Prostate Cancer 2011: To Screen or Not To Screen?

1. The benefits of PSA screening generally outweigh the limitations, and I usually recommend it to my patients (screen >66% of men over 50)

2. There are benefits and limitations to PSA screening, and deciding whether or not to recommend screening is best approached on a case-by-case basis (screen 34-66% of men over 50)

3. The limitations of PSA screening generally outweigh the benefits and I do not usually recommend it for my patients (screen <34% of men over 50)

The Party Line...

Pre-test

Prostate Cancer 2010

Estimated New Cases*

Male
- Prostate: 217,700 (20%)
- Lung & bronchus: 106,570 (14%)
- Colon & rectum: 69,400 (9%)
- Leukemia: 24,200 (3%)
- Acute myeloid leukemia: 21,100 (3%)
- Myelodysplasia: 17,900 (2%)

Female
- Breast: 207,000 (20%)
- Lung & bronchus: 105,750 (14%)
- Colon & rectum: 69,400 (9%)
- Leukemia: 24,200 (3%)
- Acute myeloid leukemia: 21,100 (3%)
- Myelodysplasia: 17,900 (2%)

Estimated Deaths

Male
- Lung & bronchus: 85,200 (20%)
- Breast: 32,900 (17%)
- Colon & rectum: 18,400 (10%)
- Leukemia: 8,300 (5%)
- Acute myeloid leukemia: 6,500 (4%)
- Myelodysplasia: 5,000 (3%)

Female
- Lung & bronchus: 71,600 (20%)
- Breast: 30,800 (15%)
- Colon & rectum: 22,600 (10%)
- Leukemia: 8,300 (5%)
- Acute myeloid leukemia: 5,400 (3%)
- Myelodysplasia: 4,000 (2%)
- Leukemia other: 3,900 (2%)
- Breast cancer: 3,000 (1%)
- Cervix: 2,200 (1%)
- Pancreas: 1,800 (1%)
- Lymphoma: 1,400 (1%)
- Prostate cancer: 1,300 (1%)
- Hodgkin lymphoma: 1,200 (1%)

*Data from: Surveillance, Epidemiology, and End Results (SEER) Program (http://seer.cancer.gov)
The Changing Face of Prostate Cancer

Cooperberg et al. J Urol 2007; 178:S14

The Good News:

Jemal et al. CA Cancer J Clin 2010; 60:277

Heterogeneity of prognosis

Esserman et al. JAMA 2009; 302:1685

But at what cost?
Overtreatment— and undertreatment

Age and risk

Natural history of conservative tx

What about RCTs?
PLCO
Prostate, Lung, Cancer, & Ovarian Cancer Screening Trial

Conclusions
After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. (ClinicalTrials.gov number, NCT00002540.)

Andriole et al. NEJM 2009; 360:1310

PLCO

- 76,693 men aged 55-74 randomly assigned to annual PSA screening for 6 years vs. “usual care” at 10 U.S. centers 1993-2001
- Up to 1995, any prior screening allowed; starting in 1995, no more than 1 PSA within past 3 years
  - 44.1% of control group had had ≥1 PSA in past 3 years; 53.9% had had ≥1 DRE
- PSA >4.0 ng/ml considered abnormal
- Cancer incidence ascertained by questionnaire

Andriole et al. NEJM 2009; 360:1310

ERSPC
European Randomized Study of Screening for Prostate Cancer

Andriole et al. NEJM 2009; 360:1310
**ERSPC**

- Population-based study at 7 European centers
- 182,160 men age 50-74 randomized (162,387 in core age 55-69)
- In 3 centers, men were randomized from population lists before informed consent; in other 4 they were identified from population lists but randomized after consent
- Screening interval 4 years at most centers (2 at one)
- Some variation in thresholds for biopsy (3.0 ng/ml vs 4.0 with ancillary tests (DRE/fPSA/TRUS) for values between 2.5 or 3.0 and 4.0.

**82% compliance with screening in screening arm**

<table>
<thead>
<tr>
<th>No major comorbidity</th>
<th>≥1 major comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivar HR 0.56 (0.33-0.95)</td>
<td>Multivar HR 1.43 (0.96-2.11)</td>
</tr>
</tbody>
</table>

**PLCO: Extrapolated follow-up**

**PLCO: Impact of Comorbidity**
Other findings from ERSPC

- No substantial heterogeneity among different centers in Europe (mortality reduction varies from 16-26%)
- Absolute mortality risk reduction 7 per 10,000 men screened
- NNS: 1,410
- NNT: 48 in excess of control group at 9 years  
  - NNT to prevent metastasis: 24
- Curves appear to be diverging; effect of screening may be greater with longer followup

ERSPC: Adjusting for compliance

<table>
<thead>
<tr>
<th>Effect measurement</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.80 (0.68-0.96)</td>
<td>0.013</td>
</tr>
<tr>
<td>NoConsent cohort</td>
<td>0.82 (0.67-1.02)</td>
<td>0.013</td>
</tr>
<tr>
<td>YesConsent cohort</td>
<td>0.78 (0.58-1.05)</td>
<td>0.013</td>
</tr>
<tr>
<td>Adjusted for nonattendance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.73 (0.58-0.93)</td>
<td>0.010</td>
</tr>
<tr>
<td>NoConsent cohort</td>
<td>0.72 (0.51-1.01)</td>
<td>0.013</td>
</tr>
<tr>
<td>YesConsent cohort</td>
<td>0.77 (0.56-1.03)</td>
<td>0.013</td>
</tr>
<tr>
<td>Adjusted for nonattendance and contamination based on PSA use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERSPC study cohort</td>
<td>0.69 (0.51-0.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>NoConsent cohort</td>
<td>0.64 (0.40-1.03)</td>
<td>0.013</td>
</tr>
<tr>
<td>YesConsent cohort</td>
<td>0.73 (0.50-1.07)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

Comparison to a low-screening population

Screened population in Rotterdam cohort vs. Northern Ireland

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
The Göteborg randomized trial

<table>
<thead>
<tr>
<th>Control group (n=9952)</th>
<th>Screening group (n=9952)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n=9952)</td>
<td>Attendees (n=728)</td>
</tr>
<tr>
<td>Number of men with prostate cancers diagnosed (%)</td>
<td>218 (2.2%)</td>
</tr>
<tr>
<td>Low risk*</td>
<td>199 (2.0%)</td>
</tr>
<tr>
<td>Moderate risk†</td>
<td>249 (2.5%)</td>
</tr>
<tr>
<td>High risk</td>
<td>126 (1.3%)</td>
</tr>
<tr>
<td>Advanced disease§</td>
<td>87 (0.9%)</td>
</tr>
<tr>
<td>Unknown†</td>
<td>57 (0.6%)</td>
</tr>
</tbody>
</table>

Hugosson J. Lancet Oncol 2010; 11:725

- 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)

RR 0.56 (0.39-0.82, p=0.002)
NNS: 293, NNT: 12

Hugosson J. Lancet Oncol 2010; 11:725
Absolute vs. relative benefit?

![Graph showing distribution of men based on relative benefit](image)

So what now?

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

What is a “normal” PSA?

<table>
<thead>
<tr>
<th>PSA Level</th>
<th>No. of Men (N=2959)</th>
<th>Men with Prostate Cancer (N=449)</th>
<th>Men with High-Grade Prostate Cancer (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.3 ng/ml</td>
<td>486</td>
<td>32 (6.6)</td>
<td>4/32 (12.5)</td>
</tr>
<tr>
<td>0.4–1.0 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

Establishing a baseline

- 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)

Vickers et al. AUA 2009 #162

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 55 and 64 is significant. 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
- Patients at risk for, but who do not have cancer may be candidates for chemoprevention

Greene et al. Urol 2009; 182:2232

High Risk Populations: SFGH

Porten et al. Urol, in press
What do PCPs do?

- Survey of UCSF internal medicine / family medicine providers (UCSF / SFVA / SFGH)
- Marked variation in confidence in knowledge, accuracy of knowledge, and aggressiveness of screening
- 86% screen <60% of men

Tasian et al. Urol Oncol 2010; epub ahead of print

Risk Assessment and Risk-Adapted Management

*Diagnosis ≠ Treatment*

SPCG-4 Update


Walter et al. JAMA 2006; 296:2336
SPCG-4 Update

Death from Any Cause, Men ≥65 Yr of Age

- Radical prostatectomy
- Watchful waiting

P = 0.89 by Gray’s test

No. at Risk
- Radical prostatectomy: 190, 185, 166, 135, 99, 42
- Watchful waiting: 182, 177, 162, 133, 101, 42

Years

Probability

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7

PIVOT Trial

Prostate cancer Mortality
All Patients

HR = 0.63; (95% CI = 0.36 to 1.09); p = 0.09

Prostate cancer Mortality
D’Amico Low Risk-Local Pathology

HR = 1.48; (0.42 to 5.42); p = 0.54
ARR = -1.4 (-6.2 to 3.2)

Prostate cancer Mortality
D’Amico High Risk-Local Pathology

HR = 0.40 (0.16 to 1.00); p = 0.04
ARR = 8.4 (-2.5 to 19.2)
Prostate Cancer Risk Assessment

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

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

CAPRA: Cancer-specific survival

- C-index = 0.80

Overtreatment– and undertreatment


Treatment Variation

### Surveillance: Recent Experiences

<table>
<thead>
<tr>
<th>Institution/PI</th>
<th>Total (n)</th>
<th>Strict (n)</th>
<th>Median age</th>
<th>Inclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal Marsden (Parker)</td>
<td>326</td>
<td>326</td>
<td>67</td>
<td>Gleason ≤3+4, PSA ≤15 ng/ml, cT stage ≤2a, ≤50% of cores positive</td>
</tr>
<tr>
<td>University of Miami (Soloway)</td>
<td>210</td>
<td>210</td>
<td>64</td>
<td>Gleason ≤6, PSA ≤10 ng/ml, cT stage ≤2, ≤2 cores, ≤20% of any core positive</td>
</tr>
<tr>
<td>Johns Hopkins (Carter)</td>
<td>769</td>
<td>633</td>
<td>64</td>
<td>Gleason ≤3+3, PSA ≤15 ng/ml, cT stage 1, ≤2 cores positive, ≤50% of any core positive</td>
</tr>
<tr>
<td>UCSF (Carnall)</td>
<td>640</td>
<td>376</td>
<td>62</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2, ≤50% of any core positive</td>
</tr>
<tr>
<td>University of Toronto (Klotz)</td>
<td>413</td>
<td>413</td>
<td>70</td>
<td>Gleason ≤3+3, PSA ≤15 ng/ml, cT stage ≤2a, ≤50% of any core positive</td>
</tr>
<tr>
<td>UCSF sites (Schneider)</td>
<td>988</td>
<td>616</td>
<td>66</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2a, ≤50% of any core positive</td>
</tr>
<tr>
<td>Memorial Sloan Kettering (Eastham)</td>
<td>238</td>
<td>238</td>
<td>64</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, cT stage ≤2a, ≤50% of any core positive</td>
</tr>
<tr>
<td>TOTAL</td>
<td>3644</td>
<td>2872</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

Cooperberg et al. J Clin Oncol, in press

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### Active Surveillance: UCSF

- Upgrading/upstaging based on preop criteria for surveillance

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### Progression vs. undersampling?

Cooperberg et al. J Clin Oncol, in press

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Active Surveillance: Anxiety

- Treatment decision driven by PSA velocity and "anxiety velocity"

<table>
<thead>
<tr>
<th>Parameter Estimate</th>
<th>p Value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA velocity (ng/mL/yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low than -0.50</td>
<td>0.05</td>
<td>1.00</td>
</tr>
<tr>
<td>-0.50-0.18</td>
<td>-0.02</td>
<td>1.00</td>
</tr>
<tr>
<td>0.01-0.50</td>
<td>0.42</td>
<td>1.00 (0.95, 1.19)</td>
</tr>
<tr>
<td>0.50-1.00</td>
<td>1.26</td>
<td>1.18 (1.10, 1.26)</td>
</tr>
<tr>
<td>CA change rate</td>
<td>0.02</td>
<td>1.00</td>
</tr>
<tr>
<td>CA change rate x PSA change rate</td>
<td>0.26</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Change nomenclature?

PUNLUMP

IDLE

PCPT The Prostate Cancer Prevention Trial

18,882 men ≥55 with normal DRE, PSA <3, and IPSS<20 randomized 1994-97 at 221 sites

Prostate cancer detected in 24.4% of placebo arm, 18.4% of finasteride arm (RR 24.8%)

Gleason ≥7 disease in 6.4% of finasteride arm, 5.1% of placebo arm

Chemoprevention?
PCPT
Early controversy

➢ Does finasteride prevent or treat?

➢ Does finasteride reduce incidence or diagnosis?

➢ Does finasteride cause high-risk disease?
  • Yes?
  • No – pathologic artifact?
  • No – artifact of impact on BPH?

PCPT
Impact on PSA ROC curves

AUC 0.76 vs 0.68         AUC 0.84 vs. 0.78 AUC 0.89 vs 0.82

Thompson et al. JNCI 2006; 98:1128

PCPT
Does finasteride prevent or treat?

Answer: BOTH!

Table 1. Effect of finasteride treatment by prostate cancer risk group of study entry

<table>
<thead>
<tr>
<th>Quatiles of Predicted Prostate Cancer Risk</th>
<th>No. of Subjects/Cases</th>
<th>Predicted Probability of Prostate Cancer Range</th>
<th>PSA (ng/mL) Range</th>
<th>Odds Ratio</th>
<th>Predicted Probability of Pathologic Risk</th>
<th>Predicted Probability of Prostate Cancer Range</th>
<th>Odds Ratio</th>
<th>Predicted Probability of Pathologic Risk</th>
<th>Predicted Probability of Prostate Cancer Range</th>
<th>Odds Ratio</th>
<th>Predicted Probability of Pathologic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>204/1,139</td>
<td>0.15-0.88</td>
<td>0.4-9.6</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.80</td>
<td>0.15-0.88</td>
<td>0.4-9.6</td>
<td>0.79 (0.65, 0.95)</td>
<td>0.80</td>
<td>0.15-0.88</td>
<td>0.4-9.6</td>
</tr>
<tr>
<td>2</td>
<td>2002/1,184</td>
<td>0.15-0.38</td>
<td>0.4-3.1</td>
<td>0.92 (0.63, 0.97)</td>
<td>&lt;0.0001</td>
<td>0.15-0.38</td>
<td>0.4-3.1</td>
<td>0.92 (0.63, 0.97)</td>
<td>&lt;0.0001</td>
<td>0.15-0.38</td>
<td>0.4-3.1</td>
</tr>
<tr>
<td>3</td>
<td>2005/1,488</td>
<td>0.18-0.23</td>
<td>0.4-1.8</td>
<td>0.98 (0.50, 0.70)</td>
<td>&lt;0.0001</td>
<td>0.18-0.23</td>
<td>0.4-1.8</td>
<td>0.98 (0.50, 0.70)</td>
<td>&lt;0.0001</td>
<td>0.18-0.23</td>
<td>0.4-1.8</td>
</tr>
<tr>
<td>4</td>
<td>2021/1,408</td>
<td>0.23-0.31</td>
<td>0.4-2.5</td>
<td>0.95 (0.54, 0.81)</td>
<td>&lt;0.0001</td>
<td>0.23-0.31</td>
<td>0.4-2.5</td>
<td>0.95 (0.54, 0.81)</td>
<td>&lt;0.0001</td>
<td>0.23-0.31</td>
<td>0.4-2.5</td>
</tr>
<tr>
<td>5</td>
<td>2023/1,676</td>
<td>&gt;0.30</td>
<td>0.4-3.0</td>
<td>0.71 (0.58, 0.86)</td>
<td>0.0003</td>
<td>&gt;0.30</td>
<td>0.4-3.0</td>
<td>0.71 (0.58, 0.86)</td>
<td>0.0003</td>
<td>&gt;0.30</td>
<td>0.4-3.0</td>
</tr>
</tbody>
</table>

PCPT
The Prostate Cancer Prevention Trial

Answer: BOTH!
Reduction by Dutasteride of Prostate Cancer Events (REDUCE)

**Effect of Dutasteride on the Risk of Prostate Cancer**

Gerald L. Andriole, M.D., David G. Bostwick, M.D., Otis W. Brawley, M.D., Leonard G. coming, M.D., Michael Marberger, M.D., Francesco Montorsi, M.D., Curtis A. Petlawa, M.D., Truro L. Trammell, M.D., Claudia Tschima, M.D., Ph.D., Donald J. Tindall, Ph.D., Matthew C. Somervelle, M.S., Timothy H. Wilson, M.S., Ivy L. Fowler, B.S.N., and Roger S. Rittmaster, M.D., for the REDUCE Study Group

**REDUCE trial**

- 8231 men 50-75 with PSA 2.5-10 (3-10 for men >60) with negative biopsy within past 6 mos, <80cc prostate, IPSS <25
- Biopsies at 2 and 4 years
- No increase in high grade cancer at 2 years; increase in GS 8-10 at 4 years only

**PCPT vs. REDUCE**

<table>
<thead>
<tr>
<th></th>
<th>PCPT</th>
<th>REDUCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>18,882</td>
<td>8,231</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;55</td>
<td>50-75</td>
</tr>
<tr>
<td>PSA</td>
<td>&lt;3</td>
<td>2.5-10 (3-10 if &gt;60)</td>
</tr>
<tr>
<td>Prior biopsy</td>
<td>No</td>
<td>Yes (x1)</td>
</tr>
<tr>
<td>Duration</td>
<td>7 years</td>
<td>4 years</td>
</tr>
<tr>
<td>Risk reduction</td>
<td>24.4%</td>
<td>22.8%</td>
</tr>
</tbody>
</table>

**Summary of 5αRI effects**

- Downsize prostate
- Reduce and stabilize PSA
- Treat LUTS, prevent BPH interventions
- Reduce prostate cancer diagnosis
- Improve ROC characteristics of PSA and biopsy

**The Risks and Benefits of 5α-Reductase Inhibitors for Prostate-Cancer Prevention**

Marc R. Thone, M.D., Yang-Min Ning, M.D., Ph.D., Jenny J. Zhang, Ph.D., Robert Justice, M.D., Patricia Kueger, M.D., and Richard Pastur, M.D.
AUA / ASCO 2008 recommendation

Should Men Routinely Be Offered Chemoprevention of Prostate Cancer?

Asymptomatic men with a PSA ≥ 3.0 with PSA or are anticipating undergoing early detection of prostate cancer may benefit from 5-ARIs for 7 years to prevent the potential risks (including the possibility of cancer) to be able to make a better-informed decision. Taking 5-ARIs for benign conditions such as benign prostatic hyperplasia is a similar discussion.

Conclusions

- Screening saves lives, period.
- Cancer 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 and chemoprevention strategies.

What do PCPs do?

- New finasteride users in the VA population

“Post-test”

1. The benefits of PSA screening generally outweigh the limitations, and I will usually recommend it to my patients (screen >66% of men over 50)
2. There are benefits and limitations to PSA screening, and deciding whether or not to recommend screening is best approached on a case-by-case basis (screen 34-66% of men over 50)
3. The limitations of PSA screening generally outweigh the benefits and I will not usually recommend it for my patients (screen <34% of men over 50)