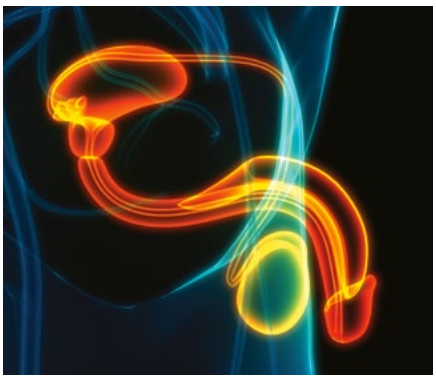
Prostate-specific antigen testing for prostate cancer

Time to reconsider the approach to screening



CPD

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Background
Prostate cancer is now the most common cancer in men in Australia. Men should be aware of the potential risk of significant prostate cancer despite the lack of symptoms. Screening for prostate cancer using prostate-specific antigen (PSA) has been controversial. General practice guidelines can be confusing leading to men not being tested for prostate cancer. Reasons cited include overdiagnosis and overtreatment with associated morbidity.

Objective
This article aims to highlight the current evidence for PSA testing and advocate for updating outdated guidelines and resources.

Discussion
Current evidence shows that a risk-stratified approach to PSA screening helps to assess that risk. Recent studies show improved survival rates with early intervention compared with observation/delayed treatment. Imaging, including magnetic resonance imaging and prostate-specific membrane antigen positron emission tomography, have made a significant difference in the management pathway. Biopsy techniques have progressed to minimise sepsis risk. Quality and patient-reported outcomes registry data highlight the increased use of active surveillance in patients with low to intermediate risk of prostate cancer, reducing treatment-associated harms in men with low risk of progression. There have also been improvements in medical therapeutics for advanced disease.

PROSTATE CANCER SCREENING has been controversial for many years, with primary care physicians uncertain about whether to offer a prostate-specific antigen (PSA) blood test to asymptomatic men.

The reasons cited have traditionally been anxiety over missing cancer in a man with a raised PSA from benign disease, the risk of infection associated with transrectal biopsy, overdiagnosis of indolent cancer and the morbidity of treatment (especially erectile dysfunction and urinary incontinence). While many men with prostate cancer might live long lives without the need for treatment, prostate cancer is now the most commonly diagnosed cancer (overtaking breast cancer) and the second-most common cause of death from cancer in Australia (Box 1).[1] Revisiting the need for early detection of a disease affecting over 24,000 men and killing over 3,500 men every year is therefore critical.

Current Australian PSA testing guidelines need updating

PSA screening guidelines were established in 2015 by the Prostate Cancer Foundation of Australia (PCFA) and the Cancer Council of Australia. These were endorsed by several organisations, including the National Health and Medical Research Council (NHMRC), The Royal Australian College of General Practitioners (RACGP) and the Urological Society of Australia and New Zealand (USANZ).[2] The guidelines recommend that men aged 50 years and over should be made aware of prostate cancer and, after discussing the risks and benefits, decide whether they wish to have a PSA test. This practice guideline, despite RACGP endorsement, is not reflected in the current (9th) edition of the Red Book and needs urgent updating.[3] For example, The RACGP's decision aid continues to reference an outdated figure depicting 'men at risk of prostate cancer', which recommends against prostate cancer screening,[4] despite being removed by its original source, the Harding Center for Risk Literacy,[5] and replaced by a figure demonstrating the survival benefit of PSA screening.[6] The

PCFA guidelines are also dated and are now being revised with recent evidence strengthening the need for a risk-stratified PSA screening approach.

How has the evidence changed?

When The RACGP guidelines were first developed, the evidence for PSA testing was based on two large, randomised trials: the European Randomised study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial. While the ERSPC trial showed a 21% reduction in prostate cancer deaths with PSA screening at 11 years, the PLCO trial failed to demonstrate a benefit,[7] thereby confusing the benefits of PSA screening. Subsequently, the PLCO study was found to be heavily flawed, as it included almost 80% of patients with at least one PSA test done in the non-PSA screening control arm (who should not have had a PSA test), thereby contaminating the findings.[8] The 16-year follow-up data from ERSPC further strengthened the argument for PSA screening, demonstrating that only 570 men needed to be screened to prevent one prostate cancer death at 16 years compared with 742 men at 13 years.[9]

The impact of radical treatment of PSA-detected prostate cancer was also unclear when the initial RACGP and PCFA PSA guidelines were developed. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) and the Prostate Testing for Cancer and Treatment (ProtecT) trial conducted in the PSA era initially did not demonstrate a survival benefit with early intervention compared with observation/delayed treatment.[10,11] However, more recent updates of these two studies and others demonstrate survival benefits with early intervention compared with observation/delayed treatment (Box 2).

The PIVOT study showed a 5.7% absolute risk reduction in prostate cancer deaths at 22.1 years follow up and one year of life gained with intervention compared with observation.[12] The number needed to treat to prevent one death was 18, and the absolute effects were greater in men with an intermediate risk of prostate cancer. The results from the ProtecT trial, in which localised prostate cancer patients were randomly allocated to active monitoring, radical prostatectomy and external beam radiotherapy, were also recently re-evaluated, as 22% of the 1643 men in the randomised trial did not receive the initially allocated treatment.[13] This exploratory analysis was performed by the treatment received and also demonstrated a 69% reduction in prostate cancer mortality with radical treatment, with metastasis and disease progression being at least twice as common in the active monitoring group. However, the absolute risk reduction of prostate cancer was modest due to the small number of prostate cancer deaths at 10 years. The Scandinavian Prostate Cancer Group-4 (SPCG-4) study from the pre-PSA screening era also reported 29-year follow-up results.[14] SPCG-4's research demonstrated an 11.7% absolute risk reduction in death from prostate cancer, with 8.4 men needing treatment to prevent one prostate cancer death and gaining 2.9 extra years of life with radical prostatectomy compared with observation at 23 years. A recent Cochrane review of these studies showed a 43% reduction in death from prostate cancer (hazard ratio [HR] 0.57 [95% confidence interval (CI): 0.44, 0.73]) and a 44% reduction in metastatic disease (HR 0.56 [95% CI: 0.46, 0.70]) at 19.5 years with treatment compared with observation.[15]

Although these studies were conducted in the pre-magnetic resonance imaging (MRI) and pre-biomarker era, they highlight the benefits of PSA screening and the importance of accurate risk stratification in identifying patients who would benefit from treatment.

Addressing the harms associated with prostate cancer testing

Significant advancements in assessment have reduced the risk of PSA testing. Men who have a raised PSA (>3) should

Box 1. Prostate cancer statistics in Australia[1]

- Prostate cancer is the most commonly diagnosed cancer in Australia and the most commonly diagnosed cancer among Australian men.
- 24,217 Australian men were diagnosed with prostate cancer in 2022.
- 3,507 Australian men died from prostate cancer in 2022.
- 240,245 Australian men are alive today after a diagnosis of prostate cancer between 1982 and 2017.

Box 2. Updates in prostate screening trials demonstrating survival benefits with the early intervention compared with observation/delayed treatment

- **PIVOT (Prostate Cancer Intervention Versus Observation Trial) study at 22 years[10,12]**
  - 5.7% absolute risk reduction in death and one year of life gained. The number needed to treat (NNT) to prevent one death = 18.
  - Absolute effects were greater in men with intermediate risk of prostate cancer.
- **ProtecT (Prostate Testing for Cancer and Treatment) study at 10 years[11,13]**
  - 69% reduction in prostate cancer mortality with radical treatment.
  - Metastasis and disease progression were at least twice as common in the active monitoring group.
- **SPCG-4 (Scandinavian Prostate Cancer Group-4). Pre-PSA screening era, at 29 years[14]**
  - 11.7% absolute risk reduction in death from prostate cancer. NNT to prevent one prostate cancer death: 8.4.
  - 2.9 extra years of life gained with radical prostatectomy at 23 years.
- **Cochrane review 2020 at 19.5 years[15]**
  - 43% reduction in death from prostate cancer 44% reduction in metastatic disease.

undergo a second test, ensuring that sexual activity did not take place for three to four days before the test as ejaculation can result in a false positive. The possibility of an asymptomatic urinary tract infection should also be excluded. A specialist urological referral is indicated if prostate cancer is still suspected.[2]

While a digital rectal prostate examination is not commonly undertaken in general practice, it is still conducted as part of a urological assessment. Where doubt remains, a multi-parametric MRI (mpMRI) scan offers an additional non-invasive and safe evaluation of relative risk.[16,17] mpMRI increases the detection of clinically significant prostate cancers and reduces the number of patients subjected to biopsy. A systematic review of mpMRI and transrectal ultrasound scan (TRUS) biopsy for the diagnosis of prostate cancer found that sensitivity was increased with the use of mpMRI in the detection of clinically significant prostate cancer compared with older TRUS-guided biopsies (87% versus 60%), and that it also had a higher negative predictive value (72% versus 65%).[17] These results showed that 27% of patients might have avoided a biopsy if mpMRI was used for diagnosis, potentially reducing both the need for a biopsy or missing a significant tumour. The superiority of MRI-guided biopsies was confirmed by a study conducted by Kasivisvanathan et al.[16] Therefore, while the PSA threshold for biopsy has not been reduced, the incorporation of MRI with PSA derivatives (free:total ratio, age-specific ranges, etc) has allowed for better risk stratification and tailoring the need for biopsy in a shared decision-making model.[18]

However, MRI is not a replacement for a biopsy, and the decision to biopsy should be made after a discussion with the patient. The European Association of Urology (EAU) guidelines suggest biopsy may be omitted following negative MRI results (prostate imaging – reporting and data system [PI-RADS] ≤2) after shared decision making, as Ahmed et al demonstrated that 5–10% of significant cancers could be missed on MRI.[17] Therefore, routinely omitting biopsies in non-PI-RADS 4/5 lesions without shared decision making is not advisable.

If a biopsy is indicated based on the above parameters, it is now commonly undertaken via the transperineal route rather than the transrectal route.[19] Transperineal biopsies significantly reduce the risk of sepsis compared with transrectal biopsies (0.3% versus 10%) as well as antibiotic resistance associated with the latter.[20,21] However, urinary retention occurs in 1.6–24% of patients following transperineal prostate biopsy.[22,23] This is largely related to the number of cores taken at biopsy and can be minimised by using modern biopsy templates and MRI-targeted biopsies.[19] While studies report rates of erectile dysfunction in up to 24% of patients following transperineal biopsy,[24] a recent, large meta-analysis demonstrated that this was usually transient and resolved within three months.[25]

Box 3. Risk-stratified recommendations based on the European Association of Urology (EAU) guidelines[10]

- Ensure prostate cancer awareness among men.
- Counsel men on the benefits and harms of prostate-specific antigen (PSA) testing.
- Offer an individualised risk-adapted strategy for early detection to men aged >50 years with a life expectancy of 10+ years.
- Offer early PSA testing to men with an elevated risk of having prostate cancer such as men aged:
  - >45 years with a family history of prostate cancer
  - >45 years from high-risk ethnicities
  - >40 years carrying BRCA2 gene mutations.
- Limit testing when life expectancy suggests unlikely benefit.

Addressing concerns of overdiagnosis and overtreatment

Even if prostate cancer is found, low-grade disease can be managed with surveillance to minimise morbidity from treatment, reducing the concerns associated with overdiagnosis.[26] Prostate Cancer Outcomes Registry – Australia and New Zealand (PCOR-ANZ) data highlight the increased use of active surveillance in patients with a low to intermediate risk of prostate cancer,[27] reducing the treatment-associated harms in men with low risk of progression.

When treatment is indicated, staging has improved with the use of prostate-specific membrane antigen positron emission tomography (PSMA PET) and various management options are available, including brachytherapy, external radiation therapy, radical prostatectomy and focal therapy. Treatment protocols benefit from multidisciplinary discussion, especially in complex cases. There have also been improvements in medical therapeutics for advanced disease and an established outcomes registry (eg PCOR-ANZ) ensures quality and reporting of treatment outcomes as well as patient-reported outcomes.[27]

Further evidence to support PSA screening came from the US Preventative Task Force (USPTF), which, in 2018, reversed a 2012 decision against PSA screening after significant increases in advanced and metastatic disease were found.[28] Additionally, long-term data from the well-designed ERSPC trial revealed significant survival advantages from appropriately performed PSA testing programs.[9]

Given the progress over the years, there should be informed discussion about the risks and benefits of diagnosing significant prostate cancer. As such, the EAU guidelines recommended a risk-stratified approach to PSA screening (Box 3).[29]

Conclusion

The inequity of access to PSA testing for men with significant prostate cancer at the primary care level must be addressed to ensure that the morbidity rate from this disease does not continue to rise and cause preventable harm.[30]

This article highlights the urgent need to update current Australian PSA screening guidelines based on the current evidence. This does not suggest replacing the need for a shared decision-making model, but rather augments the argument in favour of PSA testing for appropriately selected men. Early diagnosis of prostate cancers that will metastasise and cause morbidity/premature mortality can be prevented by timely intervention in patients with a long life expectancy who can participate in shared decision making. Men should be aware of the potential risk of significant prostate cancer despite the lack of symptoms. Current evidence shows that a PSA test helps assess that risk.[29]

Key points

- Prostate cancer is the most commonly diagnosed cancer in Australian men, often remaining asymptomatic until advanced.
- Guidelines for primary care PSA testing need to be updated as they do not reflect current evidence, including long-term data confirming significant survival advantages from appropriately performed PSA testing programs.
- Biopsy techniques and imaging modalities, including MRI and PSMA PET, have reduced risk, increased accuracy and improved staging.
- Outcomes data highlight the increased use of active surveillance in patients with low to intermediate risk of prostate cancer, reducing the treatment-associated harms in men with low risk of progression.
- Medical therapeutics for advanced disease have improved.

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Competing interests: While the article is not commissioned by the Urological Society of Australia and New Zealand (USANZ), all of the authors are senior office bearers of USANZ. WR received a Royal Australasia College of Surgeons Small Project Grant 2021/22 and an ANZUP Below the Belt Award 2022.

Funding: None.

Provenance and peer review: Commissioned, externally peer reviewed.

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