Screening for prostate cancer: explaining new trial results and their implications to patients

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ABSTRACT

- The best available evidence for making decisions about prostate-specific antigen (PSA) screening comes from two recent randomised trials, the larger and more robust of which showed that PSA screening reduced the risk of death from prostate cancer, but that the absolute benefit was small, and the chance of prostate cancer being diagnosed and treated (even if biologically unimportant) was increased by a much larger amount.
- The important question is whether the small reduction in numbers of deaths outweighs the harms inherent in the diagnosis and treatment of many additional cancers.
- Men considering screening should understand both its possible benefit and its possible harms, and that the harms are more immediate than any benefit.
- The challenge for future research is to find a test that reliably detects prostate cancers that are curable if they are treated early and life-threatening if they are not.

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Screening for prostate cancer has generated a heated and enduring controversy. Major clinical practice guidelines contradict one another on whether, how, and in whom screening should be done. Nevertheless, prostate-specific antigen (PSA) screening is common in Australia. The risk of an Australian man developing prostate cancer by age 85 is about 20%, but his risk of dying from prostate cancer is only 2%–3%,[1] and most deaths due to prostate cancer occur beyond the recommended ages for screening of 50–74 years (Box 1).[2]

Results from two randomised trials including almost a quarter of a million men[3,4] were expected to resolve this controversy, but their differing results seem to have fuelled, rather than doused, the fire. However, differences in the results and methods of these trials are more apparent than real and their results are complementary, as we explain below.

Are the results valid?

The United States cancer screening trial by the Prostate, Lung, Colorectal and Ovarian Cancer Screening Project Team recruited over 76 000 men aged 55–74 years, randomly allocated them to annual screening with PSA testing and digital rectal examination (DRE) or to usual care, and followed them for 7–15 years (median, 11 years).[3] The follow-up data were 98% complete at 7 years and, during this time, prostate cancer was diagnosed in 5142 men (6.6% of those recruited; annual rate, about one diagnosis per 100 men) and was the cause of death in 94 men (0.12% of those recruited; annual rate, about two deaths per 10 000 men). The rate of diagnosis of prostate cancer was 1.22 times higher in the screening group (95% CI, 1.16–1.29; $P < 0.001$). The rate of death from prostate cancer was 1.13 times higher in the screening group, but this was not statistically significant (95% CI, 0.75–1.70; $P = 0.6$); the confidence interval is wide and includes the result from the European Randomized Study of Screening for Prostate Cancer (ERSPC; see below). The results after 10 years' follow-up are similar (rate ratio, 1.11; 95% CI, 0.83–1.50), although the current data are only 67% complete.

The ERSPC trial recruited over 160 000 men aged 55–69 years, randomly allocated them to 4-yearly screening with PSA or usual care, and followed them for 3–15 years.[4] During the median follow-up period of 9 years, prostate cancer was diagnosed in 10 300 of these men (6.3% of those recruited; annual rate, about 0.7 diagnoses per 100 men), and was the cause of death in 540 (0.3% of those recruited; annual rate, about four deaths per 10 000 men). Prostate cancer diagnosis was 1.71 times higher in the screening group (95% CI, 1.64–1.77; $P < 0.001$). Prostate cancer death in the screening group was 0.80 times that in the control group, and was of borderline statistical significance after adjustment for repeated analyses (hazard ratio, 0.80; 95% CI, 0.65–0.98; $P = 0.04$). There was an absolute reduction of 0.7 prostate cancer deaths per 1000 men who had been offered screening over 9 years.

The methods of these trials differed in several respects. The US trial used a single protocol at 10 major centres. The European trial was conducted in seven countries according to protocols that were developed locally, but complied with core requirements set by the trial steering committee.

Screening was more frequent in the US trial, with PSA screening and DRE offered annually for 6 and 4 years, respectively; the European trial offered PSA screening every 4 years, but did not offer DRE. The threshold for an abnormal PSA screening test was 3 ng/mL in most European centres, and 4 ng/mL in all US centres.

1 Incidence of prostate cancer in 2005 and mortality from prostate cancer in 2006 in Australian men[2]

	Age (years)										
	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79	80–84	⩾ 85	Total
No. of cancers	29	235	803	2037	2592	3141	2672	2372	1474	988	16 349
Rate of cancers (per 100 000 men)	3.8	32.3	120.7	327.6	546.7	834.0	890.8	950.2	922.2	1013.7	
No. of deaths	2	6	23	77	134	228	373	572	736	801	2 952
Rate of deaths (per 100 000 men)	0.3	0.8	3.4	12.1	27.0	59.0	122.9	226.4	442.9	767.4	

Compliance with screening was excellent in the screened groups of both trials (about 85%). However, the control arm of the US trial was substantially contaminated by off-study screening, with about 50% of control participants having PSA tests and DRE during the course of the trial. This contamination of the control arm will obscure the effects of screening. In addition, 44% of men in the US trial had already had one or more PSA tests before being randomly allocated to the screening or control group in this trial, which would also reduce the observed effect of screening.

The treatment of prostate cancers appeared similar in the screening and control arms of each trial. This is clearer in the US trial, because diagnosis and treatment were arranged by the patients' primary care physicians, and the report includes data showing comparability of treatments received.[3] The types and frequencies of treatments in the European trial were also reported to be similar in the two groups. However, it is not clear whether European patients in the screening group were more likely to be treated at centres that specialised in the treatment of prostate cancer. The European trialists cite a separate article (still in press) in which they report that there was no treatment bias.

High follow-up rates and blinded outcome assessments were major strengths of both trials — diagnoses of prostate cancer and deaths from prostate cancer were adjudicated without knowledge of whether the patient was allocated to screening or usual care. However, outcomes would have been assessed with knowledge of the treatment provided, and this may have biased the results in favour of screening in both trials.

Because of its methodological problems (the high rate of screening at baseline and in the control group), the US trial is likely to have underestimated the effects of screening. The European trial was less affected by these problems, and includes twice as many events, so its results are both more reliable and more applicable. Most prostate cancers progress slowly, so many additional prostate cancers, and some additional prostate cancer deaths, will accumulate in these trials over the next 10 years. An obvious question is whether the current survival benefit associated with screening in the European trial will stay the same, increase or decrease. However, even if the benefit is maintained or increased, the more important question is whether the benefits warrant the risks, discomforts and costs of screening and treating additional cancers.

How do the results help us care for our patients?

Health care agencies (for example, the US Preventive Services Taskforce, the Cancer Council Australia, and the Urological Society of Australia and New Zealand) are likely to continue to recommend that doctors should inform men about the benefits and harms of PSA screening. Therefore, there is a pressing need for good-quality information about those benefits and harms. As it is the best available evidence, we suggest using the effects of screening shown in the European trial.

The main benefit is the reduced risk of death from prostate cancer. The most important harm is the increased risk of diagnosing and treating prostate cancer, including many prostate cancers that would not cause any symptoms or problems if left undetected. This occurs because, with screening, we diagnose many prostate cancers that would not become clinically apparent without screening; the European data suggest that about half of the prostate cancers detected in a PSA screening program would not cause symptoms or threaten life.[5] Treating them can only cause harm.

The key question is, then, the nature and frequency of harms from prostate cancer treatments. According to an evidence review by the US Preventive Services Taskforce in 2003[6] (updated in 2008), side effects of prostate cancer treatment are common. One year after radical prostatectomy, 20%–70% of men have reduced erectile function, and 15%–50% of men have persisting urinary problems. The risk of death or serious complications from prostate cancer surgery are small but real (eg, 30-day postoperative mortality rates of 0.7%–1% in large US samples). A more recent study, based on 1201 men treated by prostatectomy (603) or radiotherapy (598) in nine US university hospitals, found that 12 months after prostatectomy, 67% of men reported poor erections (14% before surgery), 16% reported leaking urine more than once a day (4% before surgery), and 24% reported using continence pads (1% before surgery).[7] Almost all the men undergoing prostatectomy had nerve-sparing surgery. There were no postoperative deaths in this study. Proponents claim that newer surgical techniques (eg, laparoscopic and robotic surgery) reduce the adverse effects of prostatectomy. This may be true, but there are several problems with this argument. First, these techniques are not widely available in Australia, and they may be difficult for some people to access or afford. More importantly, there is little or no evidence from randomised trials to support strong claims about effectiveness or adverse events. Radiation therapy increases the risk of bowel problems, erectile dysfunction, and urinary symptoms.[6,7] Adjuvant androgen deprivation therapy is frequently used with radiation therapy, and leads to hot flushes and reductions in libido.

Some men diagnosed by screening will not have immediate treatment of their prostate cancer, and instead will be followed by PSA surveillance. The prevalence of anxiety and depression among men undergoing "watchful waiting" appears to be similar to that among men treated by prostatectomy.[8]

While much less frequent, less severe and shorter lived, the adverse effects of prostate biopsy must also be considered as a harm of screening. In the European trial, 16% of PSA test results were abnormal, resulting in referral for biopsy. While less than 10% of men undergoing biopsy experience significant side effects, and less than 1% experience serious complications, including infection, many find the procedure uncomfortable, painful and worrying.[9]

So, how do you explain this information to your patients?

There is ample evidence that the best understood and least misleading way to present the benefits and risks of interventions, including screening, is to use event rates (or natural frequencies) for unscreened and screened men, using the same denominator (eg, per 1000 men).[6,10,11] The results from the ERSPC are not presented like this but the event rates can be calculated from their published data.

Box 2 shows that if you screen 1000 men, and follow them for 9 years, there will be 2.94 deaths from prostate cancer instead of 3.65 deaths. This reduction in deaths is the benefit of screening —

2 Prostate cancers and deaths from prostate cancer over 9 years among 1000 men aged 55–69 years[4]

	Control	Screened	Absolute difference
No. of cancers	48	82	34
No. of deaths	3.65	2.94	0.71

0.71 fewer deaths from prostate cancer over 9 years per 1000 men screened. The price of this benefit is that instead of diagnosing prostate cancer and treating it in 48 men, you will diagnose and treat it in 82 men — in other words, an extra 34 men diagnosed and treated over 9 years per 1000 men screened. Adverse effects from the detection and treatment of these additional men with prostate cancer (such as poor erections and incontinence) are the harms of screening.

If you prefer, you can express the same information as a number needed to screen and treat to prevent one death from prostate cancer. This is how the results were reported.[4] Expressed this way, you have to screen 1408 men and treat an additional 48 men to prevent one prostate cancer death over 9 years. In other words, only one of those 48 men is going to benefit over the next 9 years; the other 47 do not benefit because their prostate cancer was not destined to kill them in the next 9 years, and they have undergone treatment for no benefit within this period.

Doctors advising well men about PSA testing should cover the following points:

- Explain that there is a decision to make (men may think testing is mandatory and may not appreciate that their preferences matter) and that either choice (to screen or not to screen) is reasonable, and there is no right or wrong answer.
- Explain the possible outcomes, both good and bad (for men aged 50–74 years; you can use the numbers in Box 2 as described above).
- Explain the risks of prostate cancer treatment, noting that the harms are experienced much sooner than any benefit (the survival benefit in the European trial was only apparent after 7 years of follow-up).
- Mention the need for a biopsy, and its nature, if the PSA test result is abnormal.

Some men will wonder why you are saying all this when all they are thinking of at that moment is the initial test. It is important for them to understand that the test alone does nothing. It is the subsequent investigation and early treatment that leads to the benefits (and harms). So, to make an informed choice about screening (or even to give informed consent), they need to consider the benefits and harms of the whole package before having a serum PSA test.

For men aged 75 years or over, the US Preventive Services Taskforce recommends against screening because benefits are unlikely within the man's remaining lifetime.[12] Related to this, you may want to consider life expectancy. Only men with a life expectancy longer than 7 years are likely to benefit from PSA screening.

You should also consider family history. The risk of developing prostate cancer is increased twofold to fourfold with one affected first-degree relative (about twofold if that person was the patient's father and/or was older than 60 years at diagnosis, and about threefold to fourfold if the person was the patient's brother and/or was younger than 60 years at diagnosis), and is increased about fivefold with two or more affected first-degree relatives.[13]

You may want information about the benefits and harms of PSA screening specifically for men of different ages and with different degrees of familial risk, and over time frames longer than 10 years. Such information is available, but does not greatly change the balance between the likelihood of experiencing benefit versus harm from PSA screening, because any increased benefits are likely to be offset by proportionately increased harms.[14]

Some men will look at the trade-off and decide that their goal is to minimise the risk of dying from prostate cancer, that the risks are acceptable, and will opt to be tested. Others will consider the risks too great to justify the small chance of a future benefit.

How should these results affect our advice for men with lower urinary tract symptoms (LUTS), and should they be advised to have a PSA test? Men with uncomplicated LUTS appear to have little or no increased risk of prostate cancer. The aim of management in these men is to improve their symptoms and quality of life. However, LUTS are frequently mild and have minimal impact on quality of life.[15] In such cases, reassurance, lifestyle advice and follow-up to assess whether symptoms are progressing may be sufficient. A standard instrument such as the International Prostate Symptom Score (I-PSS) or American Urological Association Symptom Index[16] can be used for monitoring. In patients with troublesome symptoms requiring medical or surgical intervention, a PSA test may be warranted to help with diagnosis, management and monitoring, along with other tests recommended in urology practice guidelines.[17,18] In this context, the serum PSA test is being used to help manage a clinical problem, not as a screening test for prostate cancer.

Conclusion

The ERSPC trial has provided, for the first time, high-quality evidence that screening for prostate cancer can be effective. Unfortunately, PSA screening also entails significant risks. The challenge for future research is to find a test that reliably detects prostate cancers that are curable if they are treated early and life-threatening if they are not, thereby making the balance of benefit to harm from prostate cancer screening more favourable. In the meantime, men need to be well informed about the pros and cons of PSA screening.

Competing interests

None identified.

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