PSA SCREENING
DISTINGUISHING SIGNAL FROM NOISE

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SEATTLE, WASHINGTON
TODAY’S PRESENTATION

- Review evidence from population and trial data
- Demonstrate why it is so hard to see the signal
- Introduce the idea of using statistics to “go beyond the (empirical) data”
- Show what we can learn if we are willing to do so
PROSTATE CANCER TRENDS IN THE US POPULATION

Cases

- African Americans
- All races

Deaths

- African Americans
- All races

Prostate cancer cases per 100,000 men

- Screening begins

Prostate cancer deaths per 100,000 men

- Screening begins

52% decline

51% decline
PROSTATE CANCER SCREENING TRIALS (2012)

<table>
<thead>
<tr>
<th></th>
<th>ERSPC</th>
<th>PLCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate ratio</td>
<td>0.79</td>
<td>1.09</td>
</tr>
<tr>
<td>Lives saved per 1000</td>
<td>1.07</td>
<td>−0.03</td>
</tr>
</tbody>
</table>
DOES PROSTATE CANCER SCREENING WORK?

- *Population data* suggest a strong effect of screening
  
  BUT
  
  – There may be other explanations for the mortality decline
  – Example: changes in primary treatments for localized disease
PSA SCREENING AND PRIMARY TREATMENT TRENDS IN THE US

Initial treatments among localized cases

- Conservative management
- Surgery
- Radiation
- Radiation + hormones

Percent of men who had at least 1 PSA test

- All races
- Blacks

Year of diagnosis


Percent of cases

0% 20% 40% 60% 80% 100%

Year


Percent of cases among localized cases

- 50-59 y
- 60-69 y
- 70-84 y

Etzioni et al, submitted

SEER and CaPSURE databases
The Prostate Cancer Conundrum

Peter C. Albertsen

"The recent decline in prostate cancer mortality rates suggests that some treatment is having an impact. Whether this is the result of the early use of androgen withdrawal therapy or whether this is the result of widespread use of surgery or radiation remains to be determined."

JNCI, 2003

Prostate Cancer Screening—The Evidence, the Recommendations, and the Clinical Implications

Roger Chou, MD
Michael L. LeFevre, MD, MSPH

"ERSPC clearly showed that if PSA screening reduces prostate cancer mortality, it does not occur for 7 to 10 years. Therefore, the decline observed from the 1990s to about 2000 could not be from screening but was probably due to other factors such as more effective treatments."

JAMA, 2011
Does Prostate Cancer Screening Work?

- **Population data** suggest a strong effect of screening
  
  **BUT**
  
  - There may be other explanations for the mortality decline
  - Example: changes in primary treatments for localized disease

- **Trial data** are equivocal
  
  **BUT**
  
  - The PLCO trial did not compare screening vs no screening
  - Absolute benefit (lives saved) from trials underestimates population benefit over the long term
SCREENING IN PLCO

Assessing contamination and compliance in the prostate component of the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

Paul F Pinsky, Amanda Block, Barnett S Kramer, Anthony Miller, Philip C Prorok, and Christine Berg

Clinical Trials, 2010

Mean number of routine PSA tests:
- 2.7 in control arm
- 5.0 in screening arm

Percent with at least one test:
- 74% in control arm
- 95% in screening arm

Numbers of cancers detected:
- 1984 in control arm
- 1611 in concurrent population
After 13 years of follow-up, there was no evidence of a mortality benefit for organized annual screening in the PLCO trial compared with opportunistic screening, which forms part of usual care.
## LIVES SAVED BY SCREENING TRIAL VERSUS POPULATION

<table>
<thead>
<tr>
<th>Trial arm</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5.17</td>
</tr>
<tr>
<td>Screening</td>
<td>4.10</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>1.07</td>
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Prostate cancer deaths per 1,000 men invited in core age group after 11 years: 20%
LIVES SAVED BY SCREENING TRIAL VERSUS POPULATION

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<thead>
<tr>
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<th>Deaths</th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td>30</td>
</tr>
<tr>
<td>Screening</td>
<td>24</td>
</tr>
<tr>
<td>Absolute Difference</td>
<td>6</td>
</tr>
</tbody>
</table>
THE PROBLEM WITH THE EVIDENCE
1. Go beyond observed data to learn about underlying disease process
   – Given data on screening uptake
   – Use incidence before and after screening to learn about disease natural history
GOING BEYOND THE DATA

1. Go beyond observed data to learn about underlying disease process
   – Given data on screening uptake
   – Use incidence before and after screening to learn about disease natural history

3. Project impact of screening on (stage-specific) incidence
   – Translate drop in distant stage under screening into mortality reduction
OBSERVED AND MODELED INCIDENCE

SEER

Cases per 100,000 men age 50-84

Localized-regional

Model

Observed

1980
OBSERVED AND MODELED INCIDENCE

**SEER**

Localized-regional

Model

Observed

**PLCO screen group**

GS<7  GS=7  GS>7

Cumulative number of prostate cancers

Study year of trial

- PLCO-FHCRC

**PLCO control group**

GS<7  GS=7  GS>7

T<T2A

T>T2A

T4/N1/M1

Cumulative number of prostate cancers

Study year of trial

- PLCO-FHCRC
ROLE OF SCREENING IN MORTALITY DECLINE

Assumes prostate cancer incidence would have remained constant after 1987

Treatment effects from trials and C/E studies

Screening effect via decline in distant stage incidence

Etzioni et al., Cancer, 2012; Gulati et al Cancer 2014
The Prostate Cancer Conundrum

Peter C. Albertsen

“The recent decline in prostate cancer mortality rates suggests that some treatment is having an impact. Whether this is the result of the early use of androgen withdrawal therapy or whether this is the result of widespread use of surgery or radiation remains to be determined.”

JNCI, 2003

Editorial

The Prostate Cancer Conundrum Revisited: Further Insights

Peter Albertsen, MD, MS

“This insight carries significant practical implications. First, it refutes the notion that PSA screening is worthless. Many men do not benefit from PSA testing but those with sufficient longevity appear to benefit from having treatment initiated early in the course of their disease.”

Cancer, 2012
HOW SHOULD WE SCREEN THE POPULATION?

“Using higher thresholds for biopsy referral for older men and screening men with low PSA levels less frequently can reduce overdiagnosis while preserving the majority of lives saved”

“For PSA screening to be cost-effective, it needs to be used conservatively and ideally in combination with conservative management for low-risk disease”

Comparative Effectiveness of Alternative Prostate-Specific Antigen–Based Prostate Cancer Screening Strategies
Model Estimates of Potential Benefits and Harms
Roman Gulati, MS; John L. Gore, MD; and Ruth Etzioni, PhD

Ann Int Med, 2013

Original Investigation
Economic Analysis of Prostate-Specific Antigen Screening and Selective Treatment Strategies
Joshua A. Roth, PhD, MHA; Roman Gulati, MS; John L. Gore, MD; Matthew R. Cooperberg, MD; Ruth Etzioni, PhD

JAMA Oncology, 2016
SMARTER SCREENING = LESS SCREENING?

JAMA Oncology, 2016
LEARNING FROM CANCER INCIDENCE
ALL RACES AND BLACK NATURAL HISTORY

<table>
<thead>
<tr>
<th></th>
<th>All races</th>
<th>African Americans</th>
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<tbody>
<tr>
<td>Onset in lifetime</td>
<td>29%</td>
<td>45%</td>
</tr>
<tr>
<td>Mets at dx given onset</td>
<td>6%</td>
<td>10%</td>
</tr>
<tr>
<td>Mean lead time</td>
<td>7.3 years</td>
<td>7.4 years</td>
</tr>
<tr>
<td>Fraction of screen dx overdiagnosed</td>
<td>43%</td>
<td>40%</td>
</tr>
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</table>
SHOULD WE SCREEN BLACK MEN DIFFERENTLY?

- Suppose we agree to start screening at age 55 in the US population
- Among blacks, incidence of latent disease that would be lethal reaches a level at age 45 that matches all races at age 55
- This suggests starting screening at age 45 in black men
- This may suggest more frequent screening subject to harm-benefit analysis
**Mean lead times (years)**

<table>
<thead>
<tr>
<th></th>
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<th>ERSPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screen</td>
<td>4.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Control</td>
<td>3.0</td>
<td>0.93</td>
</tr>
<tr>
<td>Difference</td>
<td>0.9</td>
<td>3.07</td>
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Differences in observed screening benefit across trials can be attributed to differences in screening intensity as captured by the mean lead time.

Mortality risk reduced by 7% per year of mean lead time.
TAKE-HOME MESSAGES

- Empirical evidence from trials/population
  - No clear signal about screening efficacy
  - Generally also do not provide unbiased estimates of overdiagnosis

- Statistical and computer modeling is necessary to go beyond the data

- What we have learned
  - ERSPC and PLCO screening trials are more similar than they appear
  - In the general population screen conservatively and treat conservatively
  - Black men have a higher risk of developing prostate cancer at all ages
  - May be a case for earlier and more frequent screening in black men
ACKNOWLEDGMENTS

- Roman Gulati
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