

## **PSA as a screening test for prostate cancer**

*A while ago I saw a man and his wife to discuss the pros and cons of PSA testing. Having given a full explanation of the pros and cons, I asked what they thought. Without any hesitation the man looked at me and said 'Well on hearing all that it's very clear I shouldn't have the test'. His wife, who had been sitting next to him throughout, looked aghast, 'No surely you don't mean that – of course you should have the test!' Perhaps it is people's approach to risk, not the facts we give them, that makes the difference!*

### **☒ Prostate cancer statistics**

- Prostate cancer is the leading cause of cancer deaths in men in the UK
- BUT more men die with prostate cancer than of it.

Research just out adds to the debate on PSA testing as a screening test for prostate cancer.

***First I must declare an interest** – I was one of the authors of the Prostate Cancer Risk Management Programme Information Booklet for Primary Care (2002), which is currently being updated. This was commissioned by the National Screening Committee to help primary care clinicians to understand and relay to patients the pros and cons of the PSA test in relation to screening for prostate cancer.*

PSA screening is controversial for a number of reasons, as highlighted in The Prostate Cancer Risk Management Programme Information Booklet For Primary Care (2002), (available at [www.cancerscreening.nhs.uk/prostate/prostate-booklet-text.pdf](http://www.cancerscreening.nhs.uk/prostate/prostate-booklet-text.pdf)).

### **The key problems are:**

- There is no strong evidence that PSA testing reduces mortality from prostate cancer.
- Not all men with a raised PSA have prostate cancer (about 2/3rds will **not** have cancer).
- The PSA test will not detect all prostate cancers. Up to 20% of men with clinically significant cancers will have a normal PSA.
- Prostate cancers range from aggressive to slow-growing. It is difficult to separate clinically or histologically those with more aggressive disease from those with less aggressive disease.
- Slow growing tumours may not result in symptoms or shorten life expectancy. Diagnosing cancer in these men may lead to treatments that result in significant side effects (impotence, incontinence), when the tumour itself would never have become clinically apparent.
- There is limited evidence about the optimum treatment for localised prostate cancer.

**Research is underway to address some of these dilemmas, but results of the main trials will not be available for several years. Recently a couple of papers have been published that look at whether screening reduces mortality. These are summarised overleaf.**

### **Statistical note**

*These studies quote rate ratios. This is a way of quantifying differences between two groups. For example if a rate ratio is >1 it suggests an event is more likely in the treatment group than in the control group.*

## **The PLCO study in the US**

**NEJM 2009;360:1310-9**

This paper is from the PLCO (Prostate, Lung, Colorectal and Ovarian) Cancer Screening Trial, but reports only the findings in relation to PSA screening.

Over 76 000 men (aged 55-74y) were randomised to usual care or annual screening for prostate cancer (annual PSA for 6yrs, digital rectal exam for 4 years). This was a US study, so some men in the usual care group would have been offered screening too, depending on the level of their health insurance.

Compliance was good: 85% for PSA testing and 86% for digital rectal examination (DRE).

In the control group screening occurred in 40-52% of men (PSA) over the period of the trial (variation due to different uptake rates/year).

Follow up data is published here for 7yrs of follow up. However about two thirds of data is also available for 10 year follow up which shows trends consistent with the 7 year data.

- **Unsurprisingly screening picked up more cancers than usual care and this difference was statistically significant (rate ratio 1.22, CI 1.16-1.29).**

After 7 years the **incidence** of prostate cancer was:

Screening group:	116	per 10 000 person years
Control group:	95	per 10 000 person years

- **The mortality rate from prostate cancer was not reduced in those who had been screened (rate ratio 1.13 with non-significant confidence intervals CI 0.75-1.7)**

After 7 years the **mortality** from prostate cancer was:

Screening group:	2	per 10 000 person years
Control group:	1.7	per 10 000 person years

- **Screening did not appear to pick up earlier tumours (similar rates of all stages in control and screening group).**

## **So why didn't screening reduce mortality?**

The authors put forward several reasons:

- If they had used a lower threshold for diagnosis they may have picked up more early tumours by screening. *True, but they set their cut off at 4, which is considered by most to be the appropriate cut off between normal and abnormal.*
- The level of screening in the control group could have 'contaminated' the results, however the authors have calculated that there was not sufficient contamination to affect the results.
- 44% of men (in both groups) had already had a PSA at enrolment. Although the authors argue that this might eliminate some of the benefit they expected to see in the screening group, most screening programmes are a series of tests, not a single test, so the effect should not be great.
- Improvements in treatments for prostate cancer over the last 10 years may have masked improvements in survival in the screening group.
- The follow up may not yet have been long enough to detect a benefit

### **The ERSPC European study**

**NEJM 2009;360:1320-8**

The European Randomised Study of Screening for Prostate Cancer (ERSPC) was an RCT of 180 000 men aged 50-74 in 7 European countries.

Men were randomly assigned to receive a PSA every 4 years, or no screening. 82% of the men took up the offer of at least one PSA test. Follow up was for a median of 9 years.

- **Unsurprisingly almost twice as many cancers were diagnosed in the screening group compared to the control group.**  
The cumulative incidence in the screening group was 8.2%.  
The cumulative incidence in the control group was 4.8%.
- **Those who had undergone screening were 20% less likely to die of prostate cancer than those in the control group (ratio rate for death in the screening group compared with the control group 0.8 (CI 0.65-0.98)).**
- **Put another way, that's about 7 less prostate cancer deaths per 10 000 men screened after 9 years follow up.**
- **The benefit of screening (reduced mortality) was only seen in those aged 55 or more (upper age 69 in this study) and not in those aged 50-54**
- **There was a significant rate of over diagnosis (detecting tumours that would never become clinically significant).**

### **What is that in NNTs?**

- **1410 men would need to be screened to prevent one death from prostate cancer.**
- **48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer.** With most screening programmes this figure would be much lower; it reflects significant over diagnosis of prostate cancer; those with clinically unimportant disease. Most of these people have been harmed rather than helped by the screening test – they have been diagnosed with a cancer that would never have become clinically important yet they have undergone treatment and the side effects that come with treatment.

The NNT for screening is similar to those for mammography and faecal occult blood testing, but, very importantly, the NNT for additional cases to be treated to prevent one death is much lower for other screening programmes, because there is little over diagnosis and over treatment.

### **Comments on this study**

- A criticism of the study is the way deaths were attributed and the risk that they were mis-attributed away from prostate cancer (as has been demonstrated in other trials). This could have contaminated the results, possibly significantly.
- This study did use a lower cut off (3 rather than 4 ng/ml) which is likely to result in more cancers being diagnosed, although they may not be clinically significant cancers. This may 'improve' cure rates in the screening group.
- Quality of life and economic evaluations are yet to be published but these factors are really important.

### **Why the difference between the two studies?**

*When looking at these two studies together it is tempting to give up in despair as they seem to add complexity to the confusion!*

However there are several reasons why the results may be different, which are discussed in the excellent accompanying editorial (NEJM 2009;360:1351-1354).

- The studies use **different cut-off values for action** with the ERSPC using 3ng/ml and the PCLO using 4ng/ml as a trigger for further investigation. The European trial is therefore more sensitive at detecting prostate cancer, perhaps at an earlier stage. This is at a cost of reduced specificity which results in over investigation, over diagnosis and over treatment.
- There is significant “**contamination of the control group**” in the PCLO study ie. Nearly half the control group had PSA tests over the course of the trial. This may dilute any detectable benefit in the screening group.
- The **smaller size** of the PCLO study may mean it is not yet powered to detect a small improvement in mortality in the presence of control group contamination.
- **Study population selection:** In the PCLO trial 44% of men in both the screening and control arms had had at least one PSA measurement before entering the trial. This is because of the widespread use of PSA screening in the US. This may have eliminated some prostate cancers detectable on screening from the randomised population.
- **Improved prostate cancer treatment** over the course of the PCLO trial may have resulted in fewer deaths in both arms of the trial which would blunt potential benefits in screening.

### **So what does all this mean in practice?**

As the Chief Medical Officer reminded us in a letter to all clinicians (18<sup>th</sup> March 2009), all men are entitled to PSA testing on the NHS, but they need to have made an informed choice based on the material in the PCRMP (see useful websites).

**The editorial concludes** (NEJM 2009;360:1351-4):

- **Serial PSA screening has at best a modest effect on mortality from prostate cancer over the subsequent decade.**
- **This benefit should be balanced against the cost and implications of over diagnosis and over treatment.**

***The question is not, ‘Does screening for prostate cancer save lives?’ but, ‘Does screening for prostate cancer do more good than harm?’***

***At the moment, the answer isn’t clear!***

The NEJM editorial concludes that the risk-benefit analysis of screening may be in the eye of the beholder, which takes us back, rather nicely, to the case scenario with which we started!

**What will I say to my patients when I counsel them about PSA screening?**

In addition to my usual discussion about the pros and cons of prostate cancer screening, in the light of these studies, I will also say to my patients:

- There were two trials of prostate cancer screening using the PSA test, but only one showed benefit.
- The benefit was a 20% reduction in deaths from prostate cancer in men aged 55-69y, as a result of screening.
- The downside is that you are twice as likely to be labelled with prostate cancer: 48 men will be diagnosed with prostate cancer to prevent one man dying from prostate cancer. Diagnosis means treatment, and treatment means side effects.

<b>Useful Websites</b>	<p><b>For professionals and patients:</b>  <i>The Prostate Cancer Risk Management Programme has information for both patients and clinicians and is available at:</i>  <a href="http://www.cancerscreening.nhs.uk/prostate/informationpack.html">www.cancerscreening.nhs.uk/prostate/informationpack.html</a></p>	<b>Useful Websites</b>
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**Take home messages: PSA screening for prostate cancer**

- PSA testing for prostate cancer has many drawbacks: poor sensitivity and specificity and the risk of over diagnosis of clinically unimportant tumours.
- Treating men with clinically unimportant cancers exposes them to harm with no benefits.
- A US RCT shows no benefit from PSA screening.
- A European RCT shows a 20% reduction in mortality with PSA screening but with significant over diagnosis and over treatment and all the harms that involves.
- Screening *might* save lives, but we still don't know whether it actually does any good, which is the far more important question!

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