity across all age groups. However, just as important is the age-related rise in the median PSA with age.

When a man consents to have a PSA test to ascertain his risk of prostate cancer, there are two important limits to consider. Firstly, if his PSA concentration is above the median, his probability of prostate cancer is above average. Secondly, if his PSA is above the upper limit of the age-related reference range, it is unlikely to be due to chance alone. For example, a man in his early 60's with a PSA above 4.5 microgram/L has about a 25–30% chance of prostate cancer being found at biopsy – indicating a high **absolute risk**.[1]

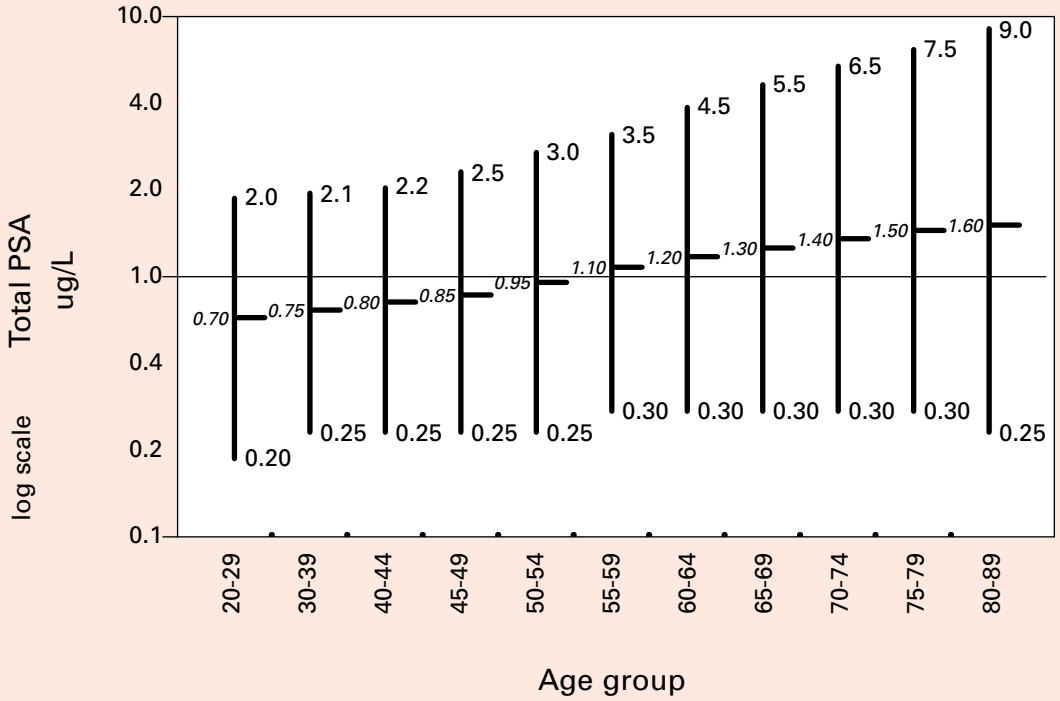
Results above the age-related upper reference limit

When the PSA exceeds the reference interval, the absolute risk of prostate cancer seems high (for example 30%), but it is still more likely that the cause is not prostate cancer. It is usually due to benign hyperplasia or prostatitis. However, a very high PSA level (above 10 microgram/L) is unlikely to be due to hyperplasia in asymptomatic men under 70 years of age. It is probably due to prostate cancer so referral to a urologist is appropriate. Clinically evident prostatitis is usually associated with PSA concentrations over 20 microgram/L so the risk of prostate cancer cannot be determined until this has fully resolved which may take one month.[2]

The most common challenge occurs when the PSA is abnormal (above the age-related upper reference limit) but not above 10 microgram/L. We need more specific approaches to reduce the false alarm caused by concentrations transiently in this range. The simplest approach is to repeat the test after two weeks. If the concentration falls it is less likely that there is a prostate cancer, and the patient may have intermittent subclinical prostatitis.

Fig. 1

Age-related rise in prostate specific antigen [3]



The central value is the median. The upper and lower values represent the 95% 'normal' range or reference interval. While these results refer to the Abbott Architect method and an Australian population, the values will be similar for any internationally calibrated (WHO standard) PSA assay on Caucasian men.

Free to total PSA ratio

The PSA in the blood is either free or bound to protein. As PSA is a protease, the anti-protease proteins of the blood will identify the molecule and bind to it inactivating its potential proteolytic actions within the body. Bound PSA is therefore active PSA molecules which have escaped from the prostate gland, but have been bound to antiproteases such as alpha-2-macroglobulin and alpha-1-antichymotrypsin. Molecules of free PSA are not bound to protein, and are not active. Free PSA is inactive because these molecules were either immature (pro-PSA) or inactivated (nicked PSA) when they escaped from the prostate gland.

The clinically important difference in these two forms of PSA is that free PSA has a short half-life (2–3 hours) whereas bound PSA has a long half-life (2–3 days). Patients who have diseases that cause intermittent 'showers' of PSA to appear in the blood will have both free and bound PSA, whereas in diseases that cause chronic release of PSA, bound PSA will accumulate in the blood due to its longer half-life compared to free PSA. Benign prostatic hyperplasia is characterised by highly variable PSA concentrations due to the intermittent physical disturbance of the enlarged gland or the increased risk of intermittent subclinical prostatitis. Cancer is the only continuously progressive disease of the prostate that constantly increases PSA release and most patients with low free to total PSA ratios (less than 10% free PSA, more than 90% bound PSA) will have prostate cancer.

Men with constantly elevated PSA concentrations (but below 10 microgram/L) should have the free to total PSA ratio estimated. If the free to total PSA ratio is below 8%, the risk of prostate cancer is almost 80%.[4] The only problem with this test is that free PSA is short-lived not only *in vivo* but also *in vitro*, so it must be measured within 24 hours of collecting the blood sample. Delay will falsely lower free to total PSA ratios which could be misinterpreted as an increased risk of cancer.

Results above the age-related median

The PSA test has 60% sensitivity using the upper reference limit, so we would miss the 40% of prostate cancers that occur in men with 'normal' concentrations. These cancers are also usually organ-confined and 'treatable'. By definition, the 50% of men with 'normal' PSA (below the age-related upper reference limit) but above the age-related median will have an above average risk of prostate cancer, but that risk is not high enough to warrant prostate biopsy. In these men with above average risk, continued monitoring with yearly measurements of PSA and digital rectal examination should be offered.

More frequent monitoring may be warranted in a man whose pre-test likelihood of prostate cancer is already high and who has a PSA above the age-related median, for example men with a family history of prostate cancer in a close relative (especially a brother). When both family history and PSA concentration suggest an increased risk, the test could be repeated within 3–6 months with a free to total PSA ratio.[5]

Results below the age-related median

If a man's PSA concentration is below the age-related median, his probability of prostate cancer is below average. Most researchers suggest that no further testing is justified for at least 3–5 years, as several studies have shown the absolute risk of prostate cancer in these men is very low (less than 1%). A man over 70 years of age is unlikely to benefit from further testing.

The rate of PSA changes

A useful refinement in predicting the clinical significance of any prostate cancer is the measurement of the rate of change of PSA concentrations. This is usually referred to as PSA 'velocity', but the 'doubling time' of PSA may be the more appropriate way to assess malignant potential.[6]

PSA concentrations may double every five years in the early stages of benign prostatic hyperplasia. If the PSA concentration is doubling faster (for example every three years or faster), this is more likely to be due to prostate cancer. When a man has had at least three PSA concentrations, several months apart and they show a rising trend, PSA doubling time can be calculated (see www.mskcc.org/applications/nomograms/prostate/). Estimating the rate of change of PSA applies both to PSA 'screening' or monitoring a known cancer.

PSA monitoring in known malignancy

A rising concentration of PSA in a man with prostate cancer suggests that the cancer is progressing.

PSA production is typically reduced by prostate cancer treatment (for example antiandrogen therapy), and the nadir can predict clinical outcome. PSA concentrations are ideally undetectable after radical prostatectomy, however men with 'biochemical recurrence' may still not have anything to worry about as a slowly rising PSA indicates their residual tissue may not be an aggressive cancer.[7] Watchful waiting should be reserved for men who are not at high risk. Men with low free to total PSA ratios or fast doubling times are at risk and should be considering treatment.[8]

Medicare Benefits Schedule

All the suggestions made in this article are currently supported by the Medicare Benefits Schedule. At least one free to total PSA ratio can be requested each year when the PSA is above the median. Should the PSA concentrations be above the age-related upper limit, several PSA tests and up to four free to total PSA ratios can be requested within each year.

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Further reading

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Conflict of interest: none declared