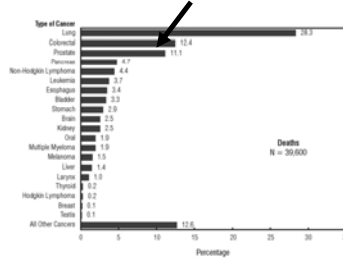


PSA: What do the trials mean? What do we tell our patients?

J Dickinson
Feb 2010

Prostate cancer in Canada

- Commonest cancer in men (apart from skin)
- 3rd commonest cause of cancer death in men



<http://www.cancer.ca> 2

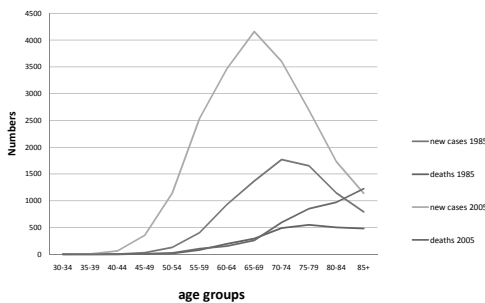
Tasks for the groups

- John aged 50 attends for a checkup. Will you recommend a PSA test? DRE?
- Peter aged 55 comes in and asks for a PSA test. How will you respond?
- Terry, aged 68, has renal failure secondary to diabetes. How do you respond to his request for a PSA test?
- Morgan has an African background. He is 60 with diabetes and calls your nurse to ask for the tests he needs before his appointment next week. Should you add a PSA to the tests you are ordering?
- Tom aged 40 His father was diagnosed with Prostate cancer at age 70. Tom wants your advice about being tested.

Decision steps

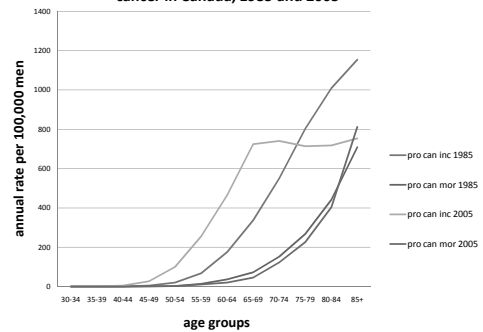
1. What is your main concern?
2. What do you know about Prostate cancer and your risk?
3. Do you know how good the tests are?
4. What are the pros and cons of early detection?
5. What is most important to you?
6. What do you want to choose now?

Age distribution of new cases and deaths from Prostate cancer reported in Canada: 1985 & 2005.*



*Data calculated from Canadian cancer statistics 2005; Cancer surveillance on-line; Cancer Mondial, IARC, 1985& WHO 1985

Age-specific incidence and mortality rates for prostate cancer in Canada, 1985 and 2005**



**Data calculated from Cancer surveillance online; Annual demographic statistics 2005; Cancer Mondial 1985; WHO 1985 & Canadian cancer statistics 2005

PSA Test

- Developed and popularised by Thomas Stamey (Stamford U)
- Available since 1987, widely used since 1990.

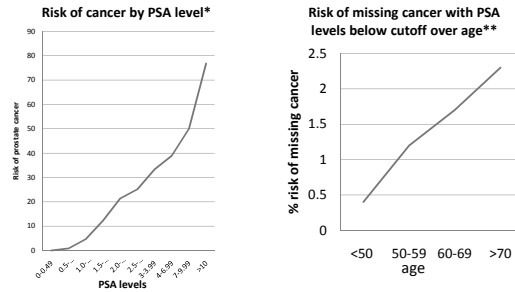
Recanted 2004

“...the relationship between prostate cancer and serum PSA is tenuous at best, especially with serum PSA less than 10ng/ml, and perhaps even less than 22ng/ml.”

“...any excuse to biopsy the prostate has an excellent, age-dependent chance of being positive.”

Stamey TA et al. J Urol 2004; 172: 1297-1301

PSA: detection of cancer



* Aus G, Damber JE, et al 2005 ** Conolly DJ, Black A et al 2007

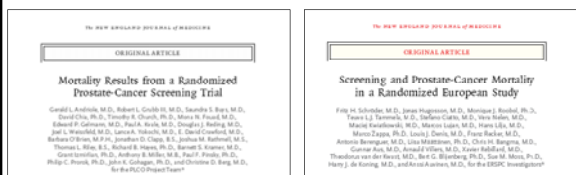
How good are the tests?

- PSA variation 40%
 - PSA velocity?
- Prostate biopsy: causes infection – rate?
- Pathology reading of biopsies
 - reliability often low
- Predictive value of Gleason score low
 - for death from cancer

Does it work?

- Non-trial data:
 - Interpreted according to preference
 - Possibility of bias
- Therefore trials were established.
 - US PLCO started: 1993
 - European started: 1991 (varied by country)
 - Opposition: testing already in wide use esp. in US.
 - Both reported early 2009

PSA screening trials – Mortality results after over 10 years of f/u, reported in March 2009



US - PLCO

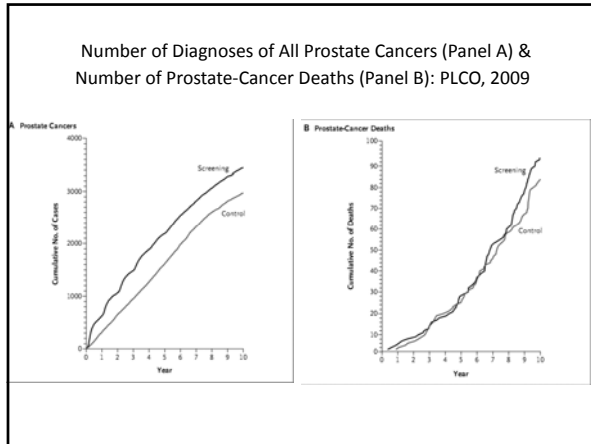
Europe - ERSPC

<http://content.nejm.org>

11

Long term trials of PSA testing

- US Trial PLCO
 - 77,000 men 55-74 yrs. Followed 11.5 years.
 - Annual PSA 6 yrs.
 - Death rate slightly higher in screened group



Long term trials of PSA testing

- European trial ERSPC
 - 182,000 men 55-70yrs Followed 9 yrs.
 - PSA 4 yearly twice.
 - Screened deaths 0.29%
 - Control deaths 0.36% p=0.04

ERSPC – Death From Prostate Cancer

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

Age at Randomization	Screening Group		Control Group		Rate Ratio (95% CI) ^b
	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)

55-69 core age group: Rate Ratio = 0.80 (CI, 0.65 – 0.98)

PLCO Death Rates

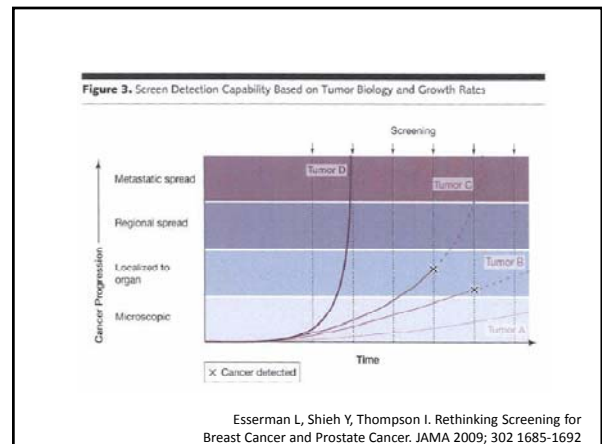
Table 3. Death Rates from Prostate Cancer per 10,000 Person-Years at 10 Years.^a

Variable	Years after Randomization									
	1	2	3	4	5	6	7	8	9	10
Screening group										
Cumulative deaths — no.	7	6	12	16	26	35	50	59	76	92
Cumulative person-yr — no.	37,864	75,292	112,234	148,635	184,490	218,752	254,295	287,194	318,244	345,230
Death rate	0.8	0.8	1.1	1.1	1.4	1.6	2.0	2.1	2.4	2.7
Control group										
Cumulative deaths — no.	1	4	12	18	23	34	44	56	65	82
Cumulative person-yr — no.	37,838	75,231	112,223	148,648	184,514	218,715	254,317	287,377	318,483	345,583
Death rate	0.3	0.5	1.1	1.2	1.2	1.6	1.7	2.0	2.1	2.4
Rate ratio (95% CI)	3.00 (0.31–28.82)	1.50 (0.42–5.31)	1.00 (0.45–2.22)	0.89 (0.45–1.74)	1.13 (0.64–1.98)	1.03 (0.64–1.65)	1.13 (0.75–1.70)	1.05 (0.73–1.51)	1.16 (0.83–1.62)	1.11 (0.83–1.50)

After 10 years, mortality rate ratio = 1.11; 95% (CI, 0.83-1.50)

Bias in the trials

- Many critics of the 2 largest RCTs
- Neither reported treatment methods used
- PLCO:
 - 40% ↑ to 52% (by 6th year) of controls underwent PSA testing
 - Dilute effect
- ERSPC:
 - Different countries with different epidemiology involved
 - Differences in
 - age-groups included,
 - schedules of PSA testing, post testing protocol & treatment offered
 - Randomization in some countries after enrolment into study
- Possible difference caused by annual vs 4 yr testing
- Low power: trials continue



Why is it so?

- Screening works for *common chronic* disease
- Range of growth rates
- Cannot work for rapidly developing disease
 - Disseminated before surgery, XRT
- No point for very slow disease
 - Still treatable at late stage
 - May never kill
- If too rare, not worthwhile

Table 1: Comparison of effects experienced by 10,000 men each screened every 4 years and not screened between ages of 55-69 years followed for 9 years

Events	Not screened	Screened	Net benefit/harm
Number of positive PSA results (>3ng/ml)*		1620	
Number of biopsies*		1393	
Number of cancers detected*	480	820	-340
Number of aggressive cancers (gleason score >7)*	217	228	+11
Number of low grade cancers*	263	592	-329
Number undergoing radical prostatectomy**	100	220	-120
Number undergoing radiotherapy**	123	227	-104
Complications of therapy***			
• Urinary problems	15	30	-15
• Sexual dysfunction	158	317	-159
• Bowel problems	62	125	-63
Number of deaths due to prostate cancer*	36	29	+7
Number of lives saved by screening	7		

(* numbers calculated based on results of Schroeder FH, Hugosson J, Roobol MJ, Tamella TJ, Clatto S, Nelen V, Kwiatkowski M, et al., 2009 ** numbers based on Barry MJ, 2009 *** numbers calculated based on results of Potosky AL, Legler J, Albersen PC, Stanford JL, Gilliland FD, Hamilton AS, Eley JW, Stenbenson RA, Harlan L, 2000)

Long term effects of Androgen deprivation for prostate cancer

- Used for advanced cancer
 - Should have become less common with more screening
 - Actually increased: more than doubled
- Antiandrogens GnRH agonists
 - Leuprolide (lupron)
 - Goserelin (Zoladex)
- 30% greater risks of Heart disease, stroke, sudden cardiac death, diabetes
- Fracture increase 23%
- Orchiectomy: higher heart dis, diabetes.
- Androgen agonists no effect
 - Flutamide(Euflex) bicalutamide (Casodex)

Albertsen JNCI Dec 2009.
Taylor L et al, Cancer 2009, 115: 2388-99

Evidence-based Health Care Policy Muir Gray (Director, NHS Screening Programs) *Aphorisms about screening*

- All screening programs do harm; some can do good as well.
- The harm from a screening program starts immediately; the good takes longer to appear. Therefore, the first effect of any program, even an effective one, is to impair the health of the population.
- Finding 'asymptomatic' disease by means of screening always increases the length of time a person knows s/he has the disease... not to be confused with increased survival.

Issues

- 55 years old: beginning of age group.
- 68: do not screen after age 75, or less than 10 years likely life span.
- African background: higher risk.
- Do not do PSA without discussion

Role of DRE?

- American Urological Association Nov 2009
- TOP Guidelines 2008
 - Must always evaluate using both
- Both *screening* trials found no additional value to DRE over PSA alone.

Helping patients to decide

Patient information aids

- Increase knowledge
- Prefer active role in decisions
- More accurate knowledge about cancer rates
- Less concerned about Prostate cancer
- Less favourable attitudes to testing
- Feel informed about testing
- Reduce rate of testing: rr 0.88
- Preferred watchful waiting

Systematic review. Volk et al Am J Prev Med 2007; 33: 428-434

My recommendations re PSA

- Do not bring up the subject.
 - Plenty of more important and valuable activities to discuss
- If asked: say that you think it is harmful.
- If someone wants it done: give information about relative risks/harms, warn them against it.
- Consider other useful preventive activities that could be done for them.



THE LANCET.

"The recommendation ... that men should be fully informed of the risks and benefits of screening and then asked to make up their own minds is perhaps disingenuous when it is clearly difficult for specialist advisers to know the best approach"

- Frankel et al. *The Lancet* 2003;361:1122

Legal Scaremongering

- You will be sued if you do not screen!
- Show me the evidence!
 - One case: Merenstein JAMA 2004; 291 (1):15-16.
 - State of Virginia. Not a precedent, since not appealed.
 - None since.
- You could be sued if you do screen inappropriately
- Especially if you do harm
- You must have evidence on your side: often uncertain
- Can get experts to support you
- Canadian Law different
 - Lewis MH, Gohagan JK, Merenstein DJ JAMA 2007; 297 (23) 2633-2637

The Drug Game

- Selling to profitable market
- Research focused on drug-treated diseases
- Distorted trials
 - Wrong comparisons, selected results
- Sell drugs to healthy
- Stretch definitions
 - HT, Diabetes, Cholesterol, osteoporosis, Depression, Dementia,
- Create new "disease"
 - menopause, Kassirer J. *On the Take*. OUP 2005
 - raised PSA, Selling Sickness: how drug companies are turning us all into patients. Moynihan R, Cassels A.
 - Erectile dysfunction. Allen and Unwin, Sydney, 2005

Angell, M. *The Truth About the Drug Companies*. Random House NY 2004

Actual Preventable Causes of Death in the United States in 2000

Mokdad AH, et al. <i>JAMA</i> 2004;291(10):1238-45.	Deaths	
	Estimated No.*	Percentage of Total Deaths
Tobacco	435 000	18.1
Diet/activity patterns	365 000	15.2
Alcohol	85 000	3.5
Microbial agents	75 000	3.1
Toxic agents	55 000	2.3
Motor vehicles	43 000	1.8
Firearms	29 000	1.2
Sexual behaviour	20 000	0.8
Illicit use of drugs	17 000	0.7
Total	1 159 000	46.7