Prostate Cancer PSA Controversy and Emergence of Active Surveillance

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Disclosures

• NCI Kidney Cancer Task Force Co-Chair
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• AMGEN honoraria
• Janssen Inc. consultant and honoraria
• Genprobe consultant
• Dendreon consultant
Prostate Cancer in Developed Countries – *Known 2012*

- 39% Reduction in mortality; Accounting for 20% of the overall reduction in cancer mortality in men.
- Half of this appears related to early detection
- Screening of healthy, young, well-informed men with serum PSA *reduces significantly the risk of dying of prostate cancer* (21% – 44%)
- It does so at the *risk of over detection*—detecting disease which would not have become clinically apparent over a patient’s lifetime if left untreated
- Detection and treatment (over-treatment) are currently, too tightly linked

**USPSTF**

- Gives prostate cancer screening a D grade.
- The definite evidence of harm far outweighs the unproven benefit of PSA screening
- 8,000 comments received concerning the recommendation in the first 30 days (comment period).
Why?

- The randomized trials of PSA screening show little improvement in mortality at a high cost of treatment
- PSA is a poor screening test with poor specificity so many men get prostate biopsies and worry and don’t have cancer
- Many men who are treated had bad side effects, surgical complications, erectile dysfunction and incontinence and don’t benefit from treatment

Recent studies

Screening revisited:


Screening

PLCO:
- Randomization 50-74 yo men from 1993-2001
  - 38,350 men to intervention vs 38,355 to control
  - Screening: Annual PSA (6 yrs) and DRE (4 yrs)
  - Control: NO screening
  - Follow for ≥ 13 years

- Goal: whether or not screening reduces Prostate Cancer Mortality

Screening

PLCO:
- Findings after median 11.5 yrs

  - Prostate Ca diagnosis:
    - Screened-9% vs Control-7.8%

  - Prostate Ca Mortality:
    - Screened-0.24% vs Control-0.21%

Andriole et al, NEJM, 2009
PLCO Contamination:

• Flaws:
  • Assumed that 10% with prev screening in control arm would continue
  • In actuality, Control Arm,
    • 44% of men in each arm had ≥1 PSA test before randomization
    • During trial, 52% had undergone PSA screening and 46% with DRE
  • Controls:
    • Only 15% decreased diagnosis
    • 93% of cancers were asymptomatic, organ-confined
  • Follow-up was 11.5 years from randomization, NOT treatment

• Re-analyzed PLCO
• Stratified by co-morbidity
• 35.7% of men had minimal co-morbidity
• Significant decreased risk of prostate cancer mortality in those with minimal or no co-morbidity, HR 0.56
• NNS/NNT 723 and 5

Crawford E D et al. JCO 2011;29:355-361
Screening

ERSPC:

- 162,243 men 55-69 yo randomized from 1991-2003
- Median follow-up - 9 years

Screening:

- Did NOT require annual PSA – only 2.1 tests averaged over course of study
- DRE variable, but usually only if equivocal PSA

ERSPC:

- Prostate Cancer diagnosis: Screened-8.2% vs Control-4.8
- Death from prostate cancer: screened arm RR was 0.80 (95% CI 0.67–0.95; P=0.01)
  - Curves began to diverge at 7-8 years
- NNS to prevent 1 death=1410; NNT=48

Schroder et al, NEJM, 2009

Figure 2. Cumulative Risk of Death from Prostate Cancer
Screening - Newer data

Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Janet Hugosson, Sigurd Carlson, Carman Alm, Owe Zetterstrom, All-Sten Stormby, Hans Jokel, Carl-Einar F. Malmström, Michael Hugosson, Lars Ljøngh

- 20,000 men aged 50-64 yrs
- Screened every 2 years
- Followed median 14 years
- Screened:
  - Prostate cancer diagnosed: Screened-12.7% vs Control-8.2%
  - Prostate cancer death: Screened-0.5% vs Control-0.9%
  - RR Reduction = 0.56 (95%CI, 0.39-0.82, p=0.002)
  - Compared to ERSPC = 0.8

Hugosson et al, Lancet Oncol, 2010

Screening - Newer data

- Younger patients – more likely to have incurable cancer at first screen
- Lower PSA threshold for biopsy (2.5-3 vs 4) and more frequent screening (2 vs 4 yrs)
- Lower contamination (3% vs 44%)
  - Longer follow-up with improved RR
  - NNS = 293 and NNT = 12 to prevent 1 Death
  - Not significantly different from Breast or Colorectal cancer
Now with 11 years of follow-up, the relative reduction in the risk of death from prostate cancer is 21% (RR 0.79, 95% CI 0.68-.91 p=0.001), 29% after adjustment for noncompliance.

NNS now 1055, NNT 37.
So in what ways were they wrong?

- There is strong evidence that radical prostatectomy saves lives over observation (38% prostate cancer mortality reduction, 25% all cause mortality reduction) at 15 years (Bill-Axelson NEJM 2011; 364:1708-17)
- Diagnostic procedures to detect prostate cancer are common in both screened and unscreened populations, they just occur later in unscreened men.
• The task force minimized the burden of living with advanced cancer and primarily looked at survival (bone mets, obstruction, fractures etc…)
• The task force did not adequately consider at risk populations (AA and FH men)
• The task force minimized the epidemiologic data that since PSA testing began in the 1990’s there has been a 40% reduction in prostate cancer mortality and 75% reduction in presentation with advanced disease.

Defining the proportion of mortality reduction from PSA screening and early detection
• Two models generated to determine the proportion of decline in mortality from early detection vs. improved treatment
• 45-70% mortality reduction from early detection

Stage Evolution

The Changing Face of Prostate Cancer in the United States
So how do we answer the screening concerns?

- Improve the specificity of PSA
- Stop screening men who are unlikely to benefit
- Diminish overtreatment by offering active surveillance more than currently

http://deb.uthscsa.edu/URORiskCalc/Page/s/uroriskcalc.jsp
Rational 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


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
Risk Stratification

- PSA
- Clinical Stage
- Gleason Grade
- Number and extent of positive biopsies
- PSA velocity/PSA kinetics
- Obesity

<table>
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<td>% pos bx</td>
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</table>

UCSF CAPRA

Score calculated by totaling each characteristic, range 0-10

Cooperberg et al J Urol June 2005
Active Surveillance

- Advantages
  - Avoids risk from surgery or radiation therapy
  - Decreased cost

- Disadvantages
  - Inaccurate staging/grading may put patient at risk for metastases
  - Stress
  - Side effects from repeat biopsy
A busy year for AS

Clinically Indolent Disease

How to define an “insignificant tumor”?  
• Clinical stage T1c or T2a, PSA under 10 ng/ml  
• PSA density < 0.15ng/ml/cm³

And absence of  
• Any Gleason pattern 4 or 5  
• 3 cores involved  
• > 50% of core involved  
• In a 12 core Bx

Epstein. JAMA 1994;271:368
### Surveillance: Recent Experiences

<table>
<thead>
<tr>
<th>Institution</th>
<th>Median follow-up (months)</th>
<th>Progress by grade</th>
<th>Progress by volume</th>
<th>Treatment without progression</th>
<th>OS</th>
<th>CSS</th>
<th>PFS</th>
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<td>18%</td>
<td>2%</td>
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<td>100%</td>
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<td>14%</td>
<td>11%</td>
<td>64%</td>
<td>98%</td>
<td>64%</td>
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### Surveillance: Recent Experiences

<table>
<thead>
<tr>
<th>Institution</th>
<th>Total</th>
<th>Median age</th>
<th>Inclusion criteria</th>
</tr>
</thead>
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<td>Royal Marsden</td>
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<td>67</td>
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<td>University of Miami</td>
<td>230</td>
<td>64</td>
<td>Gleason ≤3+4, PSA ≤10 ng/ml, Tt stage ≤2, ≤3 cores, ≤20% of any core positive</td>
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<td>Johns Hopkins</td>
<td>769</td>
<td>66</td>
<td>Gleason ≤3+3, PSA ≤0.15 ng/ml, Tt stage ≤2, ≤30% of cores positive</td>
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<tr>
<td>UCSF</td>
<td>640</td>
<td>62</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, Tt stage ≤2, ≤33% of cores positive, ≤50% of any core positive</td>
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<tr>
<td>University of Toronto</td>
<td>453</td>
<td>70</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, Tt stage ≤2, ≤33% of cores positive, ≤50% of any core positive</td>
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<td>ERSPC sites</td>
<td>988</td>
<td>66</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, PSA kinetics ≤0.2 ng/ml/ml, Tt stage 1c-2, ≤2 cores positive</td>
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<tr>
<td>Memorial Sloan-Kettering</td>
<td>238</td>
<td>64</td>
<td>Gleason ≤3+3, PSA ≤10 ng/ml, Tt stage ≤2, ≤33% of cores positive, ≤50% of any core positive</td>
</tr>
</tbody>
</table>

TOTAL: 3644 | 67 |

Outcomes of Surveillance

Economic Impact of AS

- The cost of AS is driven by repeated prostate biopsies, clinical visits and imaging
- Other treatments for low risk disease have higher up-front costs (RP<Brachy<IMRT/ADT)
- Costs for AS are lower that curative therapies through 10 years in Markov modeling
- Physician reimbursement for AS is higher than other therapies after 5 years
- Periods of AS with intensive assessment then transitioning to active treatment highest cost

Advantages to the RALP

- Data suggesting:
  - Lower blood loss
  - Earlier discharge
  - Quicker return to regular routine
  - Lower rate of bladder neck contraction
  - Earlier return of continence
  - New evidence of decreased complications and perhaps lower mortality!
- Equal cancer cure rates
  - Continence and potency data related to surgeon
  - Safety higher in high volume hospitals

Robotic Volume by Year
2012 429, 1740 cases overall
USPSTF Accountability Act

- USPSTF Transparency and Accountability Act of 2012. This bipartisan legislation, introduced today by Reps. Marsha Blackburn (R-TN-7) and John Barrow (D-GA-12), along with Donna Christensen (D-VI) and Lee Terry (R-NE-2), calls for significant changes to the U.S. Preventive Services Task Force (USPSTF) and the process by which the group makes formal recommendations regarding preventive care services.

Prasad Sm et al JAMA 2012;307(16):1692-1694.
USPSTF Accountability Act

- Most importantly, the bill strikes the language added by the 2010 Affordable Care Act (ACA) that directly ties Medicare coverage of a particular preventive service to the grade given by the USPSTF.
- Other key changes called for by the bill include a mandate to ensure a “balanced representation of primary and specialty care providers” and other key stakeholders in the healthcare community are involved in development and review of recommendations.

Summary

- PSA is an imperfect screening test. High sensitivity but low specificity
- PSA screening does save lives
- Younger men and those at increased risk of prostate cancer benefit the most
- We should stop screening men unlikely to benefit
- We should offer active surveillance to low risk men
- When we treat we should do so expertly with consistently good outcomes
Summary

• To discourage PSA screening for all men is irresponsible
• The USPSTF methodology is severely flawed
• Lets thoughtfully move forward with prostate cancer detection and treatment that keeps faith with the patients at risk for the second leading cancer killer of American Men