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# Disclosures

## (Things the listener should know)

- Employed by:
    - American Cancer Society
    - Emory University
  - Consultant for:
    - Sanofi Aventis \*
    - Glaxo Smith Kline\*
    - U.S. Department of Defense
    - U.S. Department of Health and Human Services
- \* Without Compensation



# Prostate Cancer and Chemoprevention

- Pretend you are a 50 year old male and a pill exists:
  - If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
  - If you take it, it may decrease your lifetime risk of prostate cancer death by 20% from 3% to 2.4%
- Would you take this pill?



# American Cancer Society Prostate Cancer Screening Guideline

- Within the Physician-Patient relationship, men should be offered the PSA and DRE.
- The patient should be informed of the potential risks and the potential benefits of screening and diagnosis.
- Recommend against mass or community-based screening
  - Last modified in 2000 (2010?)



# Prostate Cancer

- We need to approach this issue logically and rationally
- We must realize:
  - What we know.
  - What we do not know.
  - What we believe.



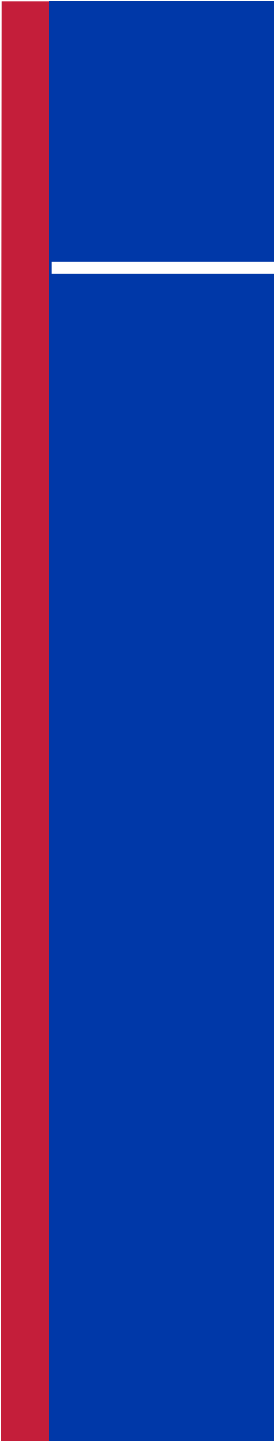
## Faith Based versus Evidence Based Medicine

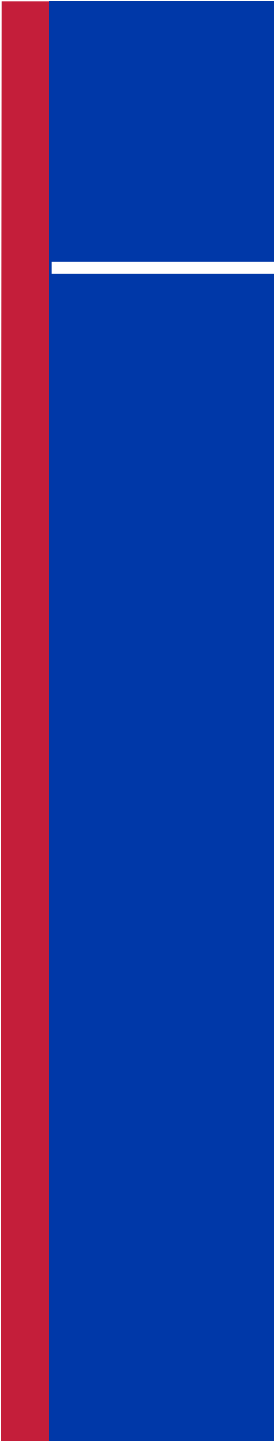
- We in medicine have a tendency to adopt things before fully accessing their benefit or harm.
- We also criticize those who question the benefit and some even praise/worship advocates with a monetary interest.
  - Bone marrow transplant for breast cancer
  - Lung cancer screening with Chest Xray
  - Neuroblastoma Screening with urine VMA
  - The Halsted Mastectomy
  - Postmenopausal hormone replacement
  - Prostate cancer screening



# Cancer Screening

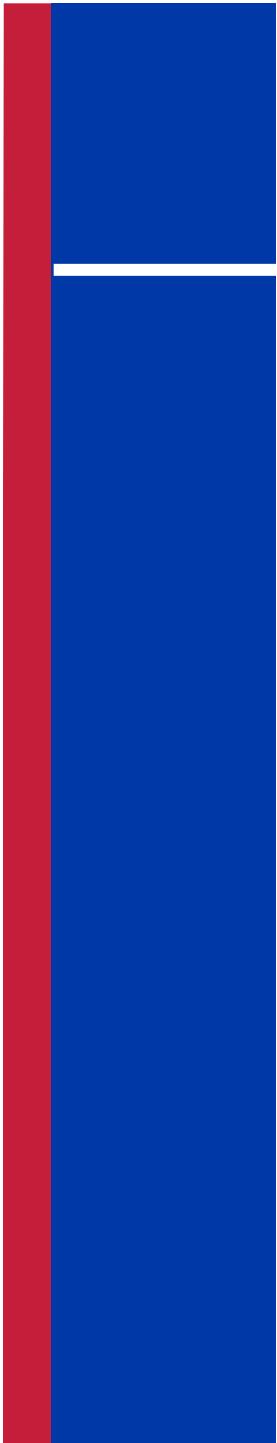
- Well designed clinical studies have demonstrated the utility of:
  - Mammography and CBE for Breast Cancer
  - Stool Blood Testing, Sigmoidoscopy and Colonoscopy for Colorectal Cancer
  - Pap and HPV testing for Cervical Cancer

- 
- Principles of Screening
  - Advanced Epidemiology
  - A Public Health Intervention

- 
- Finding disease is not a measure of success in screening

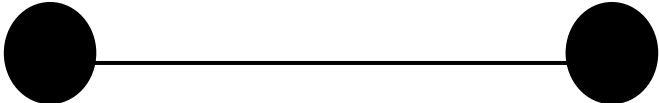
Increased survival is not a legitimate measure of success outside of a randomized clinical trial

Reduction of mortality is the proof of effective screening



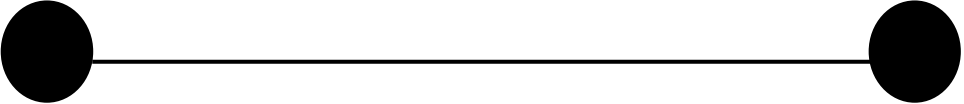
# Lead Time Bias

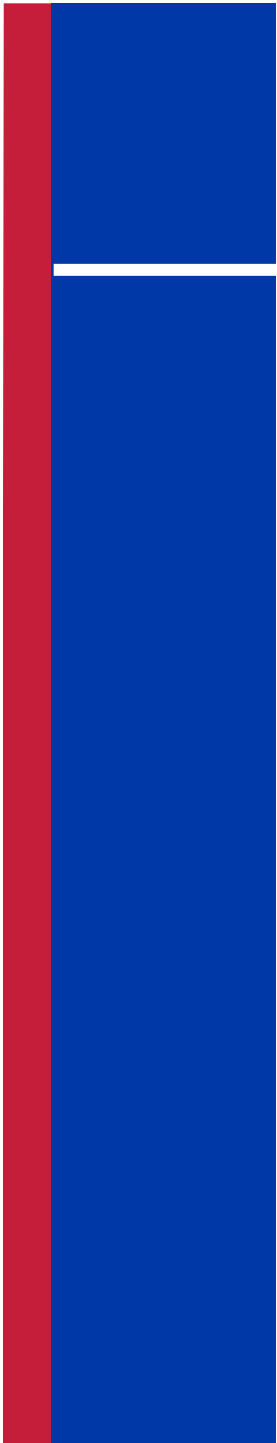
Diagnosis due to symptoms



Death due to Cancer

Diagnosis due to screening





# Length Bias

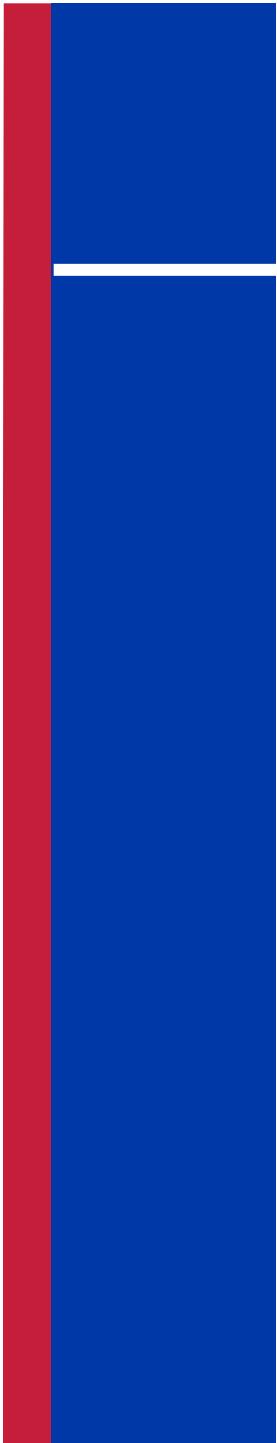


Cancer diagnosed in between scheduled screens is more aggressive than those diagnosed at scheduled screenings. Those diagnosed at initial screening are least aggressive of all.



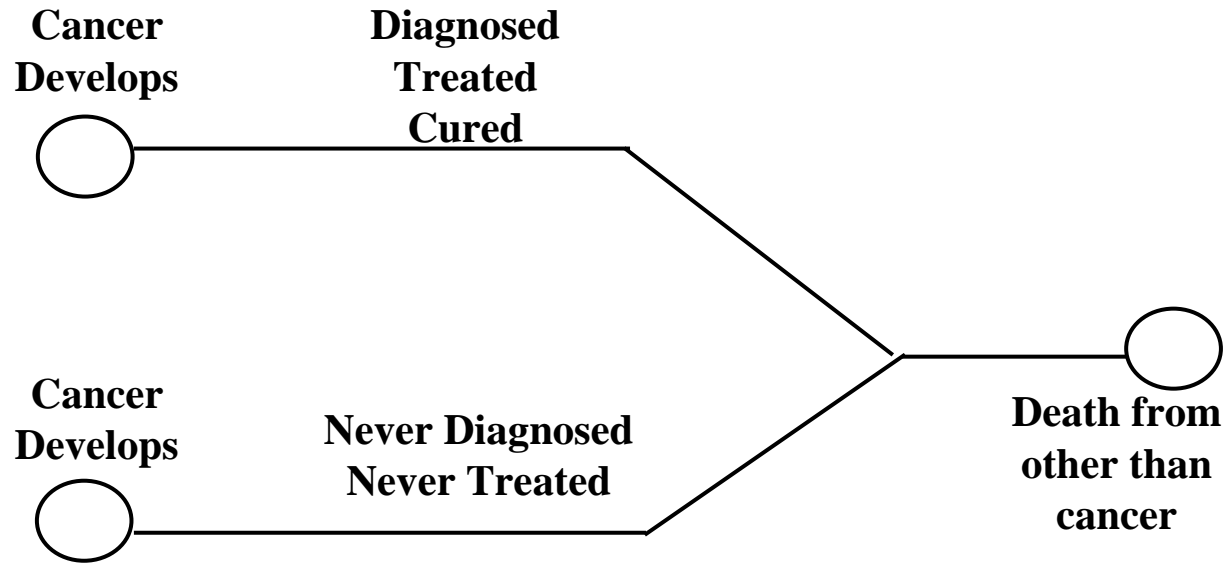
# Principles of Screening

- Screening is less effective in more aggressive cancers
- Those with comorbid diseases are less likely to benefit from screening because of competing causes of death



# Over-diagnosis

A form of length bias





“Those who do not appreciate history are destined to repeat it.”

Georg

Santianna



# The Lessons of Neuroblastoma

- Urine VMA screening was advocated for children in Japan and Quebec.
- Incidence rose dramatically as did surgical treatment.
- Mortality remained relatively stable.
- Over-diagnosis of neuroblastoma was realized.



# The Lessons of Lung Cancer Screening

- Chest X-ray Screening found disease:
  - at more favorable stage
  - increased survival
  - increased incidence of lung cancer



# The Lessons of Lung Cancer Screening

- In randomized trials the death rate from lung cancer and lung cancer diagnostic procedures was:
  - 3.4 per 1000 per year among those screened annually for ten or more years
  - 2.8 per 1000 per year in the control group



# The Lessons of Lung Cancer Screening

The completion of these randomized trials begun in the 1950's was delayed until well into the 1970's because so many people were certain that screening was superior.

Spiral CT screening is undergoing a similar experience in this decade



# Prostate Cancer Screening

- PSA discovered in 1970's
- PSA as a test shown to be a measure of disease in 1980's
- PSA shown to be associated with early detection in late 1980's
- Late 1980's -Failure to define the questions associated with early detection leads to a failure to address the questions.



# Principles of Screening

- Finding disease is not a measure of success in screening

Increased survival is not a legitimate measure of success outside of a randomized clinical trial

Reduction of mortality in a randomized trial is the only true proof of effective screening



# Principles of Screening

- Overdiagnosis is:
  - A form of Length Bias
  - The concept that there are cancers which fulfill the histologic definition of cancer but the tumor is of no risk to that specific patient.
  - The tumor will not cause death because of the seriousness of competing illnesses or the lack of aggressiveness of the prostate cancer



# The Kinds of Prostate Cancer

- Cure is possible, but not necessary
  - Proven to exist
- Cure is necessary, but not possible
  - Proven to exist
- Cure is necessary and possible
  - Hopefully exists (subject of study)



# Prostate Cancer Screening Studies

- Quebec Study (Canadian) 1998
- Norrkoping (Sweden) 2004
- PLCO (American) 2009
- ERSPC (European) 2009



# Prostate Cancer Screening Studies

- Quebec randomized study 16% excess deaths in the screening group
- Norrkoping (Sweden) study 4% excess deaths in the screening group
- PLCO (American) study 13% excess deaths in the screening group



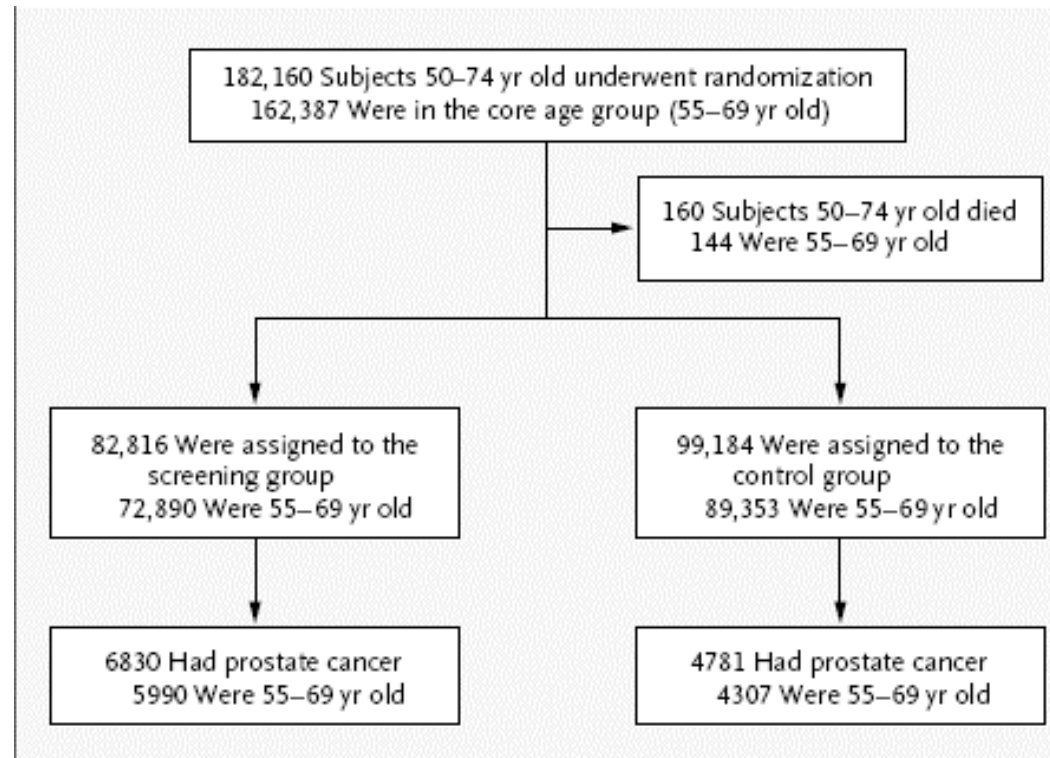
## Prostate Cancer 2009

Two prospective screening trials reported

- A European study showed a small improvement in mortality with weak statistical significance
- The American trial did not find that screening saved lives (actually found a slightly higher death rate among the screened)
- Both studies found significant overdiagnosis (unnecessary treatment). The European study reported 48 treated for every life saved.

# Screening and Prostate-Cancer Mortality in a Randomized European Study

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D.,



## The ERSPC

- 162,000 men aged 55 to 69 randomized to screening vs routine follow-up (there was no standardized protocol)
- Began in 1991, seven countries
- Median follow-up about nine years
- Death rate 20% difference favoring screening
  - $P=.04$  (minimally statistically significant)
  - NNT 48 to 1 (overtreatment)
  - Overall death rate not reported
  - Treatment differences did exist



## Issues with ERSPC

Positive finding – 20% risk reduction of prostate cancer death.

Those in the screened arms had different treatment patterns than those in the control arms

To prevent one prostate cancer death:

- Screen 1410 men
- Treat 48 men

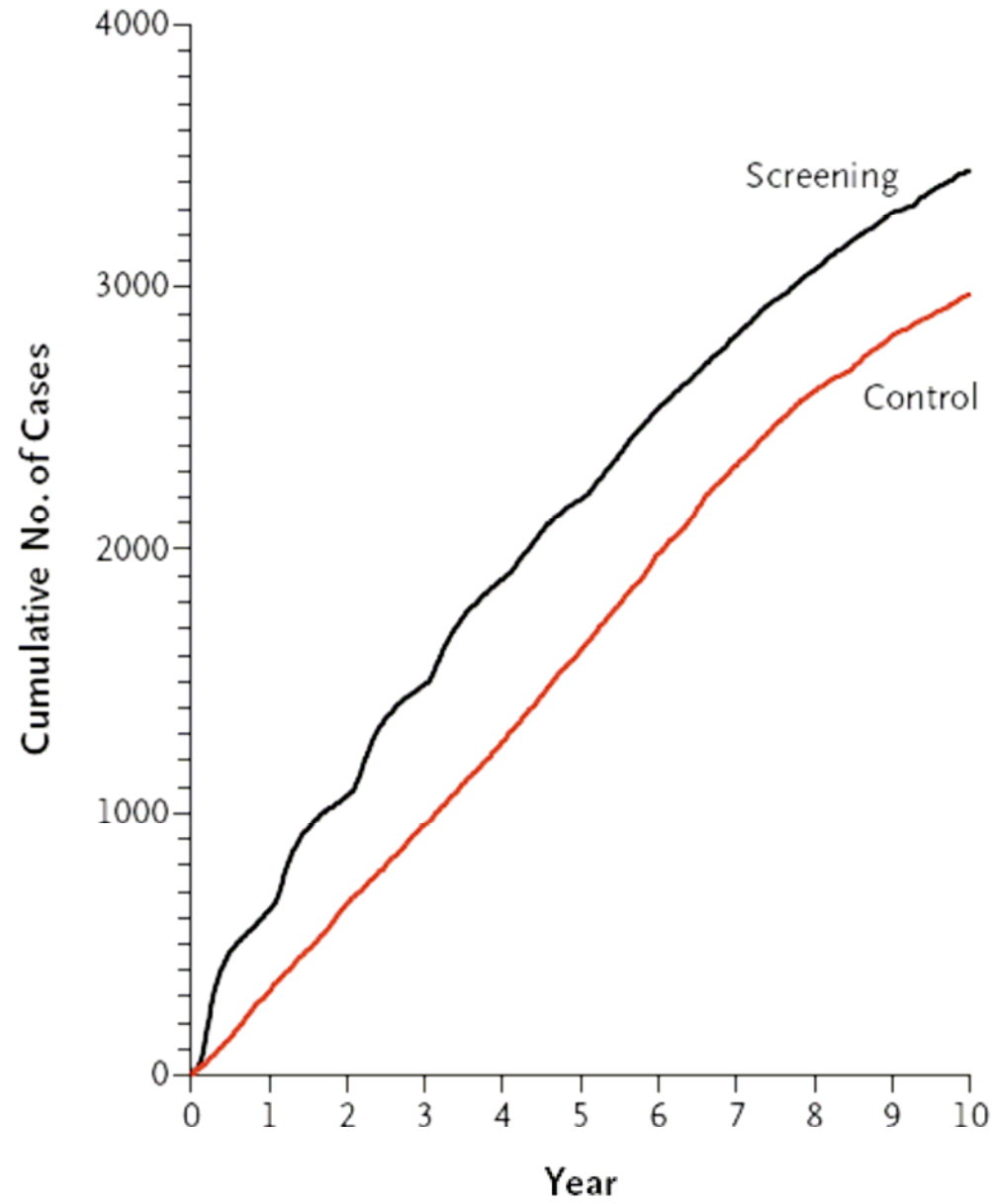
Is the study negative or positive?



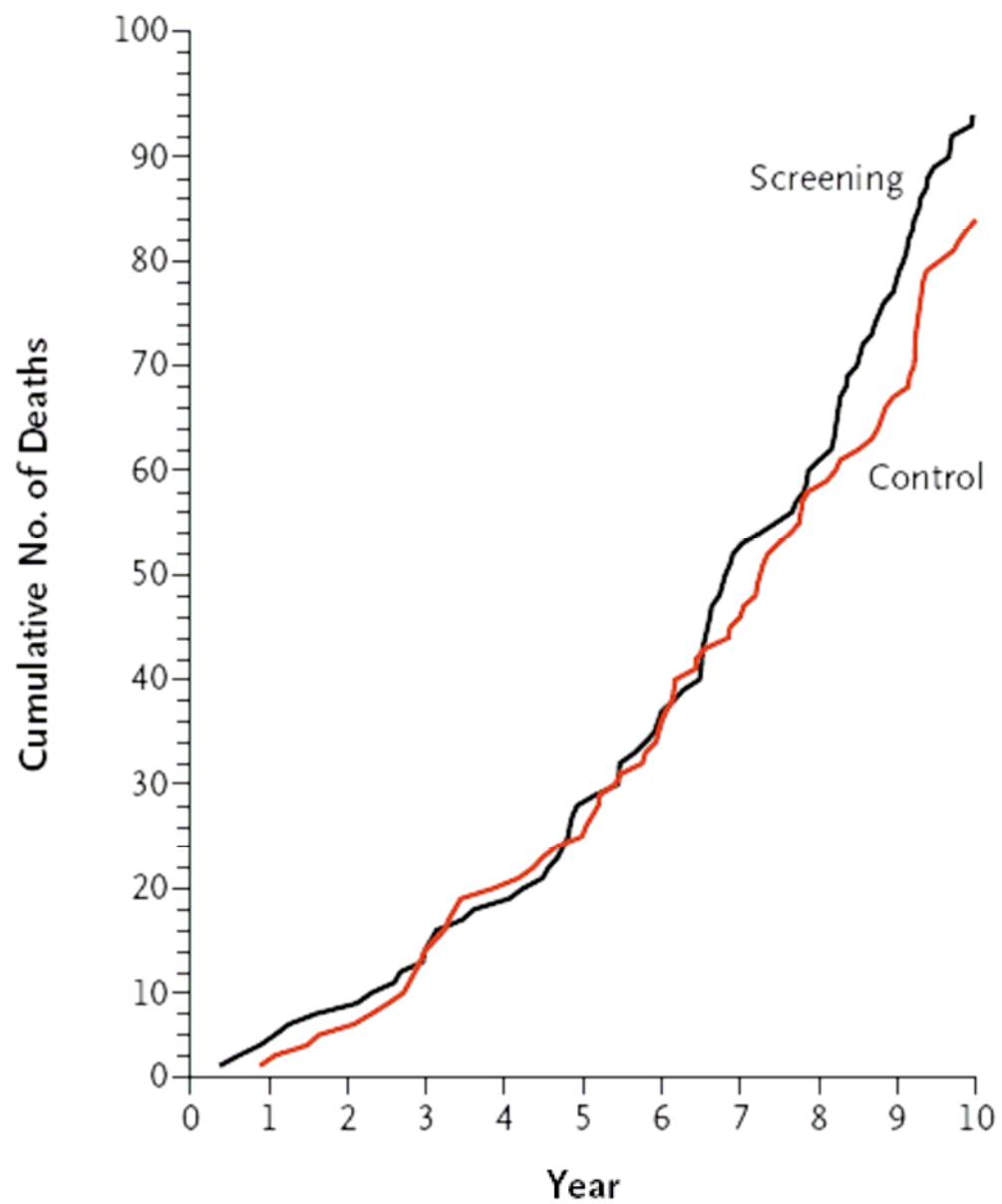
## The PLCO

- 73,000 men aged 55 to 74 randomized to screening annually vs routine follow-up
- Began in 1993, ten U.S. Centers
- Median follow-up about ten years
- Death rates not statistically significant
  - Prostate cancer and
  - Overall death rate (higher in screened)

**A Prostate Cancers**



## B Prostate-Cancer Deaths





## PLCO Issues

As high as a 52% contamination rate.

Less than 50% of those with positive screen had prostate biopsy.



## PCPT (the placebo arm)

- Median age 62 with PSA less than 3.0 and screened annually for seven years.
- 14% diagnosed with cancer due to screening during the seven years.
- 14% diagnosed with cancer on terminal biopsy done per protocol among those with a “normal screen” for seven years.

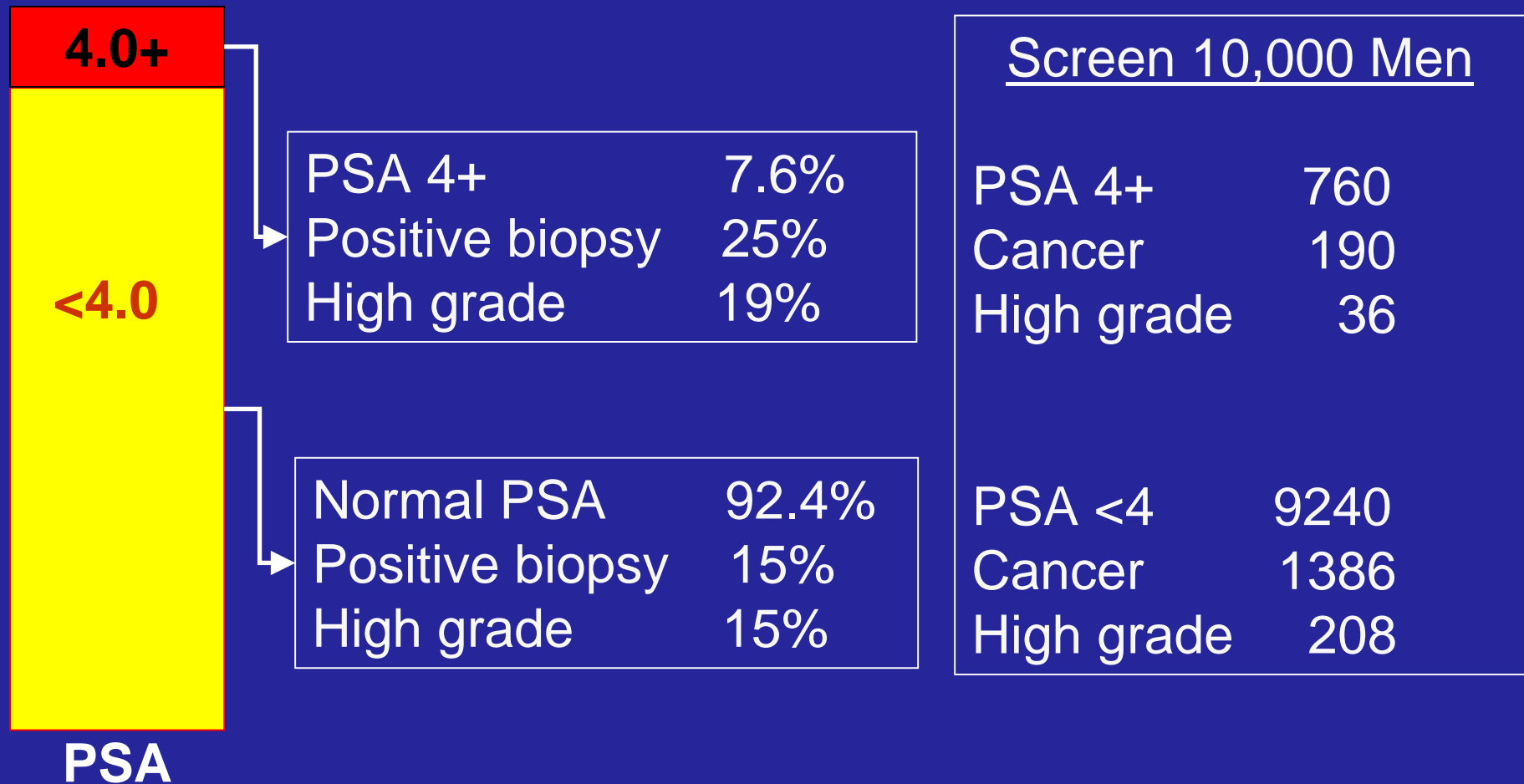


## PCPT (the placebo arm)

- A total of 28% of men median age 69 diagnosed with prostate cancer.
- PSA screening missed as much disease as it found.
- There was overdiagnosis as it is estimated that 3% of this population will die of the disease.

# Population Screening with PSA

## True Outcomes



# The Prostate Cancer Prevention Trial

- **Changing PSA Cutoffs from the traditional 4.0 ng/ml**
  - There is no clear cutpoint between normal and abnormal
  - PCPT suggests a cutoff of 1.1 ng/ml would miss 17% of cancers
    - Thompson et al, JAMA 294:66, 2005
    - Stamey et al, J RoI 167:103, 2002



# Unanswered Questions in Prostate Cancer Medicine

- In quiescent metastatic disease, does early use of hormonal disease increase survival moreso than use of hormonal disease at the time of symptoms?
  - Increasing use of hormonal therapy for a PSA rise after prostatectomy with uncertain efficacy
  - In U.S. one in three prostate cancer patients eventually is treated with hormones
  - Increasing use of hormonal therapy for asymptomatic metastatic disease to bone with uncertain efficacy



## True FACT

- Androgen Deprivation Therapy for prostate cancer has significant side effects

	HR
– Diabetes Mellitus	1.4*
– Coronary Heart Disease	1.16*
– Myocardial Infarction	1.11*
– Sudden Cardiac Death	1.16*

\* Statistically Significant Hazard Ratio

Keating et al., JCO 2006



## True FACT

- In the CAPCURE database Androgen deprivation therapy post prostatectomy or post radiation therapy increases risk of cardiac death HR 2.6 (95% CI 1.4 to 4.7) More than 5% versus 2% in five years
  - Tsai JNCI, 2007



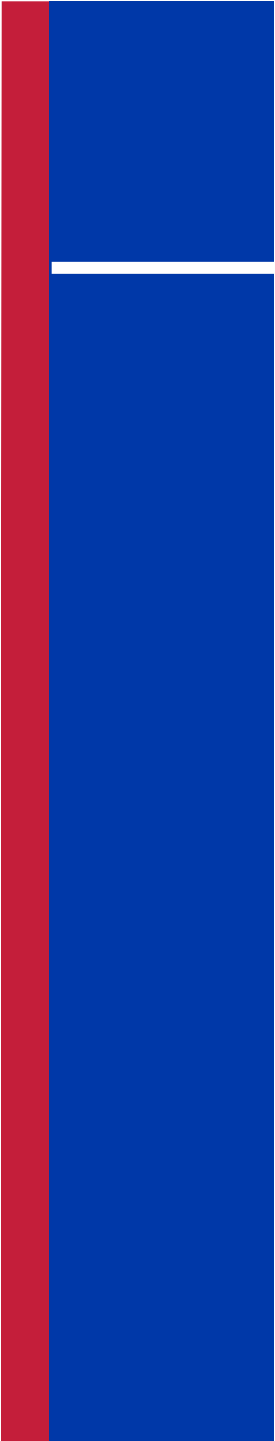
# Unanswered Questions in Prostate Cancer Medicine

- Can the decline in prostate cancer mortality be seen without screening and its inherent overdiagnosis?
- Is the decline in prostate mortality actually due to an increase in the number of men dying of cardiovascular disease due to anti-androgen therapy for prostate cancer?
- While overdiagnosis clearly exists, a small advantage to screening cannot be excluded!!!



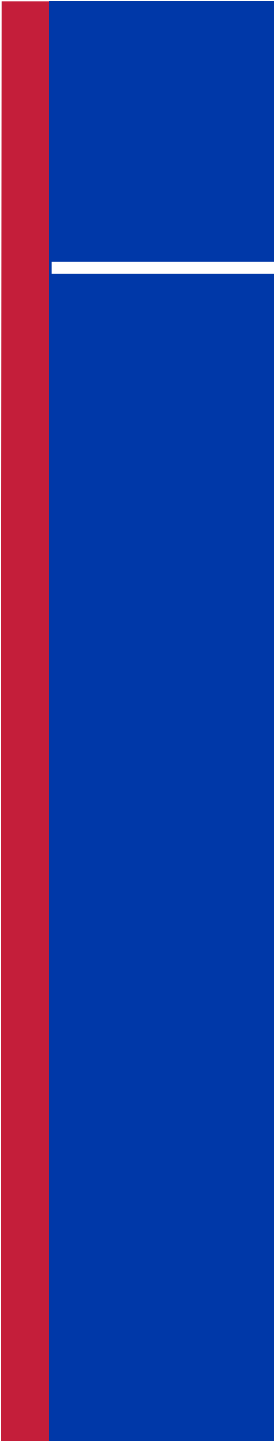
## Take Home Message

- Prostate cancer screening (within the doctor patient relationship) can be a reasonable practice
- Men should be told that its benefits are unclear
  - Some men will be diagnosed and receive unnecessary treatment
  - Some men will be diagnosed and may receive lifesaving treatment.



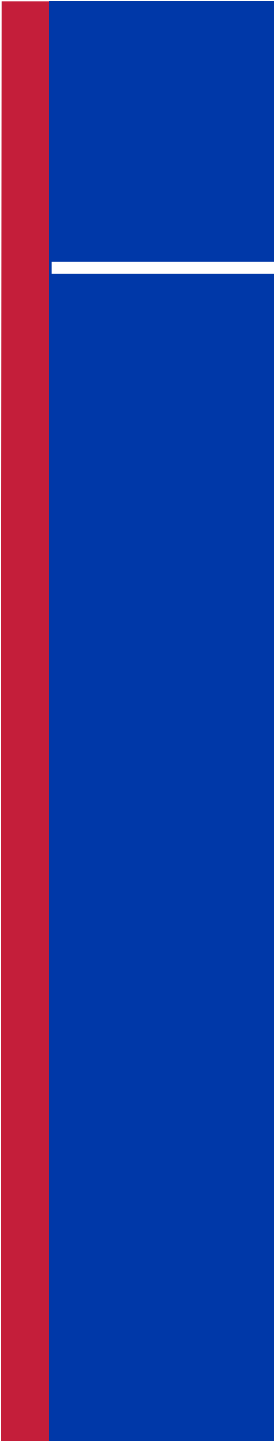
## 2010 ACS Guideline for the Early Detection of Prostate Cancer

- The American Cancer Society recommends that asymptomatic men who have at least a ten-year life expectancy have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening.



## 2010 ACS Guideline for the Early Detection of Prostate Cancer

- Men at average risk who have a life expectancy of 10 years or more should receive information about testing starting at age 50.
- Men at higher risk, i.e. African American men and men with a 1<sup>st</sup> degree relative diagnosed with prostate cancer before age 65, should receive this information at age 45
- Men at appreciably higher risk (multiple family members diagnosed with prostate cancer before age 65) should receive this information at age 40.



## 2010 ACS Guideline for the Early Detection of Prostate Cancer

- Screening should not occur without an informed decision making process
- Men should either receive this information directly from their health care providers or be referred to reliable and culturally appropriate sources.
- Patient decision aids are helpful in preparing men to make a decision whether to be tested (*examples are included in the guideline paper*)

# Summary: Core Information



## Potential Benefits

- PSA screening detects cancers earlier.
- Treating PSA-detected cancers may be more effective, but this is uncertain.
- PSA may contribute to the declining death rate but the extent is unclear

## Potential Harms

- False positives are common.
- Overdiagnosis and overtreatment are problems, but the magnitude is uncertain.
- Treatment-related side effects are fairly common.

**Bottom line: Uncertainty about degree of benefits and magnitude of harms**



## To Help Men Decide

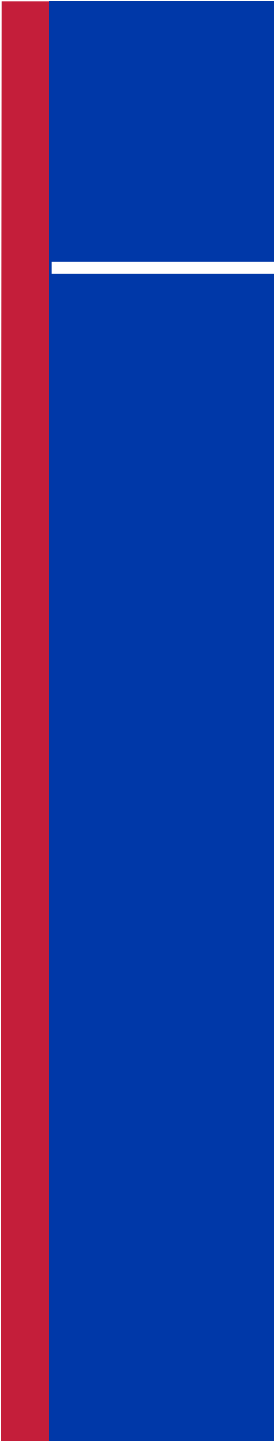
**You may wish to be tested if:**

- You value finding cancer early
- You are willing to be treated without definite benefit
- You are willing to risk urinary, sexual, or bowel injury from treating early prostate cancer

**You may *not* wish to be tested if:**

- You place a higher value on avoiding potential harms of screening & treatment, such as anxiety or injury to urinary, sexual, or bowel function

**Values clarification scenarios help to reduce “decisional conflict”**



## 2010 ACS Guideline for the Early Detection of Prostate Cancer

- The screening decision is best made in partnership with a trusted source of regular care.
- Community-based screening programs:
  - Should be limited to men with no access to a regular source of medical care
  - Must assure high-quality informed decision making
  - Must assure that participants with abnormal screening results receive appropriate counseling and follow-up care



## For Men Who Choose to be Screened

- Screening is recommended with the PSA test; DRE is now optional
- Rescreening intervals are based on the PSA result
  - $< 2.5$  ng/ml repeat screening can be safely extended to every 2 years
  - 2.5 to 3.9 ng/ml rescreen annually; individualized risk assessment
  - $\geq 4.0$  ng/ml consider referral for further evaluation and/or biopsy



# Prostate Cancer

- We need to approach this issue logically and rationally
- We must explain to patients:
  - What we know.
  - What we do not know.
  - What we believe.



# Prostate Cancer and the U.S. Food and Drug Administration (FDA)

- PSA has never been FDA approved for screening
- PSA is FDA approved for diagnosis in symptomatic men
- PSA is FDA approved for following disease



## For Men Who Choose to be Screened

- PCPT has demonstrate finasteride 5mg per day reduces period prevalence of prostate cancer.
- Dutasteride has shown it reduces risk in men at high risk.
- Neither finasteride nor dutasteride has been FDA approved for prostate cancer prevention.



## The Challenge for Prostate Cancer Scientists

- We currently use a histologic definition of cancer that was developed by German pathologists in 1845.
- We need to be able to distinguish between the localized cancers that are destined to kill and the localized cancers that are destined to stay localized.



# Prostate Cancer and Chemoprevention

- Pretend you are a 50 year old male and a pill exists:
  - If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
  - If you take it, it may decrease your lifetime risk of prostate cancer death by 20% from 3% to 2.4%
- Would you take this pill?



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