Perspective Article

To do or Not to do!

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Introduction

Prostate Specific Antigen (PSA) is a protein produced by the cells of prostate gland. It is present in small quantities in the serum of men with healthy prostate but is often elevated in presence of prostate cancer and other prostate disorders.

A Blood test to measure PSA is considered the most effective test currently available for early detection of prostate cancer but this effectiveness has also been questioned[1].

However PSA is neither specific for prostate nor cancer. Although present in large amount in prostatic tissue, semen and serum in men, it has also been detected in other body fluids and tissues including female ejaculate, breast milk, amniotic fluid, endometrium, normal breast tissue and salivary gland tissue[2].

Normal/Reference Range

Defining a normal range is difficult. Rather than attempting to define a normal range, it would probably more appropriate to provide the clinician with an appropriate PSA cut off level that affords a reasonable yield of cancer. Even more appropriate, perhaps, would be to establish additional criteria e.g. age, race, digital rectal examination results that would provide a risk assessment of prostate cancer being present.

Various factors such as benign hyperplasia, inflammation, ejaculation, cycling, prostatic massage and instrumentation have all been known to alter the PSA level. Even though there is no specific normal or abnormal PSA level, 4.0ng/ml it is generally taken as a cut off level. However prostate cancer was diagnosed in 15.2% of men with PSA level below 4.0ng/ml[3]. In another study 65-75% of men of PSA between 4.1- 9.9ng/ml did not have prostate cancer[4].

Limitation Of PSA Test

- Detecting tumour does not always mean saving lives- finding a small tumour does not necessarily reduce the chances of dying from prostate cancer. PSA testing may identify very slow growing tumours that are unlikely to threaten life.

- False positive test – False positive test occurs when the PSA level is elevated but no cancer is actually present. Only 25-35% of men who have a biopsy due to an elevated PSA actually have prostate cancer. Hence a false positive test may lead to additional medical procedures that have potential risk and significant financial cost and can create anxiety for the patient and for the family

- False negative test – False negative test occurs when the PSA level is normal range even though prostate cancer is actually present. Most prostate cancers are slow growing and may exist for decades before they cause symptoms.

Factors Enhancing Perfomance Of PSA

The major efforts to improve PSA testing have addressed enhancement of specificity. The question of whether to improve sensitivity or specificity is important as they are generally inversely related parameters. Efforts to enhance specificity would appear to be more logical because with serial testing, a false negative result is of less consequence. By increasing the PSA cut off level, specificity improves but at the cost of decreasing sensitivity. False positive test are exceedingly expensive as they mandate further testing with attendant increase in expenses and morbidity

Number of approaches have been widely used to enhance PSA performance

Age specific PSA cut off point have been used, taking into account that prostate grows with age and PSA gradually increase with age.

40-49yrs ----------2.5ng/ml

50-59yrs----------3.5ng/ml

60-69yrs----------4.5ng/ml

70-79yrs----------6.5ng/ml

The age specific ranges have not been generally favoured because their use may lead to missing or delaying detection of prostate cancer in as many as 20% of men in the 60's and 60% of men in their 70's.

- PSA velocity - change in PSA overtime may be greater in men with prostate cancer. It is generally agreed that rise of PSA over 0.7ng/ml over a period of 12 months may indicate prostate cancer
- Prostate density – Adjusts serum PSA with respect to prostatic volume, as a larger prostate may be associated with higher PSA level even though the gland is benign.
- Free/Total PSA ratio may be helpful in differentiating between benign and malignant prostate in men with PSA between 4-10ng/ml
- Alteration of PSA cut off level – reducing the cut off level will increase the chance of detection of cancer but may also increase over diagnosis and false positive results and lead to unnecessary medical procedures.

PSA In Prostate Cancer Screening

The use of PSA to screen men for prostate cancer is controversial because it is not yet known for certain whether it actually saves lives. Moreover it is not clear that the benefits of PSA screening outweigh the risk of follow up diagnostic test and cancer treatment. The PSA test may detect small cancers that would never become life threatening. This puts men at risk of complications from unnecessary treatment.

The benefits of screening for prostate cancer are still being studied. Two large trials are ongoing at the moment to look at the benefits of prostate cancer screening ie PLCO trial and ERSPC trial[1,5]. In the ERSPC trial it has been estimated that 1410 men would have to be screened and 48 additional cancers would have to be detected to prevent one death from prostate cancer.

Key Points

- It is generally accepted to use 4.0ng/ml as the cut off level.
- Many factors affect PSA levels in serum
- Single PSA test is not used as a diagnostic test
- PSA test should always be used along with digital rectal examination
- PSA should offered to well informed men aged 50 and over who have a life expectancy of more than 10years
- Decision to biopsy the prostate should take into account other additional factors, PSA velocity, PSA density, age, family history and co-morbidities[6].
- PSA on its own is more useful as a prognostic tool

References

1) Schroder FH et al'' Screening and Prostate Cancer Mortality in a Randomised European Study''. New Eng J.Med. 2009; 360: 1320 - 1328.

2) Dale L. Laux et al. Detection of PSA Using Membrane Based Test. Midwestern Assoc of Forensic Scientists 2008. http://mafs.net/pdf/forensicdetectionsemen3.pdf

3) Thompson IM et al. Prevalence of prostate cancer among men with a PSA less than 4.0 New Eng J.Med. 2004; 350 (22): 2239 - 46.

4) Smith DS et al. Early Detection of Prostate Cancer with PSA. Cancer. 1997; 80 (6): 1852 - 1856

5) Andriole G et al. Mortality results from a randomized Prostate Cancer screening trial (PLCO trial). New Eng J.Med.2009; 360 (13) : 1310 - 1319.

6) AUA (American Urological Association) Guidelines and NICE (National Institute of Health and Clinical Excellence UK) Guidelines

Belly Buddy

Not all bacteria are malevolent and harmful. Billions of those that colonise our gut maintain a relationship with us that is at least commensal and at best, mutually beneficial. One such organism goes by the name, Akkermansia muciniphila and it accounts for nearly 3-5% of gut microbial population. It is a resident of the mucus layer and it appears to degrade the mucus. Dr. Patrice D. Cani and his colleague from Belgium, have discovered that its numbers are significantly reduced in obesity and type 2 diabetes resulting in increased inflammation and defective gut barrier. When the researchers (working with rats) restored its numbers through prebiotic feeding, metabolic status of the host improved with reversal of fat-mass gain and reduction in metabolic endotoxaemia, adipose tissue inflammation, and insulin resistance. Akkermansia muciniphila apparently achieves this by increasing the intestinal levels of endocannabinoids that control inflammation, the gut barrier, and gut peptide secretion. Of course it is effective only when it is alive. Not all our true friends are easily recognisable. This one is microscopic with an unpronounceable name. But does it matter? Keep it alive in your gut and it is your friend for life. The study is published in the latest issue of Proceedings of the National academy of Sciences (PNAS 2013 ; published ahead of print May 13, 2013, doi:10.1073/pnas.1219451110)

- Dr. K. Ramesh Rao