COMPREHENSIVE
CANCER CENTERS

PSA as a prostate cancer screening tool – past, present and future.

Oscar B. Goodman, Jr., M.D., Ph.D.

Nevada Cancer Coalition

Cancer Control Summit

September 16, 2019

Disclosures

- Nothing formal to disclose.
- As a medical oncologist I rarely prescribe primary prostate cancer screening, however I use PSA as a monitoring tool.
- My practice includes men who are with regard to primary PSA screening:
  - True positives
  - False positives
  - False negatives

Objectives

- Describe the historical and present role of PSA testing as a prostate cancer screening tool.

- Characterize the realized clinical impact of decreased PSA testing on the natural history of prostate cancer.

Overview of the talk

- Historical overview of PSA as a biomarker
- Review of PSA screening prospective studies
- Overview of PSA screening guidelines
- PSA screening trends and impact on prostate cancer disease states
- Optimizing PSA screening

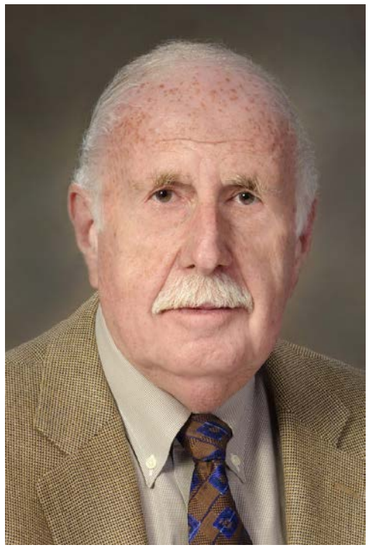
Importance of risk-benefit analysis

Sorry I'm late for your digital-rectal exam...
I slammed my finger in my car door.

Historical overview of PSA as a prostate cancer biomarker

PSA (prostate specific antigen)- a brief history

- 1970: Ablin identified PSA while searching for prostate cancer specific antigens released by cryosurgical ablation of prostate tumors.



- 1979: C hu (re)discovered PSA while searching for cancer antigens; ultimately patented as a diagnostic in 1984

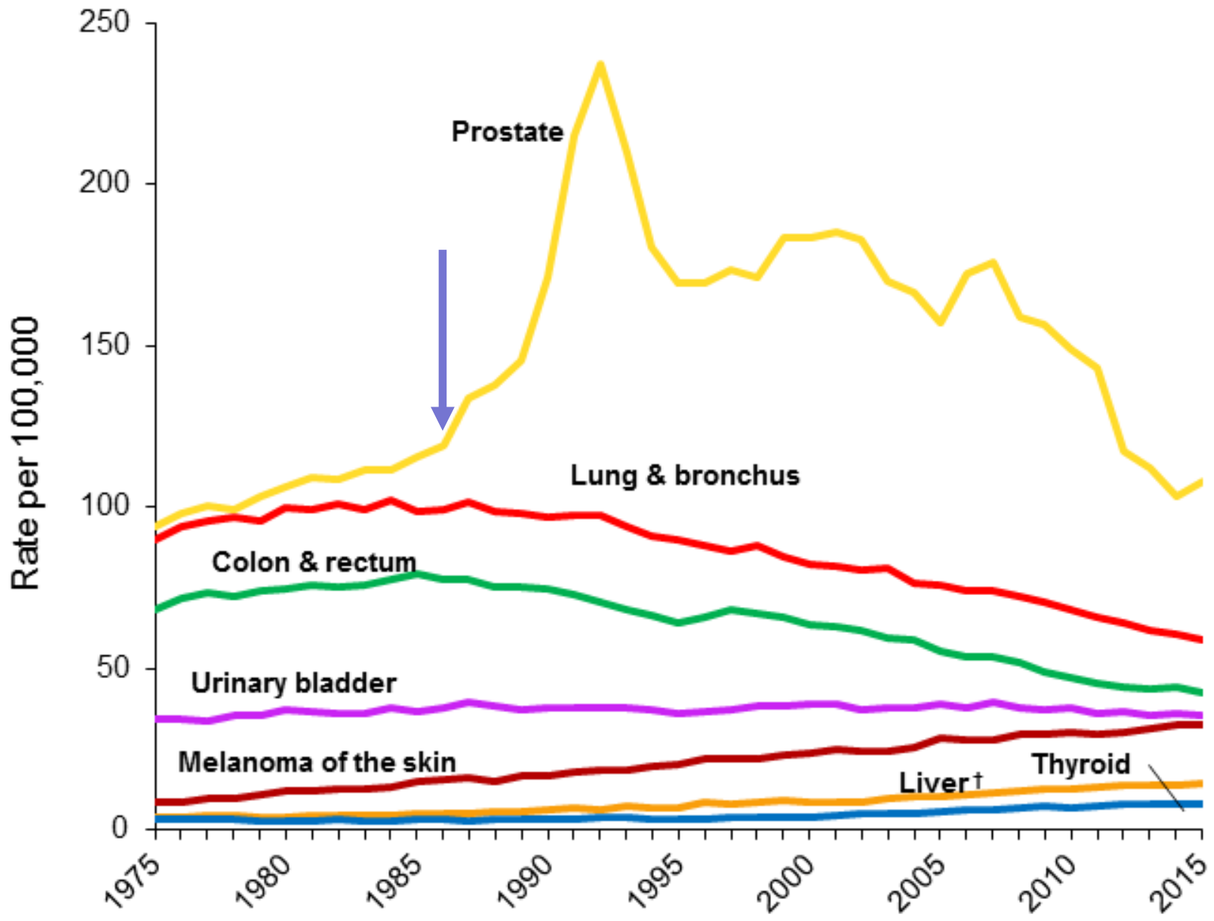
PSA- a brief history, continued

- 1981: Using hybridoma technology Hybritech developed clinically used αPSA mAb (partnering with Roswell Park).

- 1986- PSA approved by FDA for monitoring of men who had definitive therapy for prostate cancer.

- 1986-1994: Widespread off-label use of PSA screening ensues….

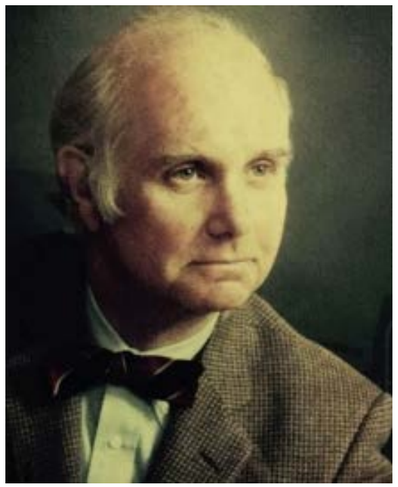
Male Cancer Incidence 1975-2015



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2018.

PSA- a brief history, continued

- 1987- Stamey et al., NEJM demonstrate PSA more sensitive than PAP in detecting cancer in a cohort with advanced disease.



- 1991- Catalona et al., NEJM propose PSA as a PC screening test.

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.

Table 4. Accuracy of Rectal Examination, Serum PSA Measurement, and Ultrasonography in Detecting Prostate Cancer on First Biopsy in 300 Men in the Comparison Group.

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

*Sensitivity was determined by dividing the number of true positive results by the number of true positives plus the number of false negatives, specificity by dividing the number of true negative results by the number of true negatives plus the number of false positives, positive predictive value by dividing the number of true positive results by the number of true positives and false positives combined, negative predictive value by dividing the number of true negative results by the number of true negatives and false negatives combined, and overall accuracy by dividing the number of true positive and true negative results by the total number tested.

†Values are based on a sample of 235 men (65 patients in the comparison group did not have serum PSA determinations).

PSA- a brief history, continued

C orrelation of screening PSA with cancer risk:

PSA ng/ml	Risk of prostate cancer	Risk of aggressive prostate cancer
<0.5	7%	1%
0.6 - 1.0	10%	1%
1.1 - 2.0	17%	2%
2.1 - 3.0	24%	5%
3.1 - 4.0	27%	7%

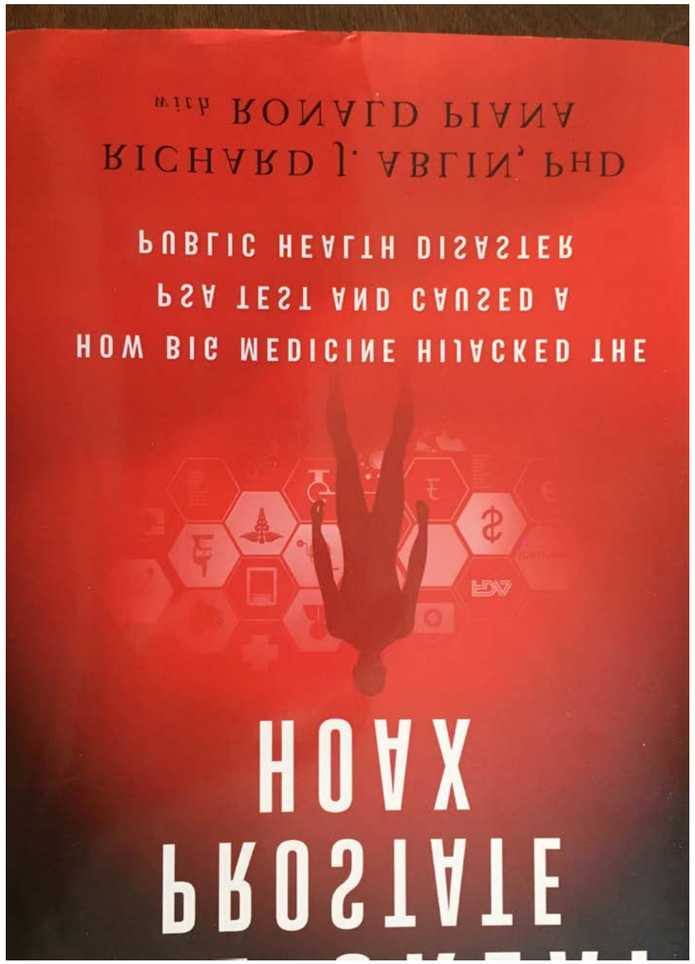
Prostate Cancer Prevention Trial (PCPT)

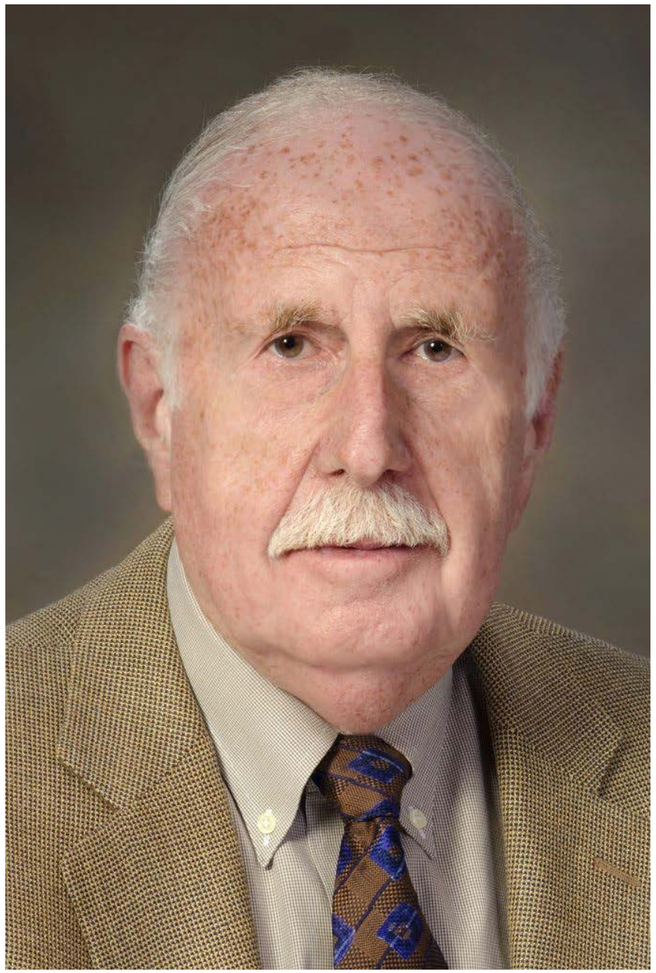
PSA- a brief history, continued

- 1994- PSA approved by FDA for the early detection of prostate cancer.

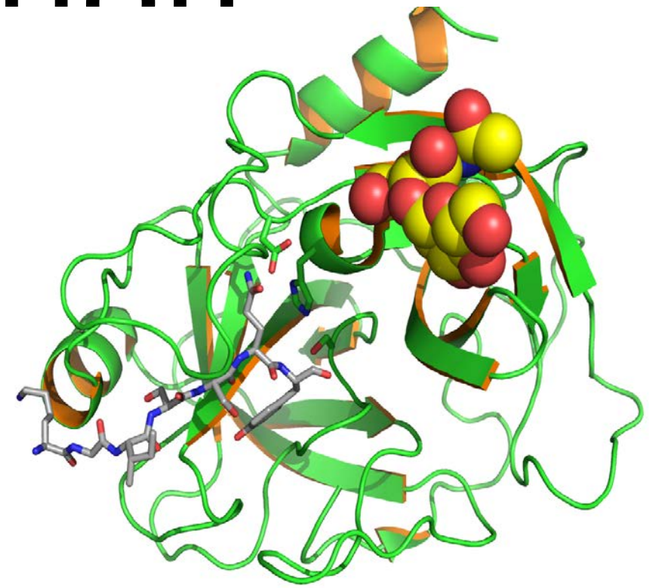
- 1996 Percent-free PSA approved by FDA as an adjunctive prostate cancer screening tool.

PSA politics





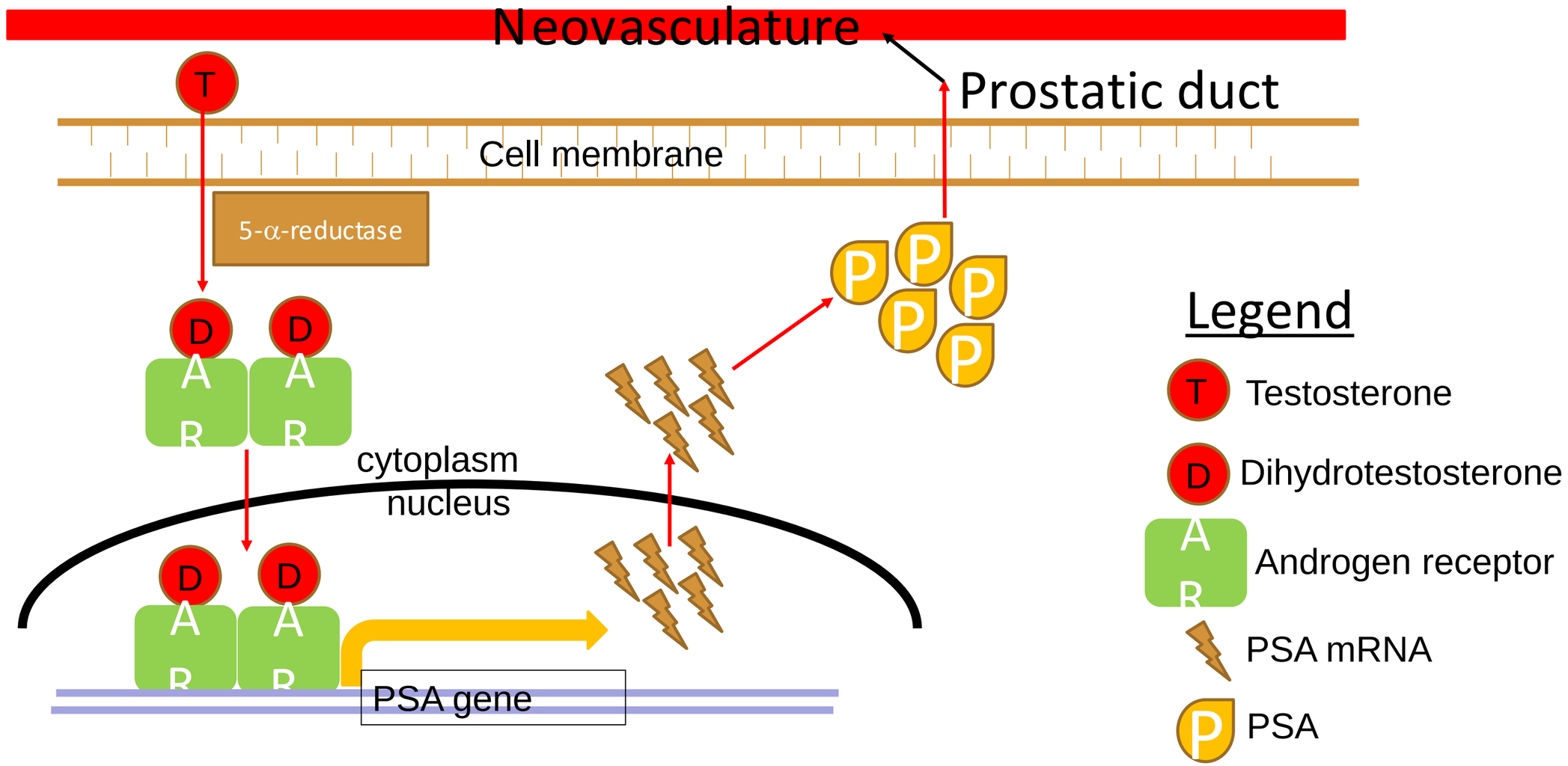
PSA structure and function



- Human kallikrein-3
- Glycoprotein serine protease.
- Secreted in seminal fluid.
- Facilitates sperm motility and uterine entry.
- Produced by both normal and malignant epithelial cells.
- Transits into circulation.

(2008) J.Mol.Biol. **376**: 1021-1033

R egulation of PSA by androgen receptor (AR) signaling



C linical sources of PSA variation

- Mechanical perturbation (e.g. truck drivers, D R E)
- B enign prostatic hypertrophy
- Prostatitis/inflammation
- Medications (5-α-reductase inhibitors, anti-inflammatories)*
- Supplements (testosterone, androgenic herbs)

* Since these lower PSA, may impact sensitivity as well

Occupation and PSA

	PSA < threshold n (%)	PSA ≥ threshold n (%)	Crude OR	95% CI	Adjusted OR	95% CI*
PSA threshold 4.0 ng/mL						
All						
Production workers	1,690 (99.5)	9 (0.5)	1.00		1.00	
Office workers	251 (96.9)	8 (3.1)	5.98	2.29-15.65	7.73	2.78-21.46
Age < 50						
Production workers	1,079 (99.6)	4 (0.4)	1.00		1.00	
Office workers	187 (99.5)	1 (0.5)	1.44	0.16-12.97	2.372	0.24-22.84
Age ≥ 50						
Production workers	611 (99.2)	5 (0.8)	1.00		1.00	
Office workers	64 (90.1)	7 (9.9)	13.37	4.13-43.33	12.90	3.65-45.64

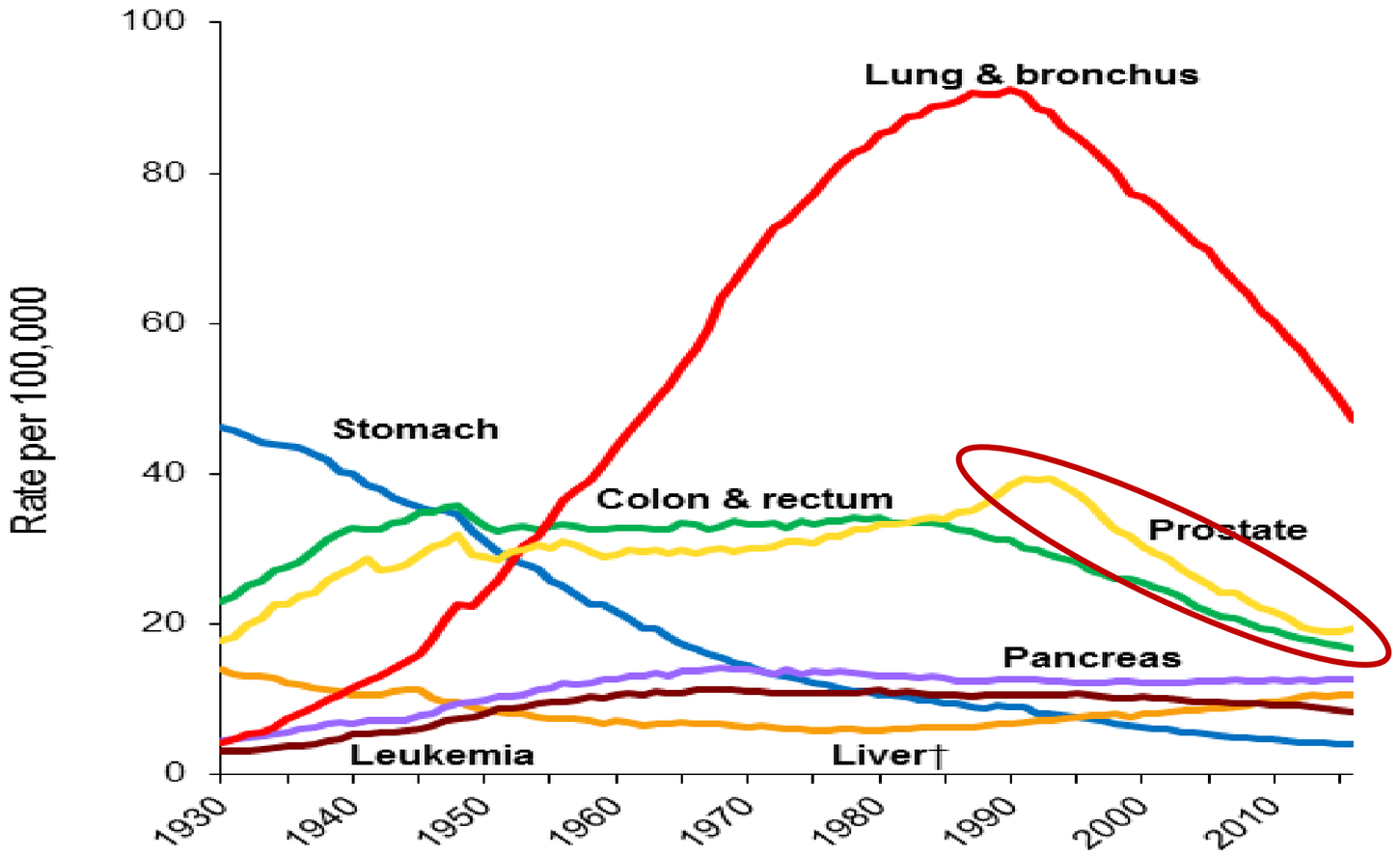
Ann Occup Environ Med. 26: 50 (2014)

Conclusions: Historical overview of PSA as a biomarker

- PSA has had a controversial history with clinical impact driven by early off label use.
- PSA is tightly regulated by AR signaling, which may be impacted by a variety of factors.
- PSA lacks specificity with many clinical sources of variation.

R eview of PSA screening prospective studies

Male cancer-specific mortality-1930-2015



*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other b
NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal,
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2018

Overview of PSA screening trials

Study	PLCO	ERSPC
Location	USA	Europe
Number enrolled	76,693	182,000
Years enrolled	1993-2001	1991-2003
Screening interval	annual	2-4 years
Ages included	55-74	55-69
PSA Biopsy threshold	4	3
Control arm PSA contamination	77%	20-25%

PLCO- prostate, lung, colon, ovarian screening

ERSPC- European Randomized study of Screening for Prostate Cancer conducted in Netherlands, Belgium, Sweden, Finland, Italy, Spain, Switzerland

Screening increases early detection of prostate cancer, but . . .

Study	US (PLCO screening)	Europe (ERSPC)
Cancer incidence in unscreened	95/10,000 person-years	49/10,000 person-years
Cancer incidence in screened	116/10,000 person-years	76/10,000 person-years
Cancer deaths in unscreened	1.7/10,000 person-years	4.1/10,000 person-years
Cancer deaths in screened	2.0/10,000 person-years	3.5/ 10,000 person-years

Impact on prostate cancer-specific survival is mixed

Study	US (PLCO screening)	Europe (ERSPC)
Cancer incidence in unscreened	95/10,000 person-years	49/10,000 person-years
Cancer incidence in screened	116/10,000 person-years	76/10,000 person-years
Cancer deaths in unscreened	1.7/10,000 person-years	4.1/10,000 person-years
Cancer deaths in screened	2.0/10,000 person-years	3.5/ 10,000 person-years

Impact on prostate cancer-specific survival is mixed

Study	US (PLCO screening)	Europe (ERSPC)
Cancer incidence in unscreened	95/10,000 person-years	49/10,000 person-years
Cancer incidence in screened	116/10,000 person-years	76/10,000 person-years
Cancer deaths in unscreened	1.7/10,000 person-years	4.1/10,000 person-years
Cancer deaths in screened	2.0/10,000 person-years	3.5/ 10,000 person-years

Number needed to treat (NNT)= 48

Number needed to screen (NNS) = 1410

ERSPC trial data used to estimate life-saving costs

- In the ERSPC study, screening correlates with a 20% decrease in prostate cancer death rates at 9 year. Assuming *NNS = 1,410, NNT = 48:*
  - PSA 1,410 x $50 x 2 tests/patient = $141,000
  - DRE 1,410 x $100 = $141,000
  - TRUS (1,410 x 0.16 x $4000/test = $902,400 Fraction with PSA> 3 ng/mL
  - Radical Prostatectomy: 48 x $12,173 = $584,304
  - Cost to prevent one PC-specific death $1,768,704
  - Cost to prevent 20% (6,400) of deaths $11,319,705,600

http://healthcarebluebook.com/page_Default.aspx
http://EzineArticles.com/6514961
http://ezinearticles.com/?Prostate-Cancer:-The-Dreaded-Prostate-Biopsy-and-Alternatives&id=6514961
Luo JL et al, ***Nature.*** **2007**
http://health.costhelper.com/blood-test.html

The unaccounted costs of biopsy

- Pain and suffering (~100%)
- Sepsis (2%)
- Theoretical concerns for seeding, local inflammation (??)

PSA screening trials: conclusions

- Screening results in the diagnosis of more prostate cancers in both studies.
- In the US (PLCO) study, screening had no impact on reducing prostate cancer death rates, with contamination felt to play a role.
- In the European (ERSPC) study, screening was associated with a 20% risk reduction in prostate cancer deaths.

Overview of PSA Screening Guidelines

Prior USPSTF PSA Screening Policy Statements

2008

- Current evidence is insufficient to assess the balance of benefits and harms of screening for prostate cancer in men younger than age 75 years (Grade C).
- Do not screen for prostate cancer in men age 75 years or older (Grade D).

2012

The U.S. Preventive Services Task Force (USPSTF) recommends against prostate-specific antigen (PSA)–based screening for prostate cancer (Grade D).

Current PSA Screening Guidelines

ENTITY	<40	MEN 40-55	55-69	>70
AUA	Against (Grade C)	Against except high risk (Grade C)	Consider (Grade B) Biennial	Against if life expectancy <10-15 years (Grade C) Consider otherwise
NCCN	No policy	Starting at 45 and based on perceived risk (FH, germline mutations, race, medications) risk stratify based on baseline PSA: •PSA<1, normal DRE: obtain PSA every 2-4 years •PSA 1-3, normal DRE: obtain PSA every 1-2 years •PSA >3 and/or suspicious DRE: biopsy		Healthy and >75: PSA >4: biopsy
ACS	No policy	Consider at: •40 if > 1 first degree relative with PC •45 if 1 first degree relative <65 or AA •50 for men at average risk and > 10 years survival •Annual for PSA>2.5, otherwise biennially	Consider	Consider (no age cap in policy)
USPSTF	No policy	No policy	Consider (Grade C)	Against (Grade D)

Early Detection of Prostate Cancer: AUA Guideline (2013)
https://www.cancer.org/cancer/prostate-cancer/early-detection/acs-recommendations.html
Screening for Prostate Cancer: USPTF *JAMA.* 2018;319(18):1901–1913. doi:10.1001/jama.2018.371
NCCN Guidelines: Prostate Cancer Early Detection (2018)

USPSTF PSA Screening Policy Statement Revised in 2018

For men aged 55 to 69 years, the decision to undergo periodic prostate-specific antigen (PSA)–based screening for prostate cancer should be an individual one. Before deciding whether to be screened, men should have an opportunity to discuss the potential benefits and harms of screening with their clinician and to incorporate their values and preferences in the decision. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy; overdiagnosis and overtreatment; and treatment complications, such as incontinence and erectile dysfunction. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening.

The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older.

Screening for Prostate Cancer: USPTF *JAMA.* 2018;319(18):1901–1913. doi:10.1001/jama.2018.371

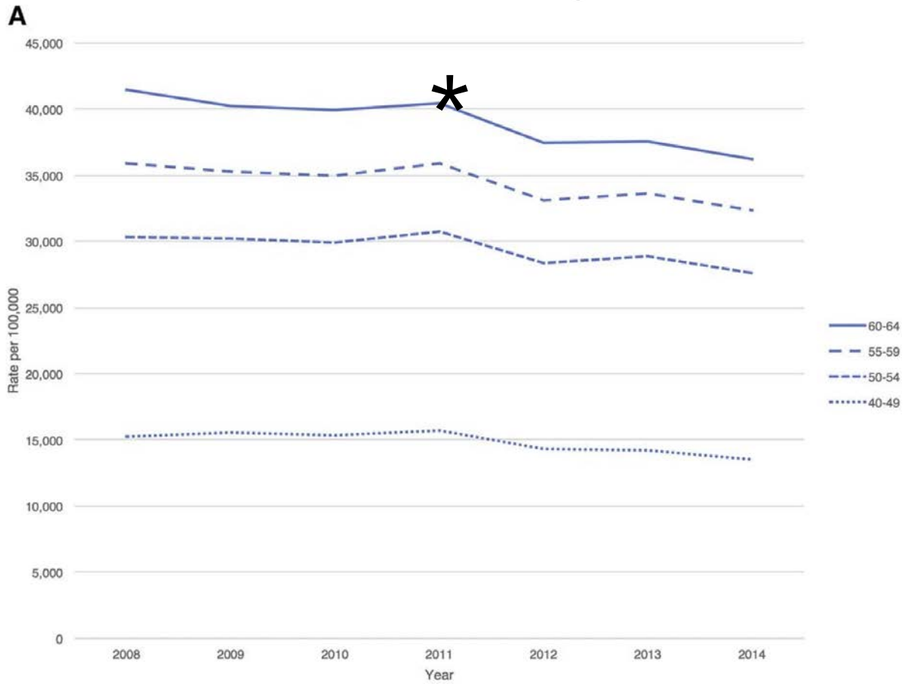
PSA Screening Summary

- In the last 10+ years guidelines for PSA screening have become increasingly conservative.
- PSA screening recommendations tend to incorporate the biases of recommending entities.
- My opinion: Age is a number. Consider all potential factors (especially race, family history- most closely mirrors NCCN).
  Counsel patients on risks and benefits of testing.

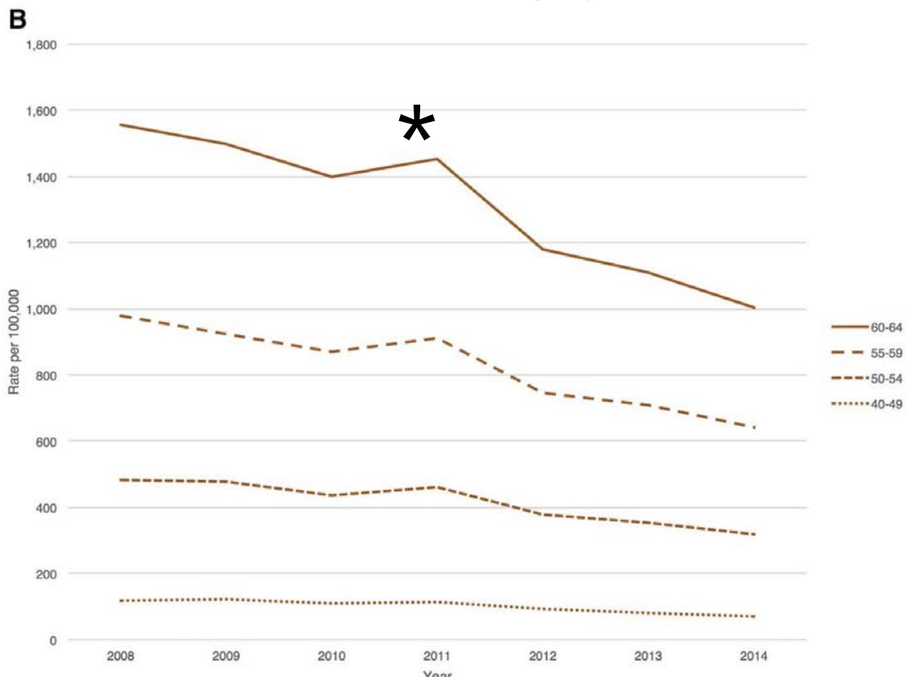
PSA screening trends and impact on prostate cancer disease states

Rates of PSA screening and biopsy

Rate of PSA testing



Rate of TRUS Biopsy

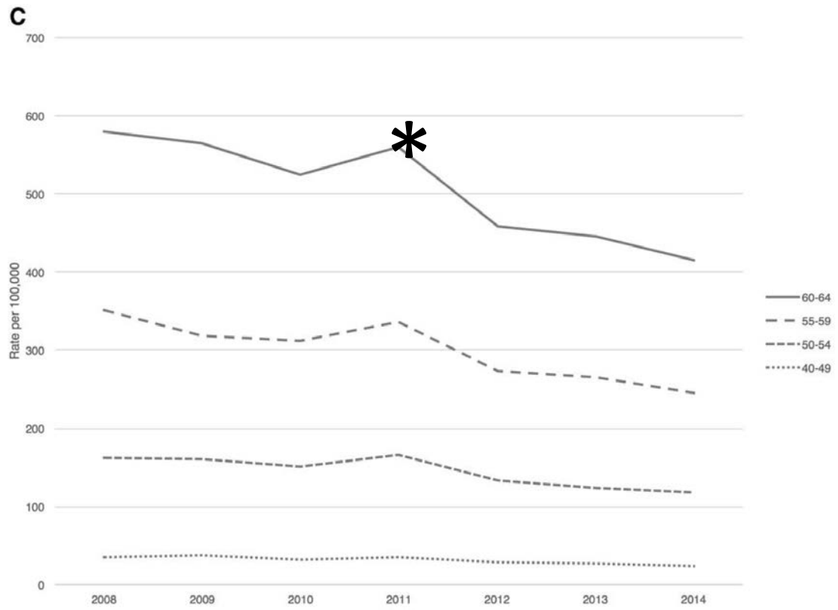


*2011 public draft of USPSTF recommendations released (no screening)

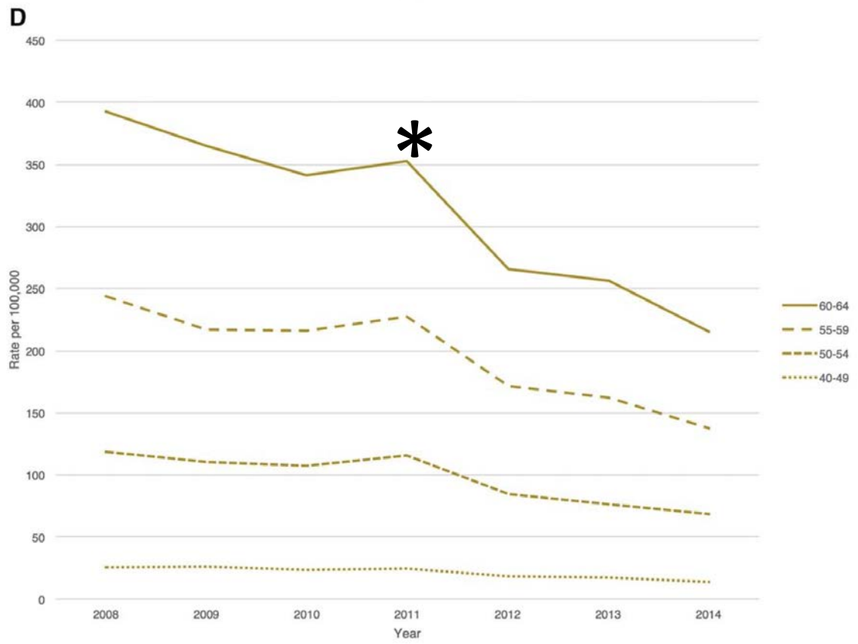
Kerns et al, Cancer 2018;124:2733-9.

R ates of prostate cancer detection and treatment

Rate of PC detection



Rate of Definitive Therapy



*2011 public draft of USPSTF recommendations released

Kerns et al, Cancer 2018;124:2733-9.

Composite Data

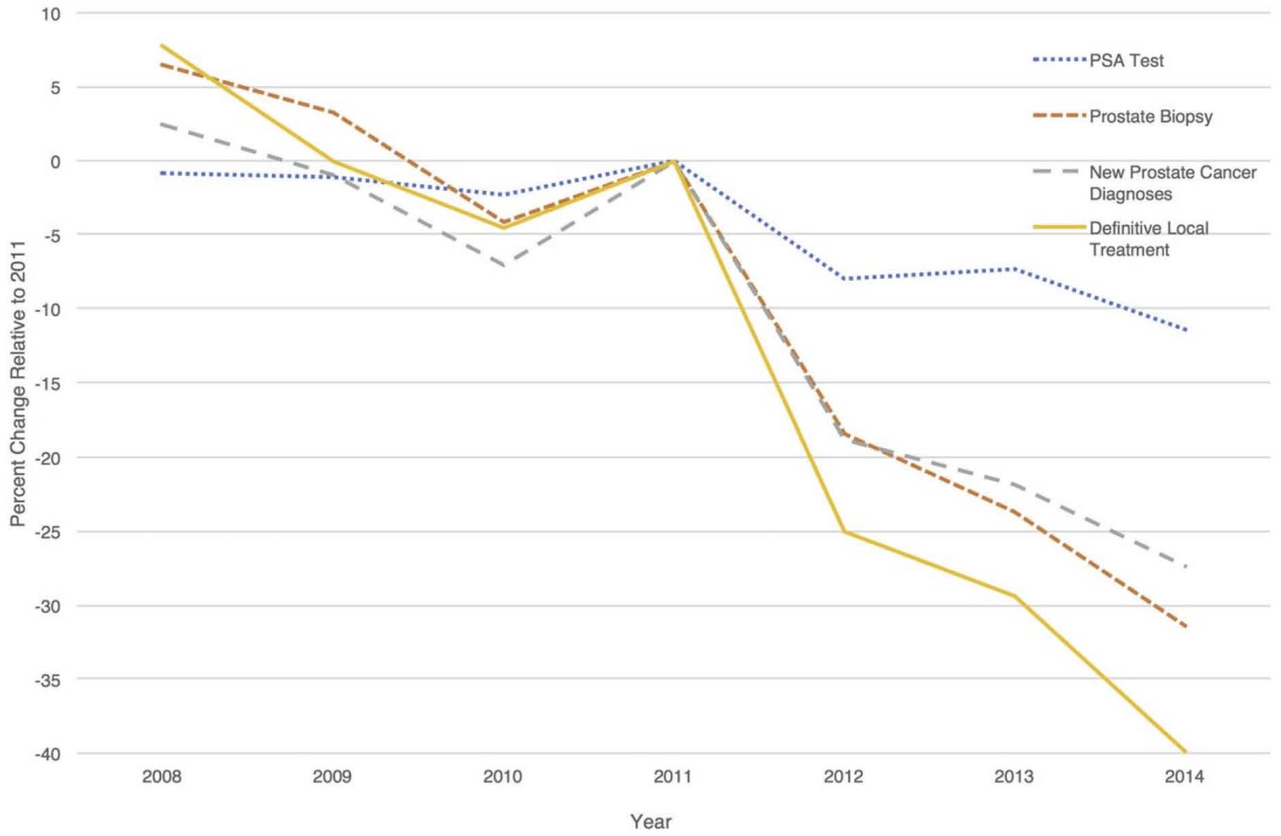
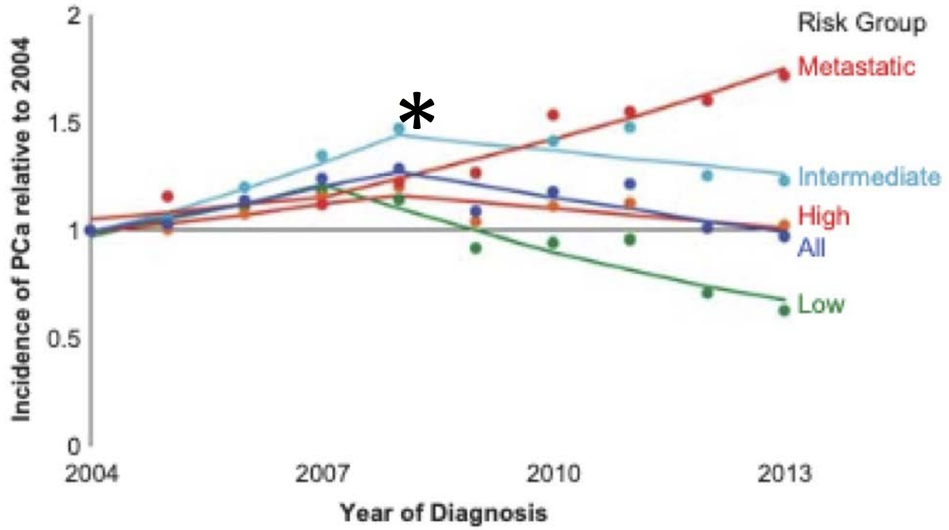


Figure 2. Changes over time relative to 2011 age-standardized rates for prostate-specific antigen testing, prostate needle biopsy, new diagnoses of prostate cancer, and definitive local therapy for prostate cancer. PSA, prostate-specific antigen.

Kerns et al, Cancer 2018;124:2733-9.

Prostate C ancer Incidence

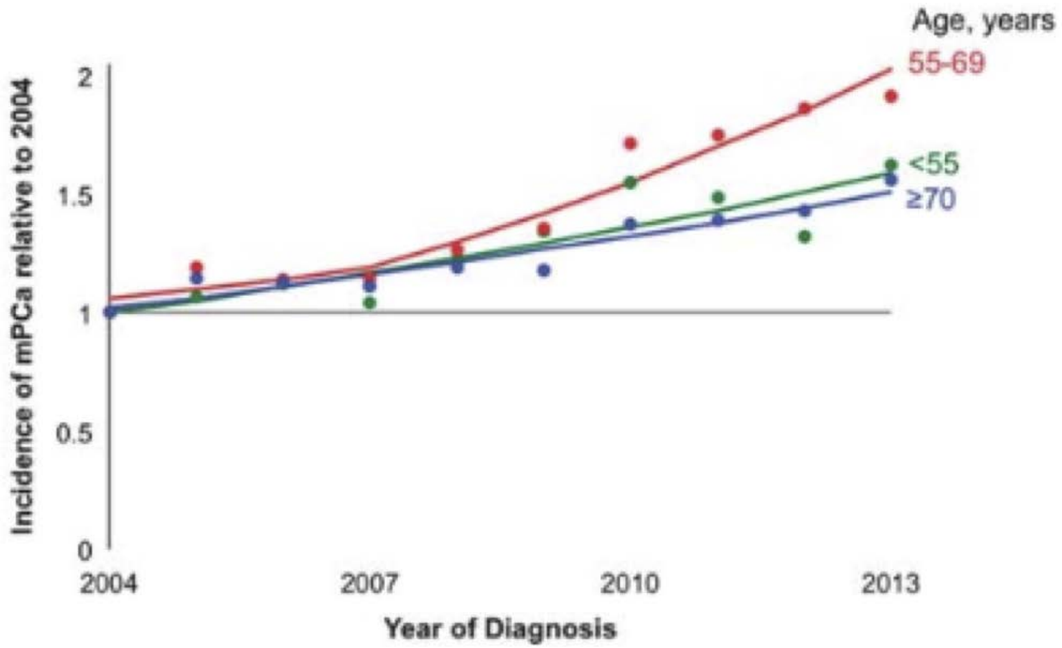


Risk Group	Trend 1			Trend 2		
	Interval	APC	p	Interval	APC	p
Low	2004-2007	7.5	0.3	2007-2013	-9.3	<0.05
Intermediate	2004-2008	10	<0.05	2008-2013	-2.7	0.3
High	2004-2008	4.1	0.1	2008-2013	-2.7	0.1
Metastatic	2004-2007	3.3	0.4	2007-2013	7.1	<0.05
All	2004-2008	6.3	0.1	2007-2013	-4.8	0.1

*2008- USPSTF states insufficient evidence to support screening

Weiner et al., *Prostate Cancer Prostatic Dis.* 2016 Dec;19(4):395-39

Metastatic Prostate Cancer Incidence as a function of age



Age, years	Trend 1			Trend 2		
	Interval	APC	p	Interval	APC	p
<55	2004-2013	5.3	<0.05			
55-69	2004-2007	4	0.5	2007-2013	9.3	<0.05
≥70	2004-2013	4.5	<0.05			

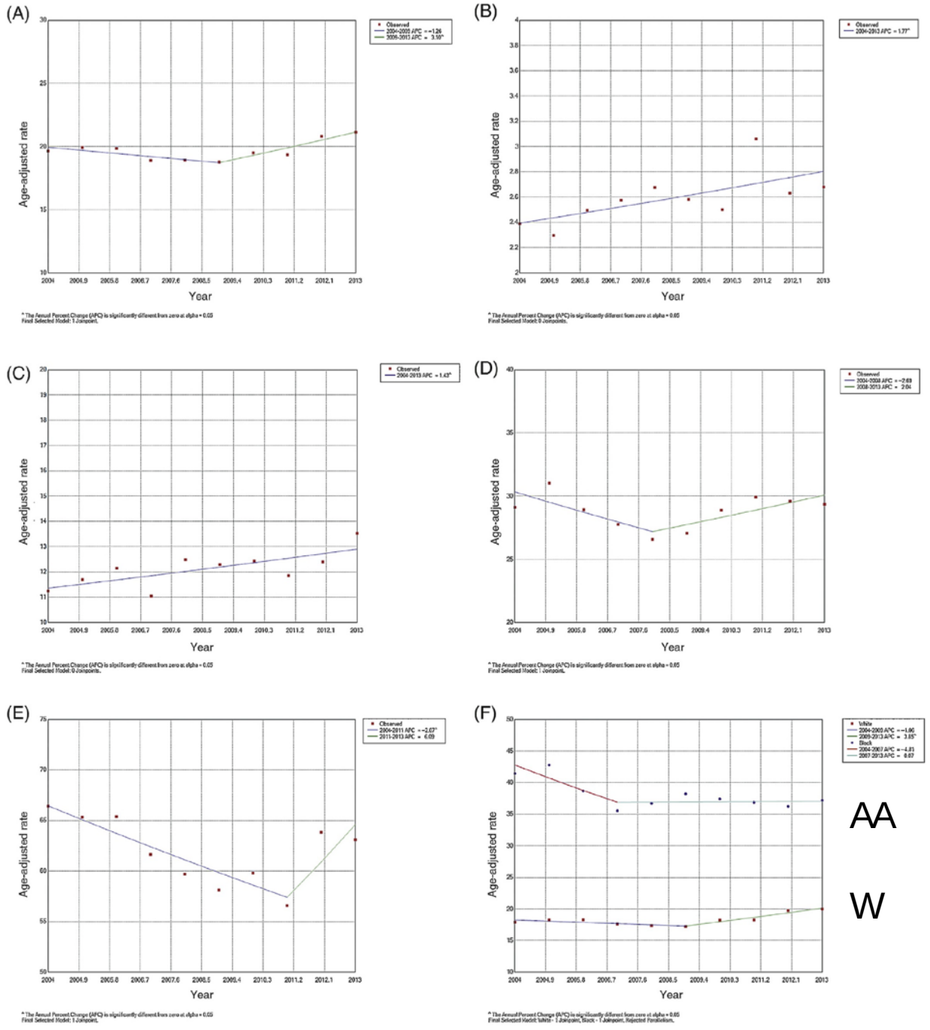
Weiner et al., *Prostate Cancer Prostatic Dis.* 2016 Dec;19(4):395-39

Metastatic prostate cancer incidence as a function of age and race

Overall

55-64

>75



45-54

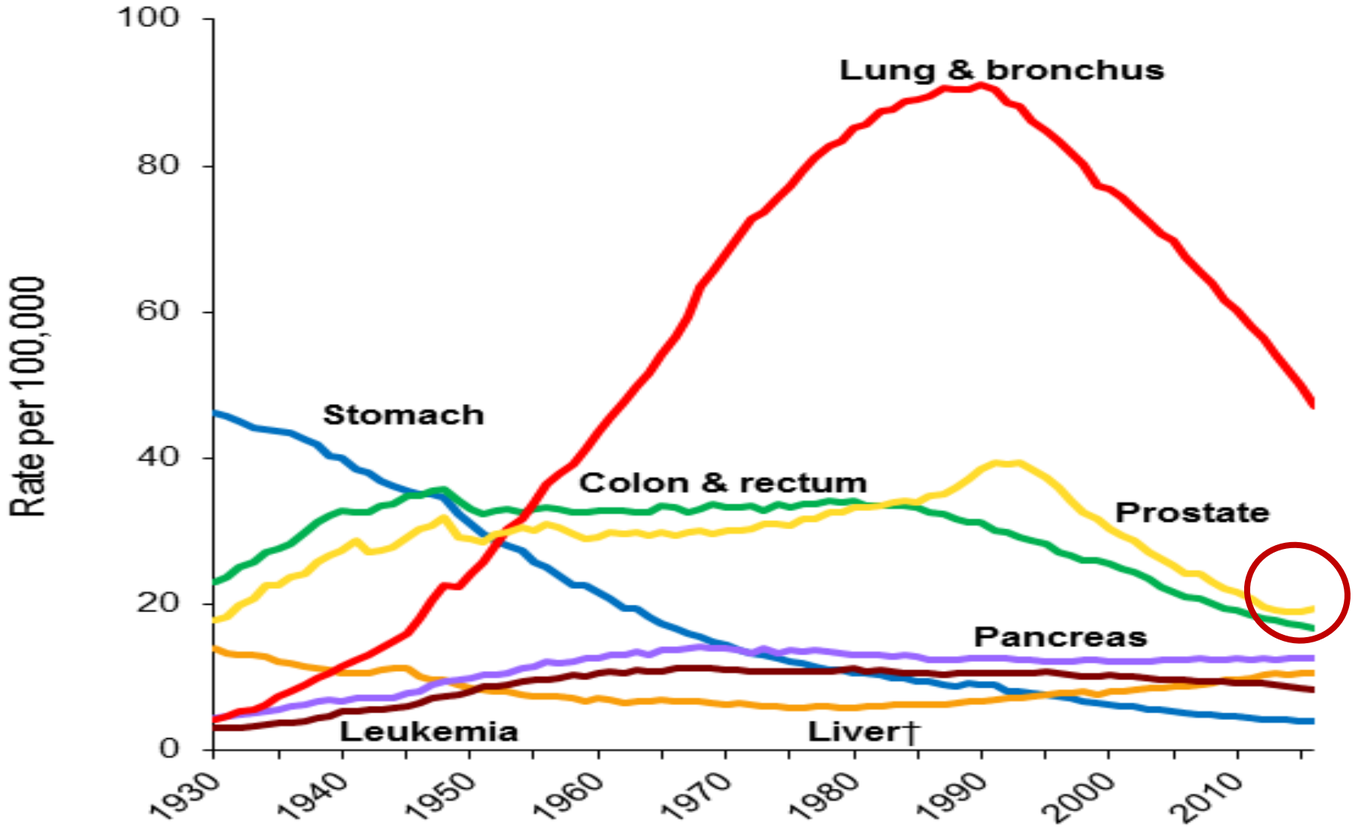
65-74

Race

Fig. 1 – Delay-adjusted incidence rates for metastatic prostate cancer. (A) The overall cohort of men aged ≥45 yr. (B–E) Rates stratified by age groups: (B) 45–54 yr, (C) 55–64 yr, (D) 65–74 yr, and (E) ≥75 yr. (F) Rates stratified by race. Data from the Surveillance, Epidemiology and End Results (SEER) database, 2004–2013. Metastatic cases were identified using the SEER Collaborative Staging system.

Delela et al., European Urology Foc 5:77-80 (2019)

Male cancer-specific mortality-1930-2015



*Age-adjusted to the 2000 US standard population. †Includes intrahepatic bile duct, gallbladder, and other bi
NOTE: Due to International Classification of Diseases coding changes, numerator information for colorectal,
Source: National Center for Health Statistics, Centers for Disease Control and Prevention, 2018

Summary-PSA screening trends and impact on prostate cancer disease states

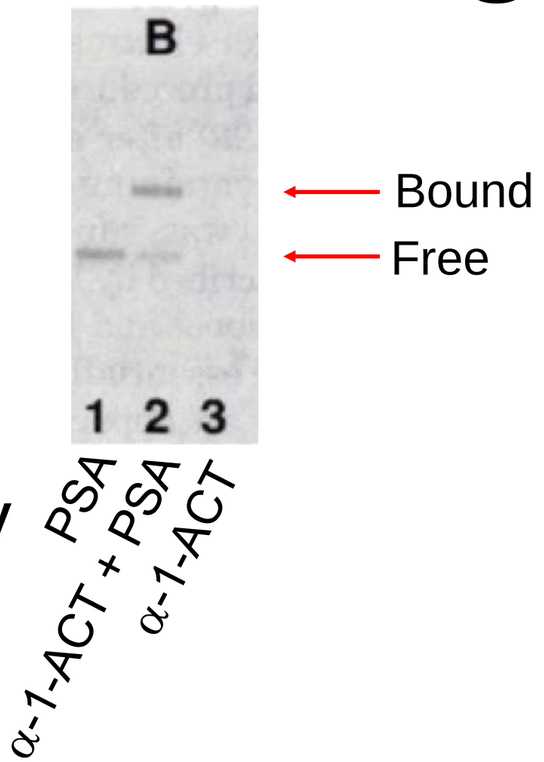
- The incidences of PSA screening, localized disease, and definitive therapy have been decreasing.
- The incidence of metastatic disease has been increasing over the last decade, particularly in populations discouraged from screening.
- There is an apparent correlation between USPSTF recommendations and acceleration of this trend.
- This is not causal proof, however.
- Possible future PC-specific mortality impact.

Optimizing PSA Screening

- Adjunctive tools
  - % free PSA
  - PSA density
  - Urinary PCA3 testing (FDA approved in 2012 for men with prior negative biopsy).

Optimizing PSA Screening

- % Free PSA
  - Circulating PSA complexes with α-1-antichymotrypsin (to prevent proteolytic inactivation).
  - Lower % free PSA increases PSA specificity



Probability of Cancer, Based on PSA[6,8] and %FPSA Results,[20] for Men With Normal Digital Rectal Examination Results*

T1

PSA (ng/mL [ng/mL])	Probability of Cancer (%)
0-2	~1
2.1-4	15
4.1-10	25
>10	>50

%FPSA	Probability of Cancer (%)
0-10	56
10-15	28
15-20	20
20-25	16
>25	8

PSA, prostate-specific antigen; %FPSA, percentage free prostate-specific antigen.
**%FPSA can further stratify risk for men with PSA values between 4 and 10 ng/mL (4 and 10 ng/mL).*

Lilja et al., Clin Chem 37/9 1618-1625 (1991)
Catalona et al., JAMA. 274(15):1214-20 (1995)
Southwick, Lab Med 32/5 259-263 (2001)

PSA Density

Table 4.

Multivariate analyses of PSA, PSA density and Gleason score in predicting positive surgical margins, extracapsular disease, seminal vesicle invasion and lymph node invasion

							95% CI for Exp(B)	
	B	SE	Wald	df	p^*	Exp(B)	Lower	Upper
Multivariate analysis for prediction of PSM								
PSA	0.001	0.013	0.004	1	0.947	1.001	0.975	1.028
PSAD	−0.884	0.264	11.191	1	0.001*	0.413	0.246	0.693
GS	0.265	0.110	5.797	1	0.016*	1.303	1.050	1.616
Multivariate analysis for prediction of ECD								
PSA	0.021	0.018	1.294	1	0.255	1.021	0.985	1.058
PSAD	−2.042	0.334	37.302	1	0.000*	0.130	0.067	0.250
GS	0.271	0.127	4.506	1	0.034*	1.311	1.021	1.683
Multivariate analysis for prediction of SVI								
PSA	0.045	0.021	4.744	1	0.029*	1.046	1.005	1.089
PSAD	−1.324	0.456	8.441	1	0.004*	0.266	0.109	0.650
GS	0.238	0.163	2.125	1	0.145	1.269	0.921	1.747
Multivariate analysis for prediction of LNI								
PSA	0.009	0.015	0.389	1	0.533	1.009	0.981	1.038
PSAD	−2.949	1.044	7.972	1	0.005*	0.052	0.007	0.406
GS	0.432	0.235	3.382	1	0.066	1.540	0.972	2.439

Sfoungaristos et al., *Can Urol Assoc J.* 2012 6:46-50

Optimizing PSA screening

- Urinary PCA3 testing
  - A lncRNA produced by malignant prostate cells (specific).
  - Urine collected following DRE
  - Prospective prostate cancer screening comparative study (n=201) vs PSA :

	PSA (<2.5)	PSA (4-10)	PCA3
Sensitivity	98%	84%	82%
Specificity	5%	80%	76%

Tinzl et al., Eur. Uro 46: 182-187 (2004)

Future screening approaches

- Multiparametric MRI- helps detect/target high grade disease
- Nuclear medical imaging of novel prostate-specific antigens
- Novel biomarkers (including PSA-based glycomic markers)

Conclusions

- PSA screening is imperfect but still a standard of care.
- PSA screening appears to save lives, but at a cost.
- Prostate cancer incidence appears to correlate with PSA prescribing practices.
- Adjunctive screening approaches may be helpful, but newer approaches are needed.

Thanks!

Questions?