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Short Communication

Free PSA as a Predictor of Prostate Cancer

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Abstract

Clinically diagnosed Prostate cancer is suspected due to raised PSA and abnormal DRE. DRE detected prostate cancer is often advanced and not amenable to curative treatment. The use of PSA as a serum marker has revolutionized PCa diagnosis. PSA is specific to the gland but not specific to cancer, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non- malignant conditions. There is no universally acceptable PSA cut off, as PCa can be diagnosed in about 7% cases, although less than 1% are clinically significant with PSA of 0-0.5ng/mL ranges. Various modifications of PSA are therefore described including PSA density, PSA kinetics (velocity and doubling time), free/total (f/t) ratio, PHI test, PCA3 etc. f/t PSA is particularly useful in differentiating BPH from PCa for 4-10ng/mL PSA range. It is, however of no use if total PSA is greater than 10ng/mL or in the follow up of patients. There is limited work to indicate its utility in the <4ng/mL group. There are many limitations to the use of f/t PSA as the values can be affected by various preanalytic and clinical factors.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in males over 50years [1]. The biological potential of PCa is variable, however most are slow growing. Early PCa may not cause any symptom and remain undetected until it is advanced. Almost all localized (organ confined) PCa are screen detected. Screening is done by digital rectal examination (DRE) and prostate specific antigen (PSA) measurement. Confirmation of diagnosis is by trans rectal ultrasound (TRUS) guided biopsy1 [2]. Screening has the potential of identification of disease early and potential benefit in improving cancer specific survival. Bergstralh et al [3] has shown that there is a potential benefit of screening by PSA testing and/or DRE on PCa mortality. However, screening has recently been criticized following two landmark population based studies i.e. ERSPC in Europe and PLCO in United States. Widespread use of PSA screening led to a decrease in mortality; however, PSA screening may have led to over diagnosis and overtreatment of clinically insignificant cancers. The US Preventive Services Task Force (USPSTF) released a statement recommending against the use of PSA, which was met with concern from professional organizations [4]. Recently Berry and Nelson noted that patients Present with More Advanced Prostate Cancer since the USPSTF Screening Recommendations [5]. One of the major reasons for this controversy is that PSA is an organ specific marker and has many limitations. In order to improve PSA based diagnosis of PCa various modifications have been suggested. PSA density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely is that the PCa is clinically significant. PSA kinetics is assessed by PSA velocity and PSA doubling time, only former is important in the diagnostic algorithm.PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year). However it has limited clinical value. PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. It is particularly useful for indicating re biopsy.

PSA is the most useful marker for the screening, early detection and follow up of PCa. First of all there is no universally acceptable cut off. PCa is present at very low PSA. The prostate health index (phi) can improve specificity over percent free and total PSA and correlates with aggressive cancer. The PHI test is a recently approved diagnostic blood test, combining free and total PSA and the (-2) pro PSA isoform (p2PSA), intended to reduce the number of unnecessary prostate biopsies in PSA tested men. A few prospective multicentre studies demonstrated that the PHI test not only outperforms free and total PSA PCa detection, but has an improved prediction of clinically significant PCa, both in men with a PSA between 4-10 ng /mL and between 2-10 ng / mL. The PHI test may therefore also have a role in monitoring men under active surveillance [6]. Its clinical impact is, as yet undetermined, given the slight net benefit for clinical decision-making [7].

The urinary PCA3 also shows its utility to detect PCa but its correlation with aggressiveness and the low sensitivity at high values are limitations. While the detection of alterations of the androgen-regulated TMPRSS2 and ETS transcription factor genes in tissue of ˜50% of all PCa patients was one research milestone, the urinary assay should only be used in combination with PCA3.

Both US FDA-approved markers phi and PCA3 perform equally [8].

PSA a Tumor Marker for screening

Prostatic acid phosphatase was used earlier as a monitoring marker for PCa. PSA was introduced in 1987, to evaluate treatment response and later on was used for screening Population based screening is defined as the systematic examination of asymptomatic men (at risk) and is usually initiated by health authorities. In contrast, early detection or opportunistic screening consists of individual case findings, which are initiated by the person being screened patient or physician.

PCa and was proposed as a screening tool due to its improved sensitivity over prostatic acid phosphatase. The American Cancer Society recommends that screening based on the PSA test and DRE should be offered annually, beginning at age 50 [9]. The economic viability of this is challenged by USPSTF following two large randomized population based trials (PLCO and ERSPC) [10,11] assessing the efficacy of PSA based screening. However screening by PSA has low specificity for PCa detection, due to its low sensitivity in localized disease and overlap in PSA levels between normal and cancer patients.

Men at elevated risk of having PCa are those over 50 years of age, or with a family history of PCa and age > 45 years, or African-Americans [12]. In addition, men with PSA > 1 ng/mL at 40 years and > 2 ng/mL at 60 years [2] are also at increased risk of PCa metastasis or death several decades later. Recently, as for breast cancer, a genetic abnormality likely to be associated with an increased risk has been shown prospectively [14]. Its everyday use requires further studies and cannot yet been recommended.

There was no evidence of a PC mortality reduction in the American PLCO trial, which investigated a screening program in a setting where opportunistic screening was already common practice. Given that opportunistic PSA screening practices in Canada are similar, it is unlikely that the introduction of a formal PSA screening program would reduce PC mortality [15]. Tawfik A [16] analyzing the economic impact of the PSA based screening in a systematic literature search noted that PSA screening is associated with significant costs to the health care system when the cost of the PSA test itself is considered in addition to the costs of diagnosis, staging, and treatment of screen-detected PCs.

Limitations of PSA

A problem with the total PSA test normally used is that, it exists in elevated concentrations in both PCa and in various non-cancerous conditions like prostatitis, following recent interventions and benign growth of the prostate (BPH). Recently Park and colleagues [17] noted that total and free PSA levels in the serum are altered by prostate massage, rigid cystoscopy, TRUS-guided prostate biopsy, and TURP. The PSA rises were related to the stimulation strength of the procedures. The total and free PSA levels were increased significantly from 10 minutes after procedures, except DRE and TRUS, and were increased to maximal level at 60 minutes after procedures.

The detection of early prostate cancer by total PSA measurement is limited by its lack of specificity, particularly when PSA levels are within the grey zone (4–10 ng/ml range). When the conventional PSA cutoff of 4ng/ml is used as the cut off between cancer and nonmalignant prostatic diseases, the false-positive rate is 77% because increased serum PSA concentrations are also found in BPH and inflammatory prostatic diseases such as prostatitis[1]and only about 30% for patients with serum PSA between 4.0 and 10.0ng/mL have prostate cancer on biopsy[2,3]. Due to aforementioned reasons a serum marker with better sensitivity and specificity was required.

To improve specificity of PSA multiple strategies are proposed including age specific PSA reference ranges, PSA velocity (serial measurement of PSA), PSA density (prostate volume determined by ultrasound divided by PSA), PSA isoforms and their ratios measurement [19].

Isoforms of PSA

In 1991, PSA isoforms were discovered. PSA isoforms to improve the diagnosis potential of total PSA: percentage of free PSA (% fPSA) complexed PSA (cPSA), ProPSA, BPSA. Since then researches have reported that the differentiation between BPH and PCa can be improved by determination of the serum PSA isoforms [20]. PSA circulates in the serum in several molecular forms unbound or free form (fPSA) and complexed with different protease inhibitors, commonest one is α1-antichymotrypsin [21]. Of the total PSA about 10–30% is not bound to serum proteins and is called free PSA (fPSA). The major form of PSA circulating in men with PCa is PSA-α1ACT while free PSA levels are increased in benign diseases related to prostate and lower fPSA levels suggests more aggressive cancer. The performance of total serum PSA still needs to be improved. Several studies show potential clinical interest of PSA isoforms to improve specificity in PCa diagnosis.

Free PSA

Investigators have begun measuring the ratio of free to total PSA for clarifying diagnosis of patients with elevated PSA levels [7]. Severalstudies have demonstrated a lower ratio of fPSA to tPSA in PCa patients, calculated as the percentage of fPSA [8]. Percent fPSA ratio is also a powerful predictor of morbidity in men with PCa and initial PSA levels of 4.1 to 10.0ng/ml. It has been considered a promising tool for distinguishing between PCa and BPH(4). Free PSA was approved by the FDA for use with total PSA for cancer detection in 1998 and <10% fPSA is suggestive of cancer while >20% fPSA suggest benign cause. Chang and colleagues [22] recently noted that the clinical application of %fPSA could help to discriminate PCa from benign prostate disease in men with a tPSA concentration below 4 ng/mL.

Evidence

Data from several studies suggest an inverse relationship between percent free PSA and total PSA [9,10,23]. This relationship suggests that men with higher PSA levels (and with more aggressive or advanced disease) have lower percentages of free PSA. Thus, age, prostate volume, and total PSA concentration are important factors that influence cutoffs for percent free PSA. A large prospective multicenter clinical trial showed that free PSA can reduce unnecessary biopsies, and is especially beneficial for improving sensitivity of PCa diagnosis in patients with PSA

ranging from 4-10ng/ml [24]. Another study by Catalona et al [25] showed that free PSA has improved sensitivity (90%) for detecting PCa in patients with tPSA between 2 to 4 ng/ml and it was able to reduce unnecessary biopsies by 10% ($p < 0.001$) [26] but the specificity was low (20%) so it cannot be used alone for screening but as an adjunct for tPSA. To summarize fPSA is a good adjunct test for diagnosing PCa along with tPSA. It has improved sensitivity especially in grey zone tPSA levels to differentiate PCa from BPH.

fPSA Testing

Sample handling is important to preserve immune-reactivity of fPSA. Researchers have shown that 30% fPSA immune-reactivity is lost if sample is stored at 2-8°C compared to 15% loss of immune-reactivity for PSA, proposing that serum sample for fPSA be frozen immediately and long term storage done at -70°C [27,28]. Keeping these in mind it is now recommended to do not use samples stored at room temperature for longer than 24 hours and store at or below -20°C if the sample is to be stored for longer period (Kit insert Free PSA; Siemens Diagnostics, US).

f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors (e.g., instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates) [29].

CONCLUSION

Free/total (f/t) PSA ratio is widely used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. PCa was detected by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 [21]. The value of f/t is only for 4-10 ng/ml range of PSA for early detection of PCa, f/t PSA has no clinical use if total serum PSA is > 10 ng/mL or during follow-up of known PCa. There is limited data to indicate its usefulness in the <4ng/mL group.

The interpretation of f/t PSA values are subject to storage and handling, f/t PSA must be used cautiously because it may be adversely affected by several preanalytical and clinical factors like instability of free PSA at 4°C and room temperature, variable assay characteristics, and concomitant BPH in large prostates [30].

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