

PSA Testing 101

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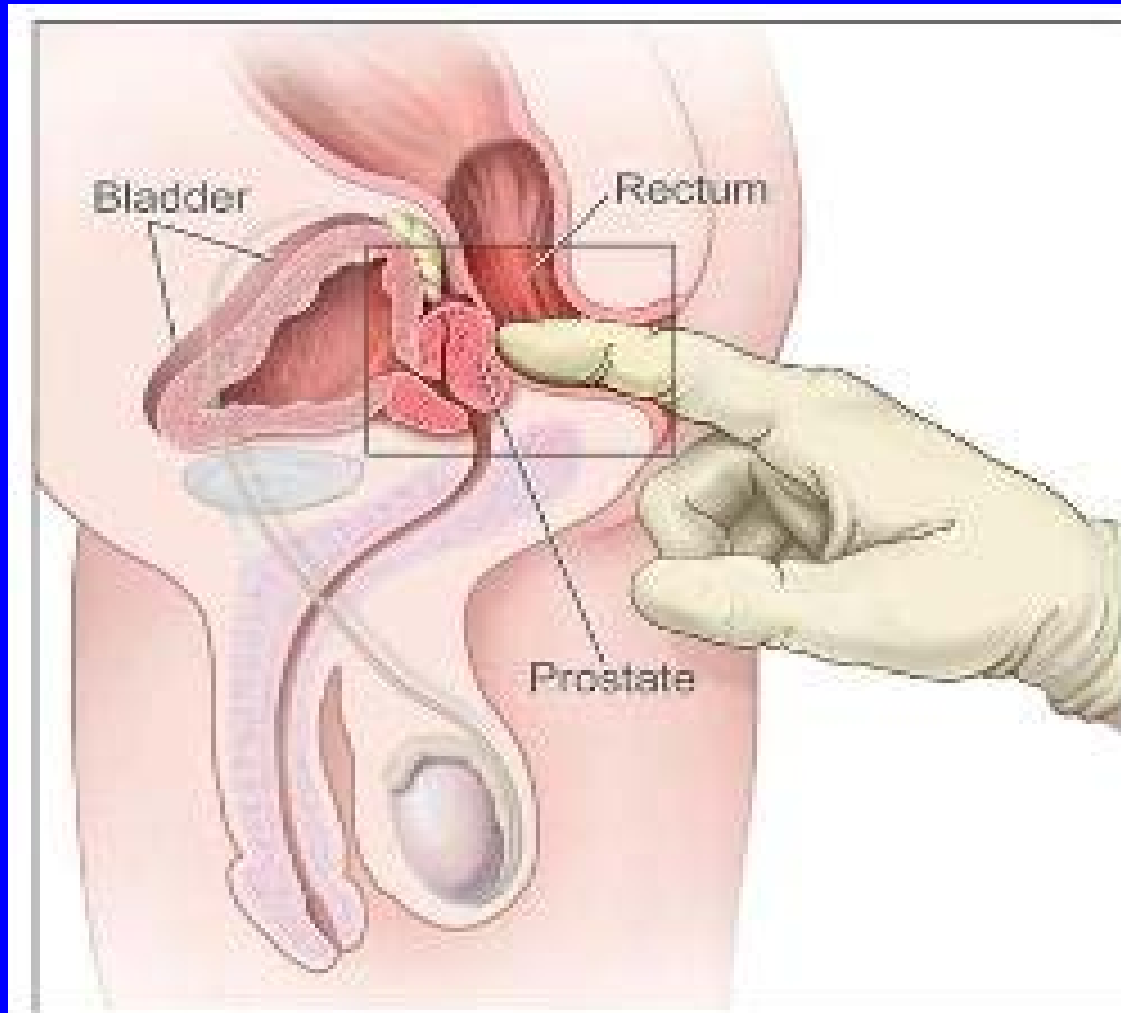
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September 23, 2010

Screening: 3 tests for PCa

- A good screening test must accurately identify persons **with** the condition (sensitivity) and those **without** (specificity).
- A good screening test must identify those with the disease **early** enough before symptoms appear to make a difference in treatment outcomes (survival and quality of life).
- A good screening test preferably has high sensitivity and high specificity **and** must be **acceptable** for the population screened, **rapid** and ideally noninvasive.

1. The **Digital Rectal Exam (DRE)** is a mainstay of PCa screening, but the examiner cannot feel the whole prostate nor small lesions



Digital Rectal Examination (DRE)

2. Blood serum test – for **Prostate-Specific Antigen (PSA)** – takes a small sample of blood and tests for the amount of a substance that is mainly produced by the prostate gland
3. **Trans-rectal ultrasonography (TRUS)** – limited value for screening; history, exam or lab findings may indicate a need for TRUS evaluation

Additional details about each follow the presentation in the supplemental slides

What are the risks & benefits of screening?

- **The value of screening can be proven only by showing a reduction in the chance of dying of prostate cancer without an unacceptable reduction in quality of life (from both the screening and increased use of treatments that can have negative side effects).**
- **Conclusive evidence for the value of prostate cancer screening has not yet accumulated.**
- **But some evidence does indicate that screening offers the possibility to diagnose early prostate cancer and to reduce deaths from this disease.**

Risks of Screening

- On the other hand, screening also detects cancers that do not threaten the patient's life.
- **Finding such cases cannot be avoided at present.**
- When screening the general population for PCa by PSA, over 50% of the PCa's detected will be minimal cancers (Draisma 2003).
- As immediate treatment of these has not been shown to be beneficial, detection and diagnosis of some tumors may be unnecessary and counter-productive, as in some patients there will be treatment-associated morbidity (and, rarely, even mortality).

Benefits of Early Treatment

- A randomized trial has demonstrated that radical prostatectomy can decrease the chance of dying of prostate cancer as compared to delayed treatment. This benefit has been attributed in part to suppression of the male hormone, testosterone. However, even in the *delayed* treatment group 8 years later, only ~ 25% are at risk of developing metastatic disease.
- Thus, a majority of those with prostate cancer die **with**, not **from**, the disease.
- Still impossible to determine up front which cases will not progress.
- It has **not** been shown that the same favorable results of surgery can be achieved when prostate cancer has been detected by screening.
- Uncertainty therefore remains.

Benefits of Screening

- Screening can find potentially lethal cancers at an early, still curable stage as well as provide an opportunity for earlier, and possibly life-prolonging, treatment of additional tumors.
- Men who decide to be screened take a chance, and need to be informed about – and balance – the potential risks and benefits of screening and subsequent treatment. The decision currently must be individualized, and men who choose to be screened should not be denied the early diagnostic tests.
- Data concerning cost efficacy – an important determinant of public policy recommendations – are limited and controversial.

European Randomised Study of Screening for Prostate Cancer (ERSPC) www.erspc.org

- ERSPC established >10 years ago
- Largest randomized study (220,000 men in eight western European countries*) on screening for prostate ca
- Prostate cancer – 2nd leading cause of cancer death in men in Western Europe and the U.S.

* Netherlands, Sweden, Finland, Belgium, France, Spain, Italy and Switzerland

European Randomised study of Screening for Prostate Cancer (ERSPC)

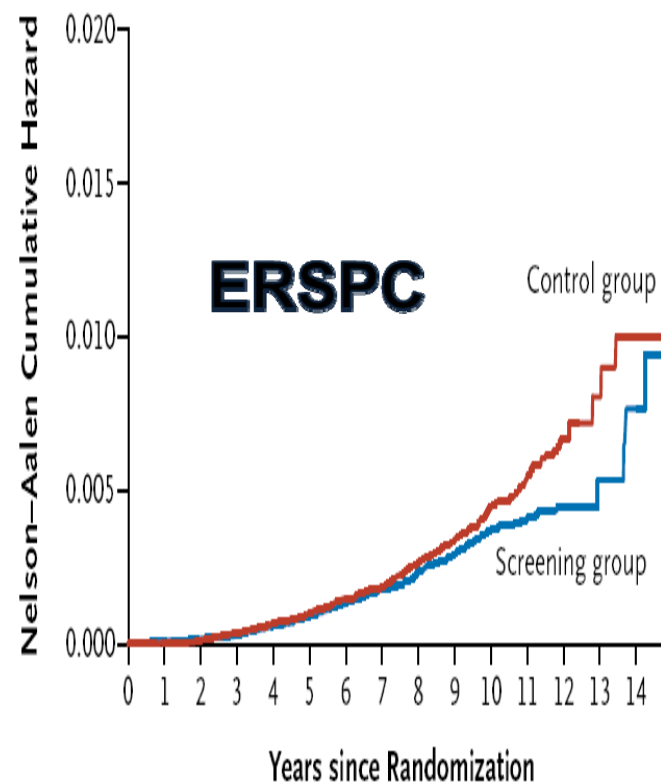
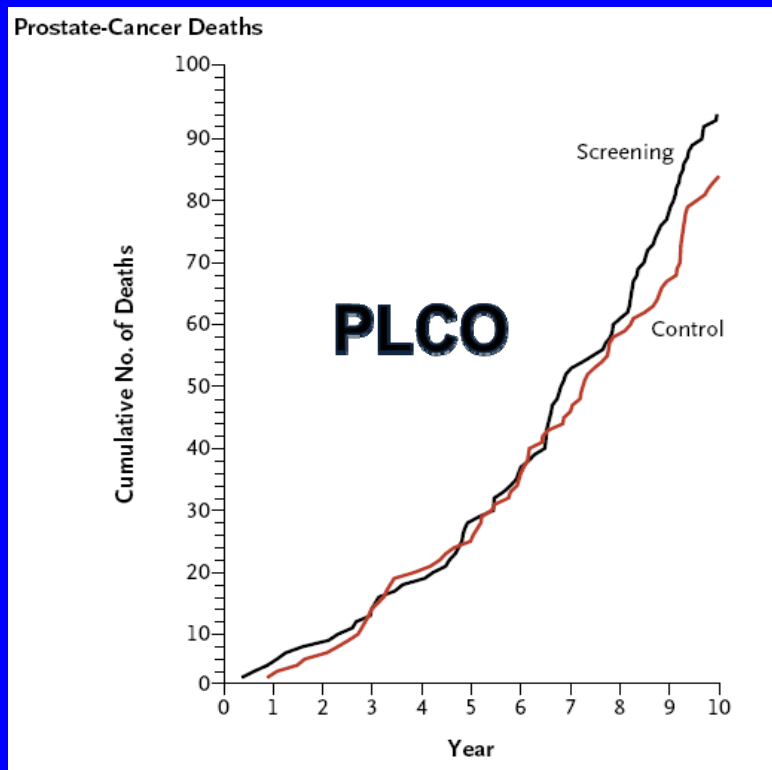
Provides some evidence-based advice to the pivotal question – does screening lead to an improvement of cancer-specific survival?

Initial results: 20 percent reduction in the rate of death from prostate cancer after first ten years of follow-up

Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial

- Objective: The PLCO hopes to provide some answers about the effectiveness of prostate cancer screening.
- Designed as a 17-year project of the National Cancer Institute (NCI).
- An initial report appeared in the *New England Journal of Medicine* online March 18, 2009 (in print – March 26 issue), to coincide with presentation of the ERSPC data at the European Association of Urology meeting in Stockholm, Sweden.
- PLCO: Six annual screenings for prostate cancer.
- **FINDINGS: More diagnoses of the disease, but did NOT lead to fewer prostate cancer deaths.**
- ***BUT there are limitations to the study...***

Randomized Screening Trials



No. at Risk

Screening group	65,078	58,902	20,288
Control group	80,101	73,534	23,758

Caveats

•PLCO

- Wrong PSA cutoff
- > 40% screened within 3 yrs of enrollment
- Half of “non-screened controls” got PSA during trial, **REDUCING** its power
- Most men not biopsied when advised
- Limited & variable # of biopsies
- Relatively short follow-up
- Variable care
- Very few A-A

•ERSPC

- Need to screen 1410 men and treat 48 with cancer to save 1 life
- Limited # of biopsy samples
- Absence of A-A
- Limited follow-up
- Underestimates effect since some controls were also screened

Summary of Concerns

- There are limitations to the protocols that may have reduced the efficacy of screening
- Based on our knowledge of the epidemiology of prostate cancer, in each trial the follow-up period is too short to have expected to see the full potential benefits, and much too short to calculate cost/benefit ratios
- The US PLCO trial was significantly under-powered to have been able to demonstrate a positive result due to PSA screening of controls – reminiscent of the classic epidemiologic limitations of the negative cardiovascular “MRFIT” trial 2 decades ago

The Göteborg Trial

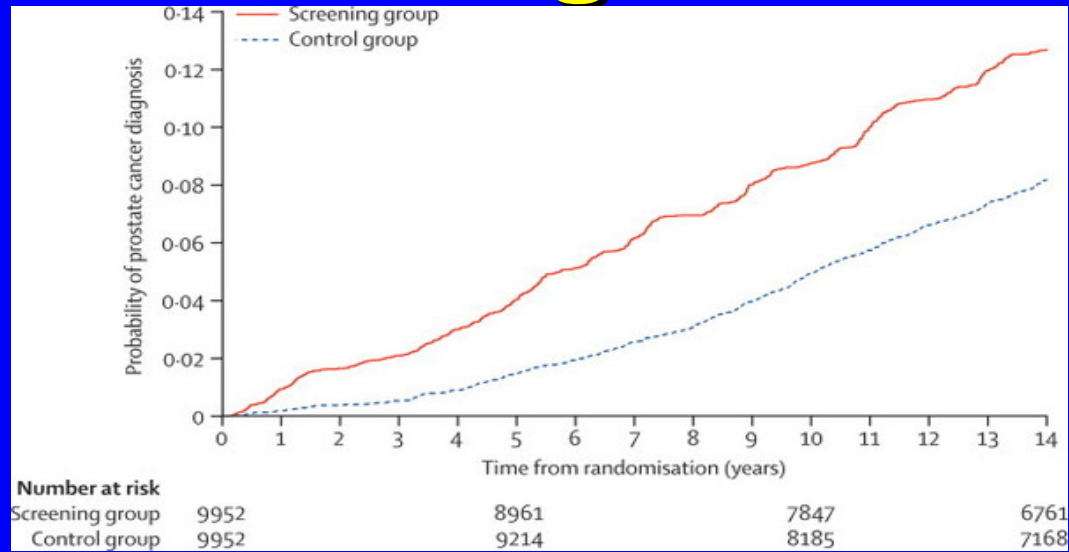
- A smaller Swedish screening trial consisting of roughly 20,000 men designed with similar criteria as the ERSPC
- Current data were reported following a total of 14 years of screenings and follow-up - in *Lancet Oncology* (online release: July 2010; journal release: August 2010)
 - Some of the data from the trial were incorporated into the ERSPC

The Göteborg Trial

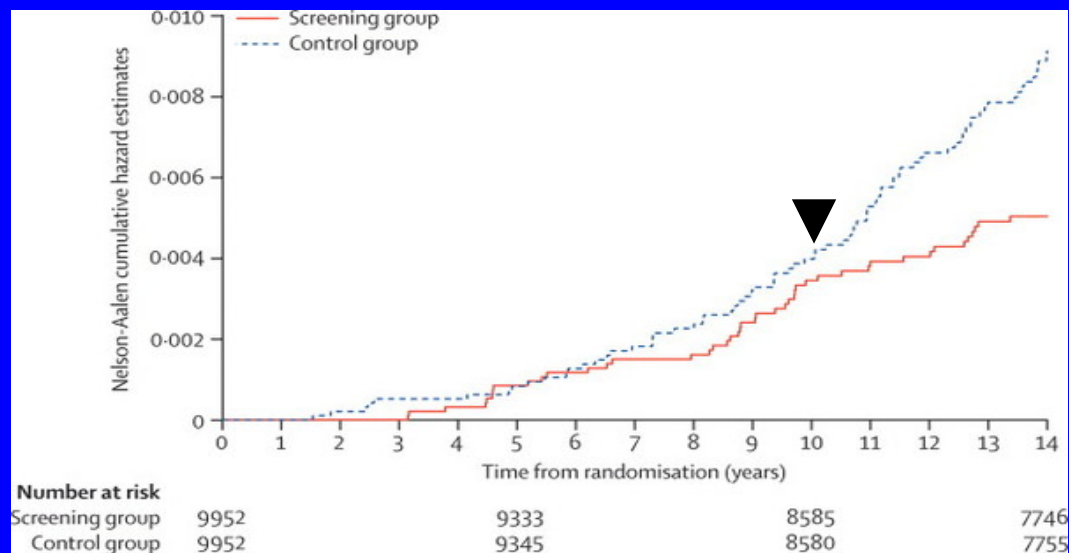
- Final results indicate a roughly **50% decrease in mortality** from prostate cancer in the screening group vs. the control group.
 - **The benefit was greatest 10+ years from the beginning of the trial**
 - Half of the attendees who died of PCa in the screening group were diagnosed in the first round of screening, and many of these men were 60+ years of age at entry
 - The number of men from the control group who may have received independent screening was not known or was not included – a bias that may underestimate the benefits of screening
 - 293 screened and 12 diagnosed or treated to prevent 1 death from prostate cancer

The Göteborg Results

Cumulative
Risk of
Diagnosis:



Cumulative
Risk of
Death:



The
approx
ten-year
point is
marked
by an
arrow

Current Screening Guidelines from Major U.S. Organizations

- **American Urological Assoc Best Practice Statement**
 - Individual decision for those with 10yr life expectancy
 - Baseline PSA at 40
 - PSA at subsequent intervals based on PSA level and risk factors
- **American Cancer Society**
 - Advises against routine screening
 - PSA should be offered as option
 - Age 45 in those with risk factors (FH, AA)
 - Age 40 in those at highest risk (multiple family members or a family member diagnosed at a young age)
- **US Preventive Services Task Force**
 - Do not screen routinely over age 75
 - Inadequate evidence regarding younger ages

If You Choose to be Screened, What's the Best Way?

- **PSA – cutoff value issues**

Should it be age and/or race dependent?

Should clinical findings be incorporated into testing algorithms as well?

(e.g., PSA rises with BPH and transiently with acute prostatitis)

- **PSA velocity issues**

Baseline value(s) – at what age?

How often to screen? What is a “rapid” rise?

- **Risk calculator or nomogram ...**

Risk of Biopsy-Detectable Prostate Cancer

Fields marked with asterisks (*) are required.

Enter Your Information	
* Race	<input type="text" value=""/> ▾
* Age	<input type="text" value=""/>
* PSA Level <small>?</small>	<input type="text" value=""/> ng/ml
* Family History of Prostate Cancer <small>?</small>	<input type="text" value=""/> ▾
* Digital Rectal Examination <small>?</small>	<input type="text" value=""/> ▾
* Prior Prostate Biopsy <small>?</small>	<input type="text" value=""/> ▾
* Is the patient taking finasteride?	<input type="text" value=""/> ▾

Calculate Cancer Risk

Figures

Disclaimer

<http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>

Example:

Your Information	
Race	Caucasian
Age	55
PSA Level	2.7 ng/ml
Family History of Prostate Cancer	No
Digital Rectal Examination	Normal
Prior Prostate Biopsy	Never Had A Biopsy
Is the patient taking finasteride?	No

Results
Based on the data provided, the person's estimated risk of biopsy-detectable prostate cancer is 27.8% .
The 95% Confidence Interval for this prediction is 26.5% to 30.1% . More information about the confidence interval
The person's estimated risk of biopsy-detectable high grade prostate cancer is 3.6% .
The 95% Confidence Interval for this prediction is 2.3% to 5.1% . More information about the confidence interval

Supplemental Slides

DRE: (digital rectal examination)

- Tendency to detect larger tumors with DRE
- Low chance of detecting clinically insignificant tumors with DRE, but risk depends strongly on the PSA level.
- Limitation: small multi focal lesions with aggressive biologic potential are **NOT** detected with DRE alone.
- The DRE is subjective = variable between different examiners.
- Several studies have questioned the use of DRE in screening programs and found little or no additional beneficial effect of a DRE in men with PSA levels ≥ 4.0 ng/ml (Catalona 1994, Rietbergen 1997).
- DRE may provide an additional value in detecting clinically significant cancer in men with a low [?“normal”} range of PSA (< 4.0 ng/ml) (Eastham 1999, Han 2004).

TRUS: (transrectal ultrasound)

- **Similar to the DRE, the interpretation of TRUS is highly dependent on the investigator.**
- **Several studies have shown that the value of TRUS has LIMITED value as a screening test to detect cancer,**
- **But is indispensable for guiding prostatic biopsies and assessing the prostate volume.**

PSA: (prostate specific antigen)

PSA

- A protein
- Almost exclusively produced by the epithelial cells of the prostate in normal and in pathologic conditions such as infection, urinary retention, enlargement of the prostate, and prostate cancer.
- Approximately 40% of patients with organ-confined prostate cancer show no elevation of serum PSA.
- *Unresolved*: At what PSA value should more invasive examinations - such as prostate biopsies - be conducted? *Not yet clear...*

PSA (continued)

F/T PSA ratio:

- Objective: To (try to) increase the specificity of PSA as a screening tool derivatives from PSA are studied.
- Total PSA consists of **c**omplex PSA (cPSA) and **f**ree PSA (fPSA).
- cPSA is serum PSA that is bound to circulating proteins.
- The proportion of circulating cPSA is higher in patients with carcinoma than in those with benign enlargement.
- Studies comparing the diagnostic efficacy of cPSA with total PSA and the free to total (F/T) ratio so far report inconsistent results.

PSA (continued)

proenzyme PSA (pro-PSA):

- Form of free PSA
- Elevated in cancerous prostate tissue
- Results from a multi-center study have validated proPSA as a detector of early stage prostate cancer.
- Findings suggest that proPSA may be associated with aggressive and significant prostate cancer, worthy of further investigation
- See: cebp.aacrjournals.org/content/19/5/1193.abstract?etoc

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