PSA Screening and Prostate Cancer

Rishi Modh, MD

ABOUT ME

- From Tampa Bay
- Went to Berkeley Prep

- University of Miami for Undergraduate - 4 years
- University of Miami for Medical School - 4 Years

- University of Florida for Urology Residency - 5 years

ABOUT ME

Why Urology

- Get to work in clinic, hospital, and operating rooms
- Numerous procedures in the clinic
- Patients are grateful
- Get to help people everyday, improve quality of life
- Very In Demand - <300 new urologist per year

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Objectives

1. Review history of PSA Screening
2. Examine 2011 USPSTF recommendations
3. Review landmark trials and evidence behind recommendations
4. Review AUA guidelines
5. Discuss current arguments for and against PSA testing

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Prostate Cancer Statistics

- Prostate Cancer is most common non-cutaneous malignancy in men in the United States
  - 233,000 men diagnosed annually (13.3% of all cancers)
  - Second most common cancer-related cause of death among US men
- Localized disease is amenable to definitive therapy
- Metastatic prostate cancer: 25%-30% 5-year survival rate

Siegel, R. Ca Cancer J Clin **64:** 9, 2014.
Holmberg L. N Engl J Med **347:** 781, 2002.
Bill-Axelson A. N Engl J Med **370**: 932, 2014
National Cancer Institute. Surveillance, Epidemiology, and End Results Registry. 2015.

Cancer Screening

- Goals of screening: identify asymptomatic men with aggressive localized tumors
  - Provide early diagnosis to improve cancer-related mortality
  - Reduce development of metastatic disease
  - Increase quality of life years and reduce morbidity of advanced disease: urinary obstruction, painful metastases

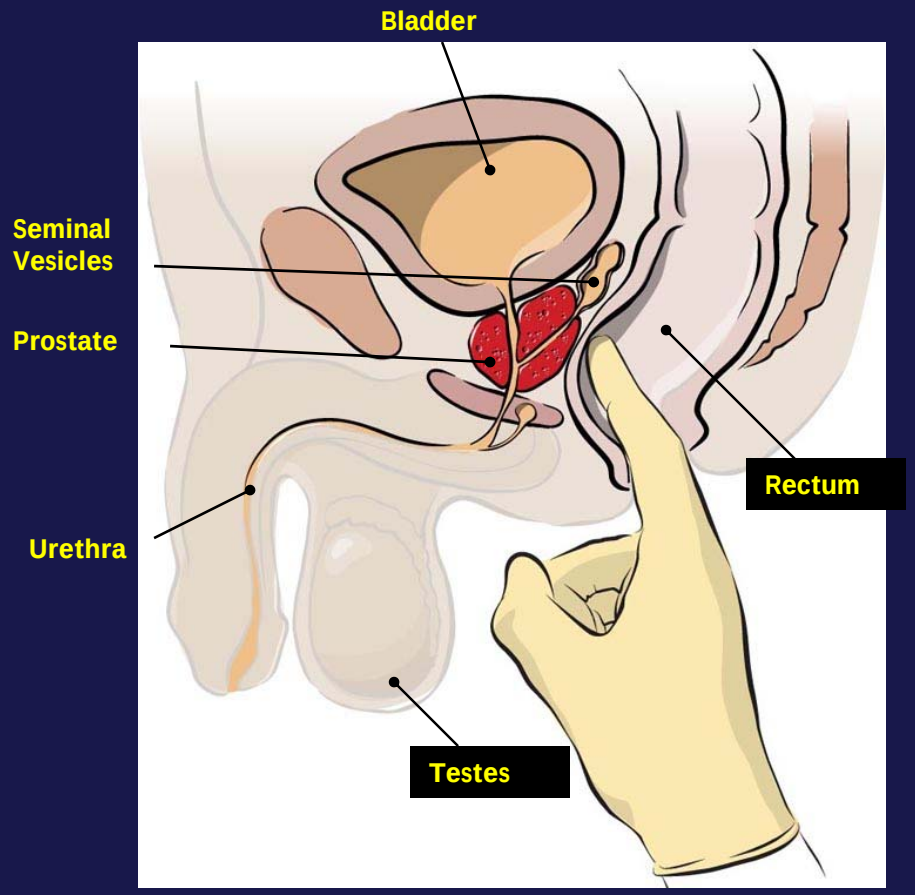
Prostate Cancer: Screening

Requires two components:

1. PSA blood test: Prostate specific antigen blood test

2. Prostate exam: Digital rectal exam

If either are abnormal
- Evaluation by a urologist
- Prostate ultrasound and biopsy



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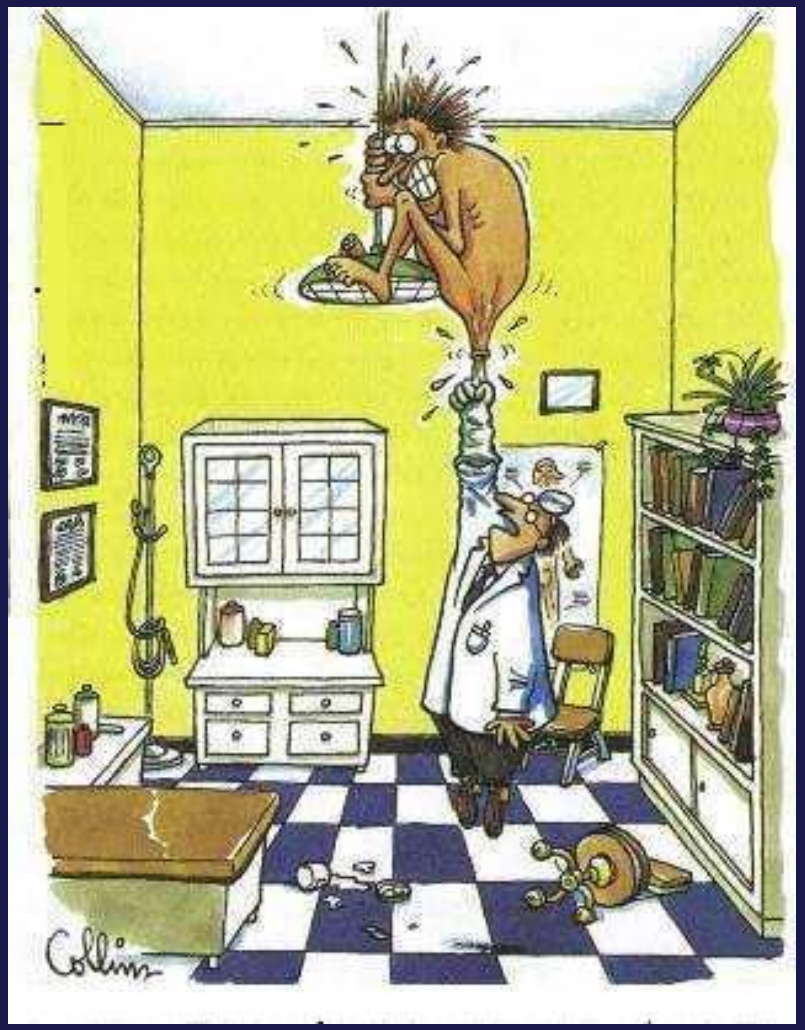
Prostate Cancer: Screening



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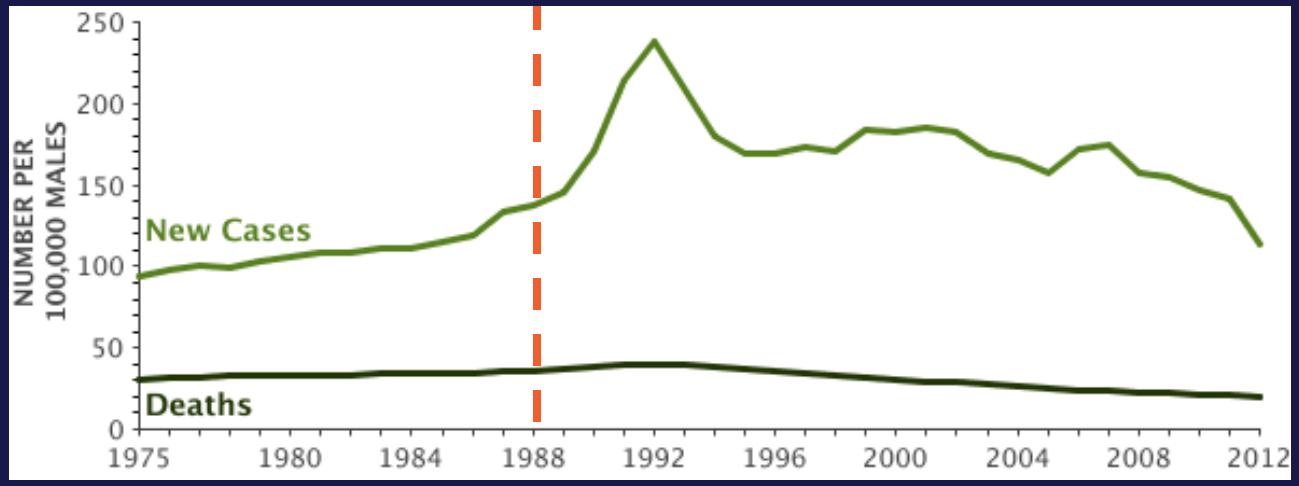
Prostate Cancer Screening

- 1986: PSA approved by FDA to monitor established disease
- 1988-1992: Widespread use of PSA to screen asymptomatic men for prostate cancer
    - Increased incidence of prostate cancer



National Cancer Institute. Surveillance, Epidemiology, and End Results Registry. 2015.

Stamey TA. N Eng J Med, **15**:909, 1987

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Effects of PSA Screening

- Majority of newly-diagnosed cancers localized
  - Aggressive treatment to cure early-stage cancers
  - Increase in radical prostatectomy and radiation
- Stage migration towards organ-confined disease
  - Decrease in advanced stage/metastatic disease: 25% (1980) to 4% (2002)
  - Annual decrease in prostate cancer mortality by 4.1% between 1994-2006

Jemal A. CA Cancer J Clin **60**: 277, 2010
Etzioni R. J Natl Cancer Inst **12**: 1033, 1999

Effects of PSA Screening

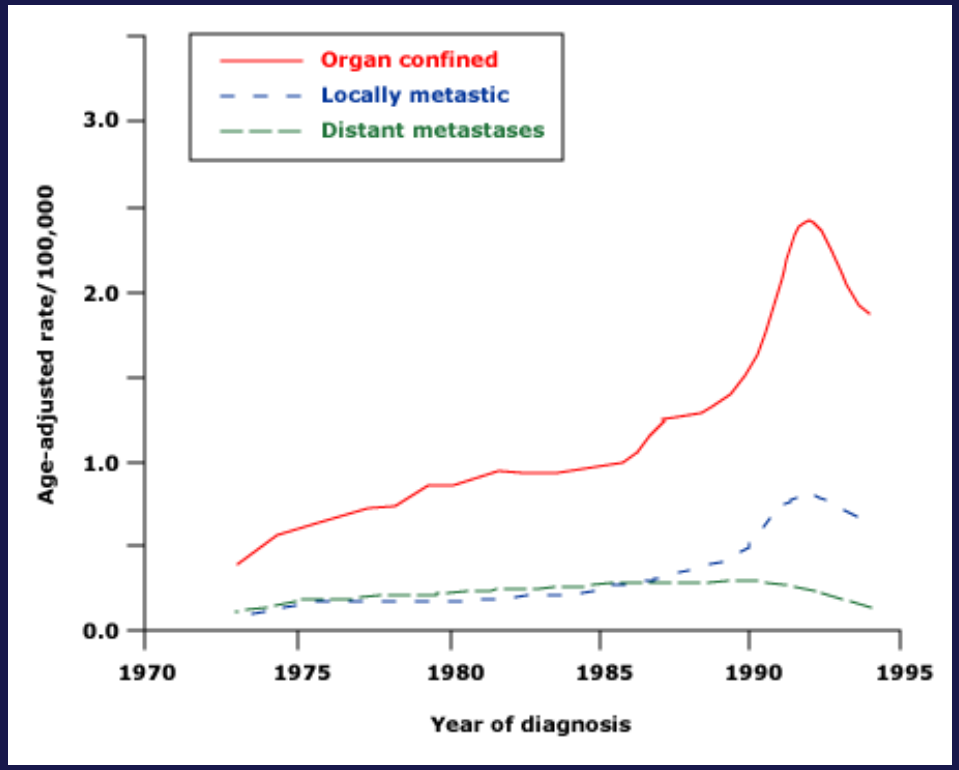

Figure: Age-adjusted rates of prostate cancer by stage and year of diagnosis in white men in the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) data base.

- 1992: AUA and American Cancer Society recommend PSA screening for all men 50 years and older

Paquette, E. L. Urology. **60:** 756, 2002
Ryan, C. J. Urol Oncol, **24:** 396, 2006

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PSA Screening Controversy

- Widespread screening → increased treatment of clinically insignificant disease
  - Lead/length time associated with screening
  - 23%-42% of PSA-detected cancers over-diagnosed
- Over-diagnosis secondary to increased rate of biopsies
  - Risks of screening and confirmatory diagnosis
  - Potential psychosocial harm and anxiety
- Side effects and cost of treatment

Essink-Bot ML, J Natl Canc Inst **90:** 925, 1998
Draisma G, J Natl Canc Inst **101:** 374, 2009

PSA Screening Controversy

- Unclear benefit of PSA screening on prostate-cancer mortality based on observational studies and meta-analyses
    - Concurrent advances in surgical/hormonal therapy
- Lack of high quality evidence → different screening recommendations between professional organizations
- Patients and clinicians: uncertainty if benefits of PSA screening outweigh harms

Ilic D. Can Causes Cont **18:** 279, 2007
Lin K. Ann Intern Med **149:** 192, 2008
Penson DF. JAMA **314:** 2031, 2015

US Preventative Services Task Force (USPSTF)

- Independent volunteer panel of experts in prevention and evidence-based medicine
  - Primary care physicians and experts in methodology and behavioral health
- Provide evidenced-based recommendations about clinical preventative services
- Positions independent of US government
- Influential among primary care physicians

Tasian, GE. Urol Oncol **30:** 155, 2012
Moyer, VA. Ann Intern Med **157:** 120, 2012

US Preventative Services Task Force (USPSTF)

- Oct 2011: Grade D recommendation to prostate specific antigen (PSA) – based screening:
  - Grade D: “There is moderate or high certainty that the service has no net benefit, or that the harms (of the service) outweigh the benefits.”

Moyer, VA. Ann Intern Med **157:** 120, 2012
Chou, R. Ann Intern Med **155**: 762, 201

US Preventative Services Task Force (USPSTF)

- Recommendation widely debated and source of controversy
- Based on two large randomized trials evaluating the effect of PSA-based screening for prostate cancer:
  - 1) United States Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial
  - 2) European Randomized Study of Screening for Prostate Cancer (ERSPC)

Moyer, VA. Ann Intern Med **157:** 120, 2012
Chou, R. Ann Intern Med **155**: 762, 201

PLCO Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- From 1993 to 2001 at 10 study centers across U.S.
- 76,693 men between ages 55-74 randomly assigned to annual screening (DRE + PSA) vs usual care
  - Screening group: Annual PSA 6 years and DRE 4 years
  - Indications for bx: PSA > 4.0 ng/mL or abnormal DRE
- Compliance: 85% PSA testing and 86% for DRE
- 90% of men with cancer diagnosis underwent treatment

Andriole GL, N Engl J Med **360**: 1310, 2009

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PLCO Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Incidence of prostate cancer per 10,000 person-years:
  116 (2,820 cancers) in the screening group vs
  95 (2,322 cancers) in control (RR 1.22 [CI, 1.16 to 1.29]

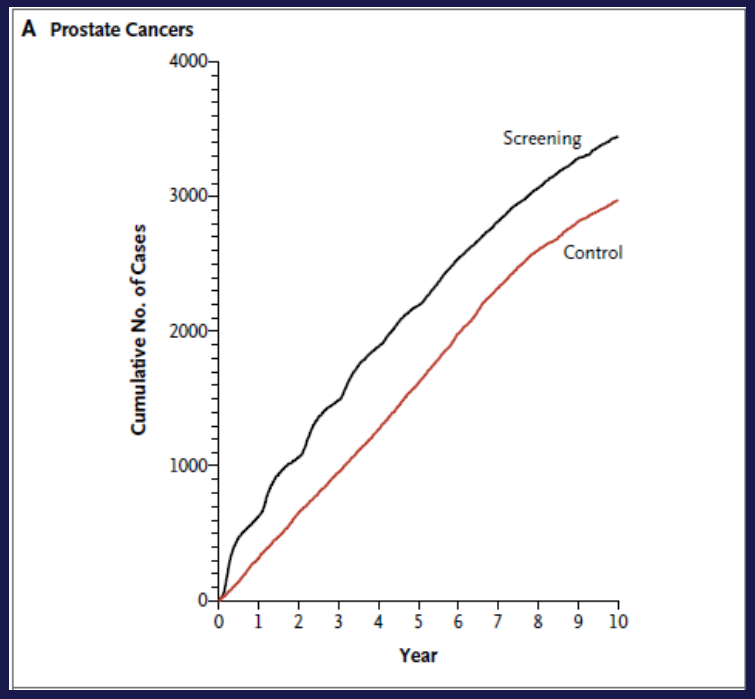

Figure A: Number of Diagnoses of All Prostate Cancers

Andriole GL, N Engl J Med **360**: 1310, 2009

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PLCO Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Prostate cancer mortality per 10,000 person-years:
- 2.0 (50 deaths) in screening group vs 1.7 (44 deaths) in control (RR 1.14 [0.75 to 1.70]) at 7 year follow-up.
- Similar findings at 13 year follow-up (RR 1.09 [CI 0.87 to 1.36]).
- = <u>lack of screening benefit on cancer mortality</u>

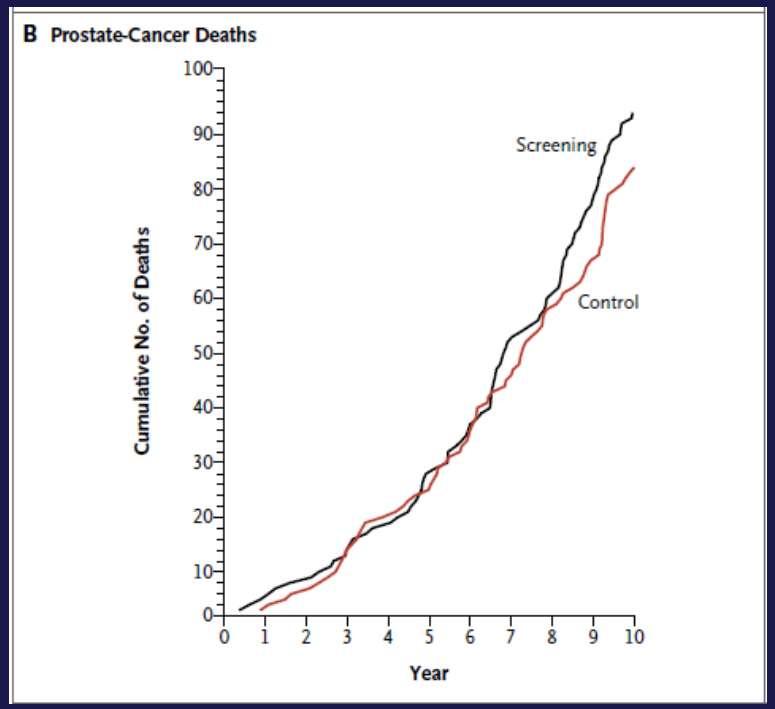

Figure B: Number of Prostate Cancer Deaths

Andriole GL, N Engl J Med **360**: 1310, 2009
Andriole GL, J Natl Cancer Inst **104:** 125, 2012

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PLCO Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Conclusion: No significant benefit in cancer-specific mortality at 7, 10, or 13 year follow-up

- Criticisms: high contamination rate: >40% men underwent PSA testing prior to randomization and 52% of control group underwent PSA testing

Andriole GL, N Engl J Med **360**: 1310, 2009
Andriole GL, J Natl Cancer Inst **104:** 125, 2012

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ERSPC Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- 182,160 men ages 50 and 74 in seven European countries randomly to screening (PSA) vs control
- Variable screening interval (country-specific): PSA every 2-7 years (mean 4 years) with cutoff ranges 2.5 to 4.0 ng/mL as indication for biopsy
    - Variable use of DRE
- 66% of men with cancer diagnosis underwent treatment
- 82% compliance rate of screening group

Schröder FH, N Engl J Med **360**:1320, 2009

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ERSPC Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Incidence of prostate cancer: 8.2% screening group and 4.8% control group
  - Gleason ≥ 7 incidence: 28% screening and 45% control

- No significant decrease in cancer-specific mortality of screening vs control for all subjects (age 50 – 74) after 9 years (RR 0.85 [CI, 0.73 to 1.00])

Schröder FH, N Engl J Med **360**:1320, 2009
Schröder FH, N Engl J Med **366:**981, 2012

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ERSPC Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Death from Prostate Cancer, According to the Age at Randomization.*

Age at Randomization	Screening Group		Control Group		Rate Ratio (95% CI)†
	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	No. of Deaths	Person-Yr (Death Rate per 1000 Person-Yr)	
All subjects	261	737,397 (0.35)	363	878,547 (0.41)	0.85 (0.73–1.00)
Age group					
50–54 yr	6	55,241 (0.11)	4	53,734 (0.07)	1.47 (0.41–5.19)
55–59 yr	60	316,389 (0.19)	102	402,062 (0.25)	0.73 (0.53–1.00)
60–64 yr	76	191,542 (0.40)	95	221,113 (0.43)	0.94 (0.69–1.27)
65–69 yr	78	135,470 (0.58)	129	162,410 (0.79)	0.74 (0.56–0.99)
70–74 yr	41	38,755 (1.06)	33	39,228 (0.84)	1.26 (0.80–1.99)

- Core group age 55-69: cancer-specific mortality decrease (RR 0.80 [CI, 0.65 - 0.98]) is statistically significant at 9 years
  - Absolute risk difference: 0.71 cancer deaths per 1,000 men
  - 1,410 men need to be screened and 48 additional men treated (NNT) to prevent one death (vs breast cancer NNT = 10 at 10 year follow-up)

Schröder FH, N Engl J Med **360**:1320, 2009

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ERSPC Screening Trial

THE LANCET

- Benefit of prostate cancer screening amplified at 13 years f/u:
  - For men age 55-69, prostate cancer mortality 21% lower compared to screening group (RR 0.79, CI 0.69-0.91).
  - Absolute rates difference = 781 men need to be screened or 27 diagnosed to prevent 1 cancer death
  - 30% decreased risk of metastatic disease

Schröder FH, Lancet **384**: 2027, 2014

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ERSPC Screening Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Conclusions: PSA-based screening reduced prostate-cancer mortality for patients between the ages of 55 to 69 by 21% (at 13 year f/u) but with a high risk of over-diagnosis.

- Criticisms: Inconsistencies in age requirements, screening intervals, PSA thresholds, and enrollment procedures.
  - 2 of 7 countries demonstrated significant reduction in prostate cancer mortality with significant magnitude

Schröder FH, N Engl J Med **360**:1320, 2009

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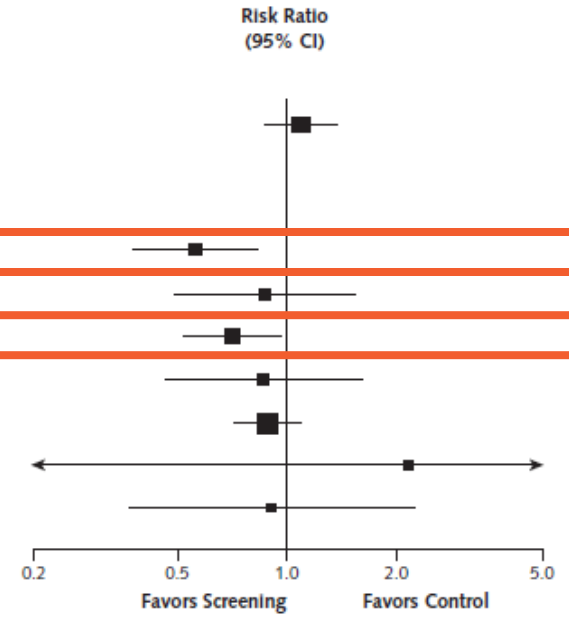
Summary of Trials

Figure 2. **Relative risk of prostate cancer death for men screened with PSA versus control participants, by country.**

Country	Screened Deaths	Screened Total	Control Deaths	Control Total	Risk Ratio (95% CI)
PLCO trial					
United States	158	38 340	145	38 345	1.09 (0.87–1.36)
ERSPC trial					
Sweden	39	5901	70	5951	0.56 (0.38–0.83)
Belgium	22	4307	25	4255	0.86 (0.48–1.52)
Netherlands	69	17 443	97	17 390	0.71 (0.52–0.96)
Italy	19	7266	22	7251	0.86 (0.46–1.58)
Finland	139	31 970	237	48 409	0.89 (0.72–1.09)
Spain	2	1056	1	1141	2.15 (0.20–23.77)
Switzerland	9	4948	10	4955	0.89 (0.36–2.20)



ERSPC = European Randomized Study of Screening for Prostate Cancer; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA = prostate-specific antigen.

- PLCO = no reduction in cancer-specific mortality
- ERSPC = 20% reduction in pts 55-69 but with over-diagnosis

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USPSTF Rationale

- Conflicting results on mortality reduction by PSA screening
  - Men aged 55 – 69 in ERSPC, a small (0.09%) absolute reduction in prostate cancer death seen at 11 years
- Time for any benefit from screening on cancer-specific mortality to emerge is long (10+ years)
- Most men with prostate cancer die of other comorbidities (no all-cause mortality reduction in any trial at 14 years)
  - Competing mortality may attenuate screening benefits

Moyer, VA. Ann Intern Med **157:** 120, 2012

USPSTF Rationale

- Potential harms/risks of PSA screening:
  - 1 in 5 men undergoing screening → elevated PSA
  - 3 in 4 men undergoing biopsy due to elevated PSA not diagnosed with cancer (= high false-positive rate)
  - Of men diagnosed with cancer, 50% to 75% have low-risk disease (Gleason ≤ 6) = minimal metastatic threat
  - Risks of biopsies (pain, infection, bleeding, anxiety)
  - Risk of over-diagnosis and consequent treatment (urinary, sexual, and bowel related symptoms)

Moyer, VA. Ann Intern Med **157:** 120, 2012
Etzioni R. Canc Cau Cont **2:**175, 2008

PSA Screening

- Is current evidence sufficient to discourage PSA screening for all asymptomatic men?
  - Lengthy natural history, complexity of tumor biology, aging population
  - One-size-fits-all policy → failure to detect high-risk cancer during window of curability?

- "Is a cure possible in those for whom it is necessary, and is it necessary for those in whom it is possible?"

  - Willet F. Whitmore, Jr., M.D.

Prostate Cancer: AUA Guidelines

- **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

- **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.

Prostate Cancer: AUA Guidelines

- **3. For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, 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.

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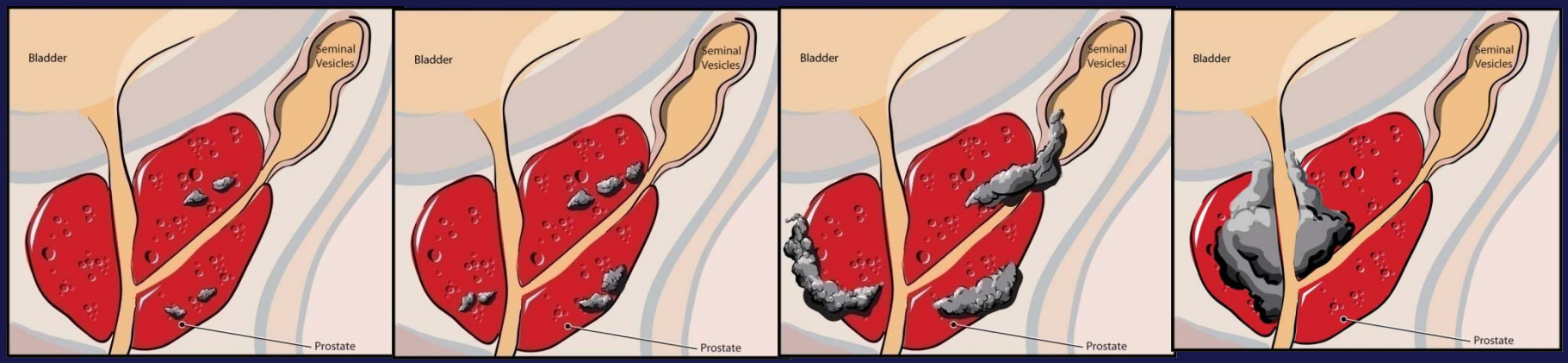
Prostate Cancer: AUA Guidelines

- **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. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce over diagnosis and false positives. (Option; Evidence Strength Grade C)**
  - Additionally, intervals for rescreening can be individualized by a baseline PSA level.
- **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.

Prostate Cancer: Staging

Assessment of the extent of cancer within the prostate



cT1 **cT2** **cT3** **cT4**

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Prostate Cancer: Options

Dependent upon:

- Stage of disease
- Patient's age and health
- Patient's personal preference and expectations
- NOT a "one size fits all" or "cookie cutter" decision
- Informed decision in conjunction with your urologist

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Prostate Cancer: Options

- **Active Surveillance**

- **Radiation**

External beam radiation therapy (IMRT)
Proton beam radiation therapy
Radioactive seed implant (Brachytherapy)

- **Surgery** (radical prostatectomy)

Open retropubic
Robotic (da Vinci® Prostatectomy)

- **Investigational**

Cryosurgery (freezing the prostate)
High Intensity Frequency Ultrasound (heating of the prostate)

Prostate Cancer: Treatment

Active Surveillance

Patients with low volume, low grade, low stage cancers who choose not to pursue treatment immediately in order to avoid side effects

Rationale:

- Many low grade cancers progress slowly with only a small chance of metastasis
- Repeat annual PSA and prostate biopsies to monitor for progression of cancer
- Treatment may be required if cancer has shown to progress
- NOT an option for patients with higher grade/volume/stage cancers

Prostate Cancer: Treatment

Radiation Therapy

- Radiation energy transmitted from an external source through the body and to the prostate gland or implanted into the prostate (i.e. radioactive seed implants)
- Less invasive than surgery
- Cure rate at 10 years similar to surgery, however long term success is less well understood
- Side effects: bladder and bowel irritation (i.e. urgency and frequency) and erectile dysfunction
- Best suited for older or frail patients or for patients who want to avoid surgery

Prostate Cancer: Treatment

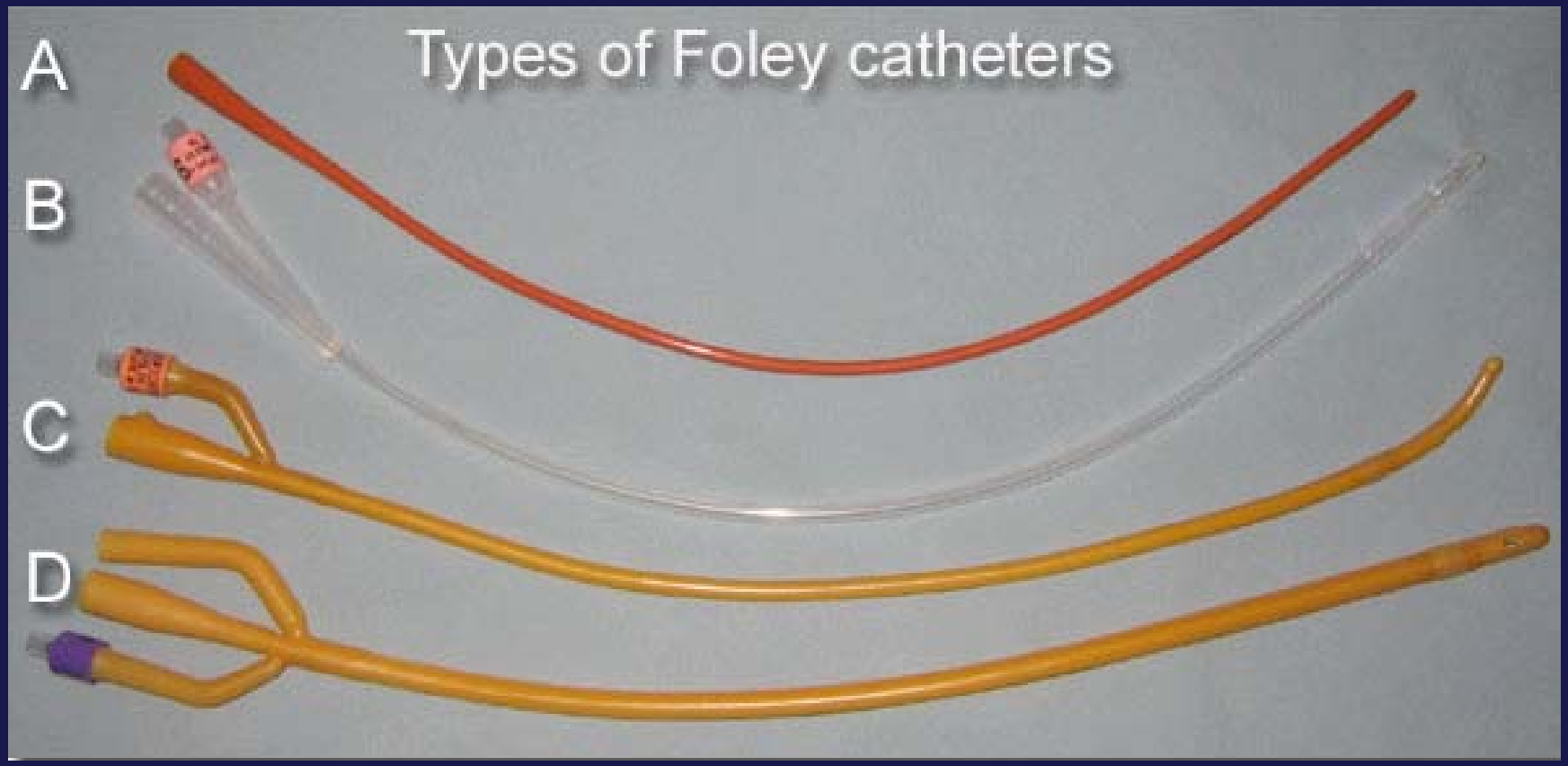
Surgery (Radical Prostatectomy)

- Prostate gland completely removed surgically and bladder drainage is restored to the urethra
- More invasive than radiation
- Robotic surgery is less invasive than traditional open surgery
- Side effects: urinary leakage and erectile dysfunction
- >90% patients recover urinary control and 70-80% recover some erectile function at one year if nerve sparing surgery is performed
- Best suited for younger, healthier patients with >15 year life expectancy

Conclusions

- Controversies over PSA use will remain
- PSA screening strategies can be adapted to decrease risk of overdetection/overtreatment
- Use of evidence to inform health policy and individual screening decisions = rational basis for moving forward
- Treatment options must be individualized

Other Issues



Catheter Irrigation Video

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