Prostate Cancer Screening

Ahmad Shabsigh, MD, FACS
Assistant Professor
Department of Urology
The Ohio State University Wexner Medical Center

The Committee:

U.S. Preventive Services Task Force

The Date:
August 2008

The Committee:

U.S. Preventive Services Task Force

The Date:
August 2008

The Committee:

U.S. Preventive Services Task Force

The issue:

Prostate Cancer Screening

U.S. Preventive Services TASK FORCE

SCREENING FOR PROSTATE CANCER
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adult males
Recommendation	**Do not use prostate-specific antigen (PSA)-based screening for prostate cancer.** **Grade: D**

U.S. Preventive Services TASK FORCE

SCREENING FOR PROSTATE CANCER
CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Adult males
Recommendation	**Do not use prostate-specific antigen (PSA)-based screening for prostate cancer.** **Grade: D**

The reduction in prostate cancer mortality 10 to 14 years after PSA-based screening is, at most, very small, even for men in the optimal age range of 55 to 69 years.

The harms of screening include pain, fever, bleeding, infection, and transient urinary difficulties associated with prostate biopsy, psychological harm of false-positive test results, and overdiagnosis.

Harms of treatment include erectile dysfunction, urinary incontinence, bowel dysfunction, and a small risk for premature death. Because of the current inability to reliably distinguish tumors that will remain indolent from those destined to be lethal, many men are being subjected to the harms of treatment for prostate cancer that will never become symptomatic.

The benefits of PSA-based screening for prostate cancer do not outweigh the harms.

The Impact of the Disease

Prostate Cancer Epidemiology

Estimated New Cases*

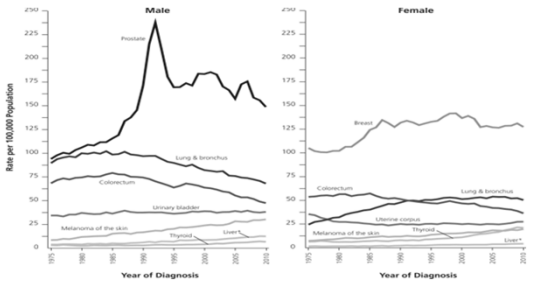
Males			Females		
Prostate	233,000	27%	Breast	232,670	29%
Lung & bronchus	116,000	14%	Lung & bronchus	108,210	13%
Colorectum	71,830	8%	Colorectum	65,000	8%
Urinary bladder	56,390	7%	Uterine corpus	52,630	6%
Melanoma of the skin	43,890	5%	Thyroid	47,790	6%
Kidney & renal pelvis	39,140	5%	Non-Hodgkin lymphoma	32,530	4%
Non-Hodgkin lymphoma	38,270	4%	Melanoma of the skin	32,210	4%
Oral cavity & pharynx	30,220	4%	Kidney & renal pelvis	24,780	3%
Leukemia	30,100	4%	Pancreas	22,890	3%
Liver & intrahepatic bile duct	24,600	3%	Leukemia	22,280	3%
All Sites	**855,220**	**100%**	**All Sites**	**810,320**	**100%**

Estimated Deaths

Males			Females		
Lung & bronchus	86,930	28%	Lung & bronchus	72,330	26%
Prostate	29,480	10%	Breast	40,000	15%
Colorectum	26,270	8%	Colorectum	24,040	9%
Pancreas	20,170	7%	Pancreas	19,420	7%
Liver & intrahepatic bile duct	15,870	5%	Ovary	14,270	5%
Leukemia	14,040	5%	Leukemia	10,050	4%
Esophagus	12,450	4%	Uterine corpus	8,590	3%
Urinary bladder	11,170	4%	Non-Hodgkin lymphoma	8,520	3%
Non-Hodgkin lymphoma	10,470	3%	Liver & intrahepatic bile duct	7,130	3%
Kidney & renal pelvis	8,900	3%	Brain & other nervous system	6,230	2%
All Sites	**310,010**	**100%**	**All Sites**	**275,710**	**100%**

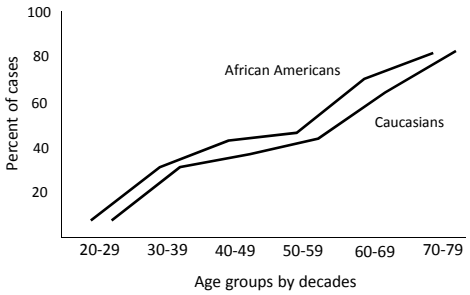
Jemal et al. Cancer statistics, 2014. CA cancer J clin, 2014 Mar-Apr;61(2):133-4

Age Adjusted Incidence

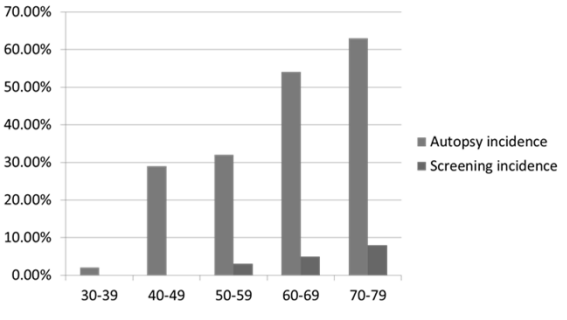


Jemal et al. Cancer statistics, 2014. CA cancer J clin, 2014 Mar-Apr;61(2):133-4.

Incidence of prostate cancer on autopsy

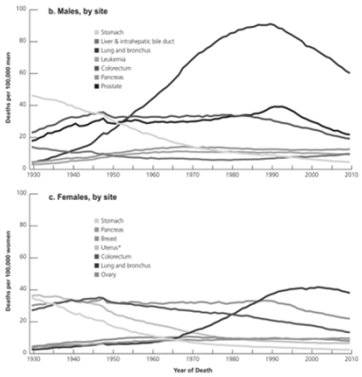


Incidence of prostate cancer on autopsy



Sakr 1993

Age Adjusted Deaths



Jemal et al. Cancer statistics, 2014. CA cancer J clin, 2014 Mar-Apr;61(2):133-4.

Lifetime Risk of Dying from CaP

- Risk of dying from prostate cancer is ~3%
- Once metastatic disease develops there is no cure
- Prior to PSA screening only 25% of CaP presented confined to prostate vs. 91% since
- 5 year CSS rates increased from ~70% to 100% (from 1980s to early 2000s)

Jemal et al. Cancer statistics, 2010. *CA cancer J clin, 2011 Mar-Apr;61(2):133-4.*
Comprehensive Textbook of Genitourinary Oncology, 3rd edition
Catalona et al. Detection of organ-confined prostate cancer is increased through prostate-specific antigen-based screening. *JAMA 1993; 270(8):948*

What is Cancer Screening?

- Checking for disease when there are no symptoms. Since screening may find diseases at an early stage, there may be a better chance of curing the disease.
- The source: NCI

What Is Prostate Cancer Screening?

- HPI
- DRE
- PSA

Prostate Specific Antigen

- Discovered in 1979 by Wang et al
- Approved by FDA in 1986
- Produced by prostate and periuretheral glands epithelial cells
- Liquefaction of seminal coagulum
- Serine protease from the kallikrein family
- In serum, most is bound

Prostate Specific Antigen

- Inflammation, hyperplasia, neoplasia lead to disruption of physiological barriers and increased serum PSA levels
- Half life is 2-3 days
- Used for
  - Initial diagnosis of disease and screening
  - Monitor for recurrence after initial therapy
  - Prognosis of outcomes after therapy

Prostate Cancer Screening

- Controversial:
  - Prostate cancer has a relatively slow course, Long term follow up is needed (>15 years).
  - Patient's age
  - Comorbidities
  - Treatments are associated with significant morbidity
  - No comparisons of efficacy between therapeutic options

Screening for Prostate Cancer: *Potential Harms*

- Additional medical visits
- Adverse effects of prostate biopsies
- Anxiety
- Over diagnosis
- Over treatment
- Morbidity and mortality associated with treatment
- Financial burden

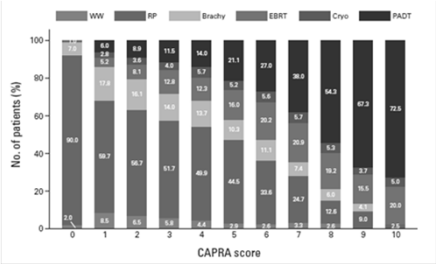
Complications of TRUS Prostate Biopsy

Complications	%
Hematospermia	37.4
Hematuria > 1 d	14.5
Rectal bleeding <2 d	2.2
Prostatitis	1.0
Fever > 101.3°F, epididymitis, rectal bleeding >2 d, retention	<1.0
Other complications requiring hospitalization	0.3

EAU Guidelines

Time Trends and Local Variation in Primary Treatment of Localized Prostate Cancer

Matthew R. Cooperberg, Jeanette M. Broering, and Peter R. Carroll



J Clin Oncol 28:1117-1123.

Screening for Prostate Cancer: *Potential Benefits*

- **Early detection and treatment**
- **Improve cancer Specific Survival**
- **Alleviate symptoms of locally advanced disease**

The Evidence

ERSPC

The European Randomized study of Screening for Prostate Cancer

ERSPC

- **Primary objective: PC mortality**
- **Ages 50-74**
- **162.387 men**
- **Screen interval every 4 yrs (87%) Sweeden every 2 yrs (13%)**
- **Sextant TURS Bx for PSA ≥ 3.0 ng/ml, abnormal DRE, F/T ratio 3-4 ng/ml**

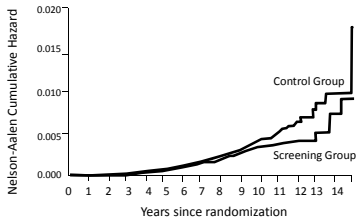
N Engl J Med. 2009 Mar 26;360(13)

ERSPC

- **Screen 72.890**
- **Control 89.353**
- **85.8% biopsied of the positive tests PPV 24.1**
- **Median F/U 9 years**
- **Screen arm: 5990 PC (8.2%), that is 71% higher, 214 deaths**
- **Control arm: 4.307 PC (4.8%), 326 deaths**

N Engl J Med. 2009 Mar 26;360(13)

ERSPC



N Engl J Med. 2009 Mar 26;360(13)

ERSPC

- **20% fewer men die of PC in the screen group (p=0.04)**
- **Adjustment for non - compliance, 27% fewer deaths in the screened men**
- **Absolute risk reduction 7 per 10.000 screened men**
- **NNS: 1.410, NNT: 48 in excess of the control arm.**
- **NNT to prevent mets 24**
- **All centers showed the same outcome (16-26%)**

N Engl J Med. 2009 Mar 26;360(13)

Number Needed to Treat (NNT)

- **Estimates Will Decrease**
- **In Northern Ireland (with very little screening), the NNT to prevent 1 case of metastatic prostate cancer was only 15**
- **THAT IS similar to the NNT to prevent 1 breast cancer death through mammography screening and follow-up surgery**
- ***The number needed to treat to save 1 life with prostate cancer screening will decrease with correction for compliance and longer follow-up***

Roobol MJ et al, Eur Urol 56: 592, 2009

Number Needed to Treat (NNT)

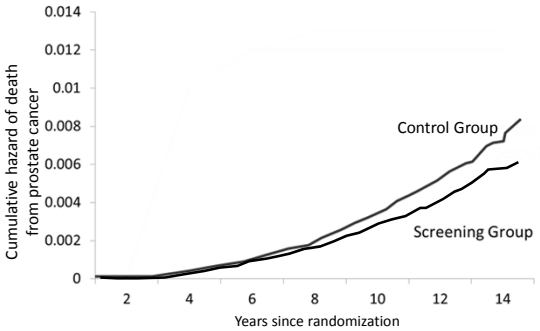
Table 1. Modeled Results Assuming a Piecewise Exponential Model

Year and Group	Hazard Function	Constant Hazard Rate	Survival	Dropout Rate	No. of Patients at Risk	NNS	NNT	Hazard Ratio	Cumulative Hazard Ratio
0									
Control	0.00000	0.00020	1.00000	0.00000	89,353	—	—	1.00	—
Screening	0.00000	0.00020	1.00000	0.00000	72,890	—	—	1.00	—
1									
Control	0.00020	0.00020	0.99980	0.02186	87,421	—	—	1.00	1.00
Screening	0.00020	0.00020	0.99980	0.02267	71,256	—	—	1.00	1.00
9									
Control	0.00344	0.00102	0.99657	0.37661	34,623	—	—	1.00	1.00
Screening	0.00264	0.00062	0.99736	0.35528	28,943	1,254	43	0.61	0.77
10									
Control	0.00446	0.00102	0.99555	0.37661	23,758	—	—	1.00	1.00
Screening	0.00326	0.00062	0.99675	0.35528	20,288	837	29	0.61	0.73
11									
Control	0.00548	0.00102	0.99453	0.37661	16,302	—	—	1.00	1.00
Screening	0.00388	0.00062	0.99613	0.35528	14,221	628	22	0.61	0.71
12									
Control	0.00650	0.00102	0.99352	0.37661	11,186	—	—	1.00	1.00
Screening	0.00450	0.00062	0.99551	0.35528	9,969	503	18	0.61	0.69

Abbreviations: NNS, number needed to screen; NNT, number needed to treat.

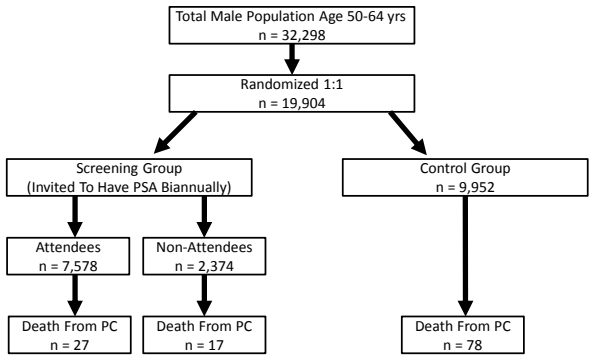
Catalona, *J Clin Oncol 2011, 29:464-467*

Prostate Cancer Mortality At 11 Years Of Follow-Up



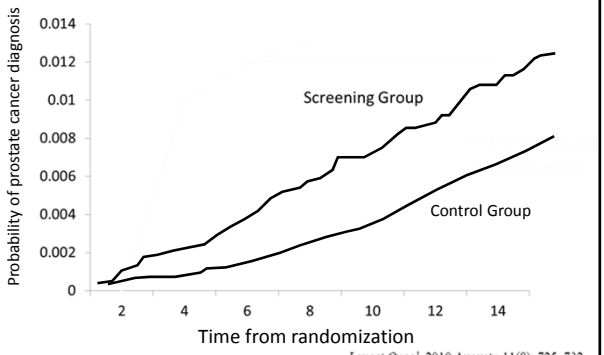
NEJM 366;11 March 15, 2012

Goteborg Randomized Prostate Cancer Screening Trial: Mortality Results



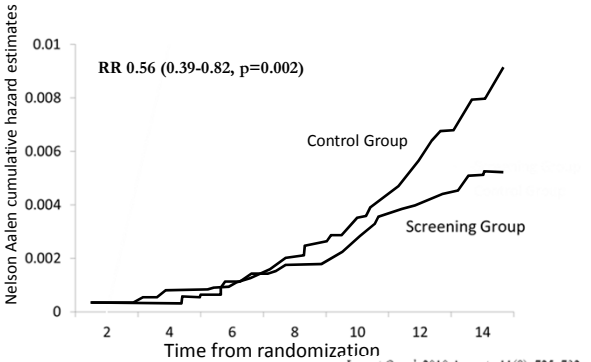
Lancet Oncol. 2010 August ; 11(8): 725–732.

Goteborg Randomized Prostate Cancer Screening Trial: Mortality Results



Lancet Oncol. 2010 August ; 11(8): 725–732.

Goteborg Randomized Prostate Cancer Screening Trial: Mortality Results



Lancet Oncol. 2010 August ; 11(8): 725–732.

PLCO

The US Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

PLCO

- **74,000 ages 55 to 74 years**
- **1:1 randomization to receive annual PSA and DRE screening to a total of 4 screens vs usual care in the community**
- **PSA cut-off is 4 ng/mL**
- **Follow-up of abnormal screening results was at the discretion of physicians**
- **In the screening group, rates of compliance were 85%**
- **Rate of screening in control arm 40$ in first year and 52% in sixth yrs**
- **Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year**
- **7 years of follow-up**

N Engl J Med. 2009 Mar 26;360(13)

Table 1. Characteristics of the Subjects at Baseline. *

Variable	Screening Group (N=38,343)	Control group (N=38,350)
	Percent	
Age		
55-59 yr	32.3	32.3
60-64 yr	31.3	31.3
65-69 yr	23.2	23.2
70-74 yr	13.2	13.2
Race or ethnic group†		
Non-Hispanic white	86.2	83.8
Non-Hispanic black	4.5	4.3
Hispanic	2.1	2.1
Asian	4.0	3.9
Other	0.8	0.9
Missing data	2.4	5.0
Enlarged prostate or benign prostatic hyperplasia	21.4	20.5
Previous prostate biopsy	4.3	4.3
Family history of prostate cancer	7.1	6.7
PSA test within past 3 yr		
Once	34.6	34.3
Two or more times	9.4	9.8
Digital rectal examination within past 3 yr		
Once	32.8	31.9
Two or more times	22.2	22.0

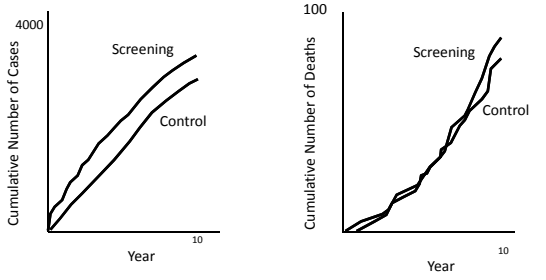
N Engl J Med. 2009 Mar 26;360(13)

PLCO

- **Screen: PC 116 per 10,000 person-years (2820), 50 deaths**
- **Control: PC 95 per 10,000 person-years (2322), 44 deaths**
- **Rate ratio, 1.13; 95% CI, 0.75 to 1.70). The data at 10 years were 67% complete and consistent with these overall findings.**

N Engl J Med. 2009 Mar 26;360(13)

PLCO



N Engl J Med. 2009 Mar 26;360(13)

PLCO

- **40%-52% of controls were screened during the study (contamination) *thus, comparing 85% vs 52% screened***
- **Poor prompt Bx compliance for PSA > 4**
- **Reported PCa mortality at 7-10 yr (med 11.5) but f/u was only 5.3 to 6.2 years for PCa patients**
- **10-year prostate cancer detection rate was only 15% higher in screened men - 9.0% vs 7.8%**
- **PCa death rate = 2.0 screened vs 1.7 control /104 per-yr**
- **Authors conclude: no mortality benefit from screening**

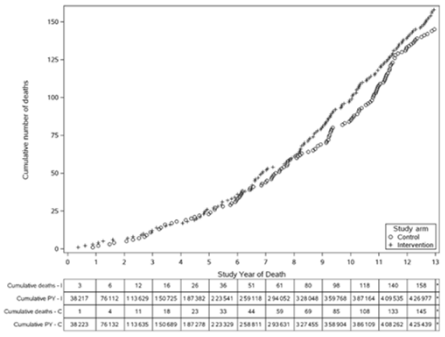
Assessing contamination and compliance in the prostate component of the prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial

		Time Period Of Latest Test				
		< 1 year	1-2 years	2-3 years	> 3 years	
PSA	# Men Surveyed	Routine Use (%)				Never Received Test (%)
0	181	33	15	3	2	38
1	422	31	14	6	5	34
2	385	41	17	5	4	24
3	410	39	16	8	5	21
4	435	46	15	7	3	17
5	392	46	18	5	3	15
0-5	2225	40	16	6	4	23
0-5 adjusted		46	14	5	4	21
0-5 screened arm		78	8	3	2	9
DRE						
0-5	2336	28	17	17	9	28
PSA or DRE						
0	196	39	16	6	10	20
1	454	37	20	8	10	15
2	415	49	17	7	6	13
3	450	43	20	10	7	12
4	466	49	17	7	6	12
5	418	52	22	5	5	8
0-5	2399	46	19	7	7	13
0-5 adjusted		51	17	6	6	12

Clinical Trials 2010; 7: 303–311

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,



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	

A Smarter Way to Screen for Prostate Cancer

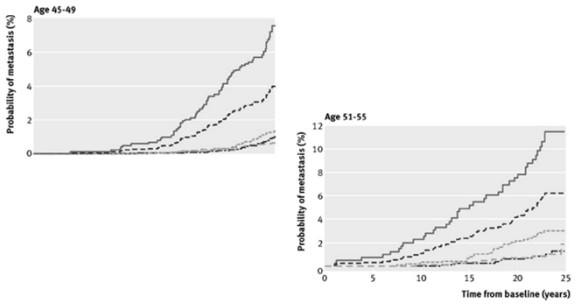
Smarter Screening

- **Risk-adjust screening by age, comorbidities, family history, ethnicity and PSA (reduce false positives)**
- **Reduce false positive PSA results by repeating (verifying) positives and by adding additional markers (reduce indications for biopsy)**
- **Active surveillance for low-risk cancers (reduce harms of unnecessary therapy)**
- **Refer patients who need treatment to experienced high-volume physicians or centers (reduce harm of necessary therapy)**

PSA concentration (µg/L)		Proportion (95% CI) Deaths	Metastases
Age 45-49 at baseline screen			
Highest 10th	≥ 1.6	44 (34 to 53)	40 (33 to 48)
Highest quarter	≥ 1.06	54 (45 to 63)	51 (44 to 59)
Below median	<0.68	28 (20 to 37)	28 (22 to 35)
Age 51-55 at second screen			
Highest 10th	≥2.4	44 (32 to 56)	42 (32 to 52)
Highest quarter	≥1.4	59 (47 to 71)	56 (46 to 66)
Below median	<0.85	16 (7 to 25)	18 (10 to 26)

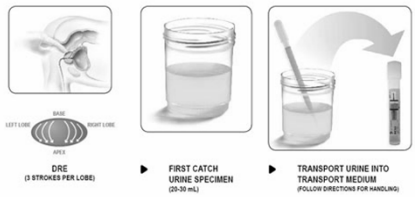
BMJ 2013;346

Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study



BMJ 2013;346

PCA3 Screening



PCA3 Screening

- **PCA3 is a non-coding mRNA molecule that is believed to be prostate specific.**
  - **It is highly over-expressed in cancerous prostate cells relative to benign tissue**
  - **Present in urine (no blood test necessary)**
- **Potential to be used as supplement for PSA testing**
  - **PSA has a 21% specificity but a 87% sensitivity for prostate cancer**
  - **Conversely, a test for PCA3 was reported to have a sensitivity of only 49%, but a specificity of 78%**
  - **Additional studies are needed**

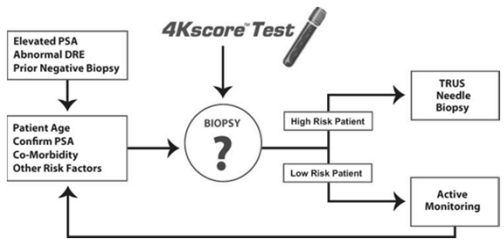
PCA3 Screening

Table 2: Operating Characteristics of PCA3 vs. PSA in 225 Men Undergoing Prostate Re-Biopsy

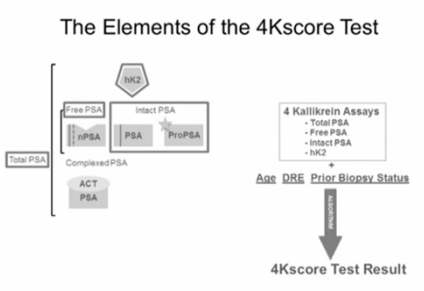
PCA3/PSA mRNA ratio vs. Serum PSA: Previous negative biopsy group

	PCA3 Assay	Serum PSA
Cutoff	PCA3/PSA = 35 x 10^{-3}	4.0 ng/mL
Sensitivity	58%	83%
Specificity	74%	17%
*ROC AUC	0.680	0.506
Odds ratio	3.6	1.2
*P = 0.002		

K4 test



K4



A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening

Andrew Vickers, PhD[1], Amit Gupta, MD[2], Caroline J. Savage, MPH[1], Kim Pettersson, PhD[5], Anders Dahlin, PhD[6], Anders Bjartell, MD, PhD[7], Jonas Manjer, MD, PhD[8], Peter T. Scardino, MD[3], David Ulmert, MD, PhD[3,6], and Hans Lilja, MD, PhD[2,3,4,6]

	Biopsies		Prostate cancers		Palpable prostate cancers		Advanced prostate cancer	
	Performed	Avoided (%)	Found	Delayed	Found	Delayed	Found	Delayed
Cancers diagnosed within 5 years from baseline								
Biopsy all (i.e., PSA ≥3.0 ng/ml)	1000	0	152	-	112	-	49	-
Biopsy based on age-specific PSA threshold*	539	461(46%)	112	40	88	24	40	9
Biopsy those with PSA ≥4.0 ng/ml	637	363(36%)	128	23	100	12	46	4
Biopsy if risk on full kallikrein panel is ≥20%	579	421(42%)	131	21	102	9	47	2

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2012 March 1.

A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening

Andrew Vickers, PhD[1], Amit Gupta, MD[2], Caroline J. Savage, MPH[1], Kim Pettersson, PhD[5], Anders Dahlin, PhD[6], Anders Bjartell, MD, PhD[7], Jonas Manjer, MD, PhD[8], Peter T. Scardino, MD[3], David Ulmert, MD, PhD[3,6], and Hans Lilja, MD, PhD[2,3,4,6]

	Biopsies		Prostate cancers		Palpable prostate cancers		Advanced prostate cancer	
	Performed	Avoided (%)	Found	Delayed	Found	Delayed	Found	Delayed
Cancers diagnosed within 10 years from baseline								
Biopsy all (i.e., PSA ≥3.0 ng/ml)	1000	0 (0%)	367	-	242	-	143	-
Biopsy based on age-specific PSA threshold*	539	461(46%)	265	103	192	50	115	28
Biopsy those with PSA ≥4.0 ng/ml	637	363(36%)	285	82	202	40	120	23
Biopsy if risk on full kallikrein panel is ≥20%	579	421(42%)	299	68	210	31	129	14

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2012 March 1.

A panel of kallikrein marker predicts prostate cancer in a large, population-based cohort followed for 15 years without screening

Andrew Vickers, PhD[1], Amit Gupta, MD[2], Caroline J. Savage, MPH[1], Kim Pettersson, PhD[5], Anders Dahlin, PhD[6], Anders Bjartell, MD, PhD[7], Jonas Manjer, MD, PhD[8], Peter T. Scardino, MD[3], David Ulmert, MD, PhD[3,6], and Hans Lilja, MD, PhD[2,3,4,6]

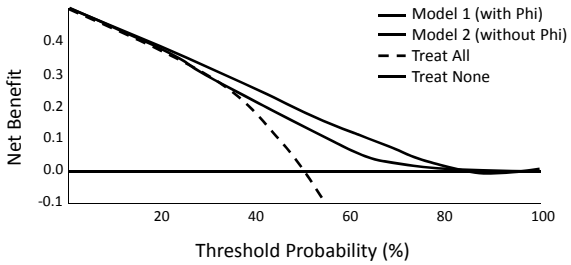
	Any Prostate Cancer	Palpable Prostate Cancer (clinical stage T2 or higher at diagnosis	Advanced Prostate Cancer (clinical stage T3 or higher or evidence of metastasis at diagnosis
Base Model	0.654 (0.621, 0.683)	0.708 (0.671, 0.741)	0.716 (0.664, 0.762)
Full model	0.751 (0.726, 0.777)	0.803 (0.774, 0.831)	0.824 (0.785, 0.858)
Full model without hK2	0.752 (0.728, 0.782)	0.803 (0.777, 0.832)	0.825 (0.784, 0.855)
Full model without intact PSA	0.711 (0.680, 0.746)	0.746 (0.706, 0.779)	0.754 (0.698, 0.801)
Full model without free PSA	0.654 (0.619, 0.689)	0.698 (0.650, 0.731)	0.695 (0.638, 0.751)
Model including total PSA, free PSA and age only	0.692 (0.664, 0.719)	0.723 (0.686, 0.764)	0.720 (0.658, 0.771)

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2012 March 1.

Prostate Health Index (PHI)

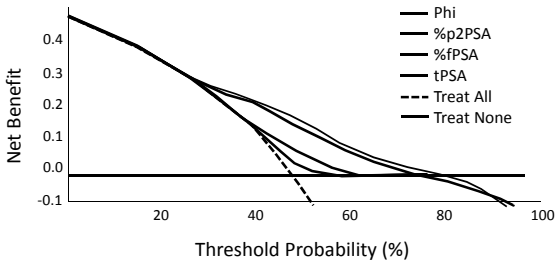
- **([-2]proPSA/free PSA) × √PSA.**

Multicenter Evaluation of [-2]Proprostate-Specific Antigen and the Prostate Health Index for Detecting Prostate Cancer



Decision Curve Analysis

Multicenter Evaluation of [-2]Proprostate-Specific Antigen and the Prostate Health Index for Detecting Prostate Cancer



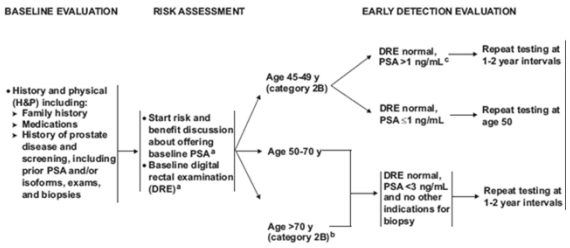
Decision Curve Analysis

Where do we stand?

AUA

- **No screening < 40 yrs.**
- **No routine screening in men 40 to 54 yrs at average risk.**
- **Individualized for high risk < 55 yrs**
- **shared decision-making for 55 to 69 yrs**
- **Every 2 or more yrs according to baseline PSA**
- **No screening for >70 yrs or any man with less than a 10 to 15 year life expectancy.**
- **Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.**

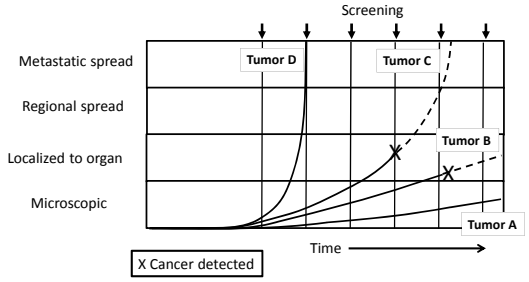
2014 NCCN Guidelines for PC



Rethinking Screening for Cancer

Rethinking Screening For Breast Cancer And Prostate Cancer

Screen Detection Capability Based On Tumor Biology And Growth Rates



Benefit and Burden of Mammographic Screening and Prostate-Specific Antigen Screening in the United States and Europe

Breast Cancer

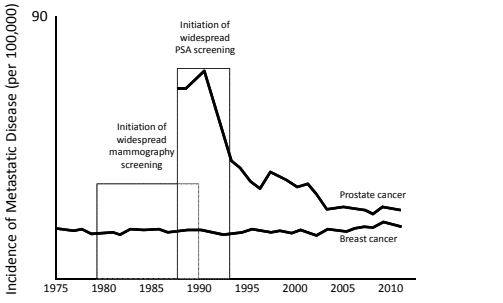
Region	Deaths Averted	Cancers Detected, Treated	Biopsies/ Recalls	Screening Visits	Individuals Screened (#)	Years Of Screening (#)
U.S.	1	18 Invasive 6 DCS	90/535	5866	838	6
Europe	1	15 Invasive 5 DCS	41/162	3352	838	6

Prostate Cancer

Region	Deaths Averted	Cancers Detected, Treated	Biopsies/ Recalls	Screening Visits	Individuals Screened (#)	Years Of Screening (#)
U.S.	0					
Europe	1	48		2397	1410	9

JAMA 2009; 302:1685

Trends in Metastatic Breast and Prostate Cancer: Lessons in Cancer Dynamics



N ENGL J MED 373;18 NEJM.ORG OCTOBER 29, 2015

Conclusions

- PSA is not a perfect screening test

Conclusions

- PSA is not a perfect screening test

  (But it is the best we have)

Conclusions

- PSA is not a perfect screening test

  (But it is the best we have)

- Yes most men will have PC and most will not die from it

Conclusions

- PSA is not a perfect screening test

  (But it is the best we have)

- Yes most men will have PC and most will not die from it
- Tens of thousands die from the disease, and the numbers will increase with increased life expectancy

Conclusions

- PSA is not a perfect screening test

  (But it is the best we have)
- Yes most men will have PC and most will not die from it
- Tens of thousands die from the disease, and the numbers will increase with increased life expectancy
- PSA screening for PC detects cancers earlier and at a lower stage where curative therapies more effective

Conclusions

- PSA is not a perfect screening test

  (But it is the best we have)
- Yes most men will have PC and most will not die from it
- Tens of thousands die from the disease, and the numbers will increase with increased life expectancy
- PSA screening for PC detects cancers earlier and at a lower stage where curative therapies more effective
- PC screening saves lives

Cracks on Airbus A380 Wings

- January 2012: Qantas A380 plane encounters severe turbulence on London-Singapore flight
  - Aircraft checked and cleared to fly on to Sydney
- February 5, 2012: Plane grounded in Sydney after further precautionary inspection finds 36 hairline cracks on the wing rib brackets similar to "Type 1" cracks found on previous A380 checks

When It Comes to Prostate Cancer:

"Diagnostically aggressive"

Peter T. Scardino, MD

When It Comes to Prostate Cancer:

"Diagnostically aggressive"

"Therapeutically conservative"

Peter T. Scardino, MD