Dr Andrew Williams

Urologist

Auckland

BPH and the PSA Debate - Concurrent Workshop Repeated

Saturday, 22 June 2013	Start 2:00pm	Duration: 55mins	Picasso
	Start 3:05pm	Duration: 55mins	Picasso

BPH and The PSA Debate

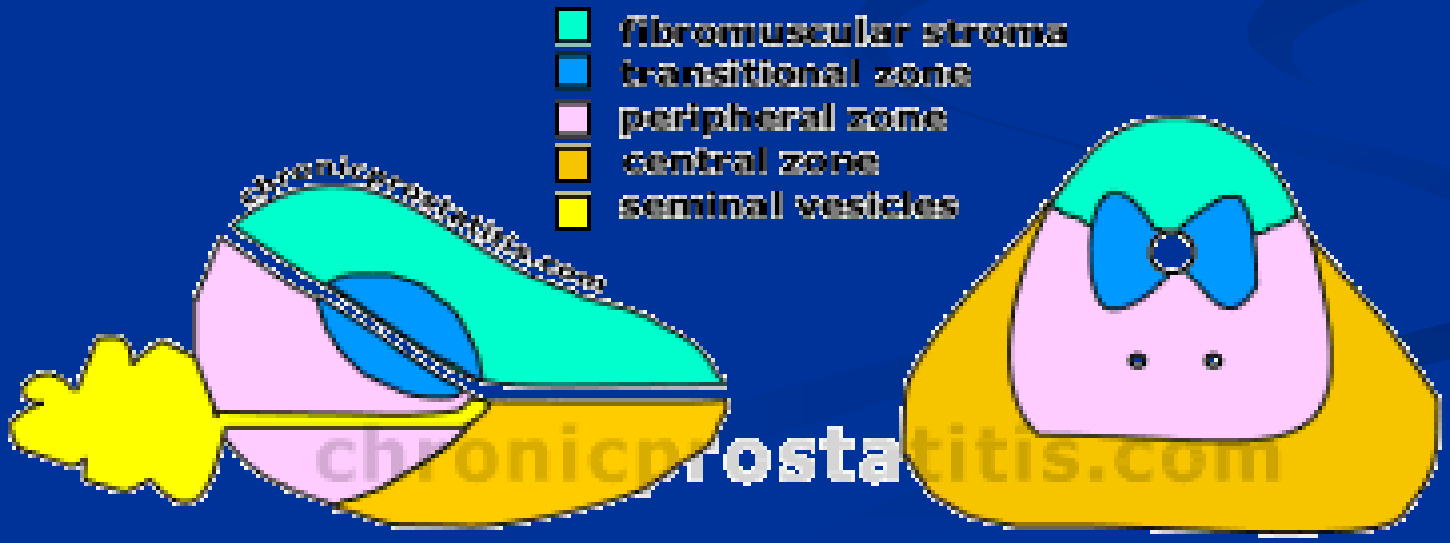
Andrew Williams FRACS

Urologist ADHB, CMDHB and

Clinics at EastCare and 161 Gillies Ave

What is BPH

- Non-malignant growth of the prostate gland particularly involving the transition zone.
- Occurs in most men to a greater or lesser degree.



Primary Symptoms of BPH

- Poor Flow
- Incomplete emptying
- Terminal dribbling
- Straining to void

- Primary treatment is α Blockers and Finasteride

Secondary symptoms

- These are due to bladder hypertrophy secondary to prolonged outlet obstruction.

- Urgency
- Frequency

- Often improve with treatment of Primary symptoms but can benefit from Anticholinergics (don't be scared).

Complications of BPH

- Urinary Retention
  - 95% of patients who go into unprecipitated retention and void with TROC will go into retention again within 1 year.
  - TURP
- Recurrent UTI's
  - More than 1 UTI in a male is abnormal and should precipitate investigations, U/S to rule out stones and if high residual volume → TURP
- Bladder Stones
  - Stasis of Urine → TURP

Standard Management of BPH

- This is a patient directed treatment.
- α Blockers can be commenced when the patient wants to trial them.
- Strongly consider Finasteride
- Be wary of patients with Parkinsons and "BPH" symptoms.
- Patients with Spinal lesions should be assessed by a Urologist

Tamsulosin

- A Selective α blocker
- Available for those that don't tolerate Doxazosin or Hytrin.
- Selective for α1a receptors
- Less effect on BP
- Great for patients with Parkinsons or postural hypotension
- 0.4mg OD, no titration required

Finasteride (Fintral or Propecia)

- 5mg OD
- 5α Reductase Inhibitor
- Available on special authority to any "relevant practitioner" for patients failing α blocker or intolerant of α blocker.
- Blocks the conversion of Testosterone to Di-hydroxy Testoterone in peripheral tissues.
- Stops male pattern baldness and shrinks prostates (Circa 40% in 6 months)

Study design: overview

Double-blind, placebo-controlled, multicentre, randomised

Average follow-up: 4.5 years

Randomised **n=3047**

Entry criteria:

- **Men ≥50 years of age**
- **AUA symptom score 8–30**
- **Q_{max} 4–15 ml/sec**
- **Voided volume ≥125 ml**

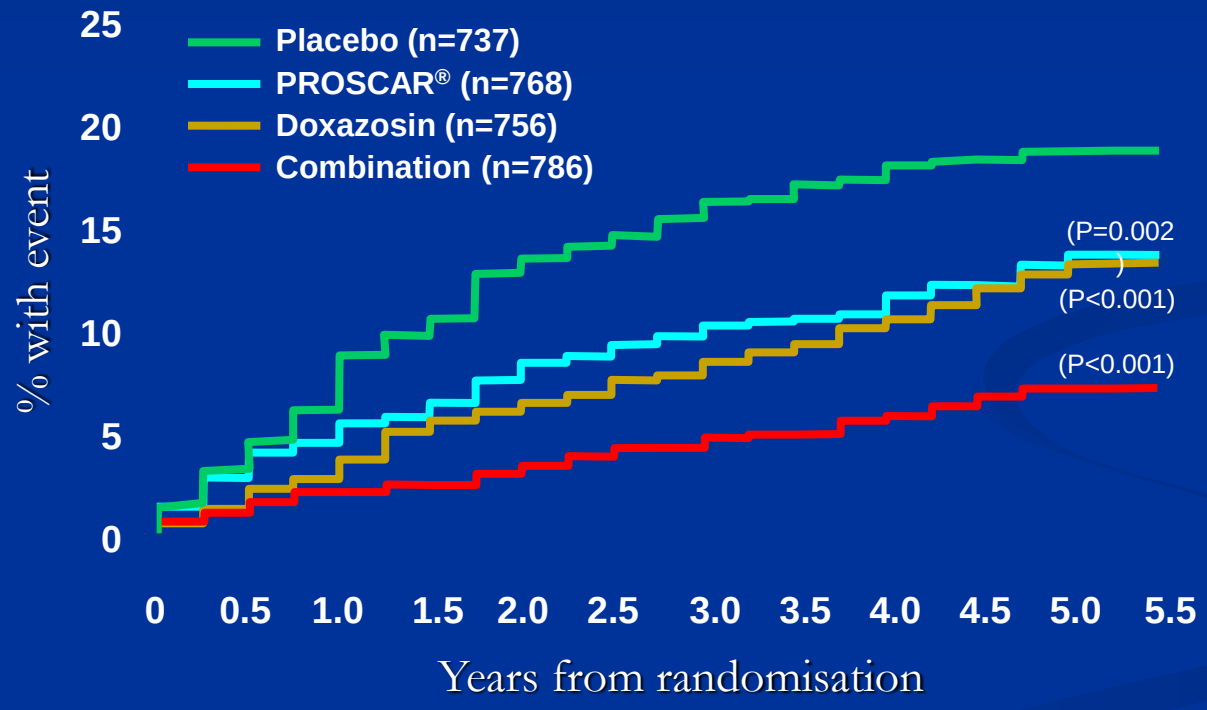
Doxazosin (n=756)	PROSCAR® (n=768)	PROSCAR® + doxazosin (n=786)	Placebo (n=737)

AUA=American Urological Association; Q_{max}=maximum urinary flow

Adapted from McConnell J et al. *N Engl J Med* 2003;349:2387-2398.

Impact of medical therapy on clinical progression of BPH

Cumulative incidence of BPH progression



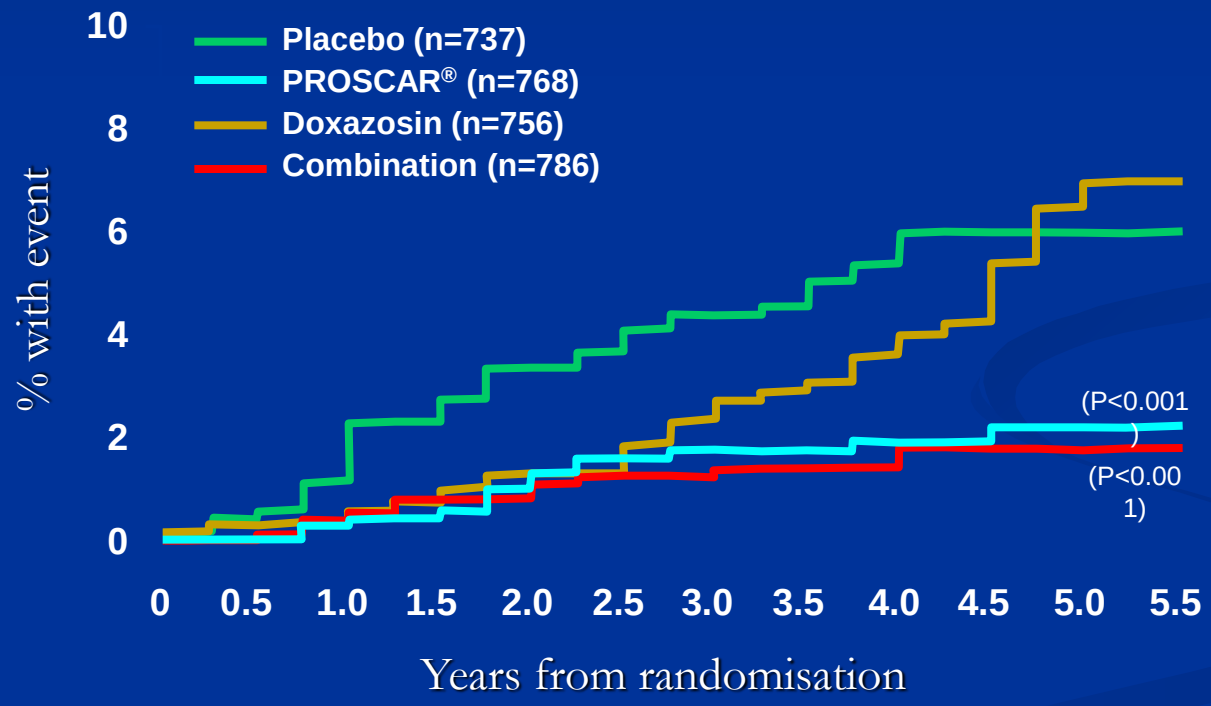
Combination vs. Placebo 66% risk reduction

- Risk reduction with PROSCAR® and doxazosin was significantly greater than with either drug alone
- PROSCAR alone vs. placebo: 34% risk reduction
- Doxazosin alone vs. placebo: 39% risk reduction.

Adapted from McConnell J et al. *N Engl J Med* 2003;349:2387-2398

Impact of medical therapy on the need for BPH-related surgery

Cumulative incidence of BPH-related surgery



Combination vs. Placebo
67% risk reduction

- PROSCAR® and doxazosin significantly reduced the incidence of BPH-related surgery vs. placebo
- PROSCAR alone significantly reduced the incidence of BPH-related surgery vs. placebo
- Doxazosin alone did not significantly reduce the incidence of BPH-related surgery

Adapted from McConnell J et al. *N Engl J Med* 2003;349:2387-2398

Side Effects

- Erectile Dysfunction – 10%
- Abnormal ejaculation – 5%
- Gynaecomastia – 2%

Caveats

- Little effect in small prostate glands
  - Should be > 40cc, one fingerprint = 10cc
- Will lower PSA by 50%, if PSA increase on Finasteride a PSA increase should be treated seriously, regardless of PSA level. Trialled as a chemoprevention treatment. Some data that it can predispose to high grade prostate cancer (but reduces risk of low grade prostate cancer) PCPT trial.

Solifenacin

- Don't be scared of trialling an AntiCholinergic if symptoms suggest its use.
- Selective Anti-cholinergic for M3 receptors
- Reduced salivary gland side effects and constipation (M1 mediated)
- Available for those that don't tolerate oxybutinin.
- 5mg OD.

PDE-5 Inhibitor

- Some evidence for effect in patients with BPH.
- Tadalafil 5mg od approved in NZ
- Evidence for improvement in erectile function in this group.
- Still expensive at circa $200 per month.

Typical Flow Male 50 + with LUTS

- Dose he want to trial treatment??
- Alpha blocker (consider tamsulosin if poorly tolerated or parkinsonism)
- If urgency, frequency add an Anticholinergic (consider solifenacin)
- If Prostate enlarged (>2 fingerprints per side), then add finasteride.
- If complications of BPH → Refer to Urologist

Groups that require Urologist for non-surgical input.

- Early referral after trial of alpha blockers.
  - Parkinsons disease.
  - Previous pelvic surgery or trauma.

- Should be referred.
  - Spinal injured patients.
  - Neurological conditions.
  - Incontinence in a male.

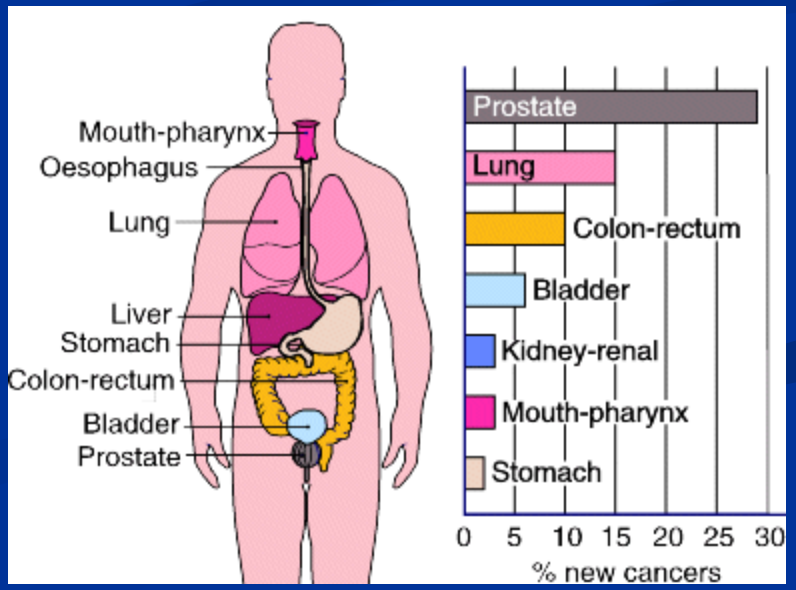
Prostate Cancer Screening

Andrew Williams FRACS

Urologist ADHB and Urology 161 Gillies Ave

Why the dilemma?

- Prostate Cancer is the most diagnosed cancer in NZ men.
- Prostate is the second most common cause of cancer death.
- Early detection tests are available – PSA, DRE, PCA-3 etc
- But…. Only 1 in 5 men diagnosed with prostate cancer will die from it.
- Overtreatment has been rife particularly in privately base medical systems (eg USA)



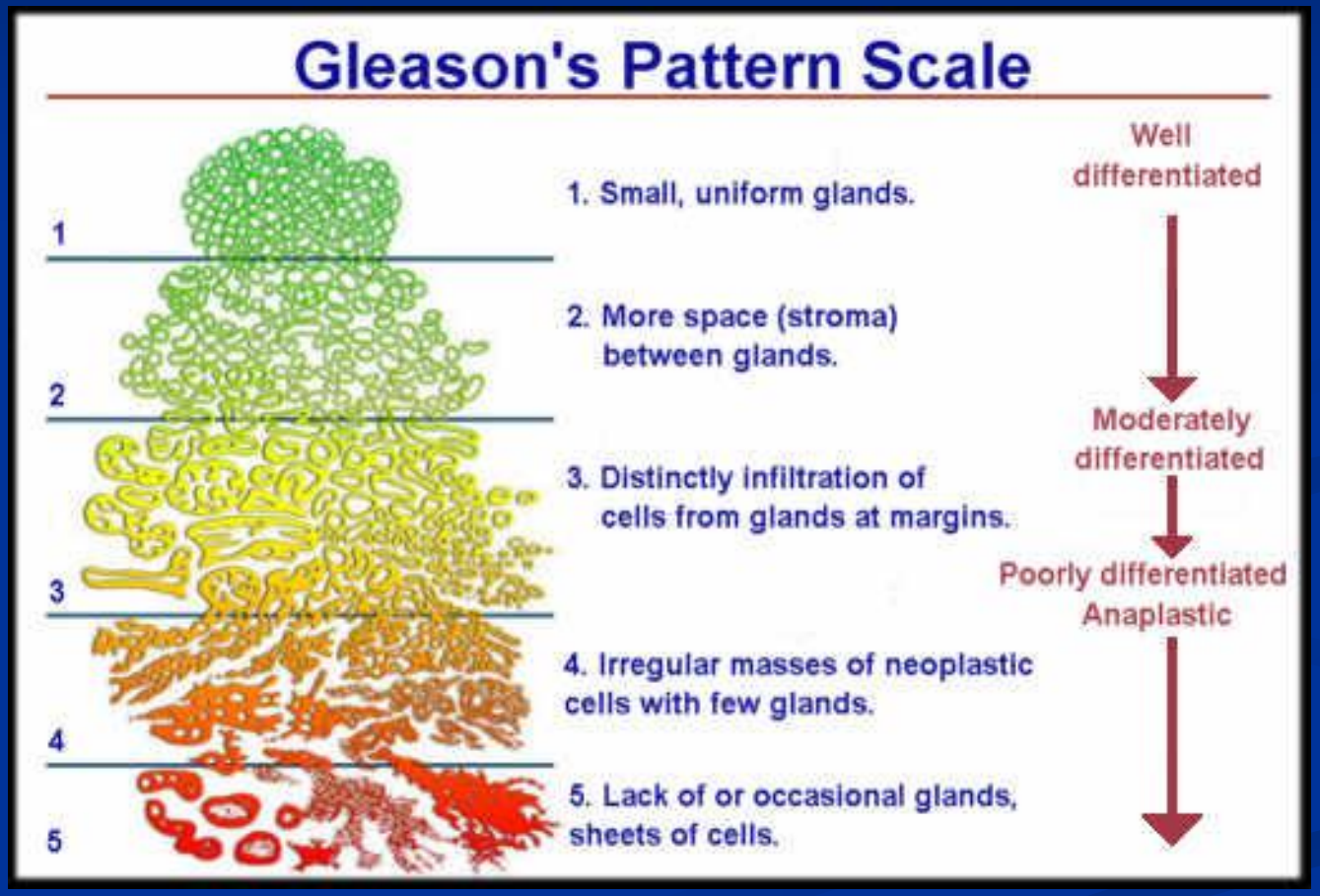
Prostate Cancer: a quick review

- Usually diagnosed by Trans-Rectal Biopsy of the prostate (TRUS).
- Clinical grading is based on
  - Impalpable T1
  - Palpable but within the prostate T2
  - Palpable and outside the prostate capsule T3
  - Fixed to adjacent structures T4.

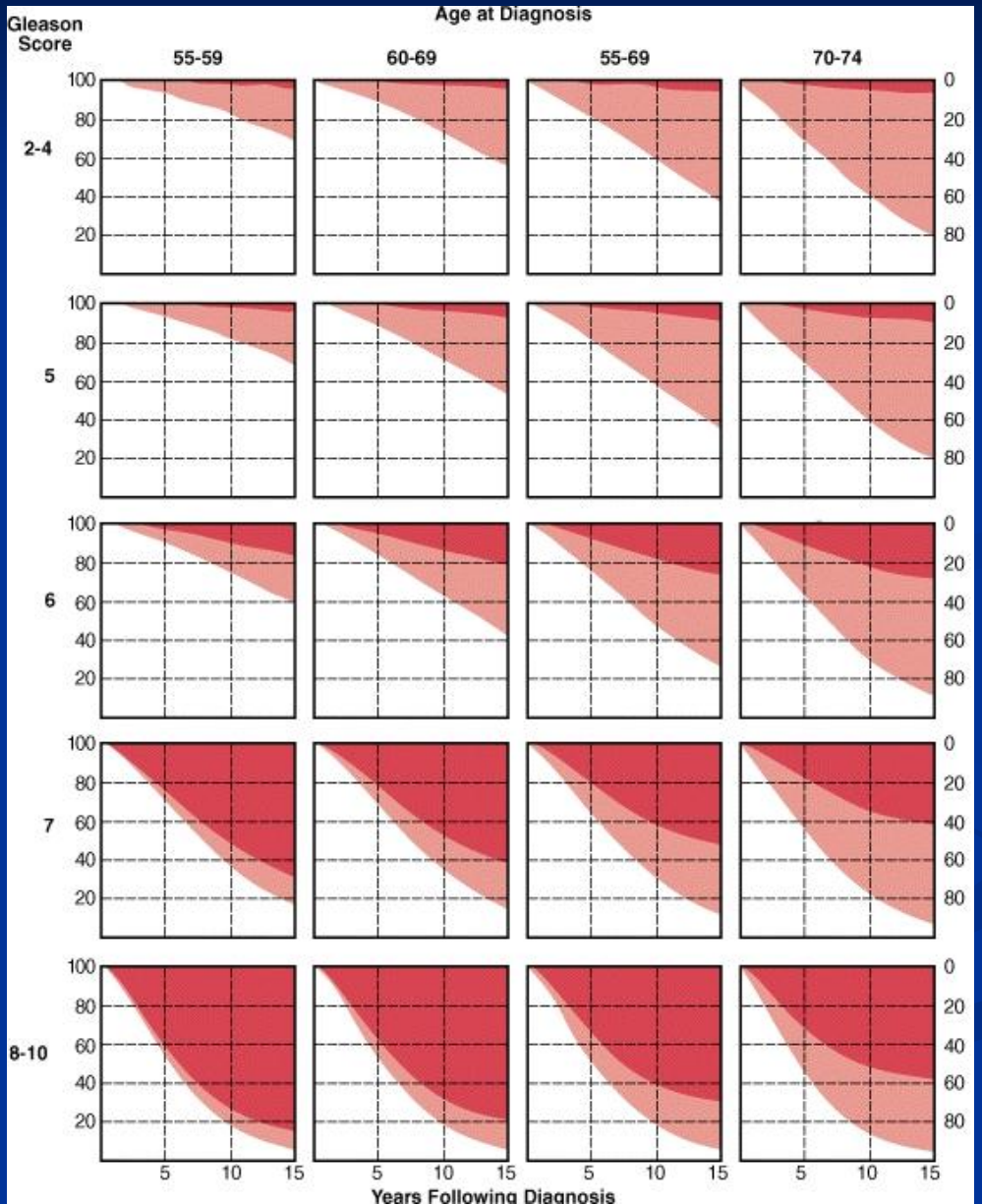
Aggressiveness is based on Gleason Score

- Most common prostate cancer morphology plus second most common.
- Tertiary score sometimes given if a small amount of aggressive prostate cancer seen.

Different Gleason grades



Why does Gleason score matter?



Low Risk Disease

- Little evidence for intervention
- PSA <10, Gleason 6, T1 or early T2.

- Surgery
- Radiation – Brachytherapy or EBRT
- Active Surveillance

Intermediate Risk

- PSA 10-20, Gleason 7, T2/T3.

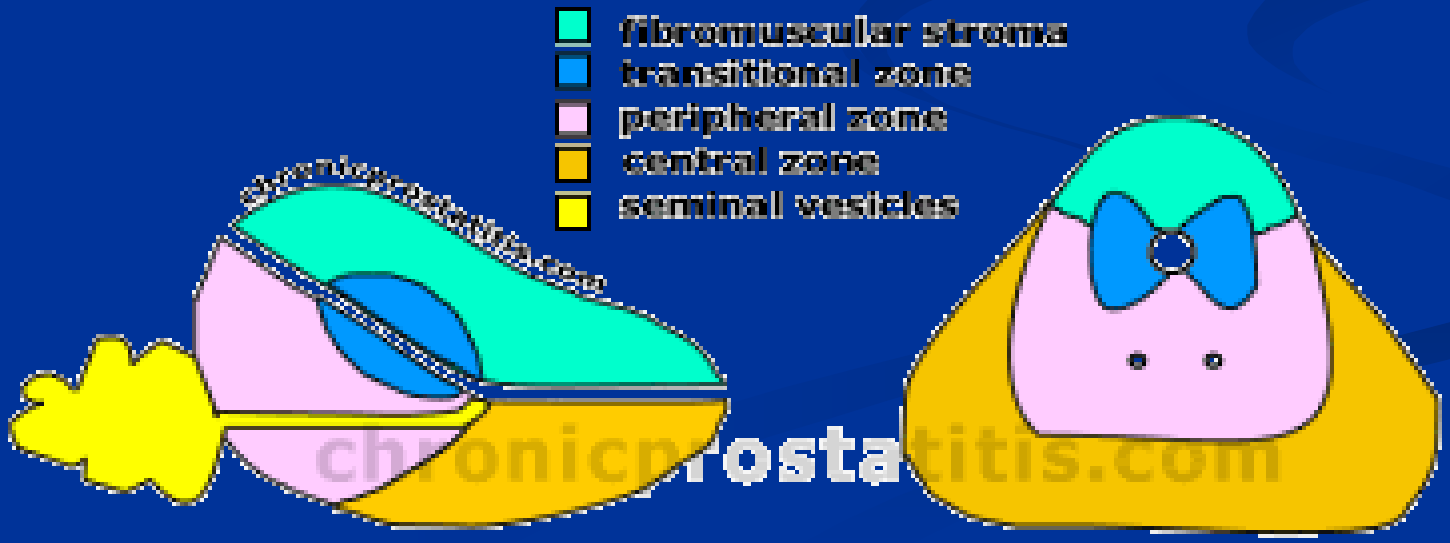
- Surgery + Node dissection +/- EBRT
- EBRT + 2 years of hormones

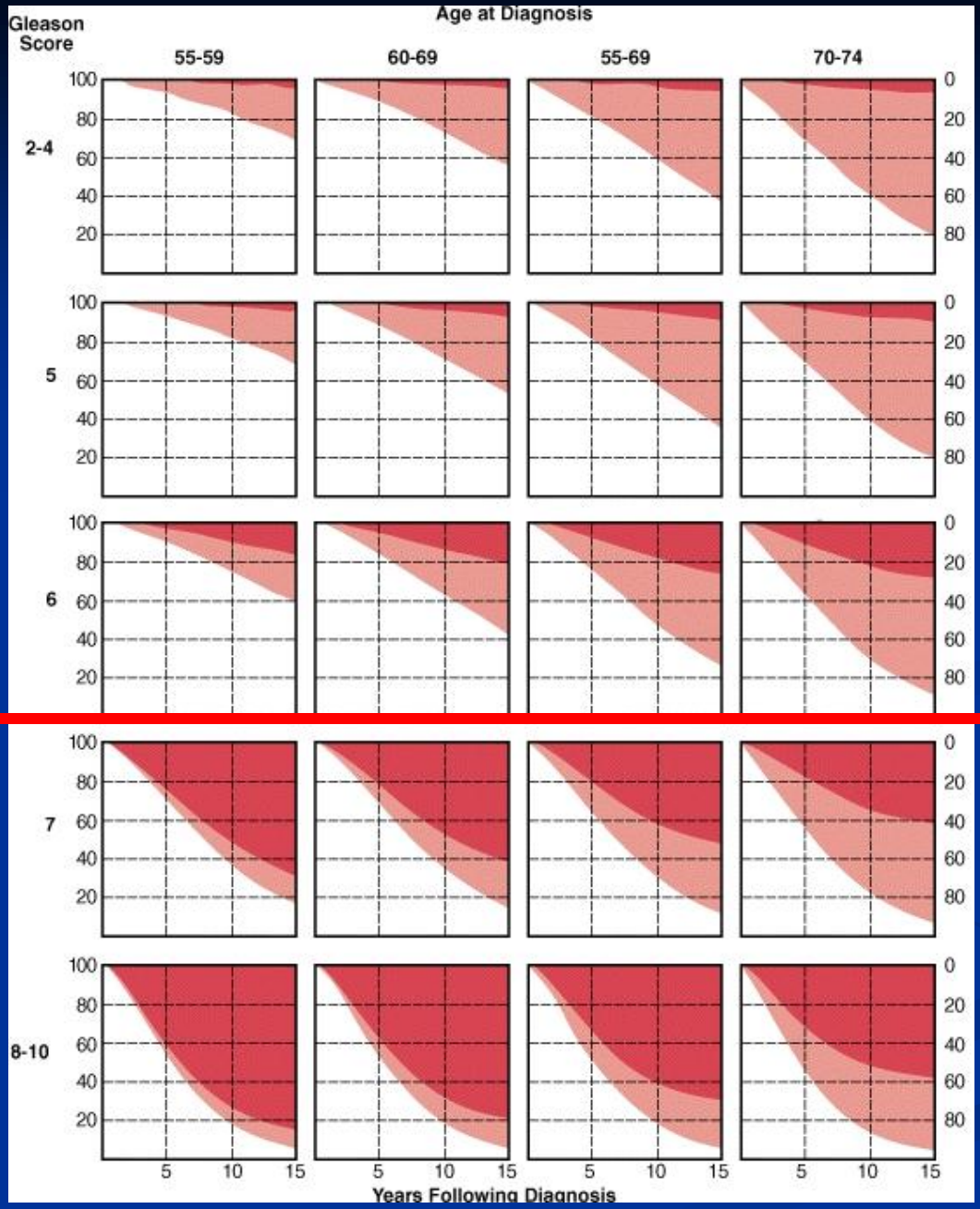
High Risk Disease

- Gleason 8+, PSA >20, T3/T4.
- Hormonal Therapy
- If T3 and negative staging
  - Surgery + Node dissection +/- EBRT.
  - Hormones + EBRT

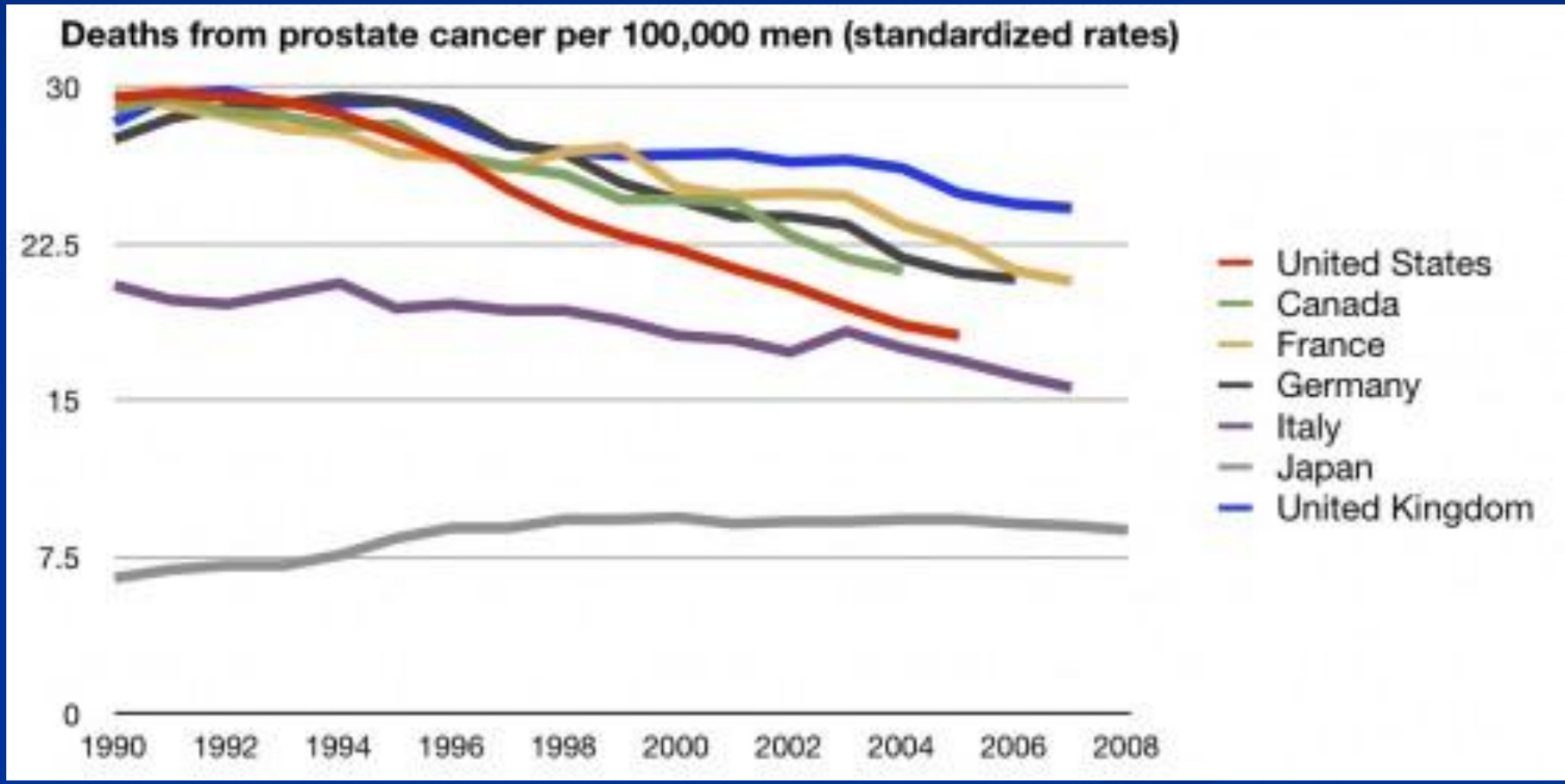
What about screening?

- Screening has been in place in a disorganised manner since the early 90's.
- PSA testing in any symptomatic individual is screening (with the exclusion of bone mets).

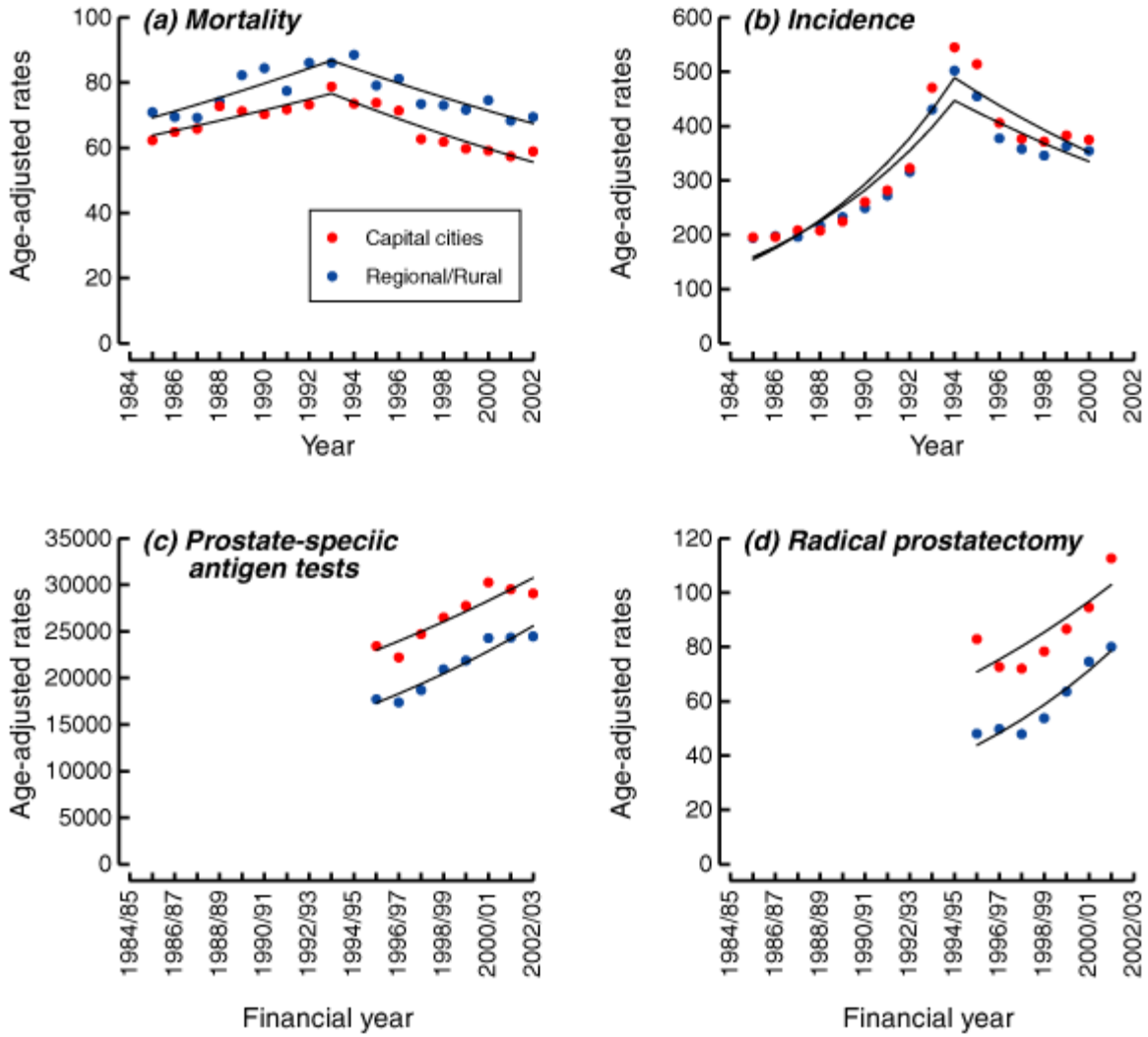



Gleason Score
Age at Diagnosis
55-59
60-69
55-69
70-74
2-4
5
6
7
8-10
100
80
60
40
20
0
20
40
60
80
5
10
15
Years Following Diagnosis

International Prostate Cancer Mortalilty rates



Australian Data

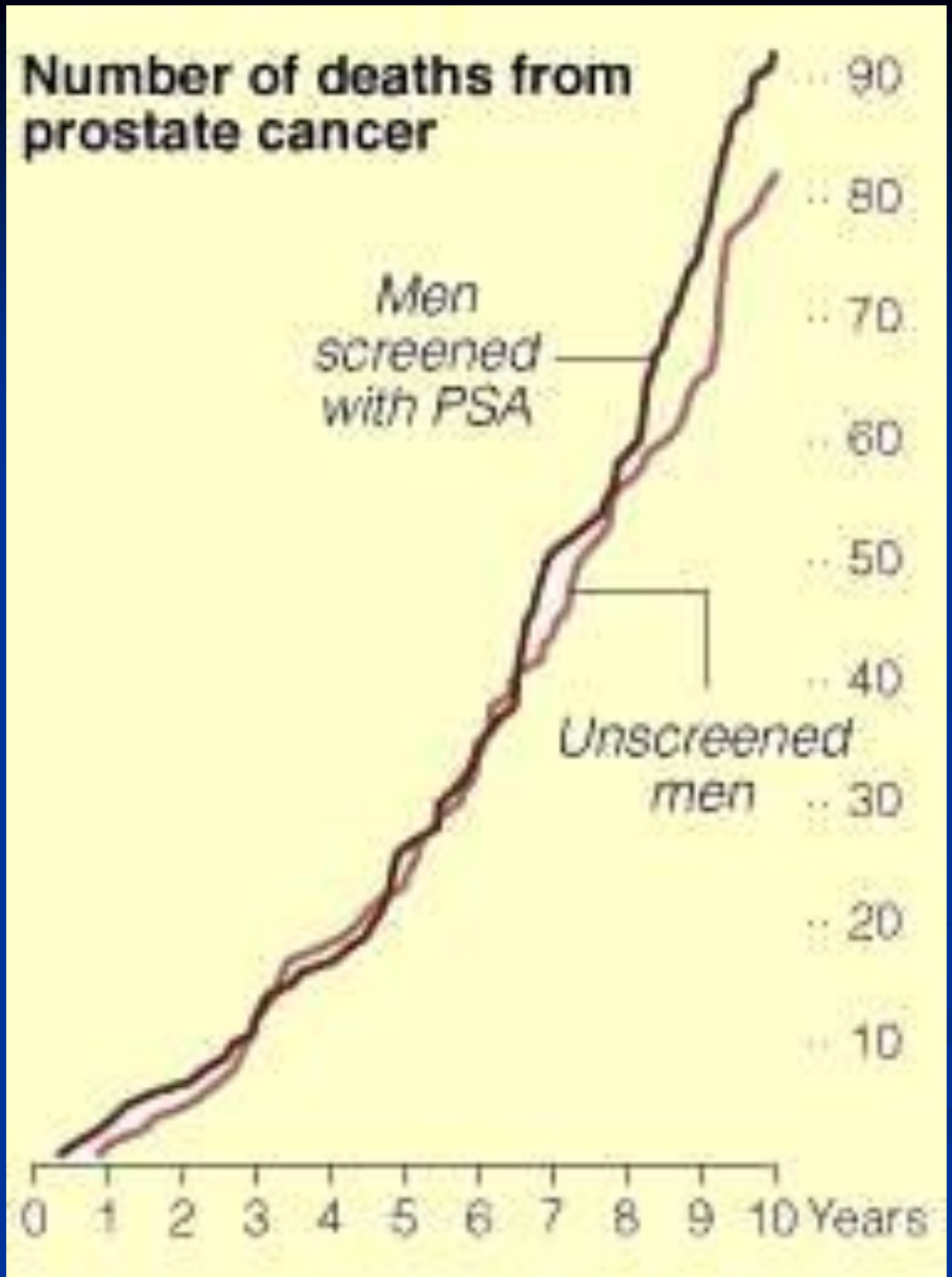


What does the research show?

- Three large studies have been performed all with varying screening methods, quality of design and contamination.
- Two large studies (ERSPC and PLCO) were prematurely rushed to publication in the same month (NEJM).
- Both of these major studies had conflicting results.
- One further study tends to be overlooked and is probably the best reflection of NZ practice.

PLCO

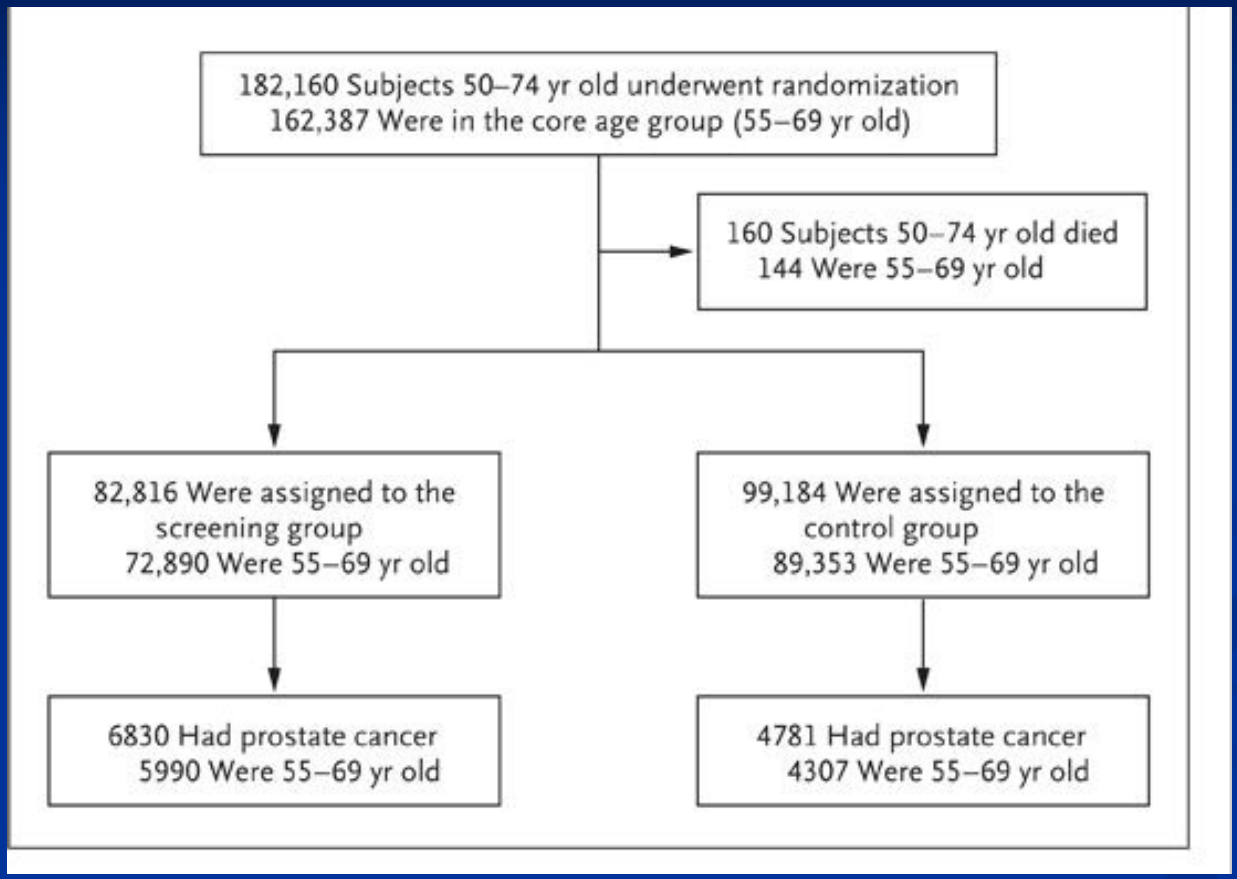
- N Engl J Med March 26 , 2009
- Found no benefit from prostate cancer.
- 76,693 men in USA 55-74
- Multiple centers
- Intervention for PSA>4 (yearly) or abnormal DRE.
- 11 years follow up
- 52% had already had PSA test performed.
- Less prostate cancers were found in the screening arm (6% vs 7.3%)


Number of deaths from prostate cancer
90
80
70
60
50
40
30
20
10
Men screened with PSA
Unscreened men
0 1 2 3 4 5 6 7 8 9 10 Years

ERSPC

- 162,243 men in Europe 55-69.
- 7 European countries.
- 9 years follow up
- PSA > 3 (every 4 years) or abnormal DRE.
- Contamination not known but thought to be circa 20%

ERSPC

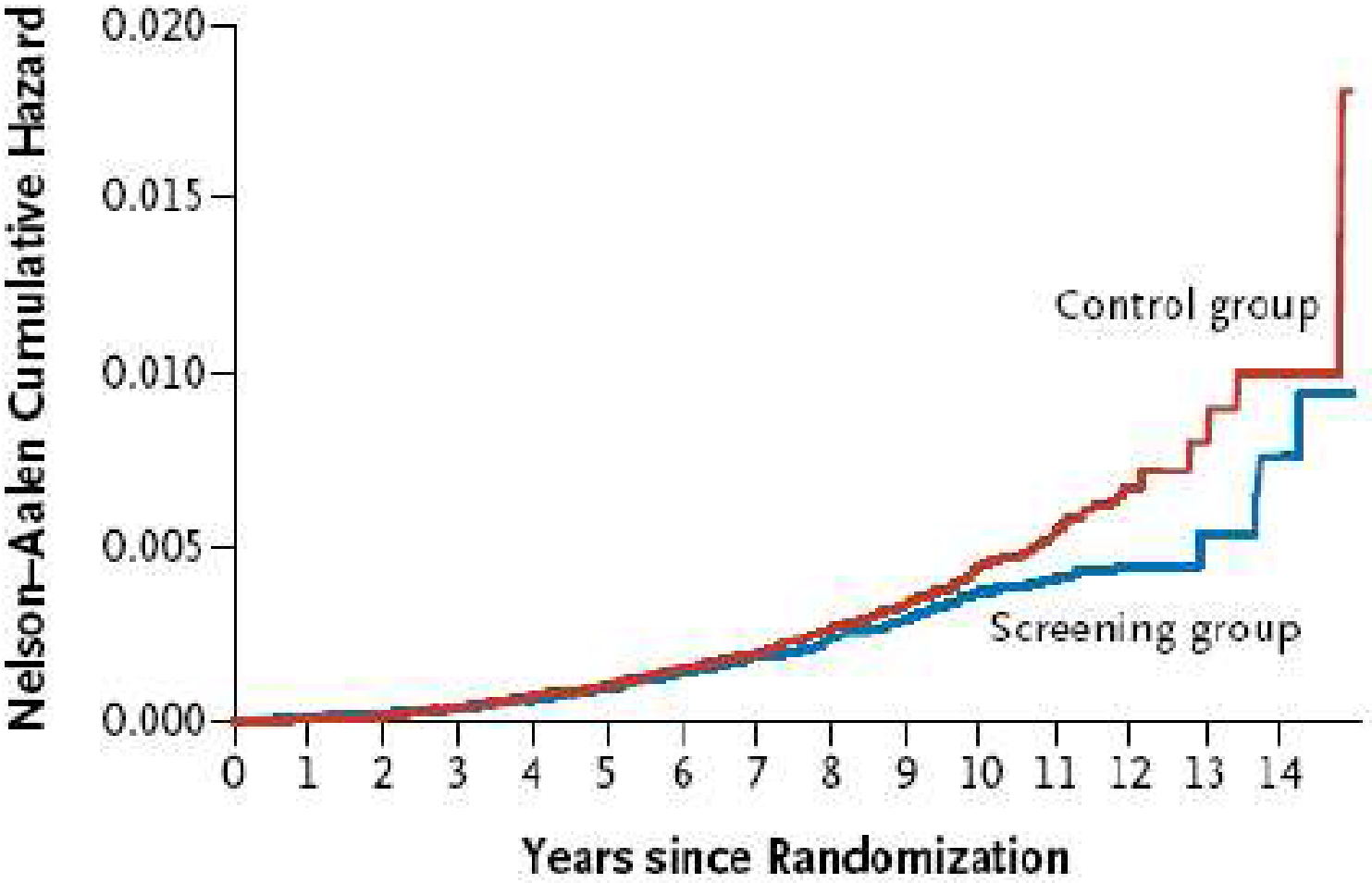


Prostate cancer was less common in screened group (8.2% vs 4.8%)

20% RR in prostate cancer mortality.

NNT were 1410 (screened) and 48 (treated) at 9 years

Data suggest this will be 503 and 18 at 12 years


Nelson–Aalen Cumulative Hazard
0.020
0.015
0.010
0.005
0.000
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Years since Randomization
Control group
Screening group

Goteborg study

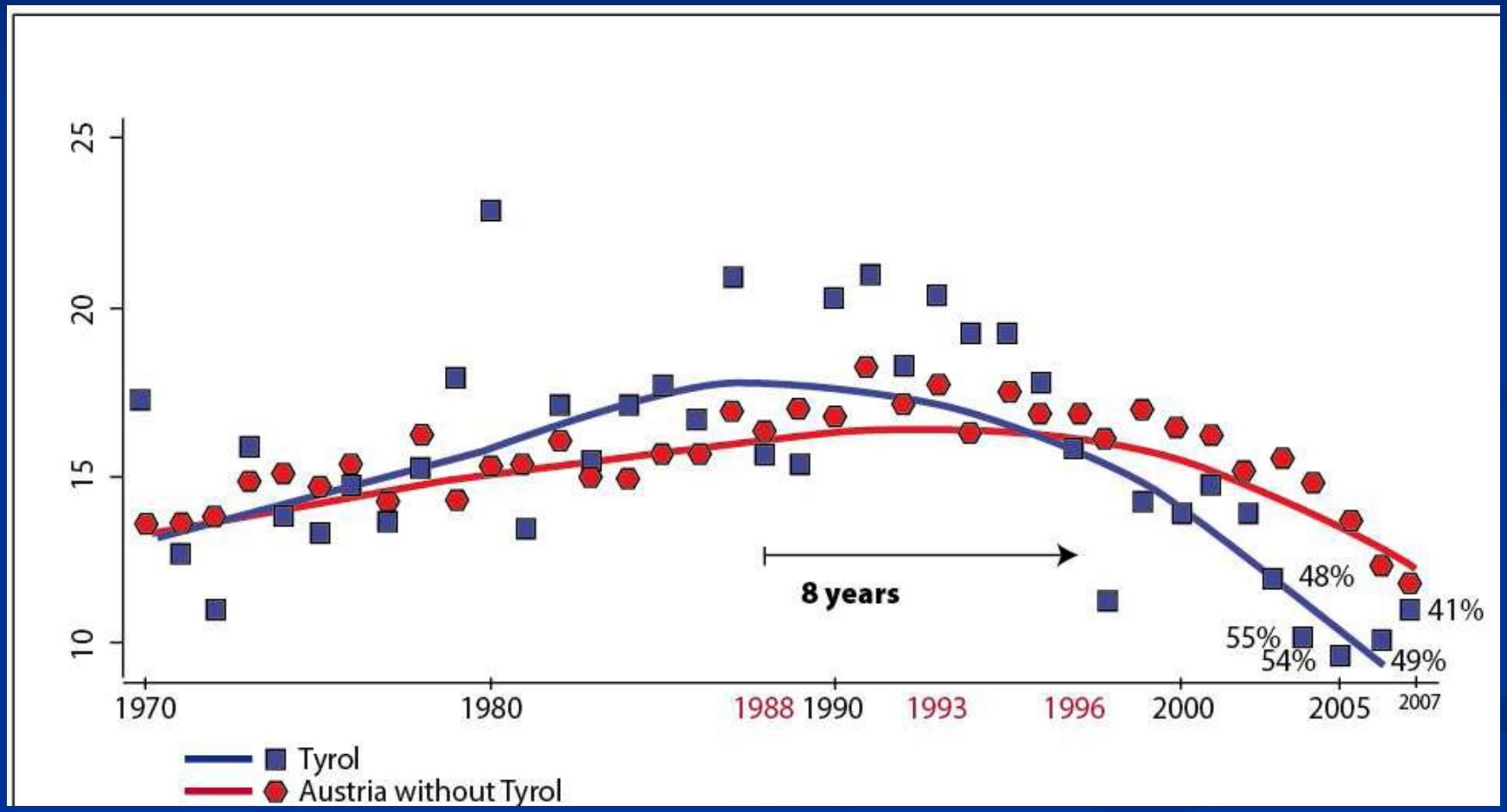
- Methodologically the best study.
- 19,904 patients
- 14 year follow up
- PSA > 2.5 (2005+) to >3.4 (1995-1998)
- Contamination 3%
- Prostate Cancer 11.4% screened vs 7.2%
- RR 44%
- NNT 293 screened 12 treated.

The Tyrol Comparison

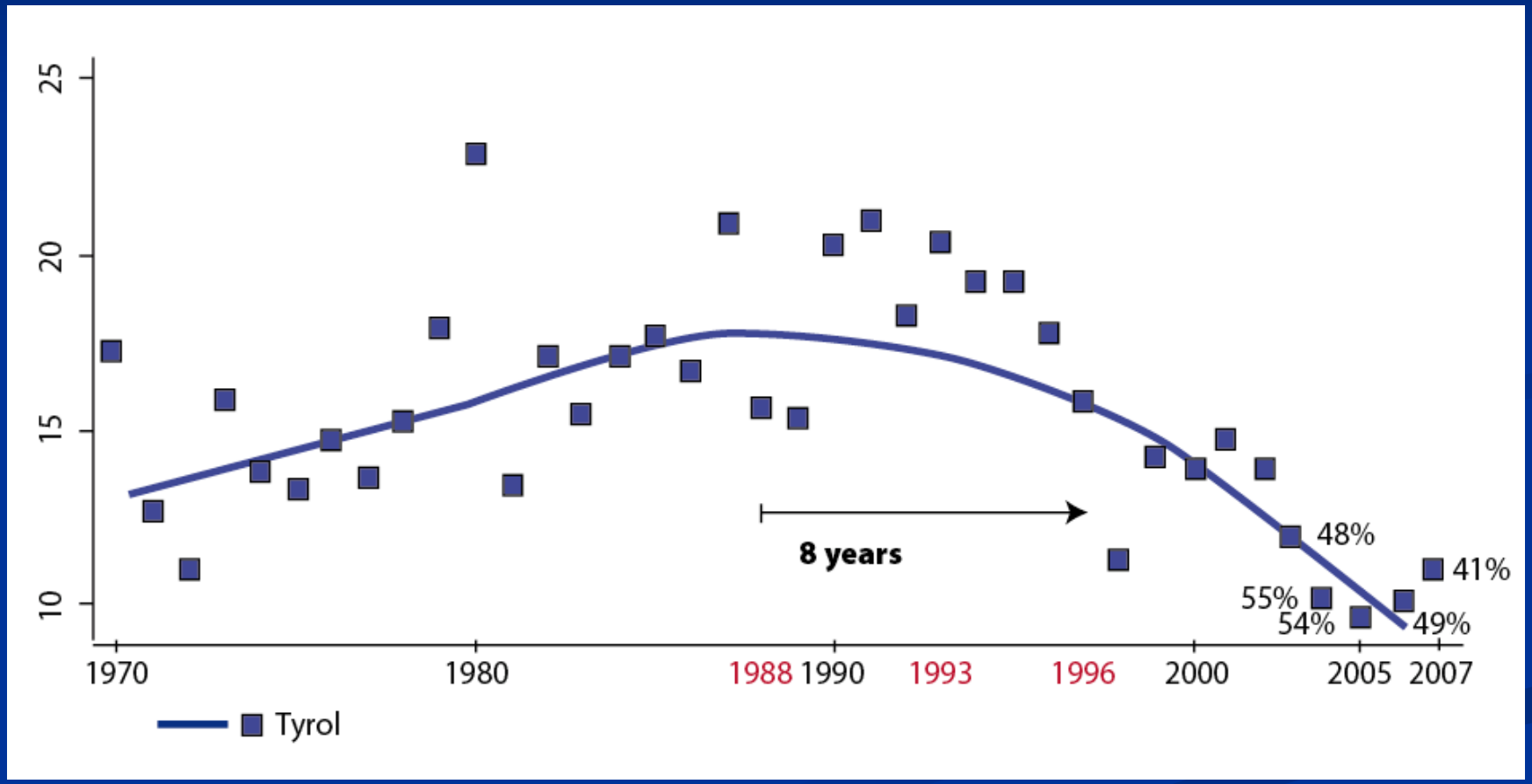
Why is Tyrol important to PSA?

- Austria maintains an entirely publically funded health system.
- Tyrol introduced PSA screening in 1988 and free testing since 1993.
- 86.6% of eligible men have had a PSA test.
- PSA screening is not available elsewhere in Austria.

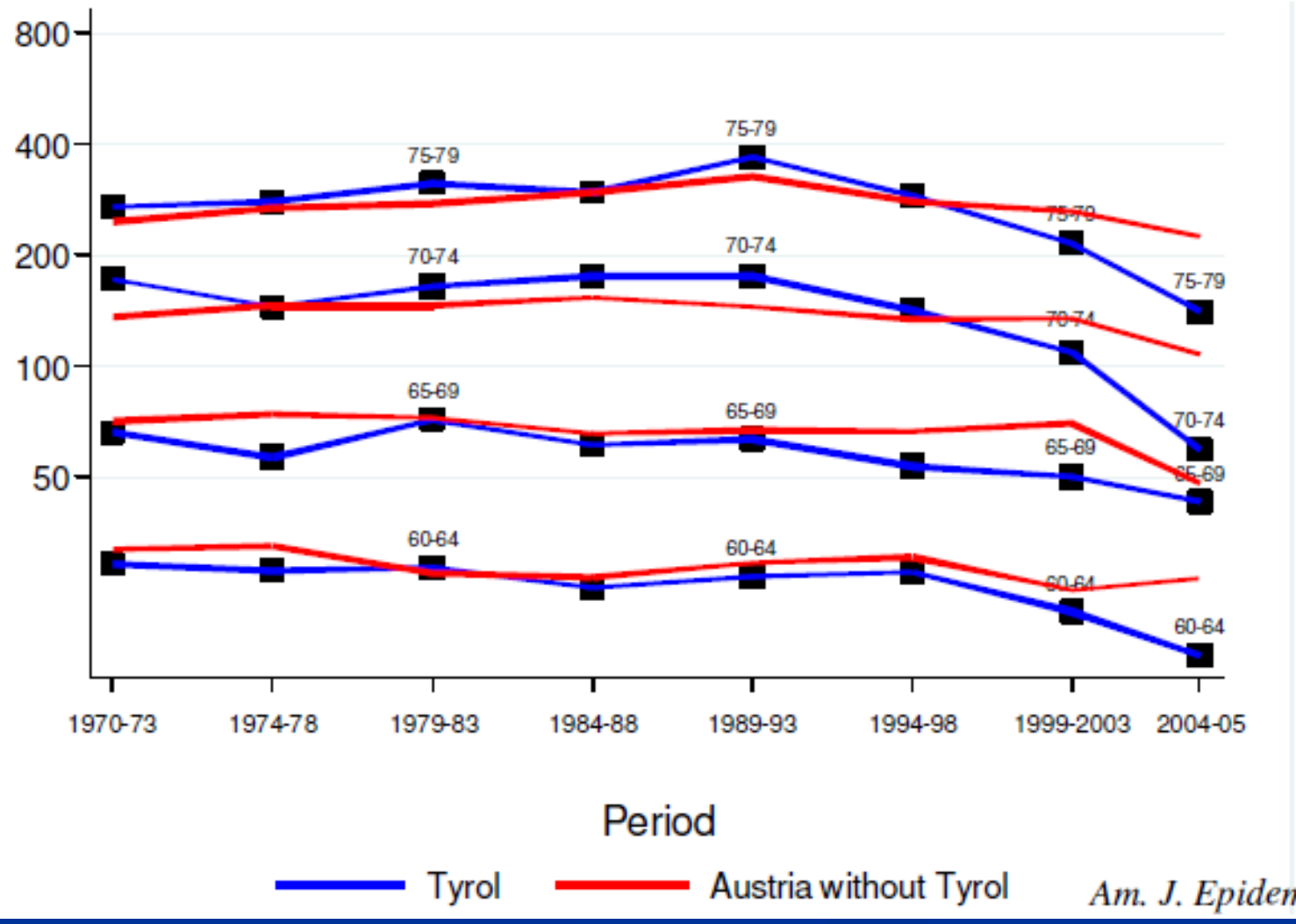
Tyrol vs Rest of Austria



Tyrol Alone


25
20
15
10
1970
1980
1988
1990
1993
1996
2000
2005
2007
8 years
48%
41%
55%
54%
49%
Tyrol

Has Tyrol been overdiagnosing and therefore overtreating?



Am. J. Epidemiology,

What harm is being done by screening?

- TRUS Biopsy
  - A local anaesthetic procedure
  - Urinary retention 2-3%
  - Sepsis 1-3%
  - Bleeding <1%
- Prostatectomy/EBRT
  - Incontinence 5%
  - Erectile dysfunction 50-70%
  - Stricture formation 2-10%

Can we improve on these screening study results?

- We can not treat insignificant or low risk prostate cancer!!!
  - Insignificant cancer is present in 24% of patients.
- We can't top taking a one size fits all approach!!!!

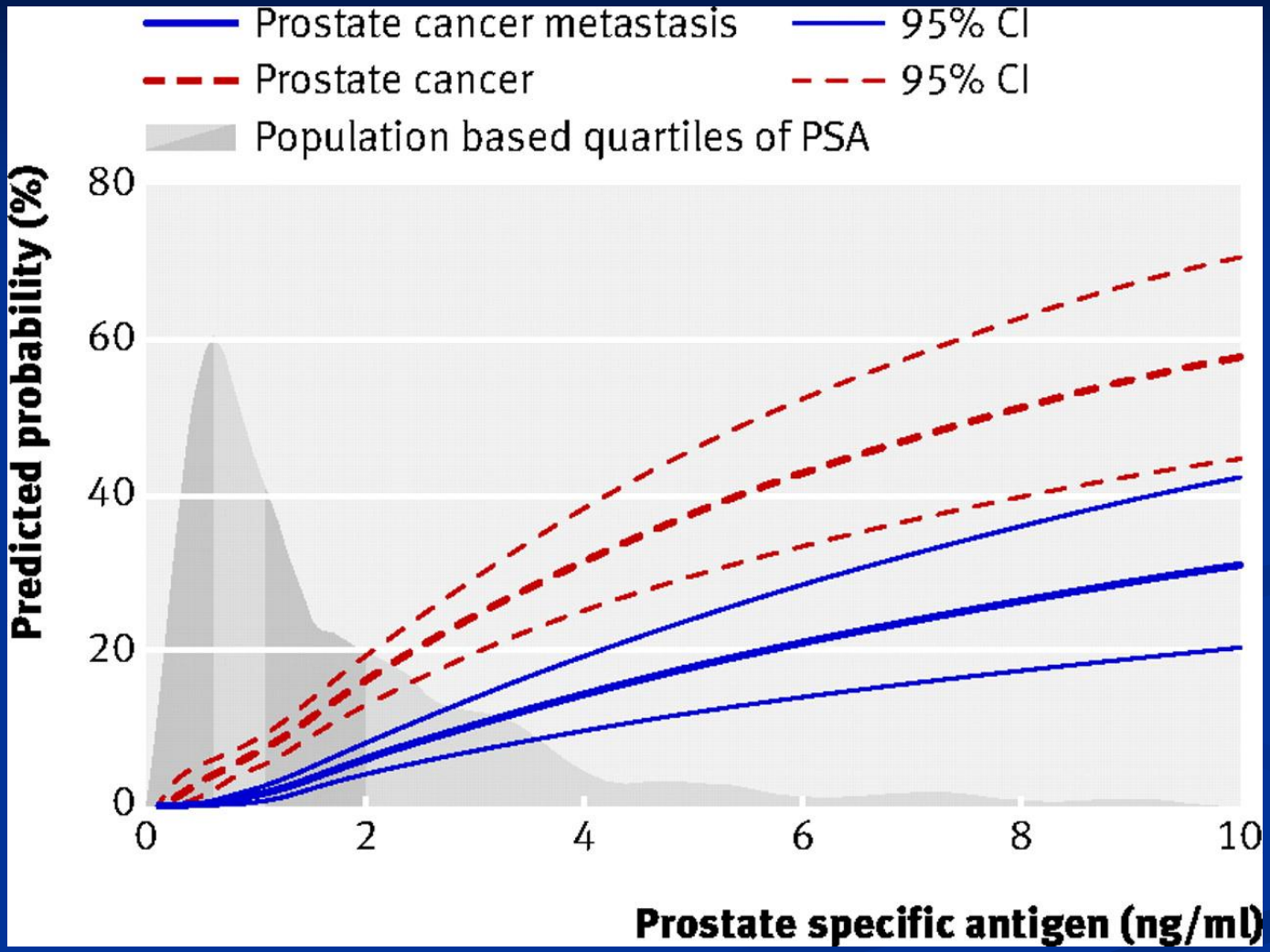
Malmo Preventative Study

- PSA at 40 -55 predicts risk of cancer
- Median PSA 0.5

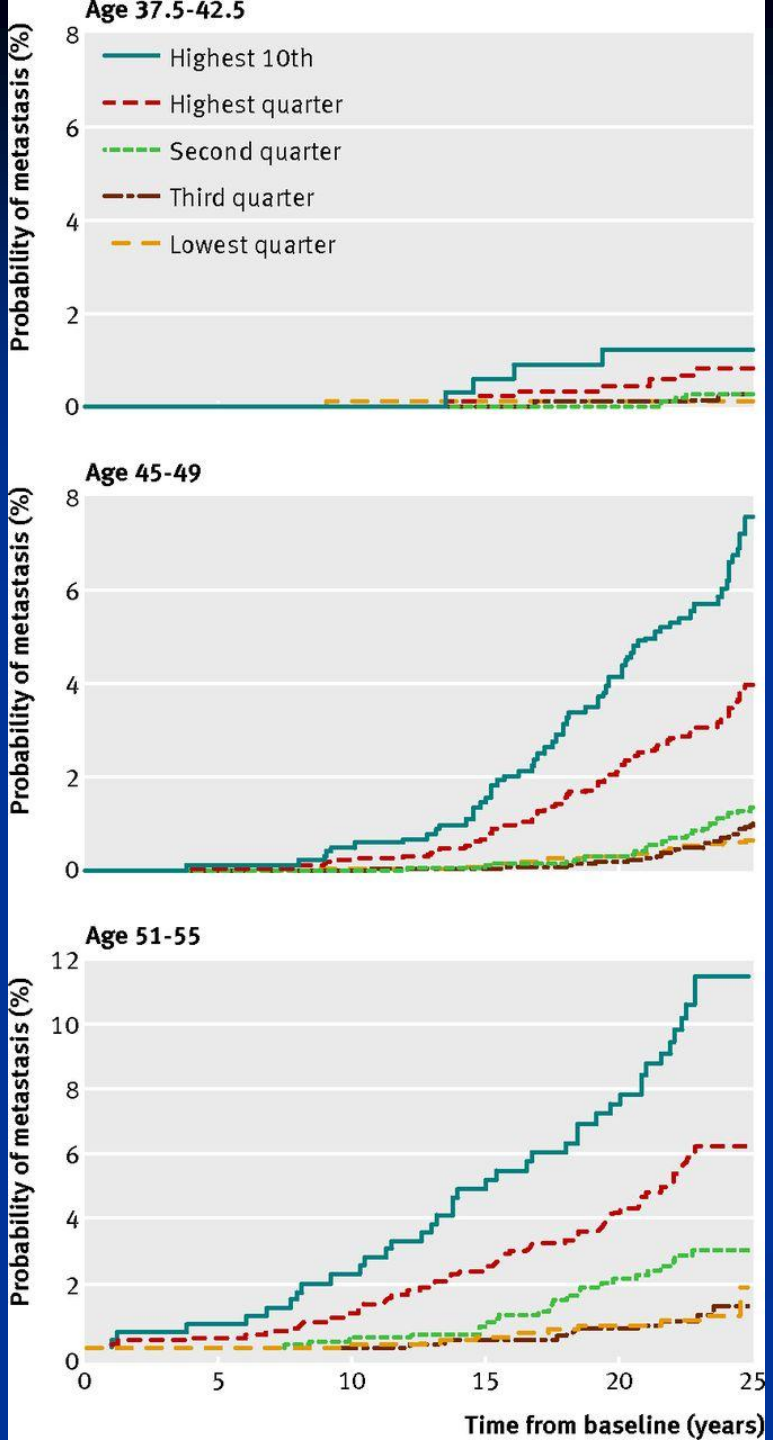
- PSA 0.5-1.0 = 2.5 x risk
- PSA 1-2 = 7 x risk
- PSA 2-3 = 17 x risk
- PSA 3+ = 39 x risk

- If you can risk stratify you can reduce cost and potentially morbidity

Fig 1 Lifetime risk of clinically diagnosed prostate cancer or prostate cancer metastasis.



Vickers A J et al. BMJ 2010;341:bmj.c4521


Age 37.5-42.5
Highest 10th
Highest quarter
Second quarter
Third quarter
Lowest quarter
Probability of metastasis (%)
0
2
4
6
8
Age 45-49
Probability of metastasis (%)
0
2
4
6
8
Age 51-55
Probability of metastasis (%)
0
2
4
6
8
10
12
0
5
10
15
20
25
Time from baseline (years)

USANZ Screening Policy

- PSA and DRE at 40
  - If < 0.5 repeat at 45 and 50 then yearly
  - If >0.5 yearly.
- If PSA >4.0 refer for discussion of biopsy.

NZ Prostate Cancer Workforce

Recommendation 15

Primary health care should provide high-quality, culturally appropriate information on prostate cancer and PSA testing to men aged 50 to 70 years.

All men who are concerned about prostate cancer or are requesting a PSA test must be presented with high-quality, culturally appropriate information.

Recommendation 17

Screening for prostate cancer must be by both PSA and DRE testing. PSA testing alone is acceptable only where DRE is considered a barrier to testing.

NZ Prostate Cancer Workforce

General practitioners should refer patients to a urologist according to the following criteria:

- 50–70 years –PSA is ≥ 4.0 ng/mL
- 71–75 years –PSA is ≥ 10.0 ng/mL
- ≥76 years PSA is ≥20 ng/mL
- Men with a palpable abnormality on DRE
- A significant PSA rise in a man whose PSA has previously been low may warrant referral.

Treatment Indicated

- 10 year life expectancy.
- Most cases
  - PSA >10
  - Gleason 7 or higher disease.
  - Palpable disease > half of prostate.
- Selected cases
  - PSA < 10, Gleason 6 and early palpable or impalpable disease.

Key Points

- Early risk stratification is becoming increasingly important.
- Although an elevated PSA (>1ng/ml) in a patient in their forties increases risk, there is no harm in waiting till >4ng/ml.
- Not all prostate cancer should be treated.
- Unfortunately for or against prostate cancer debates are moot points as it is already here.

Do I personally recommend screening?

- Difficult question, will place a huge stress on the Public Hospital.
- The bottom line is that the validity of screening is dependant on the treating physician.
- Does screening lead to increased morbidity?
  - No doubt.
- Is low risk prostate cancer worth treating?
  - In most circumstances no (but 40% will get treated even if they choose no treatment initially.)
- Is prostate cancer screening here to stay?
  - Yes, and it won't go away.

Questions / Discussion