PSA & Prostate Cancer Screening

DR JONATHAN REES MD MRCS MRCGP

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

- YES
- NO
- Maybe
- Don’t know

Do’s & Don’t’s of PSA Testing

- 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 UTI (PSA may remain raised for many weeks/months)
  - ejaculated in previous 48 hours
  - exercised vigorously in previous 48 hours
  - had a prostate biopsy in previous 6 weeks

1.6.2 Consider a prostate-specific antigen (PSA) test and digital rectal examination to assess for prostate cancer in men with:
- any lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention or
- erectile dysfunction or
- visible haematuria. [new 2015]

1.6.3 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]
“Where a man aged 70 or over decides to have a PSA test, the same referral value of 3 ng/ml should apply, but an elevated PSA should not automatically lead to prostate biopsy.”

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

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)
- GF is usually worried about prostate cancer
  - only 11% confident in distinguishing between BPH & Prostate Cancer (2)

2. prostatecanceruk.org (Prostate Action)
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


ERSPC

- 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

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 NSC

The UK NSC recommendation on Prostate cancer screening/PSA testing in men over the age of 50

- Systematic population screening programmes not recommended
- Last review completed: January 2016
- Last review due in: 2019/19
- Key downloads:
  - Recommendation statement
  - Last external review - Prostate cancer
  - Last evidence review summary

Prostate cancer is a serious public health problem. Evidence suggests that PSA screening use reduces prostate cancer mortality by 27%. However, strategies to manage the harms of overdiagnosis and overtreatment are not yet known. Information is provided on the risks and benefits of the Prostate Cancer Risk Management Programme.

http://www.screening.nhs.uk/prostatecancer

BMJ review 2013

- Increasing age the most important risk factor for prostate cancer
- Most effective way to reduce incidence of prostate cancer is:
  - Avoid sex
  - Take aspirin for heart disease
- Screening with PSA testing results in small reduction in mortality and 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)

Annals of Internal Medicine

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Grade B: Recommend against PSA testing

http://www.annals.org/content/annals/197/6/732

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’

http://www.screening.nhs.uk/prostatecancer
We currently screen the wrong patients

**TAKE HOME MESSAGE 4**

<table>
<thead>
<tr>
<th>Association of PSA testing with study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>City</td>
</tr>
<tr>
<td>Cambridge</td>
</tr>
<tr>
<td>Bristol</td>
</tr>
<tr>
<td>Leicester</td>
</tr>
<tr>
<td>Leeds</td>
</tr>
<tr>
<td>Sheffield</td>
</tr>
<tr>
<td>Newcastle</td>
</tr>
</tbody>
</table>

**Who gets screening at present?**

**Association of PSA testing (%) with Age**

- **When should we stop PSA testing?**

  **PSA without DRE for men aged:**
  - 45 – 49:
    - PSA 3.5 ng/mL or serum prostate specific antigen (PSA)
    - PSA 2.0 ng/mL or PSA levels below 2.0 ng/mL
    - PSA 1.5 ng/mL or PSA levels below 1.5 ng/mL
    - PSA 1.0 ng/mL or PSA levels below 1.0 ng/mL
  - 50 – 59:
    - PSA 3.5 ng/mL or serum prostate specific antigen (PSA)
    - PSA 2.0 ng/mL or PSA levels below 2.0 ng/mL
    - PSA 1.5 ng/mL or PSA levels below 1.5 ng/mL
    - PSA 1.0 ng/mL or PSA levels below 1.0 ng/mL
  - 60 – 70:
    - PSA 3.5 ng/mL or serum prostate specific antigen (PSA)
    - PSA 2.0 ng/mL or PSA levels below 2.0 ng/mL
    - PSA 1.5 ng/mL or PSA levels below 1.5 ng/mL
    - PSA 1.0 ng/mL or PSA levels below 1.0 ng/mL
  - 71 – 75:
    - PSA 3.5 ng/mL or serum prostate specific antigen (PSA)
    - PSA 2.0 ng/mL or PSA levels below 2.0 ng/mL
    - PSA 1.5 ng/mL or PSA levels below 1.5 ng/mL
    - PSA 1.0 ng/mL or PSA levels below 1.0 ng/mL
  - 76+:
    - PSA 3.5 ng/mL or serum prostate specific antigen (PSA)
    - PSA 2.0 ng/mL or PSA levels below 2.0 ng/mL
    - PSA 1.5 ng/mL or PSA levels below 1.5 ng/mL
    - PSA 1.0 ng/mL or PSA levels below 1.0 ng/mL

  - Age varying for each man
  - Age to be – Within a range of men in whitecell houses

PSA tests need to be targeted at the high risk patients

TAKE HOME MESSAGE 5

Who is at high risk of prostate cancer?

- Age
- "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>66</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>

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 yrs.

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>
</tr>
</thead>
<tbody>
<tr>
<td>0.65-1ng/ml</td>
<td>PSA test every 2–4 years</td>
</tr>
<tr>
<td>&gt;1ng/ml</td>
<td>Annual PSA tests</td>
</tr>
<tr>
<td>&lt;0.65ng/ml</td>
<td>Low risk, further testing 55–60 years</td>
</tr>
</tbody>
</table>

Conclusion: A baseline serum PSA should be offered to all men 40–45 yr of age to initiate a risk-adapted follow-up approach with the purpose of reducing PCA mortality and the incidence of advanced and metastatic PCAs. In the future, the development and...
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: 30-45%

FHx & Probability of Prostate Cancer

Average Population Probability at age 65

White: No Prostate Cancer
Light Grey: Low Risk Pca
Medium Grey: Intermediate Risk Pca
Black: High Risk / Metastatic PCa

Probabilities at age 65 for men with a father & 1 brother with Pca

Average Population Probability at age 75

White: No Prostate Cancer
Light Grey: Low Risk Pca
Medium Grey: Intermediate Risk Pca
Black: High Risk / Metastatic PCa
We need better tools in primary care to aid interpretation of PSA results

**TAKE HOME MESSAGE 6**

**Interpreting PSA results – difficult even for the experts**

Recommendation from 50 Nordic Prostate Cancer Specialists

Case 1
- 65 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
- 65 year old healthy man with no symptoms: He had had three PSA between 4.0-4.5 during the last year.

- **New PSA**
  - 49%

- **Biopsy**
  - 33%

- **MRI**
  - 18%

- **49%**

- **22%**

- **54%**

- **24%**

- **18%**

- **3%**
Inconsistency

- “The days of using 1 PSA threshold to trigger a biopsy for all men are over” – BJU Editorial 2015
- “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 1.8 – 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 19.3% 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 USPSTI 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 lower urinary tract symptoms, such as nocturia, urinary frequency, hesitancy, urgency or retention 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
ERSPC Risk Calculator

‘A prostate cancer risk prediction tool for primary care practice’

- Led by Chris Parker, Institute of Cancer Research & Royal Marsden
- Team includes:
  - Mike Kattan, Cleveland Clinic
  - Robert Nam, Sunnybrook, Toronto
  - Monique Roobol, Erasmus, Rotterdam
  - Ewout Steyerberg, Erasmus, Rotterdam
- Initial planning meeting also involved:
  - Freddie Hamdy, Oxford
  - Jan Adolfsson, Karolinska, Stockholm
  - Henrik Gronberg, Karolinska, Stockholm
  - Sunil Jain, Queens, Belfast
  - Peter Albertsen, Connecticut
  - Jon Rees, North Somerset, UK
We need to avoid overtreatment of men with low risk prostate cancer

**TAKE HOME MESSAGE 7**

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

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**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.

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**Prostate Cancer UK PSA Consensus Statements**

How did we gather consensus?

- Steering group with independent Chair
- Delphi consensus survey (n=335)
- Focus groups with men with prostate cancer
- Steering Group meeting
- User testing with HCPs and men without prostate cancer – inc a dedicated group for Black men
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.**

*Eur Urol. 2015 Mar 10*