PSA Screening in Primary Care

Updated USPSTF Recommendations for Prostate Cancer Screening

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Disclosure

Pfizer, Inc. – Speakers Bureau

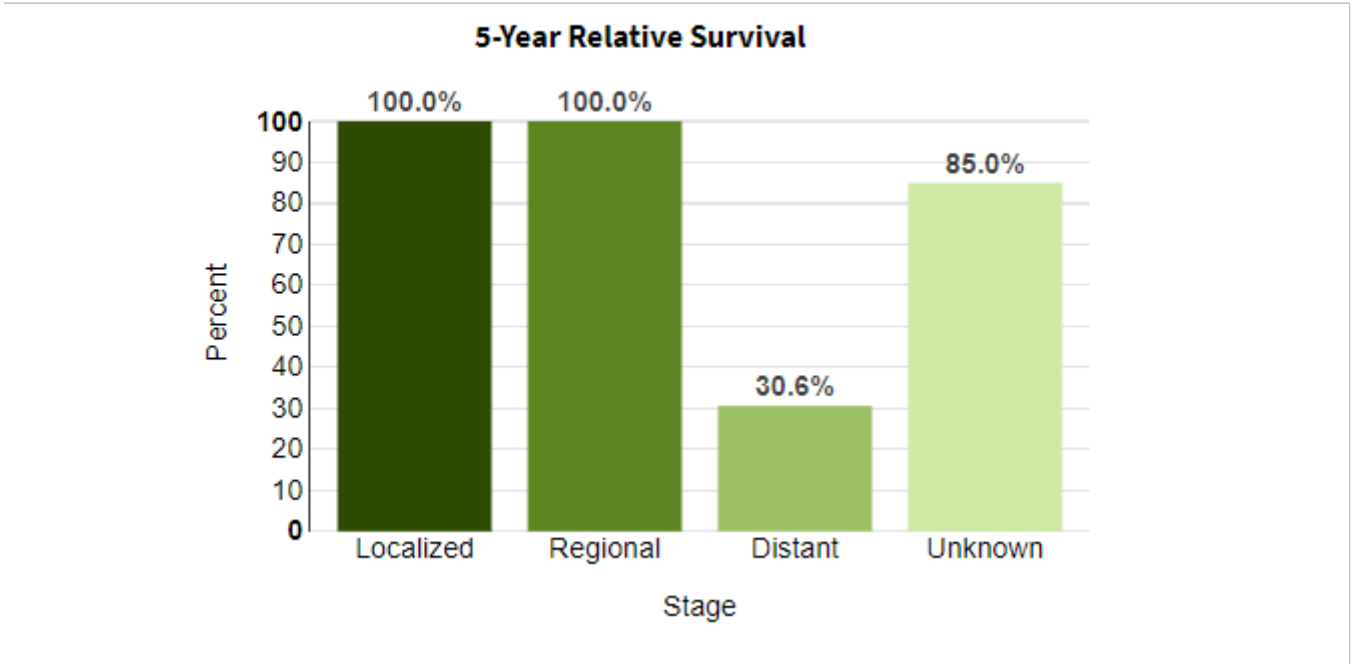
Objectives

- Discuss the recommendations for PSA screening for prostate cancer
- Review relevant literature on the risks/benefits of PSA screening for prostate cancer
- Characterize the role of the provider in shared decision making for prostate cancer screening
- Consider appropriate patients for PSA screening

Background

According to the American Cancer Society's and National Cancer Institute[1] estimates for 2021 in the United States:

- There will be approximately 248,530 new prostate cancer diagnoses
- There will be 34,130 deaths due to prostate cancer



https://seer.cancer.gov/statfacts/html/prost.html

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Background

59% of men 80 years old or older have prostate cancer at autopsy[2]

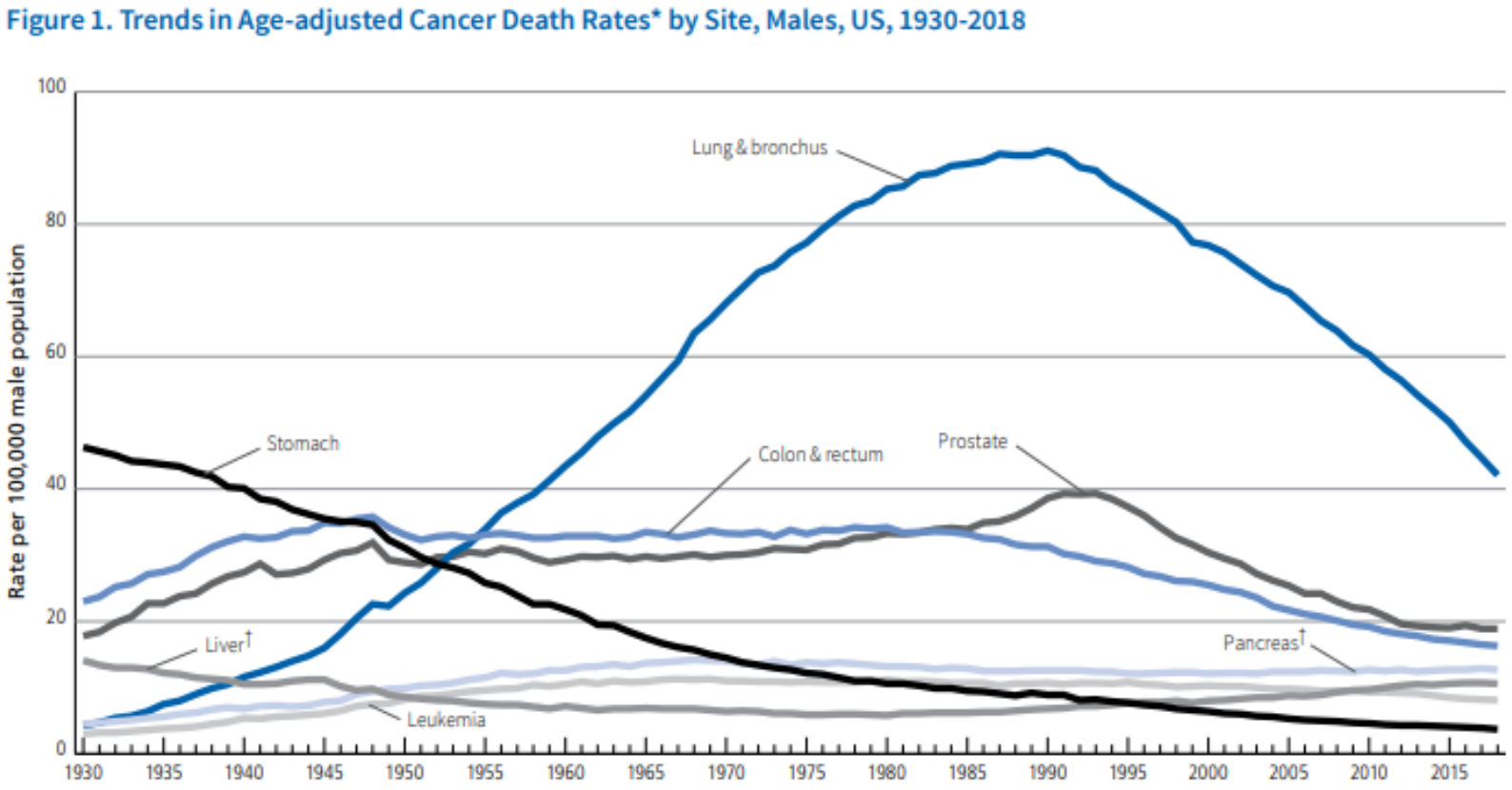
Many prostate cancers are considered low-risk disease, as they remain local, and may not require treatment

- Low risk means:
  - Not likely to give symptoms or impact mortality in 20+ years

Local intermediate to high-risk disease are more likely to progress to symptomatic or metastatic disease

- Likely to have symptoms within 10 years
- May progress to death within 15 years

Trends in Death Rates Among Males for Selected Cancers, United States, 1930 to 2018[3]



American Cancer Society. (2021). *Cancer Facts and Figures 2021*. Atlanta, GA: American Cancer Society.

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Background

The May 2012 USPSTF recommendations for screening for prostate cancer recommended against PSA-based screening for prostate cancer (grade D recommendation).

- Grade D: There is moderate or high certainty that the service has no net benefits or that the harms outweigh the benefits.

Effects of USPSTF Recommendations in the Media

- Forbes Article: “Is President Obama’s Prostate Gland More Important Than Yours?”
- CNN Article: Ben Stiller tested at 46, treated
- Concern for Medicare not covering Grade D ratings

Effects of USPSTF Recommendations in Practice

- Statistically significant decrease in DRE and PSA evaluations in primary care[4]
- Subjective reports from Urologists and Oncologists of seeing pre-PSA era rates of metastatic and high-grade prostate cancer
- Objective findings of a decrease in diagnosis of low-grade cancers and increases of metastatic and high-grade prostate cancer[5,6]

How did the USPSTF arrive at their recommendation?

Two Key Questions

1. Does PSA-based screening decrease prostate cancer-specific or all-cause mortality?
   - Nörrkoping Trial
   - Stockholm Trial
   - PLCO Cancer Screening Trial
   - ERSPC Trial
   - Djulbegovic Meta-Analysis
   - Cochrane Meta-Analysis

Two Key Questions

2. What are the Harms of PSA-Based Screening for Prostate Cancer?
   - PLCO Cancer Screening Trial
   - ERSPC Trial

Risks of PSA Screening

False Negatives

- PSA levels can be decreased for the following reasons:
  - Neuroendocrine (small-cell) differentiation of prostate cancer (rare)
  - Use of 5-alpha reductase inhibitors (finasteride, dutasteride)

False Positives

- PSA can be elevated for the following reasons:
  - Benign prostatic hyperplasia (BPH)
  - Prostatitis
  - Perineal trauma
  - Sexual activity
- False positives can lead to unnecessary prostate biopsies

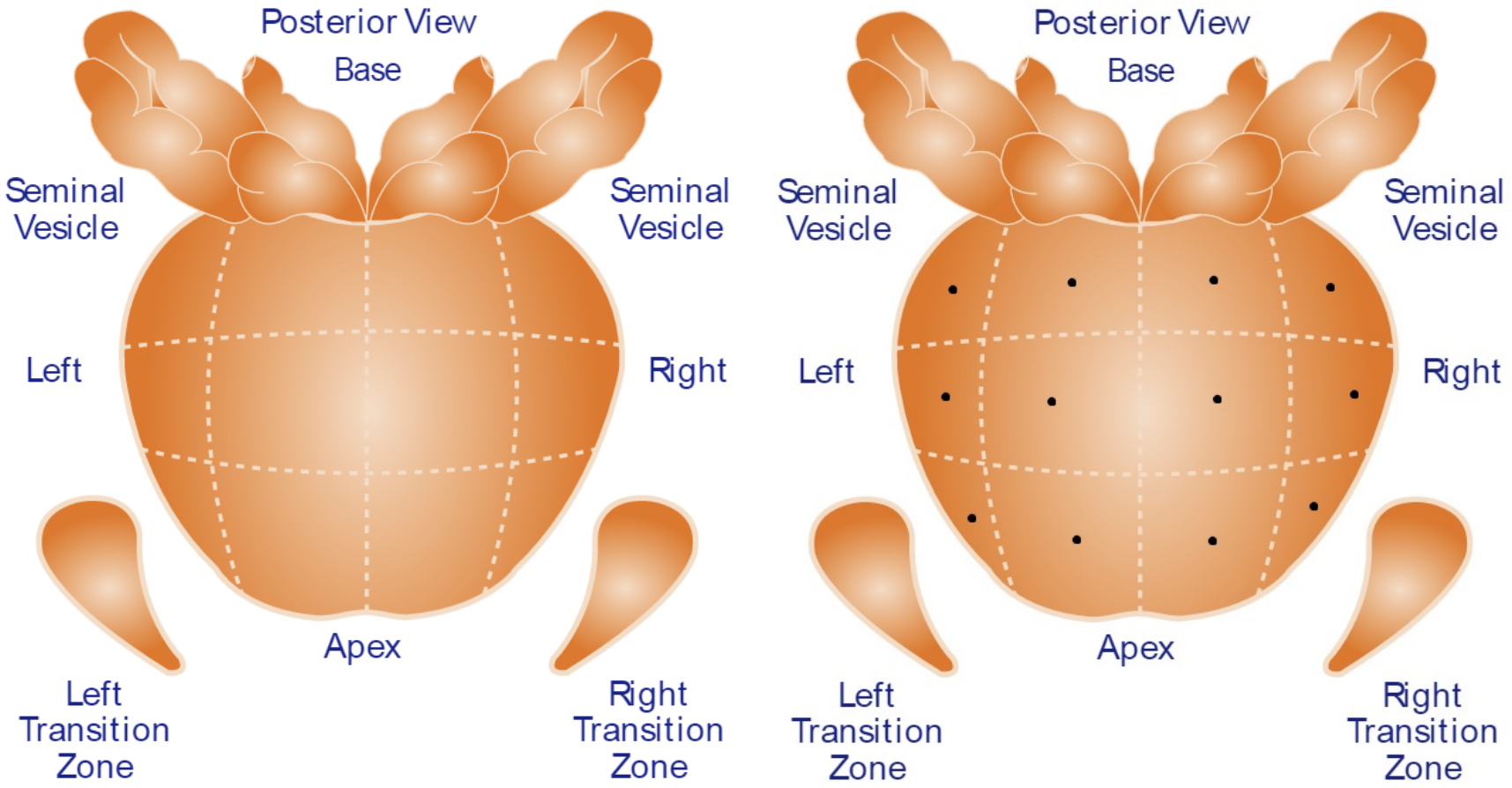
Over Treatment of Indolent Disease

Risks of Prostate Biopsy

The gold standard method of diagnosing prostate cancer is to identify the disease by prostate biopsy.

- Pain and discomfort
- Urinary retention
- Hematuria or hematospermia
- Rectal bleeding
- Infection and sepsis
  - 0.1 to 6.3 percent[7]

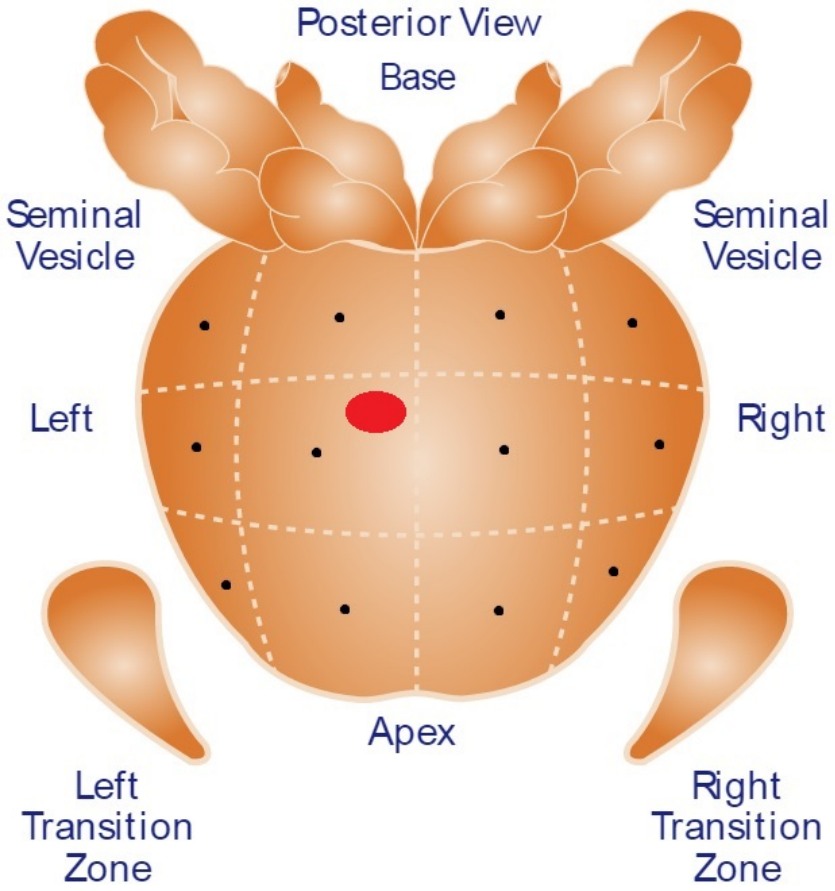
Risk of Prostate Biopsy

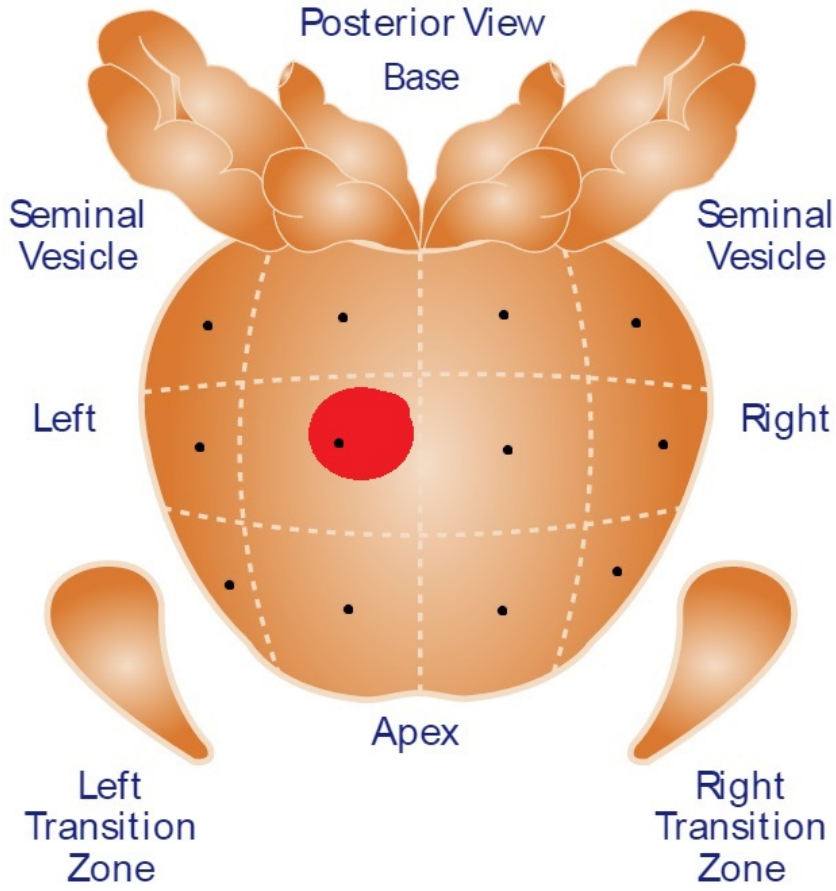


Pictures adapted from MDX Health with permission

Risk of Prostate Biopsy

False Negative





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Over Treatment of Indolent Disease

- Prostatectomy
  - Common surgical risks (complications of anesthesia, infection, etc.)
  - Incontinence
  - Erectile dysfunction
- Radiation
  - Radiation cystitis
  - Radiation colitis
  - Erectile dysfunction
  - Incontinence
  - Secondary cancers

So why was the USPSTF wrong?

Two Key Questions

1. Does PSA-based screening decrease prostate cancer-specific or all-cause mortality?

2. What are the Harms of PSA-Based Screening for Prostate Cancer?

PLCO Cancer Screening Trial

Screening Group

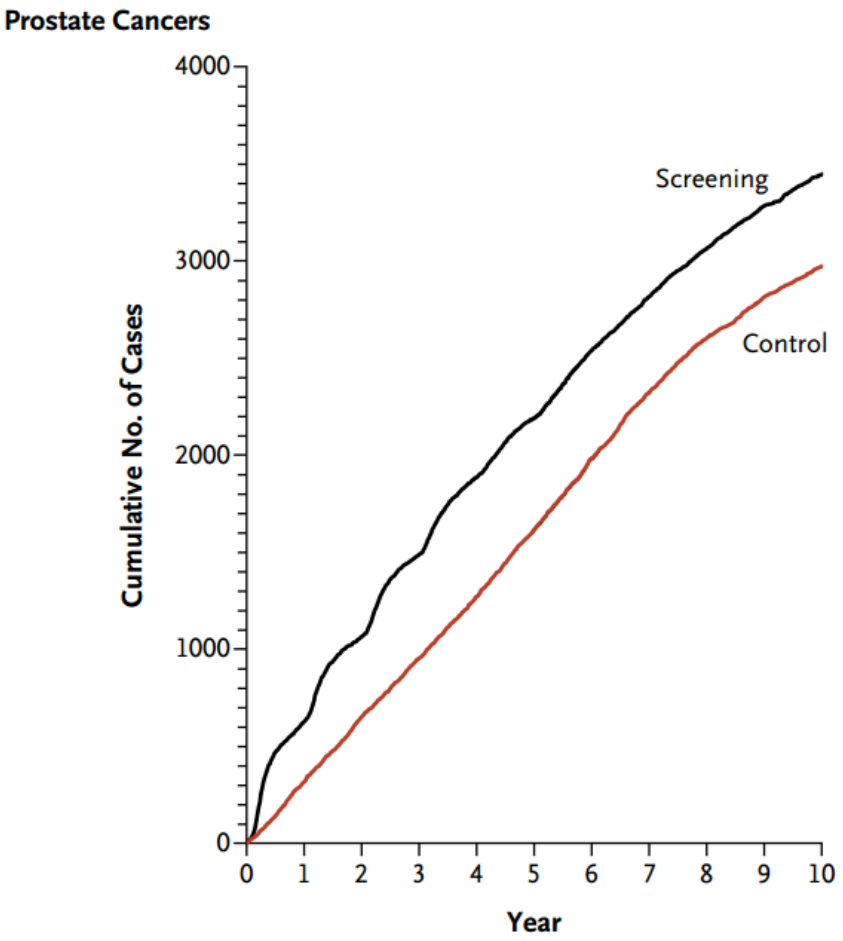
- PSA and DRE performed every year
- 38,343 subjects

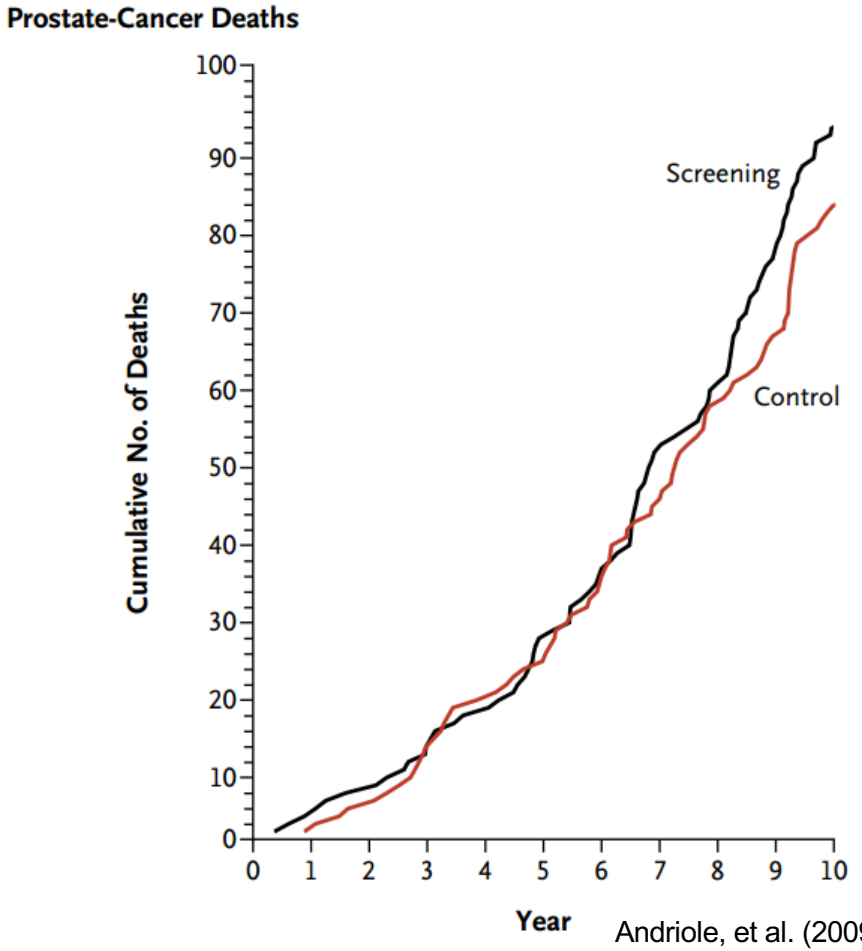
Control Group

- As per routine standard of care
  - Expectation: no PSA
  - Symptoms drive assessment and screening
- 38,350 subjects

No significant difference in demographics or characteristics at baseline.

PLCO Cancer Screening Trial





Andriole, et al. (2009).

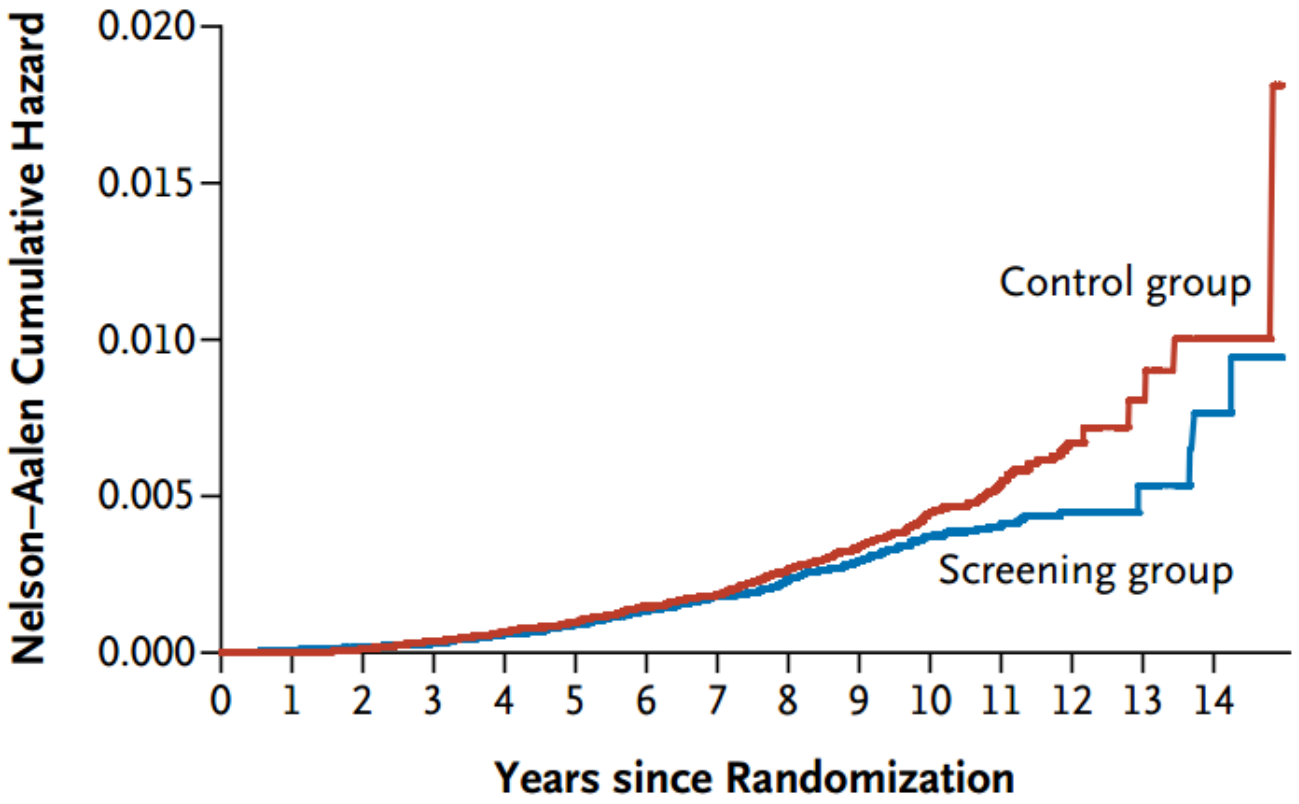
Critiques of the PLCO Trial

- High contamination
  - High rates of PSA testing performed in the control group during or before entering the trial
  - 40% in the first year of the study[9]
  - Increased to 52% by the sixth year
    - Reached as high as 80-90%[9,10]
- PSA cut-off too high (4.0 ng/mL)
- Short follow-up

ERSPC Trial

Screening Group	Control Group
• PSA performed every four years	• As per routine standard of care
• 82,816 subjects	• 99,184 subjects

ERSPC Trial



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Schröder, et al. (2009).

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ERSPC Trial Results

- Screening reduced the risk of prostate cancer death
  - HR = 0.80 [0.65-0.98], p=0.04
- 1,410 men needed to be screened to prevent one prostate cancer-related death
- 48 men needed to be treated to prevent one prostate cancer-related death

Comparing PLCO and ERSPC Trials

	PLCO	ERSPC
Benefit	No mortality benefit	20% mortality benefit
N	77,000	182,000
Age	55-74	55-69
PSA threshold	4.0 ng/mL	3.0 ng/mL
PSA contamination	52%	20%
% of patients screened before study entry	44%	6%
% screen (+) pts biopsied	40%[8]	90%
Screening interval	Annually	Every 4 years

Number needed to prevent one prostate cancer death at 9 years:

- Screen 1410 men
- Treat 48 men

Updating the ERSPC Trial

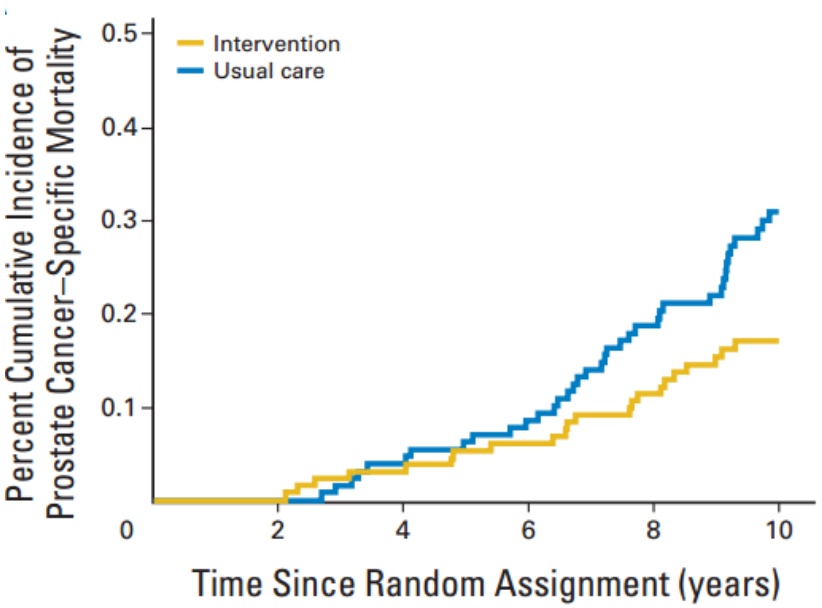
At 13 years of follow-up[13]:

- Screening continued to reduce the risk of prostate cancer death
  - HR = 0.73 [0.61-0.88], p=0.0007
- Numbers needed to prevent one prostate cancer death at 13 years:
  - Screen 781 men
  - Treat 27 men
  - Compare to initial findings of 1400 and 48

Sub-Analysis of PLCO Trial

Crawford et al. (2010)[14] re-analyzed the PLCO trial to determine whether comorbidities affect the outcomes:

- In men without major comorbidities, being assigned to the intervention group of the PLCO trial showed a significant decrease in the risk of prostate cancer specific mortality.
  - HR 0.56 [0.33-0.95], p=0.03
  - Screen 723 men
  - Treat 5 men



Two Key Questions

1. Does PSA-based screening decrease prostate cancer-specific or all-cause mortality?
   - PSA screening trials appear to show a reduction in prostate cancer death
   - Benefit likely largest in healthier men
   - Benefit increases over time

2. What are the Harms of PSA-Based Screening for Prostate Cancer?

Mitigating Risks of PSA Screening and Over-Diagnosis

Pre-Biopsy Biomarkers

- PCA3 (FDA approved)
- OPKO Diagnostics 4KScore
- Neogenomics
- PHI
- Prostarix
- SelectMDx
- Exosome DX

Post-Biopsy Biomarkers

- ConfirmMDx
- Oncotype DX
- Myriad Prolaris
- Prostate Core Mitomic Test
- Decipher

Mitigating Risks of PSA Screening and Over-Diagnosis

Role of MRI for prostate biopsy

- PROMIS study

Prophylactic antibiotics

- Pre-biopsy rectal swab and culture
- Transperineal biopsy

Better risk stratification

Over-Treatment?

Treatment options differ based on significance of disease.

- Low risk disease (a large majority of prostate cancers)
- Intermediate risk disease
- High risk disease

Treatment options change based on life expectancy.

Over-Treatment?

An emerging option for treatment of low-risk prostate cancer is Active Surveillance.[15-17]

- Routine monitoring of PSAs
- Routine DRE
- Biopsy when necessary

Active surveillance may eliminate or delay risks of treatment

Over-Treatment?

Local therapies

- HIFU
- Cryotherapy

Prostatectomy and Radiation Therapy reserved for more aggressive cancers

- Risk for direct complications of therapy are likely clinician-specific

Two Key Questions

1. Does PSA-based screening decrease prostate cancer-specific or all-cause mortality?
   - PSA screening trials appear to show a reduction in prostate cancer death
   - Benefit likely largest in healthier men
   - Benefit increases over time

2. What are the Harms of PSA-Based Screening for Prostate Cancer?
   - Newer tests may clarify risk for prostate cancer prior to biopsy
   - Over-diagnosis does not necessarily equate to over-treatment

American Urological Association Guidelines[18]

The panel evaluated the early detection of prostate cancer in average risk men by age, recognizing that the harm-benefit ratio is highly age-dependent.

- <40 years
- 40-54 years
- 55-69 years
- 70+ years

American Urological Association Guidelines

- Recommend against PSA-based screening of men under age 40 years
  - In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating a benefit for screening, and likely the same harms of screening as in other age groups
- Routine screening is not recommended in men between ages 40-54 years at an average risk
  - Low prevalence of fatal prostate cancer, long lead times, and extended time at risk for harm from treatment, all may lead to greater harm than benefit

American Urological Association Guidelines

- For men younger than age 55 years at higher than average risk, decisions regarding prostate cancer screening should be individualized based on personal preferences, and an informed discussion regarding the uncertainty of benefit and the harms of screening should take place prior to any decisions
  - African American
  - Family history of prostate cancer in first-degree relative

American Urological Association Guidelines

- Shared decision making for men age 55-69 years considering PSA testing, and proceeding based on a patient's values and preferences

- Routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared-decision making and chosen screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of benefits and reduce over diagnosis and false positives

American Urological Association Guidelines

- Do not routinely test men older than 70 years, or in any patients with less than a 10-15 year life expectancy
  - Some men over age 70 years who are in excellent health may benefit from prostate cancer screening
- For older men who have chosen screening:
  - Higher PSA thresholds (10.0 ng/mL)
  - Discontinue screening in men with lower PSA levels (less than 3.0 ng/mL)

Other Guidelines

The American Cancer Society is supportive of shared decision making, but recommend screening beginning at 50 years old.[19]

The American College of Preventive Medicine supports shared decision making, but does not endorse routine screening.[20]

The American College of Physicians does not recommend screening for average-risk men under the age of 50, men 70 or older, or men with a life expectancy of less than 10 to 15 years.[21]

Updated USPSTF Recommendations

In 2018, the USPSTF updated the recommendations for screening for prostate cancer in men aged 55-70 to reflect shared decision making between the patient and their provider.

- Grade C: The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences.

Shared Decision Making

- Clinician's role
  - Assessing risk of prostate cancer
  - Assessing comorbidities
  - Estimating life expectancy
  - Discussing risks of screening and possible future treatment
- Patient-centered
  - Account for patient's values

Take Home Points

- Long-term follow-up of PSA screening trials indicate that there is benefit, which increases over time
- Newer tests may identify patients at higher risk of prostate cancer, but PSA remains the best initial screening test
- Improved risk stratification may decrease over-treatment
- Weigh and discuss pros and cons of PSA screening with patients
- After shared decision making, PSA screening should be done every 2 years starting at age 50-55
  - May start younger in high-risk groups
  - Stop screening at 70 years old

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