Prostate Cancer Screening:  
Risks and Benefits across the Ages

7th Annual Symposium on Men’s Health  
Continuing Progress: 
New Gains, New Challenges  
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Michael J. Barry, MD  
General Medicine Unit  
Massachusetts General Hospital  
Professor of Medicine  
Harvard Medical School

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Prostate Cancer (PCA): A Major Health Problem

- 2009: 192,280 new cases expected
  27,360 deaths expected
- Most common CA and no. 2 cause of CA death in men (after lung cancer)

PCA: A Major Health Problem

- Lifetime risk of PCA dx rose from 10% to 18% in the “PSA era”
- Lifetime risk of PCA death about 3%
- By 2001, 75% of US men 50+ reported having ever had a PSA test
- Therefore, regular PSA testing at least doubles lifetime risk of “getting” PCA
US Prostate Cancer Mortality and Incidence 1987-2005

SEER Cancer Statistics Review, 1975-2005

Epidemiology of PCA

Prevalence at autopsy

<table>
<thead>
<tr>
<th>Age</th>
<th>PCA</th>
<th>PCA &gt; 0.5 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>15%</td>
<td>6%</td>
</tr>
<tr>
<td>60-69</td>
<td>22%</td>
<td>9%</td>
</tr>
<tr>
<td>70-79</td>
<td>39%</td>
<td>16%</td>
</tr>
<tr>
<td>80-89</td>
<td>43%</td>
<td>17%</td>
</tr>
</tbody>
</table>

(Coley et al, J Urol 1993, 150:379)
Epidemiology of PCA

Autopsy study, Sakr et al

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence of PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>25%</td>
</tr>
<tr>
<td>40-49</td>
<td>35%</td>
</tr>
</tbody>
</table>

(Sakr et al, J Urol 1993, 150:379)

Risk Factors for PCA

- African-American: 2-3X risk
- 1st degree relative: 2X risk
- Two 1st degree relatives: 5X risk
- Prior vasectomy: 1.5X risk?
- High fat/red meat diet raises risk?
- Obesity raises risk?
Risk Factors for PCA

**Possibly protective:**
- Tomatoes (lycopenes)
- Red wine
- Statins

**Not protective:**
- Selenium
- Vitamin E

Screening for Localized PCA

**Purposes of screening:**
- Reduce CA specific mortality
- Reduce morbidity from local progression
- Reassurance value of normal test
Screening for Localized PCA

“Costs” of screening:
- Dollar costs of screening, follow-up, treatment
- Morbidity of TRUS/biopsy
- Anxiety among false positive screenees
- Overdiagnosis and overtreatment
- Morbidity/mortality of RP or XRT

Morbidity of XRT or RP at 5 years

<table>
<thead>
<tr>
<th>Complication</th>
<th>Probability following:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XRT</td>
</tr>
<tr>
<td>Incontinence (requiring pads)</td>
<td>4%</td>
</tr>
<tr>
<td>Erections insufficient for intercourse</td>
<td>64%</td>
</tr>
<tr>
<td>Bothered by bowels</td>
<td>4%</td>
</tr>
<tr>
<td>Additional treatment (w/in 2-4 yrs.)</td>
<td>24%</td>
</tr>
</tbody>
</table>

(Potosky et al, JNCI 2000, 92:1582)
Scandinavian RCT of RP vs. watchful waiting, localized cancer

- <10% of PCA detected through screening
- Reduced PCA specific mortality from 18% to 12.5% in RP group compared to WW at 12 years (P=0.03, NNT=18)
- Overall mortality reduced 40% to 33% (N.S.)

Effectiveness of Therapy

Cumulative incidence of death from prostate cancer after 12 years, by treatment and age

(Bill-Axelson et al., JNCI 2008;100:1144)
PLCO Trial: Methods

- Randomized, annual screening vs usual care
- 10 centers in U.S.
- 38,343 screening vs 38,350 control
- Age 55-74
- Uniform screening protocol = Annual PSA for 6 yr, DRE for 4 yr
- PSA>4.0 ng/mL or suspicious DRE referred for further evaluation via usual care
- Median follow-up 11.5 yrs, range 7.2-14.8

(Andriole et al, NEJM 2009,360:1310)

PLCO Trial: Results

- Screening group: compliance 85-86% for DRE & PSA
- Controls: rate of PSA screening 40% year 1 to 52% year 6, 41- 46% for DRE
- Vital status f-up 98% at 7 yrs, 67% at 10 yrs
- 22% increase in PCA dx in screened group at 7 years
- No mortality PCA benefit was seen for combined screening with PSA and DRE over 7-10 years

(Andriole et al, NEJM 2009,360:1310)
PLCO Trial: Results, 7 years

<table>
<thead>
<tr>
<th></th>
<th>Screening group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA Incidence</td>
<td>116 /10,000 PY</td>
<td>95/10,000 PY</td>
</tr>
<tr>
<td></td>
<td>Rate ratio 1.22 (95% CI 1.16-1.29)</td>
<td></td>
</tr>
<tr>
<td>PCA Mortality</td>
<td>2 /10,000 PY</td>
<td>1.7/10,000 PY</td>
</tr>
<tr>
<td></td>
<td>Rate ratio 1.13 (95% CI 0.75-1.70)</td>
<td></td>
</tr>
</tbody>
</table>

*10 yr results, 67% complete, are consistent*

(Andriole et al, NEJM 2009,360:1310)

PLCO Trial: Limitations

- Relatively low number of endpoints so far (174 PCA deaths)
- High levels of pre-screening
- Control group contamination – about half had a PSA by year 5
- Cause of death assigned with knowledge of treatments- possible bias towards assigning PCA to those with attempted curative treatment

(Andriole et al, NEJM 2009,360:1310)
ERSPC Trial: Methods

- Randomized, offered screening vs not
- Pts. from a collection of trials in 7 countries
- 72,890 screening vs 89,353 control
- Age 55-69
- Screening protocol varied by site
- Screening group = offered PSA average of once every 4 years, no DRE
- PSA>3.0 ng/mL biopsied, local policies for evaluation and treatment
- Median follow-up 9 yrs

(Schroder et al, NEJM 2009,360:1320)

ERSPC Trial: Results

- Screening group: 82% at least one screening
- Cumulative incidence of PCA =
  8.2% screen group vs 4.8% controls
- 20% relative reduction in PCA death rate in screen group
- Rate ratio for PCA death = 0.8 (screened vs control, 95% CI 0.65-0.98, p=0.04)
- Absolute reduction =
  7 PCA deaths/ 10,000 men screened

(Schroder et al, NEJM 2009,360:1320)
ERSPC Trial: Limitations

- No information on possible control group contamination
- Possible differences in management protocols between groups make it difficult to separate benefit from screening vs subsequent management
- Cause of death assigned with knowledge of treatments- possible bias towards assigning PCA to those with attempted curative treatment

(Schroder et al, NEJM 2009, 360:1320)

Breast Cancer vs Prostate Cancer Screening

Per 10,000 screened for 10 years:

<table>
<thead>
<tr>
<th></th>
<th>Breast cancer (age 40-69)</th>
<th>Prostate cancer (age 55-69)</th>
</tr>
</thead>
<tbody>
<tr>
<td># biopsies</td>
<td>800</td>
<td>2400</td>
</tr>
<tr>
<td># extra CA diagnosed</td>
<td>50</td>
<td>350</td>
</tr>
<tr>
<td># lives saved</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td># screened/ life saved</td>
<td>2,000</td>
<td>1,400</td>
</tr>
<tr>
<td># treated/ life saved</td>
<td>10</td>
<td>50</td>
</tr>
</tbody>
</table>

Digital Rectal Exam

- Little scrutiny of operating characteristics and reproducibility
  - Suspicious results = up to 15%
  - Positive predictive value (PPV) ~ 20%
    (only half of CA in quadrant with palpable abnormality)
  - PPV ~ 10% if PSA = 4.0 or less

Prostate Specific Antigen

- Glycoprotein produced by prostatic epithelial cells
- Circulates free and complexed to macromolecules (alpha-1 antichymotrypsin)
- Numerous assays available
Prostate Specific Antigen

- PSA can be elevated after:
  - Prostatic biopsy (weeks)
  - Prostatitis (weeks)
  - Acute retention (weeks)
  - TURP (weeks)
  - Ejaculation (48 hrs.)

- NO clinically important elevation after DRE, or flexible cystoscopy

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Prostate Specific Antigen

- Prostate Cancer Prevention Trial placebo arm
- Biopsied all regardless of DRE, PSA

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Probability of PCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.6</td>
<td>7%</td>
</tr>
<tr>
<td>0.6 - 1.0</td>
<td>10%</td>
</tr>
<tr>
<td>1.1 - 2.0</td>
<td>17%</td>
</tr>
<tr>
<td>2.1 - 3.0</td>
<td>24%</td>
</tr>
<tr>
<td>3.1 - 4.0</td>
<td>27%</td>
</tr>
</tbody>
</table>

(Thompson et al. NEJM 2004;350:2239)
When is a PSA Abnormal?

- Historical cutpoint is >4.0 ng/ml (used in PLCO trial)
- Cutpoint in the ERSPC trial was >3.0 ng/mL
- Values just over biopsy threshold should be repeated

What about PSA “Velocity”?

- PSAV > 0.75 ng/ml/yr (>0.5 ng/mL/year if baseline PSA <4.0 ng/mL) suggestive of PCA; need 3 annual values
- PSAV > 2.0 ng/ml/yr: more likely to die of PCA even with early DX, aggressive Rx
- But, PSAV strongly correlates with total PSA
- Analyses from ERSPC, PCPT and a large Swedish cohort have not shown improved performance of PSAV over tPSA (for any PCA or aggressive PCA)

(Ulmert et al, JCO 2008, 26:835
Thompson et al, JCO 2007;21:3076
PCA has more complexed PSA relative to free than in BPH

- Ratio of free to total (f/T) PSA lower in PCA
- Free to total PSA ratio can increase specificity of screening

<table>
<thead>
<tr>
<th>Total PSA</th>
<th>F/T PSA</th>
<th>Bx strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1-10.0</td>
<td>&gt; 25%</td>
<td>may skip</td>
</tr>
<tr>
<td>2.5-4.0</td>
<td>&lt; 25%</td>
<td>may add</td>
</tr>
</tbody>
</table>

Complexed / Free PSA

- Catalona study, total PSA = 4.1-10.0

<table>
<thead>
<tr>
<th>Free/total PSA</th>
<th>Pr of CA at bx.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-10%</td>
<td>56%</td>
</tr>
<tr>
<td>10-15%</td>
<td>28%</td>
</tr>
<tr>
<td>15-20%</td>
<td>20%</td>
</tr>
<tr>
<td>20-25%</td>
<td>16%</td>
</tr>
<tr>
<td>&gt; 25%</td>
<td>8%</td>
</tr>
</tbody>
</table>

(Catalona et al, JAMA 1998,279:1542)
How Often to Screen?

- Historically, PSA/DRE annual (used in PLCO trial)
- In the ERSPC trial, PSA was done about every 4 years
- Strategy from the PLCO trial:
  - PSA less than 1.0 ng/mL, repeat 5 years
  - PSA 1.0-2.0 ng/mL, repeat 2 years
  - PSA>2.0 ng/mL, repeat in 1 year

(Crawford et al, J Urol 2006;175:1286)

PCA Screening Guidelines (2009)

- ACS: offer annual DRE/PSA at 50, at 45 with risk factors (40 for very high risk), if >10 yr LE
- USPSTF: no recommendation for or against DRE or PSA 74 or younger, recommends against for >75
- ACP: doesn’t recommend routine PSA
- AUA: start screening at 40! (of 23,587 PCa deaths among white men, 265 before age 55)
The ACS Recommends:

“…that health care providers discuss the potential benefits and limitations of prostate cancer early detection testing with men and offer the PSA blood test and the digital rectal examination annually, beginning at age 50, to men who are at average risk of prostate cancer and who have a life expectancy of at least 10 years.”

(Smith et al, CA Cancer J Clin 2009; 59:27)

What Should Men be Told Before a PSA?

- PSA is a blood test
- Risk factors for PCA
- Incidence and prevalence of PCA
- False positives and negatives possible
- Advantages and disadvantages to testing
- Unclear if PSA reduces PCA mortality (enough to result in more good than harm)

Ongoing Trials:
Will the PSA Controversy ever “Sleep the Big Sleep”?*

Results to look for in the next several years:

- PLCO - US screening trial: updates
- ERSPC - European screening trial: update 2011?
- PIVOT - US treatment trial: May, 2010
- ProtecT - UK screening and treatment trial

Male Life Expectancy from Birth, 2009

<table>
<thead>
<tr>
<th>Country</th>
<th>Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia</td>
<td>79.2</td>
</tr>
<tr>
<td>New Zealand</td>
<td>78.4</td>
</tr>
<tr>
<td>Canada</td>
<td>78.7</td>
</tr>
<tr>
<td>Sweden</td>
<td>78.6</td>
</tr>
<tr>
<td>Switzerland</td>
<td>78.0</td>
</tr>
<tr>
<td>France</td>
<td>77.8</td>
</tr>
<tr>
<td>Italy</td>
<td>77.3</td>
</tr>
<tr>
<td>Norway</td>
<td>77.3</td>
</tr>
<tr>
<td>Netherlands</td>
<td>76.8</td>
</tr>
<tr>
<td>Spain</td>
<td>76.7</td>
</tr>
<tr>
<td>Austria</td>
<td>76.6</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>76.5</td>
</tr>
<tr>
<td>Germany</td>
<td>76.3</td>
</tr>
<tr>
<td>Belgium</td>
<td>76.1</td>
</tr>
<tr>
<td>Denmark</td>
<td>76.0</td>
</tr>
<tr>
<td>United States</td>
<td>75.7</td>
</tr>
<tr>
<td>Ireland</td>
<td>75.6</td>
</tr>
</tbody>
</table>

*(US Census Bureau, International Data Base)
Prostate cancer
Diffusing a deadly disease