PSA screening

“To screen or not to screen, that’s the question”

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Conflict of Interest Declaration: Nothing to Disclose

Presenter: Dr. Walid Shahrour

Title of Presentation: PSA: What is it good for?

I have no financial or personal relationship related to this presentation to disclose.

Clinical scenario

- 58 years old male presenting to your clinic with LUTS. He denies any gross hematuria, UTI, fever, chills, weight loss. Symptoms have been ongoing for the past 10 months and have been getting progressively worse. What is your next step?

1. Rectal exam, ultrasound of the abdomen and pelvis
2. Ultrasound of the abdomen and pelvis, PSA
3. Rectal exam, ultrasound of the abdomen and pelvis, PSA
4. Rectal exam, PSA, IPSSS
5. Rectal exam, ultrasound of the abdomen and pelvis, start on Tamsulosin

PSA structure & biology

- Prostate specific antigen (PSA)
  - Protein
  - Protease
  - Produced in the glandular tissue of the prostate
    - Two types of tissue in the prostate: muscle and gland
  - Liquefies the semen
- 1970 – PSA first identified in human prostate extracts
- 1980 – PSA identified in the sera of prostate cancer patients
- 1981- first use of PSA as tumor marker

[Ablin RJ et al J Reprod Fertil. 22,573,1970] [Wang MC et al Invest Urol. 17: 159: 1979]

[Papsidero LD et al Cancer Res 40: 2428 1980] [Kuriyama M et al Cancer Res, 41:3874, 1981]

- February, 1986 Hybritech Tandem-R PSA test released, FDA approved for PCa recurrance testing
- 1991-94 – Catalona, Andriole publishes staged findings on 31,000 men trial for PSA testing
- 1994 – FDA approval for PSA as screening test

PSA

1156 THE NEW ENGLAND JOURNAL OF MEDICINE April 25, 199

MEASUREMENT OF PROSTATE-SPECIFIC ANTIGEN IN SERUM AS A SCREENING TEST FOR PROSTATE CANCER

WILLIAM J. CATALONA, M.D., DEBORAH S. SMITH, PH.D., TIMOTHY L. RATLIFF, PH.D., KATHY M. DODDS, R.N., DOUGLAS E. COPLEN, M.D., JERRY J.J. YUAN, M.D., JOHN A. PETROS, M.D., AND GERALD L. ANDRIOLE, M.D.

- PSA measured in 1653 volunteer men 50 or more years
- Results compared to 300 men undergoing ultrasound for abnormal exam

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MEASURE*	RECTAL EXAMINATION	ULTRASONOGRAPHY	SERUM PSA†
		percent	
Sensitivity	86	92	79
Specificity	44	27	59
Positive predictive value	33	28	40
Negative predictive value	91	91	89
Overall accuracy	58	43	64

Possible Causes for an Elevated PSA

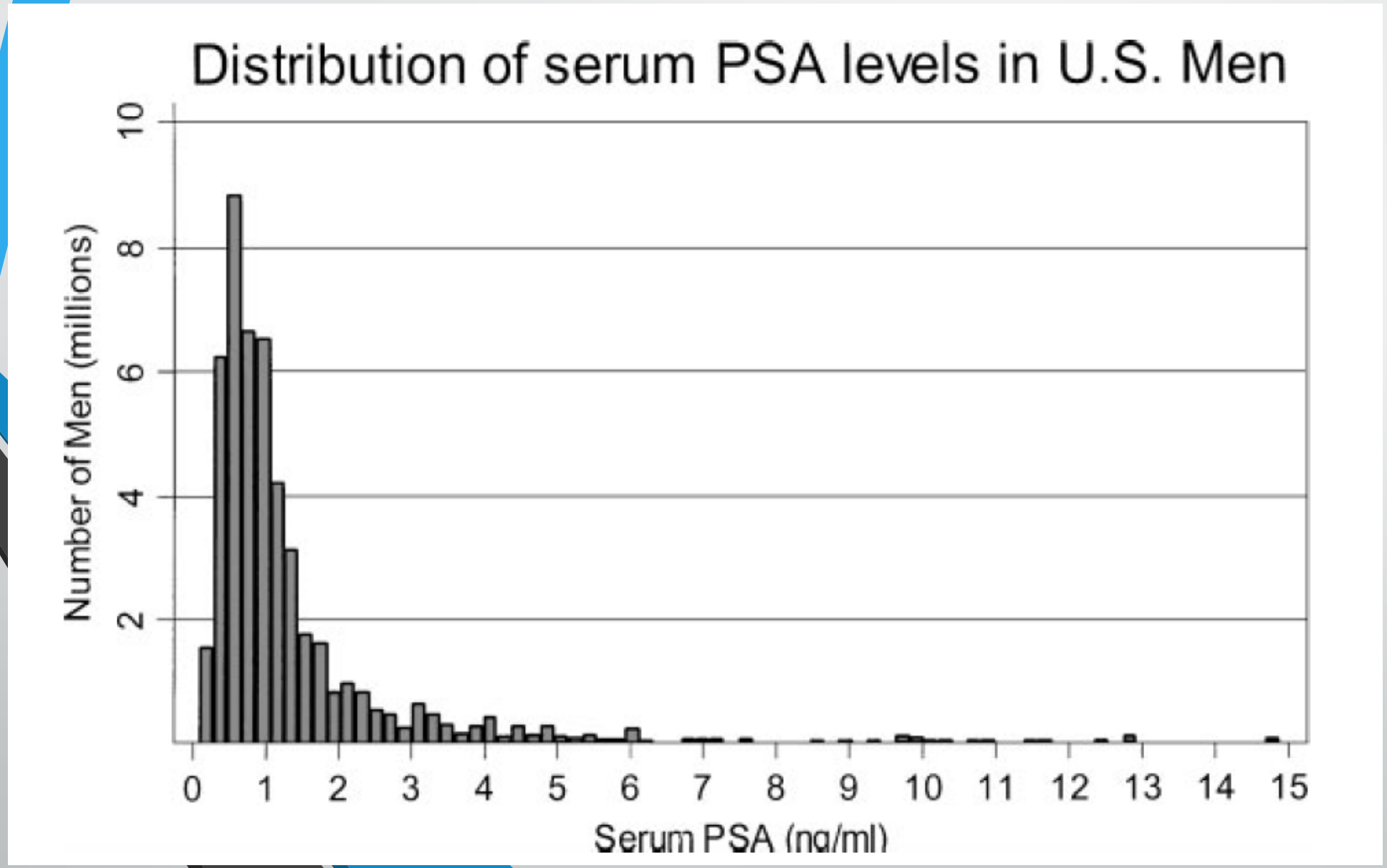
- Prostate cancer
- BPH: benign prostate enlargement
- Infection:
  - Prostatitis
  - Urinary tract infection
- Inflammation
  - Prostatitis
  - Urinary retention
- Intercourse
- Unknown

Why 4.0 ng/ml cutoff?

- 1986 Hybritech Tandem-R PSA test published result of normal is < 4.0
- Based on their study that found 99% of 472 apparently healthy men had a total PSA level below 4 ng/mL

Median PSA in Men Enrolled in PSA Study 1989-2001 (n = 36,000)

Age Group	Median PSA (ng/ml)
40s	0.7
50s	0.9
60s	1.3
70s	1.7



The Prostate 66:1044 – 1051 (2006)

Prostate Cancer in low PSA

PSA level	Prevalence of Prostate Cancer	High-Grade Disease
3.1 - 4.0	26.9%	25.0%
2.1 - 3.0	23.9%	19.1%
1.1 - 2.0	17.0%	11.8%
0.6 - 1.0	10.1%	10.0%
<0.5	6.6%	12.5%

Thompson et al, JAMA 294:66-70, 2005.

Thompson et al, NEJM 350:2239-46, 2004.

PSA Derivatives

- PSA density
  - Correlates the contribution of PCa to serum PSA values
  - Compensate for the presence of BPH and prostate size on TRUS
  - PSAD > 0.15 consistent with the presence of cancer
  - Limitations to wide spread acceptance
    - Variations in prostatic size and measurements
    - Ratios of stroma to epithelial tissue
- PSA velocity:
  - Rate of change of PSA over time
  - PSAV > 0.75 ng/ml per year, with total PSA < 10
    - 72% sensitivity
    - 95% specificity
  - Limitations:
    - Need for previous values
    - PSA variations with nonmalignant causes of PSA elevation
    - Variations between tests with sequential testing
- Age-specific cutoffs
  - Reflects increasing PSA values with age
  - Risk missing clinically significant cancers in older men

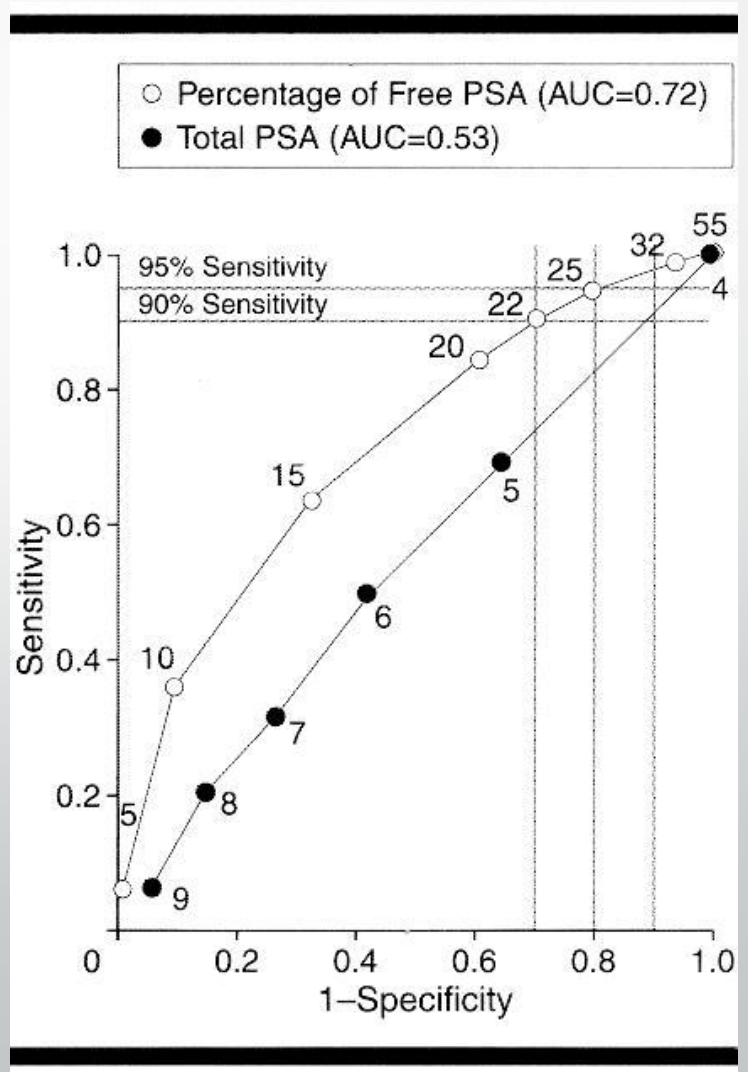
%fPSA: PCa detection tPSA 4-10 ng/ml

Catalona et al 1998

PSA, ng/mL	Probability of Cancer, %	Free PSA, %	Probability of Cancer, %
0-2	≈1	. . .†	. . .
2-4	15	. . .	. . .
4-10	25	0-10	56
		10-15	28
		15-20	20
		20-25	16
		>25	8
>10	>50	. . .	. . .

*Data are for men with normal digital rectal examination results, regardless of patient age. Data for prostate-specific antigen (PSA) results are from Catalona et al[1] and Keetch et al.[21] Percentage of free PSA can further stratify risk for men with PSA values between 4 and 10 ng/mL.

†Ellipses indicate data not applicable.



1. Catalona WJ et al JAMA 279:19:1542; 1998

Other tests

- PCA_3
- Pro-PSA
- 4K score
- Prostate Health Index

  $p2PSA/freePSA \times \sqrt{totalPSA}$

Estimated New Cases*

Males

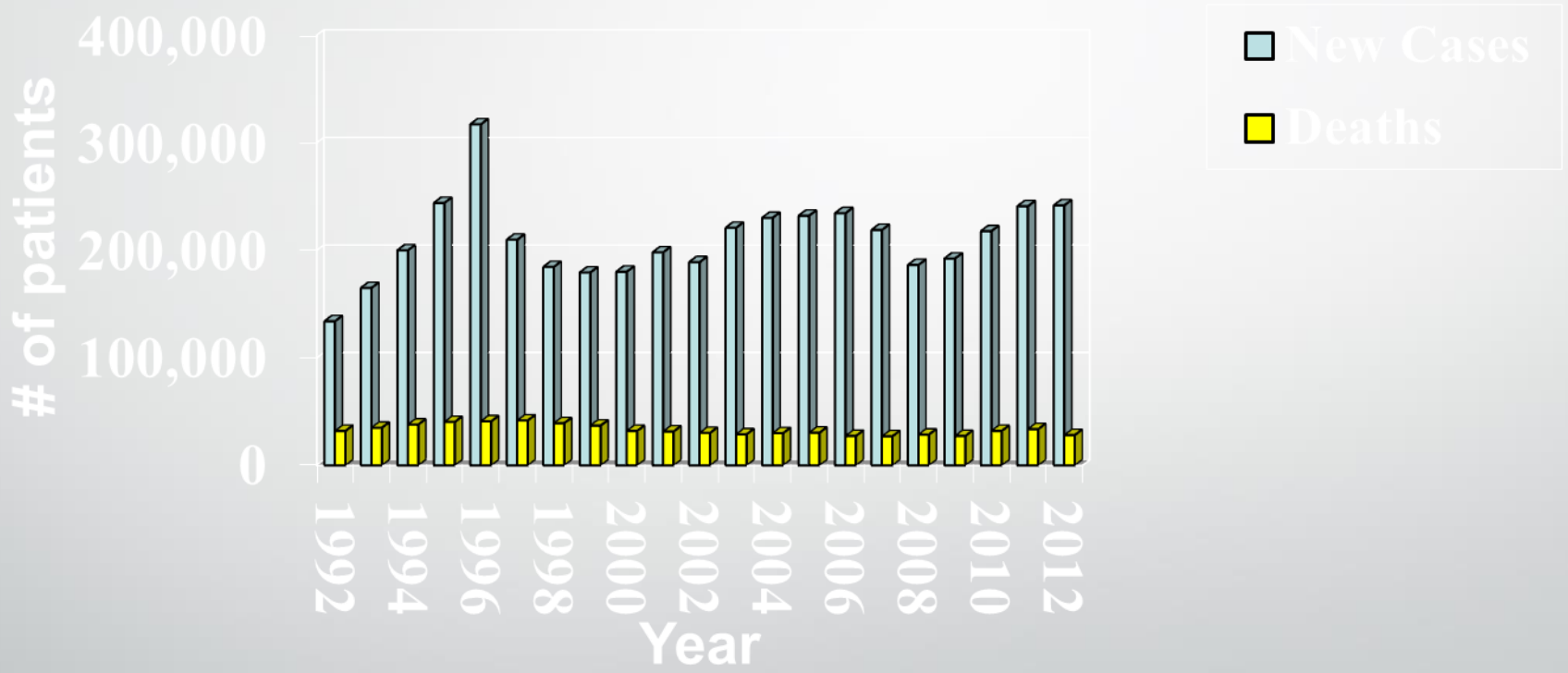
Prostate	217,730	28%
Lung & bronchus	116,750	15%
Colon & rectum	72,090	9%
Urinary bladder	52,760	7%
Melanoma of the skin	38,870	5%
Non-Hodgkin lymphoma	35,380	4%
Kidney & renal pelvis	35,370	4%
Oral cavity & pharynx	25,420	3%
Leukemia	24,690	3%
Pancreas	21,370	3%
All Sites	**789,620**	**100%**

Estimated Deaths

Males

Lung & bronchus	86,220	29%
Prostate	32,050	11%
Colon & rectum	26,580	9%
Pancreas	18,770	6%
Liver & intrahepatic bile duct	12,720	4%
Leukemia	12,660	4%
Esophagus	11,650	4%
Non-Hodgkin lymphoma	10,710	4%
Urinary bladder	10,410	3%
Kidney & renal pelvis	8,210	3%
All Sites	**299,200**	**100%**

Prostate cancer incidence with time



Prostate Cancer Screening Trials

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement DRAFT

Summary of Recommendation and Evidence

The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)-based screening for prostate cancer. **This is a grade D recommendation**.

This recommendation applies to men in the U.S. population that do not have symptoms that are highly suspicious for prostate cancer, regardless of age, race, or family history. The Task Force did not evaluate the use of the PSA test as part of a diagnostic strategy in men with symptoms that are highly suspicious for prostate cancer. This recommendation also does not consider the use of the PSA test for surveillance

USPSTF 2012 Recommendations

- "D" rating (Moyer VA. Ann Intern Med 2012;157:120)
  - Recommends against PSA screening for any man, regardless of age or risk factors
- Evidence synthesis (Chou R. Ann Intern Med 2011;155:762)
  - Systematic review of benefits and harms from screening, treatment
    - Heavily weighted PLCO and ERSPC trials

Potential Harm

- Prostate Biopsy:
  - Majority are negative
  - Bleeding
  - Infection

- Prostate Cancer Treatment
  - Erectile Dysfunction
  - Urinary Symptoms/Incontinence

USPSTF 2012 Recommendations

Benefits (screening every 1 to 4 y for 10 y)	Men, n
10-year PCa death no screening	5 in 1000
10-year PCa death with screening	4-5 in 1000
Net benefit	0-1 in 1000

Harms (screening every 1 to 4 y for 10 y)	Men, n
False positive test	100-120 in 1000
Prostate cancer diagnosis	110 in 1000
Death (treatment)	< 1 in 1000
Urinary incontinence (treatment)	18 in 1000
Erectile dysfunction (treatment)	29 in 1000

Moyer VA. Ann Intern Med 2012;157:120

ERSPC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

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.,

Schroder et al, NEJM 360: 1320-8, 2009

ERSPC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

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*

N Engl J Med 2012;366:981-90.

ERSPC

- 162,243 men randomized
- 7 countries
- Age 55-69
- Screening q 2-4 years vs. usual care
  - Compliance in screening group 82%
  - Screening in the control group ??
- 11 years of follow up (median)
- Detection was higher in screening group
  - 6963 cases vs. 5396, or cumulative incidence of 9.6% vs. 6.0%

ERSPC

- Screening reduced PCa mortality by 21%
- Absolute benefit low: 1.07 fewer deaths per 1,000
- Number needed to invite = 1055 (previous 1410)
- Number needed to treat = 37 (previous 49)
- Screening increased incidence by 63%

* Up to 29% reduction if corrected for noncompliance in the screening arm and contamination of the control arm.

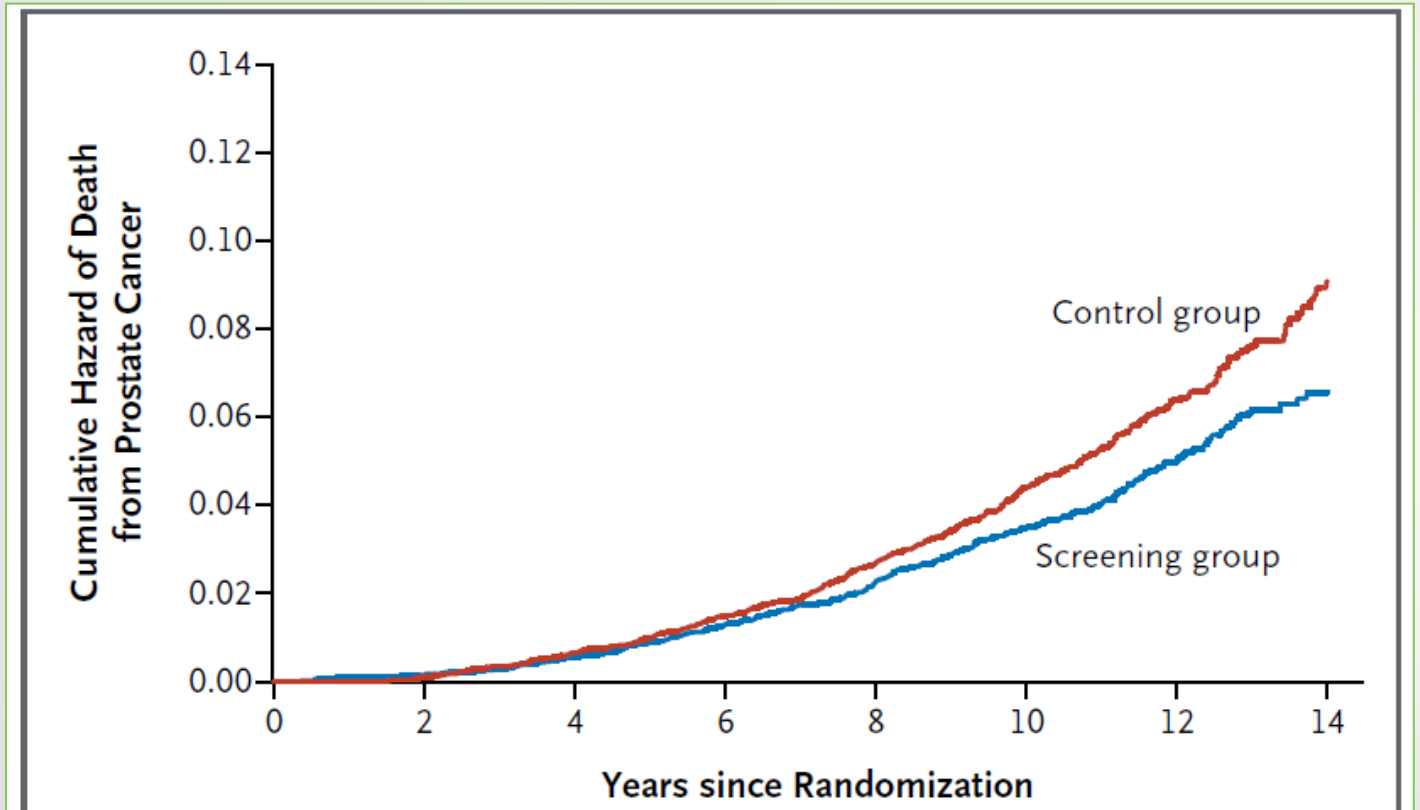


Figure 2. Cumulative Hazard of Death from Prostate Cancer among Men 55 to 69 Years of Age.

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.

At 11 years, 299 prostate-cancer deaths in screening group and 462 in the control group.

Rate ratio 0.79, 95% confidence interval 0.68-0.91, p=0.003.

ERSPC Limitations

- ERSPC criticisms
  - Variable randomization strategies, testing intervals, biopsy criteria

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Mortality Results from a Randomized Prostate-Cancer Screening Trial

Gerald L. Andriole, M.D., E. David Crawford, M.D., Robert L. Grubb III, M.D., Saundra S. Buys, M.D., David Chia, Ph.D., Timothy R. Church, Ph.D.,

Andriole et al, NEJM 360: 1310-9, 2009

Advance Access publication on January 6, 2012.

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

Manuscript received March 17, 2011; revised November 8, 2011; accepted November 9, 2011.

Correspondence to: Philip C. Prorok, PhD, Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, 6130 Executive Blvd, Ste 3132, Bethesda, MD 20892-7354 (e-mail: prorokp@mail.nih.gov).

J Natl Cancer Inst 2012;104:125–132

PLCO

- 1993-2001 randomized 76,693 men up to age 74 at 10 US centers
- Annual PSA + DRE vs. “standard care” in the community - widespread screening
- Prostate biopsy for abnormal result

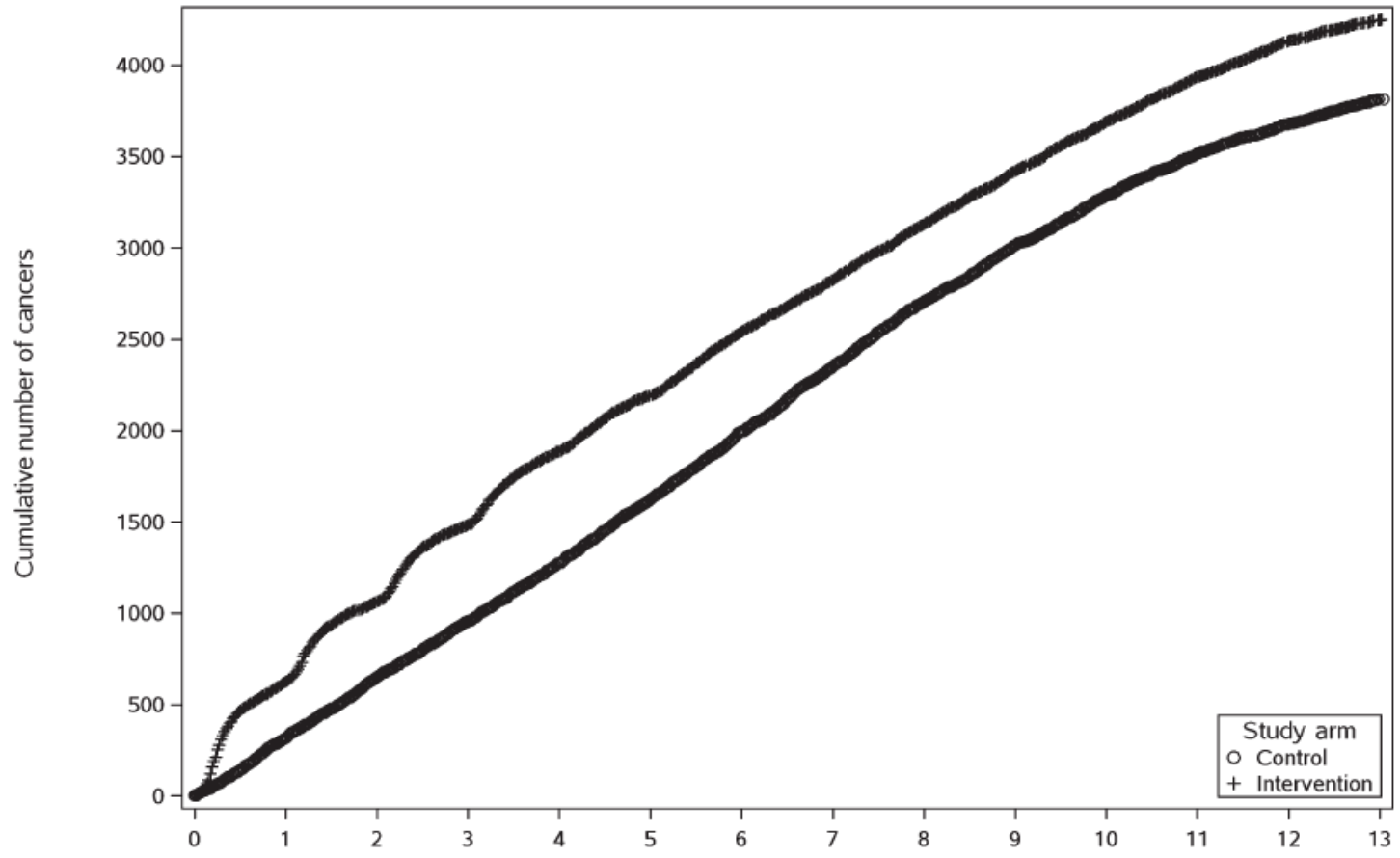
Results from PLCO screening trial

- ~85% in screening arm actually screened
- 52% of controls were screened (contamination)

Thus, comparing 85% vs 52% screened

- No mortality benefit from screening
- Complications of screening
  - PSA and DRE: minimal
  - Biopsy: 68 per 10,000; infection, bleeding, retention

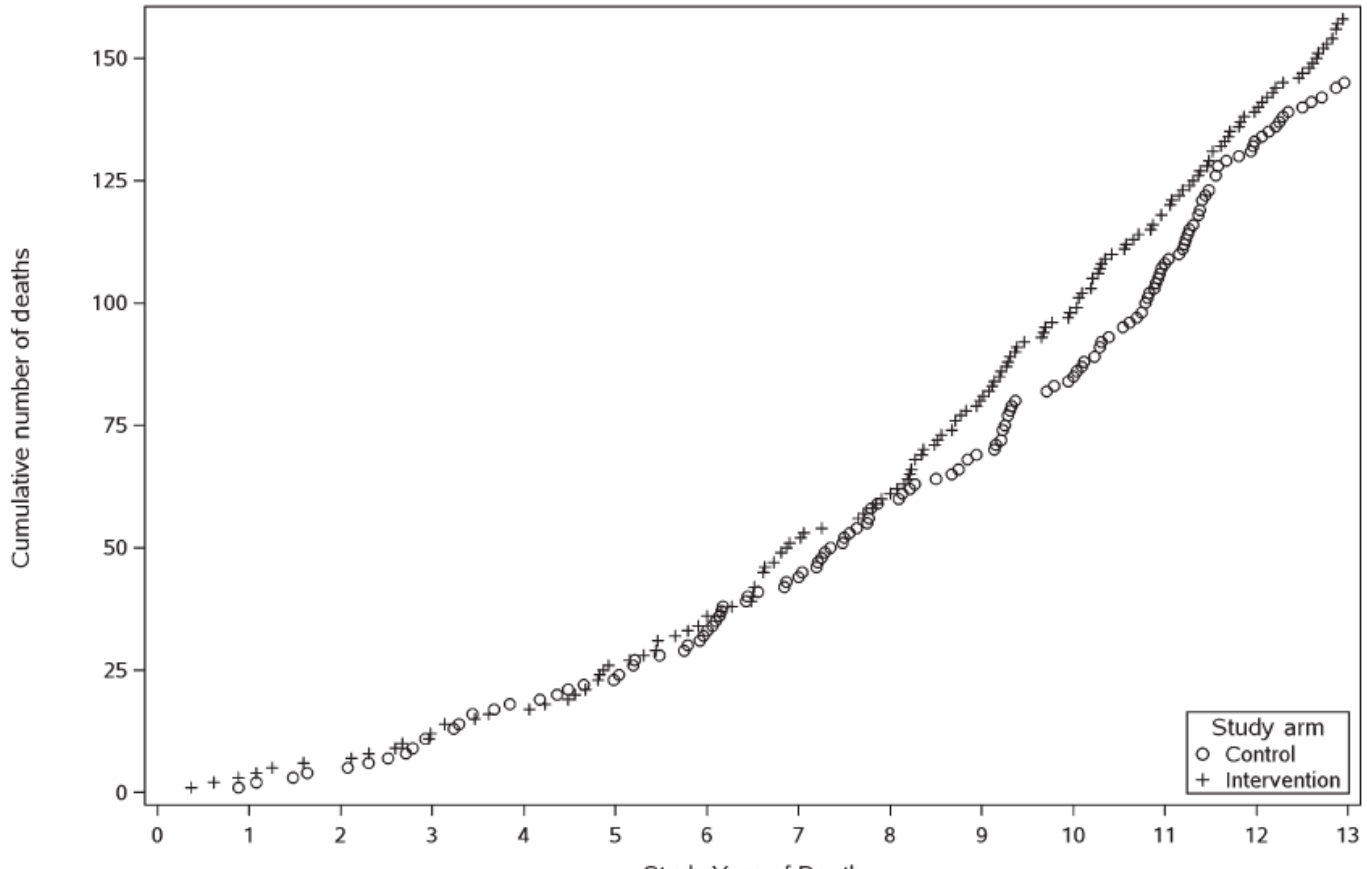
Number of Cases Identified



Cumulative cancers - I	622	1060	1485	1886	2190	2541	2830	3132	3426	3698	3939	4138	4250
Cumulative PY - I	37560	74193	109937	144808	178854	212064	244376	275790	306070	334050	357928	377196	392022
Cumulative cancers - C	313	648	953	1274	1624	1997	2351	2710	3021	3288	3521	3681	3815
Cumulative PY - C	37674	74605	110719	145980	180338	213709	246077	277429	307582	335355	359107	378262	392977

More cancers identified in the screening group (4250 vs. 3815).
Rate ratio 1.12, 95% confidence interval 1.07-1.17.

Number of Prostate Cancer Deaths



Cumulative deaths - I	3	6	12	16	26	36	51	61	80	98	118	140	158
Cumulative PY - I	38217	76112	113629	150725	187382	223541	259118	294052	328048	359768	387164	409535	426977
Cumulative deaths - C	1	4	11	18	23	33	44	59	69	85	108	133	145
Cumulative PY - C	38223	76132	113635	150689	187278	223329	258811	293631	327455	358904	386109	408262	425439

At 13 years, 158 prostate-cancer deaths in screening group and 145 in the control group.

Rate ratio 1.09, 95% confidence interval 0.87-1.36.

Limitations of PLCO

- Only ~41% of screened men with abnormal results were biopsied within 1 year
- Median f/u for men with PCa was 6.3 years in screening arm vs. 5.2 years in controls; thus, follow-up is insufficient to evaluate mortality results

Goteborg Randomized Population-Based Screening Trial

- 20,000 men aged 50-64 randomized to PSA screening or no screening
- Screened every 2 years until age 67-71
- PSA cutoff:
  - 3.4 ng/ml during 1995-8 ;

  2.9 ng/ml in 1999;

  2.5 ng/ml in 2004
- 93% complied with biopsy

Lancet Oncology 2010

Goteborg Randomized Population-Based Screening Trial

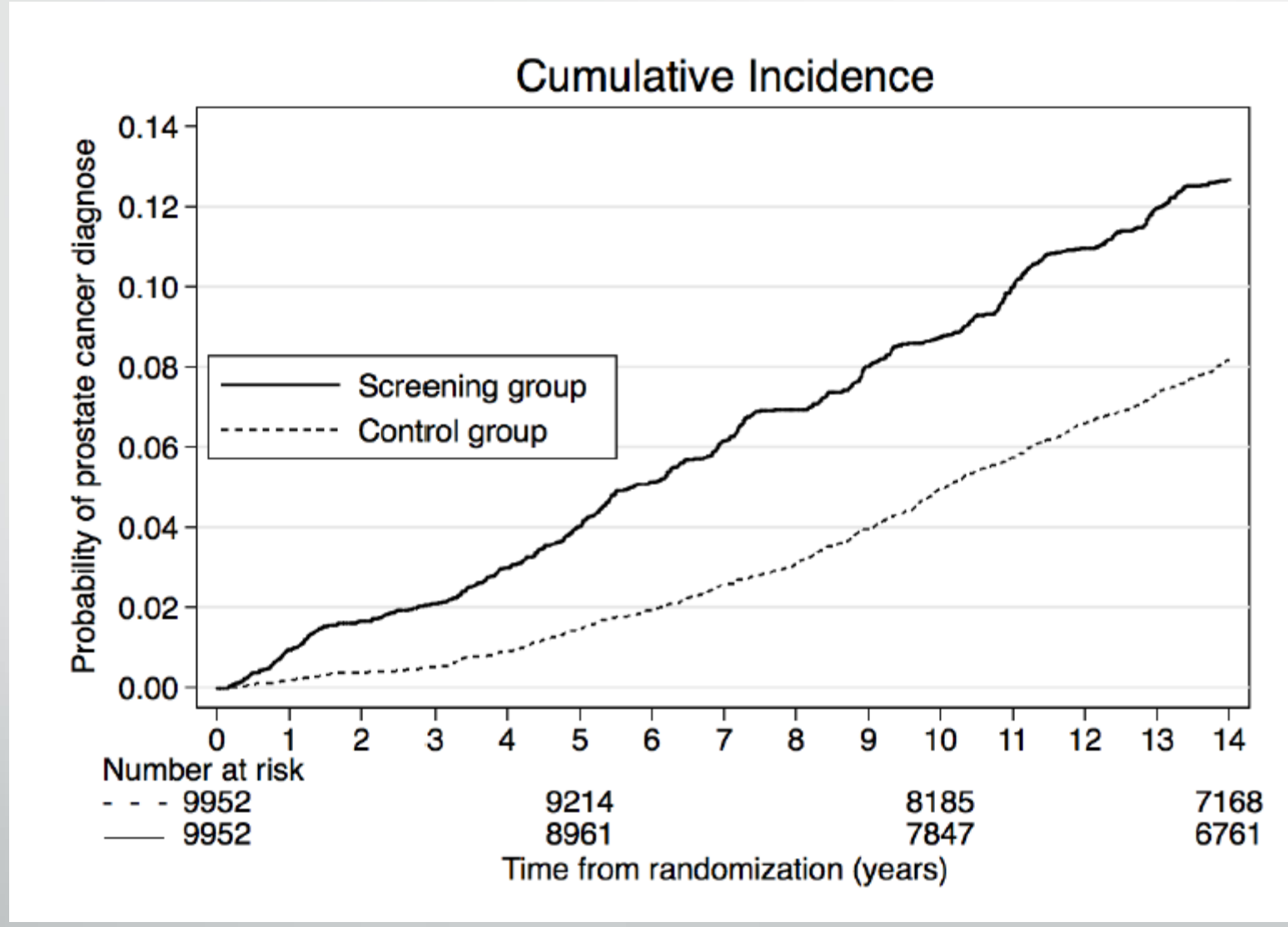
- Patients treated according to discretion of their physician
- Incidence of PCa linked to Swedish Cancer Registries
- Death certificate available on all deceased
- Median follow-up 14 year follow-up

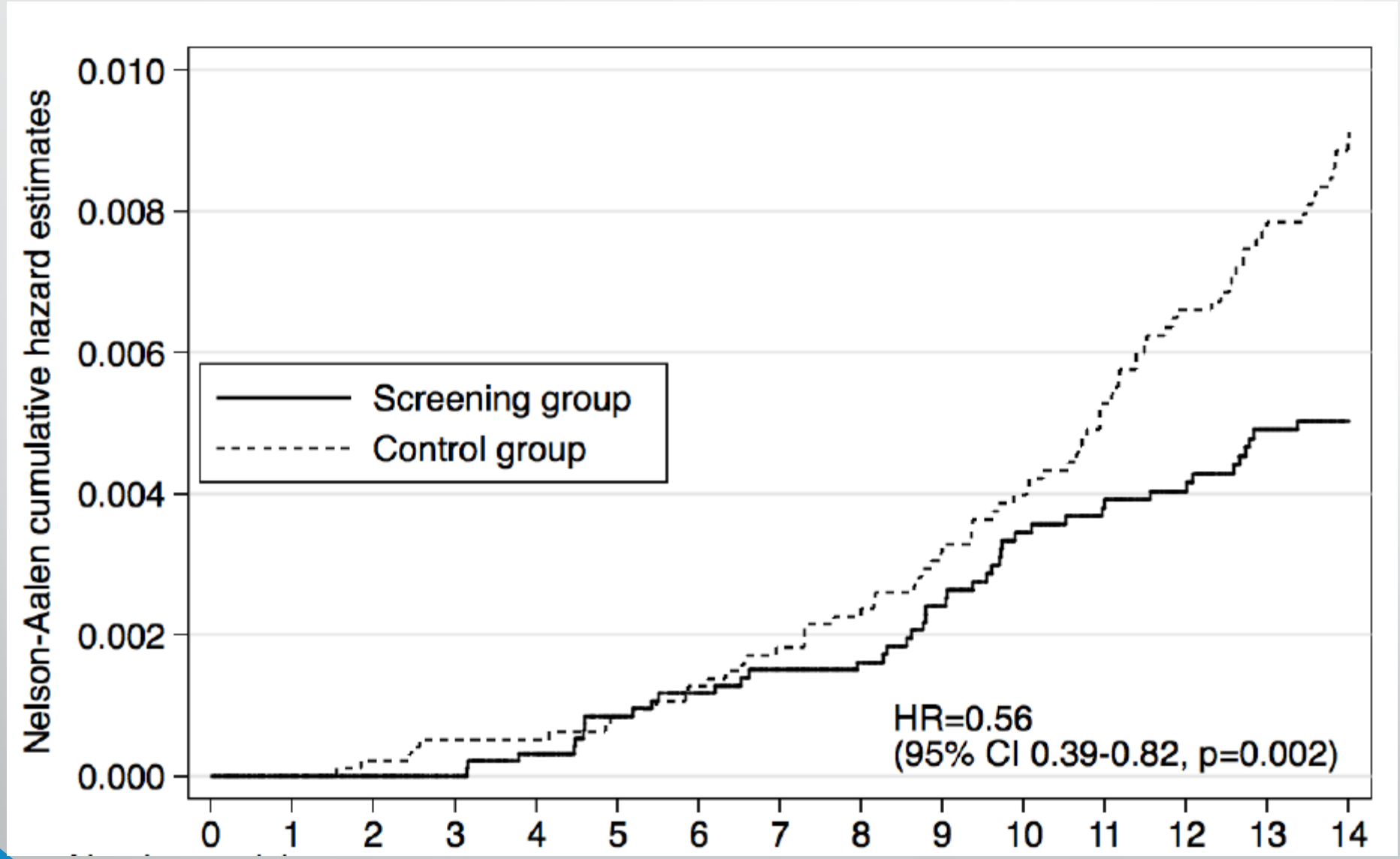
Lancet Oncology 2010

Goteborg Randomized Population-Based Screening Trial

- Dx CaP: 12.7% vs 8.2% ($p < 0.0001$)
- 44% lower mortality in screening arm
- 56% lower mortality in men actually screened

Lance t Oncology 2010


Cumulative Incidence
Probability of prostate cancer diagnose
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
Screening group
Control group
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number at risk
- - - 9952 9214 8185 7168
—— 9952 8961 7847 6761
Time from randomization (years)


Nelson-Aalen cumulative hazard estimates
0.010
0.008
0.006
0.004
0.002
0.000
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
Screening group
Control group
HR=0.56
(95% CI 0.39-0.82, p=0.002)

Goteborg Randomized Population-Based Screening Trial

To prevent 1 PCa death:

ERSPC : NNS = 1410; NNT = 48

Goteborg:

Number needed to screen = 293

Number needed to treat = 12

Why the differences?

- Gotennborg much smaller than other two (20,000 vs 77,000 and 182,000)
- More homogenous population, little baseline screening contamination
- Longer f/u (14years vs 11 and 9 years)
- Younger population (median 56 vs 60)
- Key point: > 50% of Gotenborg study were also part of ERSPC and heavily influenced outcome of that study

Gotenborg therefore is more of a subgroup analysis rather than an independent confirmatory study of ERSPC findings

Long-Term Benefits

- Modeled ERSPC data (per 1000 men followed for their entire life span)
  - Screening between ages 55 to 69 resulted in
    - 9 fewer PCa deaths (NNI 98)
    - A total of 73 life-years gained (8.4 y per death avoided)

(Heijnsdkijk EAM. NEJM 2012;367:595)

Long-Term Benefits

- Screening resulted in total of 56 QALY (95% -21 to 97) gained
  - From 73 unadjusted life-years
  - Biggest negative impact was due to long-term side effects from treating over-diagnosed cancers
    - 23% to 42% of PSA-detected cancers over-diagnosed

Draisma G. J Natl Cancer Inst 2009;101:374)

What about PSA screening in Canada

- CUA guidelines came in October 2017

CUA GUIDELINE

Canadian Urological Association recommendations on prostate cancer screening and early diagnosis

Ricardo A. Rendon, MD[1]; Ross J. Mason, MD[2]; Karim Marzouk, MD[3]; Antonio Finelli, MD[4]; Fred Saad, MD[5]; Alan So, MD[6]; Philippe D. Violette, MD[7,8]; Rodney H. Breau, MD[9]

Published October 2017

CUA guidelines

1. **The CUA suggests offering PSA screening to men with a life expectancy greater than 10 years. The decision of whether or not to pursue PSA screening should be based on shared decision-making after the potential benefits and harms associated with screening have been discussed *(Level of evidence: 1; Grade of recommendation: B)*.**

CUA guidelines

- The USPSTF is publishing its latest report which is recommending a shared decision between physician and patient despite recommending against it previously (still not published yet)

CUA guidelines

- The CTFPHC (Canadian Task Force on Preventative Health Care) is weakly recommending against PSA screening (old studies, not updated)

CUA guidelines

2. **For men electing to undergo PSA screening, we suggest starting PSA testing at age 50 in most men and at age 45 in men at an increased risk of prostate cancer *(Level of evidence: 3; Grade of recommendation: C)*.**

CUA guidelines

3. **For men electing to undergo PSA screening, we suggest that the intervals between testing should be individualized based on previous PSA levels (Fig. 1).**
   a. **For men with PSA <1 ng/ml, repeat PSA testing every four years *(Level of evidence: 3; Grade of recommendation: C)*.**
   b. **For men with PSA 1–3 ng/ml, repeat PSA testing every two years *(Level of evidence: 3; Grade of recommendation: C)*.**
   c. **For men with PSA >3 ng/ml, consider more frequent PSA testing intervals or adjunctive testing strategies *(Level of evidence: 4; Grade of recommendation: C)*.**

CUA guidelines

4. **For men electing to undergo PSA screening, we suggest that the age at which to discontinue PSA screening should be based on current PSA level and life expectancy.**
   a. **For men aged 60 with a PSA <1 ng/ml, consider discontinuing PSA screening *(Level of evidence: 2; Grade of recommendation: C)*.**
   b. **For all other men, discontinue PSA screening at age 70 *(Level of evidence: 2; Grade of recommendation: C)*.**
   c. **For men with a life expectancy less than 10 years, discontinue PSA screening *(Level of evidence: 4; Grade of recommendation: C)*.**

CUA guidelines

5a. In patients with an elevated risk of clinically significant prostate cancer (according to PSA levels and/or nomograms) who are biopsy-naive, mpMRI followed by targeted biopsy (biopsy directed at cancer-suspicious foci detected with mpMRI) should not be considered the standard of care.

CUA guidelines

5b. In men who had a prior negative TRUS-guided systematic biopsy who demonstrate an increasing risk of having clinically significant prostate cancer since prior biopsy (e.g., continued rise in PSA and/or change in findings from digital rectal examination [DRE]), mpMRI followed by targeted biopsy may be considered to help in detecting more clinically significant prostate cancer patients compared with repeated TRUS-guided systematic biopsy.

CUA guidelines

- PSA kinetics, density, F:T ratio should not be used alone.
- They can be helpful adjuncts but not the main driving factors

CUA guidelines

- PSA 3, PHI, 4K score are helpful in aggressive cancer
- Expensive and not funded.
- These tests are not to be widely used

CUA guidelines

- Biopsy or not is a shared informed decision between the patient and his doctor.

Back to our clinical scenario

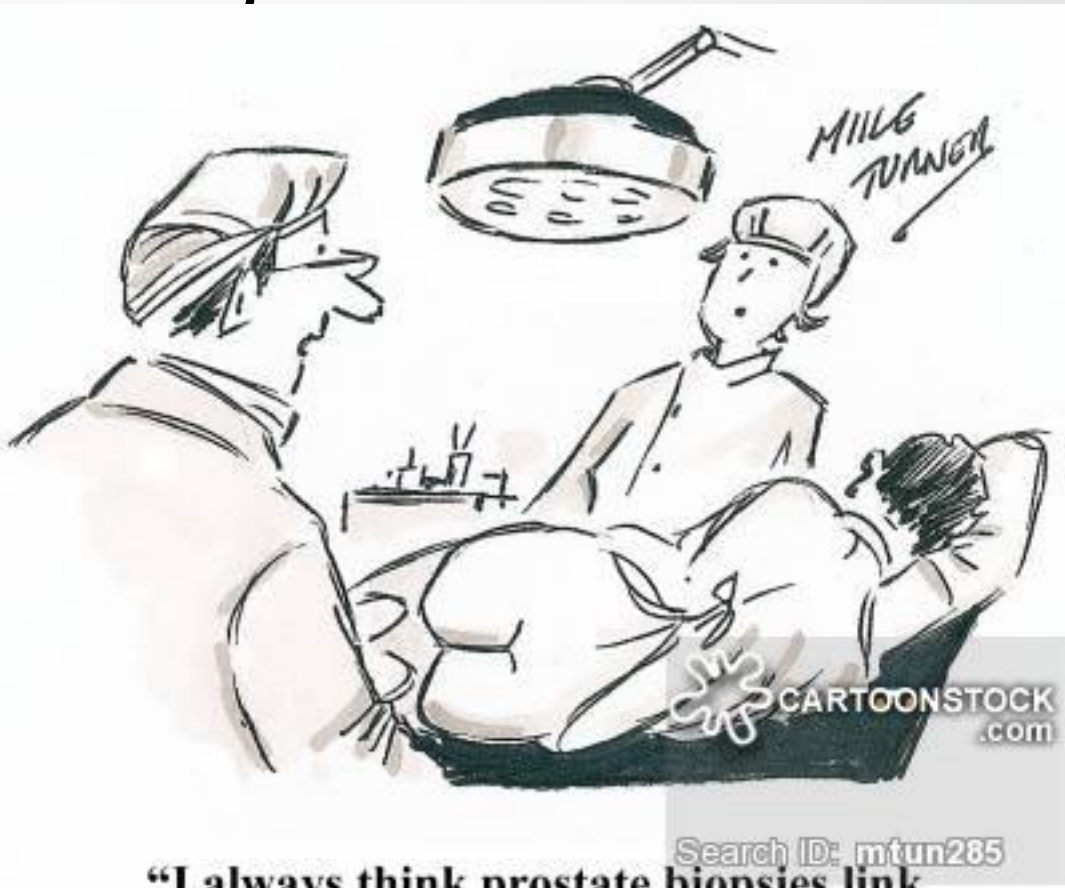
Clinical scenario

- 58 years old male presenting to your clinic with LUTS. He denies any gross hematuria, UTI, fever, chills, weight loss. Symptoms have been ongoing for the past 10 months and have been getting progressively worse. What is your next step?

1. Rectal exam, ultrasound of the abdomen and pelvis
2. Ultrasound of the abdomen and pelvis, PSA
3. Rectal exam, ultrasound of the abdomen and pelvis, PSA
4. Rectal exam, PSA, IPSSS
5. Rectal exam, ultrasound of the abdomen and pelvis, start on Tamsulosin

Take home message

1. PSA screening is not a hoax
2. DRE is always important
3. Informed discussion, not just any discussio
4. Prostate biopsy can cause trouble.
   But careful selection of patients can help



Thank you