

Prostate cancer screening: the controversy continues

Two long awaited randomised trials of PSA screening have reported this year. However, as **Jennifer Stark and colleagues** explain, the results are unlikely to end the controversy over the benefits and harms of testing

The introduction of prostate specific antigen (PSA) testing as a screening tool has transformed the clinical landscape of prostate cancer. Screening allows prostate cancer to be diagnosed many years earlier, offering hope that a newly detected cancer is still localised to the prostate when treatment is curative. However, screening has also led to considerable false positive results and extensive overdiagnosis of disease that would not otherwise emerge clinically. We summarise current screening guidelines and review the evidence of benefit and harm of PSA testing.

Current screening guidelines and practices

The US Food and Drug Administration approved PSA testing to monitor progression of cancer among men with prostate cancer in

1986 and for early detection of prostate cancer in 1994. Nevertheless, many agencies in the US and Europe do not recommend routine prostate cancer screening (box 1). The European Association of Urology, for instance, states that “Current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy due to the large overtreatment effect.” The notable exception is the American Urological Association,¹ which updated its guidelines after the publication of the results of two recent randomised trials^{2,3} of prostate cancer screening, and now recommends annual screening for men aged 40 and older who have a life expectancy of at least 10 years.

Even without consensus on routine screening, more than half of US men age 50 and older

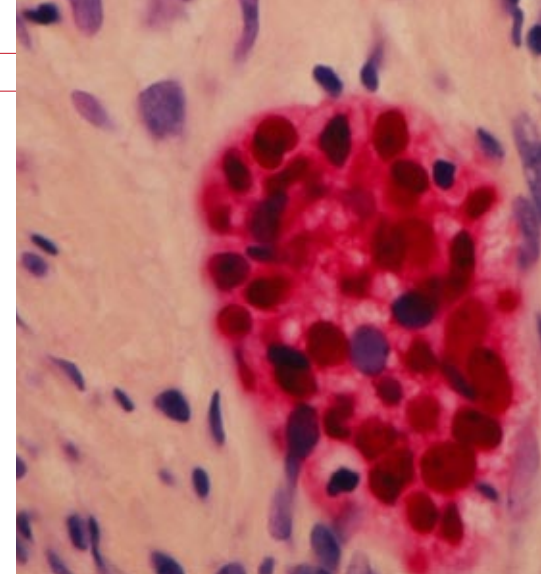
report having had a PSA test within the past year.⁴ Furthermore, a third of men screened for prostate cancer were not aware that their PSA level had been tested within the previous three months.⁵ Orders for a PSA test from primary care in the US and Europe have risen substantially in the past decade,^{6,7} indicating that primary care doctors increasingly support testing. Even in the UK, where PSA screening is less common, two thirds of men screened in 2003 did not realise that the PSA test had been done.⁸

Is prostate cancer a suitable disease for screening?

Prostate cancer is a major public health problem, affecting 679 000 men and causing 221 000 deaths worldwide each year.⁹ Both the disease and the treatment cause considerable morbidity. Some men have an aggressive form for which screening might be helpful, but many have a slow growing cancer that would never progress to cause serious illness during a man's lifetime.¹⁰⁻¹² Ideally, a screening tool would selectively identify lethal prostate cancers for which treatment would be effective but avoid detecting cancers that would not be lethal and might not ever cause symptoms. Detecting slow growing cancers causes needless anxiety and brings unnecessary medical treatment with all its attendant risks (box 2).

Is there effective treatment for prostate cancer?

The goal of screening is to lengthen life or improve its quality through early detection and treatment of disease. Mortality from prostate cancer has been falling in both the US and the UK since the early 1990s,¹³ a trend that may be due to earlier detection through screening, improved treatment, changes in exposure to risk factors associated with aggressive disease, or changes in the attribution of cause of death. Treatment of localised prostate cancer can reduce mortality. After 12 years of follow-up in a Scandinavian trial comparing radical prostatectomy with watchful waiting,¹⁴ men receiving prostatectomy had 35% lower mortality from



Box 1 | International recommendations on screening for prostate cancer

American Cancer Society—Does not support routine testing for prostate cancer. Recommends discussion with doctor regarding benefits and limitations of early detection with an offer of a PSA test beginning at:

Age 50 for average risk men with life expectancy of at least 10 years

Age 45 for men at high risk of developing prostate cancer (African-Americans and men with a first degree relative who had prostate cancer diagnosed younger than age 65)

Age 40 for men with several first degree relatives who had prostate cancer at an early age

If, after discussion, a man asks his healthcare professional to make the decision for him, he should be tested (unless there is a specific reason not to test)

American Urological Association—PSA test should be offered to well informed men aged 40 years or older who have a life expectancy of at least 10 years

US Preventive Services Task Force—For men younger than age 75 years, the benefits of screening for prostate cancer are uncertain and the balance of benefits and harms cannot be determined. For men 75 years or older, there is moderate certainty that the harms of screening for prostate cancer outweigh the benefits

Cancer Council Australia—No recommendation for or against prostate cancer screening. Men should weigh the pros and cons before deciding to be screened

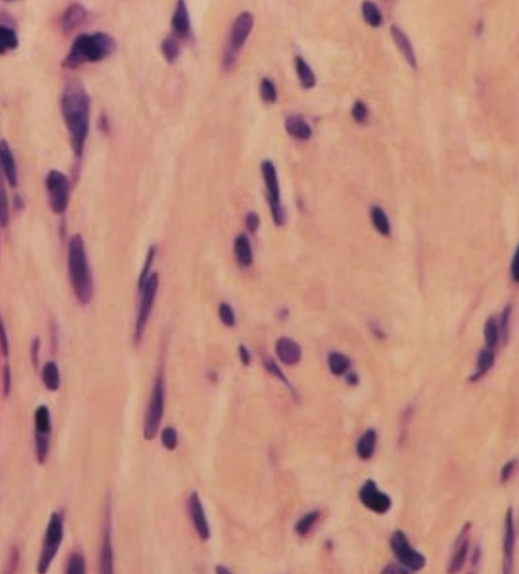
European Urological Association—Current published data are insufficient to recommend population screening for prostate cancer as a public health policy owing to the large overtreatment effect

Japanese Urological Association—The evidence for the effect of prostate cancer screening is insufficient. PSA and digital rectal examination not recommended for population based screening programmes

National Health Committee (New Zealand)—Population based or opportunistic screening for prostate cancer using PSA or digital rectal examination for asymptomatic men is not recommended given lack of conclusive evidence showing reduction in morbidity or mortality, but a man should not be denied the test if he is fully informed and requests it

Swedish Board Of Health And Welfare—No recommendations about general PSA screening for men aged 50-70, but providers should provide information to men who are interested in screening

NHS (UK)—No organised screening programme for prostate cancer but the informed choice programme, Prostate Cancer Risk Management, aims to provide high quality information about the risks and benefits to men who ask about screening in order to enable them to decide whether to have the test



MICHAEL ABBEY/SPL

Light micrograph of a section through a prostate gland with cancer using antibody labelling

Box 2 | Who would and would not benefit from routine PSA screening

Groups who benefit

- Men who would have died from prostate cancer but are cured owing to earlier detection
- Men with no prostate cancer and a normal PSA result (reassurance)

Groups who do not benefit (and may be harmed)

- Men who die from a PSA detected prostate cancer and whose clinical course has not been improved by treatment
- Men with prostate cancer who would have survived even without screening
- Men with a PSA detected prostate cancer that would have not surfaced clinically during their lifetime (overdiagnosis)
- Men with a false negative result
- Men with a false positive result

prostate cancer (a 5% drop in absolute risk). But this treatment benefit was accompanied by substantial costs. Nine in 10 treated men would have survived without intervention, and 1 in 20 died from cancer despite treatment.

Radical prostatectomy is associated with significant morbidity, including incontinence and impotence. This surgically induced morbidity is noteworthy given that in the US 168 000 men annually have radical prostatectomy¹⁵ and prostatectomy increased 19-fold in the UK between 1991 and 2004.¹⁶ Radiotherapy, the benefit of which has yet to be evaluated in a randomised trial, also substantially affects quality of life.¹⁷

Is PSA an effective test?

Unfortunately PSA screening cannot differentiate between indolent and lethal prostate cancer. Cancer raises PSA levels, but non-malignant conditions do so as well. For detecting any prostate cancer, the test characteristics are adequate. In a study population that had not been previously screened, the PSA test had a sensitivity of 56% to detect prostate cancer diagnosed clinically within two years, using a threshold of 4 µg/l.¹⁸ Nine per cent of men had raised PSA levels but no clinical diagnosis over

10 years, indicating a false positive result. In the European Randomized Study of Screening for Prostate Cancer,³ study centres used a threshold of 3 or 4 µg/l. The sensitivity of PSA to detect prostate cancer among men who agreed to biopsy was 71%, with an average positive predictive value of 24% across the seven countries in the study. As with other screening tests, PSA testing has a considerably lower sensitivity and specificity in populations that have previously been screened.¹⁹

Lead time is necessary to reduce morbidity and mortality associated with disease, but a person with a positive result spends more time with awareness of disease and the effects of treatment, regardless of treatment benefit. Pashayan and colleagues estimated that the mean lead times for PSA testing were 11-13 years among men aged 50-69, much longer than for other cancer screening.²⁰ For example, mammographic screening for breast cancer has a 2-4 year lead time.²¹

Trials of screening

Results from two randomised trials, one in Europe and the other in the US, provide the best available information on the effectiveness of PSA screening in reducing mortality.^{2,3} The European study included 162 387 men from seven countries.³ PSA screening was offered roughly every four years. Of the 16.2% positive test results, 76% were false positives as determined by biopsy. During an average follow-up of nine years, 214 men died from prostate cancer in the screening group compared with 326 in the comparison group (risk ratio=0.80, 95% confidence interval 0.65 to 0.98) a difference in risk of 0.71 cancer deaths per 1000 men screened. Thus 1000/0.71 or 1410 men must be screened to avert one death. Because screening led to the detection of 34 cases of prostate cancer per 1000 men screened, the authors estimated that 48 (1410×34/1000) cases of prostate cancer would have to be treated for every death averted.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found no benefit from screening after seven years of follow-up of men randomised to screening or not in the US.² This result was consistent with results after the same amount of follow-up in the European trial. Men in the screening group were offered annual PSA tests for the first six years and digital rectal examination for the first four years; adherence was 85% for PSA testing and 86% for digital screening. In the comparison group, half of the men sought annual PSA screening elsewhere, and about the same proportion received digital rectal examinations, blurring the differences between the randomised groups. At 10 years there were 92 and 82

deaths in the screened and comparison groups respectively (risk ratio=1.11, 95% confidence interval 0.83 to 1.50). The authors suggested several reasons for the apparent lack of benefit, including too high a threshold for the test, too much screening outside the study protocol in the comparison group, too many men having been screened before entry into the study, improvement in prostate cancer treatment, and insufficient follow-up time to see a benefit. We note that the confidence interval is wide, indicating that the data are compatible with a wide range of possibilities, including some benefit.

Unanswered questions in PSA screening

The results of these two long awaited randomised trials will not end disagreement about the effectiveness of routine PSA screening until additional questions are answered.

What percentage of men are appropriately reassured by negative screening results?

Continued follow-up of men in the trials with PSA values below the threshold should help to quantify the predictive value of a negative result.

What are the costs associated with the modest reduction in mortality observed in the European study?

Overdiagnosis—Men in the screening group were 71% more likely to have prostate cancer diagnosed after nine years than men in the comparison group. An unknown proportion of cases in the screening arm would have died of another cause before becoming aware of their cancer in the absence of screening. Estimates of overdiagnosis as a result of screening are as high as 50%.²² Additional follow up of participants should clarify the extent of overdiagnosis.

Overtreatment—Most men identified through screening are not destined to die of their prostate cancer and thus could not obtain any survival benefit from screening. Most men (72%) in the screening group had a Gleason 2-6 cancer diagnosed. This would have included many indolent cancers that did not require treatment. Other men would have died from their cancer despite treatment. Among the 28% with Gleason 7-10 cancers, some will have disease for which treatment is not likely to be effective. Quantification of overtreatment resulting from the randomised trials of screening is needed. Molecular or pathology tools to correctly classify men with lethal disease from indolent are currently lacking.

What are the long term benefits of screening?

The benefit of PSA screening on cancer mortality was not evident until after seven years' follow-up. Continued follow-up of the men

in the trials will provide valuable information about the long term benefits of screening.

How much time alive is gained by averting a death in the typical screened man?

The European study showed that cancer specific survival was improved for screened men, who were on average 61 years at randomisation.³ Life expectancy of a 61 year old man is about 21 years. Suppose that for a man who is going to die from prostate cancer without screening, his lead time is six years and survival would be five years after clinical diagnosis without screening. Screening thus adds 10 years of life for that man. Given that 1410 men must be screened to prevent one death, screening would provide an average survival gain of about 2.6 days per man screened. Furthermore, as survival after diagnosis of prostate cancer diagnosis can be considerably longer than five years, the days of life gained per man could be even lower.

Recommendations

Given the current evidence, we support the opinion of the European Urological Association that data on costs and benefits remain insufficient to support population based screening. The financial and psychological costs of false positive results, overdiagnosis, and overtreatment of prostate cancer need to be measured more precisely. Better estimates of these costs should emerge from further evaluations of the large randomised trials.

We believe that one change in current screening practice is urgently needed. Although PSA can be measured with a simple blood test, the test should be approached deliberately and with the same forethought and discussion used for screening for other cancers, such as mammography for breast cancer or endoscopy for large bowel cancer. Before testing men should be informed about the test itself and the

interpretation of a positive or negative result. Moreover, they should be advised that the test cannot tell whether they have a life threatening cancer but that it could lead them through a thicket of tests and treatments that they might have better avoided. This advice follows the basic tenets of screening programmes laid out by the World Health Organization.

Jennifer R Stark postdoctoral fellow of epidemiology, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston MA 02115, USA and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medicine School, Boston MA

Lorelei Mucci assistant professor of epidemiology, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston MA 02115, USA; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medicine School, Boston MA and Dana Farber/ Harvard Cancer Center, Boston MA

Kenneth J Rothman professor of epidemiology and medicine, RTI Health Solutions, Research Triangle Institute, Research Triangle Park, NC and Departments of Epidemiology and Medicine, Boston University Medical Center, Boston MA

Hans-Olov Adami professor of epidemiology, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston MA 02115, USA; Dana Farber/ Harvard Cancer Center, Boston MA and Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm

Correspondence to: J R Stark stark@hsph.harvard.edu

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See also **EDITORIAL**, p 759, and **RESEARCH**, p 793

ANSWERS TO ENDGAMES, p 813. For long answers use advanced search at bmj.com and enter question details

STATISTICAL QUESTION

Screening tests

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CASE REPORT

A seaman with blindness and confusion

- 1 This patient most likely has methanol poisoning.
- 2 Acid-base status and serum methanol concentration should be measured to confirm diagnosis. If the latter is not possible, calculation of the osmolal gap and the anion gap might be helpful.
- 3 The osmolal gap is the difference between the measured serum osmolality and the calculated osmolality. The anion gap is the difference between the measured serum cation concentration and the measured serum anion concentration. Measurement of the acid-base status in an individual with severe methanol poisoning is useful to determine metabolic acidosis, which was present in this patient.
- 4 Urgent treatment should include haemodynamic support with fluid and vasopressors; correction of metabolic acidosis; haemodialysis or haemodiafiltration (to enhance elimination of methanol and formate and to correct acidosis); and treatment of seizures.
- 5 Fomepizole is the treatment of choice to reduce further conversion of methanol to its harmful metabolites. Ethanol may be used if fomepizole is not immediately available.
- 6 Patients with methanol poisoning should also be given folic acid (calcium folinate) or folic acid to enhance formate metabolism.