

Prostate Cancer: Past, Present and Future

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11th October 2011



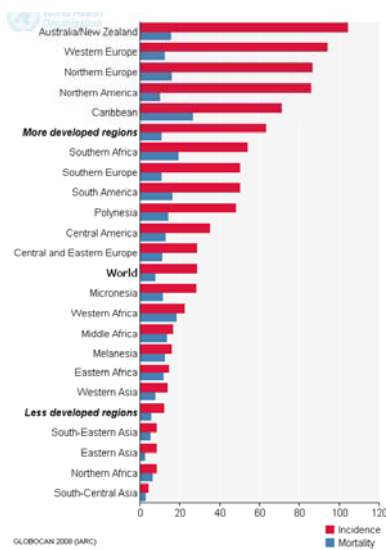
AACB 49th Annual Scientific Conference & Golden Jubilee

Laboratory Medicine: Past, Present & Future

10-13 October 2011 | Including the Toxicology Forum, 14 October 2011

Sydney Convention & Exhibition Centre | Sydney NSW

Prostate Cancer - Today



Estimated age-standardised rates (World) per 100,000

- 2nd most common cancer in Aust men (after NMSC)
- Risk of Dx increases with age
 - 1 in 554 for man in 40s.
 - 1 in 15 for man in 60s.
 - 85% cases diagnosed in M>65 yrs.
- If FHx, risk of Dx doubles; esp close relative Dx < 60 yrs.
- 90% present with localised disease.
- For localised disease, 10 yr survival = 93%
- 3,300 men die of PCa every year – now more than Breast Ca deaths.

Source: Cancer Council Australia

What are we doing about Pr Ca?

- PSA + DRE. If either abnormal → consider biopsy (TRUS)
- No national screening program
 - Testing is available for any man who wants it
 - MBS item 66655
 - Public awareness campaigns – “Be a man”, celebrity endorsement of testing.

BUT PSA testing is controversial.

“I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster ...

the test is hardly more effective than a coin toss ...

P.S.A. testing can't detect prostate cancer and, more important, it can't distinguish between the two types of prostate cancer — the one that will kill you and the one that won't.”

Richard Ablin, “The Great Prostate Mistake” New York Times March 2010

Can we justify using PSA?

- MBS changed 1st May 2009
 - **Age-related** PSA reference intervals
 - ↑ sensitivity in young men, ↑ specificity in older men
 - **Free:Total** PSA ratio (where Total PSA <10 ug/L)
 - Ratio <10%: risk of Ca = 56%
 - Ratio >25%: risk of Ca = 8%

(Catalona et al. JAMA 1998, 249 (19): 1542-1547)
 - PSA kinetics: **velocity** (0.75 ug/L/year) & **doubling time** (< 3 years)

But is this what we are actually doing?

MBS statistics for 2010 (Jan- Dec) for Item 66655

- Per capita, highest rates of testing are in SA + Tasmania
- H/e SA has the lowest rates of free PSA testing (items 66659 +66660)
- “increased use of PSA testing is less commonly followed up by modern tools such as free to total PSA ratio” (Sikaris MJA 2010)

Why do we test anyone?

- RCPA, USANZ, PCFA, Cancer Council Australia, Andrology Australia, RACGP Consensus :
 - General population screening not recommended.
 - Men need to be informed of the benefits and risks of testing & decide for themselves.
 - (? What age to start testing: 40 or 50 yrs)

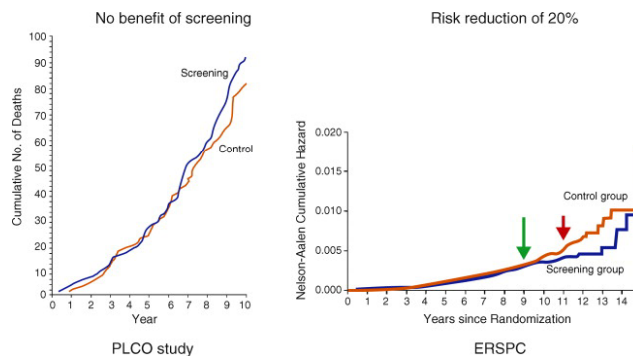
“Clayton’s” screening policy: promoting screening when you are not promoting it.” (Let Sleeping Dogs Lie? Chapman et al. 2010)

- Plans underway to develop national prostate Ca testing guidelines

“Our rush to screen for early cancer and treat ... is creating major injuries, such as impotence and incontinence ... the main contributor to this carnage is the widespread ordering of prostate-specific antigen (PSA) testing in asymptomatic men.” (A/Prof I Haines Herald-Sun 10/10/2011)

Is Pr Ca screening based on EBM?

- March 2009, NEJM published results of 2 large-scale RCT of prostate cancer screening:
- ERSPC - **Decrease in** advanced Ca by 50% & Pr Ca death by 20% at 9 yrs.
- PLCO - **No decrease** in advanced Ca or prostate Ca deaths at 7 years.





How did we get ourselves into this situation?

Prostate Cancer – early history



1853: Histologically diagnosed Prostate Cancer reported by J. Adams in Lancet as "a very rare disease".

Prostate Ca still incidental finding at surgery. Pathology: 14/100 supposed BPH actually invasive cancer (Albarran)

1500

1800

1900

2000

First descriptions & drawings of prostate gland – Massa (Italian) & Vesalius (Flemish)

1850: Life expectancy, for men who made it to 20 years of age, was just under 60 years of age.

Hugh H Young: "I was struck by the fact that had the entire prostate gland been removed with its capsule, it would have been possible to cure "

1st radical perineal prostatectomy on April 7, 1904 at Johns Hopkins Hospital

Prostate Cancer – 1930s

- “Average” Prostate Cancer patient :
 - urinary symptoms (nocturia, frequency, dysuria), backache, sciatica.
 - typically >3 symptoms.
 - time from 1st symptom to presentation = 24 mths.

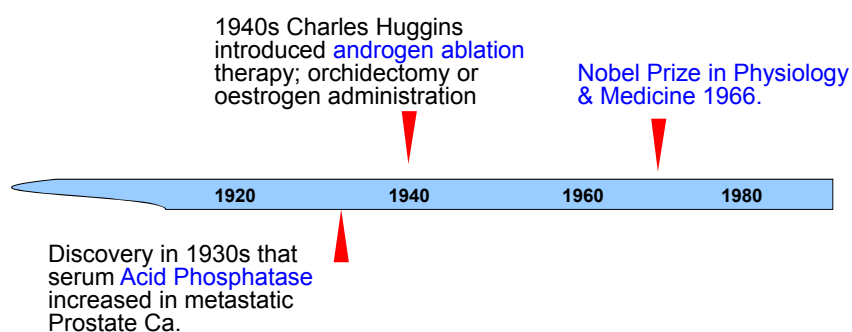
Dr B S Barringer “Carcinoma of the Prostate” CMAJ 1933:

“Prostatic carcinoma is to-day fairly firmly established in the lost-cause column. Even Young, that ardent and skilful advocate of the operative cure of prostatic carcinoma, finds but little over one case a year suitable for operative removal.”

“attention is centred wholly on the urinary obstruction which may be caused by the carcinoma, rather than upon the control of the disease.”

“Only isolated cases of cure are published.”
10-20% of cases “controlled” for >5 years.

Prostate Cancer – Rx advances



Oestrogen Rx caused cardiovascular and thromboembolic toxicity.
Androgen ablation was not sufficient to completely cure advanced disease.

Other agents tried (LHRH agonists and antagonists, Ketoconazole, cyproterone acetate) as well as Radiation Therapy (Brachytherapy & External Beam Radiation), Chemotherapy and advances in surgery.

Prostate Cancer – Need for early diagnosis

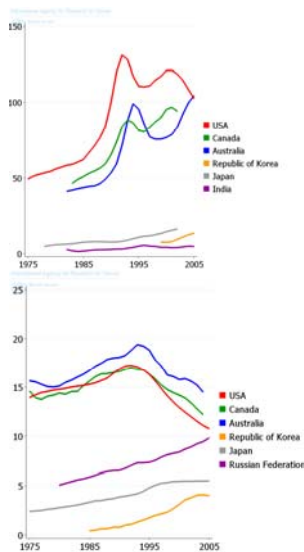
“Before 1980, there was no diagnostic test for prostate cancer; there was no effective radiation therapy; there was no safe surgery, and the only option for most men with prostate cancer was to have their testes removed — surgical castration ...

A common emergency department presentation at that time was acute paraplegia due to prostate cancer metastatic lumbar spine cord compression. This is a rare presentation in 2010.”

A J Costello & D G Murphy , MJA 2010; 193 (1): 4-5

- 1986** – FDA approved PSA testing for monitoring
 - Within a couple of years, unofficial PSA screening escalated
 - 1992 approved for diagnosis.

Introduction of PSA



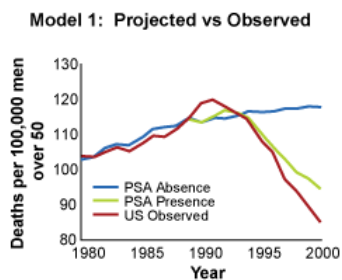
age-standardised rate (W) per 100,000. Source: Globocan.iarc.fr

- Pr Ca incidence ↑ peaking in 1992, now returned to expected rates.
- ↓ in % p/w distant metastases
 - 20.6% in 1986 to 11.6% in 1993
- ↑ in pts p/w clinically localised Ca
 - 65.4% to 74% (1986 to 1993)
- Mortality rates falling.

Is this due to PSA or Rx advances?

PSA screening decr. mortality

- Tyrol , Austria – screening introduced in 1993 (uptake 87%)
- 2005: Reduction in death rate around 54% , compared to rest of Austria - fall of 29%
- Bartsch G. BJU Int 2008: 101, 809-816.



- Modelling suggests that PSA contributed to at least some of the reduction in mortality.
- Etzioni R. Cancer Causes Control 2008 Mar;19(2):175-81

What about ERSPC & PLCO?

- PLCO criticisms:
 - 7 years too short. No diff at 7 yrs for ERSPC
 - Half the size of ERSPC (76,000 VS. 162,000)
 - 44% had a prior PSA, less likely to have Ca; ↓ power of study
 - Controls (“usual care”) contaminated; 52% had PSA
 - Only 30% PSA>4 ug/L had biopsy
 - Subsequent analysis of young healthy men showed signif ↓ in Pr Ca mortality due to screening. (Crawford. J Clin Oncol 2011,29: 355-361)
- Göteborg study
 - 20,000 young (50 – 69 yr old) men
 - Good design, long F/U (14 yrs)
 - Screening reduced mortality by 44%
 - Hugosson et al. Lancet Oncology 2010.
- **Screening does decrease Pr Ca mortality.**
- **Young men have the greatest mortality benefit from screening.**

What is the harm in screening?

- **Over-diagnosis**

Detection of Ca that would have never become clinically apparent

- Estimates of over-diagnosis: 28 – 66%. **It's significant!**

- **Over-treatment**

Treatment which does not extend the life of individual.

- Numbers Needed to Treat (NNT) to save one life
- ERSPC: NNT = 48
- NNT influenced by age, health + length of F/U
- Subsequent analysis of PLCO looking at young men NNT = 5. (Crawford et al. 2011)
- In Göteborg , NNT = 12
- Note: Breast Ca NNT = 10

Unnecessary side effects – infection, impotence, incontinence etc.

Treatment ≠ surgery

- Active surveillance:
 - Low volume (<1.3 cc), low grade (gleason 6 and less) cancers
 - Regular PSA, rpt biopsies 12-18 mthly
 - Intervene if signs of cancer progression
 - Side effect: anxiety
- Studies have shown that AS is a valid treatment choice
 - Göteborg: 28% of the screening group were managed with active surveillance (achieving 44% mortality ↓)
 - BUT cannot save all who progress, chance of undertreatment.
- Other problems: identifying those who have indolent disease
 - Biopsies can be inaccurate esp if cancer is on anterior aspect .
 - No diagnostic test (pathology or imaging) which can distinguish between aggressive and non-aggressive Ca.

The story so far ...

- Testing asymptomatic men will detect early cancer and offer the best chance of cure.
- Young men (esp. with higher grade cancers) are the ones most likely to experience a mortality benefit from screening.
- Older men (esp. with co-morbidities) are less likely to derive mortality benefit from testing.
- The downside of PSA testing is that there will be over-diagnosis and over-treatment.
- Over-treatment can be minimised by offering active surveillance to men with small volume, low grade cancers.
- However, they should be warned that biopsies may be wrong, and if the disease progresses, salvage therapy may not be possible.

Where to now?



Current challenges:

- Can we distinguish aggressive from non-aggressive disease?
- Can we predict those at highest risk of future Prostate Ca for close F/U (and conversely relax F/U of those at low risk)?
- Can we prevent Prostate Ca?

Other markers

- **ProPSA**
 - At least 3 isoforms of free PSA.
 - 2 are ↓ in Pr Ca and 1 (“proPSA”) is ↑
 - ProPSA itself exists as a no. of truncated forms & it is [-2]proPSA which is especially assoc with Pr Ca.
 - Assay available measuring [-2]proPSA for calculation of PHI:

$$\text{PHI} = (\text{proPSA}/\text{freePSA}) \times (\text{TotalPSA})^{1/2}$$

(A high PHI is bad news)

Catalona et al. J Urol. 2011 May

In the PSA 2-10 ug/L range with non-suspicious DRE, PHI was better indicator of Pr Ca, and also aggressive Pr Ca (gleason ≥ 7) than Total PSA and free PSA

Other markers

- **PCA3**

- PCA3 is a gene which has (non-coding) mRNA that is over-expressed in Pr Ca but not in health or BPH.

- Detected in urine

- High specificity for Ca.

Potential use in detecting Ca where there persistent suspicions of Prostate Ca but negative biopsies.

- Some studies suggest a correlation with Gleason score.

- **Genetic markers**

- 40-45% variability in PSA is genetically determined

- SNPs associated with higher-than-normal PSA secretion, ↑ Pr Ca risk.

- Zheng et al. NEJM 2008 looked at 5 particular SNPs which alone were each associated with moderate risk of Pr Ca. H/e in combination and with FHx the association with Pr Ca was strong.

Prostate Ca risk

- **Baltimore** Longitudinal study of aging

- PSA > median (0.6 ug/L for 40 yo, 0.7 ug/L for 50 yo), 3.5 times ↑ risk of Pr Ca over next 15 yrs

- 2011 Hans Lilja et al.

- **Malmö** Preventive Project - archived blood (1974 – 1992)

- No PSA screening. Median 27 yr F/U.

- At age 44-50, men with PSA >1.6 ug/L (top 10%) accounted for 44% of future Pr Ca deaths

- Implications:

Possible to prevent half of all deaths by intense surveillance of a small proportion of men with the highest PSA levels at age 44-50.

For men with lower PSA, testing at age 51-55 and age 60 is sufficient to capture Pr Ca mets or death 10+ years in advance.

50% of men only need have three lifetime PSA tests.

Can we prevent Prostate Cancer?

- Primary prevention – lifestyle factors can decrease your risk of Pr Ca, and even decrease advanced disease
 - Avoid **obesity**
 - Avoid deli meats
 - No charred meats
 - Eat more fruit and vegetables
 - Stop smoking.
 - Best effect is to make these lifestyle changes when you are young (20-30).
- What doesn't work:
 - Chemoprevention
 - Selenium, Vit E, Vit E+C, Zinc, Vit D, multi-vitamins
 - Chemo-prevention at 50 yrs cannot stop what has already started.
 - Finasteride

The final word ...

- The focus in prostate cancer has shifted from treatment to early detection & now, to detection of aggressive disease, future risk prediction & primary prevention.
- PSA testing remains controversial.
We embraced PSA 15 years not fully aware of the implications of testing. We now have a better understanding of what it means and how to use it and, in my opinion, we should not be abandoning it.
- Watch this space.