Prostate cancer: PSA screening

“Oh, and one more thing, should I have the PSA test? A mate of mine at the golf club has just been diagnosed and luckily they’ve caught it early. He says we should all get a test.”

I don’t know about you but a little bit inside me dies when faced with this common conundrum. It would be so easy just to say: “Quite right, thank goodness you’ve come. Hop on the couch and let’s sort you out with an examination and blood test.” But is that really what is best for the patient in front of you?

There has been a sea change in attitude to PSA screening in the last few years with even the USA (where 90% of prostate cancers are now diagnosed by screening), changing their attitude.

There is no formal prostate cancer screening programme in the UK but the National Screening Committee has a ‘risk management programme’. Men can request a PSA test but should be given a balanced view of the current evidence relating to PSA testing and this is discussed below.

Remember in this section we are discussing the use of PSA tests in asymptomatic men who ask for a test. Symptomatic men may require a PSA test as part of your clinical work-up.

An excellent BMJ review summarised the current situation and clearly explained why, in the light of current evidence, we should think very carefully about offering and accepting PSA tests (BMJ 2013;346:f325). Before we consider the evidence in more detail, consider these key messages:

- PSA testing has more than doubled the incidence of prostate cancer, identifying tumours that would never have otherwise come to clinical attention.
- At autopsy in men who have died from other diseases, occult prostate cancer is common:
  - 30% of men aged >50y
  - 70% of men aged >70y.

This suggests that indolent prostate cancers may be a ‘normal’ part of ageing.

- The absolute reduction in deaths from prostate cancer has been small in comparison to the increased incidence – only 10.4 per 100 000 men – and is this due to better treatment?
- We are not yet able to differentiate between indolent and aggressive prostate cancers (although parametric MRI may change all this). Therefore a PSA test sets off a cascade of events which may be unnecessary and even harmful for the individual patient.

Important point:

First we will discuss the reasons why we are shifting away from doing PSA tests in asymptomatic men. However, accepting that some men will already be having the test and some will continue to request it, we will go on to look at the best age to have the test and the best interval between tests.

Does PSA screening reduce mortality?

No! Well…..at the very best a very small amount!

The purpose of a screening test is to reduce disease-related morbidity and mortality, not just to identify more people with the disease and treat them, exposing them to harm.

There have now been 5 large long-term randomised trials which have looked at prostate cancer mortality in screened and unscreened populations. The two key studies and their key findings are shown in the table below.

<table>
<thead>
<tr>
<th>The Prostate, Lung, Colorectal and Ovarian screening trial (PLCO) (NEJM 2009;360:1310)</th>
<th>The European Randomised Study of Screening for Prostate Cancer (ERSPC) (NEJM 2009;360:1320)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial design: US-based RCT of 76 000 men aged 55–74y Annual PSA and DRE for 6y vs. usual care 13y follow-up</td>
<td>Trial design: European 7 country RCT of 180 000 men aged 50–74y PSA test every 4y vs. no screening 11y follow-up (NEJM 2012;366:981)</td>
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There is so much we don’t know in medicine that could make a difference, and often we focus on the big things, and the little things get forgotten. To highlight some smaller but important issues, we’ve put together a series of pearls that the Red Whale found at the bottom of the ocean of knowledge!
Why do the results differ between the two studies?

There were some differences between the two studies.

- Different PSA cut-off values were used (PLCO =4ng/ml, ERSPC =3ng/ml) – this made the ERSPC trial more sensitive at detecting prostate cancer, perhaps at an earlier stage, but at the cost of over treatment.
- There was significant contamination of the control group in the PLCO study – nearly half the control group had PSA testing over the course of the trial. This may have diluted the benefits in the screened group but the authors did statistical modelling suggesting this was not the case.
- Improved treatment of prostate cancer in the USA over the course of the PLCO trial may have resulted in fewer deaths in both arms.

So, at best using the 11y follow-up data from the one screening study we have that showed some benefit, for every 1000 men screened and followed up for 11y, we will prevent 1 prostate cancer death at the expense of treating 37 additional men. We will not affect all-cause mortality.

A systematic review of PSA screening pooled the results of these two trials and 4 others (BMJ 2010;34:c4543). The meta-analysis of more than 380 000 men also confirmed that whilst screening increased the risk of a diagnosis of prostate cancer, it had no impact on prostate cancer or all-cause mortality.

So, should men be screened with a PSA blood test?

The UK National Screening Committee and the US Preventative Services Task Force now recommend against PSA screening because the benefits are at best small and not greater than the harms. Our tables below are taken from the former and are the figures the NHS includes in its literature, but there has been further data published since. See our section on the ERSPC 13y on.

Possible benefits of screening:

<table>
<thead>
<tr>
<th>Reduced 10y mortality from prostate cancer (in men aged 55–69y)</th>
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<tbody>
<tr>
<td>Number of men who die with no screening</td>
</tr>
<tr>
<td>Number of men who die with screening</td>
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<tr>
<td>Number of men who avoid death with screening</td>
</tr>
</tbody>
</table>

*These benefits are pretty marginal!*

Harms of screening:

<table>
<thead>
<tr>
<th>Specific harms of screening</th>
<th>Number of men</th>
</tr>
</thead>
</table>
Both the PLCO and ERSPC trials suggest between 10 and 15% of men who undertake regular screening will experience a false positive result, meaning that they will go through a biopsy that will be negative (JAMA Intern Med 2014;174:1841).

**We are considering being diagnosed with prostate cancer as a harm of screening because, at present, 90% of men will undergo treatment and its associated risks and yet many of them would have done well without treatment and a substantial proportion would have remained asymptomatic for life.

ERSPC study 13 year follow-up

The ERSPC study has now reported on 13y of follow-up (Lancet 2014; 384:2027). We have not altered the data above to reflect the new data because much of the information that patients and professionals access is based on the data that was published at 9 and 11y.

So what can we learn from the European study 13y on?

* With time the absolute benefit of screening men for prostate cancer with the PSA test has increased.
* Numbers needed to invite to screening (NNI) and numbers needed to diagnose (NND) to prevent a death from prostate cancer are improving as a consequence – see table below:

<table>
<thead>
<tr>
<th>Complications of treatment:</th>
<th>Raw data results at 9y</th>
<th>Raw data results at 13y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experiencing at least one false positive screen*</td>
<td>100–120 in 1000</td>
<td>110 in 1000</td>
</tr>
<tr>
<td>Being diagnosed with prostate cancer**</td>
<td>2 in 1000</td>
<td>1 in 1000</td>
</tr>
<tr>
<td>Serious cardiovascular events due to treatment</td>
<td>29 in 1000</td>
<td>18 in 1000</td>
</tr>
<tr>
<td>DVT or PE due to treatment</td>
<td>&lt;1 in 1000</td>
<td></td>
</tr>
<tr>
<td>Erectile dysfunction due to treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence due to treatment</td>
<td></td>
<td></td>
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<tr>
<td>Death due to treatment</td>
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</table>

*Overdiagnosis rate varies with age from 27% in those aged 55y to 75% in those over 75y.
* The authors agree with current policy not to undertake population screening but to offer it to men who request it and who are fully informed of the issues.
* In a commentary the principal author suggest that because 70% of men who took part in the study are still alive the results so far published are still preliminary!

Adverse effects of prostate biopsy

About 100 000 men undergo prostate biopsy each year in the UK. This very relevant study answers the questions rarely answered in studies of PSA screening: what can a man expect if he has a needle biopsy after a raised PSA is found (BMJ 2012;344:d7894)?

* UK-based study of men recruited for a trial of treatment options following PSA screening (so-called ProtecT study).
* 1147 men who had 10 core transrectal ultrasound biopsy after raised PSA responded to questionnaires regarding their symptoms afterwards.
* Whilst only 2% of men experienced no symptoms from the biopsy, the majority (64%) considered their symptoms to be minor. Typical problems are detailed in the table below:
Adverse event (within 35d of biopsy) | Frequency (mild, moderate & severe) | Frequency (moderate or severe only)
--- | --- | ---
Haematospermia | 90% | 25%
Haematuria | 66% | 6%
Pain | 44% | 7%
Rectal bleeding | 37% | 2%
Fever | 20% | 5%

- 10% of men had to see their GP following a TRUS biopsy, most commonly for infective complications. One in 100 required hospital admission.
- Whilst 11% considered a further biopsy might be a major problem immediately after the procedure this rose to 20% by day seven. This is important as almost half of men will end up having a further biopsy within 5 years of their first.

Adverse effects of prostate cancer treatment

And what of the adverse effects of treatment itself?

These figures taken from J Natl Cancer Inst (2004;96:1358) that looked at complication rates 5y after treatment. Whilst this study is relatively old, its rates coincide closely with other newer studies such as Eur J Cancer (2011;47:545).

Adverse effects of prostate cancer treatments

<table>
<thead>
<tr>
<th></th>
<th>Radical prostatectomy</th>
<th>External beam radiotherapy</th>
</tr>
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<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>80%</td>
<td>65%</td>
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</tbody>
</table>
So what does all this mean in practice?

On the basis of this information, we should not be recommending PSA testing for asymptomatic men. The BMJ review has a useful simple set of messages we can use with men asking for the test. Here are suggestions of what you can say if asked for a test (BMJ 2013;346:f325):

"Major evidence-based guidelines recommend against PSA testing for the following reasons:

- The test is unlikely to prevent you from dying from prostate cancer over 10–15y or to help you to live longer.
- Elevated PSA values are common and lead to tests that have harms.
- PSA tests find many cancers that will never cause health problems.
- Once we find a cancer, it is difficult not to treat it.
- Treatments have harms which can be serious and may persist and yet have very little if any benefits.
- If you choose not to have a PSA test, you can live a similar length life, have little or no difference in dying from prostate cancer and avoid the harms associated with tests, procedures and treatment”.

I think this is simple, practical and useful. However, we all know that despite this information, some men will still choose to have the test and at present the Prostate Cancer Risk Management Program (PCRMP) allows men to make this choice. The real challenge for us as clinicians is discussing the concept of a “cancer that won’t kill you!”.

Additional written information can be found at the National Screening Committee website shown in the useful websites section below.

*Now, moving on to men who choose to have the test, despite all this information. Here we consider the properties of the test, age of testing and optimal interval between tests.*

### The PSA test

#### Diagnostic characteristics of the PSA test

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>≥4.0ng/ml</th>
<th>≥3.0ng/ml</th>
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<tbody>
<tr>
<td>PSA cut-off level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>21%</td>
<td>32%</td>
</tr>
</tbody>
</table>
Before having a PSA blood test men should not have:

- An active urinary tract infection (PSA level may remain elevated for months).
- Ejaculated in previous 48h.
- Exercised vigorously in previous 48h.
- Had a prostate biopsy in the previous week.
- Had a DRE in the previous week (though some contest this...).

What about free and bound PSA?

There are two types of PSA found in the blood: free PSA, which is associated with benign processes, and bound PSA, which is associated with malignancy. A low ratio of free to bound (<25%) may be indicative of cancer. Studies are on-going to determine whether this would be a more specific test and whether it might be useful to differentiate between indolent and aggressive tumours, but the results of these are not yet published. Other tumour markers are under evaluation including PCA3, HK2 and EPCA-2, and a urine based test.

Currently, these tests are not available through the NHS.

PSA at age 60 and risk of prostate cancer

Once in a while a study comes along that is so wonderfully simple and so informative you want to jump for joy (at least we at GP Update do!). In this study from Sweden, researchers followed 1167 men from the age of 60y to the age of 85y (BMJ 2010;341.c4521). At the age of 60y they had a single PSA test. The men were part of a case–control study and the follow-up was comprehensive, with very few being lost to follow-up.

- Men who had a PSA of <1ng/ml at the age of 60y had a 0.5% risk of metastatic cancer by the age of 85y and a 0.2% risk of death from prostate cancer. This level of risk was considered by the researchers to be clinically insignificant.

It’s a small study and needs validation, particularly for different racial groups and different ages but offers us a useful piece of information we can offer patients who opt for a PSA.

Would age at which you start doing PSA tests make any difference?

The BBC reported that research suggested that all men should be offered a PSA test in their late 40s – it is no wonder our patients are confused! In the light of what we have discussed above, the context of this study has to be taken in terms of men who choose, despite the current best evidence, to have a PSA test.

The same authors of the above study went on to perform a follow-up case-control study based on the same data set which was collected as part of the Malmo Preventative project (BMJ 2013;346:f2023). This study enrolled 21 000 men aged between 27 and 52y and took and stored blood samples. The majority of these men remained unscreened for prostate cancer for the >25y of follow-up. They compared PSA levels in blood samples taken at different ages with the subsequent risk of developing metastatic prostate cancer – a natural experiment!

They start from the hypothesis that current guidance on PSA testing may be focusing on the wrong age group and attempted to answer 3 important questions:

- Is there any rationale for starting PSA screening before age 45y?
- Could a single PSA test between the ages of 45 and 49y or 51 and 55y exempt some men from further screening, or identify a particularly high risk cohort?
- What is the optimal interval for screening low risk men?

They believe that in answering these questions, screening programmes can be designed to focus on men at highest risk, reducing over-diagnosis whilst still enabling early detection in those at highest risk.

They found:

- In the cohort as a whole, higher PSA concentration correlated with the risk of prostate cancer metastases documented up to
30y later.
- Concentrations became more predictive in older men.
- At age 40y, even for men with a PSA in the highest 10%, the risk of prostate cancer metastases in the following 15y was low – they concluded it was hard to justify screening at this age in average risk men.
- Between age 45–49y men with PSA in the highest 10% (≥1.61µg/L) contribute nearly half of the deaths from prostate cancer over the next 25–30y – these form a high risk group and should be offered regular screening.
- The data did not support being able to safely exempt men from further screens based on a single PSA aged 45–49y or 51–55y.
- However, the data suggested that a screening interval of more than 5y would be safe for men who had a PSA ≤1µg/L.

On the basis of this and the previous study, the authors propose the following algorithm. If having decided on the basis of the risks and benefits that he wants PSA screening a man should be offered:

The limitations of the study are that the cohort was exclusively white. Before implementation, any algorithm such as this would require prospective evaluation. The National Screening Committee have said they will incorporate these data into their review of prostate cancer screening at the end of 2013.

What does this mean in practice?

If as a result of this study we are approached by men in their late 40s requesting PSA tests:
- We should offer them the full range of information as detailed above including the fact that neither of the two large randomised studies on PSA screening included men of their age group.
- If they choose to have the test, this study helps us to advise on the best interval for further PSA tests, but we do not know if following this would have an impact on mortality, etc.
- For men currently having annual PSA tests, we may be able to lengthen the interval!

In support of this, a mathematical modelling study looked at different PSA screening strategies using US databases and RCT trial data (Ann Int Med 2013;158:145). It concluded that higher PSA thresholds for biopsy and longer screening intervals could reduce harm while preserving life – clearly this needs to be tried out in real life!

What does the future hold?

Whilst we acknowledge here that PSA screening does not seem to offer any benefits in terms of prostate cancer mortality or all-cause mortality, this is still a disease that for a group of men results in significant morbidity and ends their lives prematurely.

The future of screening continues to look for ways to identify high risk tumours and separate them out from low risk tumours. This is proving difficult.

Research is on-going to look at the use of multi-parametric MRI (MRI that looks at structure and function of the prostate gland) and new blood and urinary biomarkers in identifying the tumours that would cause problems in a man’s life time – this is the search for the Holy Grail which could lead to a more rational screening programme.
PSA screening for prostate cancer

- The PSA test has significant failings and consensus has changed – we should not recommend PSA screening.
- A meta-analysis of all PSA screening randomised trials failed to demonstrate a reduction in death rates from prostate cancer or overall mortality in screened men.
- Treating men with clinically unimportant cancers exposes them to harm.
- Over one-third (36%) of men report moderate/severe symptoms after prostate biopsy.
- Men who ask about the PSA test should continue to be offered balanced information to allow them to make an informed choice.
- A single PSA <1µg/L for a man in their 60s largely rules out the risk of clinically significant prostate cancer in the rest of his lifetime.
- If opting to have PSA tests, lower risk men defined as having PSA <1µg/L in their late 40s may just need 3 tests over their lifetimes.
- Men with a PSA >1.6µg/L in their late 40s will make up nearly 50% of future prostate cancer deaths and would benefit from more frequent screening.

For professionals and patients:
The Prostate Cancer Risk Management Programme has information for both patients and clinicians and is available at: www.cancerscreening.nhs.uk/prostate/informationpack.html

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- Lead. Manage. Thrive! The management skills course (location).............................................................   (date)..........................
- The Telephone Consultation Course (location).............................................................   (date)..........................
- The Effective Consultation Course (location).............................................................   (date)..........................
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