PSA & Prostate Cancer Screening

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“When a thing ceases to be a subject of controversy, it ceases to be a subject of interest…”

Do you think we should have a national screening programme for Prostate Cancer using PSA?

• YES – it’s an outrage, women have breast cancer screening etc
• NO – a complete waste of time, PSA is useless, overdiagnosis…
• Maybe……
• Don’t know……

PSA testing is not usually recommended for asymptomatic men with < 10 years life expectancy

Before having a PSA test men should not have:
• had a DRE in the previous week
• an active UI (PSA may remain raised for many months)
• ejaculated in previous 48 hours
• exercised vigorously in previous 48 hours
• had a prostate biopsy in previous 6 weeks

PSA can be useful in assessment of men with LUTS-BPH

TAKE HOME MESSAGE 1
Risk Factors for Progression

- Age over 70 with LUTS
- Moderate - severe symptoms i.e. IPSS > 7
- **PSA > 1.4 ng/ml**
- Prostate volume over 30ccs (i.e. feels enlarged on DRE)
- Flow rate <12 ml/sec

Should we routinely do a PSA test in a man presenting in primary care with lower urinary tract symptoms?

The man with LUTS

- Patient is usually worried about prostate cancer
- Partner is usually worried about prostate cancer
  - 71% of partners attending a LUTS clinic (1)
- GP is usually worried about prostate cancer
  - only 11% confident in distinguishing between BPH & Prostate Cancer (2)

PSA testing in men with LUTS

- Offer men information, advice and time to decide if they wish to have a PSA test if:
  - Their LUTS are suggestive of bladder outflow obstruction due to BPE
  - Their prostate feels abnormal on DRE
  - They are concerned about prostate cancer

Screening with PSA may be better than you think

TAKE HOME MESSAGE 2

ERSPC

- European Randomised Study on Screening for Prostate Cancer
- Commenced in 1993
- 162,000 men aged between 55 and 69, from 8 countries
- Offered PSA screening at an average of once every 4 years or to a control group

82% of men accepting at least one offer of a PSA test

- median follow up 9 years
- cumulative incidence of prostate cancer was 8.2% (screening group) versus 4.8% (control group)
- absolute risk difference for death was 0.71 fewer deaths per 1000 men in screening arm – 20% decrease in risk of dying (27% for those actually screened)
- 1410 screened men per CaP life saved.
- 48 treatments per life saved

‘Gothenburg study’:
Cumulative risk of death

Prostate cancer mortality
Intention to screen analysis

- Relative risk (RR) of PC death 0.56 (95% CI 0.39-0.82, P=0.002), a 44% relative reduction
- Absolute risk reduction: 34 per 10,000 men screened
- NNS: 293 (95% CI 177-799)
- NNT: 12 (in excess of control group)

PSA screening in context

NNS to prevent 1 death:

- ERSPC 1410 (offered) – 1068 (screened)
- Gothenburg 293
- Colorectal 1173
- Breast 2000

Reduction in relative risk of death:

- ERSPC 20%
- Gothenburg 44%
- Colorectal 16%
- Breast 15-20%

ERSPC at 13 years follow up

<table>
<thead>
<tr>
<th>Outcome</th>
<th>WITH screening</th>
<th>WITHOUT screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer Diagnosis</td>
<td>1.016</td>
<td>683</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- All cause</td>
<td>2,108</td>
<td>2,139</td>
</tr>
<tr>
<td>- Prostate cancer</td>
<td>49</td>
<td>61</td>
</tr>
<tr>
<td>- Other causes</td>
<td>2,060</td>
<td>2,078</td>
</tr>
</tbody>
</table>

Numbers per 10,000 men aged 55-69 years old
Derived from 13-year follow-up data ERSPC.
A national screening programme with PSA is not going to happen

UK National Screening Committee

- Estimated cost of policy of screening men aged 50-74 with PSA 4 yearly:
  - £0.8 billion p.a.
- The harms from prostate cancer screening using PSA are likely to outweigh the benefits. Screening cannot be justified on the current evidence

BMJ review 2013

- Increasing age the most important risk factor for prostate cancer
- Most effective way to reduce incidence of prostate cancer is:
  - Reduce PSA testing
  - Raise thresholds that define abnormality
- Screening with PSA results in small reduction in mortality & leads to considerable harms
- Physicians should recommend against PSA screening
- Most men diagnosed via screening have tumours that will not cause health problems (overdiagnosis) but almost all undergo early treatment (overtreatment)

Published May 2012

- "moderate or high certainty that the service has no benefit or that the harms outweigh the benefits"
- Grade D recommendation - ‘discourage the use of this service’

We currently screen the wrong patients

Who gets screening at present?
Who gets screening at present?

Association of PSA testing with study area

- Cambridge: 9.3
- Newcastle: 7.2
- Sheffield: 7.7
- Leeds: 3.7
- Bristol: 4.8
- Cambridge: 5.3

PSA tests need to be targeted at the high risk patients

TAKE HOME MESSAGE 5

Who is at high risk of prostate cancer?

- ‘Baseline PSA test’ – PSA at 40
- Race
- Family history

‘PSA at 40’

- Why might 40 be a good place to start?
  - No Benign Prostatic Hyperplasia – ‘background noise’
  - Less prostatitis
  - Early stage of disease if found
  - Excellent results of treatment
  - BUT ... Unnecessary anxiety, biopsy, treatment

Malmö Prevention Project

- PSA testing very low in Sweden, stable population
- 1974-1986, >21 000 men <50 years provided blood within a cardiovascular study
- Prostate cancers were identified in 1999 using the Swedish cancer registry.
- Archived blood samples retrieved

Odds of prostate cancer diagnosis by plasma total PSA levels at baseline venepuncture.

<table>
<thead>
<tr>
<th>Total PSA (ng/mL)</th>
<th>Controls</th>
<th>Cases</th>
<th>Odds Ratio</th>
<th>Probability of Prostate Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.50</td>
<td>543</td>
<td>68</td>
<td>reference</td>
<td>4</td>
</tr>
<tr>
<td>0.51-1.00</td>
<td>474</td>
<td>147</td>
<td>2.51</td>
<td>8</td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>173</td>
<td>146</td>
<td>7.02</td>
<td>20</td>
</tr>
<tr>
<td>2.01-3.00</td>
<td>23</td>
<td>55</td>
<td>19.1</td>
<td>41</td>
</tr>
<tr>
<td>≥ 3.01</td>
<td>9</td>
<td>46</td>
<td>38.8</td>
<td>60</td>
</tr>
</tbody>
</table>

(Oliver D, Corderia, E.N.A. et al. 'Prostate specific antigen detection age 40 as a predictor of advanced prostate cancer diagnosed at 50 years old: results of a collaborative cohort study).
MPP continued

- PSA was a very strong predictor of prostate cancer up to 25 yrs subsequently.

- Levels of 2–3 ng/mL (within normal range) associated with increase in odds for subsequent prostate cancer of more than 19-fold.

- 80% of advanced cancers occurred in men with PSA levels above the median at age 44–50 years.

A national recommendation?

- Single PSA test as predictor for the long-term risk of prostate cancer at 40–45 yrs.
- PSA >0.65 ng/mL (median) → further PSA testing should be considered.

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>Action</th>
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<tbody>
<tr>
<td>0.65–1 ng/mL</td>
<td>PSA test every 2–4 yrs</td>
</tr>
<tr>
<td>&gt;1 ng/mL</td>
<td>Annual PSA tests</td>
</tr>
<tr>
<td>&lt;0.65 ng/mL</td>
<td>Low risk, further testing 55–60 years</td>
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Family history

- Risk increases with:
  - Increasing number of affected relatives
  - Degree of relatedness
  - Younger age at diagnosis

- Lifetime absolute risk of prostate cancer:
  - Man with no FHx: 8%
  - Man with father affected >60: 12% (worse if brother)
  - Man with 3 or more affected relatives: 35–45%

Race

- Higher incidence of prostate cancer in Afro-Caribbean men
- UK age-adjusted incidence of 166 / 100,000 black men vs. 56.4 / 100,000 white men; Relative risk approx 3
- No difference African vs. Caribbean ethnic origin
- World highest – Kingston 304 / 100,000

We need better tools in primary care to aid interpretation of PSA results
Interpreting PSA results – difficult even for the experts

**Recommendation from 50 Nordic Prostate Cancer Specialists**

**Case 1**
- 62 year old healthy man with no symptoms. First PSA 14, a second PSA 10.2 after 1 month, palpable normal prostate but slightly enlarged.

**Case 2**
- 58 year old healthy man with no symptoms. He had had three PSA between 4.0-4.5 during the last year.

<table>
<thead>
<tr>
<th></th>
<th>New PSA</th>
<th>Biopsy</th>
<th>MRI</th>
<th>No</th>
</tr>
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<tbody>
<tr>
<td>49%</td>
<td>22%</td>
<td>34%</td>
<td>18%</td>
<td>12%</td>
</tr>
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**Inconsistency**

- “The days of using 1 PSA threshold to trigger a biopsy for all men are over” – BJU Editorial 2013
- “having a PSA test is consenting to having a biopsy if the result is abnormal” – Local Urologist
- ‘my PSA was 9 2 years ago, 12 last year and now it is 18 – my GP says now it is a little concerning so they decided to refer me’ – Patient
- ‘I do a PSA on everyone’ – GP
- “PSA is essentially useless” – GP

**Trends in PSA Utilisation by PCP’s:**

**Impact of the USPSTF Recommendation**
- Most significant decrease in PSA testing in 50-70 year old age group – from 17% to 8.2%
- No significant difference in PSA testing frequency for men aged 40-49 (4.2 vs 4.4%) or >70 years (10.2 vs 9.3%)
- Only 36% of men diagnosed with BPH had a PSA test
- 75% of PCP’s had changed practice as a result of USPSTF, with majority believing PSA testing does more harm than good

**NICE Suspected Cancer – 2015 update**

- Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their prostate feels malignant on digital rectal examination. [new 2015]
- Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with:
  - any bowel urinary tract symptoms, such as haematuria, urinary frequency, hesitancy, urgency of micturition or erectile dysfunction or visible haematuria. [new 2015]
- Refer men using a suspected cancer pathway referral (for an appointment within 2 weeks) for prostate cancer if their PSA levels are above the age-specific reference range. [new 2015]

**Risk based approach to screening**
Led by Chris Parker, Institute of Cancer Research & Royal Marsden

Team includes:
- Mike Kattan, Cleveland Clinic
- Robert Nam, Sunnybrook, Toronto
- Monique Roobol, Erasmus
- Ewout Steyerberg, Erasmus

Initial planning meeting also involved:
- Freddie Hamdy, Oxford
- Jan Adolfsson, Karolinska, Stockholm
- Henrik Gronberg, Karolinska, Stockholm
- Sunil Jain, Queens, Belfast
- Peter Albertsen, Connecticut
- Plus a GP from the UK!

"Aim is to produce a risk prediction tool that is applicable to the UK population and acceptable to men in the UK, their doctors and the NHS, when delivered through primary care, forming the basis for future international adoption."

Help GPs interpret PSA results & make decisions re referral / follow up interval
Reduce numbers of "unnecessary biopsies"
Identify men at higher risk for aggressive forms of prostate cancer

Figure 3: Surname-based prototypes of next generation risk calculator input screen shot. Primary care physicians can enter each factor online.

Overtreatment

- Should low grade disease (Gleason 6) be reclassified as benign / pre-malignant / non-lethal?
- NICE guideline recommending increased role for active surveillance
Melbourne Consensus Statement

1. For men aged 50–69, level 1 evidence demonstrates that PSA testing reduces prostate cancer-specific mortality and the incidence of metastatic prostate cancer.

2. Prostate cancer diagnosis must be uncoupled from prostate cancer intervention.

3. PSA testing should not be considered on its own, but rather as part of a multivariable approach to early prostate cancer detection.

4. Baseline PSA testing for men in their 40s is useful for predicting the future risk of prostate cancer.

5. Older men in good health with over ten year life expectancy should not be denied PSA testing on the basis of their age.

Conclusion

- Potential for impacting on prostate cancer mortality whilst reducing harm from overtreatment of low risk patients if:
  - PSA tests were targeted at higher risk patients
  - Referral +/- biopsy were carried out on a more sophisticated risk based model
  - Treatment was reliably reserved for those with high risk disease

Something has to change

The answer to all critics of PC screening is not to stop the use of the PSA test but to **stop the misuse of the PSA test.**