PSA testing in Primary care

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Declaration of interests

- MK has received funding from Industry for research, attending conferences, lecturing and for providing advice.
Aim of the PCRMP

- The Prostate Cancer Risk Management Programme aims to help the primary care team give clear and balanced information to men who request details about testing for prostate cancer.
2008 review of information pack

- Commissioned by the PCRMP in 2007
  - Incorporates recent research developments and recommendations of NICE; Prostate Cancer: diagnosis and treatment guidelines (Feb 2008)
  - Reviewed by GPs and members of the multi-disciplinary PCRMP Scientific Reference Group
Prostate cancer incidence

- Prostate cancer is the most common cancer in men in the UK
- In 2005, 34,302 men were diagnosed
Prostate cancer mortality

- Prostate cancer is the second most common cause of cancer-related deaths in men in the UK
- Prostate cancer claimed the lives of 10,038 men in the UK in 2006
Do you think we should have a National Prostate Cancer Screening Programme?

0% 1. YES
0% 2. NO
0% 3. Not sure
Risk factors for cancer of the prostate

- Age
- Family history
  - 5-10% have an inherited component

<table>
<thead>
<tr>
<th>Number of first degree relatives diagnosed</th>
<th>Increase in relative risk</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2.5 fold increasing to 4.3 fold if the relative was under 60 years of age at diagnosis</td>
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<tr>
<td>2</td>
<td>3.5 fold</td>
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</table>

- Ethnicity
  - risk Black men > White men > Asian/Oriental men

- Diet
  - Lycopenes and possibly selenium may have a protective effect
  - Diet high in protein or calcium from dairy products may increase risk
Clinical features of localised prostate cancer

- Localised prostate cancer (confined within the capsule) is USUALLY ASYMPTOMATIC

- Lower urinary tract symptoms (LUTS) such as frequency, urgency, hesitancy, terminal dribbling and/or overactive bladder are common in older men

- Early prostate cancer itself will not usually produce LUTS which are usually related to the presence of benign prostatic enlargement (BPE)
Key PCRMP recommendations

- Any man over the age of 50 who asks for a PSA test after careful consideration of the implications should be given one.
- The PSA test should not be added to a list of investigations without a careful explanation of why the test is being performed and its implications.
GPs urged to resist patient pressure for prostate test

GPs have been urged to resist patient demands for screening for prostate cancer with tests for prostate specific antigen (PSA).

The tests are inaccurate, uncomfortable and can result in needless worry and anxiety, says one of two reports from the Government’s health technology assessment programme at the University of York.

Meanwhile a new study has further questioned screening and early treatment of prostate cancer. It adds more weight to the traditional UK approach of ‘watchful waiting’ for prostate cancer. But it also stresses the importance of treating advanced or metastatic disease.

The study found that the same proportion of men survived for 10 and 15 years whether or not they had ‘radical early treatment’ for prostate cancer. This treatment included radiotherapy, oestrogen, estramustine, orchidectomy or a combination of these. But if patients had advanced or harm than good, creating anxiety even though the disease is causing no symptoms and is not changing. ‘Even randomised trials to assess the full impact of screening may be unethical,’ the Swedish researchers say (JAMA 1997; 277: 467-71).

The Swedish study follows the publication of health economics reports urging GPs to resist pressures to use PSA tests in the early detection of prostate cancer.

Screening, the report adds,
Assessment of prostate cancer

- PSA test
- Digital Rectal Examination (DRE)
- Transrectal ultrasound
- TRUS guided biopsy
- Imaging techniques
Prostate Specific Antigen (PSA)

- PSA is a glycoprotein responsible for liquefying semen and allowing sperm to swim freely.
- PSA is expressed in both benign and malignant processes involving epithelial cells of the prostate.
The PSA test

- The PSA test is currently the best method of identifying an increased risk of localised prostate cancer
- However, PSA is an enzyme also found in men without prostate cancer
- PSA levels tend to rise with age due to BPE
- The difficulty in using this marker comes in defining the “normal” range and knowing when referral and biopsy are appropriate
Benefits of the PSA test

- May lead to detection of cancer before symptoms develop
- May lead to detection of cancer at an early stage when the cancer could be cured or treatment could extend life
- Repeat PSA tests may provide valuable information aiding in a prostate cancer diagnosis
Limitations of the PSA test

- It is not diagnostic (a biopsy may be required)
- It is not tumour specific in the prostate
- The PSA test result may not be elevated in some cancers and provide false reassurance
- It may lead to the identification of prostate cancers which might not have become clinically evident in the man’s lifetime
- A single PSA test will not distinguish aggressive tumours which are at an early stage but will develop quickly from those which are not
Test practicalities

• Before having a PSA test a man should NOT have:
  • an active urinary infection;
  • ejaculated in the previous 48 hours;
  • exercised vigorously in the previous 48 hours;
  • had a prostate biopsy in the previous 6 weeks; or
  • had a DRE within the previous week.
• The serum PSA level alone should not automatically lead to a prostate biopsy
• Others factors that should be considered in conjunction with the PSA level are prostate size, DRE findings, age, ethnicity, co-morbidities, history of any previous negative biopsy and any previous PSA history
• The patient should be involved in any decision about referral to another healthcare provider
Referral values for total PSA

<table>
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<tr>
<th>Age</th>
<th>PSA referral value (ng/mL)</th>
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<tr>
<td>50-59</td>
<td>≥ 3.0</td>
</tr>
<tr>
<td>60-69</td>
<td>≥ 4.0</td>
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<tr>
<td>70 and over</td>
<td>&gt; 5.0</td>
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</table>

- As PSA levels rise with age, the PCRMP recommends the use of age-related referral values.
- These levels should be used for all men regardless of their weight.
Digital Rectal Examination (DRE)

- DRE is not recommended as a screening test in asymptomatic men
- DRE is a useful diagnostic test for men with lower urinary tract symptoms
TRUS biopsy & Gleason score

- 10-12 cores of prostatic tissue are taken through the rectum under ultrasound guidance
- Gleason score is a method of grading prostate cancers
  - The most common and second most common tumour patterns are analysed
  - Each is assigned a grade (1 to 5) and combined to produce the Gleason score (2 to 10)
  - The lower the score
    - the more well differentiated the tumour
    - the less likely the tumour is to progress
    - the better the prognosis.
- Full procedural details can be found at http://www.cancerscreening.nhs.uk/prostate/pcrmp01.pdf
Biopsy benefits

- Can find cancer before symptoms develop
- Can identify cancerous tissue and identify the grade of tumour
- A negative biopsy result can relieve anxiety about prostate cancer, although a second biopsy may be necessary
- The diagnosing capability of the biopsy procedure increases with the number of cores taken
Biopsy limitations

- Complications include bleeding and infection but antibiotics should be given, so infection is unusual.
- Up to 20% of tumours are missed, although the number of tumours missed decreases with increasing number of cores taken.
- Diagnosis of cancer which is not clinically significant may have a significant impact on the patient.
- Management of men with a negative biopsy but a persistently elevated PSA level is difficult.
Main options after diagnosis

Cancer diagnosed

Localised prostate cancer

Locally advanced prostate cancer

Metastatic prostate cancer

Informed choice

Active Monitoring or Active surveillance
+ Avoids overtreatment
+ Non-invasive
+ Radical, curative treatment can be given if sign of disease progression
- Metastatic cancer may develop and curative treatment may not be an option

Watchful waiting
+ Avoids overtreatment
+ Non-invasive
- Metastatic cancer may develop - curative treatment would not be an option
- Increased risk of dying from prostate cancer

Radical prostatectomy
+ Aim is to cure or control
- Up to 20% have residual tumours after the operation (approximately half these will develop biochemical or clinical recurrence)
- Possible side-effects
  o Infertility (in all cases)
  o Erectile dysfunction
  o Urinary incontinence

Radiotherapy
External Beam Radiotherapy and Brachytherapy
+ Aim is to cure or control
- Possible side-effects
  o Erectile dysfunction
  o Urinary symptoms
  o Bowel problems
  o Infertility

Hormone/chemotherapy

Palliation

Cryotherapy and High Intensity Focussed Ultrasound may be available as part of a clinical trial, but these treatments are not recommended by NICE for routine use.

PSA levels may be used to monitor disease activity in those with established prostate cancer.
The future of prostate cancer detection

- Studies are currently underway to investigate aspects of PSA levels;
  - Proportions of free and complexed PSA
  - PSA density
  - PSA velocity
  - PSA doubling time
- Alternatives to the PSA test;
  - Prostate Cancer 3 (PCA3)
  - Human Kallikrein 2 (HK2)
  - Early Prostate Cancer Antigen 2 (EPCA2)
  - 2+Edel
Screening, what is the evidence?

- US PLCO study: no benefit
- European ERSP trial showed a 21% reduction in prostate cancer specific death after 10yrs, but concern regarding over diagnosis
- Systematic review & Meta-analysis: increased probability of diagnosis, but no impact on mortality

BMJ 18 Sept 2010 Vol 341
European Screening Study  
(started 1991, 9yrs FU, screened every 4 yrs)  

- Screen 1140 to see:  
- 21% reduction in prostate cancer mortality  
- Treat 48  
- Avoid 1 death  
- 49% indolent cancers  
- 0.5 ml tumour takes 20 yrs to become dangerous  
- Update 2012: Screen 936 to find 33 cancers and prevent one death (approx half over-diagnosed)  
- All cause mortality not reduced but still 21% reduction in Ca specific death

Who wants screening?

- Cancer societies
- Cancer Charities- Prostate Action
- Medical industry (PSA, Biopsy, therapy industry)
- Urologists
- Over diagnosis has been the fear
- Overtreatment is the problem

Is it better to know?
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svanter Borgelid, Ali Khatami, Per Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

Summary

Prostate cancer is one of the leading causes of death from malignant disease among men in the developed world. One strategy to decrease the risk of death from this disease is screening with prostate-specific antigen (PSA); however, the extent of benefit and harm with such screening is under continuous debate.

Methods

In December, 1994, 20 000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10000) or to a control group not invited (n=10000). Men in the screening group were invited up to the upper age limit (median 69, range 67-71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality, analysed according to the intention-to-screen principle. The study is ongoing, with men who have not reached the
Study Design

32,298 men in Göteborg on Dec 31, 1994, aged 50–64 years

20,000 randomised in a 1:1 ratio

48 excluded
19 deceased or emigrated before randomisation date
29 men with prevalent prostate cancer

48 excluded
21 deceased or emigrated before randomisation date
27 men with prevalent prostate cancer

9,952 invited every 2 years for PSA testing 1995–2008

7,578 attendees
1,046 with PC
27 died from PC

2,374 non-attendees
92 with PC
17 died from PC

9,952 not invited
718 with PC
78 died from PC

Figure 1: Trial profile
PSA=prostate-specific antigen. PC=prostate cancer.
Cumulative risk death from prostate cancer median follow up 14.0 years

Figure 3: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates
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)
Conclusions longer follow up

- Relative and absolute reduction in prostate cancer mortality in the ERSPC will likely show a larger effect

- This will decrease the NNS and NNT.
If you are the kind of person who doesn’t wear a seat belt, (smokes) nor goes regularly to the dentist or your family doctor for a check-up and are not worried about dying from prostate cancer, do not undergo PSA testing.

On the other hand if you are a healthy man age >40 who does not want to die from prostate cancer, early PSA testing can save your life.
Why might 40 be a good place to start?

• No Benign Prostatic Hyperplasia
• Less prostatitis
• Clean PSA
• Early stage of disease if found
• Excellent results of treatment
• BUT ... Unnecessary anxiety, biopsy, treatment
• 1974-86:
  – 21,277 men aged 44-50y in cardiovascular study
  – 498 later developed prostate cancer
  – PSA and hk2 assayed on archived plasma

• Median interval between venepuncture and diagnosis = 18y
Long-Term Prediction of Prostate Cancer Up to 25 Years Before Diagnosis of Prostate Cancer Using Prostate Kallikreins Measured at Age 44 to 50 Years

Hans Lilja, David Ulnert, Thomas Björk, Charlotte Becker, Angel M. Serio, Jan-Åke Nilsson, Per-Anders Abrahamsson, Andrew J. Vickers, and Göran Berghard

Table 3. Odds of Prostate Cancer Diagnosis by Plasma Total PSA Levels at Baseline Venipuncture

<table>
<thead>
<tr>
<th>Total PSA (ng/mL)</th>
<th>Controls</th>
<th>Patients</th>
<th>Odds Ratio</th>
<th>95% CI</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>—</td>
<td>4</td>
</tr>
<tr>
<td>0.51-1.00</td>
<td>474</td>
<td>147</td>
<td>2.51</td>
<td>1.80 to 3.50</td>
<td>8</td>
</tr>
<tr>
<td>1.01-2.00</td>
<td>173</td>
<td>146</td>
<td>7.02</td>
<td>4.90 to 10.1</td>
<td>20</td>
</tr>
<tr>
<td>2.01-3.00</td>
<td>23</td>
<td>55</td>
<td>19.1</td>
<td>10.8 to 33.9</td>
<td>41</td>
</tr>
<tr>
<td>≥ 3.01</td>
<td>9</td>
<td>46</td>
<td>38.8</td>
<td>17.8 to 84.8</td>
<td>60</td>
</tr>
</tbody>
</table>

Abbreviation: PSA, prostate-specific antigen.

*Calculated by adding a Bayes factor to the log odds to adjust mean probability to 10%, the expected incidence by age 75 years in this cohort.
Long-Term Prediction of Prostate Cancer Up to 25 Years Before Diagnosis of Prostate Cancer Using Prostate Kallikreins Measured at Age 44 to 50 Years

Mia Lilja, David Ulmsten, Thomas Björk, Charlotte Becker, Angel M. Serve, Jan-Åke Nilsson, Per-Anders Abrahamsson, Andrew J. Vickers, and Göran Berglund

Fig 2. Predicted probability of a prostate cancer diagnosis before age 75 years by population-based centiles of prostate-specific antigen (PSA) measured at age 44 to 50 years, with 95% CIs.
• PSA was a very strong predictor of prostate cancer up to 25 yrs subsequently.
• Levels of 2–3 ng/mL, (often cited as within the normal range), were associated with an increase in odds for subsequent prostate cancer of more than 19-fold.
PSA testing should be tailored to individual risk at 60yrs
Swedish Cancer registry 1160 men 60-85yrs

- PSA <1, negligible risk
- PSA >2, minority will die of prostate cancer, but 90% of cancer deaths occurred in these men
- Younger men with family history or elevated PSA should be followed carefully
- Lifestyle and 5ARIs to be considered

BMJ 18 Sept 2010 vol 341
A national recommendation?

- Single PSA test as a predictor for the long-term risk of prostate cancer at 40-45 years.
- 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

• Huge numbers of men die from prostate cancer
• Population-based PSA screening remains controversial despite huge trials
• Longer follow up will see NNT fall significantly
• Risk stratification based on PSA aged 40-45 is an interesting idea
• Newer markers & MRI will help with risk stratification
• What about genetic markers?
Genome Wide Association Studies (GWAS)

- Rapidly scanning a dense set of markers across genomes of many people to find genetic variations associated with a particular disease

- Time for GWAS now due to
  - the completion of the HapMap project
  - rapidly advancing high through-put technology
Summary of loci associated with prostate cancer risk identified by our study and other GWAS studies.

ICR/CRUK novel loci (previously unpublished)

ICR/CRUK validation of previously published hits

X

Y

Adapted From
Guy et al 2009
and Eeles et al 2009
Yeager et al 2009
Amin et al 2009
Gudmundsson et al 2009
The Pattern of Genetic Predisposition to Prostate Cancer

High-risk??
*Family linkage studies*

Common low risk
*Association studies*

Rare low/moderate risk
*Candidate resequencing/haplotype studies*

Risk allele frequency

<table>
<thead>
<tr>
<th>Gene or Region</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2</td>
<td>High-risk??</td>
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<tr>
<td>BRIP1, NBS1, BRCA1, CHEK2</td>
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</tr>
<tr>
<td>8q24 HapC rs1601975</td>
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<tr>
<td>17q24, 11q13, 8p21, 11p15, 22q13</td>
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</tr>
<tr>
<td>19q13</td>
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<td>8q24 rs 620861</td>
<td>Common low risk</td>
</tr>
<tr>
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<td>HNF1B, 4q22, 4q24</td>
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<tr>
<td>MSMB</td>
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<tr>
<td>ITGA6</td>
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<tr>
<td>KLK2/3</td>
<td>Common low risk</td>
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<tr>
<td>3p12</td>
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<tr>
<td>CTBP2</td>
<td>Candidate resequencing/haplotype studies</td>
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<tr>
<td>6q25</td>
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<td>2p15, 3q21</td>
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NEWS
Adding age and genetic risk to PSA test could improve screening for prostate cancer
BMJ 2012; 345 doi: http://dx.doi.org/10.1136/bmj.e7467 (Published 6 November 2012)
Cite this as: BMJ 2012;345:e7467
Do you think we should have a National Prostate Cancer Screening Programme?

1. YES 0%
2. NO 0%
3. Not sure 0%
References

- PCRMP pack

- PCRMP booklet
  - Burford DC, Kirby M, Austoker J. Prostate Cancer Risk Management Programme Information for Primary Care; PSA testing in asymptomatic men. Sheffield; NHS Cancer Screening Programmes, 2008
To obtain a copy of the pack, please

• download from the NHS Cancer Screening Programmes website
  http://www.cancerscreening.nhs.uk/prostate/index.html

• or contact the Department of Health publications order line quoting PROSCANRMT
  0300 123 1002
dh@prolog.uk.com
www.orderline.dh.gov.uk