What's new in prostate cancer testing?

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Prostate-specific antigen (PSA) testing can be an effective tool to detect prostate cancer if the appropriate men are targeted. However, over-detection and over-treatment of men with prostate cancer can be a consequence of widespread testing.

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Interest in the use of prostate specific antigen (PSA) as a screening tool for prostate cancer began in 1993 when it was introduced as a free test to the population of Tyrol in Austria.[1] Intuitively it was thought that the earlier cancer was detected, the greater the chance for cure. This trial demonstrated a 25% improved prostate cancer survival rate in those undergoing PSA screening with prolonged follow up compared with the rate in the general male population in Austria. However, randomised controlled studies comparing death rates of men who have had PSA tests with those who had not have only recently been published.

Surprisingly, the US Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial found no difference in death rates between men who had had their PSA levels tested and those men who had not.[2] One limitation of this trial was that the follow-up period was short, with men only being watched for an average of seven years. Also, at least half the men were tested before entry into the trial, so many who had prostate cancer had already been diagnosed before entry and as such were pre-screened. In the group of men who were not supposed to have had a PSA test during the trial, about 50% actually had, which largely invalidates the results of this study.

The second recently published study is the European Randomised Study of Screening for Prostate Cancer (ERSPC) and this trial showed a survival benefit in the long term (with more than nine years' follow up) in men who had had a PSA test.

It showed a reduction of 31% in prostate cancer death rate in men who had been tested compared with those who had not, taking into account both contamination (those who had been tested in the control arm) and noncompliance (those who were supposed to have been tested but who had not complied).[3] Another recent study from the Swedish arm of the ERSPC followed men for 14 years and found a further improvement with a 44% reduction in prostate cancer death rate.[4]

What is clear from all these studies is that unless a patient has a life expectancy of at least eight to 10 years, routine screening is unlikely to provide a survival benefit. This has particular implications for those men older than 75 years of age with comorbidities who, based on average life tables, are unlikely to survive another 10 years and therefore cannot be expected to obtain a survival benefit. The same cannot be said for younger patients with longer life expectancies.

However, these studies also demonstrated a phenomenon called overdetection and overtreatment – that is, detecting and treating a cancer when that cancer may not have caused a clinical problem during the patient's lifetime. In the ERSPC, 48 men needed to be treated to save one life, although that number decreased to 12 men in the Swedish arm of the trial with a longer follow up.[4]

ACTIVE SURVEILLANCE

Prostate cancer treatments such as surgery and radiotherapy can cause erectile dysfunction and/or bowel and urinary problems in a small percentage of patients, which can significantly reduce their quality of life. So attempts have been made to reduce overtreatment with urologists being more selective in which men they offer treatment to, based on the patients' age, PSA levels and aggression of the cancer as determined by biopsy results.

'Active surveillance' is a process whereby patients are monitored but not immediately treated. For example, about 30% of new prostate cancer diagnoses in Victoria are of small, relatively nonaggressive prostate cancers and patients are being managed by active surveillance. The urologist will continue to monitor the disease in these patients and if it appears to be getting worse, based on serial PSA measurements and repeat biopsies, the patients will be treated actively with surgery (radical prostatectomy) or radiotherapy, otherwise monitoring continues.

Most studies show that after 10 years of active surveillance, the prostate cancer death rate is as low as 0 to 1%, with only 30 to 50% of patients requiring treatment during that period.[5] As such, many men avoid the morbidity of unnecessary treatments, while preserving their chance for cure and long-term disease control. Studies have shown that men who have a delayed radical prostatectomy do not have a higher histological grade, an increased risk of extracapsular disease or positive surgical margins compared with those treated with immediate surgery.[6]

SMARTER TESTING

It is critical that the correct men are referred for testing. A recent US study showed that only 24% of men aged 50 to 54 years had undergone a PSA test, even though this is the population group that would most benefit from prostate cancer testing.[7]

In comparison, 46% of men aged 70 to 74 years and 24% of men older than 85 years of age had undergone PSA testing. These men are far less likely to benefit from prostate cancer testing because at that age the threat of death from prostate cancer is surpassed by the risk of death from heart disease and other causes. In fact, a large Swedish study has shown that early treatment with radical prostatectomy beyond the age of 70 years confers relatively little survival benefit compared with surgery in younger men.[8]

Studies show that a single PSA test at the age of 40 years predicts the likelihood of developing prostate cancer over the next 10 to 15 years. Numerous studies have shown that men with PSA levels of more than 1.5 ng/mL at age 40 to 45 years – that is, in the top 10% of PSA levels for this age group – comprise almost half of those who eventually die from prostate cancer.[9] Clearly these men need to be monitored closely, whereas those with lower PSA levels can afford to be tested less frequently.

Men with PSA levels below the median for their age (for example, a man aged 40 to 50 years of age demonstrating a PSA level of less than 0.7 ng/mL) have a low risk of prostate cancer in the short to medium term and only need repeat testing in five to 10 years time, not annually.[10] Other studies have shown that a man aged 60 years with a PSA level of less than 1 ng/mL need not be tested ever again due to the low likelihood of developing clinically significant prostate cancer.[11]

Some new tests are being introduced that may have a beneficial effect in the early detection of prostate cancer. The prostate health index (PHI) is a serum-based test measuring truncated proPSA (p2PSA), which has been found in higher levels in the free PSA fraction in men with prostate cancer compared with men with benign prostatic hyperplasia. PCA3 testing (prostate cancer antigen) is a

urine-based marker collected after a digital rectal examination. Both PHI and PCA3 testing are now available through some laboratories in Australia. The role of these tests is still being determined at this stage, but they may have a larger role in the future in determining which men who have a borderline PSA and equivocal free/total ratio proceed to biopsy.

Testing 'smarter' and using resources responsibly is clearly appropriate public policy. This is achieved by:

- testing younger men who will potentially benefit from early detection
- placing men into a risk category for future prostate cancer to determine their frequency of PSA-based testing
- reducing or ceasing testing of those men who would not benefit, namely the elderly with a less than 10-year life expectancy.

However to do this, all health agencies must provide a clear and consistent message to consumers and guidelines to GPs, which is something that has been lacking in this debate for the past 20 years.

The efficacy of government-funded population-based screening needs to demonstrate not only a survival benefit but also cost effectiveness, and the latter has not been fully evaluated for prostate cancer screening. It will be difficult to fully recommend population-based screening until it has been proven to be cost effective and, as such, population-based screening for prostate cancer is currently not endorsed by the Urological Society of Australia and New Zealand.

CONCLUSION

Individual early investigation should not be refused to a well-informed man who requests a PSA test, based on the results of the recent evidence. It can save lives in some but not all men; however, all risks and benefits of such testing need to be discussed, including the fact that not every man in whom prostate cancer is detected will need immediate therapy. MT

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