St Vincent's Prostate Cancer Update

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ST VINCENT'S HOSPITAL SYDNEY

Learning Objectives

1. Prostate Cancer Diagnosis

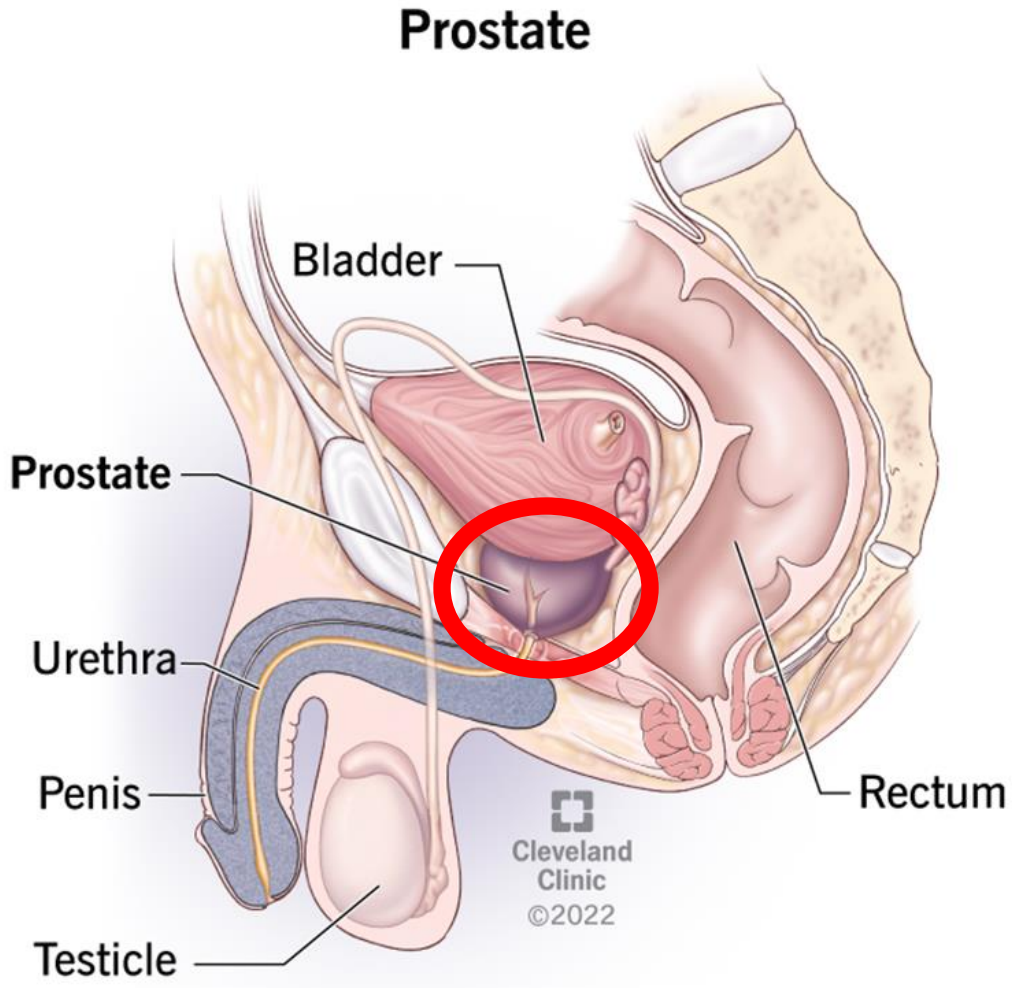
2. PSA Screening

Example:

- 53M
- Benign DRE
- No family Hx

Prostate – location, function

- Gland beneath bladder, in front of rectum
- Provides seminal fluid (30% ejaculate) to support sperm health and transport during ejaculation (contraction)
- Pathology:
  - Enlargement (BPH)
  - Prostatitis (Inflammation/Infection)
  - Cancer



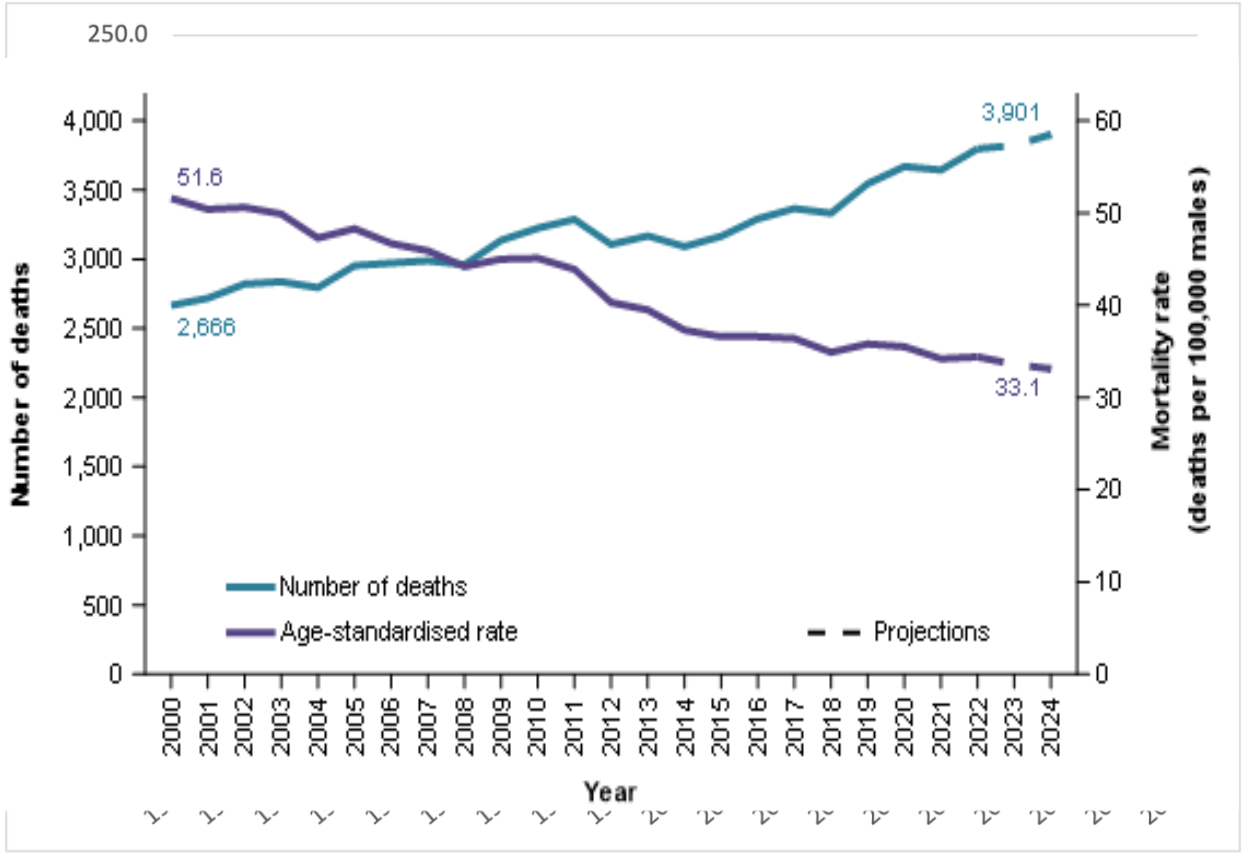
Cross section of the pelvis

Prostate Cancer Epidemiology

- Most common non-cutaneous malignancy since 1984
- Most common cancer in Australia in 2024
  - 19% of all cancers, 28% of all male cancers
  - Third leading cause of cancer death
  - Australia has equal highest incidence
- Of men alive today - 1 in 8 men will be diagnosed with PCa (12.9%) and 1 in 40 will die of PCa (2.5%)
  - However lowest expected years of life lost
- Of men diagnosed, prostate cancer accounts of 35% of deaths
  - Most common single cause, but still more likely to die of other causes

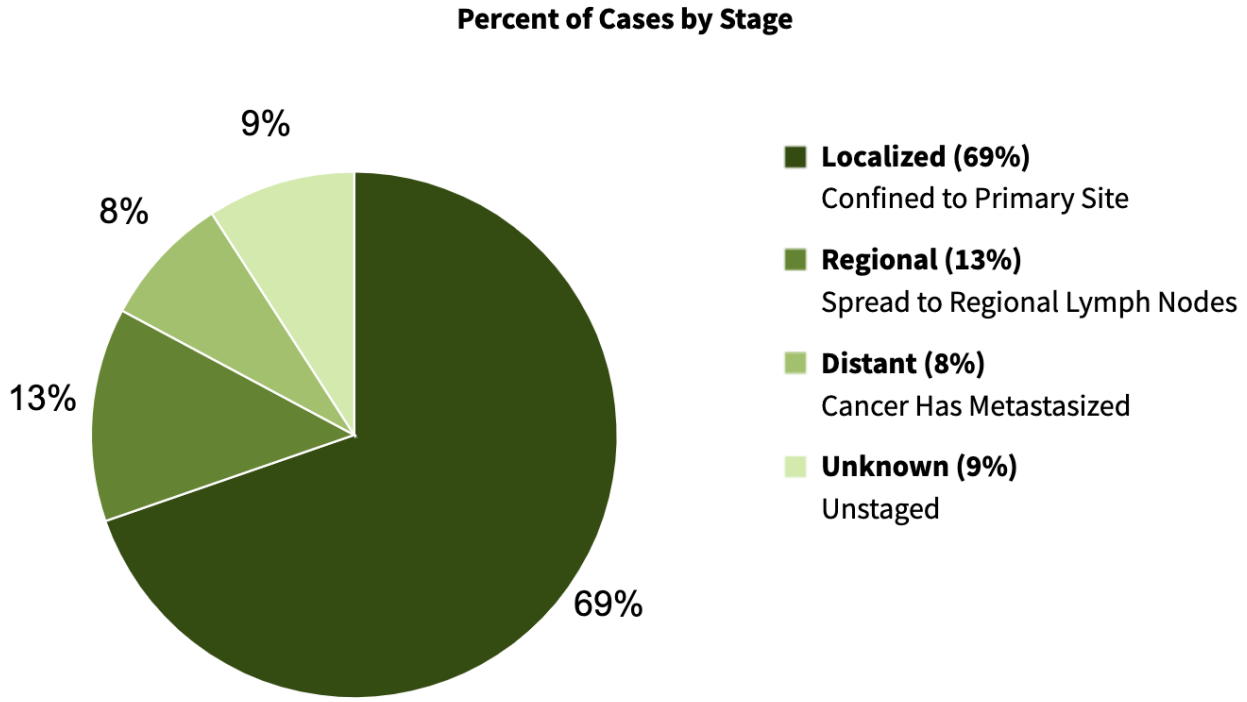
Epidemiology

- Large swings in incidence and mortality
  - Increasing incidence after introduction of TURP
  - Very large increase after introduction of PSA



- Since 1991 mortality has decreased by 4% per year
  - 62 to 33 deaths per 100000 men
  - Early decline reflects change in late 1980s – much more aggressive treatment, doubling of rate of curative intent therapy
  - Since then better screening and better treatments

Stage migration



- Substantial change since PSA
- Now up to 80% have localised disease at diagnosis
  - Nonpalpable disease – 60-75%
- Incidence of metastatic disease has decreased by 75%
- Lifetime risk of prostate cancer has doubled (~7%>12%)
  - Risk of death 3% > 2.5%

Survival

- Overall prostate cancer 5-year survival rates of 97.5%
- Neuroendocrine tumours 5-year survival in 2016–2020 was 9.9%

Risk Level	PSA	Gleason	Clinical T Stage	10 yr DFS
Low	<10	≤6	T1 to T2a	83%
Intermediate	10-20	7	T2b	46%
High	>20	≥8	T2c +	29%

Risk Factors

Prostate Cancer Risk Factors

- Age: Uncommon <50, >90% of cases in men >50 years
- Family History: (1 relative: 2x risk, 2 relatives: 4x risk)
- Genetic Predisposition: BRCA1/2, MMR, HOXB13, CHEK2, HNPCC(Lynch)

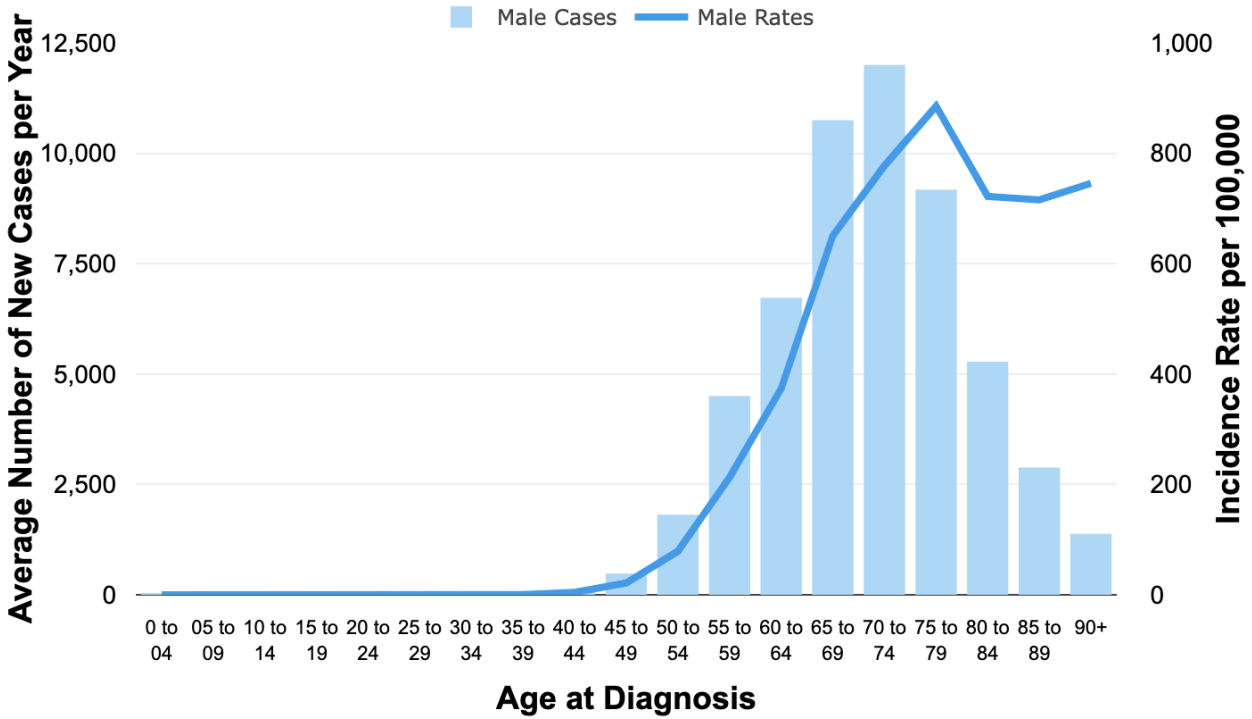
Associations

- Chronic Infection: STI/Prostatitis 1.5x risk
- Diet – Fatty diet predictive, antioxidants/Meformin protective
- Ejaculation protective
- No association with smoking

ST VINCENT'S HOSPITAL SYDNEY

Age

- <2% in <50yo men
  - Highly correlated with age of first screening however
- Prior to PSA – median age of diagnosis 70
  - >65% still diagnosed after 65



- Diagnosed earlier in patients with familial or germline risk
- Average age of death is 77

Race

- African descent
  - Highest incidence rate in world
  - Death rate 2.3 times higher
    - Though greater decline in mortality over time compared to Caucasians
  - Genetic component
  - Less aggressive therapy at all stages in America contributes
  - Sub-Saharan African men highest risk and mortality
- Other ethnic groups
  - Lower incidence and mortality than Caucasians
  - Asian men lower – but raises when move to west

	INCIDENCE[a]	MORTALITY[a]
White	114.8	18.7
African-American	198.4	42.8
Hispanic/Latino	104.9	16.5
Asian-American and Pacific Islander	63.5	8.8
American Indian and Alaska Native	85.1	19.4

Genetic influences

- Strong familial component
  - Inherited risk up to 60%
- 5-10% of cancers are primarily caused by inherited risk
- Many studies trying to identify responsible genes
  - Little applicable use beyond BRCA1, BRCA2, HOXB13
  - Widely polygenetic - multiple SNPs
  - Cumulative risk

FAMILY HISTORY	RELATIVE RISK	95% CONFIDENCE INTERVAL
Father affected at any age	2.35	2.02–2.72
Brother(s) affected at any age	3.14	2.37–4.15
One affected first-degree relative diagnosed at any age	2.48	2.25–2.74
Affected first-degree relatives diagnosed <65 years	2.87	2.21–3.74
Affected first-degree relatives diagnosed ≥65 years	1.92	1.49–2.47
Second-degree relatives diagnosed at any age	2.52	0.99–6.46
Two or more affected first-degree relatives diagnosed at any age	4.39	2.61–7.39

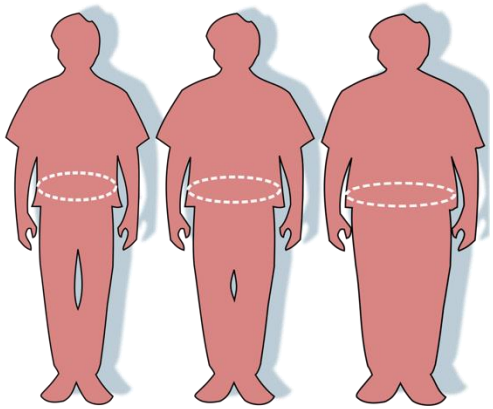
Genetic influences

- BRCA1/2
  - Unrelated proteins but similar function
  - Tumour suppressor genes – specifically ‘Caretaker genes’
  - Form genome surveillance complexes – involved in DS-DNA break repair, mismatch repair
  - BRCA1 – 3.5x higher risk
    - 10% lifetime prostate cancer risk (c.f. 65% breast cancer)
  - BRCA2 – 5-9x higher risk
    - 15% lifetime prostate cancer risk (c.f. 55% breast)
- HOXB13
  - Tumour suppressor gene of unknown function
  - 10-20x higher risk
  - Not known to be associated with any other cancers apart from prostate

Androgens

- Essential for maintenance of prostate and prostate cancer
- Minimal significance in carcinogenesis
  - Saturation effect
- Androgen receptor mutations OR 1.21
- High circulating androgen levels not correlated
- Circulating estrogen levels may act as carcinogens
  - May party explain age related increase

Factors found not to be associated



- STIs, any specific intraprostatic infections
- IGF axis
- Vasectomy
- Smoking
- Diet
  - Maybe? Extremely complex with contradictory studies
  - First generation immigrants Japan to west have large increase in risk
  - But no specific factor
- Obesity
  - No change in incidence but higher stage at presentation and more treatment failure
- Alcohol
- Testosterone replacement

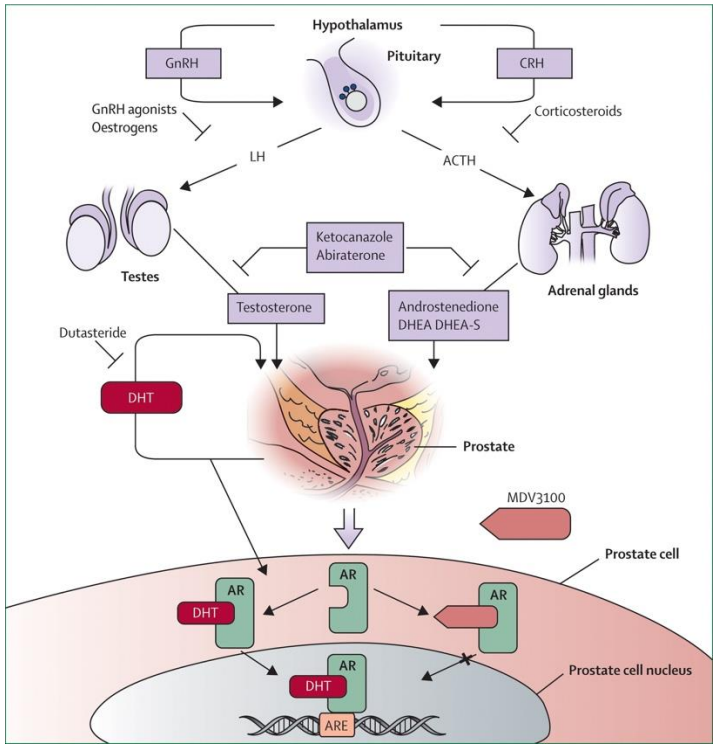
Chemoprevention

- Would be ideal candidate tumour as premalignant changes appear 20-30 years prior to clinical malignancy
- PCPT
  - 20,000 men, PSA <3, 7 years of finasteride vs placebo
  - 25% reduction in prevalence (18.4 vs 24.4) on biopsy of all patients at end of trial
  - Increase in more severe tumours on initial analysis
  - Subsequent analyses have shown it may have decreased high grade tumour (controlling for certain biases and basing on RRP specimens)
  - No OS differences

Chemoprevention

- Statins
  - Reduce inflammation
  - 20% reduction in advanced cancer in epidemiological studies
  - No RCTs
- SELECT trial
  - Selenium and Vitamin E
  - Based on two other large studies that on secondary analysis showed 30% and 46% reduction in PCa incidence
  - No effect on RCT

Pathogenesis

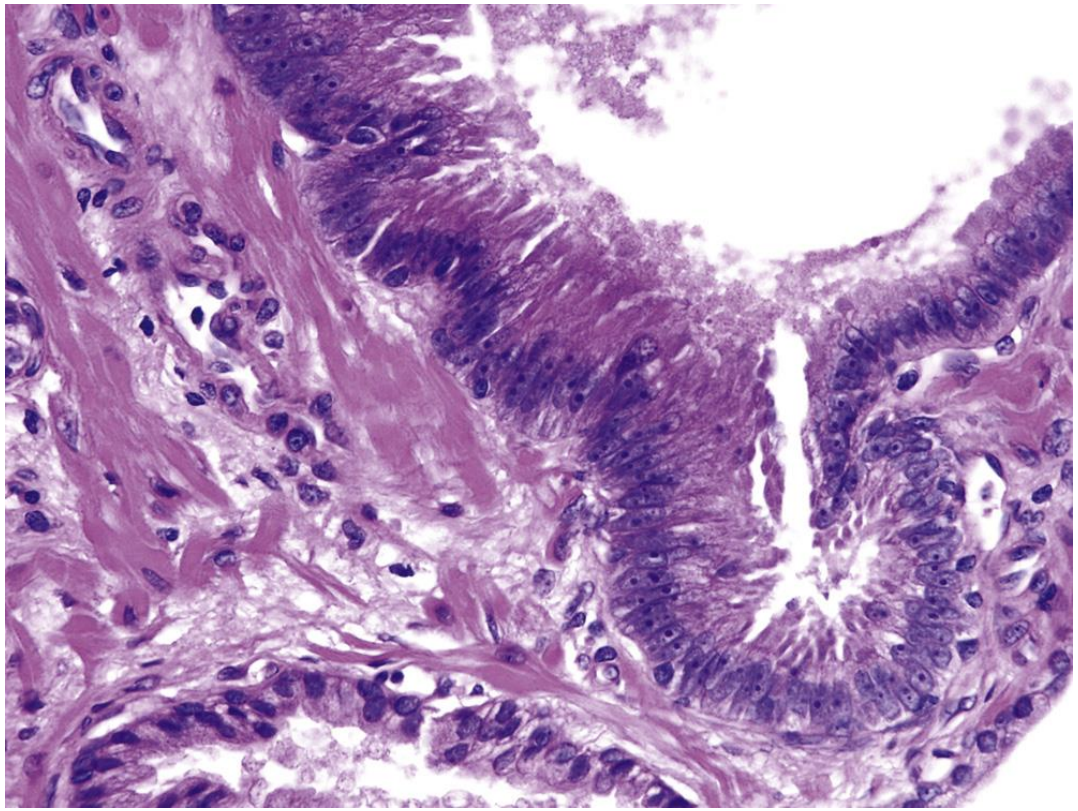


Pathogenesis - initiation

- TMPRRSS2
  - Androgen responsive serine protease
- ETS
  - Normally androgen indifferent cellular growth promoting signalling protein family – ERG is a member
- Fusion of TMPRRSS2 onto multiple growth promoters
  - Most common fusion is ERG
- 50-60% of all prostate cancer involves TMPRSS2:ERG fusion
  - Probably seminal early event
- Limited prognostic value but potential therapeutic target

Pathogenesis - PIN

- Prostatic intraepithelial neoplasia
- PIN – architecturally benign but lined with cytologically atypical cells
- Subclassified into LG and HG PIN
  - Diagnostic reports should not comment on LG PIN – pathologists can’t distinguish well enough, and no greater risk
- Does not raise PSA



Pathogenesis – HG PIN

- HG PIN precursor to at least some prostate cancers
- 20-30% risk of cancer on subsequent biopsy 1 year after diagnosis
  - However >80% Gleason 6
  - Not significantly higher rates than risk of repeat biopsy in benign finding
  - Guidelines do not recommend routine follow up biopsies
- 20% have TPMRSS2:ERG fusion
- If found on TURP – significance unclear
  - Evidence conflicting but in younger patients – workup for prostate cancer is probably warranted

Pathogenesis - intraductal

- Intraductal carcinoma also grows along normal ducts but significantly more abnormal
- Poor prognostic factor at RRP
- Almost always represents intraductal spread of high grade cancer rather than intraductal origin
- Treat as evidence of HG prostate cancer – not preinvasive malignant lesion
  - If biopsy shows only intraductal – do not perform repeat biopsy, proceed to active treatment

Grading

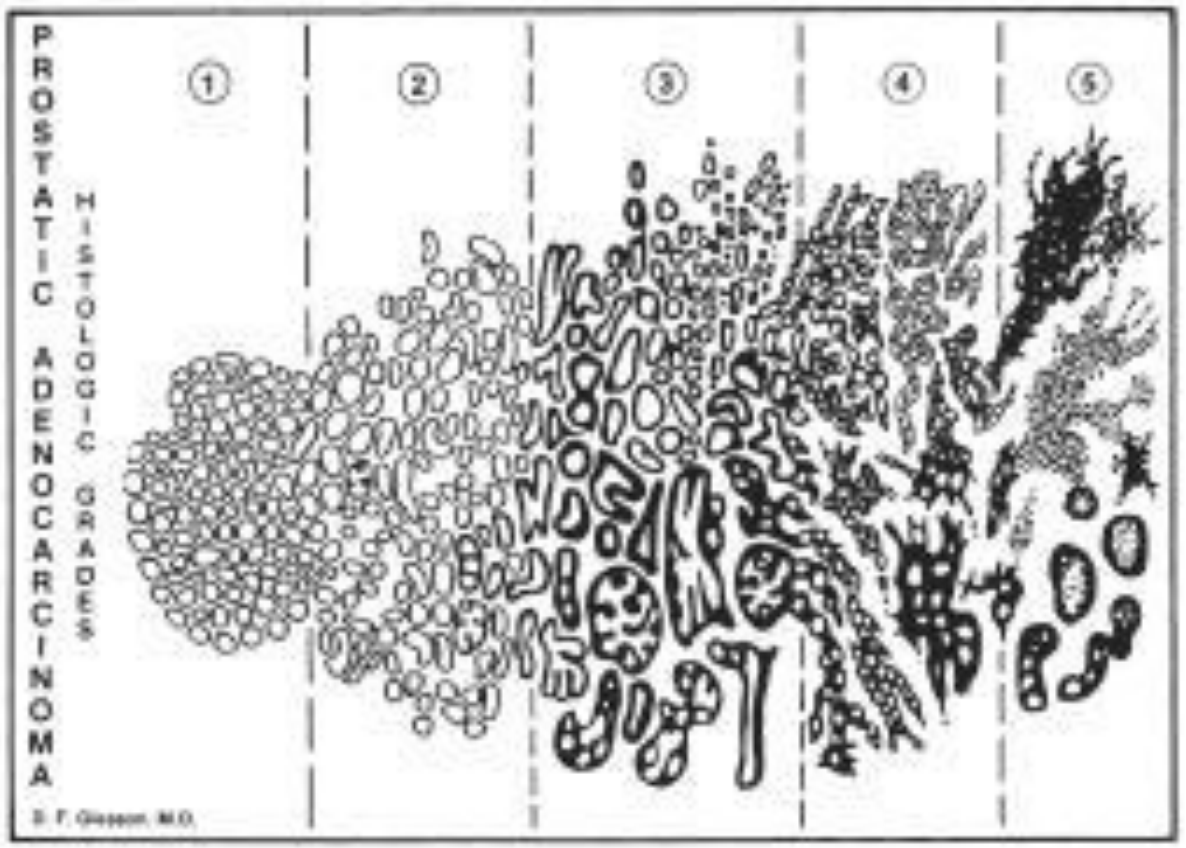
- Gleason grading (Pathologist in 1960s)
- Low magnification only – no cytological features play a role
- Architectural patterns
  - Graded 1-5
  - Originally most common and second most common – now most common and highest grade
- Gleason score 1-4 no longer applied
  - Most graded higher when reviewed by experts
  - Difficult to apply to core biopsies
  - Poor reproducibility even between experts

Adenocarcinoma

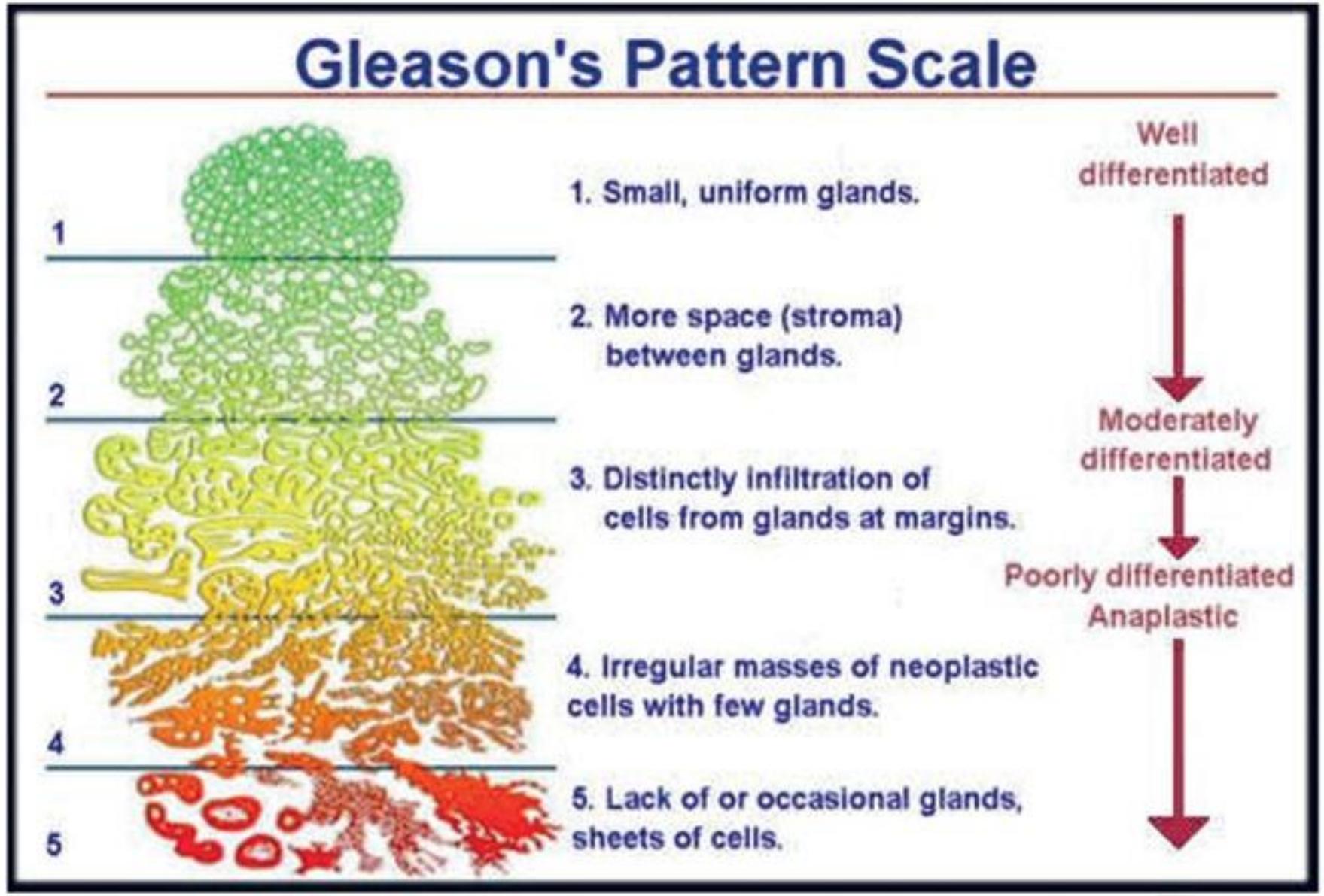
Cytological atypia and architectural changes

- 1: small uniform glands
- 2: more stroma between small/medium sized glands
- 3: Infiltrative, heterogenous size
- 4: Large irregular cribriform glands
- 5: No glandular differentiation, sheets/cords,single cells

- Normal glands have a basal cell layer, absent in adenocarcinoma



Gleason purely architectural: degree relates to glandular differentiation, independently prognostic – Gleason 1974



Source: John Murtagh, Jill Rosenblatt, Justin Coleman, Clare Murtagh: *John Murtagh's General Practice, 7e*
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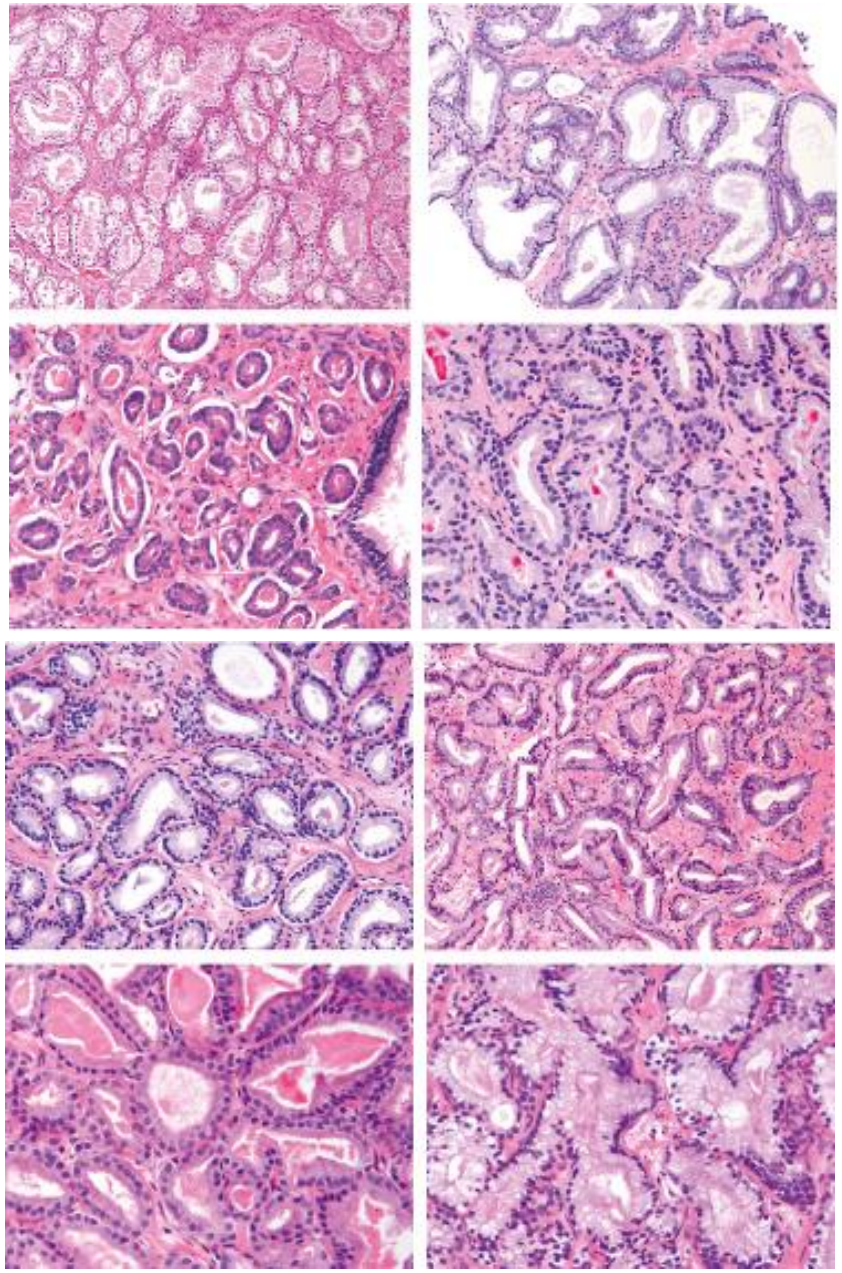
Grading

- Other changes
  - Many former Gleason 6 changes have been re-classified to 7
  - In order to leave Gleason 6 homogenous and favourable patterns only
  - This has prognostic consequences
    - Previously Gleason 6 tumours progressed and metastasised
    - In modern classification <0.02% have EPE and none metastasise
    - Gleason 3+4 tumours have also become more favourable overall as a result



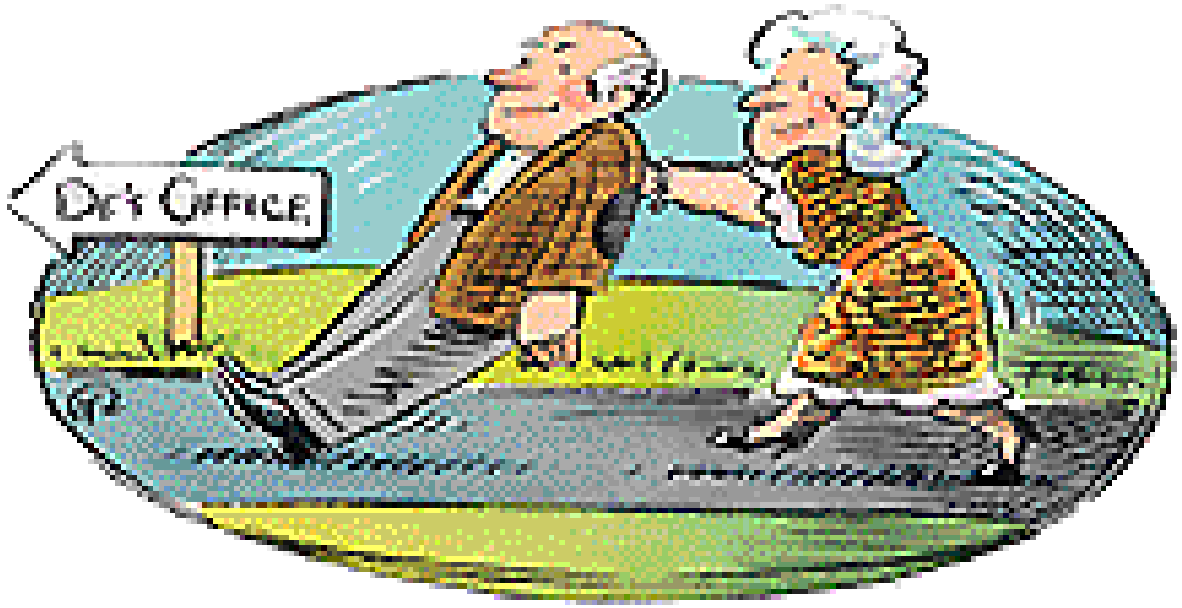
Grading

- Grade group system
  - 1: Gleason scores less than or equal to 6
  - 2: 3 + 4 = 7
  - 3: 4 + 3 = 7
  - 4: 8
  - 5: 9 to 10
- Risk of death increases rapidly with grade group
  - 1: 97% cure after RARP
  - 2: 88% cure after RARP, 83% no progression 5 years after biopsy
  - 3: 69.7%
  - 4: 63.7%
  - 5: 34.5% - grade group 5 is twice the risk of 4

Grade Group	Gleason Score	Gleason Pattern
1	6	3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9-10	4+5, 5+4, 5+5

Diagnosis

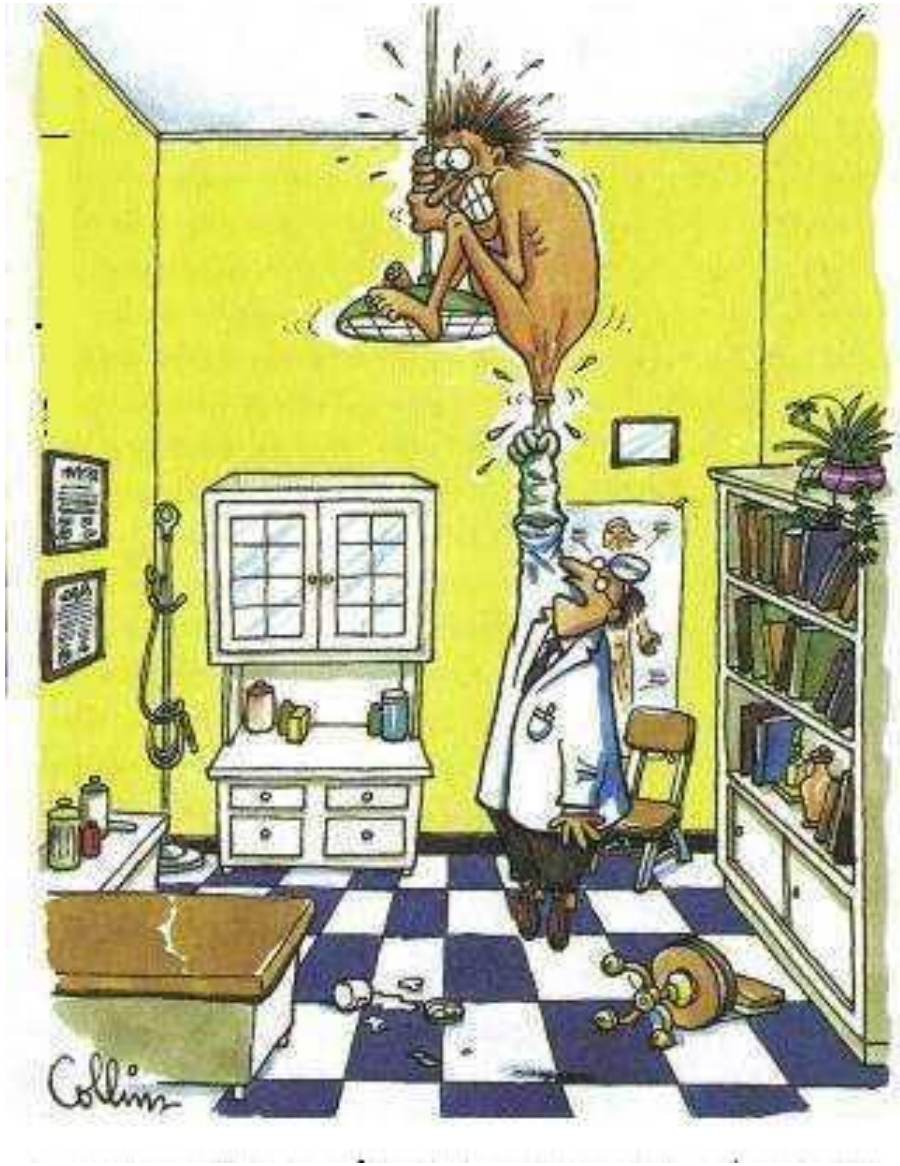
Diagnosis?


Dr's Office

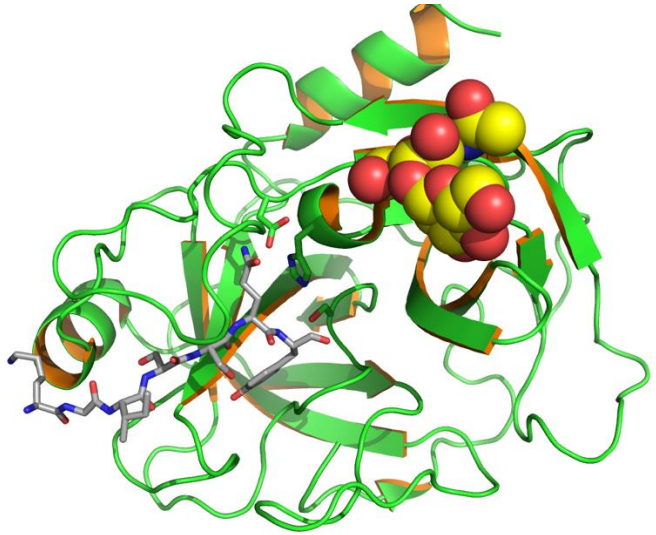

A HANDY GUIDE
INDEX
RING
1 Measure from crease at bottom of finger to tip
2 Men with longer index fingers than ring fingers significantly less likely to get prostate cancer
AT LESS RISK
INDEX
RING
AT MORE RISK

Diagnostic Pathway

- DRE (does not impact PSA value):
  - Low sensitivity (50%), Specificity 80%
  - Used with PSA to improve PPV
  - Schroder: ERSPC 1998 (n = 473)
    - PPV 4-11% with PSA <3
    - PPV 33-80% with PSA <10
    - 17% tumours missed by PSA alone
- PSA and variants
- Other biomarkers (PCA3, PHI Test…)
- Imaging: U/S, MRI
- Biopsy



Prostate Specific Antigen

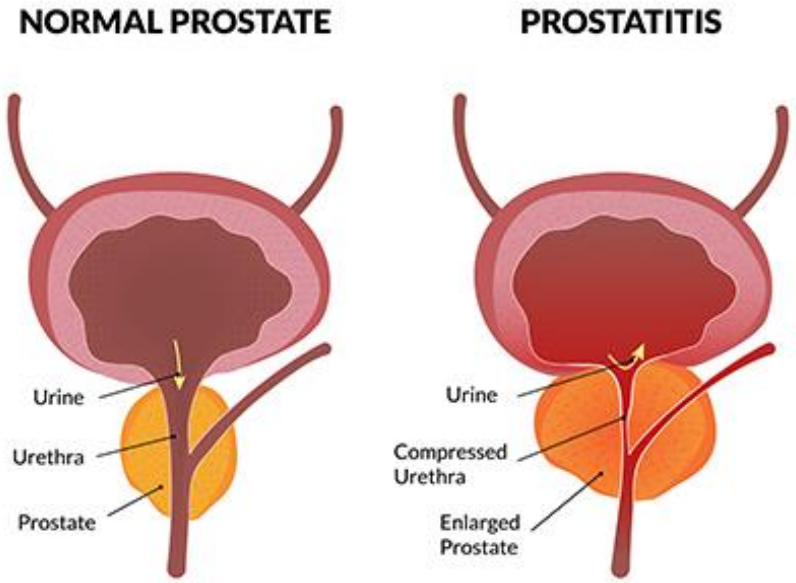


- Tumour Marker

Prostate specific, NOT cancer specific

- Liquefies semen
- Normal cells and cancer cells release the same amount of PSA on a per cell basis
- Disruption of normal architecture is what causes PSA rise
  - Loss of basement membrane
  - This is why after injury or infection PSA remains elevated for much longer than half life of PSA
  - Half life 2-3 days

Diagnosis: PSA Influences



- Elevation
  - Prostate Ca
  - BPH
  - Infection: prostatitis, bacterial cystitis
  - Manipulation: cystoscopy, biopsy
  - Age
- Reduction
  - 5α-reductase inhibitor (50% over 9-12 months)
  - Androgen deprivation
  - Prostatic surgery
  - Radiation therapy, initial elevation then depression

PSA predictive values

- Gerstenbluth 2002
  - ≤4ng/ml 27%
  - 4.1-10 ng/ml 41%
  - >10 ng/ml 69%
  - >20 ng/ml 87%

  - 20-29 ng/ml 74%
  - 30-39 ng/ml 90%
  - 50-99 ng/ml 100%

Table 2: PSA value and risk of CaP

PSA ng/mL	PPV for cancer
0-1	2.8-5%
1-2.5	10.5-14%
2.5-4	22-30%
4-10	41%
> 10	69%

PPV = positive predictive value; PSA = prostate-specific antigen.

Thompson PCPT 2003

PSA Specifics

- Age/Race range:

- Free PSA (4-10)
  (Catalona 1998)

- Velocity: >0.35-0.75?
- Density: >0.15? (Basinet 1994)

Age	"Normal" PSA	
	Caucasian	Asian
40-49	0-2.5	0-2.0
50-59	0-3.5	0-3.0
60-69	0-4.5	0-4.0
70-79	0-6.5	0-5.0

% Free PSA	Pr Ca Risk
<10%	56%
10-15%	28%
15-20%	20%
20-25%	16%
>25%	8%

Walz 2008

Diagnosis: Others

PHI	<25	25-34.9	35-54.9	>55
RR PrCa	Ref	1.6	3.0	4.7
% Pr Ca Prob	11	18	33	52

- Prostate Health Index (PHI)
  - PHI = (proPSA/freePSA) x $\sqrt{}$PSA (PSA 2-10)
- 4kscore (composite)
  - Total/free/intact/hK2
- Prostarix (Sarcosine)
  - DRE expressed metabolite on mass spectrometry
- PCA3
  - Cells analysed for overexpression of PCA3 gene
- Germline SNP Panels (only 10-15% heritable)
  - BRCA1 (RR 3.8x), BRCA2 (RR 8.6x)

PCA3 Score	Risk of Pr Ca
<5	12%
5-19	17%
20-34	23%
35-49	32%
50-100	45%
>100	50%

mpMRI – Prostate

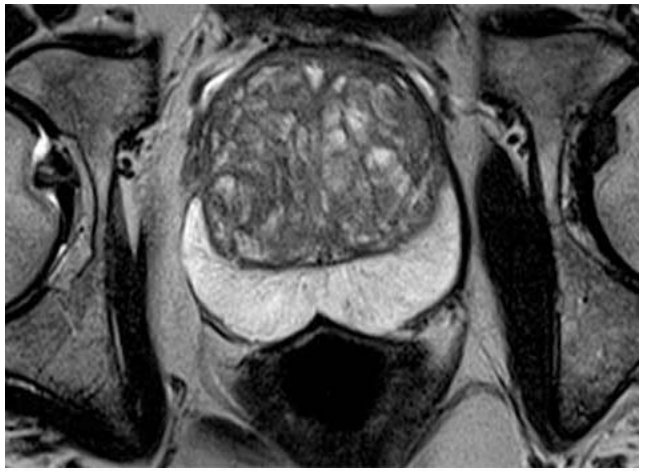
PI-RADS V2.1 SCORES

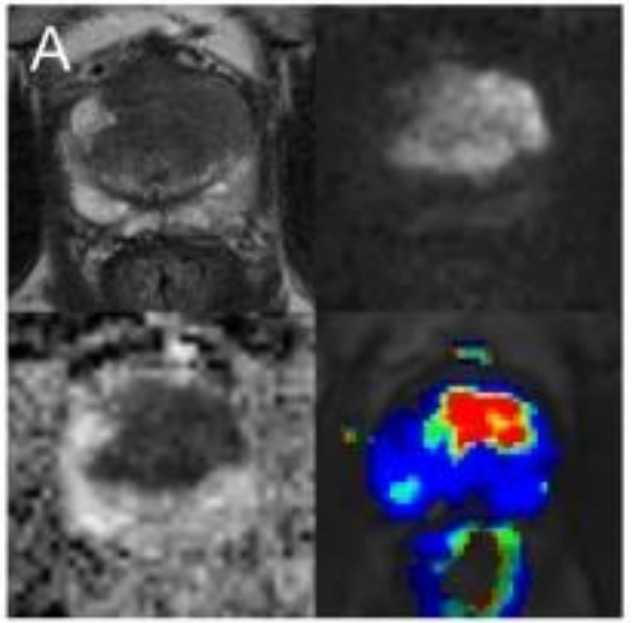
The PI-RADS scores categories based on the lesions score depending on their location

Peripheral zone (PZ) - DWI/ADC	PI-RADS score	Transitional Zone (TZ) - T2 WI
DWI/ADC - Normal	1	Normal
DWI/ADC - Indistinct hypointense	2	Circumscribed hypointense or heterogeneous encapsulated nodules (BPH)
ADC - focal mild / moderate hypointense DWI - iso /mild hyperintense	3	Heterogeneous signal intensity with obscured margins or lesions that don't fall into other categories
ADC - focal markedly hypointense DWI - markedly hyperintense	4	Lenticular or noncircumscribed, homogeneous, moderately hypointense and < 1.5cm
Similar to previous but ≥ 1.5cm or definite extraprostatic extension	5	Similar to previous but ≥ 1.5cm or definite extraprostatic extension

DCE -
DCE +
DWI ≤ 4
DWI = 5

Quantib





mpMRI – Prostate

PIRAD (prostate imaging reporting and data system)

- 1: most probably benign
- 2: probably benign
- 3: Indeterminant
- 4: Probably malignant
- 5: Most probably malignant

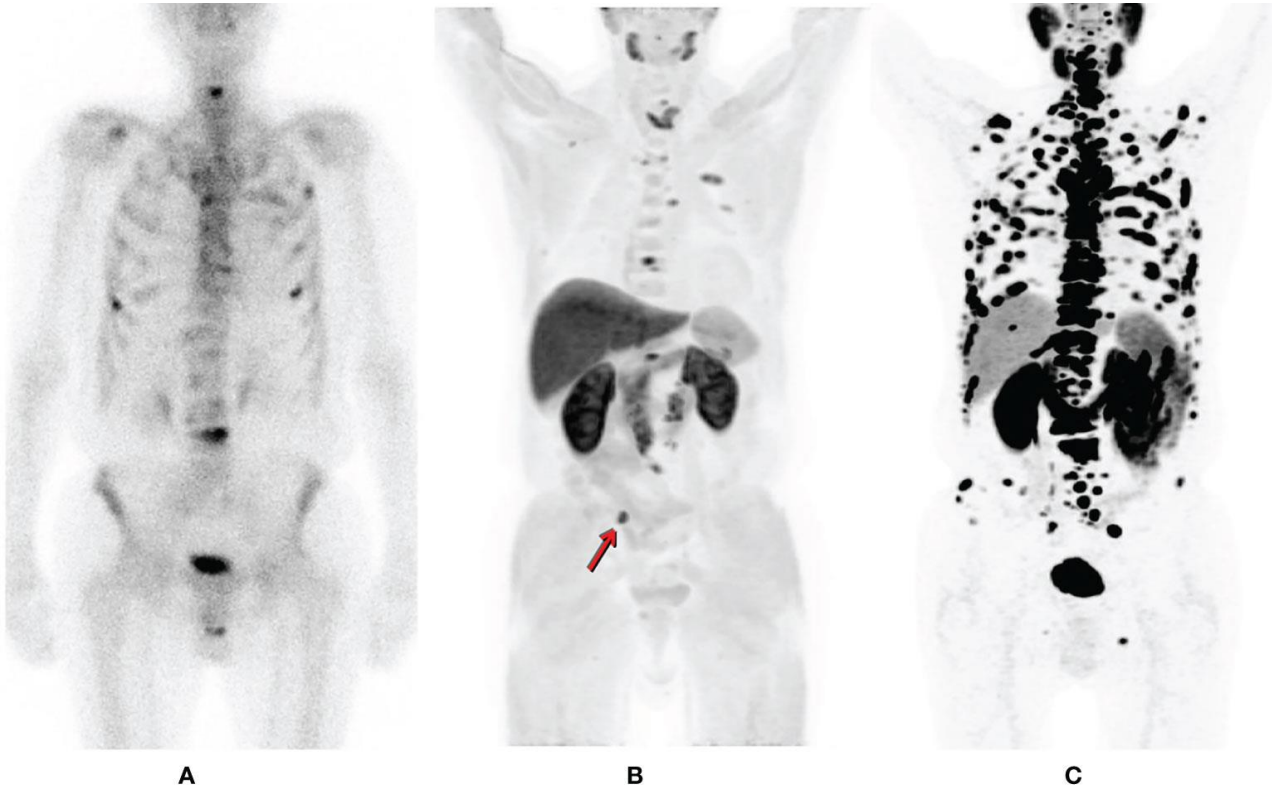
PIRAD	GI >6 (%)	GI >7 (%)
1	0	0
2	24	15
3	40	33
4	79	71
5	91	91

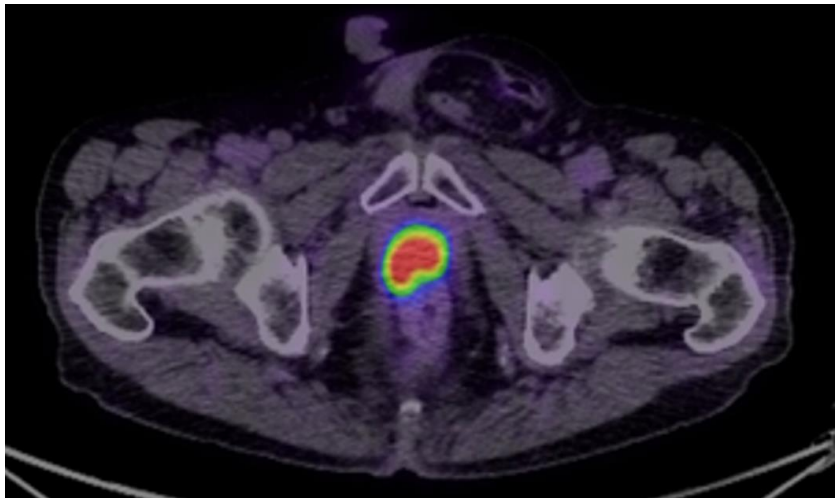
Greer et al. Validation of the Dominant Sequence Paradigm and Role of Dynamic Contrast-enhanced Imaging in PI-RADS Version 2
July 2017 Radiology 285(3):161316

PSMA PET

- PRIMARY Study
  - PSMA + MRI improved NPV and sensitivity for csPCa in an MRI triaged population

- PRIMARY-2 Study
  - Screen men with PIRAD 2/3 to see if PET can safely reduce biopsies

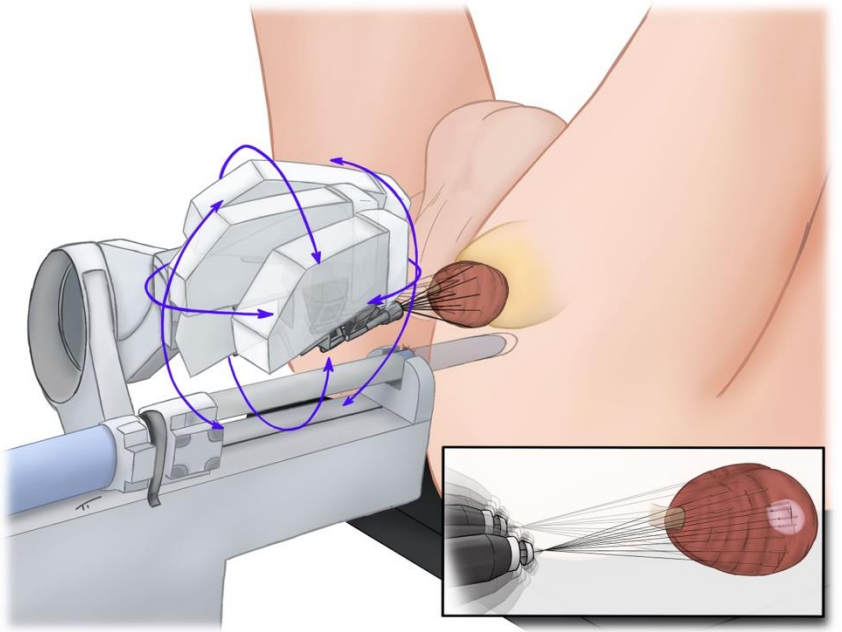


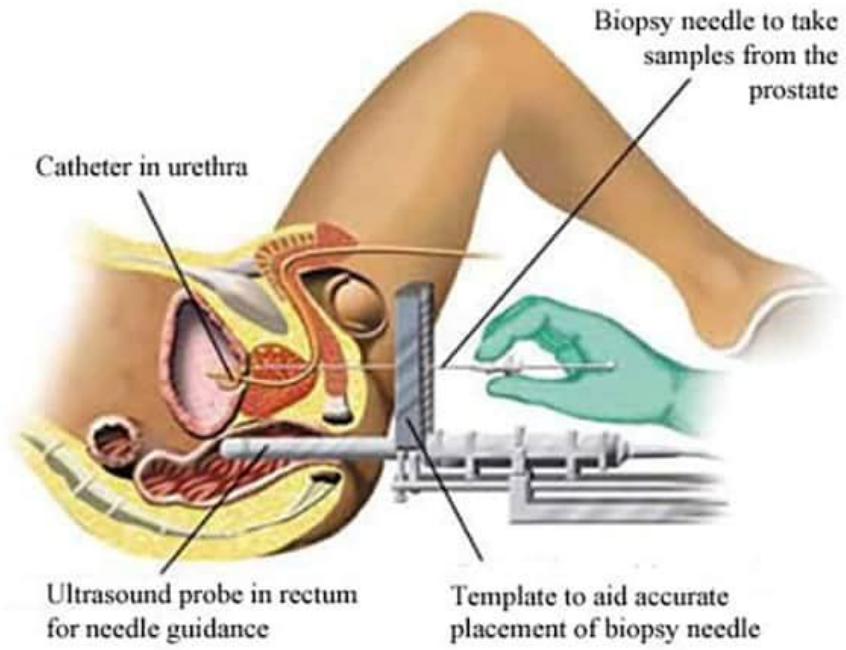


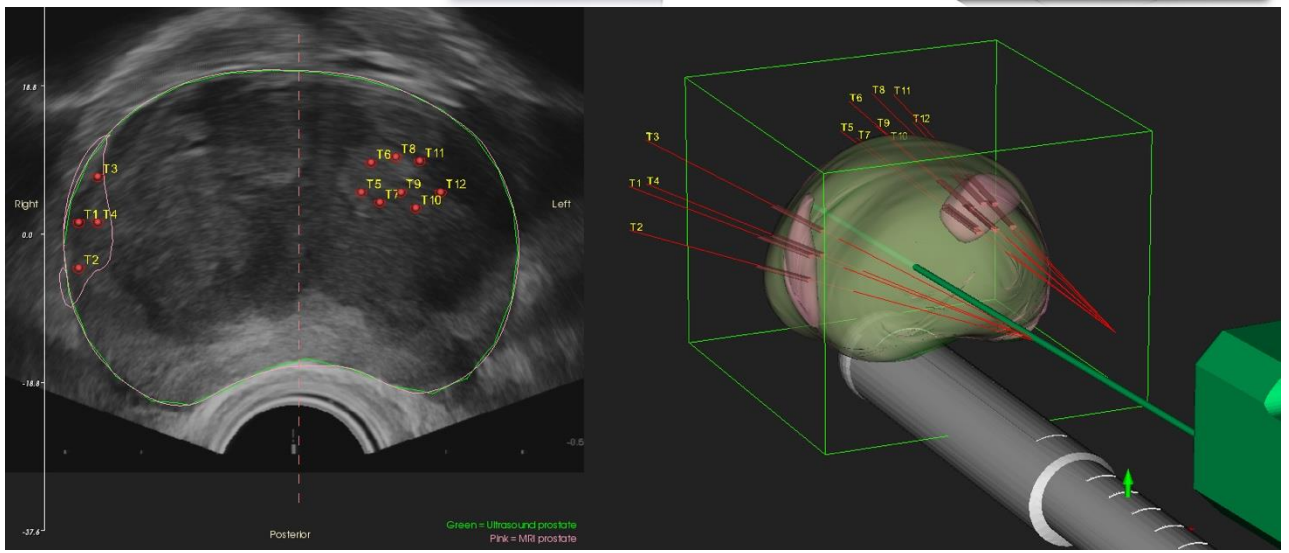
Emmet et al, Eur Urol 2021 Dec;80(6):682-689. The Additive Diagnostic Value of Prostate-specific Membrane Antigen Positron Emission Tomography Computed Tomography to Multiparametric Magnetic Resonance Imaging Triage in the Diagnosis of Prostate Cancer (PRIMARY): A Prospective Multicentre Study

Diagnostics – Transperineal Biopsv

- Grid Biopsy
- Precision Point
- Fusion







Decision Point

1) Treatment or not

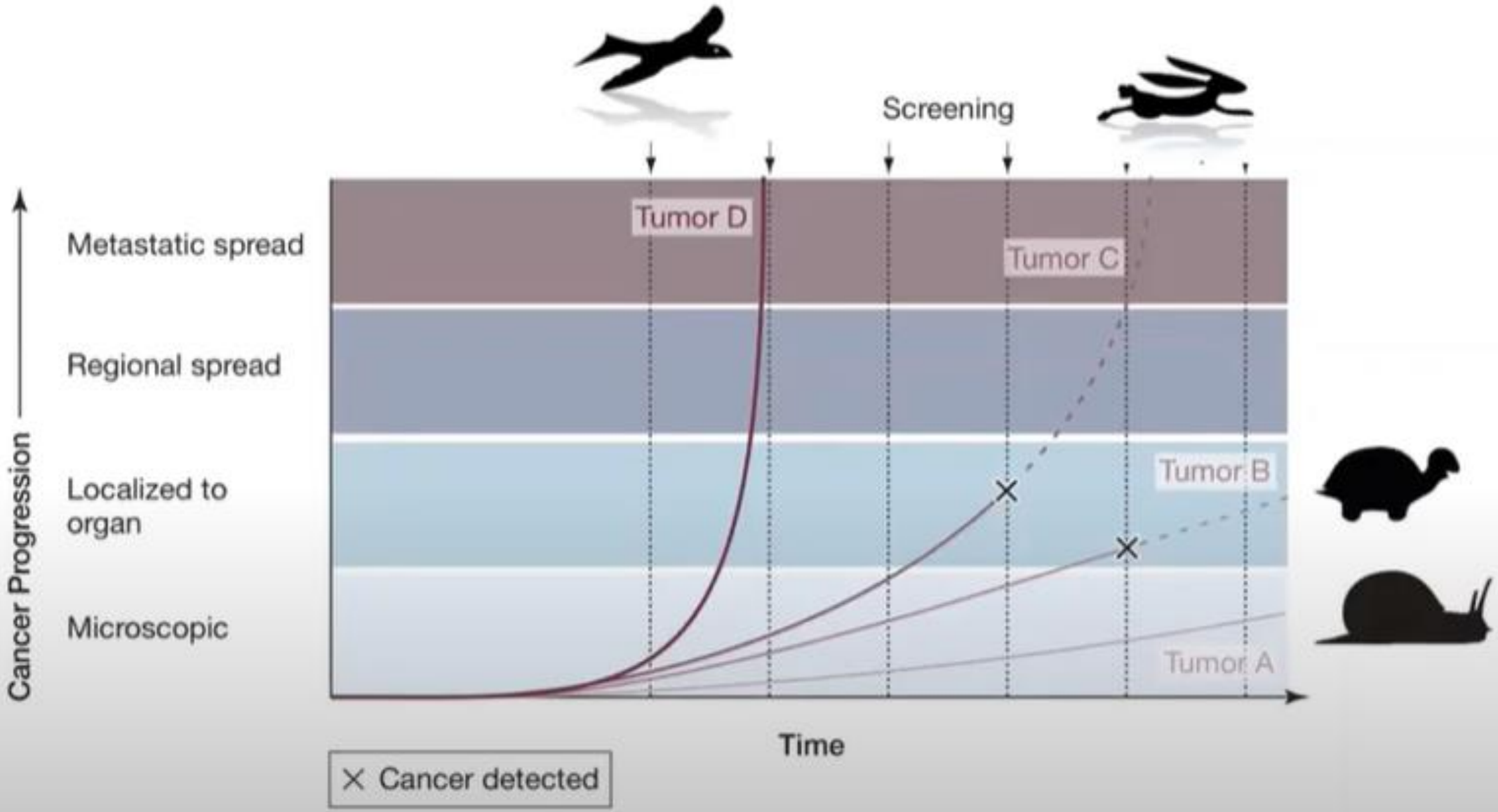
- 1/3 of localized disease appropriate for surveillance

	Low	Mid	High
PSA	<10	10-20	>30
Gleason	6	7	8-10
Stage	1	2	3/4

2) What?

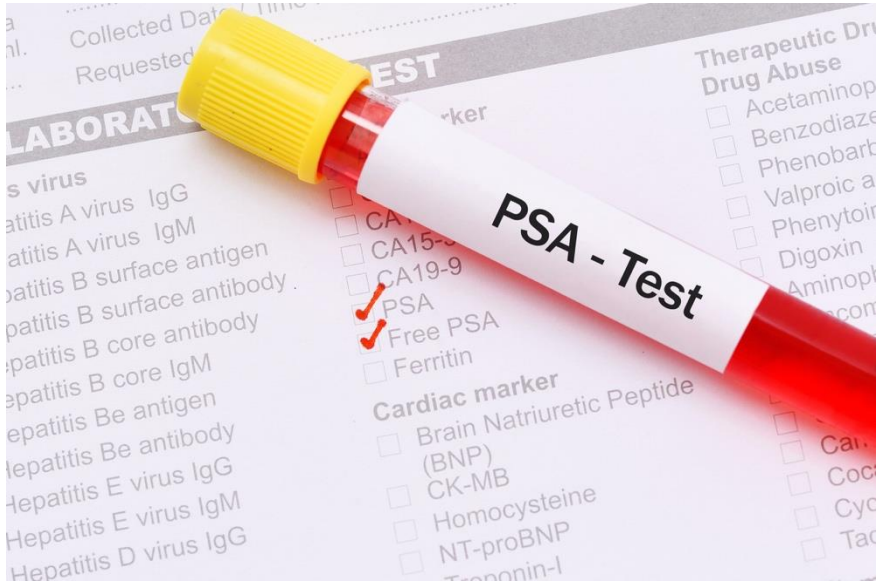
- Active Surveillance
- Radical Prostatectomy
- Radiotherapy
  - Brachytherapy (low/high dose)
  - External beam
  - MRI-LINAC
- Focal Therapy

PSA Screening


Screening
Tumor D
Tumor C
Tumor B
Tumor A
Metastatic spread
Regional spread
Localized to organ
Microscopic
Cancer Progression
Time
× Cancer detected

International Screening Recommendations

- Early ERSPC data
- RACGP recommends against PSA screening
- US Preventative Services Task Force
  - 2012 recommended against PSA screening
  - 2017 recommended individual decision making



- ACS Update: 3% increase in prostate cancer diagnoses 2014-2019, particularly more advanced cancers

Siegel et al, **Cancer statistics, 2023;** Volume 73, Issue1, January/February 2023, 17-48

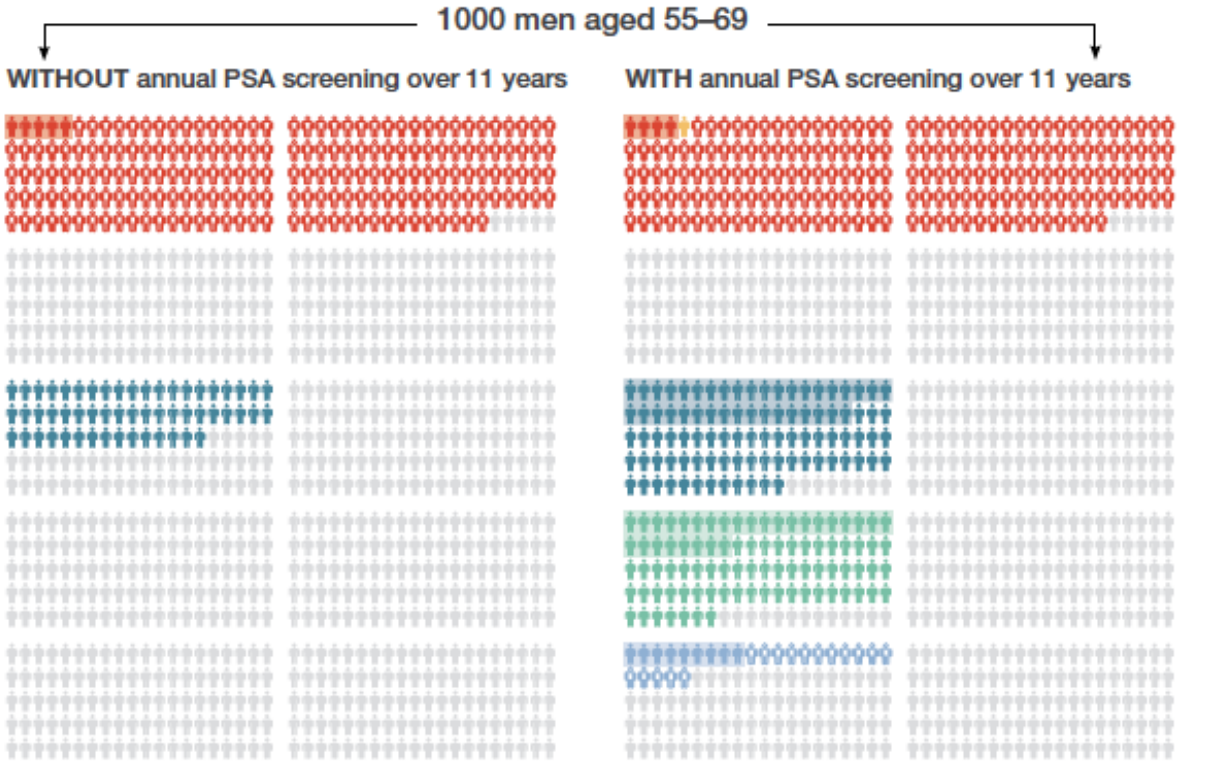
RACGP

- Recommend against PSA Screening

- 11 year data only…
- Projected outcomes only with impact/morbidity…

Figure 1. Risks and benefits of PSA screening

Adapted with permission from Harding Center for Risk Literacy.



5 men **die** from **prostate cancer**

190 men **die** from **other causes**

55 men alive with symptomatic prostate cancer

782 men alive with no prostate cancer

4 men **die** from **prostate cancer**, **1** man is **possibly saved through testing**

190 men **die** from **other causes**

55 men alive with symptomatic prostate cancer

715 men alive with no prostate cancer

87 men learned after biopsy their PSA result was a false positive

28 men have side effects that require healthcare or hospitalisation after a biopsy

25 men will choose to have treatment due to uncertainty about which cancers need to be treated. Many of these men would do well without treatment (ie. they are over-treated)

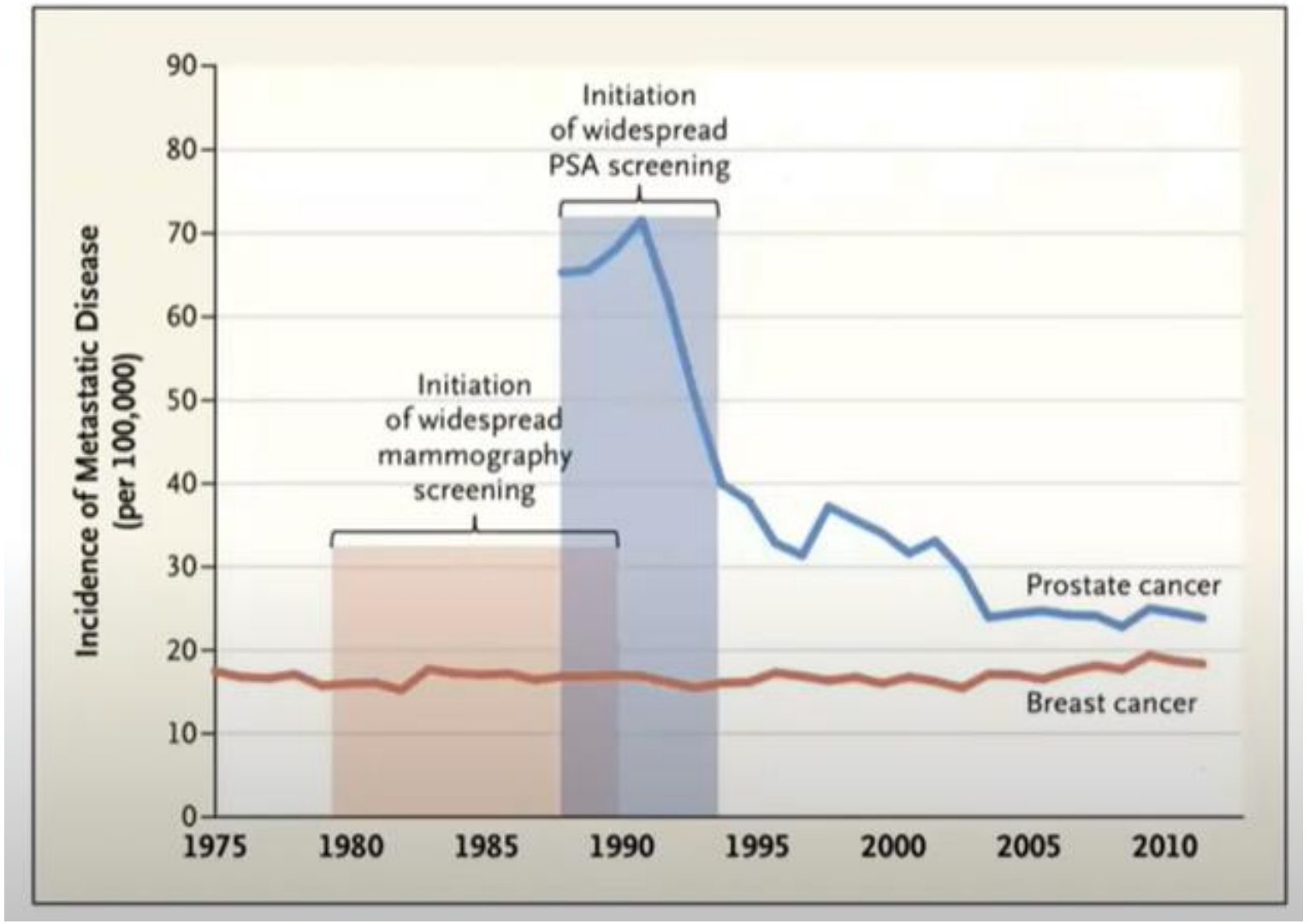
37 men with an elevated PSA were found to have **slow-growing cancers** (ie harmless and therefore over-diagnosed)

7–10 men who have treatment will experience impotence and/or urinary incontinence or bowel problems. 0.5 men could have a heart attack due to treatment.

References

1. NHMRC PSA testing for Prostate Cancer in Asymptomatic men available at **www.nhmrc.gov.au/_files_nhmrc/publications/attachments/men4d_psa_testing_asymptomatic_men_140304.pdf**
2. Schroder FH, Hugosson J, Roobol MJ, et al. NEJM 2012;366:981–90.
3. Harding Center for Risk Literacy. Available at **www.harding-center.mpg.de/en/health-information/facts-boxes/psa**
4. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. The Lancet 2014; 384(9959):2027–35.
5. Guidelines for preventive activities in general practice, 8th edn, Royal Australian College of General Practitioners, 2012.

- PSA is the best screening biomarker in the history of oncology



Then why was prostate cancer screening stopped in the USA?

- 2012 US-PSTF gave PSA screening a Grade D recommendation – do not screen anybody

- Combination of many factors
  - Natural history of prostate cancer
  - Poor implementation of screening
  - Over (and under) treatment throughout the 1990s and 2000s
  - One slightly poorly designed and very poorly interpreted trial

The trials:

- ERSPC 👍
  - 20-30% relative risk reduction
- Goteburg 👍
  - 42% relative risk reduction
- PLCO 👎
  - Doesn’t answer the question of utility of prostate cancer screening

ERSPC 👍

- In males ages 50-74, does offering PSA screening every 4 years reduce the risk of death from prostate cancer?
- Randomised, multi-centre
- Enrolled 182,000 men ages 50-74
- Started enrolling in 1991
- PSA cut off of 3.0ng/ml for biopsy

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

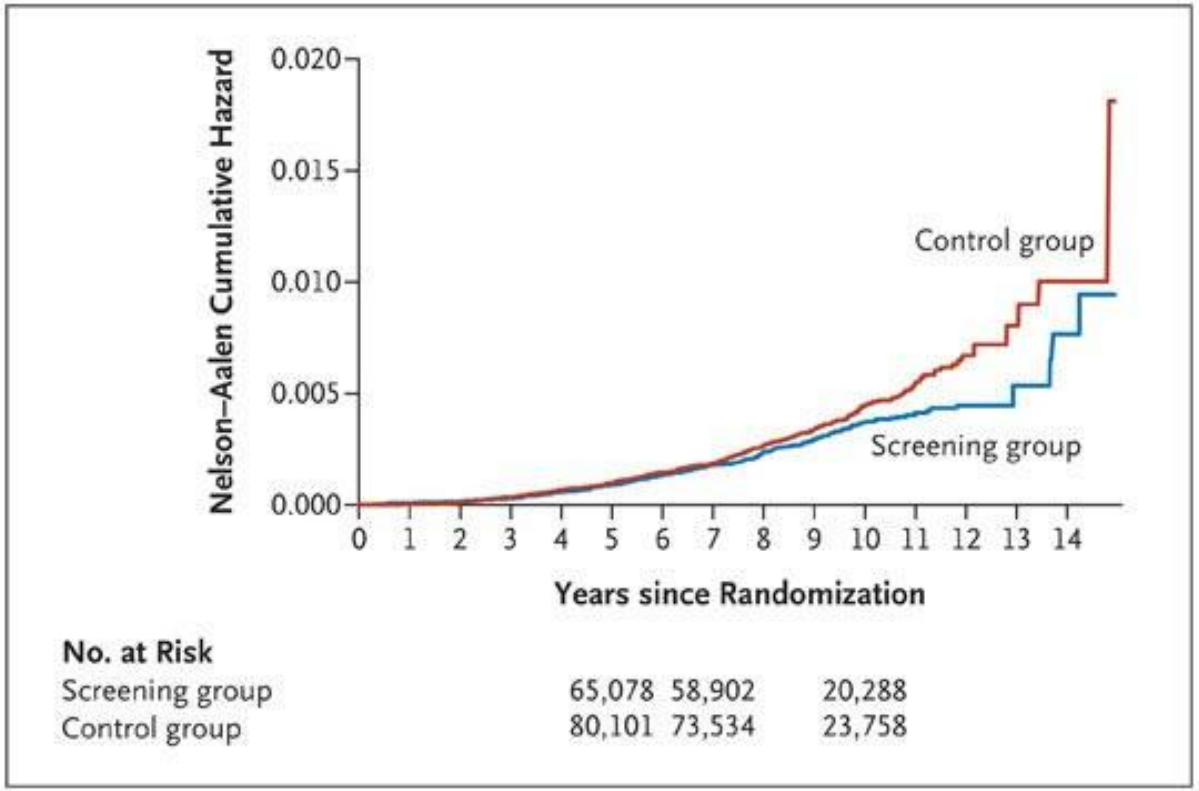
Screening and Prostate-Cancer Mortality in a Randomized European Study

Authors: Fritz H. Schröder, M.D., Jonas Hugosson, M.D., Monique J. Roobol, Ph.D., Teuvo L.J. Tammela, M.D., Stefano Ciatto, M.D., Vera Nelen, M.D., Maciej Kwiatkowski, M.D., +16, for the ERSPC Investigators* Author Info & Affiliations

Published March 26, 2009 | N Engl J Med 2009;360:1320-1328 | DOI: 10.1056/NEJMoa0810084

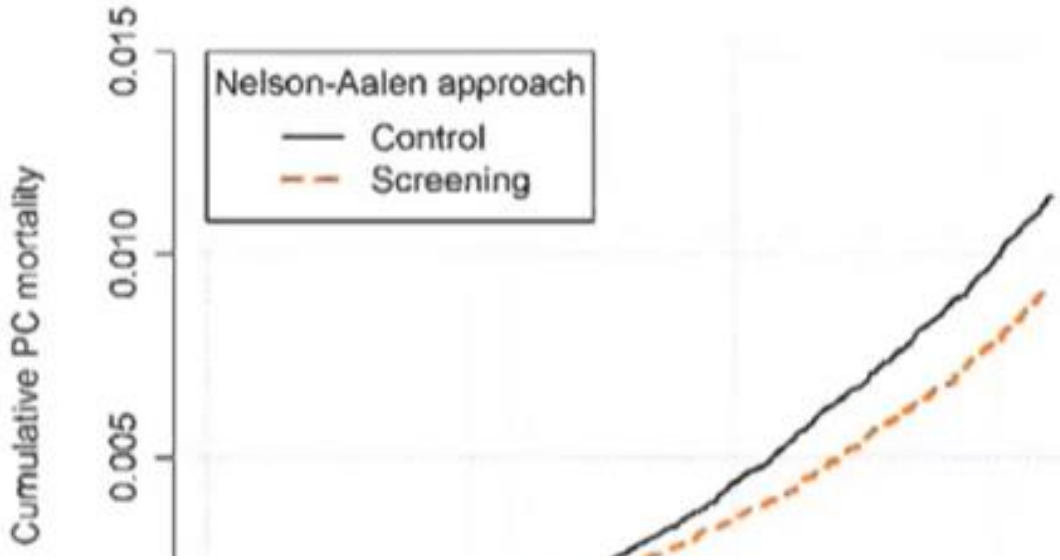
Initially reported data 👎

- Reported 2009 (same day as PLCO)
- Average follow up time of 8.8 years
- Hazard ratio of 0.8
- Number needed to invite – 1947
- Number needed to treat - 48



Updated data

- Number needed to invite – 570 (from 1947)
- Number needed to treat – 18 (from 48)



	Short-Term	Long-Term
Lives saved	0.7	6
Overdiagnoses	34	42
Overdiagnoses/Lives saved =NND	48	7

Probably an underestimate of benefit

- 20% contamination
- Screening started late
  - Average age of first screening in 60s
- Treatment was not of standard of today
  - Low volume surgery
  - Low radiation doses
- Benefit continues to increase

PLCO 👎

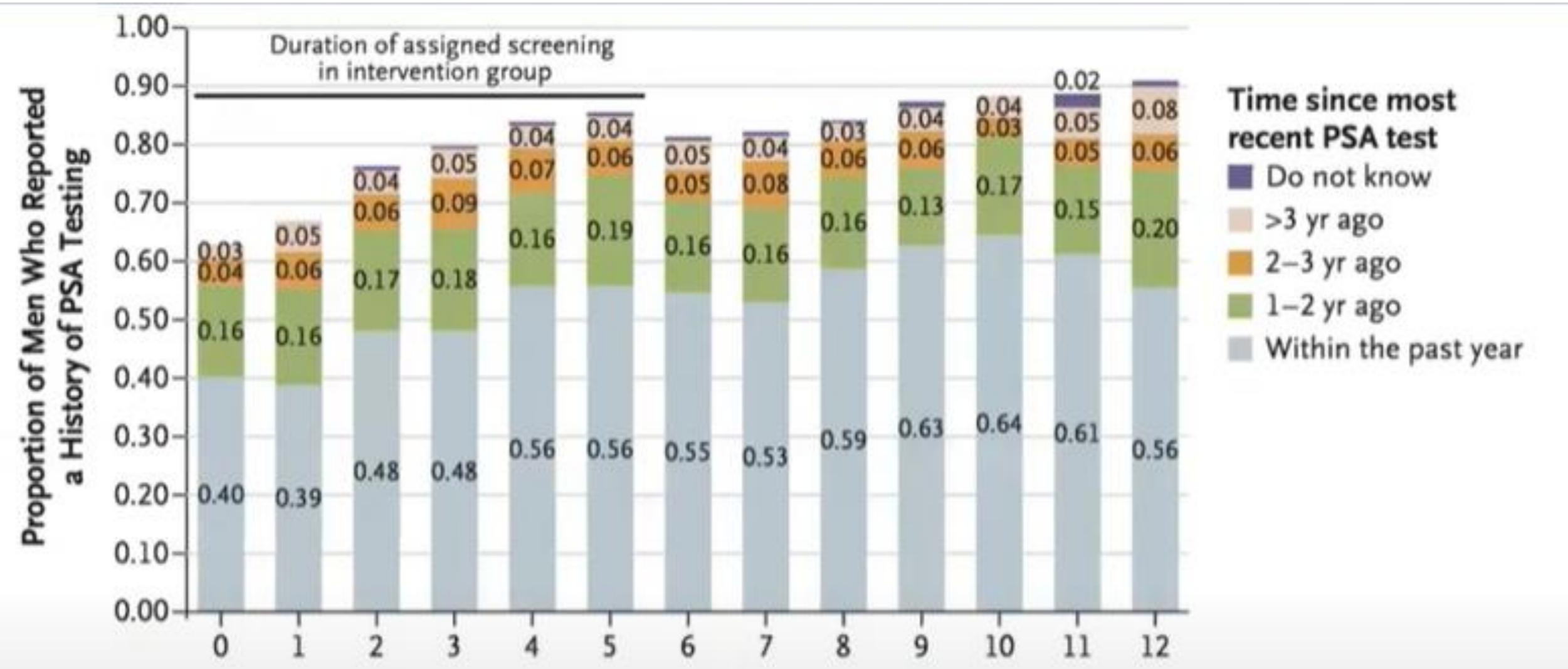
- Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial
- 76,693 men, age 55-74
- Prostate arm was assigned to annual PSA screening for 6 years vs usual care
- Found some difference in incidence, no difference in prostate cancer deaths

RESULTS

In the screening group, rates of compliance were 85% for PSA testing and 86% for digital rectal examination. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41 to 46% for digital rectal examination. After 7 years of follow-up, the incidence of prostate cancer per 10,000 person-years was 116 (2820 cancers) in the screening group and 95 (2322 cancers) in the control group (rate ratio, 1.22; 95% confidence interval [CI], 1.16 to 1.29). The incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (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.

Several problems

- Usual care in the 1990s in USA was a lot of PSA testing
- As a result pre-enrolment PSA testing was allowed
  - 52% had a PSA prior to enrolment
- >90% of patients **in the control arm** had at least one PSA during the study
- Only 30-40% of men with high PSAs went on to have a biopsy


Proportion of Men Who Reported a History of PSA Testing
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Duration of assigned screening in intervention group
0 1 2 3 4 5 6 7 8 9 10 11 12
0.03 0.04 0.16 0.40
0.05 0.06 0.16 0.39
0.04 0.06 0.17 0.48
0.05 0.09 0.18 0.48
0.04 0.07 0.16 0.56
0.04 0.06 0.19 0.56
0.05 0.05 0.16 0.55
0.04 0.08 0.16 0.53
0.03 0.06 0.16 0.59
0.04 0.06 0.13 0.63
0.04 0.03 0.17 0.64
0.02 0.05 0.05 0.15 0.61
0.08 0.06 0.20 0.56
Time since most recent PSA test
Do not know
>3 yr ago
2–3 yr ago
1–2 yr ago
Within the past year

What does PLCO tell us?

- Not a trial of screening vs no-screening
- A trial of organised vs opportunistic screening

- Has polluted meta-analyses for years – if a meta-analysis includes this data, ignore it 👎

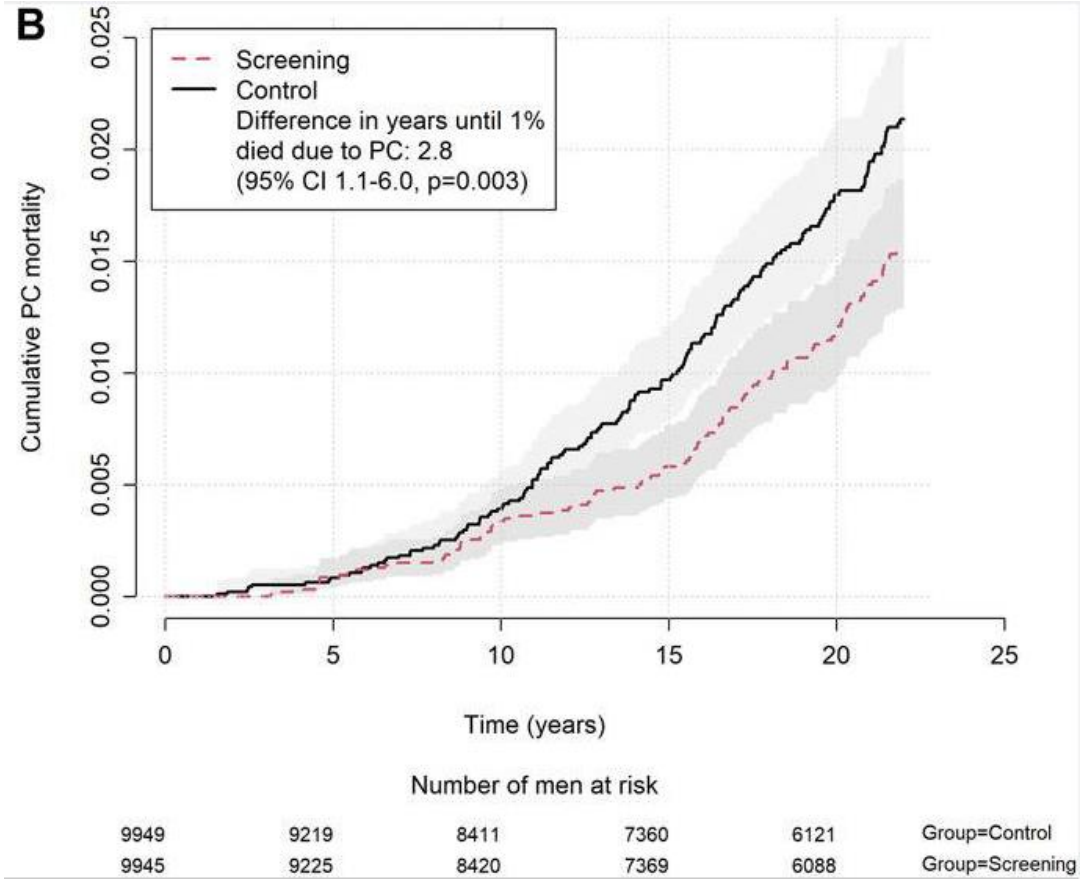
Goteburg RCT 👍

- Sometimes described as a subset of ERSPC – is not actually
- 20,000 men in across Sweden
- Randomised to screening or control
- Analysed on intention to screen bases

- Contributed a subset of patients to ERSPC
  - Half of patients
  - Had younger starting age, only older patients were contributed to ERSPC
- Average age of starting screening 52
- Very little contamination

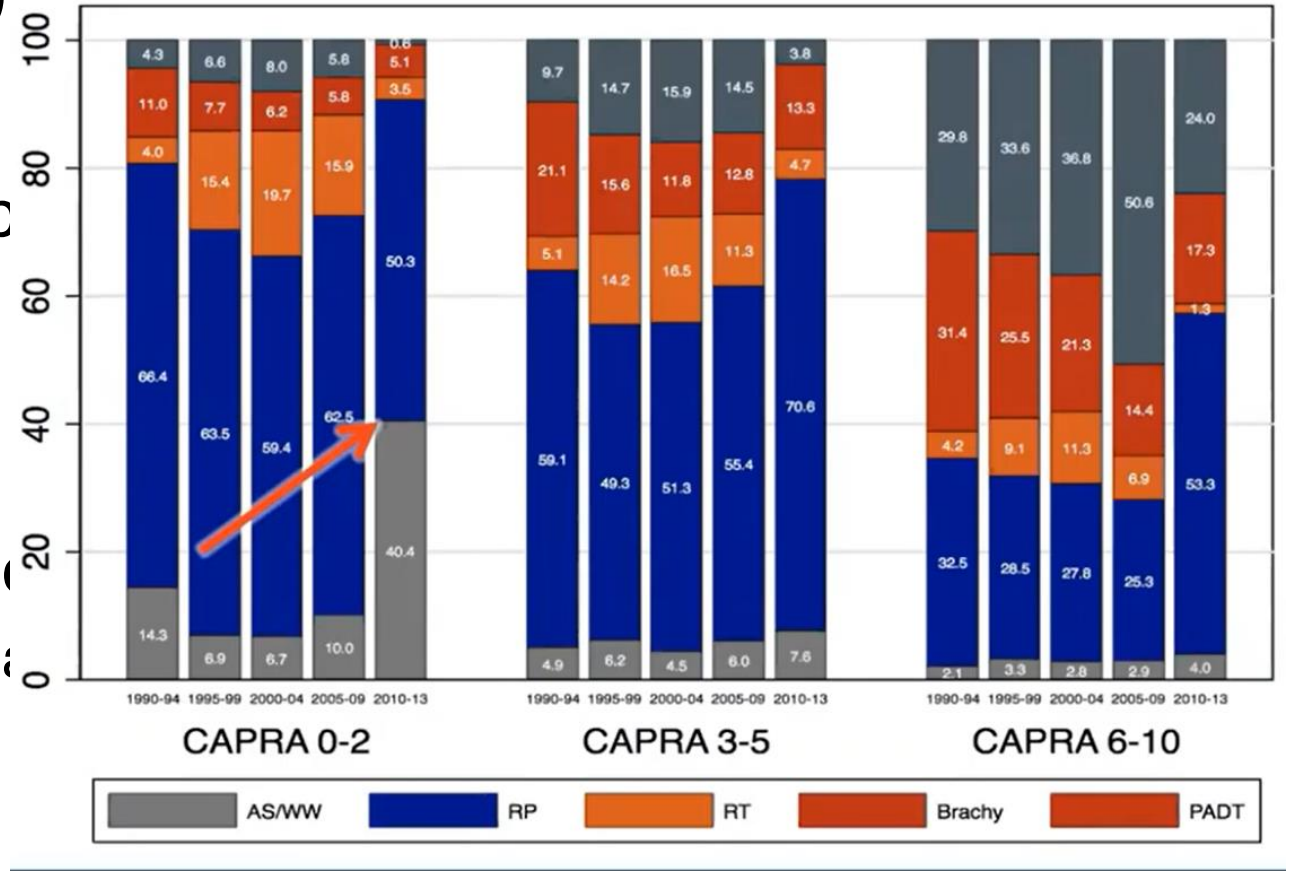
Goteburg RCT

- 22 year follow up reported in 2022
- Incidence rate ration of 1.42
- **RR of death - 0.56**
- NNI 221
- NNT 9
- First screening after age 60 associated with increased risk of death



PSA Screening in 1990s

- Screening was implemented p
  - Older men were overscreened
  - Younger men underscreened
- Treatment was poorly calibrat
  - Low risk disease hugely overtrea
  - High risk disease undertreated



- **Despite all of this – mortality rates decreased by >50%**

So how do we do it better?

Start earlier

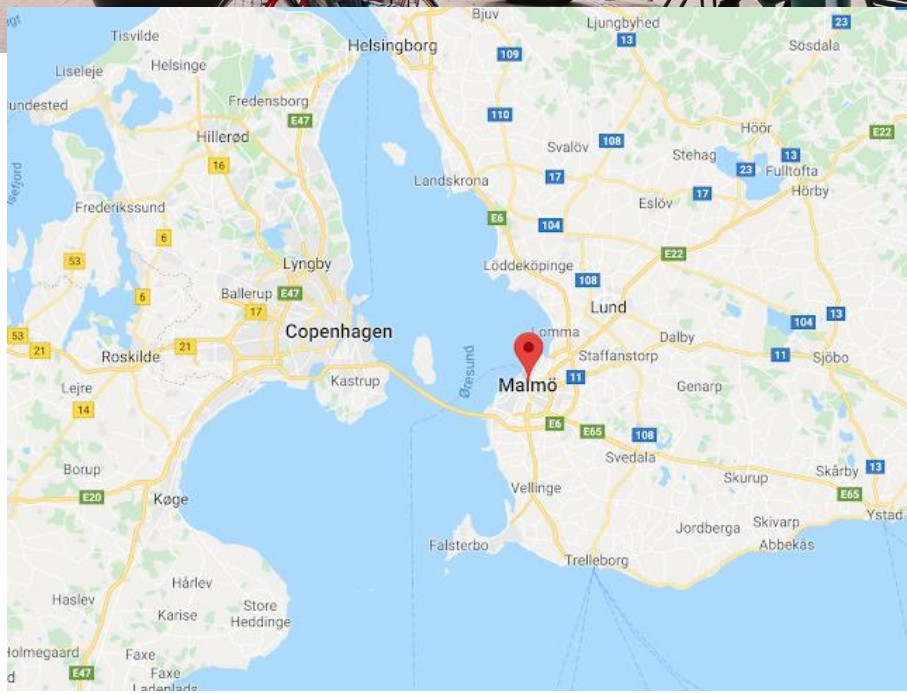
- PCFA – 50
- EAU – 50, 45 with risk factors
- AUA – shared decision making from 55
- NCCN – shared decision making from 45
- American cancer society - 50, 45 if risk factors
- USPSTF – age 55

Early baseline testing

- Based on Malmo study
  - Early 1980s prior to PSA
  - Blood drawn from population
  - Later checked for PSA

- If PSA:
  - <1.0 at 60 - <0.3% risk of PCa death
  - >2 (top quartile) – 90% of deaths occurred in this range
    - Almost all mortality is in top quartile

- Large proportion of the population can stop worrying about prostate cancer



What about even earlier?

- PSA between 40-55 remains very predictive
- 15 year risk of prostate cancer if below median PSA – 0.09%
  - ~50% of metastasis or death in top 10%

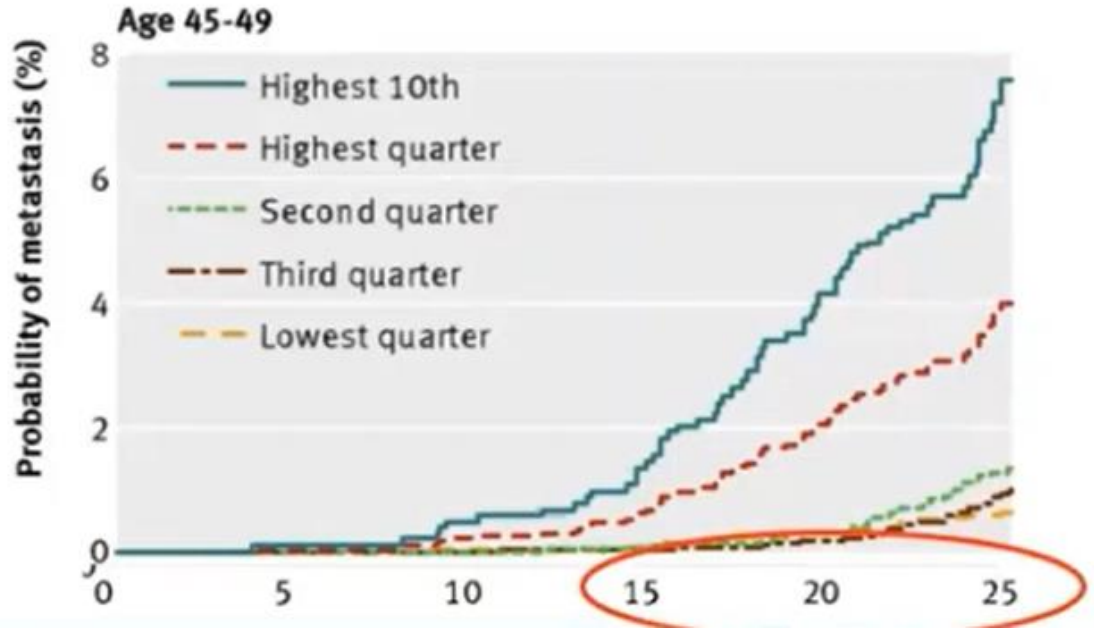
Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40-55 and long term risk of metastasis: case-control study

BMJ 2013 ; 346 doi: https://doi.org/10.1136/bmj.f2023 (Published 16 April 2013)
Cite this as: *BMJ* 2013;346:f2023

Article | Related content | Metrics | Responses | Peer review

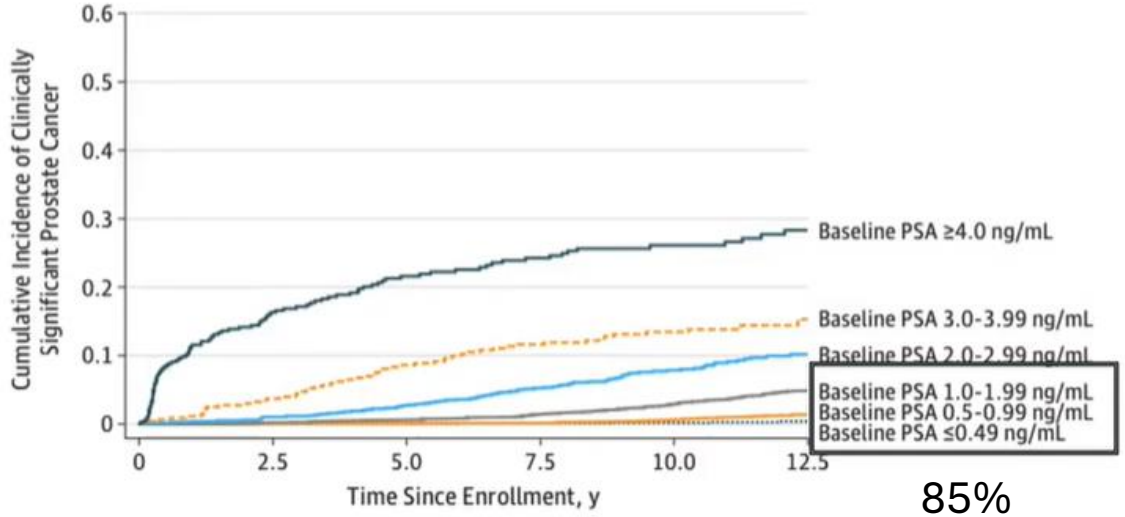
Andrew J Vickers, attending [1], David Ulmert, research fellow [2 3], Daniel D Sjoberg, research biostatistician [1], Caroline J Bennette, PhD student [4], Thomas Björk, associate professor [3], Axel Gerdtsson, resident [3], Jonas Manjer, associate professor [5], Peter M Nilsson, professor [6], Anders Dahlin, data manager [7], Anders Bjartell, professor [3], Peter T Scardino, chair [2], Hans Lilja, attending clinical chemist, professor [2 8 9 10 11]

Conclusion Measurement of PSA concentration in early midlife can identify a small group of men at increased risk of prostate cancer metastasis several decades later. Careful surveillance is warranted in these men. Given existing data on the risk of death by PSA concentration at age 60, these results suggest that three lifetime PSA tests (mid to late 40s, early 50s, and 60) are probably sufficient for at least half of men.



Value of being below median

- Repeated around the world – very si
  - Below median – very low risk
- Medians are very stable
  - Late 40s - ~0.7
  - 50s - ~ 0.8
  - 60 – 1.0



85%

Age 45-49 at baseline screen				
Highest 10th	≥1.60	0.74 (0.31 to 1.57)	2.42 (1.48 to 3.75)	5.14 (3.63 to 7.04)
Highest quarter	≥1.10	0.31 (0.13 to 0.66)	1.18 (0.75 to 1.77)	2.67 (1.97 to 3.54)
Second quarter	0.68-1.10	<0.01 (<0.01 to 0.07)	0.24 (0.09 to 0.56)	0.72 (0.40 to 1.21)
Third quarter	0.44-0.68	0 (NA)	0.09 (0.02 to 0.34)	0.54 (0.28 to 0.96)
Lowest quarter	≤0.44	0.08 (0.01 to 0.30)	0.24 (0.09 to 0.54)	0.52 (0.26 to 0.96)
Below median	≤0.68	0.04 (0.01 to 0.16)	0.17 (0.08 to 0.34)	0.55 (0.35 to 0.83)
≤66th centile	≤0.90	0.03 (0.01 to 0.12)	0.14 (0.07 to 0.28)	0.51 (0.34 to 0.74)
≤73rd centile	≤1.00	0.03 (0.01 to 0.11)	0.17 (0.09 to 0.30)	0.56 (0.39 to 0.79)

Table 5 – Distribution of total PSA (ng/ml) by age group and race among controls from case-control studies of prost

Age group	Race	*n*	Study population	Total PSA, ng/ml 25th percentile	50th percentile	75th percentile	90th percentile	
40–49 yr								
40–49	Black	110	SCCS	0.44	0.72	1.15	1.68	Curr
40–55	Black	69	CHDS[b]	0.24	0.41	0.72	–	Whit
40	White	228	VIP	0.50	0.70	0.90	–	Statt
40–55	White	78	CHDS[b]	0.27	0.48	0.87	–	Whit
40–49	White (94%)	104	PHS	0.52	0.68	1.04	1.68	Prest
45–49	White	514	Malmo	0.41	0.60	0.94	–	Vick
50–55 yr								
50–54	Black	143	SCCS	0.46	0.80	1.08	1.85	Curr
50	White	1157	VIP	0.60	0.80	1.20	–	Statt
50–54	White (94%)	202	PHS	0.59	0.88	1.40	1.96	Prest
51–55	White	3970	Malmo	0.52	0.84	1.36	–	Vick
55–59 yr								
55–59	Black	172	SCCS	0.52	0.94	1.65	2.73	Curr
55–59	White (94%)	405	PHS	0.60	0.96	1.64	2.88	Prest

CHDS = Child Health and Development Study; PHS = Physicians' Health Study; PSA = prostate-specific antigen; SCCS = Southern Co
VIP = Västerbotten Intervention Project.
[a] PSA levels by race among controls from all nested case-control studies of baseline PSA that reported PSA levels by age group.
[b] PSA values for both races were low in this study, possibly due to differences in laboratory assay or storage of blood samples, which w
1960s.

Free:total

Urology. 2002 Dec;60(6):1034-9. doi: 10.1016/s0090-4295(02)01997-0.

Substratification of stage T1C prostate cancer based on the probability of biochemical recurrence

Matthew B Gretzer [1], Jonathan I Epstein, Charles R Pound, Patrick C Walsh, Alan W Partin

Affiliations + expand

PMID: 12475665 DOI: 10.1016/s0090-4295(02)01997-0

- PSA produced in malignant cells escapes proteolytic processing
  - Greater fraction complexed
- Significantly improves AUC
  - Cut off of 25% - avoids 20% of biopsies with very low miss rate
  - 18% cut off is proposed as optimal AUC – maintains 95% sensitivity
- Reasonably reliable at predicting aggressiveness
- Probably most useful in negative biopsy

- F:T ratio remains reliable with 5ARIs

PSA Density

Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer

Tobias Nordström ✉, Olof Akre, Markus Aly, Henrik Grönberg & Martin Eklund

Prostate Cancer and Prostatic Diseases **21**, 57–63 (2018) | Cite this article

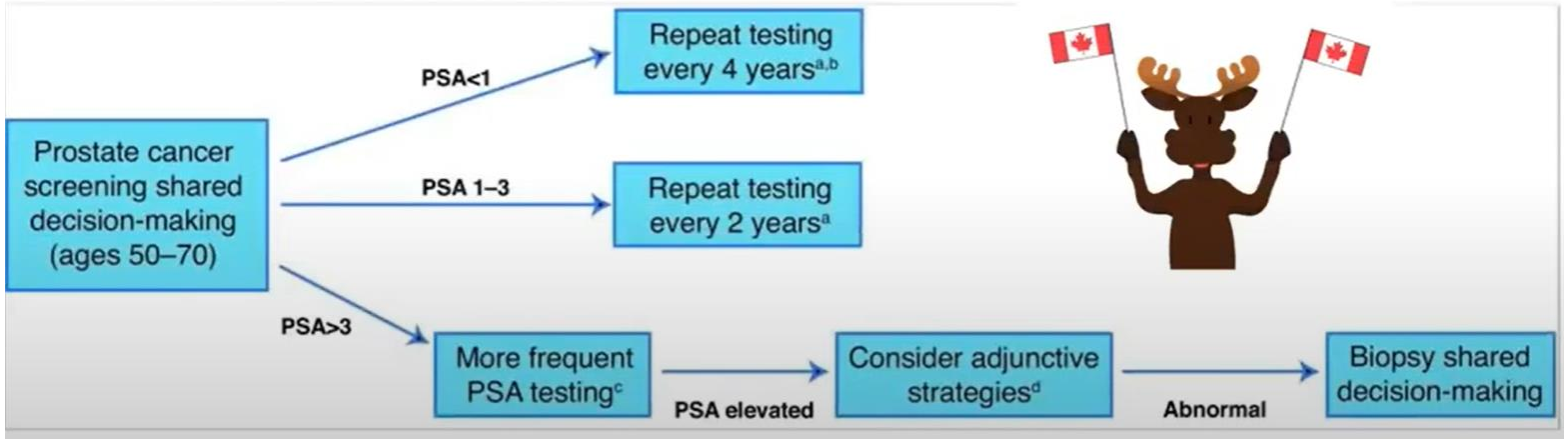
2895 Accesses | **124** Citations | **13** Altmetric | Metrics

- Literature supports mildly better predictive value than PSA alone
- Requires the patient to have had imaging however
- Proposed cut-off values are not settled
  - Values between 0.08-0.15 argued for

- PSAD higher than 0.19 have 30% to 60% chance to be diagnosed with PCa, while patients with PSAD less than 0.09 have low probability (4%)
- Using PSA density cut off of 0.07 would save 20% of biopsies at the cost of missing 7% of clinically significant cancers

Improved screening intervals

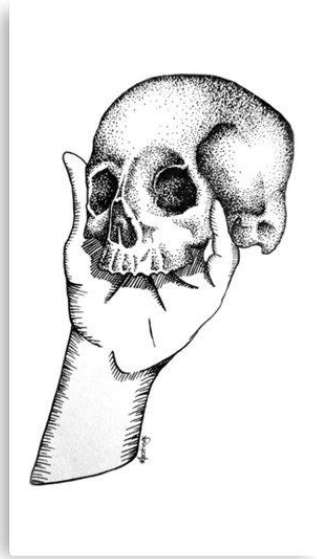
Age	PSA	Protocol
45-60	<1	Recheck in 5+ years
	1-2	Recheck in 6-12 mos vs. early referral based on family history, anxiety, etc + SDM
	>2	Referral
61-75	<1	Recheck in 5+ years
	1-3	Recheck in 6-12 months vs. early referral based on family history, anxiety, etc + SDM
	>3	Referral



To Screen or Not to Screen: The Wrong Question…

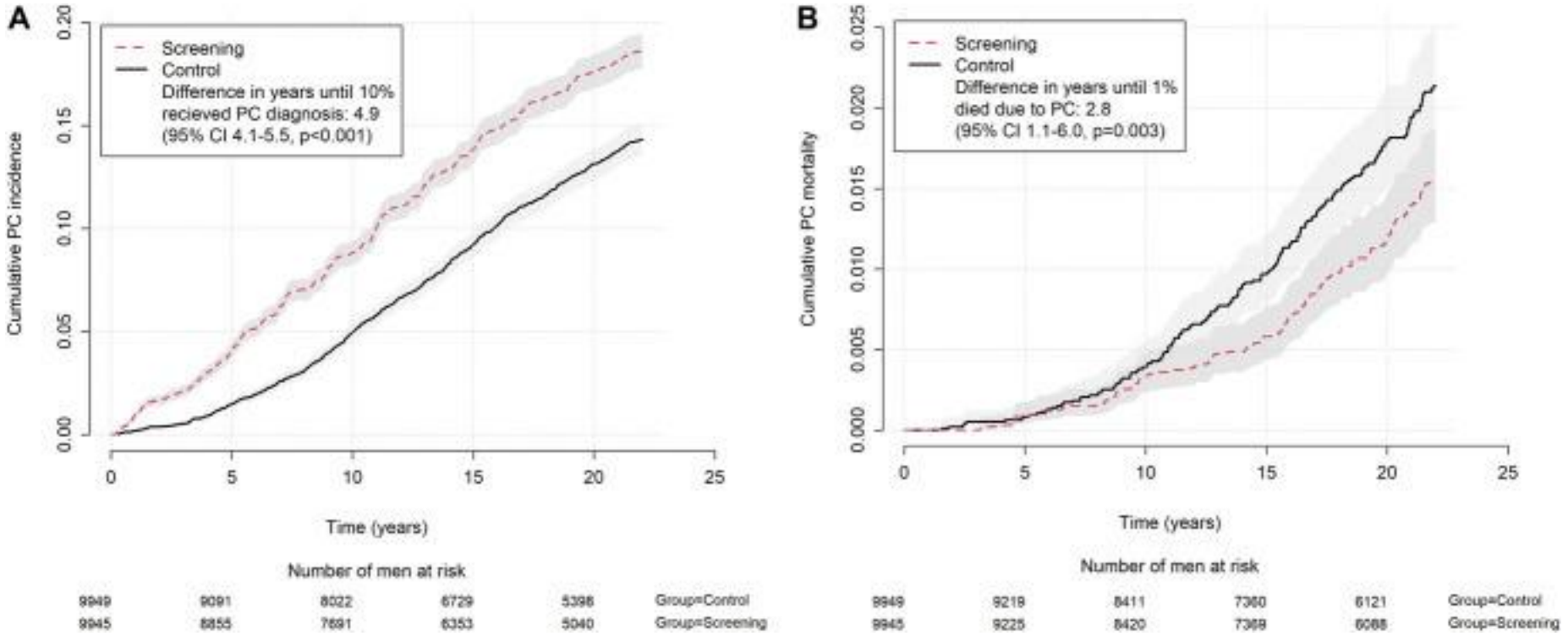
- Matured data (22 years) shows >30% reduction in mortality in the screened cohort (Goteborg)

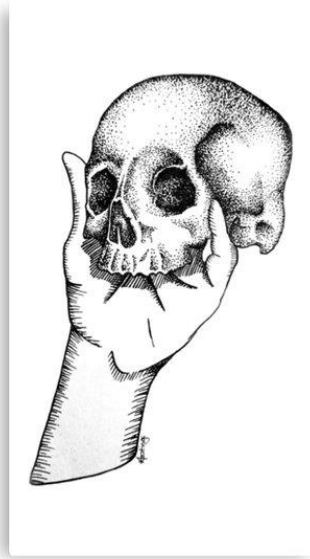
- Update at 22 years (long term disease)
  - PC Incidence 1.42
  - PC Mortality RR 0.56
  - Caveats – Starting late >60



Franlund et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. J Urol 2022 Aug;208(2):292-300.

To Screen or Not to Screen: The Wrong Question…

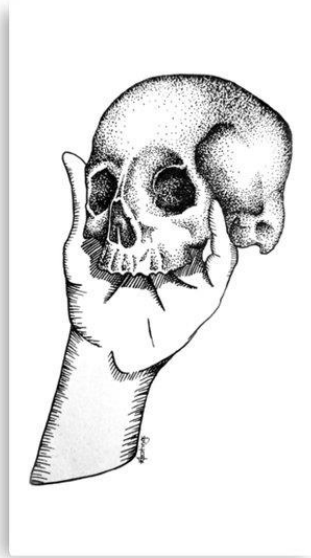




Franlund et al. Results from 22 years of Followup in the Göteborg Randomized Population-Based Prostate Cancer Screening Trial. J Urol 2022 Aug;208(2):292-300.

To Screen or Not to Screen: The Wrong Question…

- Issues:
  - Overdiagnosis
  - Consequent overtreatment with morbidity



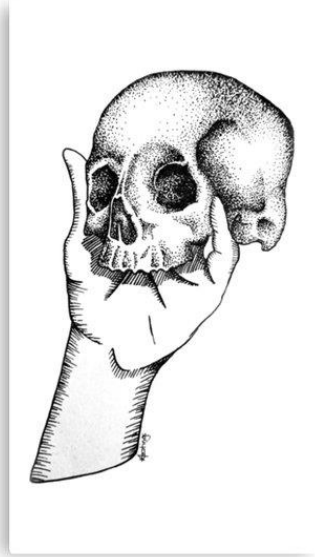
- Key is to uncouple diagnosis from treatment

ST VINCENT'S HOSPITAL SYDNEY

To Screen or Not to Screen: The Wrong Question…

- Issues:
  - Overdiagnosis
  - Consequent overtreatment with morbidity
  - Uncouple diagnosis from treatment

  - Screening:
    - Early detection
    - Before symptoms
    - Treat early to cure or reduce cancer morbidity/mortality
    - Only if minimal treatment morbidity



Clinical Practice Guidelines on PSA Testing

Australian Government
National Health and Medical Research Council

NHMRC

Prostate Cancer Foundation of Australia

PSA TESTING AND EARLY MANAGEMENT OF TEST-DETECTED PROSTATE CANCER

CLINICAL PRACTICE GUIDELINES

An overview of the recommendations approved by the National Health and Medical Research Council

Screening

- Offer testing to those aged 50 – 70+ years
  - At least a 7 years life expectancy
- Offer to those with increased risk from 40 years
- Repeat every two years
- DRE considered

— Men should be offered the opportunity to consider and discuss the benefits and harms of PSA testing before making the decision whether or not to be tested.

— The harms of PSA testing may outweigh the benefits, particularly for men aged 70 and older.

— Men at average risk of prostate cancer who decide to undergo regular testing should be offered PSA testing every 2 years from age 50 to 69.

— Men with a family history of prostate cancer who decide to be tested should be offered PSA testing every 2 years from age 40/45 to 69, with the starting age depending on the strength of their family history.

— Digital rectal examination is not recommended for asymptomatic men as a routine addition to PSA testing in the primary care setting, but remains an important part of specialist assessment.

— The recommendations in the guidelines are approved by the CEO of the National Health and Medical Research Council (NHMRC). In granting approval NHMRC is satisfied that the guideline recommendations are systematically derived, based on the identification and synthesis of the best available scientific evidence, and developed for health professionals practicing in an Australian health care setting.

Thank You