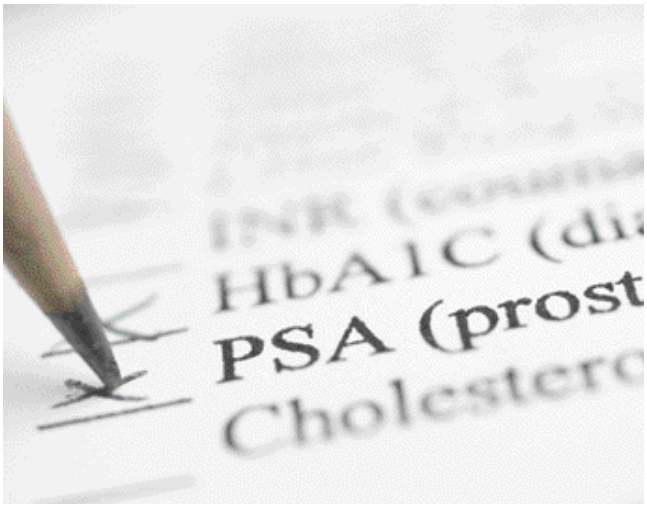
A practical guide on PSA testing

PHILLIP STRICKER MB BS, FRACS

Screening for prostate cancer is not a simple case of performing a blood test to check the PSA level. A digital rectal examination must also be included and the patient must be prepared in advance to deal with the results of the test.



Prostate specific antigen (PSA) testing has been responsible for the earlier detection of prostate cancer, which has led to increased success of curative treatment. There is an increasing body of evidence that suggests the use of PSA testing leads to the detection of cancers at an earlier and more curable stage. Furthermore, there is increasing evidence that the falling death rate from prostate cancer can, at least in part, be attributed to the efforts of testing and early treatment. Also, in countries with a high uptake of PSA testing, there has been a consistently lower death rate from prostate cancer.

Recently, the European Randomised Study of Screening for Prostate Cancer published its results in the *New England Journal of Medicine*.[1] This landmark study demonstrated unequivocally that PSA screening saves lives. This enormous undertaking was carried out in seven European countries and involved about 162,000 men aged between 55 and 69 years who either were offered screening with PSA testing every four years (with a cut-off value of 3 ng/mL indicating the need for biopsy) or were not screened. The study was scheduled to report in two years' time, but results were published early because a statistically significant decrease in the death rate from prostate cancer was found in the screened group. The median follow up in this group was nine years, with a maximum of 14 years of follow up.

The patients who were offered screening experienced a 71% increase in prostate cancers detected, a 41% reduction in advanced disease, as defined by a positive bone scan or a PSA level greater than 100 ng/mL, and a 20% decrease in deaths from prostate cancer compared with patients who were not offered screening. If only men who actually underwent screening were included in the results, the decrease in deaths from prostate cancer was 27%. It is highly likely that the mortality benefit will increase further as this study matures. This result is very similar to the 30% reduction in mortality in patients with breast cancer following screening with mammography[2] and the 33% reduction in prostate cancer-specific mortality that occurred in the USA from 1994 to 2003 following the introduction of PSA screening.[3]

The authors of the recent European study point out that to prevent one prostate cancer death at 10 years of follow up, 1410 men would need to be screened and 48 additional men would need to be treated. These numbers are very similar to those that need to be screened with mammography for breast cancer and faecal occult blood testing for colorectal cancer to prevent one death. The European study has come under harsh criticism because of the side effects associated with the treatment of prostate cancer, which, in many men, might have been unnecessary. It is for this reason that there is continuing controversy about prostate cancer screening.

The controversy about PSA testing is further compounded by another trial, which was published in the same edition of the *New England Journal of Medicine*.[4] The conclusion of this US study was that after seven to 10 years of follow up, the rate of death from prostate cancer was very low in both screened and unscreened patients and did not differ significantly between the two study groups. Unfortunately, this study has been criticised because not only did it have a poor method of testing, but also 52% of the controls were screened outside the trial protocol so the results were compared with a background of a heavily screened population, follow up was too short and very few people underwent biopsies.[5]

PSA testing, therefore, is not a perfect science, for the following reasons:

Associate Professor Stricker is Consultant Urologist, Prostate Cancer Surgeon and Specialist and a Robotic Surgeon at St Vincent's Hospital, Darlinghurst, NSW.

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Table. Useful resources for patients

- Stricker P, Phelps K. Prostate cancer for the general practitioner. 2nd edition. 2008. Available online at: http://prostate.com.au/pdf/pc_gp guide.pdf
- PSA Decision Card. Available online at: www.andrologyaustralia.org/docs/psadecisioncard20041007.pdf
- Stricker P. Prostate cancer treatments: so how do you choose? (DVD) Mens Health Matters. (www.menshealthmatters.com.au)
- Urological Society of Australia and New Zealand – www.usanz.org.au
- St Vincent's Prostate Cancer Centre, Darlinghurst, NSW – www.prostate.com.au
- Prostate Cancer Foundation of Australia – www.prostate.org.au

- a PSA test can be abnormal when cancer is not present
- a PSA test can be normal even when cancer is present.

If prostate cancer is found to be present after an abnormal PSA test, the following issues may arise:

- some prostate cancers are latent and slow growing, and do not require treatment (overdiagnosis and possibly over treatment)
- some prostate cancers are incurable, even with early detection (underdiagnosis)
- all treatments have potential side effects.

Overdiagnosis

Overdiagnosis occurs to differing extents, depending on the age group and general health of the men being tested. To avoid overdiagnosis, those people who are unlikely to have a survival benefit from early detection of prostate cancer should not undergo PSA testing. This includes men who are too old or too ill to live longer than 10 years and those who are unlikely to have a significant cancer. Avoiding overdiagnosis can be achieved by concentrating testing on those men with a life expectancy of more than 15 years.

To prevent overdiagnosis, we can use new information suggesting that a 65-year-old man with a PSA level of less than 1 ng/mL or a 75-year-old man with a PSA level of less than 3 ng/mL has such a low risk of developing clinically significant prostate cancer that testing is unnecessary.[6] We can also target younger patients and higher risk groups who are more likely to have significant cancers and in whom early detection will be of major benefit. Clearly patients with a family history of prostate cancer are at greater risk and African-American men are also at increased risk. A further useful piece of information is the level of PSA at the age of 40 years, which can help categorise men into high-risk and low-risk groups.[7]

Over treatment

The best way to avoid over treatment is to avoid treating older men with low-volume less-aggressive prostate cancers. This is particularly so in those over the age of 65 years. Increased use of active surveillance, even in younger patients with low-volume low-grade tumours, should also minimise treatments in patients with these less-aggressive potentially non-life-threatening tumours.

Active research into biomarkers to distinguish potentially aggressive from non-aggressive tumours needs to be prioritised. The use of biomarkers and functional imaging both have the potential to minimise over treatment by predicting the natural history of the patient with prostate cancer and helping to tailor therapy.

Underdiagnosis

Underdiagnosis occurs to varying degrees and can be minimised by having a lower PSA threshold and a lower PSA velocity for biopsy in younger patients.[8] As more accurate imaging techniques, such as magnetic resonance imaging-guided biopsies, become more widespread, the risk of missing significant cancer will become lower and early detection of aggressive tumours will become more accurate.

Treatment side effects

Although all treatments of prostate cancer carry potential side effects, such as impotence and incontinence, there have been significant improvements in surgical and radiotherapeutic techniques (e.g. better nerve-sparing techniques, laparoscopic techniques, robot-assisted techniques, brachytherapy and conformal radiotherapy such as intensity-modulated radiation therapy and radiosurgery techniques). Furthermore, treatments are more likely to be successful and cause fewer side effects if they are performed on cancers that are detected at an earlier stage.

There is now also strong evidence that better results are achieved in high-volume units – that is, units performing large numbers of procedures.[9] Finally, tailoring the treatment to the patient's individual circumstances is essential. (A useful resource is the DVD, *Prostate Cancer Treatments: So How Do You Choose?* See the Table for other useful patient resources.)

Inaccuracy of PSA testing

The PSA test is not a perfect test and is not specific to prostate cancer – for example, only one in three patients with a PSA test result of between 4 and 10 ng/mL will prove to have prostate cancer. A recent Australian audit detected cancer in 40% of patients with a PSA test result of between 4 and 10 ng/mL. Importantly, 20% of patients with a PSA level of less than 4 ng/mL, will prove to have cancer. This issue is currently addressed with yearly monitoring of PSA levels and watching the PSA velocity. Therefore, cancers are detected at an earlier stage, even when the total PSA level is within normal ranges, particularly in younger men.

The position of the Urological Society of Australia and New Zealand

The official position of the Urological Society of Australia and New Zealand is that PSA-based testing together with digital rectal examination should be offered to men between the ages of 55 and 69 years after providing information about the risks and benefits of such testing. Men under 55 years of age are less likely to be diagnosed with prostate cancer. However, if they are diagnosed, they are more likely to die from prostate cancer than men older than 55 years of age due to a reduced likelihood of dying from comorbid illnesses.

Men in the younger age group who are interested in their prostate health could have a single PSA test and digital rectal examination performed at or beyond the age of 40 years to provide an estimate of their prostate cancer risk over the next 20 years. At this stage, population screening in asymptomatic men is not recommended as a public health policy. A complete executive summary of the position of the Urological Society of Australia and New Zealand on PSA testing is available on its website (www.usanz.org.au).

Discussing PSA testing

Although formal, structured, informed consent is generally reserved for more invasive procedures than PSA testing, each individual should provide some form of informed consent before undergoing a PSA test. Generally, the patient's main concerns (e.g. family history of prostate cancer, cause of urinary symptoms or fear of cancer) should be established and he should be provided with some basic information about prostate conditions and prostate cancer, and the associated risks of PSA testing for the individual. The GP should have a brief discussion with the patient about the pros and cons of PSA testing and clarify the patient's values and whether he is comfortable with PSA testing.

The book *Prostate Cancer for the General Practitioner* by Professors Stricker and Phelps and the PSA Decision Card are useful resources (Table).

All men who undergo PSA-based screening must understand that the decision to undergo PSA testing is different to the decision to undergo biopsy, and this is again different to the decision to undergo treatment. It is particularly important that men who undergo screening also understand that the diagnosis of prostate cancer does not necessarily lead to immediate treatment and that the option of active surveillance for certain men diagnosed with prostate cancer is totally appropriate.

The decision to undergo PSA-based testing in an individual should therefore be made after appropriate informed consent has been given. Men who wish to be tested should have both a PSA test and a digital rectal examination. The form of case selection should not be confused with issues relating to population screening.

Once an individual wants to proceed with PSA testing, I suggest the following:

- take an initial PSA test at the age of 40 years
- monitor the PSA velocity rather than using absolute PSA cut-off values
- include a digital rectal examination and do not act on an isolated PSA reading
- stop PSA testing once the patient's life expectancy is less than 10 years or possibly 15 years
- stop PSA testing if the PSA value is less than 1 ng/mL at the age of 65 years or less than 3 ng/mL at the age of 75 years, and consider less frequent testing if the PSA value is less than 1 ng/mL.

The decision process

Several factors should be considered when discussing with a patient the decision to undergo PSA testing.

Clarify the patient's concerns

Find out if he is worried about the presence of urinary symptoms or truly concerned about cancer.

Provide basic information

Describe the prostate and discuss prostate cancer. Explain how accurate the PSA test is and the fact that PSA testing and digital rectal examination need to be performed together.

Provide an estimate of risk

Describe the patient's lifetime risk of having prostate cancer and what his lifetime risk is of dying of prostate cancer, particularly in the context of any family history of prostate cancer. Explain that a person's PSA level at the age of 40 years gives an estimate of his lifetime risk. Generally, at least a 10-year life expectancy, and preferably a 15-year life expectancy, is needed to benefit from early detection. Men aged between 50 and 75 years are most likely to benefit from early detection, although men with a significant risk factor, such as a family history of prostate cancer, are also likely to benefit from the age of 40 years.

Explain the pros and cons of early detection

Pros

- Early stages of cancer have no symptoms and PSA testing can detect prostate cancer before there are symptoms, thus increasing the chance of detecting prostate cancer at an earlier stage.
- Prostate cancer may progress over time. Modern treatments have a high cure rate for the majority of tumours detected by PSA testing.
- Prostate cancer that has spread beyond the prostate is more difficult to cure.
- The side effects of treatment are fewer with earlier diagnosis and treatment and the treatment of advanced cancer has significant side effects.
- It has now been established that the treatment of localised prostate cancer by surgery decreases the chance of metastatic disease and death from prostate cancer compared with simple observation.

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- Most prostate cancers detected in patients with more than a 15-year life expectancy are, indeed, significant cancers and will lead to morbidity.
- A very low PSA level of less than 1 ng/ml and a normal digital rectal examination can be very reassuring.
- Side effects of treatment have particularly reduced in the past two decades in high-volume centres.
- A European randomised control trial confirms a survival benefit of early detection.

Cons

- Abnormal PSA levels are not specific to prostate cancer. Indeed, only 40% of people with a PSA level of between 4 and 10 ng/ml, will prove to have cancer.
- Some prostate cancers grow slowly and are not a threat to life.
- A US randomised clinical trial has not demonstrated a survival benefit of PSA testing.
- Even with early detection, a cure cannot be guaranteed.
- The biopsy process itself can cause infection in a small number of people.
- As with many cancers, if prostate cancer is diagnosed, treatment decisions can be quite difficult and patients will need time to consider their options.

Explain treatment side effects

There are many potential treatment options for localised prostate cancer and each has the potential to cause side effects, in particular erection, urinary and bowel problems. It should, however, be mentioned that these problems have markedly reduced in incidence in recent times, particularly in experienced units.

Help clarify the patient's values

Try and work out whether the patient is the type of person who would rather be tested or not. For example, a man focused on minimising the chance of dying or developing advanced prostate cancer is clearly a candidate for testing. However, a man who feels his chance of developing prostate cancer is low and who is particularly concerned about potential side effects of treatment or is not convinced of the effectiveness of testing may choose to not be tested.

Describe the sequence of events after testing

It is important to describe what happens after the PSA test and digital rectal examination. If either result is abnormal, particularly the digital rectal examination, the patient will be referred for biopsy. If the PSA level is abnormal, it may need to be monitored or the test repeated; if the level is still elevated, a referral for biopsy may be necessary. If a biopsy is recommended, the patient must understand that this is performed under light anaesthesia and there is a small risk related to the procedure, particularly regarding infection. If a cancer is detected, treatment options will need to be carefully discussed, and the patient may wish to have a second opinion.

Decision confirmation

Ensure that the patient has asked all the questions he had regarding PSA testing. It is also important to emphasise that there should be no ejaculation for 48 hours before a PSA test. It is ideal to make another appointment for discussion of the results.

Using the PSA test

What is PSA?

PSA is a protein called 'prostate specific antigen' and is made exclusively in the prostate. It is present in very high concentrations in the ejaculated fluid, which is completely normal. When the prostate is abnormal, some PSA leaks into the bloodstream and can be detected in a blood test. Levels of up to 4 ng/ml in the bloodstream are generally normal (although younger men have lower limits). The conditions that cause an elevated PSA level in the blood are prostate cancer, prostate enlargement and prostatitis. The level of PSA, therefore, is specific to the prostate, but not to prostate cancer.

How to test

A blood test is performed to measure PSA levels and it is important to advise men to avoid ejaculation, either by masturbation or intercourse, for 48 hours prior to testing. Long-distance bike riding should also be avoided. A digital rectal examination can be performed at the same time as PSA testing without affecting the results.

A digital rectal examination must also be performed. The patient lies on his left side and the GP feels, with a gloved finger and plenty of lubricant, the back of the patient's prostate. When the patient has relaxed the posterior surface of the prostate will be felt bulging into the rectum, 3 to 5 cm inside the anus. It has two symmetrical lobes and feels like a rubbery gland. It should never be hard. An enlarged prostate is not of any concern, but severe asymmetry, a nodule or hardness are of concern.

PSA testing can be performed annually and attracts a Medicare rebate. If the PSA level is less than 1 ng/ml, less frequent testing, such as every two to four years, can be performed.

When to refer a patient for a biopsy

A patient should be referred for a biopsy if:

- digital rectal examination is abnormal
- the PSA level is above the age-specific reference range
- the yearly rate of rise of PSA level is more than 0.5 ng/mL in a man under the age of 55 years or more than 0.75 ng/mL in a man over the age of 55 years
- the free to total PSA ratio is less than 10%, even if the PSA level is within the normal range, particularly in younger patients.

The final decision to proceed to biopsy must not only take into consideration the above but also the patient's age, family history of prostate cancer, ethnicity, prior biopsy history and general health. It must be a shared decision between doctor and patient.

Active surveillance

Careful monitoring of patients should be considered if:

- the PSA level is between 4 and 10 ng/mL in a man over the age of 60 years with an enlarged, benign prostate and a high free to total PSA ratio of more than 25%
- the PSA level has increased by more than 0.5 ng/mL but less than 0.75 ng/mL in one calendar year in a man over the age of 55 years.

Interpreting the PSA test

Factors that need to be considered when interpreting a PSA test result include:

- a single PSA test at the age of 40 years can provide an idea of the likelihood of a man developing cancer in his lifetime. A man with a PSA level of more than 0.6 ng/mL is 3.5 times more likely to develop cancer in his lifetime than a man with a PSA level of less than 0.3 ng/mL. This can help guide the frequency of PSA testing
- age has an effect on the PSA level. If a man is under 50 years, his PSA level should be less than 2.5 ng/mL. If he is between the ages of 50 and 59 years, his PSA should be less than 3 ng/mL. For all other patients, the PSA should be less than 4 ng/mL
- if the PSA is in the upper range of normal, watch the PSA velocity carefully. If the patient is less than 55 years of age, a yearly PSA velocity of up to 0.5 ng/mL is acceptable; however, if he is over the age of 55 years, a velocity of up to 0.75 ng/mL per year is acceptable
- if the PSA level is in the upper range of normal or only just elevated in an older man it may be worthwhile measuring the free to total PSA ratio. If this is more than 25%, it is very reassuring; however, if it is less than 10%, it is very concerning
- remember, there are many causes for an elevated PSA level other than prostate cancer. These include prostatic enlargement, urinary infection, prostatitis, prostate biopsies, very long-distance bike riding and recent ejaculation
- if infection occurs, particularly in the prostate, it often takes three to six months before the PSA level settles
- some drugs, such as dutasteride or finasteride, affect PSA levels. Finasteride halves the level of PSA and when calculating the risk of cancer, the PSA measurement therefore needs to be doubled in a patient taking finasteride
- if the PSA level is in doubt, it is mandatory to repeat the PSA test and preferably do a urine test at the same time. This should be performed before referring the patient to a urologist for a biopsy
- remember that lower urinary tract symptoms bear no relation to PSA levels. If the prostate is enlarged and this is leading to urinary symptoms, the PSA may be moderately elevated. Clearly, the prostate size needs to be taken into consideration to some degree in a patient with a modestly elevated PSA level, before referring the patient for biopsy
- a negative biopsy, unfortunately, is not foolproof. Ongoing monitoring of the PSA level is mandatory and if the PSA velocity is high, re-referral is necessary. A new test, the PCA3 urine test, may help establish whether there is truly a cancer that has been missed
- after treatment, such as surgery, the PSA level should remain below 0.1 ng/mL, whereas after radiotherapy or brachytherapy, the PSA level should preferably drop to below 0.5 ng/mL and should never go above 2.0 ng/mL.

Take home messages

- Always repeat the PSA test prior to referral, particularly if there are any other reasons for an increased level.
- Ensure no ejaculation occurs for 48 hours before PSA testing.
- Be more vigilant in young men, particularly those with a family history of prostate cancer.
- Use the same laboratory each time to measure the PSA level.
- Tailor the PSA testing to the individual (depending on factors such as age, anxiety levels, family history of prostate cancer, prostate size and PSA velocity). MT

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