Current Controversies in Prostate Cancer Screening

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Disclosures:
Dr. Lilly is on the Speaker’s Bureau for Ferring Pharmaceuticals. He is also a Proctor for Intuitive Surgical.
Doctors have an image problem...
Urologist- image problem
Prostate cancer by race
Famous prostate cancer patients
Risk of Death for 40 year old U.S. Men, to End of Life, by Leading Causes

- Heart Disease: 341
- Lung Cancer: 80
- Stroke: 62
- Chronic Obstructive Pulmonary Disease: 55
- Pneumonia & Influenza: 38
- Prostate Cancer: 34

Number of Men per 1,000
Prostate Cancer stats

- USA lifetime risk of prostate cancer *diagnosis* 15.9%
- USA lifetime risk of *dying* of prostate cancer 2.8%
- 70% of deaths from prostate cancer occur after age 75
Why screen for prostate cancer

- Prevalent disease
- 2nd most common cause of Ca deaths in men
- No known prevention
- Early disease is curable
- High morbidity/cost of advanced disease
- Data show a decreased death rate, likely due to PSA-led screening
What’s the catch?
Potential harms of screening

- False positives
  - Unnecessary biopsies
  - Stress

- Overdiagnosis
  - Cancers which would have remained asymptomatic
  - Cancers which would have not killed?

- Side-effects of biopsy, treatment

- Death rate decline may be from something else
The goal of prostate cancer testing is not only to prevent mortality, but even more so to prevent the attendant morbidity that comes with metastatic prostate cancer.

- Urinary tract obstruction, bleeding
- Bone pain and fractures
- Side effects of androgen deprivation, chemotherapy, immune therapies
PSA- Prostate Specific Antigen

- Most widely available test to identify changes in the prostate
- Prostate-specific, not cancer-specific
- When used appropriately, the PSA test provides clinicians with valuable information to aid in the diagnosis and treatment of prostate cancer.
Before the “PSA Era”

- Prostate cancers were most commonly found following the onset of symptoms from advanced disease, or as a nodule found on DRE.

- Symptomatic tumors were of a higher grade, more advanced and often deadly.

- Many men got only hormonal therapy, with significant side-effects and limited benefits.
During the “PSA Era”

- SEER data demonstrates:
  - 75 percent reduction in proportion who present with metastatic prostate cancer.
  - 42 percent reduction in age-adjusted prostate cancer mortality over the most recent 20 years.
Is PSA screening responsible for the decrease in prostate cancer mortality?

DOI 10.1007/s10552-007-9083-8

Quantifying the role of PSA screening in the US prostate cancer mortality decline

Ruth Etzioni · Alex Tsodikov · Angela Mariotto · Aniko Szabo · Seth Falcon · Jake Wegelin · Dante diTommaso · Kent Karnofski · Roman Gulati · David F. Penson · Eric Feuer

Independent NCI mathematical modeling teams- U.Mich and FHCRC
Mathematical modeling of CaP mortality with and without PSA

45-70% of decreased CaP mortality attributed to screening

About the USPSTF:

• “... an independent panel of non-federal experts in prevention and evidence-based medicine and is composed of primary care providers (such as internists, pediatricians, family physicians, gynecologists/obstetricians, nurses, and health behavior specialists).”

• Chairman is Virginia Moyer, Professor of Pediatrics, Baylor College of Medicine

• **Did not include a prostate cancer expert (urologist or oncologist) in the development of recommendations for PSA testing.**
USPSTF and the Affordable Care Act

- The ACA broadened the scope of the USPSTF, mandating that the group must assess, develop and update clinical preventive recommendations.

- The ACA requires that Medicare and qualified commercial plans cover those preventive services graded A and B by the USPSTF at 100 percent.

- Services with grades of “C” or “D” will require a co-pay.
Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

**Description:** Update of the 2008 U.S. Preventive Services Task Force (USPSTF) recommendation statement on screening for prostate cancer.

**Methods:** The USPSTF reviewed new evidence on the benefits and harms of prostate-specific antigen (PSA)-based screening for prostate cancer, as well as the benefits and harms of treatment of localized prostate cancer.

**Recommendation:** The USPSTF recommends against PSA-based screening for prostate cancer (grade D recommendation).

This recommendation applies to men in the general U.S. population, regardless of age. This recommendation does not include the use of the PSA test for surveillance after diagnosis or treatment of prostate cancer; the use of the PSA test for this indication is outside the scope of the USPSTF.

www.annals.org  
For author affiliation, see end of text.  
* For a list of the members of the USPSTF, see Appendix 1 (available at www.annals.org).  
This article was published at www.annals.org on 22 May 2012.
USPSTF and prostate cancer screening 2012

- “D” Grade
- The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.

Other “D” recommendations

- Testis cancer screening - physician or self-exam
- Breast cancer screening with self-exam
- Ovarian cancer screening
- COPD screening with spirometry
CaP screening studies used by USPSTF

- Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)

- European Randomized Study for the Screening of Prostate Cancer (ERSPC)

Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial

- More than 76,685 men ages 55-74, randomly assigned to annual screening for 6 years or “usual care”.
- By 2009, 57% had been followed for at least 13 years
- Prostate cancer detection rate was 12 percent higher in the screening arm.
- No decrease in prostate cancer mortality or overall mortality between arms
Problems with the PLCO

- Contamination by “prescreening” of 40% in both arms
- Contamination by nonprotocol PSA measures in 50% of the control arm patients
- Less than 40% with elevated PSA had biopsy
- No conclusions can be drawn about mortality rates from this study (Fred Hutchinson CRC)

Cancer Causes Control (2012) 23:827–835
European Randomized Study for the Screening of Prostate Cancer (ERSPC)

- 162,000 men randomly assigned to PSA screening every 4 years vs no screening
- Lower PSA cutoff (3.0) than US trial
- Only 15% contamination
- After median 11 years of f/u, incidence of CaP was 8.2% screened and 4.8% controls
Updated data demonstrates a 21 percent risk reduction in prostate cancer-related death (up to 29 percent after accounting for noncompliance).

To prevent one death from prostate cancer at 11 years of follow-up:

- 1055 men would need to be invited for screening
- 37 cancers would need to be detected
- Numbers are decreasing with longer follow-up

There was no significant difference in all-cause mortality.
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja
Goteborg trial- CaP incidence

Figure 2: Cumulative incidence of prostate cancer in the screening group and in the control group

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<th>Time from randomisation (years)</th>
<th>Screening group</th>
<th>Control group</th>
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<tr>
<td>7</td>
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</tbody>
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Number at risk:
- Screening group: 9952
- Control group: 9952

Additional information:
- Number of males followed: 19,904
- Number of prostate cancer cases: 4660
- Median follow-up: 11 years
Goteborg - risk of CaP death

Figure 3: Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates
Goteborg study

- 44% decrease in CaP-specific mortality at a median of 14 years

- To prevent one prostate cancer death
  - 293 men screened
  - 12 men treated
  - Similar to breast cancer screening stats
Goteborg study - why the big differences

- Less contamination with prescreening (3% vs 44%)
- Younger men - avg age 56
- Longer follow-up
- 93% of men with high PSA had a biopsy
  - (30-40% in PLCO)
Göteborg Randomized Population-Based Prostate Cancer Screening Trial:

- Population-based trial of 20,000 men ages 50-64.
- Demonstrated a 41 percent decrease in advanced disease.
- Showed a 44 percent relative risk reduction in prostate cancer mortality in men ages 50-64 after a median of 14 years.
Screening Decreases Prostate Cancer Mortality: 11-Year Follow-Up of the 1988 Quebec Prospective Randomized Controlled Trial

Fernand Labrie,* Bernard Candas, Lionel Cusan, Jose Luis Gomez, Alain Bélanger, G. Brousseau, Eric Chevrette, and Jacques Lévesque

Oncology and Molecular Endocrinology Research Center and Departments of Medicine and Radiology, Laval University Medical Center (CHUL), and Laval University, Quebec, Canada
Laval University Prostate Cancer Screening Program
(November 15, 1988 to December 31, 1999)

46,486 men aged 45-80 years with no diagnosis of CaP

Randomization
Invited

31,133 men

7,348
Screened men
Median age [Q1-Q3]
60 [55.2-65.8]
10 deaths
/ 50,433 m-y
19.8 deaths
/ 100,000 m-y

23,785
Unscreened men
Median age [Q1-Q3]
59.7 [52.5-67.8]

1,122
Screened men
Median age [Q1-Q3]
61.1 [56.5-66.2]

14,231
Unscreened men
Median age [Q1-Q3]
59.0 [52.0-66.8]
74 deaths
/ 141,535 m-y
52.3 deaths
/ 100,000 m-y

0.38 [ 0.20 – 0.73 ]
p < 0.002
Relative Risk [ 95% C.I. ]
Quebec Study Highlights

- Prostate cancer specific death rate 62% lower in screened vs unscreened
- Only 1/159 cancers diagnosed at follow-up visits was metastatic
Quebec Study Strengths

- Large prospective trial
- Annual screening
- Only 7% contamination with “prescreening”
- Same advantage for those invited for screening and those screened despite randomization to nonscreened arm
Quebec Study Weaknesses

- Not a true randomized prospective trial
- Randomization was for *invitation* for screening
- Introduces potential biases
- This study was not used by USPSTF
Does treatment of early prostate cancer save lives?
PIVOT trial

- Prostate Cancer Intervention vs Observation Trial
- 731 men randomly assigned to RP or observation
- Mean age 67
- Follow-up so far is 10-12 years

PIVOT results

- No difference in all-cause or prostate cancer specific mortality in whole group
- But, improved all cause and CaP specific mortality for PSA $>10$ and intermediate and high-risk cancers

PIVOT trial results: 2012
PIVOT: Subgroup analysis
Bill-Axelson et al- RP vs WW

- 695 men with clinically localized CaP, mean age 65, low or intermed grade CaP on biopsy
- 14 hospitals in Sweden, Finland, Iceland
- Randomized to WW or RP
- Endpoints- Local progression, distant mets, CaP-specific mortality, overall mortality
- Median f/u 12.8 years

New Engl J Med 2011; 364:1708-17
Bill-Axelson results 2011

- Reduction in all indices in RP group including overall mortality
- Difference between RP and WW increased for all indices between 5 & 10 year analyses, consistent with natural history of CaP
- RR of death due to CaP 0.62 in RP group
- Benefit primarily seen in men <65
Bill-Axelson
CaP deaths
Benefit primarily in men <65

New Engl J Med 2011; 364:1708-17
Bill-Axelson

Any cause deaths

Benefit primarily in men <65
Bill-Axelson results 2011

- incidence of death from CaP at 15 years of 14.6% (RP) and 20.7% (WW)
- number needed to treat to avert one death was 15 overall and 7 for men younger than 65 years of age
New AUA Guidelines 2013

- Recommends against screening age <40
- Recommends against screening age 40-54 at average risk of CaP (no fam hx or AA)
- Shared decision making for men 55-69
- Routine screening interval of 2 years
- Screening over age 70 only with expected longevity >10-15 years
What I recommend about screening

- Use the PSA to aid in finding a diagnosis in men with symptoms (this is not screening)
- Discuss prostate cancer screening with men 55 and over who have a good 10-15 year longevity, and men over 40 who are African-American or have a 1st degree family history, especially of cancer early in life or multiple generations
Summary - What can PSA screening do for you as a patient?

- Improved yield of CaP in screening - yes
- Detect earlier stage cancers - yes
- Detect more curable cancers - yes
- Reduce risk of CaP progression, mets - yes
- Reduce death rate from prostate cancer - yes, but how much?
- Reduce overall mortality (death from any cause) - probably yes, especially if <65
REMEMBER THE TWENTY EXTRA YEARS YOU ADDED TO YOUR LIFE THROUGH CLEAN, HEALTHY LIVING? - WELL, THESE ARE THEM.
Take-home points

- Don’t throw out the baby with the bath water
- Risk of returning to pre-1980’s medicine
- Consider screening for healthy men with a good 10-15 yr projected longevity, especially those at increased risk
- Low-risk prostate cancers can often be safely managed with surveillance
- For those who need RP, robotics is a step forward
Questions?
Treatment of localized prostate cancer- noncurative

- Watchful waiting (active surveillance)
- Hormonal therapy
- Dietary manipulation?
- Herbals?
Natural History of Early CaP

- 223 consecutive patients with clinically localized CaP Dx 1977-1984
- No initial therapy
- Hormonal therapy if they developed symptoms
- 21 year follow-up

JAMA 2004; 291(22):2713-9
Natural History - results

- 17% developed metastatic disease
- Most had indolent course 10-15 years
- Worse from 15-20 years
  - Progression free survival 45 down to 36%
  - Survival without mets 77 to 51%
  - Prostate-specific mortality increased
    - 15/1000 person-years in first 15 years
    - 44/1000 person-years after 15 years
Treatment of localized prostate cancer - potentially curative

- Surgery - radical prostatectomy
  - Open (with an incision)
  - Laparoscopic (robotic-assisted)

- Radiation
  - External beam
  - Implants

- Cryotherapy (freezing)
What’s new in surgery for prostate cancer: The surgical “robot”
Robotic-assisted radical prostatectomy
Robotic tools
DaVinci ports

(five tiny ports inserted into abdomen)

(five tiny ports in preparation for robot docking)
DaVinci docked
DaVinci tools
Potential benefits over open RP

- Lower blood loss
- Shorter hospital stay (1 vs 2 days)
- Shorter catheterization (1 vs 2 weeks)
- Less pain
- Quicker return to activity
- Better continence and potency?