Prostate Cancer Screening

Ahmad Shabsigh, MD, FACS
Assistant Professor
Department of Urology
The Ohio State University Wexner Medical Center

The Committee:
U.S. Preventive Services Task Force

The Date:
August 2008

The Committee:
U.S. Preventive Services Task Force

The issue:
Prostate Cancer Screening
The Impact of the Disease

The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 50 to 60 years. The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harms of false-positive test results, and overstaging.

Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for prostate cancer death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

The benefits of PSA-based screening for prostate cancer do not outweigh the harms.

Prostate Cancer Epidemiology

**Lifetime Risk of Dying from CaP**

- Risk of dying from prostate cancer is ~3%
- Once metastatic disease develops there is no cure
- Prior to PSA screening only 25% of CaP presented confined to prostate vs. 91% since
- 5 year CSS rates increased from ~70% to 100% (from 1980s to early 2000s)

Comprehensive Textbook of Genitourinary Oncology, 3rd edition
Catalona et al. Detection of organ-confined prostate cancer is increased through prostate-specific antigens-based screening JAMA 1995; 274(8):908

**What is Cancer Screening?**

- Checking for disease when there are no symptoms. Since screening may find diseases at an early stage, there may be a better chance of curing the disease.
- The source: NCI

**What Is Prostate Cancer Screening?**

- HPI
- DRE
- PSA

**Prostate Specific Antigen**

- Discovered in 1979 by Wang et al
- Approved by FDA in 1986
- Produced by prostate and periurethral glands epithelial cells
- Liquefaction of seminal coagulum
- Serine protease from the kallikrein family
- In serum, most is bound
**Prostate Specific Antigen**

- Inflammation, hyperplasia, neoplasia lead to disruption of physiological barriers and increased serum PSA levels
- Half life is 2-3 days
- Used for
  - Initial diagnosis of disease and screening
  - Monitor for recurrence after initial therapy
  - Prognosis of outcomes after therapy

**Prostate Cancer Screening**

- Controversial:
  - Prostate cancer has a relatively slow course, Long term follow up is needed (>15 years).
  - Patient’s age
  - Comorbidities
  - Treatments are associated with significant morbidity
  - No comparisons of efficacy between therapeutic options

**Screening for Prostate Cancer: Potential Harms**

- Additional medical visits
- Adverse effects of prostate biopsies
- Anxiety
- Over diagnosis
- Over treatment
- Morbidity and mortality associated with treatment
- Financial burden

**Complications of TRUS Prostate Biopsy**

<table>
<thead>
<tr>
<th>Complications</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematospermia</td>
<td>37.4</td>
</tr>
<tr>
<td>Hematuria &gt; 1 d</td>
<td>14.5</td>
</tr>
<tr>
<td>Rectal bleeding &lt;2 d</td>
<td>2.2</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever &gt; 101.3°F, epididymitis, rectal bleeding &gt;2 d, retention</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Other complications requiring hospitalization</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*EAU Guidelines*
Screening for Prostate Cancer: Potential Benefits

- Early detection and treatment
- Improve cancer Specific Survival
- Alleviate symptoms of locally advanced disease

The Evidence

ERSPC

The European Randomized study of Screening for Prostate Cancer
ERSPC

- Primary objective: PC mortality
- Ages 50-74
- 162,387 men
- Screen interval every 4 yrs (87%) Sweeden every 2 yrs (13%)
- Sextant TURS Bx for PSA ≥ 3.0 ng/ml, abnormal DRE, F/T ratio 3-4 ng/ml

ERSPC

- Screen 72,890
- Control 89,353
- 85.8% biopsied of the positive tests PPV 24.1
- Median F/U 9 years
- Screen arm: 5990 PC (8.2%), that is 71% higher, 214 deaths
- Control arm: 4,307 PC (4.8%), 326 deaths

ERSPC

- 20% fewer men die of PC in the screen group (p=0.04)
- Adjustment for non-compliance, 27% fewer deaths in the screened men
- Absolute risk reduction 7 per 10,000 screened men
- NNS: 1,410, NNT: 48 in excess of the control arm.
- NNT to prevent mets 24
- All centers showed the same outcome (16-26%)
Number Needed to Treat (NNT)

- Estimates Will Decrease
- In Northern Ireland (with very little screening), the NNT to prevent 1 case of metastatic prostate cancer was only 15
- THAT IS similar to the NNT to prevent 1 breast cancer death through mammography screening and follow-up surgery
- The number needed to treat to save 1 life with prostate cancer screening will decrease with correction for compliance and longer follow-up


---

**Prostate Cancer Mortality At 11 Years Of Follow-Up**

Cumulative hazard of death from prostate cancer:

- Control Group
- Screening Group

NEJM 366;11 March 15, 2012

---

**Goteborg Randomized Prostate Cancer Screening Trial: Mortality Results**

- Total Male Population Age 50-64 yrs n = 32,298
- Randomized 1:1 n = 19,984
- Screening Group (Invited to Have PSA Biannually)
- Attendees n = 7,578
- Non-Attendees n = 2,374
- Death From PC n = 27
- Death From PC n = 17
- Control Group n = 9,952
- Death From PC n = 78

Lancer Oncol 2010 August; 11(8): 725-732.
Goteborg Randomized Prostate Cancer Screening Trial: Mortality Results

PLCO

The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

PLCO

- 74,000 ages 55 to 74 years
- 1:1 randomization to receive annual PSA and DRE screening to a total of 4 screens vs usual care in the community
- PSA cut-off is 4 ng/mL
- Follow-up of abnormal screening results was at the discretion of physicians
- In the screening group, rates of compliance were 85%
- Rate of screening in control arm 40% in first year and 52% in sixth yrs
- Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year
- 7 years of follow-up


RR 0.56 (0.39-0.82, p=0.002)
PLCO

- Screen: PC 116 per 10,000 person-years (2820), 50 deaths
- Control: PC 95 per 10,000 person-years (2322), 44 deaths
- Rate ratio, 1.13; 95% CI, 0.75 to 1.70). The data at 10 years were 67% complete and consistent with these overall findings.

**Table 1. Characteristics of the Subjects at Baseline.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Screening Group (N=38,343)</th>
<th>Control Group (N=38,350)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-59 yr</td>
<td>32.3</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>60-64 yr</td>
<td>31.3</td>
<td>31.3</td>
<td></td>
</tr>
<tr>
<td>65-69 yr</td>
<td>23.2</td>
<td>23.2</td>
<td></td>
</tr>
<tr>
<td>70-74 yr</td>
<td>13.2</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Race or ethnic group†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>96.2</td>
<td>93.8</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>4.5</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>2.1</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4.0</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.8</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Missing data</td>
<td>2.4</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Enlarged prostate or benign prostatic hypertrophy</td>
<td>21.4</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>Previous prostate biopsy</td>
<td>4.3</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Family history of prostate cancer</td>
<td>7.1</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>PSA test within past 3 yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>34.6</td>
<td>34.3</td>
<td></td>
</tr>
<tr>
<td>Two or more times</td>
<td>9.4</td>
<td>9.8</td>
<td></td>
</tr>
<tr>
<td>Digital rectal examination within past 3 yr</td>
<td>32.6</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>Once</td>
<td>32.6</td>
<td>31.9</td>
<td></td>
</tr>
<tr>
<td>Two or more times</td>
<td>22.2</td>
<td>22.8</td>
<td></td>
</tr>
</tbody>
</table>

**PLCO**

- 40%-52% of controls were screened during the study (contamination) thus, comparing 85% vs 52% screened
- Poor prompt Bx compliance for PSA > 4
- Reported PCa mortality at 7-10 yr (med 11.5) but f/u was only 5.3 to 6.2 years for PCa patients
- 10-year prostate cancer detection rate was only 15% higher in screened men - 9.0% vs 7.8%
- PCa death rate = 2.0 screened vs 1.7 control /104 per-yr
- Authors conclude: no mortality benefit from screening
### Smarter Screening

- Risk-adjust screening by age, comorbidities, family history, ethnicity and PSA (reduce false positives)
- Reduce false positive PSA results by repeating (verifying) positives and by adding additional markers (reduce indications for biopsy)
- Active surveillance for low-risk cancers (reduce harms of unnecessary therapy)
- Refer patients who need treatment to experienced high-volume physicians or centers (reduce harm of necessary therapy)
### PCA3 Screening

**PCA3** is a non-coding mRNA molecule that is believed to be prostate specific.

- It is highly over-expressed in cancerous prostate cells relative to benign tissue
- Present in urine (no blood test necessary)

**Potential to be used as supplement for PSA testing**

- PSA has a 21% specificity but a 87% sensitivity for prostate cancer
- Conversely, a test for PCA3 was reported to have a sensitivity of only 49%, but a specificity of 78%
- Additional studies are needed
Table 2: Operating Characteristics of PCA3 vs. PSA in 225 Men Undergoing Prostate Re-Biopsy

<table>
<thead>
<tr>
<th>PCA3 Assay</th>
<th>Serum PSA</th>
<th>PCA3/PSA mRNA ratio vs. Serum PSA: Previous negative biopsy group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutoff</td>
<td>PCA3/PSA = 35 x 10^{-3}</td>
<td>4.0 ng/mL</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>58%</td>
<td>83%</td>
</tr>
<tr>
<td>Specificity</td>
<td>74%</td>
<td>17%</td>
</tr>
<tr>
<td>*ROC AUC</td>
<td>0.680</td>
<td>0.506</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>3.6</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*KP = 0.002*
A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening

Andrew Vickern, PhD 1, Anil Gupta, MD 1, Caroline J. Spring, MPH 1, Kim Peterson 2, PhD 2, Andrew Cudnik, MB 3, Jack W. Wang, MD 3, PhD 3, Peter T. Scardino, MD 1, David Uramen, MD, MD 1, 2, 3, and Hans Lilja, MD, PhD 1, 4, 5

Prostate Health Index (PHI)

• ([-2]proPSA/free PSA) × √PSA.

Multicenter Evaluation of [-2]Prostate-Specific Antigen and the Prostate Health Index for Detecting Prostate Cancer

Decision Curve Analysis
Multicenter Evaluation of [-2]Prostate-Specific Antigen and the Prostate Health Index for Detecting Prostate Cancer

**Where do we stand?**

**AUA**
- No screening < 40 yrs.
- No routine screening in men 40 to 54 yrs at average risk.
- Individualized for high risk < 55 yrs
- Shared decision-making for 55 to 69 yrs
- Every 2 or more yrs according to baseline PSA
- No screening for >70 yrs or any man with less than a 10 to 15 year life expectancy.
- Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

**2014 NCCN Guidelines for PC**
Rethinking Screening for Cancer

Benefit and Burden of Mammographic Screening and Prostate-Specific Antigen Screening in the United States and Europe

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths Averted</th>
<th>Cancers Detected, Treated</th>
<th>Biopsies/Recalls</th>
<th>Screening Visits</th>
<th>Individuals Screened (#)</th>
<th>Years Of Screening (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>1</td>
<td>18 Invasive 6 DCIS</td>
<td>90/535</td>
<td>5886</td>
<td>838</td>
<td>6</td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>15 Invasive 5 DCIS</td>
<td>41/162</td>
<td>3352</td>
<td>838</td>
<td>6</td>
</tr>
</tbody>
</table>

Prostate Cancer

<table>
<thead>
<tr>
<th>Region</th>
<th>Deaths Averted</th>
<th>Cancers Detected, Treated</th>
<th>Biopsies/Recalls</th>
<th>Screening Visits</th>
<th>Individuals Screened (#)</th>
<th>Years Of Screening (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
<td>48</td>
<td>2397</td>
<td>1410</td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

Trends in Metastatic Breast and Prostate Cancer: Lessons in Cancer Dynamics

JAMA 2009;302:1685
Conclusions

- PSA is not a perfect screening test
- (But it is the best we have)
- Yes most men will have PC and most will not die from it
- Tens of thousands die from the disease, and the numbers will increase with increased life expectancy
Conclusions

• PSA is not a perfect screening test
  (But it is the best we have)
• Yes most men will have PC and most will not die from it
• Tens of thousands die from the disease, and the numbers will increase with increased life expectancy
• PSA screening for PC detects cancers earlier and at a lower stage where curative therapies more effective

Conclusions

• PSA is not a perfect screening test
  (But it is the best we have)
• Yes most men will have PC and most will not die from it
• Tens of thousands die from the disease, and the numbers will increase with increased life expectancy
• PSA screening for PC detects cancers earlier and at a lower stage where curative therapies more effective
• PC screening saves lives

Cracks on Airbus A380 Wings

• January 2012: Qantas A380 plane encounters severe turbulence on London-Singapore flight
  – Aircraft checked and cleared to fly on to Sydney
• February 5, 2012: Plane grounded in Sydney after further precautionary inspection finds 36 hairline cracks on the wing rib brackets similar to “Type 1” cracks found on previous A380 checks
When It Comes to Prostate Cancer:

“Diagnostically aggressive”

“Therapeutically conservative”