

Prostate cancer

Part 1. issues in screening and diagnosis

Prostate cancer is common, affecting about 13% of Australian men at some stage in their lifetime. In the face of continuing debate about screening asymptomatic men for the disease, it remains the primary physician's responsibility to make appropriate patients aware of the potential benefits and risks.

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Prostate cancer is the most common malignancy after skin cancer in Australian men. In 1995, about 12,000 cases were reported and the disease was responsible for 2564 deaths (13.3% of all cancer deaths in men). A patient who has a first degree relative with prostate cancer has twice the risk, and five to eight times the risk if a second relative is also affected. The inherited form accounts for 43% of prostate cancers in men before the age of 55 years, but only 9% of all cases.

The likelihood that a patient's cancer will cause him problems is related to his age (younger age increases the likelihood) and the aggressiveness of the cancer. Many prostate cancers in older men

never cause problems because the cancers generally grow slowly and patients die as a result of other causes.

Prognostic markers

Reliable prognostic markers to separate individuals with potentially fatal disease from those who will not die from prostate cancer are crucial in developing management strategies for prostate cancer. Several markers for prostate cancer are currently used to predict the natural history of the disease, select appropriate treatments and compare treatment outcomes.

A patient's blood PSA level is a useful prognostic

IN SUMMARY

- A man's lifetime risk of developing prostate cancer is about 13%, and his chance of dying of the disease is about 2%. As the population ages, these statistics are likely to deteriorate further.
- Patients should be made aware of the PSA test, but should undergo an informed consent process prior to screening.
- Screening (if elected for by the patient) should commence at the age of 50 years with a digital rectal examination and a serum PSA test. A biopsy should be performed if the rectal examination is abnormal or if the PSA reading is greater than the age specific reference range.
- If a patient has a family history of prostate cancer, screening should commence at 40 years of age and continue annually until his life expectancy falls below 10 years.
- Of patients with a PSA level between 4 and 10 ng/mL, 25% have prostate cancer. The use of free/total PSA ratios can improve test accuracy.
- PSA levels may be elevated significantly by complicated benign prostatic hyperplasia (associated with retention, infection or prostatitis) or by prostate manipulation, such as biopsy or transurethral resection. Recent ejaculation may also increase PSA levels.

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marker. The range of normal values varies with age (Table), with levels over 10 ng/mL considered to be high. Trans-rectal ultrasound-guided biopsy provides other prognostic information, such as the Gleason sum (calculated using a histological grading system). Clinical staging provides additional information, and is described in the box on this page.

When a diagnosis of prostate cancer is made, the markers can help to predict the likelihood of spread beyond the capsule, spread to lymph glands and the likelihood of cure. Further staging involves the use of bone scans and abdominal/pelvic CT scans, but these have a very limited role unless the PSA level is above 10 ng/mL or the cancer is high grade.

Screening for prostate cancer

Screening for prostate cancer attempts to diagnose cancers in the asymptomatic population earlier and improve the cure rate. Individuals may also request PSA screening or be selected for screening when they present with urinary symptoms.

Histological evidence of prostate cancer is present in 30 to 40% of men over the age of 50 years, but only one-quarter of these cancers become clinically evident. Very few 'autopsy tumours' result in an elevated PSA level, and so these are rarely picked up by screening programs.

What is the controversy?

At present, there are two schools of thought about PSA testing for prostate cancer.

Advocates cite the large number of patients who die of the disease as sufficient justification to initiate screening programs, arguing that lives can be saved by early detection and treatment. Their case has recently been strengthened by evidence for the following:

- the so called latent cancer or 'autopsy' cases do not appear to be detected by PSA screening
- watchful waiting in younger patients with less differentiated tumours has a

high mortality over time

- modern treatments give long term control of most tumours detected by screening and produce fewer side effects than earlier techniques
- the falling death rate from prostate cancer may be attributable to screening
- screening is most likely to benefit patients who have at least 10 years of life expectancy (and inappropriate screening in the much older age group can thus be avoided).

Critics of prostate cancer screening argue that the associated complications and costs are not sufficient to justify widespread implementation of aggressive screening programs. They point out that:

- only 25% of men who have a PSA level in the suspicious range (i.e. between 4 and 10 ng/mL) will have cancers detected on biopsy
- if the PSA level is greater than 10 ng/mL, 50% of men will already be incurable
- 25% of men with prostate cancer have a PSA level below 4 ng/mL (that is, cancers that can be detected only by rectal examination).

Until better data become available, such as trends in prostate cancer mortality and results from ongoing clinical trials, the debate about screening for prostate cancer cannot be resolved.

How do we advise our patients?

Ideally, physicians should discuss the benefits and risks of screening with each patient. Many men have preconceived ideas about prostate cancer and screening that have been formulated from incomplete or inaccurate information from acquaintances, advertisements and the media. In general, patients should be made aware that the PSA test exists, but they should undergo an informed consent process prior to screening (the discussion points in the box on page 5 may be helpful). In particular, patients need to be given information about:

Table. Age-specific PSA reference ranges

Age (years)	PSA level (ng/mL)
40 to 49	0 to 2.5
50 to 59	0 to 3.5
60 to 69	0 to 4.5
70 to 79	0 to 6.5

Clinical staging for prostate cancer

The TNM staging system for prostate cancer is used to describe the extent of the primary tumour (T), the presence of metastasis to nearby lymph nodes or glands (N), and the presence of distant metastasis (M).

The four stages of the primary tumour are explained below.

Stage T1. Tumour not clinically apparent and not detected by digital rectal examination.

Stage T2. Tumour confined within the prostate and detectable by digital rectal examination.

Stage T3. Tumour extending through the prostate capsule without spread to other organs.

Stage T4. Tumour fixed or invading adjacent structures other than seminal vesicles.

- the overall incidence of cancer and death rate from untreated prostate cancer – an individual's lifetime risk of developing prostate cancer is about 13%, and his chance of dying of the disease is about 2%
- the accuracy of the PSA test (see the section 'What is the controversy?')
- the side effects of investigations

- the rates of cure, survival and side effects of each form of treatment (to be discussed in part 2 of this article)
- the possibility that treatment (if selected) may be initiated for an insignificant tumour (10%).

Patients should also be informed that screening may be contributing to the decreasing death rate from prostate cancer, as well as the fact that a negative biopsy does not totally exclude the risk of prostate cancer. Finally, each patient should be informed about particular risk factors for prostate cancer (such as a strong family history), and understand if he is at high risk.

How should we screen?

Screening, if elected for by the patient, should commence at the age of 50 years (and possibly earlier) with a digital rectal examination and a serum PSA test. A biopsy should be performed if the rectal examination is abnormal or if the PSA reading is greater than the reference range for his age.

There is increasing evidence that PSA testing beginning as early as the age of 40 years may predict the likelihood of later clinical cancer. For example, if a patient's PSA level between the ages of 40 and 50 years is greater than 0.6 ng/mL, he is seven times more likely to develop prostate cancer than if his level is less than 0.3 ng/mL. If a patient has a family history of prostate cancer, screening should commence at 40 years of age and continue annually until his life expectancy falls below 10 years. Currently, 25% of Australian men over the age of 40 years are having regular PSA tests.

Who should we screen?

Assessing a patient's preferences and determining the likelihood that he will benefit from screening are part of the physician's responsibility. For example, a patient who has a life expectancy of less than 10 years is unlikely to benefit from screening and may suffer a significant

reduction in his quality of life. The final decision about whether or not to screen will depend on each man's goals, fears and willingness to accept risks.

Screening should include:

- patients at high risk – that is, those with a strong family history
- patients presenting with irritative or obstructive urinary symptoms who wish to be screened after being informed about the benefits and risks
- asymptomatic patients between the ages of 50 and 70 years who wish to be screened after being informed about the benefits and risks.

Can we make PSA screening more accurate?

Approximately 25% of patients with a PSA level between 4 and 10 ng/mL have cancer (note that this percentage is higher if the digital rectal examination is abnormal). This means that 75% of patients with a PSA level in this range will be subjected to unnecessary prostatic biopsies. Furthermore, most prostate cancer patients who have a PSA reading under 10 ng/mL have early stage disease, whereas more than 50% of patients who have a level above 10 ng/mL have extracapsular disease.

The detection of prostate cancer in its curable stages thus requires the use of relatively low PSA cut-off levels for screening. Unfortunately, low cut-off levels produce high numbers of false positive results (benign prostatic hyperplasia and prostatitis are the most common causes), which lead to even more unnecessary biopsies.

There are several ways of reducing the rates of false positive results. One technique is to use age-specific reference changes – a lower PSA cut-off level in younger age groups and higher one at older ages is less likely to miss the important tumours in the younger groups or result in unnecessary biopsies in the older groups (Table). A second technique involves consideration of the size of the

prostate, a correction that allows for the fact that a patient with a very large prostate is more likely to have a slightly higher PSA level.

Use of the free/total PSA ratio can also improve specificity while leading to a small compromise in the detection of prostate cancer for patients with a PSA between 4 and 10 ng/mL (the ratio is not valid outside of this range). The free/total PSA ratio can reduce the number of unnecessary biopsies – using a ratio of 25% as a lower cut-off level, for example, will miss 8% of cancers in this PSA range yet will save up to 30% of the unnecessary biopsies.

Common clinical PSA problems

An elevated PSA! What should I do next?

In general, an elevated PSA test should be repeated with a free/total PSA ratio. The PSA level can be elevated by urinary infection, so a urine analysis by microscopy is essential. If the patient has any suggestion of prostatitis (such as a raised urinary white cell count or tender prostate), a 2- to 4-week course of a quinolone antibiotic should be given and the test repeated in three months.

Referral to a urologist is indicated if the PSA level is elevated above the age-specific reference range on two occasions, especially if the free/total PSA ratio is less than 25%. There is no benefit to be gained from a transrectal ultrasound of the prostate because this investigation does not add any information to the PSA test and the digital rectal examination. It is important to realise that the biopsy – not the ultrasound – gives the diagnosis of prostate cancer.

Should patients with urinary symptoms have PSA tests?

In patients with prostatism, informed consent prior to PSA testing is necessary, with the same argument applying here as for screening. The general consensus, however, is that one is much more likely

to recommend PSA testing when a patient has urinary symptoms because the result is likely to influence management.

If the PSA level is elevated after infection, how long will it take to drop?

The rate of decline of the PSA level after an infection such as acute prostatitis depends on many factors (including the virulence of the organism and the selection of antibiotics), but it may take 3 to 6 months to drop completely. If the PSA level does not completely drop to normal despite long courses of antibiotics, referral to a urologist is indicated.

Can the PSA level help to assess the extent of the cancer?

Yes, the PSA level can help to assess the extent of the cancer.

The best chance of detecting organ-confined cancer is when the PSA is less than 10 ng/mL (preferably less than 7 ng/mL). If the PSA level is greater than 10 ng/mL, the risk that the cancer has microscopically extended beyond the capsule is greater than 50%.

Surgery and radiotherapy have a very low cure rate if the PSA level is greater than 20 ng/mL. If the level is greater than 50 ng/mL, the cancer is almost always metastatic.

What else can affect PSA levels?

PSA levels may be elevated significantly by complicated benign prostatic hyperplasia (associated with retention, infection or prostatitis) or by prostate manipulation, such as biopsy or transurethral resection. Recent ejaculation may also increase PSA levels. Gentle digital rectal examination and transrectal ultrasonography alone do not appear to cause a raised PSA level.

Alpha blockers do not affect the PSA level. Finasteride usually results in a 50% drop in PSA levels over a six-month period. Saw palmetto does not result in a drop in PSA levels. A modest decrease in PSA levels can result from some Chinese

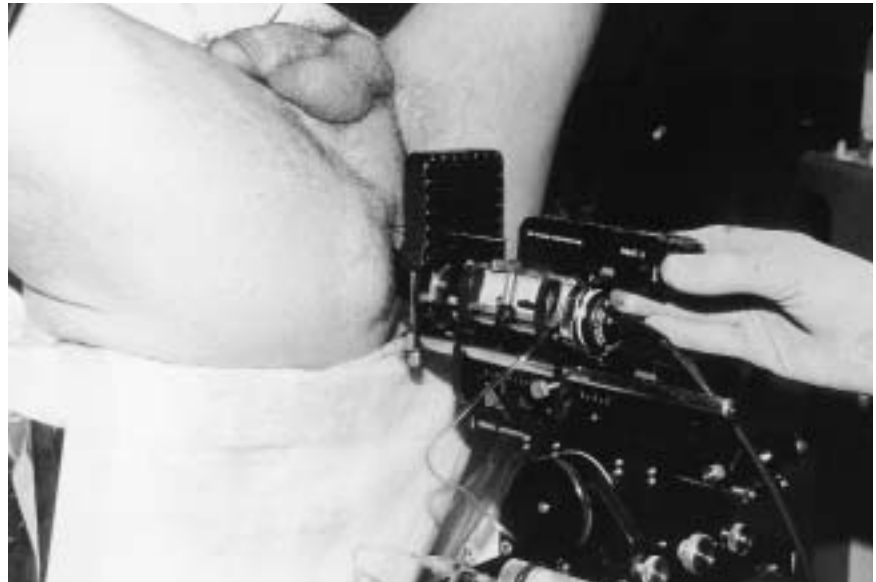


Figure. Transperineal biopsy has been described for patients in whom the transrectal route does not find cancer and the PSA level continues to rise.

herbal treatments, especially those containing strong phyto-oestrogens.

Does the PSA response to treatment help to predict outcome?

Yes, the PSA level after treatment can help to predict outcome.

- After radical prostatectomy, the PSA level should essentially become zero. A level above 0.4 ng/mL suggests clinical failure in the future – on average, this takes eight years to manifest.
- After radiotherapy, the PSA level should plateau below 1.0 ng/mL (ideally below 0.5 ng/mL) and should not subsequently rise.
- After hormone therapy for advanced cancer, a better prognosis is conferred by a PSA level less than 4.0 ng/mL.

How do we follow a patient with an elevated PSA and negative biopsy?

Follow up of a patient with an elevated PSA and negative biopsy will depend on the patient's age, PSA level and biopsy result. In general, the younger the patient,

the higher the PSA level and the more suspicious the biopsy result, the more frequent the follow up should be. If suspicious cells are visible, three-monthly follow up visits with PSA measurements should be arranged; otherwise, yearly visits should be sufficient.

A technique of transperineal biopsy has recently been developed for patients who have a PSA level that continues to rise despite previous negative biopsies. Tumours that are located more anteriorly and missed by the transrectal route are often picked up by the transperineal route (Figure). Approximately 15% of patients who have previously had a negative biopsy will be found to have a cancer.

What about PSA testing and medicolegal concerns?

Informed consent is essential because the consequences of a raised PSA test are far reaching. The implications of either a positive or negative result must clearly be explained. Furthermore, grounds for litigation could arise from failure to perform a digital rectal examination or to order a PSA test in a situation where it

Prostate cancer screening and your patients: points for discussion

There is still disagreement about whether men without symptoms of prostate cancer should be tested for the disease. The debate cannot be resolved until better data become available, but studies to assess the value of screening will not be completed for another five to 10 years. In the meantime, patients need to decide whether they want to be tested.

The information on this page is intended to prompt discussion about prostate cancer and screening that will help your patients to make an informed choice.

The case for screening

- Prostate cancer is common, causing about 2500 deaths per year in Australia. It is the second most common cause of cancer death in men.
- Screening for prostate cancer is probably the best way to minimise the risk of death from the disease. The fall in the death rate and number of cases of advanced cancer may be a result of the screening process.
- Screening for prostate cancer is safe, acceptable and relatively accurate. It involves a digital rectal examination (finger test) and a blood test for prostate specific antigen (PSA).
- The PSA test will find some prostate cancers that cannot be felt by the digital rectal examination and improves the detection of early curable disease. It is simple, inexpensive and minimally invasive.
- About 25% of patients with a PSA reading between 4 and 10 ng/mL have cancer; about 10% of the tumours detected by the test are unimportant (that is, will not cause problems).
- A large percentage of tumours detected by screening can be cured. Many cancers (especially poorly differentiated ones) that are not treated will lead to death over 10 to 15 years.
- In the absence of screening, only a small percentage of men who develop prostate cancer are diagnosed when the disease is in the curable stages. The cost of treating advanced cancer is high. Improvements in surgery and radiotherapy mean that modern treatments produce fewer side effects.
- Screening for prostate cancer once in a man's lifetime may offer little benefit. However, sequential testing is likely to offer better results.

The case against screening

- No study has yet proven that screening reduces population mortality from prostate cancer.
- Many older men with prostate cancer will die from other causes before the cancer produces symptoms.
- Early detection does not necessarily guarantee a cure.

- Screening is not always accurate – there are false positives and false negatives. About 75% of men with an elevated PSA result do not have cancer and may suffer unnecessary anxiety.
- Treatments and investigations have significant side effects, such as impotence, incontinence and bowel damage.
- The course of prostate cancer is unpredictable.
- Screening for prostate cancer involves a significant cost to the community.

What patients should know

In the face of these conflicting ideas, the following information about screening for prostate cancer is offered:

- The decision about whether or not to be screened depends on each man's goals, fears and willingness to accept risks. Screening should be performed if he wants to minimise his risk from prostate cancer and maximise his chance of living as long as possible; it should not be performed if he wants to maximise his immediate quality of life, minimise his risks of treatment complications, or only undergo medical tests that are clearly proven to be beneficial.
- In the Australian population, one man in every 18 will be found to have prostate cancer. One man in every 65 will die of prostate cancer.
- If a patient undergoes screening, a rectal examination and PSA testing should both be performed. If he has a normal result on rectal examination but abnormal PSA test, his chance of prostate cancer on biopsy is about one in four. If either his PSA test or rectal examination is abnormal, he should be offered a biopsy.
- The actual screening causes little discomfort. However, a biopsy (if necessary), may lead to a risk of infection (in less than 1% of cases). Treatment for the cancer (such as surgery or radiotherapy) may result in varying degrees of impotence, incontinence or bowel damage.
- There is no consensus about the best treatment for each man's prostate cancer. Today's options include surgery, radiation, radioactive seeds, hormone therapy and simple observation.
- A man's likelihood of benefit from screening decreases as he gets older. Screening is most likely to benefit men with at least 10 years of life expectancy, which means it is most appropriate in those aged 50 to 70 years and least appropriate in those over 75 years. Screening may also benefit men who are at increased risk of prostate cancer, especially those with a family history of the disease (such as a father or brother with known prostate cancer).

could be argued that the investigations were indicated – for example, a patient who is diagnosed with advanced cancer and was previously not informed that a PSA test existed.

What rate of change in the PSA level on yearly screening is of concern?

If the rate of change of the PSA level is greater than 0.75 ng/mL per year over a three-year period, it is much more likely that the patient has cancer than benign prostatic hyperplasia. This rate of change should therefore be an indication for biopsy in a patient who is having annual screening.

Prevention and aetiology

The aetiology of prostate cancer is not known, but is believed to be influenced by genetic and dietary factors. Factors that increase the risk of prostate cancer

include:

- a family history
- excessive dietary fat
- Afro-American race
- lack of selenium
- lack of exercise.

Factors that may reduce the incidence of prostate cancer include the administration of selenium, vitamins E and D, soy protein and lycopenes. However, most of the evidence supporting these dietary suggestions comes from epidemiological studies and is therefore not compelling.

Diagnosis and staging

Systematic core biopsy of the prostate under ultrasound guidance is the most accurate way of diagnosing prostate cancer. The procedure may be performed as an outpatient or under day-only general anaesthesia, and is undertaken if the PSA level is in the abnormal range or if the rectal examination is abnormal.

The risk of septic complications arising from biopsy has decreased to less than 1%, and is as low as 0.1% in modern series. The incidence can be minimised by use of prophylactic antibiotics, careful technique and careful patient selection (avoiding those with prostatitis). The ultrasound itself rarely gives further information beyond the digital rectal examination and PSA test.

Summary

Prostate cancer is a common and complex disease. It is the primary physician's responsibility to make appropriate patients aware of the potential benefits and risks of screening with digital rectal examination and PSA testing. MT

Part 2 of this article will discuss the current treatment options for patients with localised prostate cancer or advanced disease.