Peter R. Carroll, MD, MPH
Matthew R. Cooperberg, MD, MPH
Dept of Urology
San Diego, 2010

Prostate Cancer Screening:
Always, Never or Only Sometimes

The Good News:

Age-adjusted Cancer Death Rates,* Males by Site, US, 1930-2006

*Per 100,000 age-adjusted to the 2000 US standard population

Jemal et al. CA Cancer J Clin 2010; 60:277
But at what cost?

The Changing Face of Prostate Cancer

Risk distribution by year of diagnosis

- Low
- Intermediate
- Hgh
- Advanced

Cooperberg et al. J Urol 2007; 178:S14
Treatment Variation

So controversy rages...

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

Rethinking Screening for Breast Cancer and Prostate Cancer

Laura Esserman, MD, MBA
Yiwei Shi, BS
Jae Thompson, MD

Breast cancer and prostate cancer account for 26% of all cancers in the United States, with an estimated 388,560 patients diagnosed annually. 194,280 for breast cancer and 192,280 for prostate cancer. For both, there are remarkable differences between outcomes of localized vs advanced disease (breast cancer: 5-year relative survival of 98.1% vs 27.1%; prostate cancer: 100% vs 85%).

After 20 years of screening for breast and prostate cancer, several observations can be made. First, the incidence of these cancers increased after the introduction of screening but has never returned to prescreening levels. Second, the increase in the relative fraction of early-stage cancers has increased. Third, the incidence of regional cancers has not decreased at a commensurate rate. One possible explanation is that screening may be increasing the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers and therefore not resulting in the anticipated reduction in cancer mortality. To reduce morbidity and mortality from prostate cancer and breast cancer, new approaches for screening, early detection, and prevention for both diseases should be considered.

Amazon rank #219
Prostate Cancer Screening RCTs: Two important studies—two different results?

- One performed in US and one in Europe
- One protocol vs. several
- One shows no benefit, one shows substantial mortality reduction
- Rates of pre-screening and control group contamination markedly different
- One most often quoted

Andriole et al. NEJM 2009; 360:1310; Schröder et al. NEJM 360:1320
Screening Concerns (Risks)

- Reduction in mortality shown *conclusively*
- However, to save one man’s life
  - 1068 men screened
  - 48 treated
- Therefore, *over-detection* a problem

Number needed to treat to avoid metastases - 24

The reduction in risk even greater if one only analyzes those who actually complied with the testing

The risk of metastases was reduced by 53%

Eur J Cancer. 2010 Jan;46(2):377-83
**PLCO vs. ERSPC**

<table>
<thead>
<tr>
<th>Setting</th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>76,793</td>
<td>182,160</td>
</tr>
<tr>
<td>Interval</td>
<td>annual</td>
<td>4 years (87%) or 2 years</td>
</tr>
<tr>
<td>Biopsy</td>
<td>per clinician preference (PSA 4 / + DRE)</td>
<td>Recommended for PSA ≥ 3.0 (± DRE / f/t findings for PSA 3-4)</td>
</tr>
<tr>
<td>Biopsy compliance</td>
<td>30-40%</td>
<td>85.8%</td>
</tr>
<tr>
<td>Followup</td>
<td>6.3y screening, 5.2y control</td>
<td>Mean 8.8, median 9 years</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>6.1% control, 7.3% screening</td>
<td>4.8% control, 8.2% screening</td>
</tr>
<tr>
<td>CSM</td>
<td>1.9% control, 1.8% screening</td>
<td>7.6% control, 3.6% screening</td>
</tr>
<tr>
<td>ITS: rate ratio</td>
<td>1.13 (0.75-1.70)</td>
<td>ITS: 20% fewer cancer-specific deaths (27% if adjusted for noncompliance)</td>
</tr>
</tbody>
</table>

**Why discordant results?**

- PLCO followup shorter (insufficient?)
- Low compliance with biopsy in PLCO
- Lower rates of cancer-specific mortality
- High rates of “contamination” in PLCO
  - 44% of men tested within 3 years prior to randomization
  - Unknown % of men tested >3 years prior to randomization
  - 52% of “control” men were PSA tested within 6 years
  - Assessment of contamination by patient survey only
  - Likelihood of diagnosis only 22% higher among screening group
  - 94.3% of tumors in “control” group were clinical stage I/II
  - PLCO really tested annual vs. ad hoc screening, not screening vs. no screening
The Göteborg trial
*(the best prostate cancer screening RCT you’ve never heard of)*

- Men 50-64 (median 56) in a single Swedish city randomized without consent in 1994 to biannual screening until age 69 vs. no screening
- 9952 men in each arm
- Referral to urologist at PSA 3.4, later reduced to 2.9 then to 2.5 ng/ml. Biopsies used sextant template
- 76% of men in screening arm were screened at least once; 93% of men with elevated PSA had at least one biopsy

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### The Göteborg randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=9952)</th>
<th>Screening group (n=9952)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=9952)</td>
<td>Attendees (n=778)</td>
</tr>
<tr>
<td>Number of men with prostate cancers diagnosed (%)</td>
<td>718 (7.2%)</td>
<td>1138 (11.4%)</td>
</tr>
<tr>
<td>Tumour grouping (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk*</td>
<td>199 (2%)</td>
<td>604 (5.1%)</td>
</tr>
<tr>
<td>Moderate risk†</td>
<td>249 (2.5%)</td>
<td>353 (3.6%)</td>
</tr>
<tr>
<td>High risk</td>
<td>125 (1.3%)</td>
<td>96 (1%)</td>
</tr>
<tr>
<td>Advanced disease§</td>
<td>87 (0.9%)</td>
<td>46 (0.5%)</td>
</tr>
<tr>
<td>Unknown†</td>
<td>57 (0.6%)</td>
<td>29 (0.3%)</td>
</tr>
</tbody>
</table>

*Hugosson J. Lancet Oncol 2010; 11:725*
The Göteborg randomized trial

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=718)</th>
<th>Screening group (n=1138)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n=1138)</td>
<td>Attendees (n=1046)</td>
</tr>
<tr>
<td>Primary radical prostatectomy*</td>
<td>241 (33.6%)</td>
<td>468 (41.1%)</td>
</tr>
<tr>
<td>Primary radiation</td>
<td>75 (10.4%)</td>
<td>91 (8.2%)</td>
</tr>
<tr>
<td>Primary endocrine treatment</td>
<td>162 (22.6%)</td>
<td>86 (7.9%)</td>
</tr>
<tr>
<td>Primary surveillance followed by curative treatment</td>
<td>36 (5.6%)</td>
<td>142 (12.5%)</td>
</tr>
<tr>
<td>Primary surveillance followed by endocrine treatment</td>
<td>20 (2.8%)</td>
<td>23 (2.0%)</td>
</tr>
<tr>
<td>Surveillance at last follow-up</td>
<td>152 (21.2%)</td>
<td>314 (27.6%)</td>
</tr>
<tr>
<td>Not treated</td>
<td>32 (4.5%)</td>
<td>18 (1.4%)</td>
</tr>
</tbody>
</table>

RR 0.56 (0.39–0.82, p=0.002)
NNS: 293, NNT: 12
The Göteborg randomized trial

- Göteborg vs. PLCO & ERSPC
  - Younger mean age at start of screening
  - Lower PSA threshold for referral
  - Q2 year interval
  - Much higher rate of biopsy among those with high PSA
  - Much lower rate of pre- and intra-study PSA contamination
  - Much longer followup (though still relatively short)

So what now?
Updated AUA Screening Guidelines

- The age for obtaining a baseline PSA has been lowered to 40 years
- No longer recommends a single threshold value of PSA which should prompt prostate biopsy
- The decision to proceed to prostate biopsy should be based primarily on PSA and DRE results, but should take into account multiple factors
  - free and total PSA
  - patient age
  - PSA velocity and density
  - family history
  - ethnicity
  - prior biopsy history
  - comorbidities

What is a “normal” PSA?

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>No. of Men (N=2950)</th>
<th>Men with Prostate Cancer (N=449)</th>
<th>Men with High-Grade Prostate Cancer (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.5 ng/ml</td>
<td>486</td>
<td>32 (6.6)</td>
<td>4/32 (12.5)</td>
</tr>
<tr>
<td>0.5–1.0 ng/ml</td>
<td>791</td>
<td>80 (10.1)</td>
<td>8/80 (10.0)</td>
</tr>
<tr>
<td>1.1–2.0 ng/ml</td>
<td>998</td>
<td>170 (17.0)</td>
<td>20/170 (11.8)</td>
</tr>
<tr>
<td>2.1–3.0 ng/ml</td>
<td>482</td>
<td>115 (23.9)</td>
<td>22/115 (19.1)</td>
</tr>
<tr>
<td>3.1–4.0 ng/ml</td>
<td>193</td>
<td>52 (26.9)</td>
<td>13/52 (25.0)</td>
</tr>
</tbody>
</table>
Multivariable risk assessment

Rationale for Including Multiple Risk Factors

*Single Cut - Point/DRE vs. Calculator*

<table>
<thead>
<tr>
<th>Age</th>
<th>Race</th>
<th>PSA</th>
<th>DRE</th>
<th>Family History</th>
<th>Risk</th>
<th>Risk High Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>55</td>
<td>White</td>
<td>0.3</td>
<td>Pos.</td>
<td>Neg.</td>
<td>13%</td>
<td>1%</td>
</tr>
<tr>
<td>55</td>
<td>Black</td>
<td>2.4</td>
<td>Neg.</td>
<td>Pos.</td>
<td>31%</td>
<td>8%</td>
</tr>
<tr>
<td>73</td>
<td>Black</td>
<td>2.4</td>
<td>Neg.</td>
<td>Pos.</td>
<td>31%</td>
<td>13%</td>
</tr>
</tbody>
</table>
Confounders/Improvements

- BMI
- Statins
- 5ARI
- PCA - 3
- Gene fusions

Oncogene 26: 4596
J Urol 180: 1303
JNCI 100: 1511
JNCI 98: 1126

Rationale for Earlier Screening

- A baseline PSA level above the median for age 40 is a strong predictor of prostate cancer
- The age adjusted mortality rate for prostate cancer between ages 50 and 65 is not insignificant. Such men may have been cured by earlier diagnosis and treatment
- Younger men are more likely to have curable cancer
- PSA is a more specific test for cancer in younger men
- Earlier and less frequent testing might reduce mortality and costs compared to annual testing beginning later
- Men at risk of, but do not have prostate cancer may be candidates for chemoprevention

Screening at Earlier Ages

Based on an unscreened cohort from Malmö, a single PSA before age 50 is a strong predictor of advanced CaP occurring up to 25 years subsequently.

Data from PCPT were used to model chemopreventive treatment strategies based on PSA level.

Treating men at a certain PSA level reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men.

Chemoprevention Before Age 50

*Focusing on high-risk subgroups*

- Based on an unscreened cohort from Malmö, a single PSA before age 50 is a strong predictor of advanced CaP occurring up to 25 years subsequently.
- Data from PCPT were used to model chemopreventive treatment strategies based on PSA level.
- Treating men at a certain PSA level reduced the treatment rate by 83% and resulted in a cancer rate only 1.1% higher than treating all men.

BMC Med. 2008; 6: 6

J Clin Oncol. 2010 Mar 1;28(7):1112-6
Variations in testing

- PSA derivatives (i.e. PSAV, PSAD, PSADT) correlate with PSA and do not improve operating characteristics enough to likely replace PSA
- PSAC, AMACR, EPCA, EPCA - 2, HK2, hepsin, GSTPI are undergoing validation
- New approaches - autoantibody signatures, proteomic and genomic undergoing discovery and validation
- All require standardized evaluation and validation

When to stop?

Bechis et al. J Clin Oncol, in press
**Stopping?**

- PSA at 60 predicts long-term prostate cancer mortality
  - Analysis of 1167 samples from 1981-2 matched to Malmö registry data
  - 11.4% diagnosed, 2.7% died of prostate cancer
  - If PSA <1.0 at age 60, likelihood of prostate cancer death <0.3%
  - 90% of prostate cancer deaths occurred in men with PSA >2.0 (top quartile)

**Unresolved Issues**

- Frequency of testing
  - Clearly not necessary yearly in all patients
- End of testing
  - PSA values consistently normal up to an age may define a very low risk group
- Beginning of testing
  - Impact of chemoprevention
- Impact of DRE
- How best to advise/have men decide?
- Over - detection and resultant over - treatment
  - Cost (physical, psychological, monetary)
Better Early Detection

- Baseline PSA in 40s
  - If > mean, follow yearly
  - If ≤ mean, screen less often (4 or 5 years?)
- Use PSAV in younger men (no BPH)
- Identify all risk factors
- Use calculator
- Refine calculators with new markers
- Consider stopping, screening less often men with stable/low PSAs (<1 ng/ml)

Do Not Overestimate the Benefit of Early Detection

The risk of dying of prostate cancer is very low, screening lowers it further

Absolute reduction in prostate cancer mortality.
Based on data from the Göteborg trial, screening would reduce prostate cancer mortality from 9 men per 1000 to 4 per 1000 at 14 years followup. Gray boxes indicate men who would not die of prostate cancer in this time period regardless of screening. Solid red boxes indicate men dying of prostate cancer despite screening; hollow red boxes indicate those among whom prostate cancer-specific mortality would be prevented by screening.
Possible solutions

1. Tailor treatment to biology; reduce treatment for minimal-risk tumors
2. Identify high-risk populations and target prevention and screening efforts
3. Identify new screening markers better able to identify high-risk cancer early
4. Develop clinical and patient tools to support informed decision-making about prevention, screening, biopsy, and treatment

Esserman et al. JAMA 2009; 302:1685

Risk Assessment and Risk-Adapted Management

Diagnosis ≠ Treatment
Prostate Cancer Risk Assessment

- **Goal:** inform physician-patient decisions about optimal initial treatment approach and timing

- Numerous existing instruments
  - D’Amico
  - Kattan
  - UCSF-CAPRA

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The UCSF-CAPRA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Points</th>
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<tbody>
<tr>
<td>PSA</td>
<td>2.0-6</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>6.1-10</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10.1-20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>20.1-30</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt;30</td>
<td>4</td>
</tr>
<tr>
<td>Gleason</td>
<td>1-3/1-3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-3/4-5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4-5/1-5</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Points</th>
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<tbody>
<tr>
<td>T-stage</td>
<td>T1/T2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
<td>1</td>
</tr>
<tr>
<td>% pos bx</td>
<td>&lt;34%</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>≥34%</td>
<td>1</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;50</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>1</td>
</tr>
</tbody>
</table>

*Sum of points from each variable for 0-10 score*

CAPRA: Cancer-specific survival

C-index = 0.80

CAPRA: Overall survival

C-index = 0.71

Cooperberg et al. JNCI 2009; 101:878
Conclusions

- Screening saves lives. Don’t overestimate benefit.

- Management must be risk-adapted. If diagnosis does not lead inevitably to treatment then “overdiagnosis” will be less of a problem.

- Decisions should be driven by health and risk, not age.

- *Stay tuned* for emerging biomarkers.