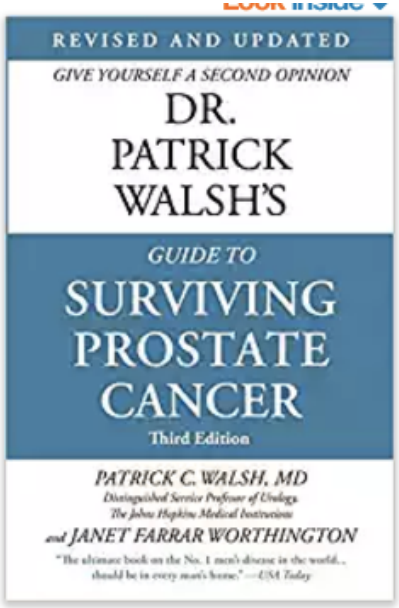
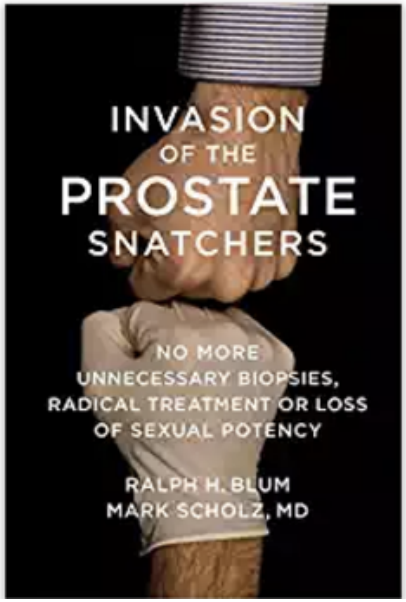
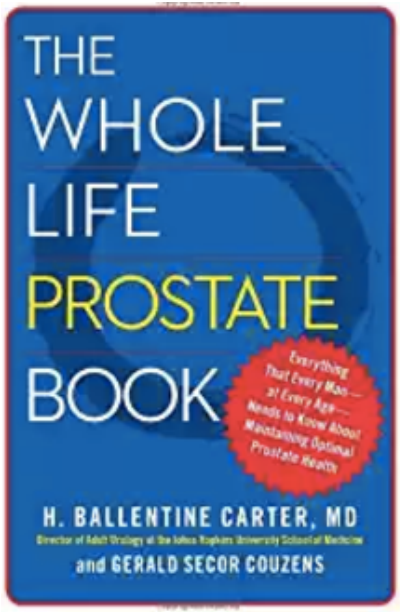

# Prostate Cancer: 2017

## Why the Controversy?

Michael S. Cookson, MD, MMHC

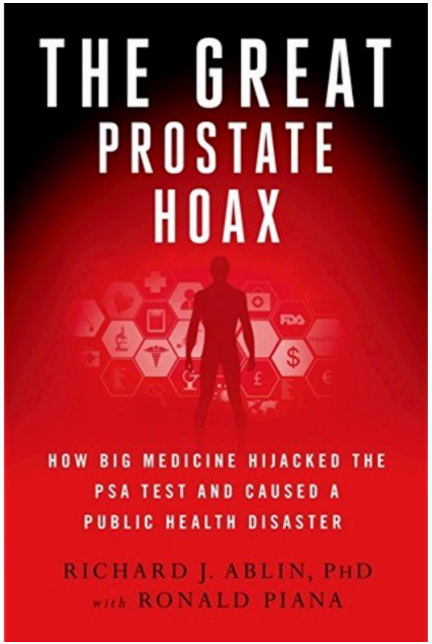



# Objectives

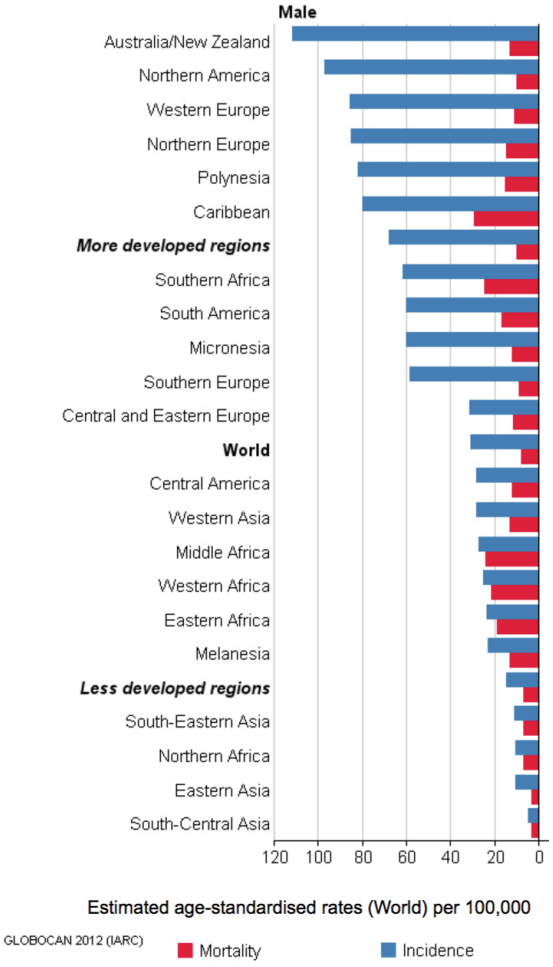
- Update the latest prostate cancer statistics
- Review data concerning PSA screening:
  - PLCO
  - ERSPC
- PSA controversy since 2012
- Latest AUA Recommendations




"*The Great Prostate Hoax* is the answer to my prayers, finally getting the message out to millions of men in jeopardy of undergoing unnecessary and debilitating treatments. *Hoax* sends a clear message that those who profit from PSA testing are doing so at the expense of countless men. A must-read."
—ALVIN COX, PROSTATE CANCER SURVIVOR WHO DEFIED
A NATIONALLY RENOWNED UROLOGIST

# Epidemiology

- Prostate cancer is a global problem
- Today we focus on the debate of prostate cancer in the US and Europe
- We often overlook the fact that prostate cancer is really a global phenomenon
- Some of the highest mortality rates found in the least developed regions of the world: Caribbean, South America, and Africa



# Epidemiology

- Prostate cancer is the most common
- 116,360 cases
- 26,150 deaths
- Now third leading cause of cancer deaths (lung and colon kill more men)

**Estimated New Cases**

| Males | | | Females | | |
|---|---|---|---|---|---|
| Prostate | 161,360 | 19% | Breast | 252,710 | 30% |
| Lung & bronchus | 116,990 | 14% | Lung & bronchus | 105,510 | 12% |
| Colon & rectum | 71,420 | 9% | Colon & rectum | 64,010 | 8% |
| Urinary bladder | 60,490 | 7% | Uterine corpus | 61,380 | 7% |
| Melanoma of the skin | 52,170 | 6% | Thyroid | 42,470 | 5% |
| Kidney & renal pelvis | 40,610 | 5% | Melanoma of the skin | 34,940 | 4% |
| Non-Hodgkin lymphoma | 40,080 | 5% | Non-Hodgkin lymphoma | 32,160 | 4% |
| Leukemia | 36,290 | 4% | Leukemia | 25,840 | 3% |
| Oral cavity & pharynx | 35,720 | 4% | Pancreas | 25,700 | 3% |
| Liver & intrahepatic bile duct | 29,200 | 3% | Kidney & renal pelvis | 23,380 | 3% |
| **All Sites** | **836,150** | **100%** | **All Sites** | **852,630** | **100%** |

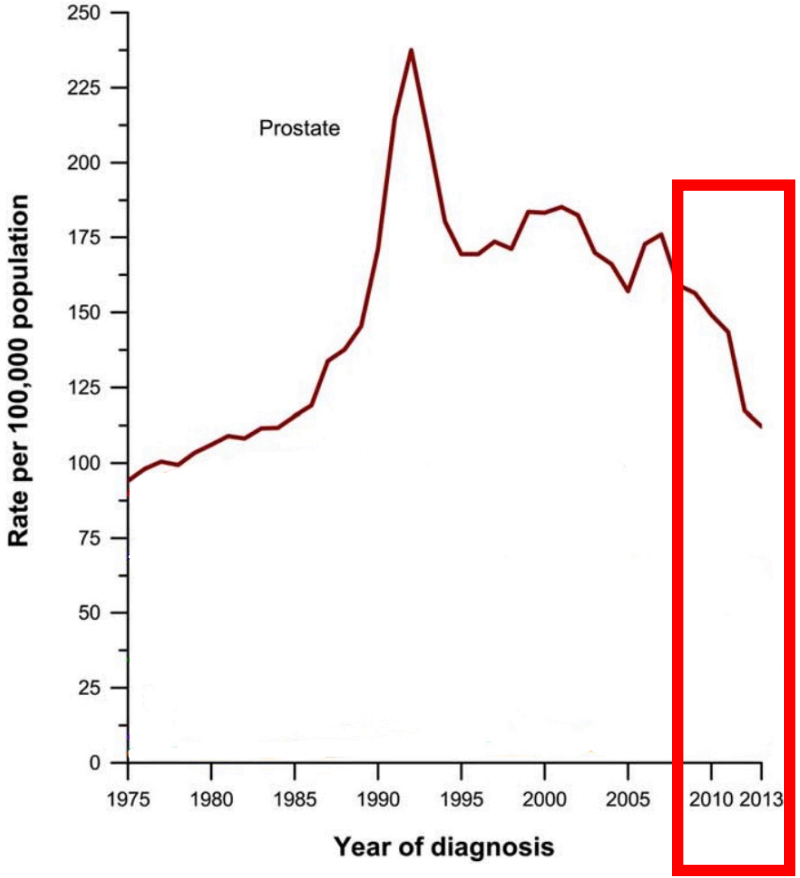
**Estimated Deaths**

| Males | | | Females | | |
|---|---|---|---|---|---|
| Lung & bronchus | 84,590 | 27% | Lung & bronchus | 71,280 | 25% |
| Colon & rectum | 27,150 | 9% | Breast | 40,610 | 14% |
| Prostate | 26,730 | 8% | Colon & rectum | 23,110 | 8% |
| Pancreas | 22,300 | 7% | Pancreas | 20,790 | 7% |
| Liver & intrahepatic bile duct | 19,610 | 6% | Ovary | 14,080 | 5% |
| Leukemia | 14,300 | 4% | Uterine corpus | 10,920 | 4% |
| Esophagus | 12,720 | 4% | Leukemia | 10,200 | 4% |
| Urinary bladder | 12,240 | 4% | Liver & intrahepatic bile duct | 9,310 | 3% |
| Non-Hodgkin lymphoma | 11,450 | 4% | Non-Hodgkin lymphoma | 8,690 | 3% |
| Brain & other nervous system | 9,620 | 3% | Brain & other nervous system | 7,080 | 3% |
| **All Sites** | **318,420** | **100%** | **All Sites** | **282,500** | **100%** |

**FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.**
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

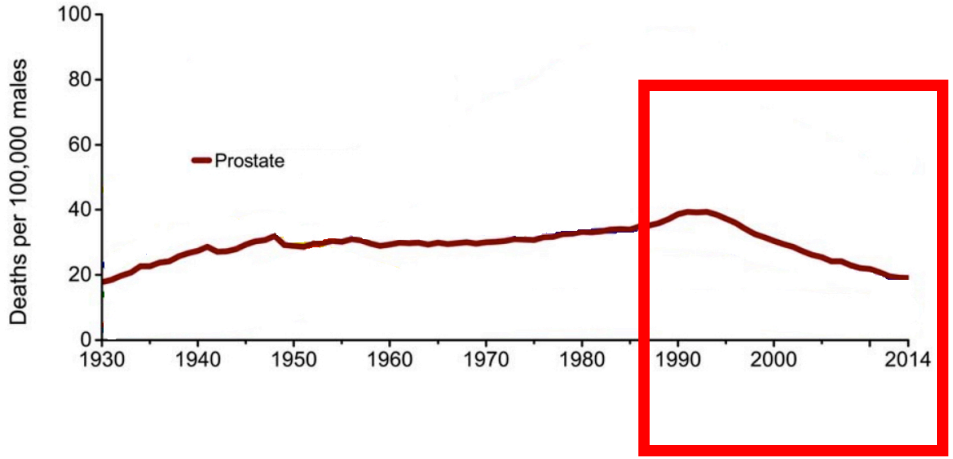
# Epidemiology

- Prostate cancer projections, 2017
  - Highest incidence among men
  - Third leading cause of cancer death in men (down from #2)
- Nevertheless, the number of men diagnosed is decreasing, compared to the 1990s



# Epidemiology

- Mortality rates are declining in the PSA era
- APC -3.4% (2005-2014)
- 10,000 lives saved




PSA
I think we should invest
in this PSA company.

# RCT's Prostate Cancer Screening

Two studies:

US – PLCO. Rigorous. Conducted in US

*Problem: PSA testing had already taken off like wildfire in the U.S.*

Europe – ERSPC – PSA testing. A*dvantage: little background PSA testing.*

*Problem: almost a meta-analysis of several different trials.*

# Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force

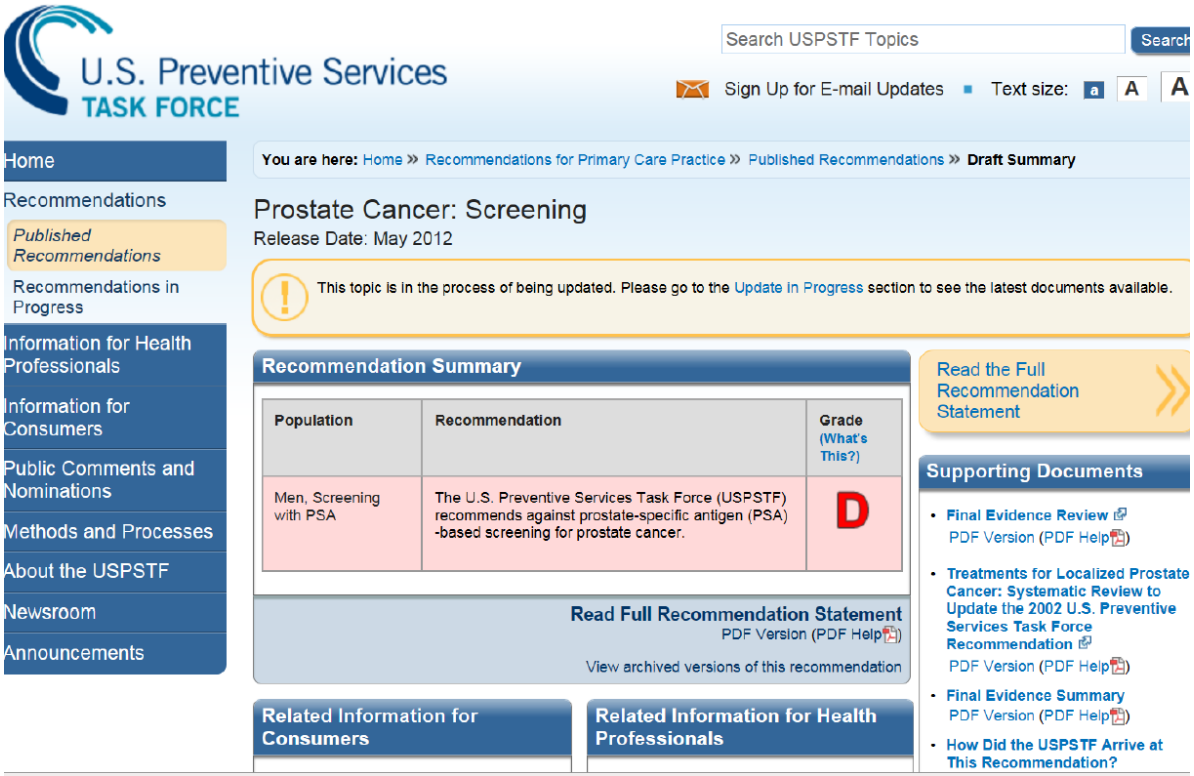
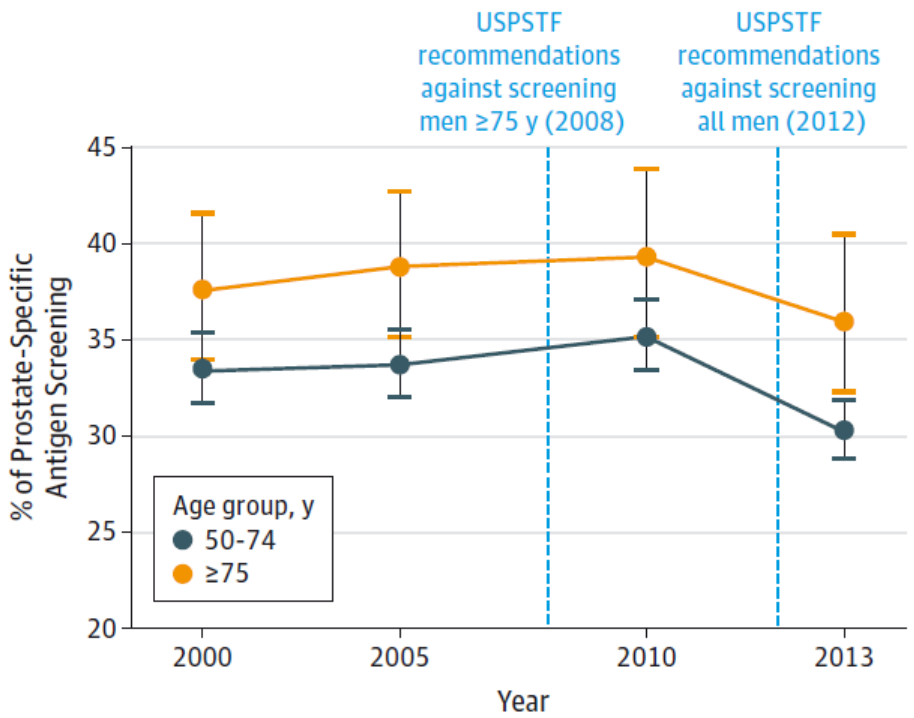
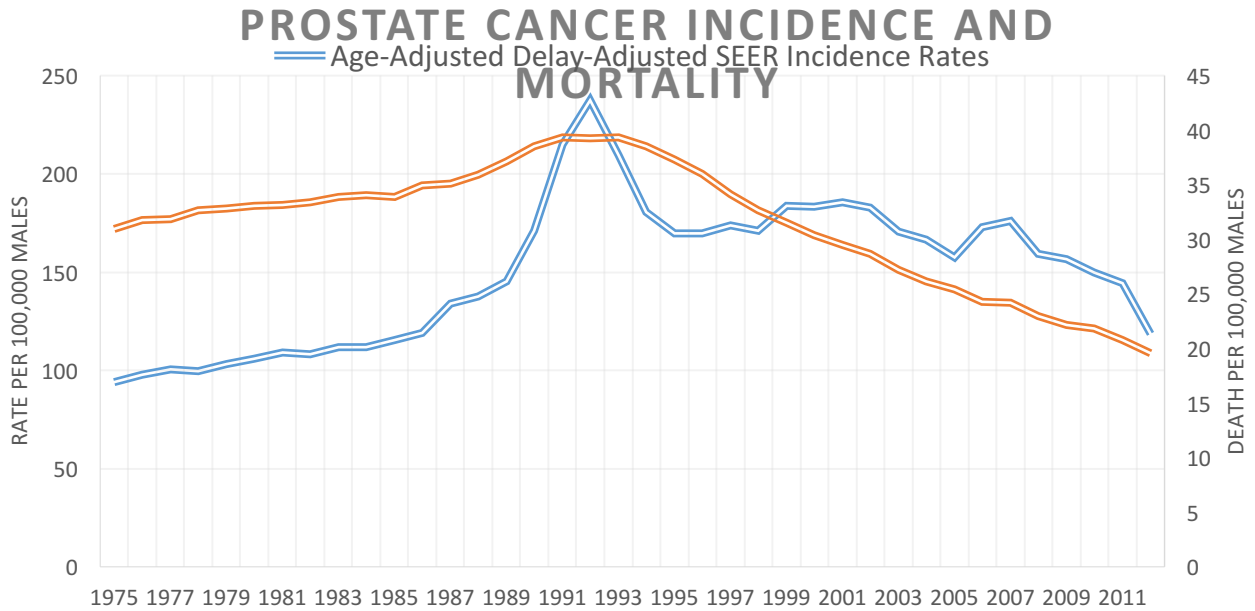


Figure. Prevalence of Prostate-Specific Antigen Screening From National Health Interview Survey (2000, 2005, 2010, and 2013)



# But, a fact:  SEER, 2015



# Screening Trials

ARTICLE

## Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

Gerald L. Andriole, E. David Crawford, Robert L. Grubb III, Saundra S. Buys, David Chia, Timothy R. Church, Mona N. Fouad, Claudine Isaacs, Paul A. Kvale, Douglas J. Reding, Joel L. Weissfeld, Lance A. Yokochi, Barbara O'Brien, Lawrence R. Ragard, Jonathan D. Clapp, Joshua M. Rathmell, Thomas L. Riley, Ann W. Hsing, Grant Izmirlian, Paul F. Pinsky, Barnett S. Kramer, Anthony B. Miller, John K. Gohagan, Philip C. Prorok; for the PLCO Project Team

The NEW ENGLAND JOURNAL of MEDICINE

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## Prostate-Cancer Mortality at 11 Years of Follow-up

Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Marcos Lujan, M.D., Hans Lilja, M.D., Marco Zappa, Ph.D., Louis J. Denis, M.D., Franz Recker, M.D., Alvaro Páez, M.D., Liisa Määttänen, Ph.D., Chris H. Bangma, M.D., Gunnar Aus, M.D., Sigrid Carlsson, M.D., Arnauld Villers, M.D., Xavier Rebillard, M.D., Theodorus van der Kwast, M.D., Paula M. Kujala, M.D., Bert G. Blijenberg, Ph.D., Ulf-Hakan Stenman, M.D., Andreas Huber, M.D., Kimmo Taari, M.D., Matti Hakama, Ph.D., Sue M. Moss, Ph.D., Harry J. de Koning, M.D., and Anssi Auvinen, M.D., for the ERSPC Investigators*

## 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*

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ORIGINAL ARTICLE

# Mortality Results from a Randomized Prostate-Cancer Screening Trial


## METHODS

From 1993 through 2001, we randomly assigned 76,693 men at 10 U.S. study centers to receive either annual screening (38,343 subjects) or usual care as the control (38,350 subjects). Men in the screening group were offered annual PSA testing for 6 years and digital rectal examination for 4 years. The subjects and health care providers received the results and decided on the type of follow-up evaluation. Usual care sometimes included screening, as some organizations have recommended. The numbers of all cancers and deaths and causes of death were ascertained.

# PLCO Design

- 1993-2001
- 77,000 men randomized to annual screening for 6 years vs. “usual care”
- Men w/ PSA WNL prior to enrollment included
- Men w/ elevated PSA prior to enrollment excluded

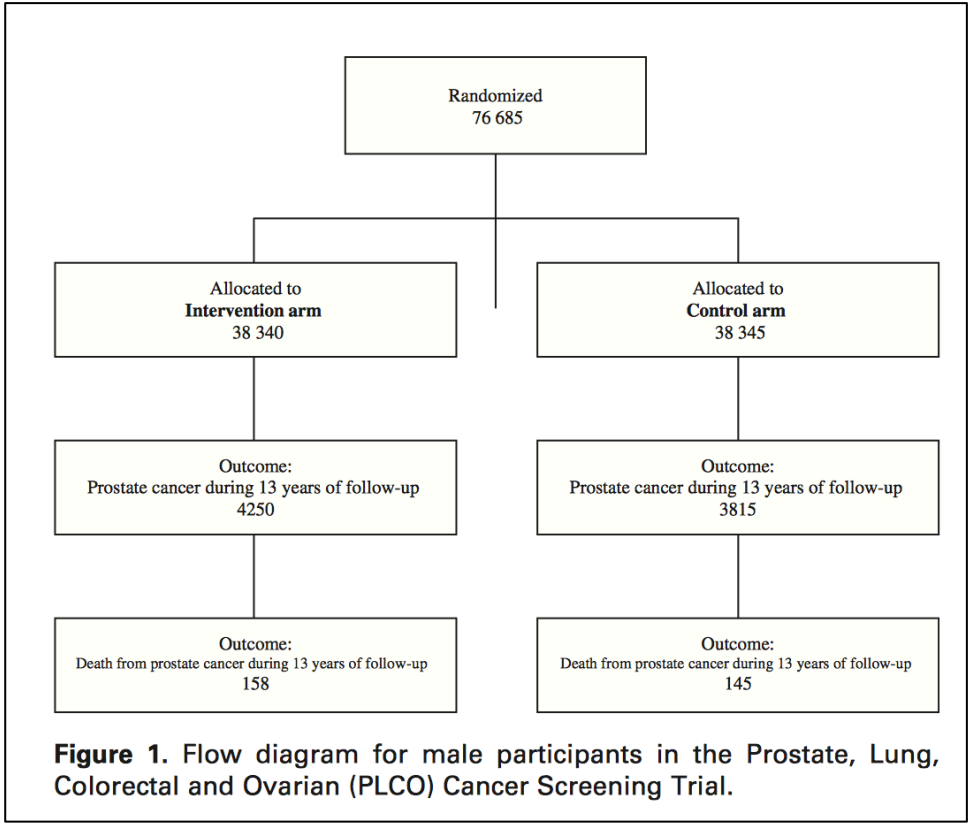
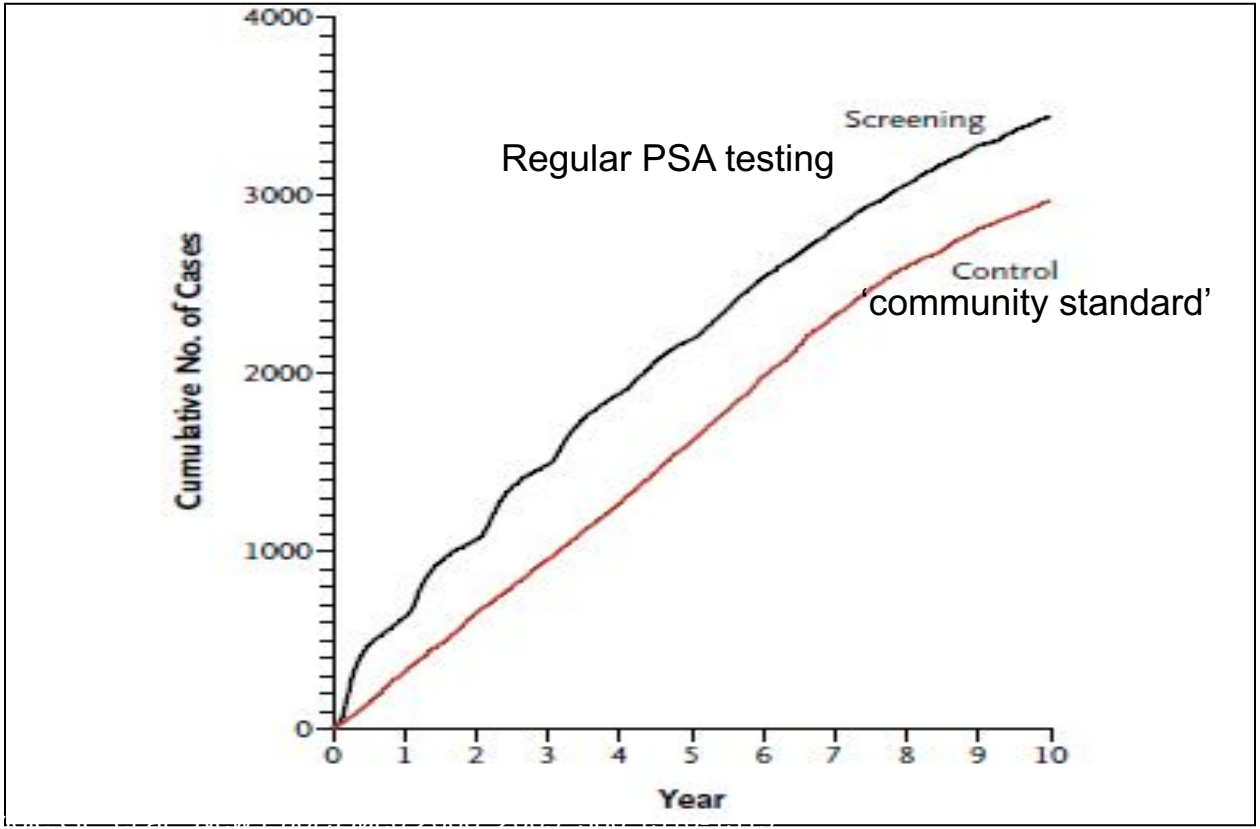
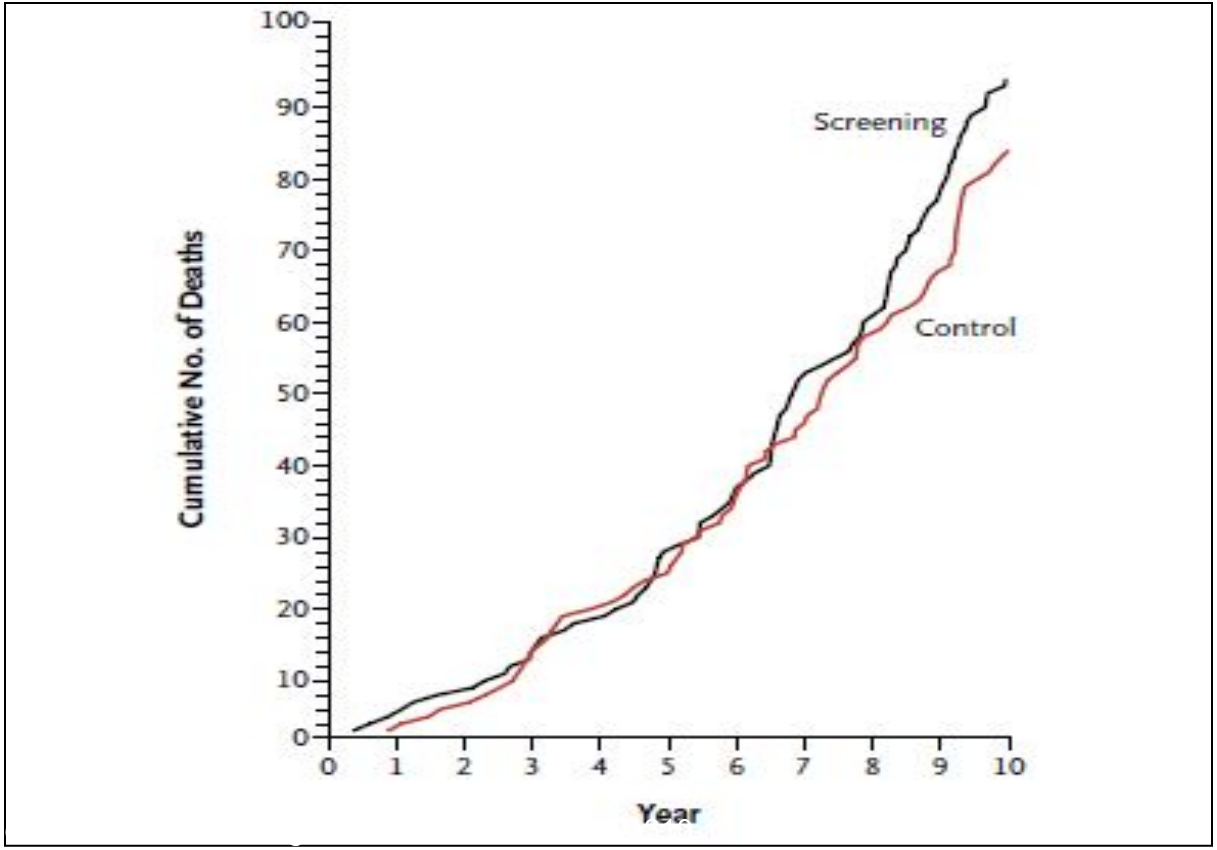



**Figure 1.** Flow diagram for male participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

# PLCO: More cancers detected



# PLCO: No reduction in deaths



# PLCO Summary

## Criticisms

- Changing definition of “usual care” in the 1990s
- 44% of participants had >/ 1 PSA prior to enrollment
- 90% contamination of “usual care” group
  - Shoag, Mittal NEJM 2016
- Biopsy rates for elevated PSA only 30-40%

## Conclusions

- PLCO is not “screening vs. no screening”
- More accurate: “annual vs. opportunistic” screening
- PLCO should not be included in analysis of screening trials
- PLCO is not evidence that screening doesn’t improve PCSM

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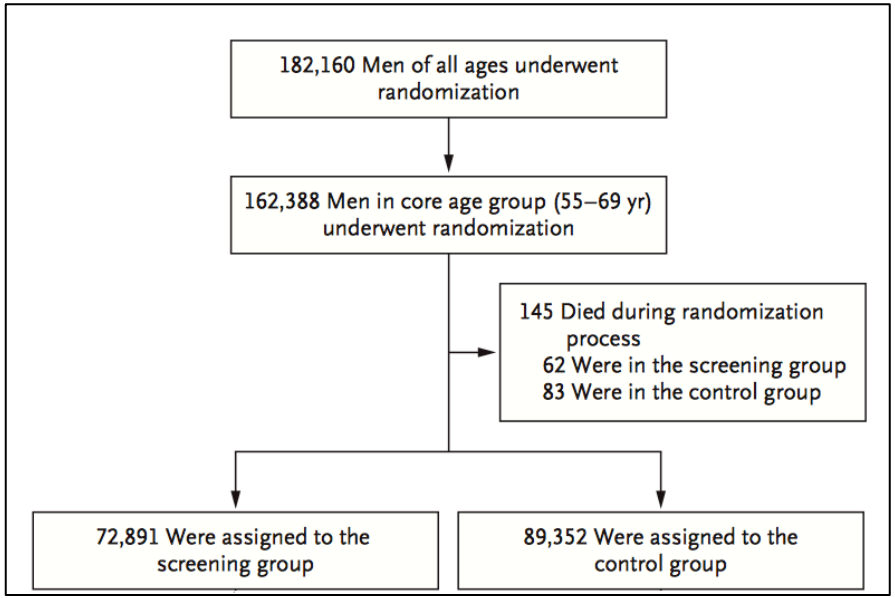
# ERSPC Design

- 1991-2003
- 182,000 men randomized
- Majority screened every 4 years
- Majority biopsied for PSA >/4
- Less contamination, larger risk profile differences between groups



# ERSPC Results

- At 9 years, 21% relative risk reduction in PCSM
- After adjustment for contamination, even higher risk reduction (29%)
- NND = 37 at 11 years follow-up

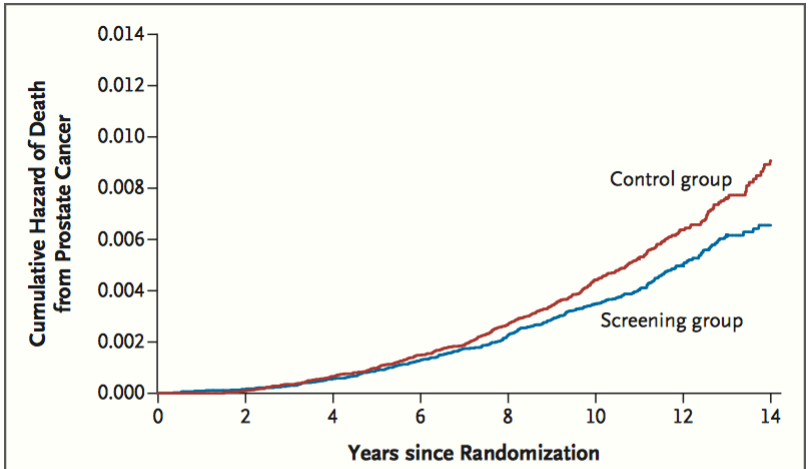



**Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.**

Values are not included for centers in France because of the short follow-up period (median, 4.6 years). The Nelson–Aalen method was used to calculate the cumulative hazard of death from prostate cancer.

# ERSPC Summary

**Criticisms**

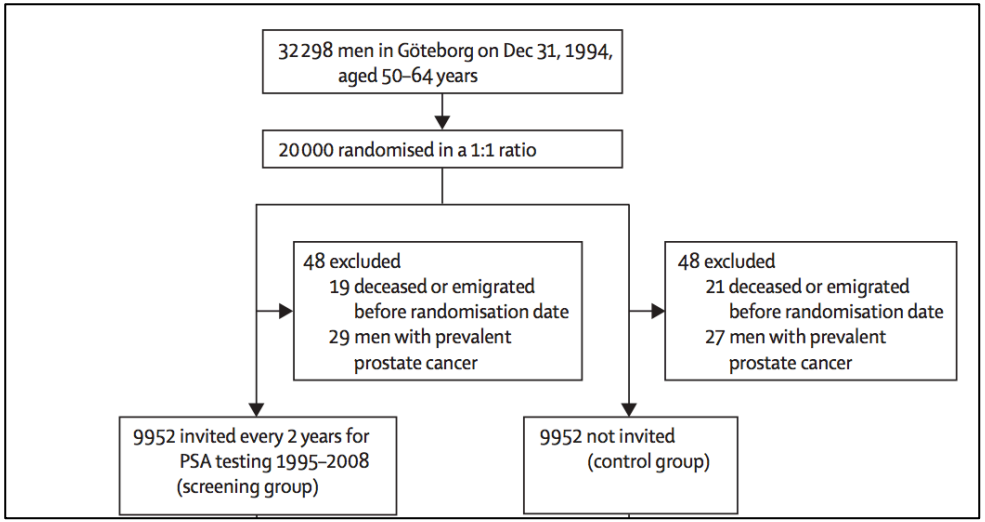
- NND at 11 years follow up is still too short to be accurate
- Predictive models with 25 years follow up show NND = 2-9

**Conclusions**

- ERSPC is an imperfect but valid study of prostate cancer screening
- The true magnitude of screening benefit is unknown because of inadequate follow-up

# Goteborg Design

- 1994-2008
- Nearly 20,000 men randomized to PSA screening every 2 years, or no screening until age 69
- Median age was 56: youngest of 3 major trials



# Goteborg Results

- 14 years of follow-up
- 44% relative risk reduction in PCSM
- NND = 12
- Diverging survival curves at the end of follow-up period

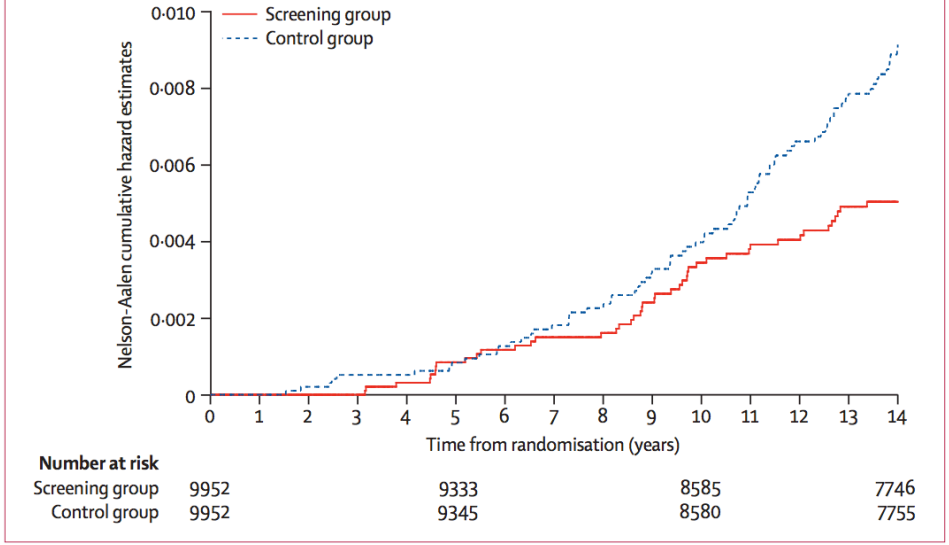



*Figure 3:* **Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates**

# Summary of RCTs in Prostate Cancer Screening

- Of the 3 major screening trials, only 2 are valid to answer the question
  - Conclusions from ERSPC and Goteborg are concordant

- Data from PLCO should not be included in the discussion
  - This is *not* controversial

- Bottom Line: PSA screening reduces prostate cancer specific mortality

# May, 2012: USPSTF Recommendations

- Outcome:
  - The USPSTF recommends against PSA-based testing for prostate cancer (Grade “D”)
- Origin of Controversy
  - Underappreciation of benefit
    - Emphasis on PLCO and ERSPC trials
    - No extrapolation of ERSPC data via modeling for NND
    - Goteborg Trial ignored

# May, 2012: USPSTF Recommendations

## Origin of Controversy

Overestimation of Harms

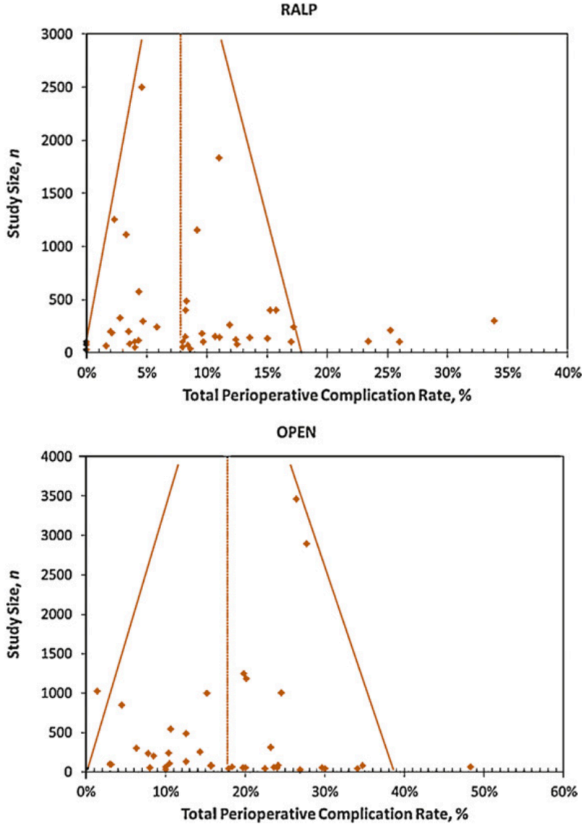
- Emphasis on false positives
- Men prefer to be designated cancer free, even if negative biopsy required.

| Screening health state | Ranked as 'best' state | Ranked as 'worst' state |
|---|---|---|
| A | 7 (4.2%) | 146 (86.9%) |
| B | 96 (57.1%) | 3 (1.8%) |
| C | 65 (38.7%) | 19 (11.3%) |

A = no cancer, no PSA test and no biopsy; B=no cancer and a favourable (negative) PSA test; C = no cancer, an unfavourable (positive) PSA test and a favourable (negative) biopsy.

# May, 2012: USPSTF Recommendations

- Origin of Controversy
  - Overestimation of Harms
    - Focus on morbidity data from treatment of prostate cancer
      - Cites 0.5% complication rate from Medicare data in open prostatectomy era
      - More contemporary data shows lower morbidity rates (<0.1%)



# May, 2012: USPSTF Recommendations

- Origin of Controversy
  - Overestimation of Harms
    - Ignores contemporary attitude that uncouples diagnosis from intervention
    - Men who enlist in active surveillance avoid operative morbidity

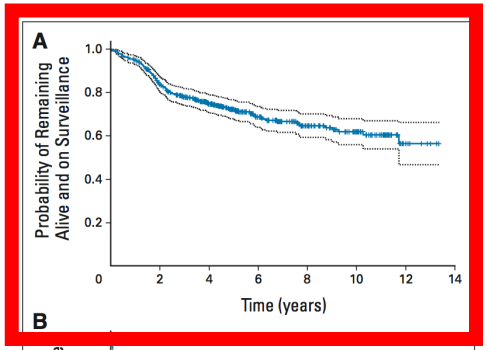



**Fig 2.** (A) Likelihood of remaining alive and on surveillance. (B) Prostate-specific antigen (PSA) failure in 117 patients treated with surgery or radiation after a period of surveillance.

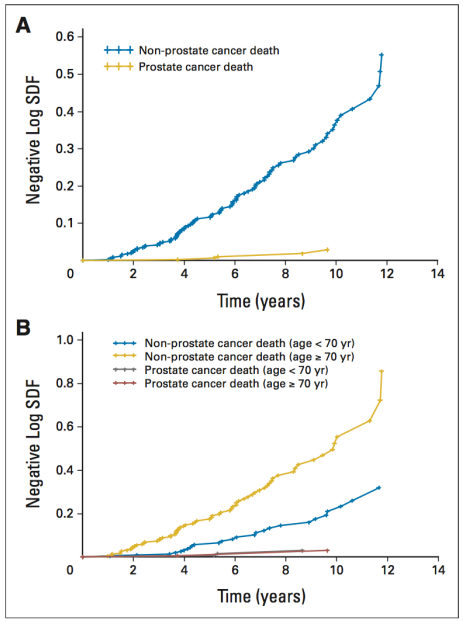
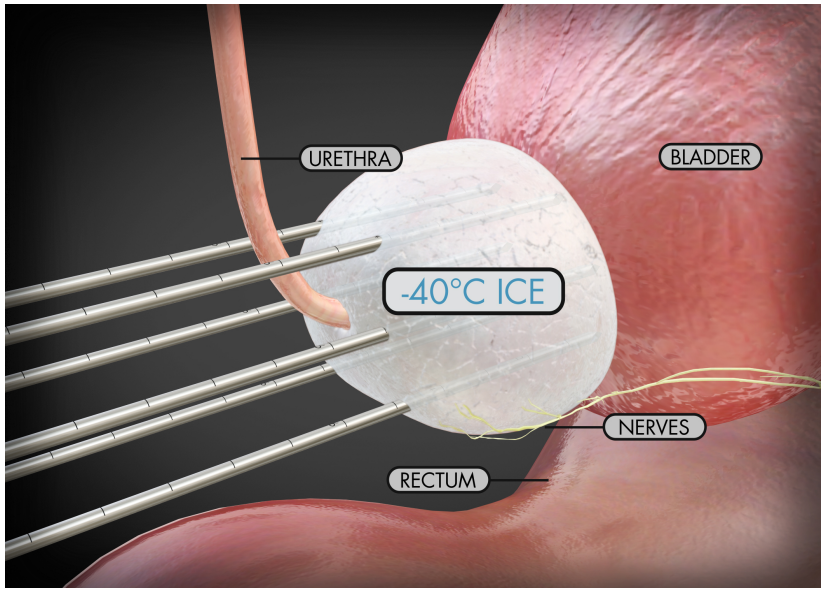



**Fig 3.** (A) Cumulative hazard ratio for non–prostate cancer to prostate cancer mortality. (B) Cumulative hazard ratio for mortality by cause and age, stratified around age 70 years.

# May, 2012: USPSTF Recommendations

- Origin of Controversy
  - Overestimation of Harms
    - Ignores contemporary attitude that uncouples diagnosis from intervention
    - Emergence of less invasive/morbid treatment options
      - Focal therapy
        - Cryo
        - HIFU
    - Numerous options reflect the heterogeneity/complexity of localized prostate cancer!

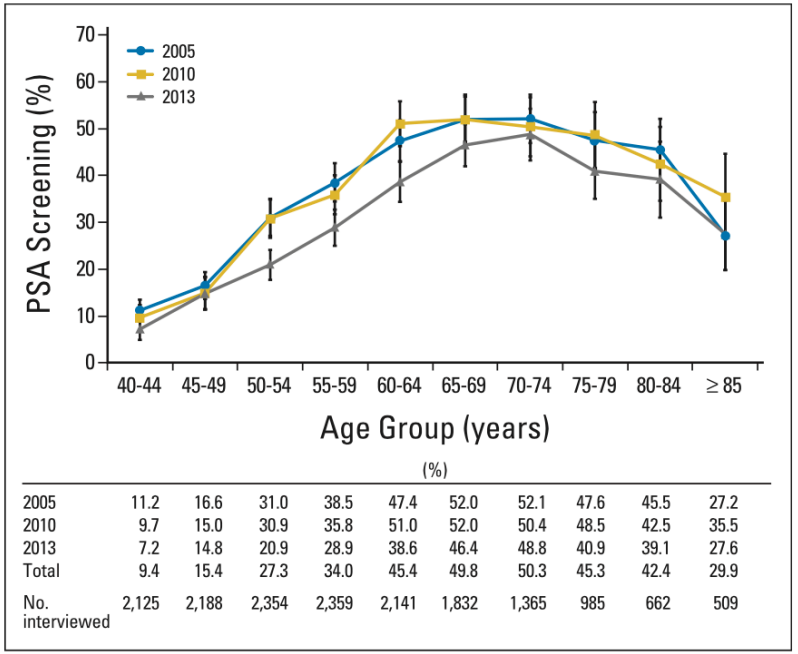


# Impact of the USPSTF Recommendation

- Screening
- Biopsy
- Diagnosis
- Stage Migration

# Impact of the USPSTF: Rates of screening across age groups- Survey Data

- Prostate cancer screening rates have declined since 2012
  - NHIS used to estimate screening rates based on 9-year mortality index for men >40
  - 2005, 2010, and 2013 compared
    - Age 50-59 rates 33→24% (p<0.01)
    - Age 60-74 rates 51→43% (p<0.01)
    - Age >75 rates 44→27% (p=0.03)



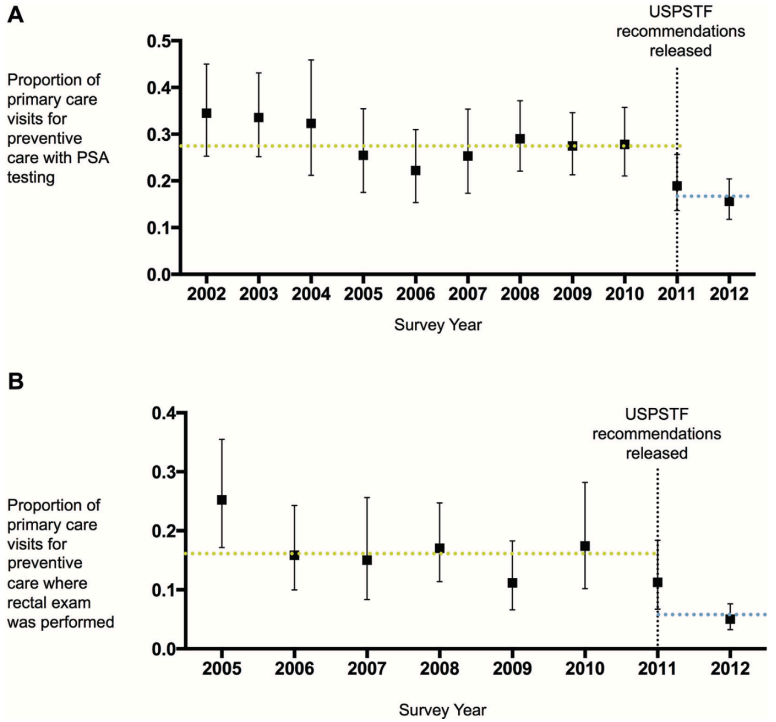

(%)

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 2005 | 11.2 | 16.6 | 31.0 | 38.5 | 47.4 | 52.0 | 52.1 | 47.6 | 45.5 | 27.2 |
| 2010 | 9.7 | 15.0 | 30.9 | 35.8 | 51.0 | 52.0 | 50.4 | 48.5 | 42.5 | 35.5 |
| 2013 | 7.2 | 14.8 | 20.9 | 28.9 | 38.6 | 46.4 | 48.8 | 40.9 | 39.1 | 27.6 |
| Total | 9.4 | 15.4 | 27.3 | 34.0 | 45.4 | 49.8 | 50.3 | 45.3 | 42.4 | 29.9 |
| No. interviewed | 2,125 | 2,188 | 2,354 | 2,359 | 2,141 | 1,832 | 1,365 | 985 | 662 | 509 |

**Fig 1.** Proportion of men, by 5-year age group, who saw a physician in the year prior and received a prostate-specific antigen (PSA) test for screening purposes.

# Impact of USPSTF: Rates of screening across age groups- Survey Data

- Prostate cancer screening rates have declined since 2012
  - NAMCS of primary care visits where DRE and PSA performed
  - DRE rates 65% decrease
  - PSA rates 39% decrease



# Impact of USPSTF: Rates of screening across age groups- Claims/EMR data

- Prostate cancer screening rates have not declined since 2012
  - UTSW review of institutional PSA orders and urology referrals
  - The number of PSAs per ambulatory visit and urology referrals were unchanged

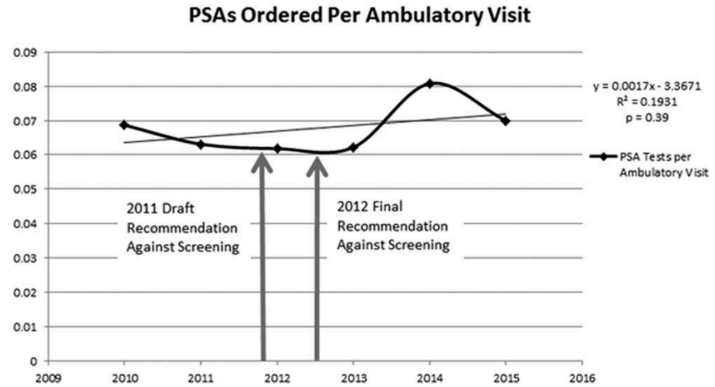



**Figure 3.** PSA tests ordered per ambulatory visit. PSA indicates prostate-specific antigen.

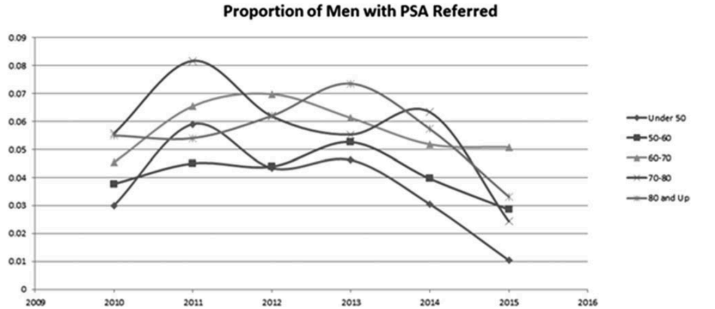
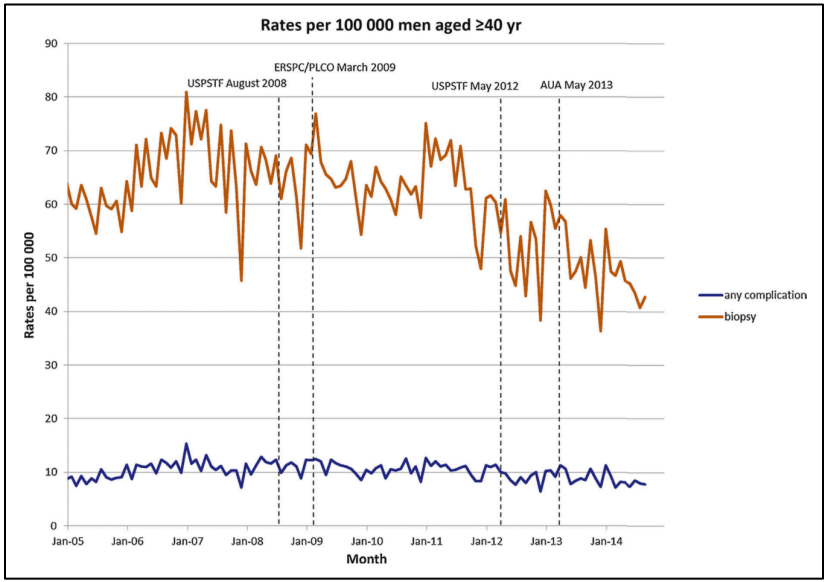



**Figure 7.** Proportion of men with a prostate-specific antigen test referred to urology, stratified by age.

# Impact of USPSTF: Rates of prostate biopsy

- Prostate biopsy rates have declined
  - Claims data from >5 million men with Medicare and private insurance
  - 2005-2014:  33% drop in prostate biopsies
  - 64→43 biopsies per 100,000 men



# Impact of USPSTF: Rates of diagnosis-localized disease

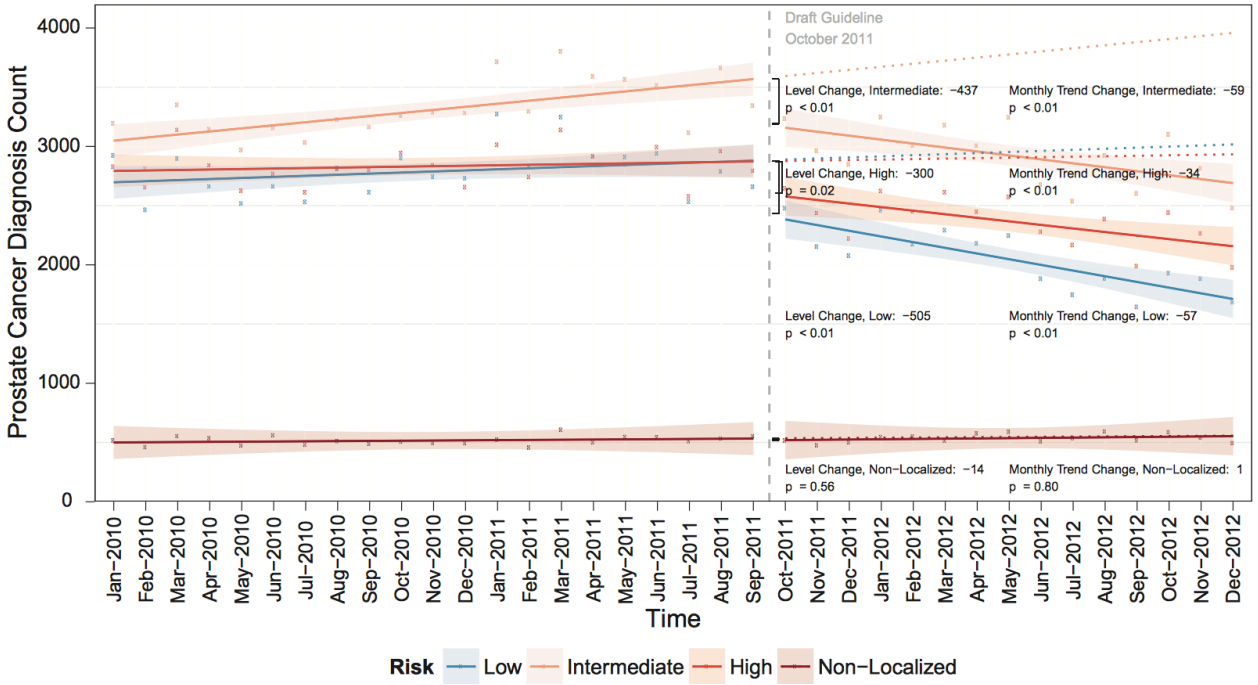
Barocas et al, JUrol, 2015

- NCDB Analysis
- 2010-2012

| Group | Monthly Slope before Guideline Change* | | Level Change Immediately after Guideline Change† | | Monthly Slope Change after Guideline Change Relative to before Guideline Change‡ | | Estimated Change in Monthly Diagnoses 1 Yr after Guideline Change§ | |
|---|---|---|---|---|---|---|---|---|
| | Absolute Change | % Change | Absolute Change | % Change | Absolute Change | % Change | Absolute Difference | % Difference |
| Cancer type: | | p(int)=0.31‖ | | p(int)=0.04 | | p(int)=0.03 | | |
| Prostate | 39 | 0.4 | −1,373 | −12.2 | −164 | −1.8 | −3,181 | −27.9 |
| Colon | 3 | 0.1 | 4 | 0.2 | −27 | −0.5 | −298 | −5.1 |
| Prostate cancer subgroup: | | | | | | | | |
| Disease risk stratum: | | p(int)=0.31 | | p(int)=0.30 | | p(int)<0.01 | | |
| Low | 9 | 0.3 | −505 | −16.9 | −57 | −2.7 | −1,134 | −37.9 |
| Intermediate | 26 | 0.8 | −437 | −12.9 | −59 | −1.9 | −1,090 | −28.1 |
| High-risk | 4 | 0.1 | −300 | −10.1 | −34 | −1.4 | −674 | −23.1 |
| Non-localized | 2 | 0.3 | −14 | −2.7 | 1 | 0.1 | −6 | −1.1 |

# Impact of USPSTF: Rates of diagnosis-localized disease

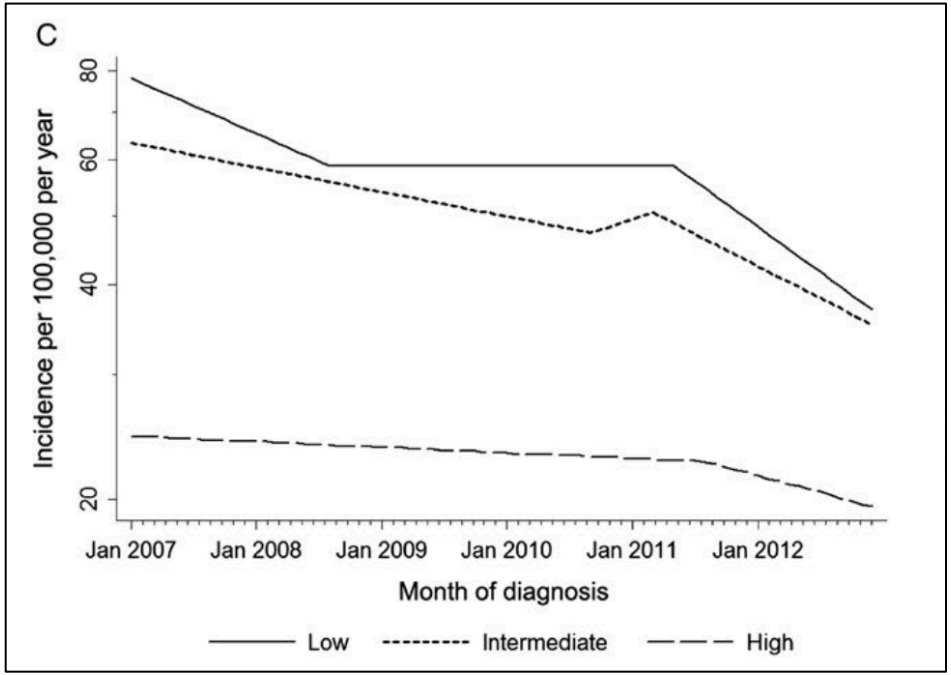
Barocas et al. JUrol, 2015



# Impact of USPSTF: Rates of diagnosis-localized disease

Herget et al, JUrol, 2016

- SEER analysis
- 2007-2012
- Rate of decline by risk group
  - Low risk
    - 18% 2007-2008, then 29% after 2011
  - Intermediate risk
    - 8% 2007-2010, then 21% after 2011
  - High Risk
    - 2% 2007-2011, then 11% after 2011



# Impact of the USPSTF: Reverse stage migration

- Statistical models exist to project effect of screening discontinuation
  - As high as 50% increase in metastatic cases at presentation
  - 20% increase in prostate cancer deaths

- Actual data to evaluate this is immature and inconclusive

# Impact of the USPSTF: Summary

- The USPSTF recommendations had notable effects on screening/biopsy/diagnosis rates in a very short time period

# AUA Guidelines Update 2013

- Meanwhile, the AUA released an updated guideline in 2013
- Represented a systematic review of the evidence by noted experts
- Emphasis on an individualized, risk adapted approach through shared decision making

# AUA Guidelines: Statement 1

- The Panel recommends against PSA screening in men under age 40 years. (Recommendation; Evidence Strength Grade C)
  - In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

# AUA Guidelines: Statement 2

- The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk. (Recommendation; Evidence Strength Grade C)
  - For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

# AUA Guidelines: Statement 3

- For men ages 55 to 69 years the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences. (Standard; Evidence Strength Grade B)
  - The greatest benefit of screening appears to be in men ages 55 to 69 years.

# AUA Guidelines: Statement 4

- To reduce the harms of screening, a 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 decided on screening.

# AUA Guidelines: Statement 5

- The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy. (Recommendation; Evidence Strength Grade C)
  - Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

# Other agencies follow suit…

- American College of Physicians, 2013
  - "ACP recommends that clinicians base the decision to screen for prostate cancer using the prostate-specific antigen test on the risk for prostate cancer, a discussion of the benefits and harms of screening, the patient's general health and life expectancy, and patient preferences."

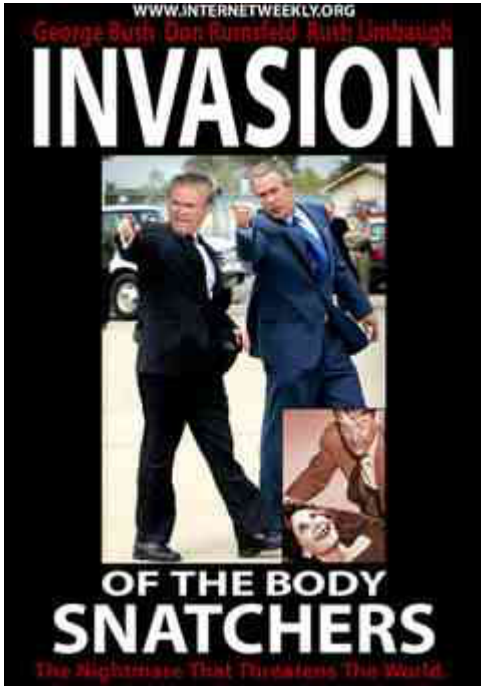
  - "ACP recommends that clinicians should not screen for prostate cancer using the prostate-specific antigen test in average-risk men under the age of 50 years, men over the age of 69 years, or men with a life expectancy of less than 10 to 15 years."

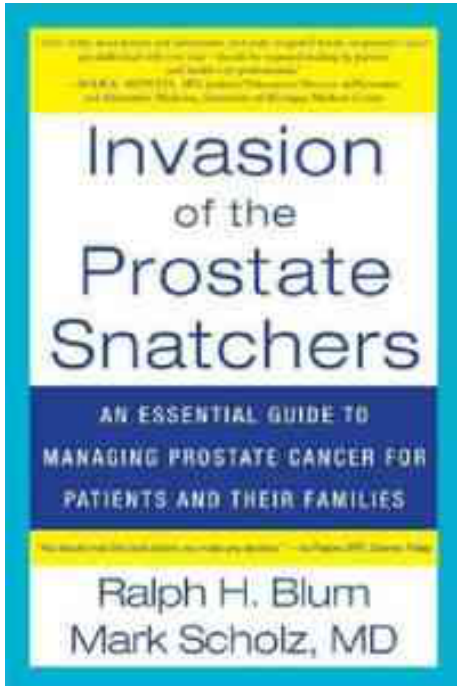
# Update to USPSTF Recommendations

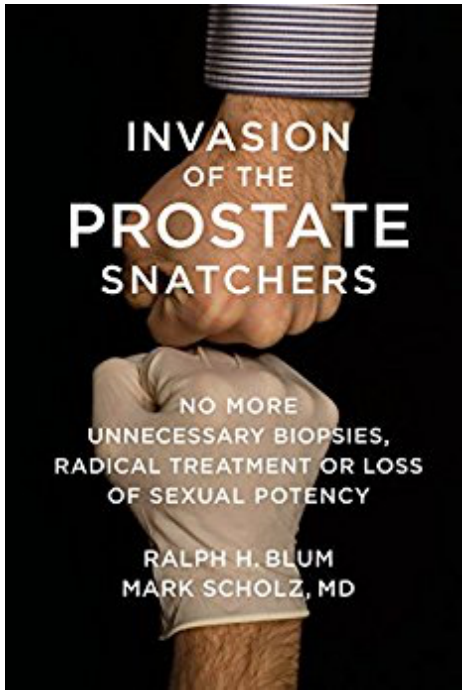
- May 8, 2017
  - USPSTF releases draft update upgrading screening recs for men 55-69 to grade “C”
  - For men >70, grade remained “D”.

> *“The decision about whether to be screened for prostate cancer should be an individual one. The USPSTF recommends individualized decision making about screening for prostate cancer after discussion with a clinician, so that each man has an opportunity to understand the potential benefits and harms of screening and to incorporate his values and preferences into his decision.”*

# Need to Message Right…or Risk Losing our Voice to



# Thank You