Investigating **prostate cancer**

CONTROVERSY RAGES OVER THE PSA TEST TO HELP DETECT CANCER OF THE PROSTATE, AND HOW TO PROCEED IF CANCER IS DIAGNOSED. **TONY JAMES** LOOKS AT THE ISSUES.

PHOTOGRAPHER: EAMON GALLAGHER AND PAUL JONES

Two men are comparing their latest prostate specific antigen test results, and joke that they have more in common than they thought – both had a result of 3.9 micrograms per litre (µg/L).

One is 75 years old, has diabetes and has suffered a heart attack. The other is 56 and in good health, but his older brother was recently diagnosed with advanced prostate cancer.

PSA is one of the best available blood tests to assist in cancer diagnosis, but the numerical result in these two men might have profoundly different implications. In the older man, the result is unlikely to reflect serious disease, and the chances are that he will die from causes other than prostate cancer.

In the younger man with a family history of cancer, the result would be concerning and should prompt follow-up investigations. There is the potential to diagnose a treatable cancer in its early stage, and extend his life. In either case, a PSA test cannot diagnose cancer – that requires a biopsy and microscopic investigation of sample tissue.

Despite rapid progress in understanding prostate cancer, its diagnosis and its treatment, controversy still rages on who should have a PSA test, at what age men should be tested, how "normal" results are defined, and how to follow up "abnormal" results.

Even more surprisingly, there is debate about how the cancer should be treated once diagnosed, and if early cancer should be treated at all: tumours often grow slowly and allow time for repeated review, and many men die "with" rather than "from" the cancer.

Dr Ken Sikaris, a chemical pathologist at Melbourne Pathology and an expert on the PSA test, says it is essential for doctors and their patients to understand the meaning of a result, and use the information as just one factor in the difficult decisions that might follow.

"Australia is lucky to have access to very high quality pathology services, and PSA is an extremely useful test, but decisions can't be made on the basis of PSA alone," he says. "Our aim is to help patients and their doctors to discuss the options on the basis of the best possible information."

Unlike many markers of disease detected by blood tests, PSA is a normal glandular product. "Usually just one in a million molecules of PSA will escape into the bloodstream," Dr Sikaris says. "One of the features of cancer cells is that they promote the growth of new blood vessels around them. It's thought that this process is responsible for the increase in PSA levels in blood that occur when cancer develops."

The upper limit of normal for PSA of 4 µg/L was determined in the late 1980s, but concentrations can be thousands of times

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higher in advanced cancer. The 4-µg/L threshold was established as a reasonable compromise between detecting as many cases as possible (that is, being sensitive), but not labelling too many healthy men as requiring further investigations (that is, being specific).

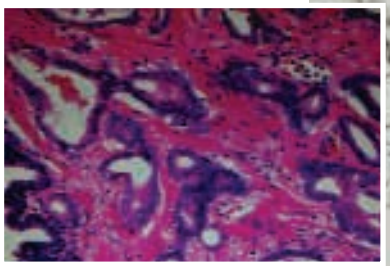
On average, PSA levels increase slowly with age. One response was to develop age-specific upper limits of normal – for example, from 2.5 µg/L for men in their 40s ranging up to 6.5 µg/L for men in their 70s. This method is still used, but Dr Sikaris says it raises some important philosophical questions about the risks of missing treatable cancer in older patients.

"Recent information suggests that up to 30% of significant cancers are associated with a PSA in the range of 2.5 to 4 µg/L," he says. "These are likely to be highly responsive to treatment, and it is a challenge to define patients in this range who are at risk."

Several techniques have been used to add value to a standard PSA test. The ratio between "free" and "bound" PSA is one option. Blood levels of free PSA are increased by events such as exercise, ejaculation and a digital rectal examination but return to baseline within about 12 hours.

PSA that circulates in the blood bound to an inhibitor is more long lasting, and therefore a more stable indicator of long-term leakage from the prostate into blood. "If the PSA is more than 2.5 µg/L and more than 90% is in the bound form, then the patient is very likely to have cancer," Dr Sikaris says.

The rate of increase in PSA over time – the PSA velocity – can be used to interpret changes in the prostate when men have chosen "watchful waiting" or to check for recurrence of cancer after treatment. An increase of more than 0.85 µg/L per year



is a marker of high risk, but does not account for whether the starting point was low or high (say 2 µg/L or 8 µg/L).

"A much more useful concept is the time it takes for PSA to double, for example from 3 µg/L to 6 µg/L," Dr Sikaris says. "If the doubling time is less than about two years, then the cancer is likely to be an aggressive one." Although there are no firm recommendations, four measurements taken three months apart are probably required to accurately calculate doubling time.

Dr Warick Delprado, an anatomical pathologist at Douglass Hanly Moir Pathology in Sydney, has a special interest in genitourinary disease, and examines prostate biopsy specimens. "The usual path is for patients to be referred by their GP to a urologist, prompted by concerns such as prostate cancer in their father or a brother, a high PSA result, abnormal findings on a digital rectal examination, or lower urinary tract symptoms," he says.

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In a procedure that's hardly appealing but generally well tolerated, the urologist uses a large-bore needle inserted through the rectum and guided by ultrasound to cut anywhere between six and 20 cores of prostate tissue for the pathologist. Like core samples of earth taken by geologists - but fortunately only about 1 mm in diameter and 10-15 mm long – they can give a representative but not necessarily complete picture of the prostate's structure.

Apart from discomfort at the time and some pain and bleeding in following days there is also a risk of infection and other complications, so the procedure is not performed without careful discussion of the need for biopsy, and the consequences of finding a tumour.

Pathologists like Dr Delprado report on the biopsy samples in a standardised, structured format. A list of criteria about the extent and nature of any abnormalities provides essential prognostic information, including a statistical probability of disease progression.

The Gleason score grades changes on a 10-point scale, with scores of 5 or less reflecting low-risk tumours and no increase in mortality, 6 suggesting that cancer is more advanced but still confined

within the prostate, and scores of 7 to 10 reflecting higher-grade tumours that may extend outside the prostate. Sophisticated programs are available to calculate risks of death, taking account of factors such as the number of cores that include abnormal cells and the proportion of each core that is affected.

The patient and his doctors then need to interpret the findings and decide on the next step. “This can be very complex and must consider not just the pathology report but other factors such as the man’s age and health and his attitude to the risk of cancer progression,” Dr Delprado says. For a low-grade tumour, some men will be content to adopt watchful waiting while others will want it removed; for high-grade tumours or prostate cancer that has started to spread, active treatment is much more likely.

Pathologists also examine the entire prostate and associated tissues if patients have a radical prostatectomy. Using up to 50 cross-sectional slides to obtain a full view of the organ, this provides information such as a definitive Gleason score, the extent of the cancer within the prostate, and whether it has spread to surrounding tissues and lymph nodes.

The information helps inform patients about their outlook and guide future treatment, which may involve radiotherapy, hormonal therapy or palliative care.

In some types of cancer, it is now possible to identify molecular markers to define the exact disease process and guide specific treatment. Prostate cancer is not yet at that stage, but there is interesting research in the area, Dr Delprado says. For example, Sydney-based researchers are investigating alternatives to PSA that might distinguish between cancerous and non-cancerous prostate changes from blood samples, and whether pre-malignant changes can be detected in prostate cells obtained by biopsy.

“We still have many unanswered questions about the most basic aspects of prostate cancer,” Dr Delprado says. “These include when to biopsy, how do we identify life-threatening cancer in a needle biopsy, and finally, who will benefit from treatment and what type of treatment should be chosen?” A number of large, long-term clinical trials currently in progress will help resolve the uncertainties.

What is PSA?

Prostate specific antigen (PSA) is a normal product of the prostate gland and an essential component of semen. PSA has a vital role in maintaining a man’s fertility, breaking down the gel-like structure of semen as it nears the cervix, allowing sperm to move more freely and increasing their chance of reaching their target egg.

How is PSA measured?

Measurement involves a simple blood test, usually organised by a GP. “Normal” levels are below 4 µg/L, but this limit can be adjusted to account for a man’s age. Other techniques, such as PSA velocity and PSA doubling time, can be used (see main story for details).

Should every man have a PSA test?

Screening of the whole population is not currently recommended. The decision to have a test requires careful discussion between patient and doctor about the implications of an abnormal result, and is usually addressed once men reach 50 (in the absence of warning signs such as a family history of the disease or significant urinary tract symptoms).

Does an elevated PSA indicate cancer?

Moderately elevated PSA levels indicate only that cancer is more likely, but a minority of men with a high PSA will actually have the disease.

How is prostate cancer diagnosed?

Men with an elevated PSA and/or other features suggesting prostate cancer will require a biopsy of the gland before cancer can be diagnosed. One-third or fewer of men having a biopsy will have cancer.

How is prostate cancer treated?

Options include watchful waiting for apparently low-grade cancer (usually involving careful follow-up with repeated PSA measurements), active treatment (radical prostatectomy to surgically remove the gland and associated tissues, radiotherapy or hormonal therapy, either alone or in combination), or palliative care for advanced disease. Treatment decisions must be individualised.

Why is prostate cancer diagnosis and treatment controversial?

Unresolved questions include:

- Whether widespread screening of PSA would save lives.
- How to interpret moderately elevated PSA levels.
- Whether treatment of cancer will save an individual’s life, and the risks of unnecessarily treating men with prostate cancer that would never have killed them or caused serious symptoms.

Both Dr Delprado and Dr Sikaris are keen for pathologists to contribute to the debate about prostate cancer. “The issues need to be discussed and publicised, and it is now clear that early diagnosis and treatment can lead to improved survival in some patients,” Dr Delprado says.

Dr Sikaris emphasises the need for men and their doctors to work together to make decisions. “This can’t happen if both have their heads in the sand,” he says.

GPs NOTE: This article is available for patients at http://pathway.rcpa.edu.au