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Early Detection of Prostate Cancer: Immunoassay for Serum Prostate Specific Antigen (PSA) Tumor Marker

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Background: Serum tumor markers are widely used clinically for monitoring response to therapy and detecting cancer recurrence. However, only a limited number of them have been effectively used for the early detection of cancer.
Objective: To review serum tumor markers used clinically, for the early detection of prostate cancer.
Methods: Literature review of serum tumor marker that have been widely accepted for the early detection of prostate cancer.
Results: In Nigeria only prostate specific antigen (PSA) has been clinically used for the early detection of prostate cancer. The analytical and clinical issues linked to its use were discussed.
Conclusion: Few serum tumor markers have been used effectively for the early detection of cancer, mainly due to their limited diagnostic sensitivity and specificity. PSA is the only tissue-specific marker identified, but it is not specific for prostate cancer. Various approaches have been developed to improve the clinical performance of PSA for the early detection of prostate cancer.

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1. INTRODUCTION

Prostate cancer is a significant health care problem in Nigeria due to its high incidence and mortality. It is the most common cancer in Nigeria males having overtaken liver cancer. Excluding superficial skin cancer, prostate cancer is the most common malignancy afflicting American men [1,2]. Since the advent in the late 1980s of prostate specific antigen (PSA) level as an effective screening test, the medical community has witnessed dramatic increase in the incidence of prostate cancer cases.

Prostate cancer screening or early detection has been accomplished using direct rectal examination (DRE), measurement of serum PSA (and its various forms), transrectal ultrasonography (TRUS) and combinations of these tests. Although DRE can detect prostate cancer, it detects fewer cancer cases than does PSA testing and, unfortunately, many cancer cases detected using DRE are either locally or regionally advanced [3]. Although serum PSA is a better screening test than DRE, DRE should not be abandoned as it may detect some cancers associated with a normal serum PSA level. Therefore, DRE should be combined with serum PSA testing. TRUS should not be used a first-line screening study as it lacks high specificity, is relatively expensive, and adds little information to that already gained by the use of serum PSA Testing and DRE [4].

An ideal serum tumor marker for the early detection of cancer should have several characteristics. It should be sensitive enough to detect small tumor at an early stage. It should be specific for a given type of cancer, not present in non-cancer (healthy and benign) conditions and released only in response to cancer. Currently, most serum tumor markers are neither sensitive nor specific enough for this purpose. PSA has been recommended for early detection in conjunction with digital rectal-examination, the application of this is discussed.

2. PROSTATE SPECIFIC ANTIGEN

PSA is a serine protease produced by benign and malignant prostate tissues. Although it is produced in small amounts elsewhere, including breast tissue, endometrium, and in a few malignancies other than prostate cancer, it should be considered to be organ-specific clinically [5,6,7,8,9]. PSA circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms [10,11,12]. Serum PSA is largely complexed by endogenous prostrate inhibitors, the most common being alpha 1 antichymotrypsin. Other proteins bind a smaller fraction.

Serum PSA may be elevated transiently in cases of prostatitis and after endoscopic urethral manipulation, prostatic biopsy and to a more limited extent, ejaculation [13,14].

Routine DRE actually has little effect on serum PSA, but most physicians defer PSA testing after such examination [15]. The half-life of serum PSA is 2.2 to 3.2 days [16,17]. Therefore one should wait approximately 4-8 weeks after significant prostate manipulation, such as that which occurs with prostatitis or prostate biopsy, before obtaining serum PSA. It should be emphasized that the most common cause for an elevated serum PSA level is BPH, the incidence of which increases with age as does the incidence of prostate cancer.

2.1 Total PSA for Early Detection

The risk of prostate cancer correlates with PSA concentrations and DRE findings. The positive predictive value of a serum PSA level between 4.0 ng/ml and 10 ng/ml is approximately 20% to 30% [18,19,20,21,22]. For levels in excess of 10ng/ml, the positive predictive value increases to 42% to 71.4%. The use of DRE complements serum PSA testing (Table 1).

The majority of cancers (>80%) detected by serum PSA are clinically significant as defined by cancer grade and volume (23). In contrast to the use of DRE alone for early detection of prostate cancer, the majority of PSA-detected cancers are confined clinically. However, as many as 40% of cancers detected by the use of serum PSA and DRE may have evidence of ECE, usually capsular penetration, if the prostate is removed surgically and examined pathologically [23].

The frequency of PSA testing remains a matter of some debate. In men with a normal DRE and a PSA level in excess of 2.5 ng/ml, PSA testing should be performed annually as approximately 50% of these patients may convert to having a PSA level exceeding 4.0 ng/ml [24,25]. The test can be performed biannually in those with a normal DRE and serum PSA level lower than 2.5 ng/ml, as conversion in this group is much less likely.

Table 1. Probability of prostate cancer based on serum prostate-specific antigen and digital rectal examination

Study	PSA < 4.0 ng/ml		PSA> 4.0 ng/ml	
	-DRE	+DRE	-DRE	+DRE
Cooner et al. 1990	9%	17%	25%	62%
Catalona et al. 1994	-	10%	32%	49%
Hammerer and Huland	4%	21%	12%	72%
Ellis et al. 1994	6%	13%	24%	42%

DRE, digital rectal examination; PSA, prostate-specific antigen
Adapted from ref (5)

Table 2. Age-adjusted prostate-specific antigen reference ranges

Age range (y)	White		African America	
	Reference range (ng/ml)	Specificity%	Reference range (ng/ml)	Specificity%
40-49	0.0-2.5	95%	0.0-2.0	93
50-59	0.0-3.5	95%	0.0-4.0	88
60-69	0.0-4.5	95%	0.0-4.5	81
70-79	0.0-6.5	95%	0.0-5.5	78

Adapted from ref (5)

Total PSA levels in serum have been classified into three categories: 0-4 ng/ml, 4.0 ng/ml, and >10.0 ng/ml. The risk of prostate cancer and necessity of a biopsy are accessed based on these categories. When the total PSA level is less than 4.0 ng/ml, the risk of cancer is considered to be low. However a recent study showed that up to 27% of men with the total PSA in the 3.1-4.0 ng/ml range had cancer [26]. When the total PSA is greater than 10 ng/ml, 40-50% of patients have cancer [27]; and biopsy is typically performed. When the total PSA level is in the 4.0-10.0 ng/ml range. However, only 25-35% of patients have cancer based on biopsy [28]; therefore this range is referred to as the diagnostic gray zone of total PSA [29].

3. ENHANCING PSA TEST PERFOR-MANCE

A number of different strategies have been developed to enhance PSA test performance, by increasing sensitivity in certain populations or specificity in others. These strategies include use of age-specific reference ranges, PSA velocity, PSA density, and its molecular forms of PSA (free or complexed PSA).

Perhaps the greatest enhancement of PSA testing has been based on the knowledge that PSA exists in the serum in both free and complexed forms (bound to serum protein). Stedman et al. [10] made the observation that the free form of serum PSA exists in a higher fraction in men without prostate cancer than in those with the disease. Others observed that the specificity of PSA testing for the detection of prostate cancer could be enhanced by calculating the free-to-total PSA ratio as compared to using total PSA alone [29].

3.1 Percent Free PSA for Early Detection

Percent free PSA (free PSA/total PSA x 100) recommended is for the risk assessment of prostate cancer when total PSA concentrations are between 4-10 ng/ml A % free PSA of > 25% indicates a low risk of cancer (e.g. probability = 8%) whereas a% free of < 10% suggests a high risk (e.g. probability = 56%) [28]. Percent free PSA has significantly increased efficacy of the early detection of prostate cancer by reducing unnecessary biopsies. A cut off of 25% detected 95% of cancers and reduced the biopsy rate by 20% when total PSA levels were between 4-10 ng/ml [30]. However, percent free PSA is not perfect. It is recommended that the percent free PSA be calculated using free and total PSA immunoassays from the same manufacturer. High analytical precision is important for free PSA especially at low levels to reduce overlays between men with and without cancer [31,32].

The percent free PSA has been used to improve the sensitivity and specificity in detecting prostate cancer, particularly for patients in the diagnostic “gray” zone of the PSA between 4 and 10 ng/L. [33,34].

4. PSA VELOCITY

PSA velocity is the rate of PSA increase as a function of time by establishing a baseline level of PSA in each patient, the rate of increase of PSA is then calculated. The increase of PSA in health, BPH and prostate cancer appears to be different with the highest rate (greater than 0.75 ng/L/Yr) observed in patients with prostate cancer [35]. A 1996 study of free PSA velocity found that percent free PSA is the earlier serum marker for predicting subsequent diagnosis of prostate cancer [36].

PSA velocity calculates changes in total PSA levels overtime. The rationale for PSA velocity is based on the assumption that prostate cancer increase PSA levels in blood faster than other benign prostate conditions do. There are many ways to calculate PSA velocity [37]. Carter et al used the equation as follows [38]:

PSA Velocity = ½ x PSA2 – PSA 1/Time1 x ½ x (PSA3 – PSA2)/Time 2

PSA1 is the first total PSA measurement, PSA2 the second and PSA3 the third in two-year period or at least 12 to 18 months apart. Time 1 and 2 are differences in time expressed in years. PSA velocity has significantly improved the cancer specificity of PSA especially in differentiating between cancer and BPH [39].

5. AGE-SPECIFIC REFERENCE RANGES FOR PSA

The age-specific reference ranges are attempt to compensate for the fact that the standard reference range of 0.0 to 4.0 ng/ml does not reflect age related volume changes in the prostate due to BPH. A single cut off may therefore be inappropriate for all ages. Many investigators have proposed age-related reference ranges to improve test sensitivity in younger men (who have less BPH and therefore would be expected to have BPH and higher PSA values that accompany it [40].

The biopsy rate has been shown to decrease approximately 21% in older men undergoing screening if age-specific reference ranges remains controversial: some investigators have shown no benefit to their use as compared to use of the standard cut off point of 4.0 ng/ml. There are contradictory guidelines by medical organizations on screening for prostate cancer. The recommendation for prostate cancer screening by the American Urological Association and the American Cancer Society is for all men aged 50 years and above with life expectancy >10 years and starting at age 40-45 years for high-risked men (e.g. African Americans and those with affected first degree relatives) [41,42].

However the national Cancer Institute [43] and the United States Preventive Service Task Force [44] do not recommend screening for prostate cancer in the general population or high risk individuals. Prostate cancer screening may reduce mortality from the disease almost by half but with a substantial risk or over diagnosis [45]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) also demonstrated that population-based screening of men aged 55-75 years can reduce prostate cancer mortality [46,47].

6. DATA ON PROSTATE CANCER IN NIGERIA

Prostate cancer is a leading cancer diagnosis and cause of cancer-related deaths among men. It is the most commonly diagnosed cancer among Nigerian men [48,49]. An estimated hospital prevalence of 127 per 100,000 in Lagos Nigeria was reported in 1997 [50]. A recently published data from South-western Nigeria also reported a hospital prevalence rate of 182.5 per 100,000 male admissions in the Hospital [51]. However, the true prevalence in the Nigerian community is not known. In the United States, prostate cancer has been described to be more prevalent among the African-Americans. The incidence of prostate cancer among white American men is 156.7 per 100,000 population compared with 248.5 for Black Americans [52]. However, the incidence among the black African community may be underestimated [53,54]. Prostate cancer screening is not a common practice in Nigeria in spite of prostate cancer being the most commonly diagnosed cancer in Nigeria. Awareness about prostate cancer is also poor [55,56]. A community based testing for prostate cancer in Lagos, Nigeria has created more awareness about the disease in the community and also helped to show the status of the disease in the community better than a hospital-based study. The estimated prevalence of prostate cancer in this study was at least 104.6 per 100,000 men of age 40 years above. This value is much greater than the previously reported in a hospital-based study in Lagos and appears similar to report from Saudi Arabia [57]. Most men with prostate cancer in the study

(74%) already have advanced disease. This is a very high figure when compared to only 4% of prostate cancer patients with metastatic disease at the time of diagnosis in United States where PSA testing is a common practice [58]. The normal range of serum total PSA values in our community is generally not known. Values≤4 mg/L are generally used as the normal range. These are suggestions that African men may have a higher PSA value than what is a generally accepted value for Caucasian possibly because of a higher prostate volume or chronic prostate inflammation [59] in a recent study conducted in a community-based screening in Nigeria using serum prostate specific antigen and digital rectal examination. The 95th percentile PSA value reported was 4.5 ng/L and 13.4 ng/L for men aged, 40-49 years and 70 years respectively, while the overall 95th percentile PSA Value was 10 ng/L [60]. This may suggest that men in our environment generally have a higher PSA value than the Caucasian counterpart.

7. CONCLUSION

One minimally invasive method for early detection and therapeutic monitoring of prostate cancer involves measurement of PSA. Many strategies have been used to improve the sensitivity or specificity of PSA. Immunologic assays measuring total, free and complexed are commercially available. Measuring the percentage of free PSA or the amount of complexed PSA may improve the specificity of the assay and the ability to detect prostate cancer is greatly enhanced.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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