PROSTATE-SPECIFIC ANTIGEN (PSA) SCREENING – CURRENT VIEWS
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Physiology of PSA

PSA is produced in the ductal epithelium of the prostate. PSA is secreted into the lumen of the prostatic ducts and plays a very important role in the prostatic fluid to release spermatozoa for fertilisation.

A small amount of PSA is reabsorbed through the ductal epithelial cells and circulated through the blood stream. The concentration of PSA is one million times higher in the prostatic fluid than in the blood.

Factors affecting PSA levels

Prostatitis
Clinical and subclinical prostatitis may elevate PSA levels up to 30 ng/ml. It takes six to eight weeks for PSA concentrations to return to baseline levels after treatment of prostatitis.

Ejaculation
There is a definite rise in PSA with a peak increase within one hour following ejaculation. The mean rise of PSA is 0.8 to 2 ng/ml but increase in levels as much as 9.2 ng/ml has been recorded. Therefore, men should abstain from ejaculation for at least 48 hours prior to PSA determination.

Prostate biopsies and TURP
There is a median increase of 7.9 ng/ml. It takes six weeks to return to baseline levels after these procedures.

Physical exercise, prostatic massage and digital rectal examination
Minor, transient increase may occur.

PSA testing for early detection of prostate cancer

Median PSA
Median PSA levels in men without prostate cancer (1,2,3):

Age	Median PSA in men without prostate cancer
40 to 49 years	0.7 ng/ml
50 to 59 years	0.9 ng/ml
60 to 69 years	1.2 ng/ml
≥70years	1.5 ng/ml

Any PSA level above the Median PSA may be an indication of early prostate cancer.

PSA velocity (PSAV)
PSA velocity = yearly change in PSA expressed in ng/ml/year
Calculation of PSAV: [(PSA 2 – PSA 1) / (months between PSA 1 and PSA 2)] x 12

For PSA levels less than 4ng/ml any consistent yearly increase in PSA of more than 0.35ng/ml/year, is associated with a five-fold increased risk of prostate cancer death in the next two to three decades.

Age-adjusted PSA velocity threshold values (4):

Age	PSA velocity threshold
40 to 59 years	0.25 ng/ml/year
60 to 69 years	0.50 ng/ml/year
≥70years	0.75 ng/ml/year

To correctly measure PSA velocity, it is recommended to use at least three PSA values over a time period of at least 18 months.

Age-specific PSA

The traditional age-specific thresholds for recommending a prostate biopsy of 2.5, 3.5, 4.5, and 6.5 ng/ml for men aged 40-49, 50-59, 60-69 and 70-79 years respectively, have now been replaced by any level of PSA above the age-specific median PSA levels and two measurements of PSA velocity above the age-adjusted threshold. The aim is to diagnose early stage prostate cancer at a much lower PSA level.

PSA threshold for recommending referral for possible prostate biopsy:

Age	Calculation (Median PSA+2 x PSAV)	PSA threshold
40 to 49 years	>0.7 + 0.25 + 0.25	>1.2 ng/ml
50 to 59 years	>0.9 + 0.25 + 0.25	>1.4 ng/ml
60 to 69 years	>1.2 + 0.5 + 0.5	>2.2 ng/ml
70 to 75 years	>1.5 + 0.75 + 0.75	>3.0 ng/ml

Free PSA

Prostate cancer tends to produce PSA that binds to alpha-1-antichymotripsin in the blood (Complexed PSA) and therefore less PSA will be in the free form. Free PSA levels below 10% to 15% are more indicative of cancer but not as specific or sensitive as PSA velocity.

PSA density (PSAD)

An elevated PSA level in a small prostate is more indicative of prostate cancer than the same PSA level in a large benign prostate.
PSAD = serum PSA / TRUS prostate volume. <0.15 in BPH and >0.15 in cancer

Current policy of American Urological Association (4,5)

The decision to proceed to prostate biopsy should be based on PSA and digital rectal examination (DRE) results, but should take into account multiple factors including patient age, PSA velocity, free and total PSA, PSA density, family history, ethnicity, prior biopsy history and comorbidities.

Current recommendations for the use of PSA to diagnose prostate cancer at an early stage in patients who have a normal digital rectal examination (DRE) and where prostatitis is excluded:

Establish a baseline PSA at age 40 before men have benign prostatic enlargement (age 35 in men with a family history of early-onset prostate cancer ≤ 60 years). If the PSA is higher than the median for the age group, immediate repeat testing should be performed to verify the result. Patients should avoid ejaculation, prostate manipulation or physical activity for 48 hours. If infection is suspected, the patient should be treated with Ciprofloxacin for 14 days followed by a PSA test (Catalona).

A single PSA test in middle age appears highly predictive for the long term risk of clinically significant prostate cancer and can be used to risk-stratify population-based screening (6).

Although the current recommendation is to perform PSA testing annually among men who decide to be tested, there is strong evidence that re-screening intervals should be based on the results of the initial PSA test (4).

The exact intervals between PSA testing have not been established yet but the possible recommendations for a 40 year old man would be as follows:

PSA level	Action
<0.6 ng/ml	Low cancer risk (6.6%). Further testing every one to ? five years.
0.6 to 1 ng/ml	Cancer risk 10%. PSA test every one to two years
1.1 to 2.4 ng/ml	Cancer risk +/-17-23%. PSA testing every six to twelve months
≥2.5 ng/ml	Immediate referral for possible prostate biopsy

If two subsequent PSA tests confirm an increase of more than the PSA velocity threshold (0.25 – 0.35 ng/ml/year), the patient should be referred for further investigation and possible prostate biopsy.

A suspicious digital rectal examination at any PSA level should be referred even with a normal PSA as there is no “safe” PSA level where cancer is excluded. Some of the highly malignant cancers produce little or no PSA.

Studies looking at relationship between initial PSA level and subsequent prostate cancer detection

Malmo, Sweden (7,8)

Between 1974 and 1986, 21,277 men aged 33 to 50 provided blood within a cardiovascular study. Prostate cancers were identified in 1999 using the Swedish Cancer Registry. Archived blood samples were retrieved in 462 patients subsequently diagnosed with prostate cancer. (2.2%) Their PSA levels were compared with 1,000 controls who did not develop prostate cancer. They found PSA was a very strong predictor of prostate cancer up to 25 years subsequently. Levels of 2 to 3 ng/ml, often cited as within normal range, were associated with an increase in odds for subsequent prostate cancer of more than 19 fold. For patients with PSA between 0.51 to 1 ng/ml there was a 2.5 fold increase in prostate cancer risk.

Median PSA in patients with prostate cancer was 1.07 ng/ml (range 0.63 to 1.79). Median PSA for controls was 0.55 ng/ml (range 0.37 to 0.81).

Eighty percent of advanced cancers in 1999 (T3, T4 or metastatic disease) occurred in men with PSA levels above the median for their age.

Chicago, Illinois, USA (1,2,3)
Professor William Catalona and Associates conducted a study between 1991 and 2001 on 26,000 men aged 40 to >70 years. PSA testing and DRE was performed at six to 12 month intervals. Prostate biopsy was recommended if DRE findings were suspicious or PSA level of ≥2.5 ng/ml. Cancer was detected in 1101 men (8%). They found that the median PSA for people who did not develop prostate cancer was 0.7 at age 40 to 59 and 0.9 age 50 to 59 and 1.2 for age 60 to 69 and 1.5 for age >70.

For men in the 40s with a PSA of 0.7 to 2.5 there was a 14.6 fold increased risk of later prostate cancer diagnosis.

Reduction in prostate cancer death rate due to PSA testing and curative treatment of cancer with radical prostatectomies or radiotherapy.

United States of America (9)
There was a 33% reduction in death rate from 1995 to 2007 (40,400 deaths/year in 1995 compared to 27,000 deaths in 2007). This is the largest decline of any cancer – male or female. They found 75% reduction in metastatic disease at presentation.

Tyrol, Austria (10)
Between 1993 and 2005 86,000 men aged 45 to 75 underwent PSA testing in the province of Tyrol. They found a reduction of 38.8% in death rate compared to the period 1986 to 1990 prior to PSA testing. The death rates were also significantly lower than in the rest of Austria where PSA testing was not free of charge and not actively promoted.

ERSPC (European randomized study of screening for prostate cancer) (11)
There was a 20% reduction in death rate. 214 patients in the screened group compared to 326 patients in the control group. There was a 70% reduction in metastatic disease at presentation.

REFERENCES

1. Loeb S, Roehl A, Catalona W J and Nadlert R B. Is the utility of prostate-specific antigen velocity for prostate cancer detection affected by age? British Journal of Urology International 2008; 101: 817-821

2. Antenor J, Han M, Roehl K, Nadler R and Catalona W J. Relationship between initial prostate-specific antigen level and subsequent prostate cancer detection in a longitudinal screening study. The Journal of Urology July 2004; 172: 90-93

3. Loeb S, Roehl K A, Antenor J A, et al. Baseline prostate-specific antigen compared with median prostate-specific antigen for age group as predictor of prostate cancer risk in men younger than 60 years old. Urology 2006; 67: 316

4. Greene K L, Albertsen P C, et al. Prostate Specific Antigen Best Practice Statement 2009 Update: The Journal of Urology 2009; 182: 2232-2241

5. Carroll P, Albertson P, Greene K, et al. Prostate-Specific Antigen Best Practices Statement: 2009 update. http://www.auanet.org

6. Challacombe B, Murphy D, et al. The continuing role of Prostate-Specific Antigen as a marker for prostate cancer: Do not throw the baby out with the bath water. British Journal of Urology International 2009; 104: 1553-1554

7. Lilja H, Ulmert D, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol 2007; 25: 431-436

8. Ulmert D, Cronin A, et al. Prostate-specific antigen at or before age 50 as a predictor or advanced prostate cancer diagnosed up to 25 years later: A case-control study. BMC Medicine 2008, 6:6

9. Walsh P (Professor). Prostate Cancer Conference 2008 Melbourne Australia.

10. Bartsch G, Horninger W, et al. Tyrol Prostate Cancer Demonstration Project: early detection, treatment, outcome, incidence and mortality. British Journal of Urology International 2008; 101: 809-816

11. Schroder, F H, Hugosson J, et al. Screening and prostate-cancer mortality in a randomized European study. New England Journal of Medicine 2009; 360(13): 1320-8.