Prostate Cancer: Prevention, Screening and Treatment

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Prostate Cancer Incidence

Year

New Cases
Deaths

192,280 cases
27,360 deaths
Case 1: A 50 year old man with a positive family history of prostate cancer says he would like to do anything he can to prevent prostate cancer.

You recommend:

1. A heart healthy diet
2. A heart health diet and antioxidants
3. A heart health diet and a 5-alpha reductase inhibitor
4. None of the above
Prevention

Prevention: The SELECT Trial

- Selenium and Vitamin E Cancer Prevention Trial
- 32,400 men
- 2 x 2 factorial design
  - Vitamin E vs placebo
  - Selenium vs placebo
- Endpoint: prostate cancer incidence
Prevention: The SELECT Trial

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  - Selenium vs placebo
- Endpoint: prostate cancer incidence
- **No difference in incidence detected**

Prevention: 5-Alpha Reductase Inhibitors

- Androgens necessary for the development of the prostate gland
- Higher levels of androgen in the physiologic range increase risk of CaP-PHS
- 5-alpha reductase inhibitors reduce conversion of T to DHT
Finasteride Chemoprevention Study (PCPT)

18,000 Men > 55 nl
DRE and PSA < 3

Finasteride

CaP

Placebo

CaP

NEJM 2003
**PCPT-Conclusions**

- Finasteride reduces risk of prostate cancer
  - Reduce PSA anxiety, diagnosis and treatment
- Morbidity is minimal-high in placebo arm
- 20% more Gleason 8-10
  - Probably mostly explained by a pathologic artifact
- Merck is applying to the FDA for an indication for finasteride as preventive agent for prostate cancer

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**REDUCE Trial**

- 8,200 men who had PSA between 2.5 ng/mL and 10 ng/mL
- All men had one negative prostate biopsy within six months prior to study entry.
- Participants were randomly assigned to dutasteride (D) or placebo (P); the study mandated 10 core biopsies at two and four years.
- (D) was associated with a 23% reduction in prostate cancer cases compared with (P).
- While there were more high-grade cancers with (D), this was not statistically significant
- CHF was more common with (D) than (P) 0.7 versus 0.4%
Prevention-Conclusions

• No evidence that antioxidant supplements decrease prostate cancer incidence
• Strong evidence that 5-alpha reductase inhibitors reduce incidence by about 25%
• Will these drugs be used?
  – What indication? What level of risk?
  – Side effects?
  – Cost?

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Prostate Cancer Screening

- Should we screen?
- If so – who?
- If we find cancer, who should be treated?
- If we decide treatment is indicated, do we know what the best treatment is?

- Do we alter mortality?
  - Many prostate cancers may do fine without treatment
  - Aggressive prostate cancer may metastasize despite treatment
Does PSA based Screening Reduce Mortality?

- ERSPC study
- PLCO

European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 162,243 men age 50 and 69 from seven different European countries starting in the early 1990s
- Randomly assigned to a screening group or control
- Men in the screening group had a PSA test on average every 4 years and the men in the control group did not get PSA tests.

Schroeder NEJM 2009
European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 82 percent of men assigned to the screening group accepted at least one screening.
- The cumulative incidence of prostate cancer in the screened group was 8.2 versus 4.8 percent in non-screened arm with a median follow-up of 9 years.
- 214 prostate-cancer deaths in the screened group and 326 in the control group.
- The HR for death in the screened group as compared to the control group was 0.71, 20% reduction in prostate cancer mortality p=0.04 (few events).
- To prevent one death from prostate cancer, 1,410 men need to be screened and 48 cases of prostate cancer would need to be treated.

PLCO

- 150,000 persons 55 to 74 years old at entry were randomized to two study arms, half to undergo cancer screening.
- Screening was annual PSA and DRE.
- There was an 86 percent compliance rate for annual PSA and DRE testing in the screening group.
- Rates of PSA testing in the control group ranged from 40 percent in the first year to 52 percent in the sixth year and for DRE testing in these men they ranged from 41 percent in the first year to 46 percent in the fourth year; i.e., approximately half of the men in the control group were screened.
**PLCO**

- At 7 years of follow-up, the incidence of prostate cancer in the screened group was 116/10,000 person-years and the incidence of prostate cancer in the control group was 95/10,000 person-years.
- The incidence of prostate cancer-specific death was 2.0/10,000 person-years (50 deaths) in the screening group and 1.7/10,000 person-years (44 deaths) in the control group.
- *Post hoc* analysis of PLCO with longer follow-up suggests that mortality rates diminished in those with low comorbidity (yet to be published).  

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**Problems With PSA Screening**

- Disappointing performance of PSA as screening test
- Overdiagnosis
Big Problem-PSA Anxiety
False Positive PSA

- Benign Prostatic Hyperplasia (BPH)
- Prostatitis

Problems With PSA Screening

- Disappointing performance of PSA as a screening test
- Overdiagnosis-many men who are diagnosed do not have potentially lethal disease
  - Over-treatment
Impact of Screening

• Diagnosis made 5-10 years earlier (Gann et al)
• Average age at diagnosis has fallen
• Proportion of advanced cases at diagnosis has decreased
• Proportion of “good risk” patients at diagnosis has increased
• Mortality rates have decreased in US by 25%
  – Not necessarily corresponding to screening

Conclusions

• Accuracy of PSA screening in detecting cancer is 67% (AUC)
• Low mortality of prostate cancer in first 10 years (few events)
• PSA screening probably reduces mortality but longer follow-up needed to be sure
• Apparent large amount of overtreatment
Conclusions

• Accuracy of PSA screening in detecting cancer is 67% (AUC)
• Low mortality of prostate cancer in first 10 years (few events)
• PSA screening probably reduces mortality but longer follow-up needed to be sure
• Apparent large amount of overtreatment
• The debate has shifted from do we screen to do we treat (particularly low risk patients)

Does Treatment Reduce Mortality?
Randomized Study: Surgery Versus Watchful Waiting

- 695 Scandinavian men, 1989-1999
- Median f/u 8.2 years
- Mean age: 64.7 years
- Mean PSA: 12.8 ng/ml
- Stage T1b (12%), T1c (11%), T2 (76%)
- Gleason: 2-6 (61%), 7 (23%), 8-10 (5%)

Bill Axelson
NEJM 2005
Overall Survival

Cancer Specific Survival

RR 0.56, p=0.01
Cancer Specific Survival Based On Age

Increased Risk Of Metastases With Watchful Waiting

RR 0.60, p=0.004
Conclusions

- Radical local treatment in a largely non-screened population with localized cancer leads to improved OS, PFS, decreased distant metastases and local progression
- The absolute benefit remains small, but is more significant in men < 65 yrs old
- At this point in follow-up, 17 RPs for 1 life saved

Bill Axelson
NEJM 2005

Watchful Waiting

- 767 patients in CT
- Mean age: 68 years
- Mean f/u: 15.4 years
- Diagnosis: TURP (60%), needle bx (26%)
- Stage: 21% had no bone scan
- Death certificates, path reviewed

Albertson JAMA 2005
Case 2

- A 63 year old man who has been serially screened with PSA has a PSA change from 1.5 to 3.0 in one year and undergoes a biopsy. 2/12 cores show Gleason 3+3 in 5% and 10% of the positive cores
Case 2-You recommend:

1. Radical prostatectomy
2. External beam XRT
3. Seeds (brachytherapy)
4. Active Surveillance

Management Options for Low Risk Prostate Cancer: A Report on Comparative Effectiveness and Value
Hayes et al

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW
Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>PSA Criteria</th>
<th>Gleason Criteria</th>
<th>Stage Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>PSA &lt; 10</td>
<td>Gleason &lt; 7</td>
<td>T1c or T2a</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>PSA 10-20</td>
<td>Gleason 7</td>
<td>T2b</td>
</tr>
<tr>
<td>Poor Risk</td>
<td>PSA &gt; 20</td>
<td>Gleason &gt; 7</td>
<td>T2c</td>
</tr>
</tbody>
</table>

Overview

- This review focused only on low-risk prostate cancer.
- Options evaluated: active surveillance, open and robotic/laparoscopic radical prostatectomy, brachytherapy, intensity-modulated radiation therapy (IMRT), and proton beam therapy.
- There are no published reports of randomized controlled trials directly comparing these treatment options.
Findings

- Evidence from individual case series reports indicates comparable rates of disease recurrence as well as overall and cancer-specific mortality for all forms of surgery and radiation therapy.

Outcomes of Active Surveillance
Findings

• Active surveillance as compared to “watchful waiting,” entails enhanced monitoring to retain the goal of curative treatment should clinical progression occur.

• Older studies of watchful waiting suggest a modest survival benefit for surgery.

• More recent studies of active surveillance are case series with outcomes limited to 5-7 years.

• Approximately 30% of patients on active surveillance progress to or choose definitive treatment within 5 years, but overall survival rates appear comparable to those patients who opt for immediate radical prostatectomy.

Side Effects of Treatment
Quality of Life for Prostate Cancer Survivors

- Between 2003-2006, 1200 pts with localized prostate cancer, not yet treated, and 600 spouses, were enrolled.

- Patients elected either prostatectomy (radical, nerve sparing, robotic), external beam RT, or brachytherapy.

Sanda, NEJM 2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radical Prostatectomy (N=600)</th>
<th>External-Beam Radiotherapy (N=392)</th>
<th>Brachytherapy (N=106)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59</td>
<td>69</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age group — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 yr</td>
<td>304 (50)</td>
<td>41 (14)</td>
<td>67 (22)</td>
<td></td>
</tr>
<tr>
<td>60-69 yr</td>
<td>253 (42)</td>
<td>116 (40)</td>
<td>346 (48)</td>
<td></td>
</tr>
<tr>
<td>&gt;70 yr</td>
<td>46 (8)</td>
<td>135 (46)</td>
<td>93 (30)</td>
<td></td>
</tr>
<tr>
<td>Race — no. (%)†</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>548 (91)</td>
<td>213 (82)</td>
<td>260 (83)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>31 (5)</td>
<td>47 (16)</td>
<td>36 (11)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15 (2)</td>
<td>2 (1)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td>9 (1)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td></td>
</tr>
<tr>
<td>College graduate or postgraduate education — no. (%)</td>
<td>375 (62)</td>
<td>152 (52)</td>
<td>169 (55)</td>
<td>0.009</td>
</tr>
<tr>
<td>Married or with partner — no. (%)</td>
<td>323 (87)</td>
<td>126 (77)</td>
<td>242 (79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean number of consulting physicians</td>
<td>1.0±1.1</td>
<td>1.4±1.2</td>
<td>1.3±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean body mass index</td>
<td>28.0±4.5</td>
<td>28.6±5.4</td>
<td>28.5±4.7</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean prostate size — ml</td>
<td>42±19</td>
<td>49±23</td>
<td>40±19</td>
<td>0.001</td>
</tr>
<tr>
<td>PSA (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean — ng/ml                                   | 6.7±5.7                       | 9.1±10.1                          | 5.8±3.6               |         |

Sanda, NEJM 2008
Post therapy side effects

Sanda, NEJM 2008

Comparative Effectiveness of Minimally Invasive vs Open Radical Prostatectomy

Hu, Harvard, JAMA 2009
Comparative Effectiveness of Minimally Invasive vs Open Radical Prostatectomy

- Population based SEER-Medicare database
- MIRP – 1938; RRP – 6899
- Compared
  - 30 day complications
  - Anastomotic strictures
  - Incontinence and erectile dysfunction more than 18 months post-op
  - Use of additional cancer therapies

Side Effect of Robotic versus Open RP

- SEER comparing RRP (6899) to MIRP (1038)
- MIRP-shorter LOS (3 vs. 2 days), lower transfusions rates (20.8% vs. 2.7%) and strictures (14% vs. 5.8%)
- MIRP-more incontinence (15.9% vs. 12.2%) and ED (26.8% vs. 19.2%)
- Conclusions
  - Rapid adoption of new technology
  - How much is operator dependent?
Range in Estimates of Long-term Incontinence, by Surgical Approach

ORP (n=15,181)  RALP (n=2,550)  LRP (n=0,183)

ORP: Open radical prostatectomy; RALP: Robot-assisted laparoscopic prostatectomy; LRP: Laparoscopic radical prostatectomy

NOTE: Diamonds represent pooled mean rates; rectangles represent full range of estimates
Comparative Side Effects - Findings

- Comparisons are challenging because of the lack of head-to-head trials.
- Nonetheless, radiation has a higher rate of short and long-term bowel side effects than surgery, and, among radiation options, IMRT has a higher rate than brachytherapy.
- Surgery has higher risks than radiation therapy of causing short-term (0-3 months) urinary incontinence and sexual dysfunction, with longer-term sexual dysfunction data very hard to interpret.
- The data on robotic-assisted prostatectomy are too preliminary to be able to make a judgment of any differences in clinical outcomes compared to traditional open prostatectomy.
Key Findings

- Approximately 40% of patients aged 65 and older who begin active surveillance will die of other causes before their cancer progresses to require definitive treatment.
- Even if a survival benefit of immediate surgery or other definitive treatment is assumed, the lower risk of complications and side effects associated with an active surveillance strategy produces more quality-adjusted life years (QALYs) for an entire population.
- There is high confidence that for patients aged ≥65 the average net health benefit of active surveillance is comparable to immediate definitive treatment for patients with low-risk localized prostate cancer.

Key Findings

- For men younger than 65 and/or for patients who have a life expectancy greater than 20 years, the limitations in longer-term outcome data from active surveillance reduce the certainty to “moderate” that active surveillance produces mortality outcomes not substantially inferior to radical prostatectomy, while maintaining the quality-of-life advantages of having many patients never require definitive treatment.
Findings

• The management options for localized prostate cancer differ substantially in terms of the cost to third party payers. Using Medicare reimbursements as a basis, treatment costs range from ~$10,000 for brachytherapy and radical prostatectomy to $20,000 for IMRT and $50,000 for proton beam therapy.

Risk/Benefit
Table 5. Lifetime quality-adjusted life expectancy and costs for 65-year-old men with clinically-localized, low-risk prostate cancer, by treatment type.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>QALYs</th>
<th>Incremental QALYs</th>
<th>Cost</th>
<th>Incremental Cost</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>8.97</td>
<td>1.16</td>
<td>$30,422</td>
<td>$2,074</td>
<td>$1,803</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>8.12</td>
<td>0.30</td>
<td>$25,484</td>
<td>($2,864)</td>
<td>N/A*</td>
</tr>
<tr>
<td>IMRT</td>
<td>8.09</td>
<td>0.27</td>
<td>$37,881</td>
<td>$9,513</td>
<td>$35,233*</td>
</tr>
<tr>
<td>Proton Beam</td>
<td>7.97</td>
<td>0.15</td>
<td>$53,828</td>
<td>$25,480</td>
<td>$163,867*</td>
</tr>
<tr>
<td>RP</td>
<td>7.82</td>
<td>Reference</td>
<td>$28,348</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

All incremental costs and QALYs calculated relative to radical prostatectomy.

NOTES: RP: radical prostatectomy; AS: active surveillance; IMRT: intensity-modulated radiation therapy.

QALY: quality-adjusted life years.

*Incremental cost-effectiveness ratios presented for purposes of transparency; findings of the ICER systematic review do NOT support substantial differences in overall effectiveness.

†Strategy is less costly and more effective than reference strategy.
Case 2

- A 63 year old man who has been serially screened with PSA has a PSA change from 1.5 to 3.0 in one year and undergoes a biopsy. 2/12 cores show Gleason 3+3 in 5% and 10% of the positive cores.
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