Chapter 10 – PROSTATE CANCER PART ONE: DETECTION

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I. INTRODUCTION AND BACKGROUND

Prostate Cancer is an increasingly common diagnosis in Western societies with over 240 000 diagnoses made in the the US each year [1]. There is a wide range in the incidence of prostate cancer across the globe with the highest rates in western countries although non-westernised societies are changing as reported recently in relation to the Asia-Pacific region [2] (Figure 1).

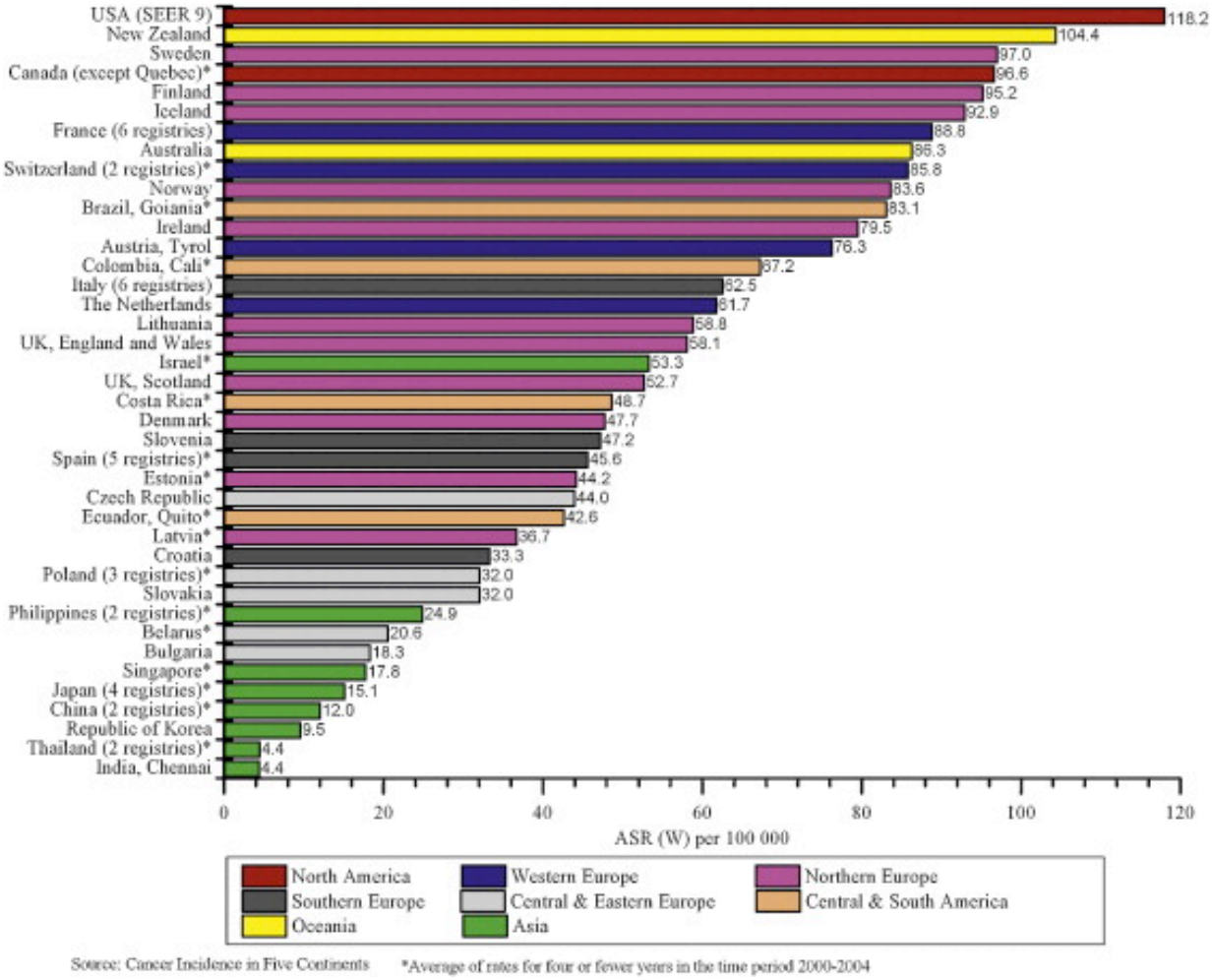


Figure 1: Prostate cancer incidence rates for select registries, 2000–2004 [3]

Mortality rates vary from country to country as well [4, 5] with prostate cancer following lung and bowel cancers in Europe and Australia in terms of mortality rates.

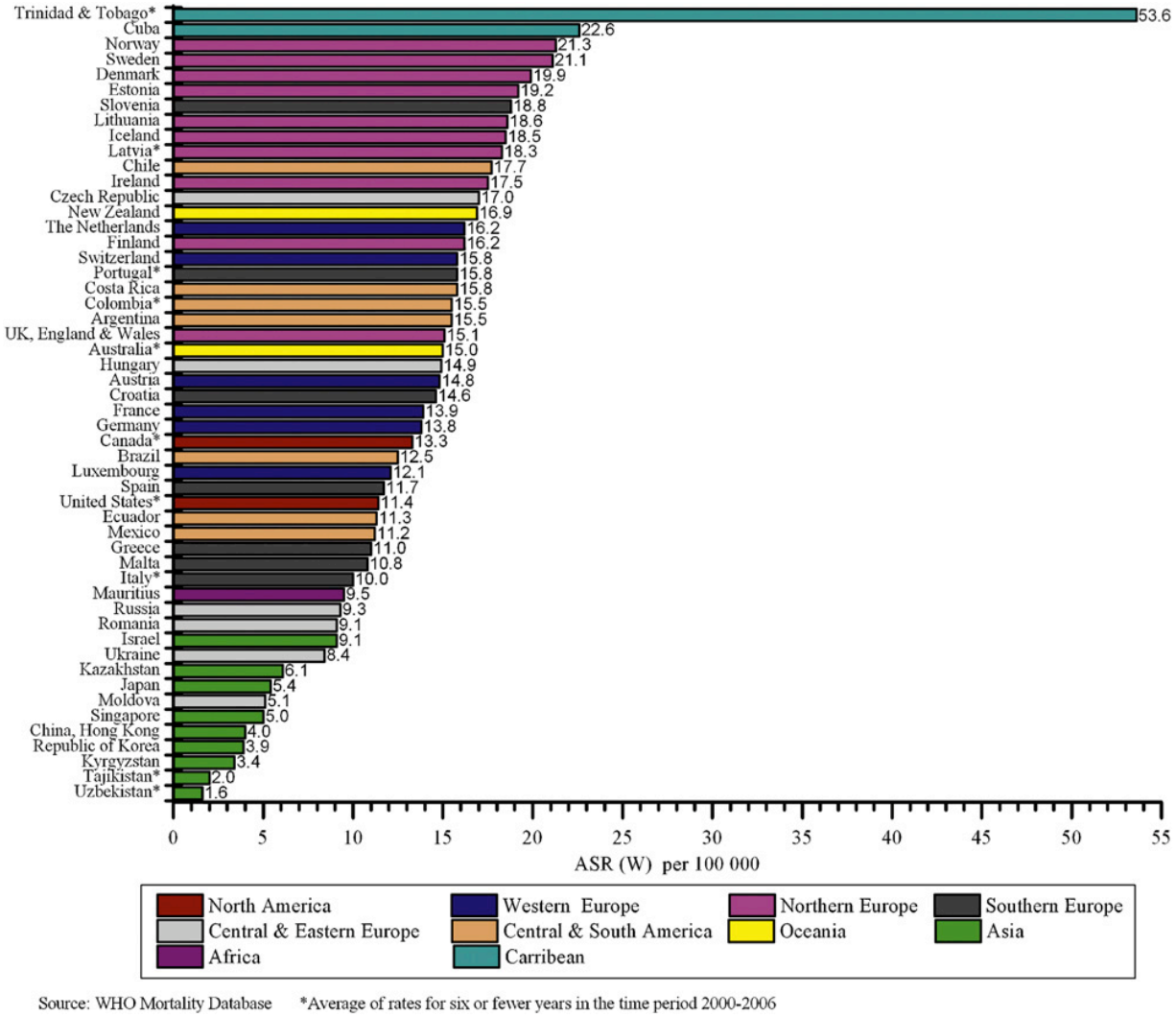


Figure 2: Prostate cancer age-standardised mortality rates for selected registries, 2000–2004 [3]

Despite advances in prevention and early detection, refinements in surgical technique and improvements in radiotherapy and chemotherapy, the ability to cure many patients remains elusive. However, mortality rates are changing albeit slowly as illustrated in blue below for Australia. A 2013 report by the Australian Institute of Health and Welfare predicts that by 2020 only 26 out of 100,000 Australian men will die from the disease compared with 34 in 1982 [6].

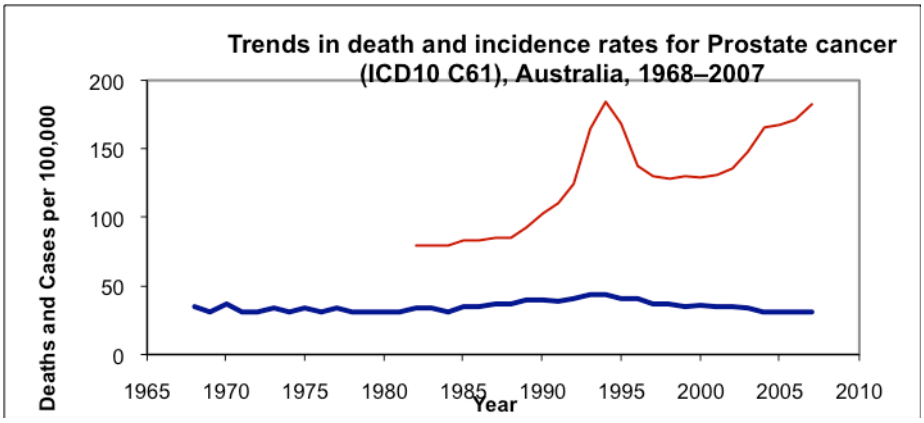


Figure 3: Incidence (red) demonstrating a rise after widespread availablitly of PSA testing with a dip after the prostate cancer backlog was addressed: mortality (blue) has been falling slowly since the mid-1990s

This phenomenon is not peculiar to Australia. Baade et al reviewed international trends in prostate cancer mortality and reported significant reductions in prostate-cancer mortality in the UK, USA, Austria, Canada,

Italy, France, Germany, Australia and Spain with downward trends in the Netherlands, Ireland and Sweden [7].

Earlier detection of this disease, as a consequence of introduction of the prostate specific antigen (**PSA**) blood test, has been acknowledged by the NCI as one factor contributing to lowering the mortality rate over the past few years [8-11]. The use of PSA testing has been estimated to provide a diagnostic lead-time of up to 10 years [12-16]. In the mid to late 1980s only one third of prostate cancers were diagnosed at curable stages compared with today when 80% are staged clinically as organ-confined and potentially curable [17-19]. Unfortunately, however, even when the tumour is thought to be localized, up to 25% of men have non-localised disease which declares itself subsequently [20].

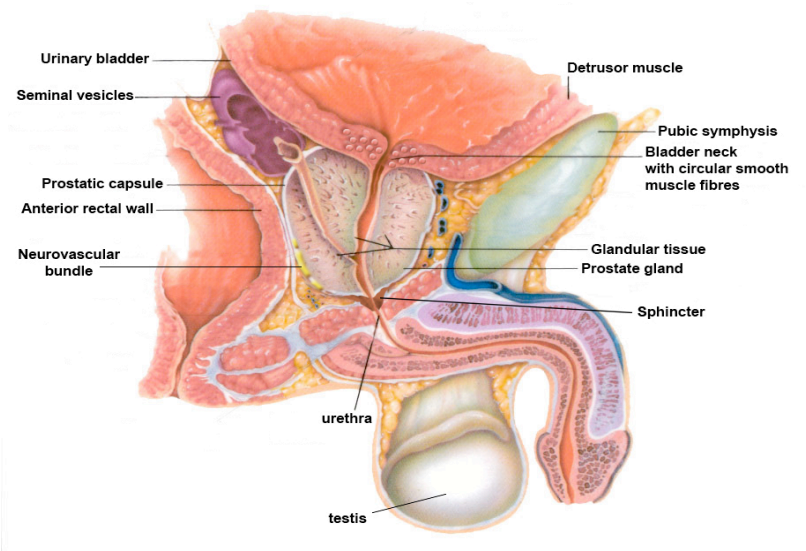
Since curative treatments are limited to localised tumours [8, 9, 12, 21], extending effective but non-invasive treatments to include both primary and secondary lesions remains a major goal and challenge. Once prostate cancer metastasizes, apart from causing loss of life, its toll is often considerable with regard to morbidity from both the disease itself and administered therapies.

As a result of increasing numbers of men having their prostate cancers diagnosed earlier, more patients are now eligible for treatment with curative intent. Improved surgical and radiation-based treatments have been developed so that the prognosis of a man diagnosed today with prostate cancer is better than ever before.

II. ANATOMY AND PHYSIOLOGY

The word "prostate", originally derived from the Greek prohistani which means "to stand in front of," has been attributed to Herophilus of Alexandria who used the term in 355 BC to describe the small organ located in front of the bladder [22]. The prostate gland is a small firm gland, about the size of a chestnut, located below the bladder and in front of the rectum. The urethra, the channel through which urine is voided, passes from the bladder through the prostate and penis.

Figure 4: the normal prostate & its relationship to other pelvic structures



The primary function of the prostate gland, which contracts with ejaculation, is to provide enzymes to maintain the fluid nature of seminal fluid and to nourish sperm as they pass through the the prostatic and penile urethra to outside the body.

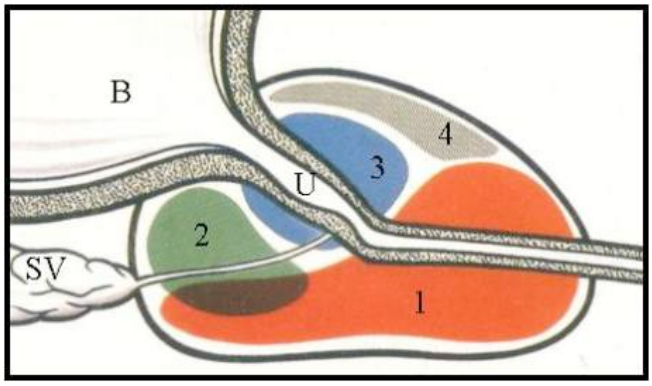


Figure 5: Zonal anatomy of the prostate (sagittal depiction)
1 = peripheral zone - the zone where most cancers originate
2 = central zone – zone in which middle lobe develops
3 = transition zone – zone in which BPH 'lateral lobes' form
4 = anterior zone
B = bladder
U = urethra

III. NATURAL HISTORY OF PROSTATE CANCER

Traditionally, prostate cancer was considered to be a disease of "older men." As such, it was generally accepted that "men never died from prostate cancer, they died of other conditions *with* prostate cancer." Consequently, treatment was conservative and directed toward palliation and management of any debilitating and painful sequelae. In addition, diagnosis from histopathology from a biopsy was generally made after palpating a rock-hard and nodular prostate on digital rectal exam [**DRE**] or by symptoms and signs of primary or secondary tumours, such as urinary obstruction, back pain, nerve root or, less commonly, spinal cord compression. In a large majority of cases, tumours had already disseminated at the time of diagnosis and, therefore, were incurable. It was in the mid-1980s, with the introduction of the PSA blood test that prostate cancer began to be diagnosed earlier and in younger men.

Prostate cancer is usually slow in its development and in the majority of cases, slow to progress as is illustrated in the figure below from Surveillance Epidemiology and End Results (**SEER**) registry**:** SEER collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 28% of the population of the United States.

Figure 6: Analysis of US SEER data from 2005-2009

Cancer	Median Age at Diagnosis	Median Age at Death	Diagnosis to Death
Lung	70	72	2
Prostate	67	80	13
Breast	61	68	7
Bowel	69	74	5
Lymphoid	64	75	11
Pancreas	71	73	2
Myeloid	69	74	5
Melanoma	61	68	7
Ovary	63	71	8

http://seer.cancer.gov/statfacts/html/prost.html

If autopsy findings are an indication, premalignant and inapparent tumours are very common with one United States study indicating that, of 249 cases examined, 70% of the prostates with the premalignant

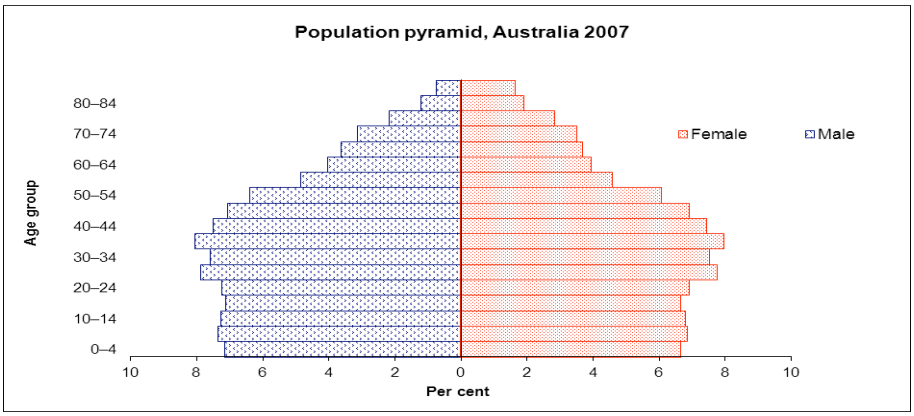
condition high grade prostate intra-epithelial neoplasoia (**HGPIN**) harboured adenocarcinoma, whereas the frequency of cancer in prostates without HGPIN was 24%. HGPIN was encountered in 0, 5, 10, 41 and 63% of men in the 3rd, 4th, 5th and 7th decades, respectively. The corresponding figures for invasive carcinoma were 2, 29, 32, 55, and 64% respectively [24].

Although methods of diagnosis and treatment of localized disease have become well-established, they are beginning to change. Both early detection through PSA screening and the management of prostate cancer remain controversial due to its variable biologic course, the invasive, costly and imprecise nature of biopsy and clinical staging as well as limitations in prediction of the clinical outcome of patients with both organ-confined and locally-invasive disease - not to mention the morbidity associated with all currently established treatments. It is sobering to muse that, were the unwanted effects of diagnosis and treatment insignificant, the dilemma of whether or not to diagnose and treat would not be issues.

IV. COMPETING MORBIDITIES AND LIFE EXPECTANCY: COMPARISONS

The likelihood of men dying from causes other than from prostate cancer increases with ageing because of competing mortalities (as indicated by Figure 7 below), in particular cardiovascular and cerebrovascular diseases (Figure 7 below) : the fact that most prostate cancers progress slowly compared with other cancers needs to be considered in terms of life expectancy from competing causes of death..

Figure 7:



http://www.aihw.gov.au/cancer-data/ [25]

If death from prostate cancer is compared with the likelihood of death from other conditions, the older a man, the greater is the likelihood that another condition will be the cause of his demise; in Australia in 2009, one in three male deaths was attributed to cardiovascular disease [25].

The following graphs (Figures 8 & 9) from the Australian Government website [25] show approximately parallel increases for incidence and death from prostate cancer, estimated to be 23 years apart. Consequently, if death is the endpoint being addressed, the patient's life expectancy, based on his age and comorbidities, needs to be considered in the context of the natural history of his disease.

Figure 8:

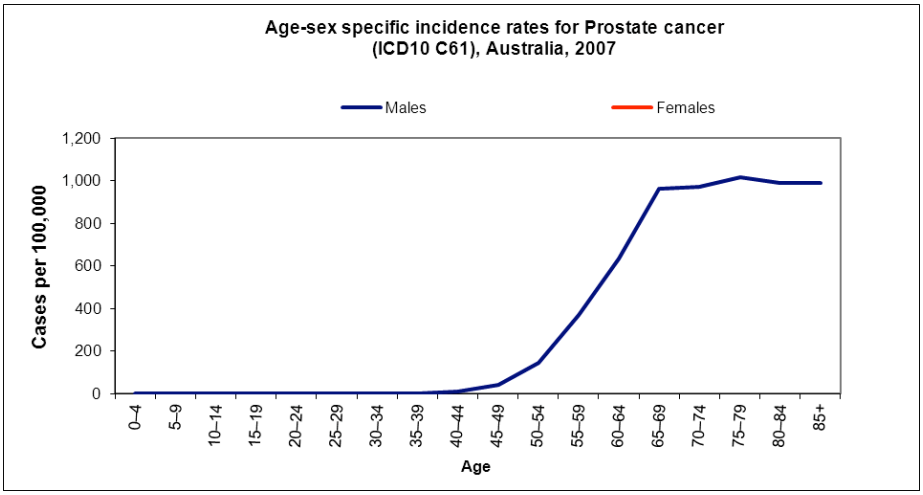
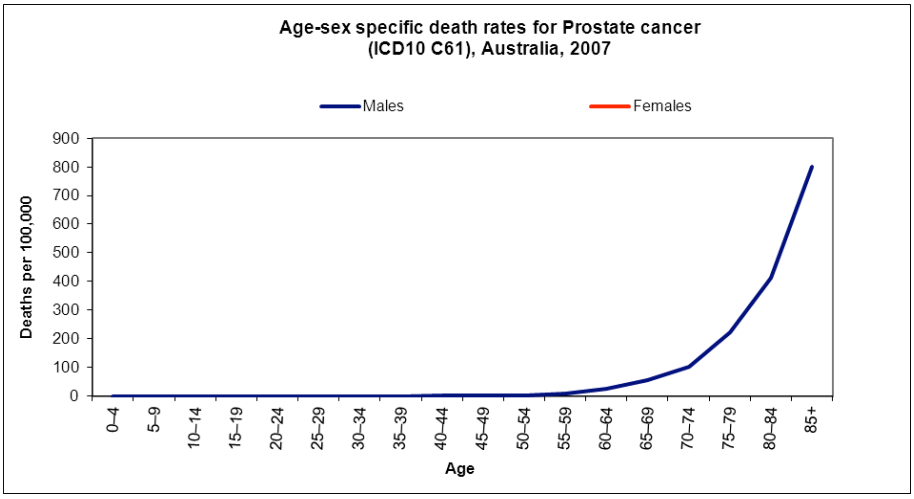


Figure 9:



http://www.aihw.gov.au/cancer-data/ [25]

Targetting Prostate cancer at-risk populations: Major genetic epidemiologic studies published in the last two decades support the notion that prostate cancer may exist as clusters in families. In the 1980s, a Utah Mormon genealogy study found that prostate cancer exhibited the fourth strongest degree of familial clustering after lip, melanoma, and ovarian cancers [26]. Prostate cancer, interestingly, had a higher familial association than either colon or breast carcinoma, which are known to be predisposed by genetic or familial components. A later study, determined cancer pedigrees in 691 men with prostate cancer and 640 spouse controls, and found that men with an affected father or brother were twice as likely to develop prostate cancer as men with no affected relatives [27]. Although these findings strongly suggest that familial clustering of prostate cancer risk does exist, they did not address the underlying aetiological mechanisms. Indeed, familial clustering can reflect either shared environmental and lifestyle risk factors, or a genetic mechanism, or both.

To determine what might distinguish hereditary prostate cancer from its sporadic counterparts, a number of clinical features of prostate cancer were examined by Carter, et al.[28]. Clinical stage at presentation, pre-operative PSA, final pathologic stage, and prostate weight were examined in a series of approximately 650 patients divided among three categories. Individuals were classified as having hereditary disease if 3 or more relatives were affected in a single generation, prostate cancer occurred in each of 3 successive generations in either paternal or maternal lineages, or 2 relatives were affected under the age of 65 years. For the other groups, either no other family members were affected (sporadic disease), or other family members were affected but not to the extent found in families classified as hereditary. In summary, no unique clinical or pathological characteristics distinguished hereditary prostate cancer in this group of patients. This parallel between hereditary and sporadic prostate cancer extends to the incidence of multifocality found in both of these categories.

These findings were supported by Brandt et al (2011) in an analysis of the nationwide Swedish Family-Cancer Database between 1961 and 2006. They found that the age-specific hazard ratio of prostate cancer diagnosis increased with the number of affected relatives and decreased with increasing age. The highest hazard ratios were observed for men <65 yr of age with three affected brothers (approximately 23) and the lowest for men between 65 and 74 yr of age with an affected father (HR: approximately 1.8). The hazard ratios increased with decreasing paternal or fraternal diagnostic age. The pattern of the risk of death from familial prostate cancer was similar to the incidence data [29].

However, there are differences between hereditary and sporadic prostate cancers. The onset of hereditary prostate cancer is, on average, 6 years earlier than of sporadic cancer and, although the clinical course is in no way different and the pathological characteristics are the same in most instances [30], patients with a family history of germ-line mutations in the family-susceptibility genes BRCA1 and BRCA2 , in particular the latter, have a significantly increased susceptibility for developing this malignancy and, when they do, tend to present at a younger age, have more aggressive disease with poorer survival outcomes [31-6].

V TESTS USED IN DIAGNOSING PROSTATE CANCER

In evaluating this issue, it is important to appreciate that the diagnostic approach is a two-step process that begins with the decision about whether or not to have a Prostate Specific Antigen (**PSA**) blood test (+/- other investigations) and, secondly, to confirm a suspected diagnosis of prostate cancer by biopsy for histopathology. Most men with a PSA level less than 10ng/ml will have a normal feeling prostate on digital rectal examination (**DRE**).

The FDA initially approved PSA testing in 1986 for monitoring the disease status of prostate cancer patients and, subsequently in 1994, it was endorsed as a screening method for prostate cancer [37]. The PSA blood test is a continuous variable with no cut point [38] so that very low levels don't completely exclude the possibility that prostate cancer is present [39-41], but the higher the serum PSA, the greater the likelihood of prostate cancer being detectable. Importantly, PSA doesn't distinguish between those who do and do not have cancer or identify those whose cancers will benefit from curative treatment. PSA increases with a number of conditions including prostate cancer, but the most common associated pathology is the non-cancerous condition benign prostatic hyperplasia (**BPH**) which is the cause, in most instances, of bladder outlet obstruction in men.

Factors affecting PSA measurements:
The medication finasteride which targets the 5-α-reductase type 2 enzyme and the more recently available drug, dutasteride, which inhibits both type 1 and type 2 enzymes, affect conversion of testosterone to dihydrotestosterone (**DHT**) in prostatic cells. They reduce prostate volume with comparable effectiveness, with their designated clinical role being to decrease bladder outflow obstruction responsible for lower urinary tract symptoms (**LUTS**) present in a large number of men. In reducing the benign prostatic hyperplasia (**BPH**) component of the prostate, both finasteride and dutasteride also reduce serum PSA levels by ~50%, the full effect taking at least 12 months before a PSA nadir is reached. However, with the influence of the non-cancer BPH component significantly reduced, PSA changes are more likely to reflect non-transition zone/BPH effects. An increase in PSA of $\geq$0.3 ng/ml from nadir is generally regarded as an indication for biopsy based on the findings of Marks et al (2006) who determined that applying this recommendation resulted in a 71% sensitivity and a 60% specificity for prostate cancer being detected in men receiving dutasteride [42].

Concerns with respect to finasteride use and subsequent prostate cancer were addressed by long-term data from the Prostate Cancer Prevention Trial. Results confirmed that finasteride reduced the risk of prostate cancer by about one third but also found that high-grade prostate cancer was more common in the finasteride group than in the placebo group. However, after 18 years of follow-up, there was no significant difference between-groups in the rates of overall survival or survival after the diagnosis of prostate cancer [43].

Other non-malignant causes affecting serum PSA levels include infection, BPH and ageing since prostates tend to become larger as men get older [44]. Instrumentation of the prostate and urinary tract can also raise PSA levels [45] as can bacterial prostatitis, both of these capable of resulting in sudden rises in this enzyme.

Figure 10: Factors affecting levels of serum PSA

- Ageing
- Benign prostatic hyperplasia (BPH)
- Finasteride and dutasteride medications
- Ejaculation (both free & total) up to 48 hours
- Bacterial infection of prostate
- Prostatic massage
- Instrumentation (including catheterisation) of prostatic urethra

AGE-RELATED PSA LEVELS

Figure: 11 Age-based PSA ranges for men in western societies [16, 46-8]

AGE-BASED RANGES FOR PSA FOR WESTERN MEN

Age range	50th percentile (median)	95th percentile (upper limit of normal)
40-49	0.65	2.0
50-59	0.85	3.0
60-69	1.39	4.0
70-79	1.64	5.5

- Between 50th & 95th percentile, higher long-term risk of cancer
- PSA increases at ~3.3% pa – if rate of increase is greater, the risk of cancer is greater

Oesterling et al, 1995; Fang et al, 2001; Gann et al, 1995; Carter et al, 1992

Figure 12: Age-based PSA ranges for Japanese men [49-52]

AGE-BASED 95TH PERCENTILE FOR PSA FOR JAPANESE MEN

Age range	Imai 1994	Imai 1995	Oesterling	Ito
40-49	1.33	2.1	2.0	
50-59	3.65	2.9	3.0	
60-69	4.06	4.0	4.0	3.0/3.5
70-79	5.09	5.2	5.0	4.0
80-89	5.66	5.9		7.0

Ku (2006) citing Imai et al, 1994 & 1995; Oesterling et al, 1995; Ito et al, 2000

Figure 13: Age-based PSA ranges for Chinese Men [49, 53]

AGE-BASED 95TH PERCENTILES FOR PSA IN CHINESE MEN

Age range	PSA in ng/ml
20-29	1.20
30-39	1.21
40-49	1.23
50-59	2.35
60-69	3.20
70-79	3.39
80-89	3.39

Ku (2006) citing He et al, 2004

Figure 14: Age-based PSA ranges for Taiwanese men [49, 54-6]

AGE-BASED 95TH PERCENTILE FOR PSA FOR TAIWANESE MEN

Age range	Lin	Kao	Wu
20-29	1.92	1.50	
30-39	1.85	1.50	
40-49	2.59	1.88	
50-59	3.31	2.37	4.0
60-69	5.03	4.82	6.0
70-79	5.73	5.96	5.0

Ku (2006) citing Lin et al, 1996; Kao, 1997; Wu & Huang, 2004

Figure 15: Age-based PSA ranges for Singaporean men [49, 57, 58]

AGE-BASED 95TH PERCENTILE FOR PSA FOR SINGAPOREAN MEN

Age range	Tay	Saw
30-39		1.4
40-49		1.7
50-59	3.51	2.3
60-69	3.78	4.0
70-79	6.02	6.3
80-89	6.02	6.6

Ku (2006) citing Tay et al, 1996; Saw & Aw, 2000

Figure 16: Age-based PSA ranges for Korean men [49, 59, 60]

AGE-BASED 95TH PERCENTILE FOR PSA FOR KOREAN MEN

Age range	Lee	Ku
20-29		2.25
30-39	1.8	2.35
40-49	2.0	2.36
50-59	2.5	2.96
60-69	3.9	3.78
70-79	5.8	7.49

Ku (2006) citing Lee et al, 2000; Ku et al, 2002

Attempts to improve the predictability of serum PSA for prostate cancer have included measuring the rate of PSA change (**PSA velocity**) and its relationship to the size of the prostate (**PSA density**) since prostates vary a lot in size and tend to become bigger as men age. This variable, but overall increase, in prostate size with ageing prompted the introduction of **age-related PSA** values by laboratories, based on the populations tested. The free or unbound PSA and its relationship to total PSA (**free: total PSA**) is another variation with the higher the free component, the lower the likelihood of cancer: most recently, the prostate health index (**PHI**) has become available and has been promoted. These are discussed in some detail (below).

1. Total PSA: Of the tests available, total serum PSA is generally regarded as having the greatest utility, maintaining its predictive value for the detection of prostate cancer [61] even after a first biopsy shows no evidence of cancer in which setting its performance characteristics are only slightly decreased [62]. However, as stated above, PSA is far from a perfect test with most men with a serum PSA less than 10 ng/ml not having prostate cancer detected with biopsy, while conversely the possibility that prostate cancer remains even with very low PSA levels. In the Tyrol project, Pelzer et al (2005) found that prostate cancers detected in men with PSA levels <4 ng/ml were in younger patients and at lower stages [63].

In terms of reassurance, a PSA $\leq$1 ng/ml in a man aged 60 years has been reported to indicate an extremely low risk of clinically important prostate cancer in his lifetime although a 25-30 year risk of

prostate cancer metastases could not be excluded by concentrations below the median at age 45-49 (0.68 µg/L) or 51-55 (0.85 µg/L), the 15 year risk remained low at 0.09% (0.03% to 0.23%) at age 45-49 and 0.28% (0.11% to 0.66%) at age 51-55 [64]. This finding was supported by Aus et al (2005) who failed to find a single case of prostate cancer detected in 2950 screened men with a PSA <1ng/ml over a 3 year period [65].

Figure 17: Current status of serum PSA in relation to prostate cancer detection

- **Is a continuous variable with no cut point** [38]
- **Lodding et al (1998) found 15% of prostate cancers detected by investigating a PSA between 3 & 4 ng/ml had extraprostatic growth** [39]
- **In the Tyrol project, prostate cancers detected in men with PSA levels <4 ng/ml were in younger patients and at lower stages with smaller prostate volumes** [63]
- **Doesn't indicate who will benefit from curative treatment** [40]
- **Total PSA remains the single most significant, clinically used predictive factor for identifying men at increased risk of harbouring cancer** [61]
- **For men 50-70 years, a PSA >1.5 ng/ml is a marker for greater than average risk up to 8 years (7.5-times greater risk versus 1.5 ng/ml or less)** [61]
- **Sustained rises in PSA indicate a significantly greater risk of PCa, particularly high-grade disease**
- **A PSA ≤1 ng/ml in a man aged 60 years has been reported to indicate an extremely low risk of clinically important PCa in his lifetime [41]**
- **Not a single case of prostate cancer was detected in in 3 years in 2950 screened men with a PSA <1ng/ml** [65]

2. PSA Velocity (PSAV): PSA is a labile enzyme with falsely high readings as a result of ejaculation within the previous 48 hours, vigorous (non-sexual) exercise, urethral instrumention and prostatic infections (Figure 10), as well as different assays providing slightly different readings. Therefore, a single PSA level should not be relied upon to indicate an increase in level. A rate of change of PSA (PSAV) >0.75 ng/ml in year in the absence of another contributing cause equates with an increased risk of a patient having cancer [66]. Men taking the taking 5-α-reductase inhibitors finasteride and dutasteride have their serum PSA levels reduced to approximately 50%, once the nadir is reached after up to 6 months. However, as stated above in this section (V) any sustained subsequent increase is more predictive for prostate cancer with an increase in PSA of 0.3 ng/ml from its nadir as a trigger for biopsy reported to provide a 71% sensitivity & 60% specificity for prostate cancer for men who were receiving dutasteride [42].

For men not taking 5α reductase inhibitors, PSA increases >3.3% per annum have been reported to be associated with an increased risk of prostate cancer being detected by biopsy [16, 47] and Makarov et al (2011) identified a preoperative PSA velocity >0.35 ng/ml/year to be associated with an increased risk of biochemical progression following radical prostatectomy [67]. A more sinister association was observed by D'Amico et al (2004) who found that a PSA increase >2 ng/ml in the year before diagnosis conferred a high risk of death from prostate cancer despite radical prostatectomy [68]. Loeb et al (2012) confirmed the adverse significance of a rapidly rising PSA, reporting that patients with two PSA velocity measurements of >0.4 ng/mL/year had an 8-fold increased risk of prostate cancer and a 5.4-fold increased risk of Gleason 8-10 disease on biopsy, adjusting for age and PSA level [69]. The same author also concluded from an analysis of the Baltimore Longitudinal Study of Aging that, since PSAV rose continuously with increasing PSA and was significantly higher in cancers than controls for PSA levels <3 ng/mL and 3-10 ng/mL, the PSA level should be taken into account when interpreting PSAV [70].

Figure 18: PSA Velocity summary

- **A PSA increase >0.75 ng/ml in year = an increased risk of having cancer** [66] **but, for men with LUTS taking 5-α-reductase inhibitors (finasteride & dutasteride) which reduce serum PSA by ~50%, sustained increases are more predictive for prostate cancer**
- **An increase in PSA of 0.3 ng/ml from nadir as a trigger for biopsy maintained 71% sensitivity & 60% specificity for PCa in men receiving dutasteride** [42]
- **A PSA increase of >3.3% pa = an increased risk of cancer** [16, 47]
- **A preoperative PSA velocity >0.35 ng/ml/year = increased risk of biochemical progression following RP** [67]

3. Free/total PSA: This test measures the percentage of free (or unb
ound) PSA in the blood, and compares it with the percentage bound to proteins (α1 antichymotrypsin and α2 macroglobulin). Most of the PSA in blood is bound so the lower the ratio of free to total PSA or the percentage of free PSA, the higher the likelihood that the patient has prostate cancer. The proportion of free PSA in seminal fluid is much higher than in serum, consistent with its physiological role in liquefaction [71]. Although levels of complex-PSA do not significantly correlate with PSA in semen in young men, levels of free PSA do. With ageing, blood levels of complex-PSA, but not free-PSA, increase [72]. The free/total PSA blood test can help to discriminate between patients with indeterminate PSA levels (4-10.0 ng/ml) indicating those who are at the greatest risk of having prostate cancer, in particular aggressive disease [73, 74]. However, as with all these modifications to PSA, the predictability remains less than perfect.

Figure 19: Free/Total PSA summary

- **Men with prostate cancer have a greater fraction of complexed PSA and a lower free PSA than men without prostate cancer**
- **Free:Total PSA can be helpful in the case of a high PSA and a negative prostate biopsy**
- **Free PSA is unstable: the assay must be frozen to -20°C within 3 hours otherwise the free fraction reduces**
- **Chronic prostatitis may also cause a reduced Free:Total ratio**

4. PSA density: PSA density relates the concentration of serum PSA to the volume of the prostate and is thus a measure of serum PSA in relation to prostatic size [75]. Most neoplastic prostate glands produce higher serum PSA levels per unit mass than do non-malignant glands. Consequently, a serum PSA of 5.0 ng/ml in a patient with a 20 gram prostate is more worrisome for cancer than that a PSA of 5.0 ng/ml in a man with a 60 gram prostate, especially if there is a predominance of transitional zone tissue (BPH) in the latter.

To determine the PSA density, a PSA level is obtained and is divided by the volume of the prostate, as estimated by transrectal ultrasound (**TRUS**). A value >0.15 ng/ml per gram of prostate tissue is considered worrisome for prostate cancer. PSA density has been extended to include transition zone measurements in relation to the overall size of the prostate as the transition zone is the site in which BPH develops with ~25% of prostate cancers also arising in this zone. The larger the transition zone in relation to the overall size of the gland, the lower the likelihood of prostate cancer, other things being equal.

Figure 20: PSA Density summary

-PSA Density = PSA divided by prostate volume determined by TRUS

5. Prostate Health Index: The most recent variation on the PSA blood test is the Prostate Health Index or ***phi***., formulated by having the value of a truncated form of the the PSA molecule (proPSA) as the numerator and the free PSA value as the dominator multiplied by the total PSA level to give a *phi* reading. *phi* is claimed to better predict prostate cancer risk than the total PSA, but this contention needs to be confirmed in large, multicentre, prospective trials. A potential advantage of *phi* is that it stratifies according to risk

Figure 21: Prostate health index [*phi*] = [−2]proPSA / fPSA) × PSA$^{1/2}$

- **For PSA 2–10 ng/ml, sensitivity, specificity and AUC (0.703) of *phi* exceeded those of total PSA and % fPSA. Increasing *phi* was associated with an increased risk of prostate cancer** [76]
- **Including the prostate health index in a multivariable logistic regression model based on patient age, prostate volume, digital rectal examination and biopsy history significantly increased predictive accuracy by 7% from 0.73 to 0.80 (p <0.001)** [77]
- ***phi*** **0-22.9 = low probability of prostate cancer (8.4%)**
  23-44.9 = moderate probability of cancer (21%)
  >45 = high probability of cancer (44%)

However, claims for phi remain to be verified through large, multicentre, prospective trials with detailed health economic analyses to determine clinical applicability [78]

Figure 22: Summary: Prostate Specific Antigen (PSA) & Derivatives

- **Is a continuous variable with no cut point** [38]
- **Doesn't distinguish between those with and without cancer or identify those with cancer who will benefit from curative treatment** [40]
- **PSA Velocity = rate of change of PSA: A PSA increase >0.75 ng/ml in year = an increased risk of having cancer** [66]
- **PDA Density: PSAD = PSA divided by prostate volume determined by TRUS**
- **Free:total PSA: The higher the free component, the lower the likelihood of cancer but chronic prostatitis may also cause a reduced Free:Total ratio**
- **Prostate Health Index (*phi*) : may predict the risk of prostate cancer better compared with total PSA, but its role in prostate cancer screening remains to be verified through large, multicentre, prospective trials**
- **Total PSA = the single most significant, clinically used predictive factor for identifying men at increased risk of harbouring cancer [61]**

6. Digital Rectal Examination: Traditionally, palpation of the prostate by digital rectal examination (**DRE**) was the manner by which a diagnosis of prostate cancer was suspected. In historical series, up to 50% of

palpable masses were attributable to prostate cancer [14,79, 80]. Although DRE by itself is a poor method for diagnosing this malignancy [81, 82], it does still have an important diagnostic role, reflected by its continued inclusion in prostate cancer guidelines, as up to 25% of tumours are detected in men with normal PSA levels [83]. Unfortunately, when a prostate cancer is diagnosed based on a palpable tumour, the risk of the patient already harbouring metastatic or locally advanced malignancy is considerable [84-6]. **However, a PSA-based prostate cancer detection strategy which omits DRE runs the low risk of missing some curable cancers** [39].

7. The PCA3 test: The non-coding RNA PCA3, originally called DD3, is highly specific to prostate cancer, with over-expression [87-90] in a number of different cohorts. The first part of a voided urine specimen is collected immediately following firm rectal examination or prostatic massage [91, 92] and PCA3 RNA measured using a PCR-based assay. One criticism of the PCA3 test is that is unlikely to obtain prostatic fluid from the anterior part of the prostate, mirroring a deficiency with TRUS-guided biopsies which are also posteriorly-focussed, especially in large prostate glands. Although the "PCA3 urine test" has been reported to improve identification of serious disease compared with total PSA in a pre-screened population, its role in initial assessment of patients suspected of having PCa has yet to be established [93, 94].

Figure 23: PCA3 results in Post-Prostatic Massage Urines [88, 90, 95-7]

Study	Sensitivity	Specificity	Neg Predictive Value	Number
Hessels et al, 2003	67%	83%	90%	108
Fradet et al, 2004	66%	74%	84%	517
Tinzl et al, 2004	82%	76%	87%	158
Van Gils et al, 2007	65%	66%	80%	534
Van Gils, et al 2007	65%	82%	80%	67

Recently, data from analysis of the fusion gene TMPRSS2:ERG and PCA3 from prostatic fluid obtained following firm digital rectal examination/prostatic massage, has been combined with serum PSA to produce a test which is being marketed commercially. Published supportive data is limited but preliminary findings indicate that the combination provides an 80% sensitivity and 90% specificity with an AUC of 0.88 for the 3 parameters [98-100].

However, Stephan *et al.* [101] examined PCA3, TMPRSS2:ERG and *phi* in an artificial neural network. The addition of TMPRSS2:ERG to PCA3 in urine following firm digital rectal examination only marginally improved detection of 110 men with PCa compared with 136 with non-cancer. PCA3 had the largest AUC (0.74) which was not significantly different to the AUC of *phi* (0.68) although the latter showed somewhat lower specificities than PCA3 at 90% sensitivity. A combination of PCA3 and *phi* only moderately enhanced diagnostic power with modest AUC gains of 0.01-0.04 for PCa at first or repeat prostate biopsies.

8. Magnetic Resonance Imaging (MRI): The role of MRI in prostate cancer is emerging rapidly [102-5]. As an initial form of detection, cost is the biggest handicap to widespread application with this factor compounded if MRI-guided biopsies are performed on the MRI examination table. A combination of anatomical (T2-weighted) images with at least two of the three functional MRI parameters (diffusion-weighted imaging, dynamic contrast-enhanced imaging and spectroscopy) has been estimated to identify approximately 90% of moderate to high risk lesions but is less reliable for detecting small (<0.5 cc) and lower risk tumours [103]. At a European Consensus Meeting, a structured reporting scheme, prostate imaging-reporting & data system (**PI-RADs**), based on the BI-RADS classification for breast imaging [102], was agreed for communicating the probability of malignancy. In this 5-point scheme PI-RADS 1 lesions are categorised as most probably benign, PI-RADS 2 probably benign, PI-RADS 3 intermediate, PI-RADS 4 probably malignant and PI-RADS 5 highly suspicious of malignancy [106].

MRI has the potential to improve the sensitivity of detection of intermediate and high risk prostate cancer, especially in the anterior zone of the prostate where cancers may not be detected by transrectal ultrasound guided biopsy techniques.

In patients with a rising PSA and previous negative prostate biopsies, MRI followed by MRI guided biopsies has identified prostate cancer in 41-59% of this patient cohort [107, 108]. MRI guided biopsies also

improves the pre-treatment accuracy of Gleason grade compared with a standard 10 core TRUS technique. [109]. However, targeted biopsies will miss up to 10% of significant tumours [110].

Interpretation of prostate imaging requires expertise and collaboration [111. 112]. Although the degree of restriction of the tumour with diffusion-weighted imaging can give a guide to the aggressiveness of the malignancy, mpMRI is not accurate enough to consistently grade tumour aggressiveness so biopsies continue to be required [113] .Both MRI-TRUS fusion and cognitive approaches to transrectal and transperineal biopsies continue to be performed with the risk of urosepsis lower with the latter, but transperineal biopsies require a general anaesthetic. In addition, the considerable costs of mpMRI are compounded if MR-guided biopsies are performed on the MR table. Experience to date indicates fewer than 30% with a 'normal' PIRADS 1-2 MRI will have prostate cancer detected, with the majority of these reported as low grade or low-volume disease. Thus, MRI has great potential for second-line screening.

Using MRI in a screening setting has the potential to decrease the number of men with an elevated PSA requiring a biopsy. As MRI aids in identifying low risk, low volume prostate cancer, MRI in a screening program promises to decrease the number of men diagnosed with insignificant prostate cancer and minimise overtreatment in this cohort. However the results of large multi-centre trials are required before the utility of multi-parametric MRI (**mpMRI**) can be determined and its optimal role in the diagnostic process established.

9. Definitive diagnosis requires biopsies: Once the possibility of prostate cancer is raised, whether by rectal examination, PSA parameters, or a combination of both, prostate biopsies are required as part of the contemporary two-step early-diagnostic approach. TRUS imaging permits spatial positioning of spring-loaded biopsy needles to provide a methodical approach for obtaining tissue cores for standard histopathology**.** With few exceptions, TRUS imaging by itself is non-diagnostic as only gross changes register as an abnormal appearance on the monitor. The number of biopsy cores taken is important with the chance of missing a cancer by standard sextant biopsy estimated to be approximately 25% [114] so that, more recently, the numbers of cores recommended are at least 8 and preferably a minimum of 10-12. In addition, it is advocated that biopsies should be directed laterally and that they should include the anterior horns of the peripheral zone [114-121]. Many urologists routinely take 12 biopsy cores now to minimise the likelihood of missing cancer.

The issue of repeat biopsies was addressed by Djavan *et al* (2001) particularly in relation to when it is reasonable to stop repeating the biopsies. Cancer-detection rates in 1051 men biopsied were 22%, 10%, 5% and 4% with 1-4 TRUS biopsy sessions with 58%, 60.9%, 86.3% and 100%, respectively, having organ-confined disease. Recently, Yanke et al (2005) extended experience with the Kattan Nomogram to predict the likelihood of a positive finding at a subsequent biopsy session. Predictor variables studied in the nomogram were patient age, family history of prostate cancer, prostate specific antigen slope, months from initial negative biopsy session, months from previous negative biopsy session, cumulative number of negative cores previously taken and previously detected high grade PIN or atypical small acinar proliferation. The authors evaluated a total of 356 repeat biopsy procedures for 230 patients. The mean number of total cores per patient was 17.9 with 78 men having biopsies positive for cancer. The area under the ROC curve was 0.71, which was greater than any single risk factor [122].

One of the problems facing clinicians is when to stop from recommending biopsy not only in terms of patient age and overall life-expectancy but also with respect to the increasing likelihood of a positive histological diagnosis in those biopsied. Schaeffer et al (2009) attempted to address this issue by sourcing the Baltimore Longitudinal Study of Ageing. Their patient group consisted of 849 men, 122 with and 727 without prostate cancer. They reported that no participants between 75 and 80 years old with a PSA lower than 3.0 ng/ml died of prostate cancer, but men of all ages with a PSA of 3.0 ng/ml or greater had a continually increasing probability of death from prostate cancer. Not unexpectedly, the time to death or diagnosis of aggressive prostate cancer after age 75 years was not significantly different between PSA categories of 3 to 3.9 and 4 to 9.9 ng/m.l. Of the 108 subjects older than 75 years with a PSA of 3 ng/ml or greater, 10 died of prostate cancer and 18 had high risk disease. In this group, 90 men did not have a diagnosis of high risk prostate cancer, including 75 who were never diagnosed with cancer (median time to censoring 12.5 years) and 15 who were diagnosed with non-high risk cancer (median time to censoring 17 years) [123].

Routine practice involves peri-operative antibiotic prophylaxis with a pre-procedural enema to ensure that the rectum is empty. Since TRUS biopsies are unpleasant and uncomfortable, many urologists use anaesthesia (local or neurolept 'light' general) as a routine.

Changing morbidity of biopsy diagnosis: Periprocedural symptoms such as haematuria, rectal bleeding and haematospermia are frequent, being experienced by over 50% of men having TRUS biopsies, but are almost always benign and self-limiting [124-36]. Infectious complications following this procedure are less common but are being reported more often, with the causative mechanism believed to be inoculation of the prostate, blood vessels and urine with bacterial flora from the rectal mucosa and subsequent systemic dissemination [127, 128]. The most usual clinical manifestations are fever and urinary tract infection, with hospital admission and bacteraemia occuring less frequently (0.3%): urosepsis requiring Intensive Care Unit admission (0.08%) or rarely death [127, 128]. More recently, there has been concern expressed that hospital admissions due to post-TRUS biopsy may be rising, with one study reporting a 3-fold increase from 0.55% across 2002-2009 to 2.15% across 2010-2011 [127, 129]. Changing bacterial resistance patterns and antibacterial practices have contributed to the spectrum of infectious complications with the infection rate being much higher in certain population groups such as men who have been taking antibacterial drugs prior to the biopsy and people who have been in South East Asia and Mediterranean countries within the past 6-12 months [130-132].

A recent prospective New Zealand study reported that drug resistance rates for patients who required intensive care admission for sepsis following TRUS biopsy were 43% for gentamicin, 60% for trimethoprim-sulphamethoxazole (60%) and 62% for ciprofloxacin as well as 19% for all 3 agents in combination. E. coli sequence type 131 clone was implicated as being particularly problematic, accounting for 41% of all E. coli isolates after TRUS biopsy [133]. The changing patterns of drug sensitivities and reports of low resistant rates to drugs such as carbopenems for patients with unresolving sepsis [134] has resulted in some advocating for the use of these drugs as prophylactic agents just prior to TRUS biopsy. However, adoption of such a strategy runs the risk of decreasing the number and effectiveness of those pharmaceutical agents currently kept in reserve for patients with overwhelming sepsis. An alternative approach being used by a number of urologists is to employ a transperineal approach for prostatic biopsies as routine, despite a longer procedural time compared with TRUS biopsy in addition to a need for deeper anaesthesia.

Gleason scoring: The biopsy result provides important information for the patient and clinician on which to base management decisions [135, 136]. In addition to the pre-biopsy PSA level, important prognostic factors include tumour volume (percentage of the core involved and the number of positive cores) and the histological grade of the tumour. Increasing tumour burden and poor histological differentiation are associated with a higher risk of metastatic disease, an increased chance of post-treatment failure, and a worse overall prognosis [137-9].

Histological analysis is based on the Gleason grading system that is regarded as the 'gold standard' for classifying prostatic adenocarcinoma [140]. Using architectural patterns, the tumour is assigned a rating between 1 and 5, with higher numbers representing less differentiated, more aggressive tumours (see Table 1.). A single prostate can harbour multiple foci of different histologic patterns of adenocarcinoma, and it is possible to have Gleason grade 3, 4 and 5 patterns in the same specimen: 85% of prostate tumours are multifocal. The Gleason score (or Gleason sum) is generated by combining the values of the first and second most common (dominant and subdominant). grades (i.e.: in a tumour with mostly Gleason grade 3 and some Gleason grade 4 disease, the Gleason score will be 3+4 = 7), assessed by the uropathologist using low-power light microscopy. The Gleason score provides important prognostic information.

Table 1: Gleason grading system

Grade	Histology	Biologic Behaviour
1 & 2	closely-packed glands forming a nodule	Indolent disease, rarely progressive
3	small infiltrating glands, complete lumen formation	most common pattern; less aggressive than pattern 4

4	fused glands, incomplete lumen formation	indicates tumour progression
5	solid sheet or single cells, no lumen formation	Very aggressive, late stage

The presence of Gleason grade 4 or greater histology carries a significantly poorer prognosis [141, 142**]**. Stamey demonstrated that Gleason score 7 tumours can be stratified, based on the amount of grade 4 disease [143]. Those with <50% grade 4 behave similarly to Gleason score 6 (more favourable), while those with >50% grade 4 act like Gleason score 8 (unfavourable) cancers. The transition from Gleason 3 to Gleason 4 appears to be a common event and represents a critical juncture in which the tumor acquires a significantly more aggressive phenotype. In the large majority of instances, gray-scale TRUS does not permit differentiation between cancer and non-cancer so TRUS and transperineal biopsies are taken blindly. Consequently, there is a possibility that small tumours may be missed, despite careful spatial positioning of biopsy needles with multiple cores taken. Furthermore, in large glands especially, the anterior part of the prostate may be poorly sampled via the transrectal route so, for these reasons, it is not surprising that the histology from biopsies and radical prostatectomies may differ. In these instances, the Gleason score from the radical prostatectomy specimen is usually higher (upgrading) but downgrading is also observed.

PIN: Prostatic intraepithelial neoplasia [PIN] is believed to be a precursor of prostate cancer, given the strong association between high grade PIN and prostatic adenocarcinoma [144-6]. The presence of high grade PIN is often indicative of the presence of prostate cancer. It has been shown that more than 80 percent of prostates with adenocarcinoma also contain high-grade PIN (PIN-11 & III). High-grade PIN has cytologic features resembling cancer and carries many of the genetic alterations of prostate cancer. The finding of high-grade PIN alone in a biopsy has been cited as an indication to proceed with repeat biopsies given the high co-frequency between high-grade PIN and carcinoma. However, in current practice, the predictive value of PIN in finding cancer on subsequent biopsies has declined, probably due to the extended biopsy techniques yielding higher rates of initial cancer detection [147]. A diagnosis of PIN by itself is certainly insufficient for a patient to undergo either radical prostatectomy or radiotherapy.

Atypical prostatic glandular proliferations: Foci of atypical glands, also labeled 'atypical small acinar proliferation of uncertain significance', have features suspicious for, but not diagnostic of, cancer. These encompass a variety of lesions including benign mimickers of cancer, high-grade prostatic intraepithelial neoplasia (PIN), and small foci of carcinoma which, for a variety of reasons, cannot be accurately diagnosed. The reported incidence of these lesions on prostate needle biopsies is 1.5% to 5.3% [147]. Patients with atypical glands on needle biopsy have a high risk of harbouring cancer. The reported incidence of prostate cancer from repeat biopsies has ranged from 34 to 60%. [14-9]. Following an atypical diagnosis, biopsies need to be repeated [150].

TNM Staging system: Once a diagnosis of prostate cancer is made, it must be determined whether the patient is a candidate for potentially curative treatment (surgery or radiation). This depends upon several factors, including general health and projected longevity in conjunction with the likelihood that the cancer is still localized within the prostate and has not yet metastasized. The most important factor, however, is the patient's decision after he has considered the 'pros and cons' of the various choices as they relate to him (see below).

Currently, the TNM system (Table2.) is used for staging, and prostate cancers can be assigned both a *clinical stage* and, subsequently should the prostate be removed surgically, a *pathologic stage*. This differentiation is important with the clinical and pathological stage designated by the letters 'c' and 'p', respectively, preceding the stage denotation (e.g. cT2a = clinically, tumour is palpably involving one lobe of the prostate or less).

Table 2. TNM staging classifications	
Primary Tumour	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour

T1	Clinically inapparent tumour not palpable not visible by imaging
T1a	Incidental tumour in < 5% of TUR tissue
T1b	Incidental tumour in > 5% of TUR tissue
T1c	Needle biopsy prompted by elevated PSA
T2	Organ confined
T2a	Tumour involves one half of one lobe or less
T2b T2c	Tumour involves more than half of one lobe but not both lobes Tumour involves both lobes
T3	Tumour extends beyond the prostatic capsule
T3a	Extracapsular, unilateral and bilateral
T3b	Tumour invades seminal vesicles (s)
T4	Tumour invades bladder neck, sphincter, rectum, pelvic side wall
Lymph Nodes	
Nx N0	Regional nodes were not assessed No regional nodes
N1	Regional node metastases
Distant Metastases	
Mx M0	Regional nodes not assessed No Metastases
M1 M1a M1b M1c	No distant Non-regional lymph nodes Bone(s) Other site(s) with or without bone disease

VI. POTENTIAL BENEFITS & HARMS FROM PSA TESTING

One of the most contentious topics in medicine is whether or not to test for prostate cancer. The key question that needs to be answered is whether a diagnosis of prostate cancer is going to benefit the patient with the qualification that the diagnostic process and treatment should not be worse than the unwanted effects of the disease. Determining who will benefit from testing is very difficult as it is impossible to know exactly how long an individual patient will live and generally both patients and clinicians tend to be optimistic in their estimations.

(A) Early diagnosis and treatment with curative intent and prevention of subsequent death from Prostate Cancer

In addition to attributing a slow but continuing reduction in prostate cancer mortality in many western countries to, at least in part, widespread PSA testing, most of the evidence proffered in support is from low-level cohort studies, many of which have been retrospective. One notable, large study undertaken prospectively has been in the the Tyrol. Unlike in the rest of Austria, PSA testing has been freely available in Tyrol since 1993 for men 45-75 years with 86.6% of eligible men having been tested at least once since its inception 151[]. Compared with the rest of the country, there has been a decreasing trend in prostate cancer mortality which, in 2005, was significantly greater in the Tyrol compared with the rest of Austria (P = 0.001). Prostate cancer deaths were 54% lower than expected in this region compared with the rest of Austria, with a significant migration to lower stage disease. These better results in Tyrol have been attributed to early detection, consequent down-staging and effective treatment.

Population studies: However, the evidence for and against PSA screening is usually based on the findings from 6 mass or whole of population screening trials and meta-analyses of their findings. These studies were the Prostate Lung, Colorectal and Ovarian (**PLCO**) Screening Trial [152, 153], the European Randomised Study of Screening for Prostate Cancer (**ERSPC**) [40, 154], Göteborg [155], Norrköping [156], Stockholm [157] and Quebec trials [1518]

The studies were very different in design and in adherence to protocols. For example, men were invited only once in Stockholm Study and a minority of those with screen-detected prostate cancer were treated

with curative intent [157]. The participation rate was only 24% in the Quebec study [158]. The Norrkoping Study commenced in 1987 with DRE as the only screening test performed up to the third (1993) and the final fourth screening time (1996) when PSA was included. Fewer than 500 men had two PSA measurements & none had more than two. Furthermore, final results were adjusted for the large difference in age at randomisation between the study groups [156].

Thus, in terms of trials with reasonable rigour, there are only 3 viz. the ERSPC, the Göteborg (which is also included as part of the larger ERSPC study) and the the PLCO trial. In the PLCO trial only 85% in the screening arm had a PSA test. In addition 52% of the control arm had a PSA test, significantly contaminating this arm of the trial and resulting in the study being underpowered [153]. Furthermore, the follow-up for these trials varied greatly with only one (Göteborg) having an adequate median follow-up period, detailed below (Table 3.)

PLCO: **median 11.5 years, maximum 13 years** [152]
ERSPC: **median 9.8 years, maximum 11 years** [154]
Göteborg: **median 14 years, maximum 14 years** [155]
Norrköping: median 6.3 years, maximum 20 years [156]
Stockholm: median 12.9 years, maximum 15 years [157]
Quebec: median 7.9 years, maximum 13 years [158]

Table 3	**ERSPC**	**PLCO**	**Göteborg**
Number studied	162 243	76,693	20,000
Recruitment sites	8 countries	10 US centres	one
Age	50-69	55-74	50-64
PSA screening interval	4 yearly	yrly x6 DRE x4	2 yearly
Biopsy trigger	3.0 ng/ml	>4 ng/ml	3.4, 2.9, 2.5 ng/ml
Contamination rate	15%	52%	3%

Since the studies are so different in so many ways, the validity of including them in a meta-analysis has been questioned [159] Given the long natural history of prostate cancer in comparison with those of other malignancies and the prevalence of the disease with increasing age, few would advocate screening each and every member of a population [160-2] i.e. mass population screening as reported in these trials.

Figure 24: Mortality findings summary from 3 most relevant RCTs

- **-None of these trials had adequate statistical power to detect an overall survival benefit with PSA screening**
- **-deaths from conditions other than prostate cancer dominated causes of death undermining ability to show an advantage for PSA screening**
- **-PLCO* At a median follow-up of 11.5 years, of 76 685 men randomised (38 340 in the intervention arm and 38 345 in the control arm)** [152]
  - deaths from all causes other than prostate, lung, and colorectal cancers were 5783/38 340 (15%) in the intervention arm: 5982/38 345 (15.6%) in the control arm
  - Of those who died, 158/5783 (2.7%) & 145/5982 (2.4%) in the control arm, died from prostate cancer, respectively
  - cumulative mortality rates from prostate cancer in the intervention and control arms were 3.7 and 3.4 deaths per 10 000 person-years
  * "Approximately 92% of the study participants were followed to 10 years and 57% to 13 years."
- **-ERSPC At a median follow-up of 11 years, 31 318 of 162,388 (19.3%) of men between 55 & 69 yr who underwent randomization had died** [154]
  - 13 917/72 891 (19%) in screening group: 17 256/89 352 (19%) in control group

- Of those who died, 299/13 917 (<u>0.4%</u>) & 462/17 256 (<u>0.5%</u>) died from prostate cancer, respectively
- The absolute reduction in mortality in the screening group was 0.10 deaths per 1000 person-years or 1.07 deaths per 1000 men who underwent randomization.
- To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected

- **<u>Göteborg</u> At a <u>median follow-up of 14 years</u>, 3 963 of 20 000 (<u>19.8%</u>) of men between 50 & 64 who underwent randomisation had died** [155]
  - 1981/10 000 (<u>19.8%</u>) in the screening group: 1982/10 000 (<u>19.8%</u>) in the control group died
  - Of those who died, 44/1981 (<u>2.2%</u>) & 78/1982 (<u>3.9%</u>) died from PCa, respectively
  - **Overall the relative risk reduction in mortality was 44% for men randomised to screening compared with controls at 14 years.**
  - **Overall, 293 men needed to be invited for screening and 12 to be diagnosed to prevent one prostate cancer death (Figure 25)**

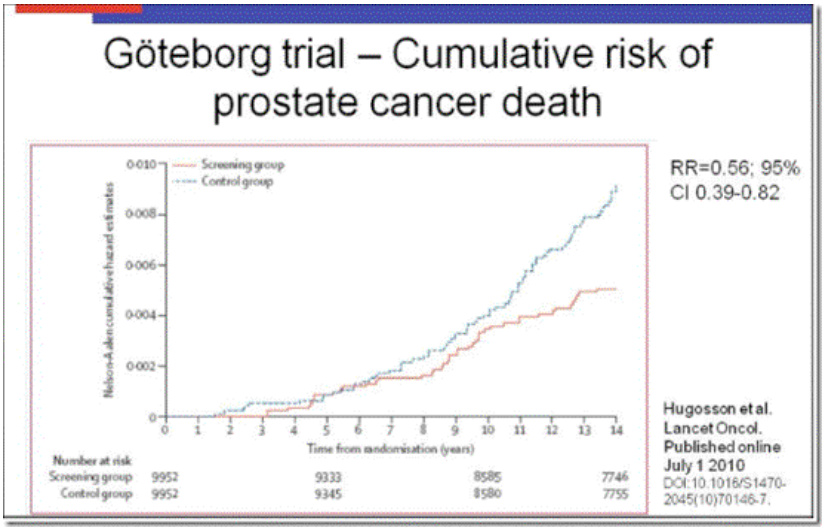


Figure 25: Other factors to be appreciated when relating to individual patients: the longer the time from randomisation, the further apart are the tracings

Findings are based exclusively on systematic reviews (meta-analyses) of 6 randomised controlled [RCTs] PSA screening trials with 8 systematic appraisals of these RCTs [163] **<u>but</u>**

- **RCTs are not the only form of evidence: absence of RCT evidence does not equal evidence of absence**
- **These were <u>mass population</u> screening trials** – no patient selection - **as opposed to <u>opportunistic & selective</u> screening** (which most people advocate)

Survival estimation: There are several approaches that can be used to improve a rough clinical estimation of a patient's life-expectancy. Validated instruments are available such as a modified form of the Total Illness Burden Index for prostate cancer by Litwin (et al, 2007) [164] and the Charlson Comorbidity Index, which seems to be most useful in men<65 years undertaking initial treatment, in particular radical prostatectomy [165, 166]. Although these are not used commonly in clinical practice, they do provide one option. Froehner et al (2013) recently examined available comorbidity assessments to determine which may best assist in the treatment choice for elderly men with prostate cancer. A total of 1,106 men aged 65 years or older who underwent radical prostatectomy for clinically localized prostate cancer was examined with overall survival as the study endpoint. They concluded that the American Society of Anesthesiologists (ASA) physical status classification tool, supplemented by a list of more clearly defined concomitant diseases, could be useful in clinical practice and outcome studies [167].

Another approach is to refer to Life Expectancy Tables (such as Table 4 below modified from the Australian Bureau of Statistics website 2013). Such tables do not take into account an individual's comorbidities.

Table 4 Life Expectancy table for Australia

Age	2000-2002	2001-2003	2002-2004	2003-2005	2004-2006
35	44.08	44.36	44.61	44.96	45.17
36	43.14	43.41	43.67	44.02	44.22
37	42.20	42.47	42.72	43.07	43.27
38	41.25	41.52	41.77	42.12	42.32
39	40.31	40.58	40.83	41.18	41.37
40	39.37	39.63	39.88	40.23	40.43
41	38.43	38.69	38.94	39.29	39.49
42	37.49	37.75	38.00	38.35	38.55
43	36.56	36.82	37.06	37.42	37.61
44	35.63	35.89	36.13	36.49	36.68
45	34.70	34.96	35.20	35.56	35.74
46	33.78	34.04	34.28	34.64	34.82
47	32.86	33.12	33.36	33.71	33.89
48	31.94	32.20	32.44	32.80	32.98
49	31.02	31.29	31.53	31.88	32.06
50	30.11	30.37	30.62	30.97	31.15
51	29.21	29.47	29.71	30.06	30.24
52	28.30	28.56	28.81	29.16	29.34
53	27.41	27.67	27.91	28.26	28.45
54	26.52	26.77	27.02	27.37	27.55
55	25.64	25.89	26.13	26.49	26.67
56	24.76	25.01	25.25	25.61	25.79
57	23.90	24.15	24.38	24.74	24.92
58	23.05	23.29	23.52	23.87	24.05
59	22.20	22.44	22.67	23.02	23.20
60	21.37	21.61	21.83	22.18	22.35
61	20.55	20.78	21.00	21.35	21.51
62	19.73	19.97	20.18	20.52	20.69
63	18.94	19.17	19.37	19.71	19.87
64	18.15	18.38	18.58	18.91	19.07
65	17.37	17.60	17.79	18.13	18.27
66	16.61	16.84	17.02	17.35	17.50
67	15.87	16.09	16.26	16.59	16.73
68	15.14	15.35	15.52	15.84	15.97
69	14.42	14.62	14.79	15.10	15.23
70	13.72	13.92	14.08	14.38	14.51
71	13.04	13.23	13.38	13.68	13.80
72	12.38	12.56	12.71	12.99	13.10
73	11.74	11.90	12.05	12.32	12.42
74	11.11	11.27	11.41	11.67	11.76
75	10.51	10.65	10.78	11.04	11.12
76	9.92	10.06	10.18	10.43	10.50
77	9.36	9.49	9.60	9.83	9.90
78	8.82	8.93	9.03	9.26	9.32
79	8.29	8.40	8.49	8.70	8.76
80	7.79	7.89	7.97	8.17	8.22
81	7.31	7.39	7.47	7.66	7.70
82	6.84	6.92	6.99	7.18	7.21
83	6.40	6.47	6.53	6.72	6.75
84	5.98	6.04	6.10	6.28	6.31
85	5.59	5.64	5.69	5.87	5.90
86	5.23	5.27	5.32	5.49	5.50
87	4.90	4.93	4.98	5.12	5.12
88	4.61	4.63	4.66	4.77	4.77
89	4.34	4.35	4.38	4.46	4.45

90	4.10	4.10	4.12	4.18	4.17
91	3.89	3.88	3.88	3.93	3.92
92	3.69	3.67	3.67	3.72	3.71
93	3.51	3.48	3.47	3.52	3.53
94	3.34	3.30	3.30	3.33	3.37
95	3.18	3.14	3.13	3.16	3.24
96	3.03	2.99	2.98	3.00	3.13
97	2.89	2.85	2.84	2.85	3.04
98	2.76	2.72	2.71	2.72	2.94
99	2.65	2.60	2.58	2.59	2.84

In terms of likelihood of dying from cardiovascular disease, whether or not a man has started to have erectile dysfunction may serve as a surrogate indicator. One recent large study indicated that the median time to death from a cardiovascular cause from the onset of erectile dysfunction (**ED**) was 10 years [168] since the reason for ED in the majority of cases is impaired arterial flow [169].

Figure 26: Factors to consider when deciding to test for prostate cancer include

- **In the Scandinavian randomised trial of Radical Prostatectomy & watchful waiting**
  At a median follow-up of 13.4 years, 63 in the surgery group and 99 in the watchful-waiting group died from prostate cancer; the relative risk was 0.56 (95% confidence interval [CI], 0.41 to 0.77; P=0.001). The number needed to treat to prevent one death was 8 [170]
- The benefit of surgery with respect to death from prostate cancer was largest in men younger than 65 years of age (relative risk, 0.45) and in those with intermediate-risk prostate cancer [170]

  At a median of 12.8 years of follow-up in an earlier report on this trial, men with more than 2 significant co-morbidities did not benefit from PSA testing [171]

- **In a follow up analysis of the PLCO study, there was a striking mortality benefit in men with minimal or no co-morbidities** viz. a 44% drop in PCa-specific mortality & a number needed to treat of only 5. However, for men with at least one significant co-morbidity, there was no significant difference in PCa mortality [172]

But what constitutes a significant comorbidity? "a condition or complaint either coexisting with the principal diagnosis or arising during the episode of care or attendance at a health care facility" [173]
How do you assess it?

- **Crawford et al chose an expanded definition** that included both 'standard' Charlson comorbidity index conditions and hypertension (even if well controlled), diverticulosis, gallbladder disease and **obesity [172]**
- **But when the analysis was repeated using only validated measures of comorbidity (Charlson comorbidity index conditions only), there was no interaction** [174]
- **A simple patient-reported index, a modified form of the Total Illness Burden Index modified for prostate cancer** [164 **vs Charlson Comorbidity Index** [165, 166]
- **The American Society of Anesthesiologists (ASA) physical status classificationhas been recommended to serve as a basis of assessing suitability for radical prostatectomy in men >65 years** [167]
- **Onset of erectile dysfunction may serve as an indictor of limited life expectancy due to cardiovascular death** [168, 169]
- **Morbidity of (frequently repeated) TRUS & T/P biopsies** TRUS biopsy infections in 4.5%: 48% had rectal swabs showing Ciproflaxacin resistant bacteria [128-132]
- **High over-diagnosis rate: active surveillance may decrease the concern of over detection and over treatment**

Psychosocial aspects pervade all aspects of detection & treatment

Recent studies have reported psychological distress levels indicative of 'caseness' close to the time of diagnosis from 10% to 23% [175]. Bill-Axelson and colleagues in an eight year longitudinal study reported that although extreme distress was not common in men with localised prostate cancer, 30–40% of men reported ongoing health-related distress and worry about their health, feeling low, and sleep disturbance [176]. Risk of suicide may be increased in the first six to twelve months after the

diagnosis of prostate cancer [177, 178]. Screening for distress and referral to appropriate support services is recommended in men diagnosed with prostate cancer [179].

Decisional conflicts impact upon continuation of Active Surveillance [180, 181]

When making decisions about treatment for prostate cancer men tend to rely on lay beliefs about cancer with the opinion of the clinician highly influential [181]

A systematic review of psychosocial interventions for men with prostate cancer and their partners found that group cognitive-behavioural and psychoeducational interventions were helpful in promoting better psychological adjustment and quality of life (QOL) for men with prostate cancer. [182]

- **Reassurance: PSA level <1ng/ml at the age of 65 years** [41] **or <3 ng/ml at the age of 75 years have a very low chance of contracting fatal cancer** [123]

(B) Early diagnosis and treatment with curative intent and lessening the likelihood of metastases occurring

The recently completed PSA Evaluation Report by the National Health and Medical Research Council (**NHMRC**) of Australia concluded that, although there was some inconsistency in the definition of prostate cancer metastases across the RCTs, overall, the evidence indicates that PSA testing reduces the risk of having metastases present at the time of diagnosis of prostate cancer. The NHMRC review focused on the RCTs above in its considerations, but did not conclude that intervention with curative intent reduces the likelihood of *subsequent* metastases [163]. However evaluation of evidence from multiple non-RCTs has reported that PSA testing and intervention with curative intent does reduce the likelihood of subsequent metastases.

There are very few RCTs for prostate cancer treated with curative intent. Bill Axelson et al (2014)[170] recruited patients from 14 centres in Sweden, Finland and Iceland: The trial is noteworthy since the study included patients detected with prostate cancer at a later stage than is currently diagnosed: only 12% had impalpable disease on DRE - detected by what are now outmoded methods. The results are summarised below:

Figure 27: Swedish trial of Radical Prostatectomy versus Watchful Waiting [170, 183]

- **From October 1989 through February 1999, 695 men with 'early' PCa were randomly assigned to watchful waiting or radical prostatectomy**
- **Eligibility required patients to be**
  - **<75 yrs of age and a life expectancy >10 years: mean age was 65 yrs**
  - **Clinically localised disease (T1 or T2, using IUCC 1978 criteria)**
  - **Diagnosis by core biopsy or fine needle aspiration cytology**
  - **Well or moderately differentiated adenocarcinoma (WHO classification)**
  - **PSA <50 ng/ml : mean PSA was 13 ng/ml**
  - **a negative bone scan**
- **During a median of 13.4 years, 200 of the 347 men in the RP group and 247 of the 348 in the watchful-waiting group died** [170]

  In the case of 63 men assigned to surgery and 99 men assigned to watchful waiting, death was due to PCa (P = 0.001) [170]
- **The survival benefit was largest in men younger than 65 years of age and those with intermediate-risk prostate cancer** [170]
- **The number needed to treat to avert one death at 18 years of follow-up was 8 (P=0.001) and 4 for men younger than 65 years of age** [170]
  Among men who underwent radical prostatectomy, those with extracapsular tumour growth had a risk of death from PCa that was 7 times that of men without extracapsular tumour growth [183]

- **Distant metastases were diagnosed in 89 men in the RP group and 138 in the watchful waiting cohort resulting in a relative risk of metastases in the RP group of 0.57 (P <0.001)** [170]

However, by contrast, in the Prostate Cancer Intervention versus Observation Trial (**PIVOT**) of radical prostatectomy versus observation for localized prostate cancer found differently [184]. Between November 1994 and January 2002, 731 men with localized prostate cancer (mean age, 67 years; median PSA value, 7.8 ng per milliliter) were randomly assigned to radical prostatectomy or observation and followed to January 2010. The primary outcome was all-cause mortality; the secondary outcome was prostate-cancer mortality

During the median follow-up of 10.0 years, 171 of 364 men (47.0%) assigned to radical prostatectomy died, compared with 183 of 367 (49.9%) assigned to observation (P=0.22). Among men assigned to radical prostatectomy, 21 (5.8%) died from prostate cancer or treatment, compared with 31 men (8.4%) assigned to observation (P=0.09). The effect of treatment on all-cause and prostate-cancer mortality did not differ according to age, race, coexisting conditions, self-reported performance status, or histological features of the tumour. Radical prostatectomy was associated with reduced all-cause mortality among men with a PSA value greater than 10 ng per milliliter (P=0.04 for interaction) and possibly among those with intermediate-risk or high-risk tumors (P=0.07 for interaction). Adverse events within 30 days after surgery occurred in 21.4% of men, including one death.

Figure 28: U.S. PIVOT –Radical Prostatectomy versus observation [184]

- **Recruitment difficulties and patient compliance issues affected numbers so that only 731 of the proposed 2000 men could be recruited to the trial and hence this study is considered to be underpowered to detect a difference in overall survival** [185]
- **Median follow-up period was only 10 years**
- **Differences between histological reporting at participating sites and by a central pathologist affected risk stratification and, consequently, secondary endpoint results**

- **A less predictive pre-2005 ISUP Consensus Gleason classification was used with ~25% of patientswith Gleason scores of 7 or higher reported at the peripheral sites compared with 48% with Gleason scores 7 or higher by a central pathologist**
  Consequently, the answer based on RCT evidence remains uncertain
  (C) Early diagnosis and treatment with curative intent. Avoiding the late clinical problems resulting from a large pelvic tumour

There is a paucity of high level evidence that early diagnosis of prostate cancer will prevent or minimise the problems resulting from a large pelvic tumour (outlined in **Treatment of Prostate Cancer**). Anecdotally, managing patients with disabling symptoms from advanced local prostate cancer constituted a considerable part of a urologist's workload. Frequent visits to hospital for interventions together with burden of clinical symptoms such as unremitting day and night frequency, incontinence and bleeding, impact significantly on the dignity and quality of life of these men [186]. However, although evidence is lacking, absence of evidence is not the same as evidence of absence.

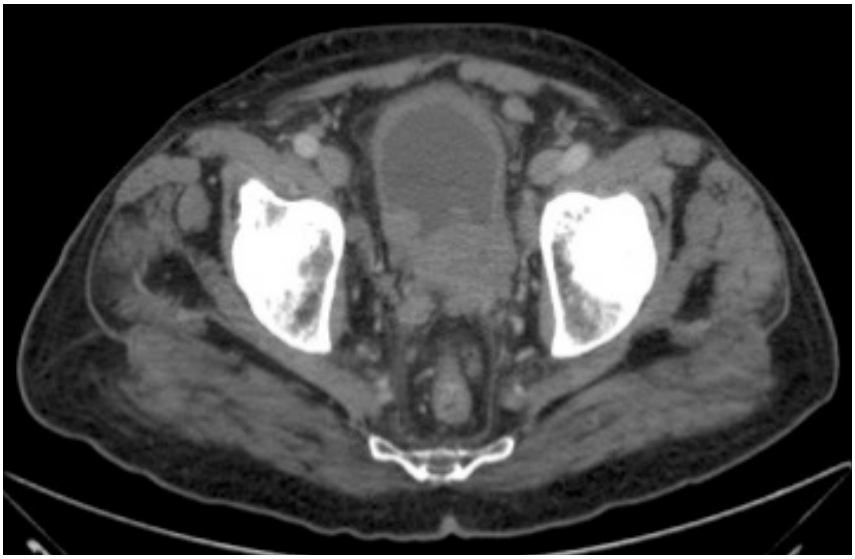


Figure 29: CT of pelvis showing prostatic tumour which has extended into the (thick-walled) bladder and spread to involve pelvic lymph nodes: the patient had multiple lower urinary tract symptoms

VII WHETHER TO TEST FOR PROSTATE CANCER

While prostate cancer is the most common male malignancy in the developed world and the second most common cause of cancer deaths, uncertainties remain about management practices at several points in the illness continuum. For example, owing to controversies regarding the outcomes of screening trials for prostate cancer reducing the death rate from this disease, population-based screening for prostate cancer in asymptomatic men is not currently recommended in most countries [187]. Rather, it is suggested that men should be able to access PSA testing as long as they are fully informed of the pros and cons of testing.

For those diagnosed with localised prostate cancer, the next decision is which pathway of management to choose, with many possible treatment options, including, but not limited to, active surveillance, watchful waiting, radiation therapy (including brachytherapy) or radical prostatectomy - extending more recently to include laparoscopic and robotic surgery [188]. Men who are diagnosed with advanced disease will also face difficult treatment decisions such as when to commence palliative treatment with androgen deprivation therapy (**ADT**) and what method of ADT to select, each with various quality of life 'trade-offs', to accept [189]. In the setting in which no one treatment approach is clearly superior with regards to cancer cure and where quality of life outcomes differ markedly, the quality of patients' decision making about medical treatments is critical. As a result, strategies to assist them in meaningfully considering prostate cancer treatment options, and the risks and benefits of these options in order to achieve high quality patient decisions, are essential [190].

The approach that is considered to be optimal for achieving high quality patient decisions is shared decision making [191].

Shared decision making *is defined as a process carried out between a patient and his health care professional where both parties share information and the patient understands the risks and benefits of each treatment option, participates in the decision to the extent that he desires and makes a decision consistent with his preferences and values, or defers the decision to another time* [192].

Shared decision making may not be easy to achieve for all patients [192]. For example, although many patients with cancer indicate a preference for sharing decision making with their clinicians, some, in the case of prostate cancer between 8% to 58% of men, prefer a passive decision making role where clinicians make treatment decisions on their behalf [193, 194]. However, clinicians still need to understand patients' preferences to ensure that they are making quality decisions on behalf of their patients. As well, there is often a gap between the clinical ideal of shared decision making and actual clinical practice where decision

complexity and time constraints may make this approach difficult for both parties to achieve [195, 196]. There are, however, defined strategies and decision aids that can facilitate this process [197].

Supporting Patient Choice about Testing for Prostate cancer

Many groups advocate an informed decision-making process as an evidence-based approach and necessary precursor to screening for early prostate cancer [187, 198-200]. Others have suggested that informed decision-making on this health topic is also necessary as a medico-legal risk management strategy [201, 202]. While some researchers have suggested a set of information that needs to be communicated to men about this health decision ([203, 204], there are few explicit guidelines on this subject [205]. Problematically, patients and clinicians do not agree on core content [206]. It has been advised that, for any screening test, patients need to understand the purpose of the test, the likelihood of false-negatives and false-positives, the uncertainties and risks associated with testing, significant medical, social or financial implications of testing and any possible sequelae and follow up care plans [207] www.ipdas.ohri.ca.

Such information needs to be communicated to patients in a logical and balanced sequence in order to promote better understanding and increased decisional control by men. One approach that has been proposed in primary care in Australia is the use of six decision steps. Each decision step logically follows to prompt the clinician to overview important health information, with tailoring suggested in Step 1 to ensure the discussion is consistent with the patient's concerns. For example, for a man with a significant family history of prostate cancer, this factor is likely to be central to the patient discussion [208]. Men who experience uncomplicated LUTS often worry about prostate cancer, so addressing this concern first may be priority [209, 210]. In this regard, resources for patients that explain about male reproductive health problems such as urinary symptoms and sexual dysfunction are available at www.andrologyaustralia.org. As well, National Health and Medical Research Council guidelines are available about the management of LUTS
http://www.health.gov.au/nhmrc/publications/synopses/cp42syn.htm
Other overseas websites include:
http://www.cancer.org
http://www.cdc.gov/cancer/prostate/
http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Prostate/Prostatecancer.aspx
www.cancerscreening.nhs.uk/prostate/prostate-patient-info-sheet.pdf
http://www.npc.nhs.uk/therapeutics/other/prostate/resources/pda_prostate_cancer.pdf

Six Decision Steps (Table 5)

Table 5. Six Decision Steps for Informed Choice about PSA Testing in Asymptomatic Men

1. Identify the patient's main concern
2. Explain where the prostate is and tests available to detect prostate cancer
3. Discuss prostate cancer risk and risk factors
4. Explain the pros and cons of early detection of prostate cancer
5. Identify patient's personal preferences
6. Support the patient's choice, and if requested implement a prostate cancer risk management plan

Source: Steginga S, Pinnock C, Baade P. "The early detection of prostate cancer in general practice: supporting patient choice ", practice resource in "Supporting patients' choice about PSA testing in general practice" A collaborative project of the Queensland Cancer Fund. Brisbane, 2005
http://www.prostate.org.au/articleLive/attachments/1/GP%20Show%20Card%20041007.pdf

From this point, checking to ensure the patient has a basic understanding of both the prostate and possible tests is needed and, given many men may be unaware of the location and function of the prostate gland, an anatomical diagram may be a useful teaching tool here. Next, a consideration of individual risk with regard to both the incidence and mortality of prostate cancer is needed. Communicating health risks effectively is a challenge in the provision of effective decision support. In general people find probabilities hard to understand, often estimate their level of risk incorrectly, and tend not to weigh up pros and cons in a systematic way when deciding about treatments [180, 211, 212]. As well, population-based statistics provide data about populations, not individuals, so risk communication needs to acknowledge this as a

limitation and, where possible, refer to age-based risk estimates and relevant individual factors such as family history)[213].

There are a number of communication strategies that have been suggested to help patients understand risk. These include

- using numbers as well as words to explain risk
- where possible providing the absolute risk or benefit
- using frequencies rather than single event probabilities
- using consistent denominators
- putting the risk into context by comparing it to other life events
- offering both the possible negative and positive outcomes to balance the message frame [214-6].

However, a quality health decision goes beyond the simple transfer of information and includes consideration and incorporation of each patient's values and personal preferences [190]. Thus, Step 5 in Box 1 prompts the clinician to discuss each man's individual preferences. A number of strategies can be used to do this, most commonly the use of a pros and cons exercise in which patients are encouraged to explicitly consider the factors that matter most to them personally in this decision, and the direction and leaning of their preferences either for or against each possible option. One approach to support this process for this health topic is the inclusion of a values table within a decision card (see Table 1). A decision aid that incorporates both the six decision steps and this values clarification exercise can be found on the Andrology Australia website at:
http://www.prostate.org.au/articleLive/attachments/1/GP%20Show%20Card%20041007.pdf

What is most important to you? (Table 6.)

Table 6. FOR: Is this like you?	***AGAINST: Is this like you?***
I'm concerned that I might get prostate cancer	I think my chance of getting prostate cancer is low
I want the best chance of finding it early, if I do get it	I am not convinced about the effectiveness of testing
I'm not interested in waiting for all the proof to be in	I am more concerned about avoiding treatment side effects, if there's no guarantee I'd be reducing my risk of dying from prostate cancer
I want to do everything possible to reduce my risk of dying from prostate cancer	

Decision aids are also effective in supporting patients to make informed choices. With regards to PSA testing, patient-focussed decision aids and decision counselling or support interventions have been found to be effective in increasing men's knowledge about PSA testing and decreasing decision-related distress [205, 217-21], with a variable effect on actual testing behaviour.

A range of aids is freely available from the web (**www.prostatehealth.org.au; www.cdc.gov/cancer/prostate; www.cancerbacup.org.uk**).

Cancer helplines also often provide such information, for example, The Cancer Council Australia Cancer Helpline on 13 11 20; the UK helpline on 0808 800 1234; the USA Cancer Helpline on 1800 227 2345.

Emerging Work

A current national project is underway in Australia to develop national guidelines about PSA testing for the early detection of prostate cancer that will include when released clinical practice recommendations for decision support for this health decision http://www.nhmrc.gov.au/your-health/testing-prostate-cancer. A PSA Information Document is expected in mid 2014 and guidelines in late 2014.

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