

**EARLY DETECTION OF PROSTATE CANCER: IMMUNOASSAY FOR SERUM
PROSTATE SPECIFIC ANTIGEN (PSA) TUMOR MARKER.**

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.

Keywords

Serum, tumor marker, early detection, prostate cancer.

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 than does PSA testing and, unfortunately, many cancers 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, and 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 4.0ng/ml and 10ng/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 2.5ng/ml, PSA testing should be performed annually as approximately 50% of these patients may convert to having a PSA level exceeding 4.0ng/ml [24,25]. The test can be performed biannually in those with a normal DRE and serum PSA level lower than 2.5ng/ml, as conversion in this group is much less likely.

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

3. Enhancing PSA Test Performance

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 4-10ng/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 4-10ng/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 10ng/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 0.75ng/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]:

$$\text{PSA Velocity} = \frac{1}{2} \times \frac{\text{PSA}_2 - \text{PSA}_1}{\text{Time}_2 - \text{Time}_1} \times \frac{1}{2} \times \frac{\text{PSA}_3 - \text{PSA}_2}{\text{Time}_3 - \text{Time}_2}$$

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].

5.0 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 4.0ng/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 4.0ng/ml

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.

Table 1 Probability of Prostate Cancer

Based on serum prostate-specific Antigen and Digital Rectal Examination

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

DRE, digital rectal examination; PSA, prostate-specific antigen

Adapted from ref (5)

150 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

151 Adapted from ref (5)

152 **REFERENCES**

- 153 1. Landis SH, Murray T, Bolden S, et al: Cancer statistics,. CA cancer J Clinical 1998 48:6,.
- 154 2. Cancer statistics. CA cancer J clin 1999; 49:8
- 155 3. Thompson IM, Eruct JJ, Gangai MP, Spence CR Adenocarcinoma of the prostate results
- 156 of routine urological screening. J. urol 1984; 132:690.
- 157 4. Coley CM Barry MJ, Fleming C should Medicare provide reimbursement for prostate-
- 158 specific antigen testing for early determination strategies. Urology 1995;46:125
- 159 5. Polascik TJ, Oesterling JE, Partin AW. Prostate-specific antigen: a decade of discovery –
- 160 what we have learned and where we are going. J .urol 1999; 162-293.
- 161 6. Yu H, Diamondis EP, Sutherland DJ. Immunoreactire prostate-specific antigen levels in
- 162 female and male breast tumors and its association with steroid hormone receptors and
- 163 patient age. Clin Biochem 1994; 27:75.
- 164 7. Yu H, Diamondis Ep, prostate-specific antigen in milk of lactating women. Clin Chem.
- 165 1995;41;54
- 166 8. Yu H, Diamondis EP. Measurement of serum Prostate- specific antigen in level women
- 167 and in prostatectomized men with an ultrasensitive immunoassay technique J. Urol 1995;
- 168 153:1004
- 169 9. Levesque M, Hu H, D' Costa M, Diamondis EP. Prostate-specific antigen expression by
- 170 various tumors. J Clin Lab Anal 1995;9:123
- 171 10. Sterman UH, Leinonen J, Alfhian H,. A complex between prostate-specific antigen and
- 172 alpha 11. Anti-chymotrypsin is the major form of prostate-specific antigen in serum of
- 173 patients with prostatic cancer assay of the complex improves chemical sensitivity for
- 174 cancer. Cancer Res 19991; 51:222
- 175 11. Lilja H, Christenson A Dahlen U,. Prostate-specific antigen in serum occurs
- 176 predominantly in complex with alpha 1- antichymotrypsin Clin 1991;37:1618
- 177 12. MC Cormack RT Ritten house HG, Finlay JA Molecular Forms of Prostate-Specific
- 178 Antigen and the Human Kallikrein gene family: a new era. Urology 1995;45:729

- 179 **13.** Nadler RB, Humphrey PA Smith DS Catalonia WJ, Ratliff. TL. Effect of Inflammation
180 and Benign Prostatic Hyperplasia on elevated Serum Prostate-Specific Antigen Levels. J.
181 Urology 1995;154:407
- 182 **14.** Tchetgen MB, Song JT, strawderman M, Jacobsen SJ, Oesterling JE. Ejaculation
183 Increases the Serum Prostate-Specific Antigen Concentration. Urology 1996;47:511
- 184 **15.** Chybowski FM, Bergstralh EJ. O sterling JE. The Effect of Digital Rectal Examination
185 on the Serum Prostate-Specific Antigen Concentration: Result of randornized study. J.
186 Urology 1992; 148:83
- 187 **16.** Oesterting JE, Chan DW, Epstein JI. Prostate-specific antigen in the preoperative and
188 postoperative evaluation of localized prostatic cancer treated with radical prostatectomy.
189 J .urol 1988;139:766
- 190 **17.** Stamey TA, Yang N Hay AR. Prostate-specific antigen as serum markers for
191 adrenocarcinoma of the prostate. N. Engl J.Med 1987;317:909
- 192 **18.** Woolf SH screening for prostate cancer with prostate –specific antigen: An examination
193 of the evidence N. Engl J.Med 1995; 33; 1401
- 194 **19.** Cooner WH, Mosley BR R Rutherford CL Jr. Prostate cancer retraction in a clinical
195 urological practice by ultrasonography digital rectal examination and prostate-specific
196 antigen. J urol 1990; 143: 1146
- 197 **20.** Catalona WJ Richie JP; Ahmann FR. Comparison of digital rectal examination and serum
198 prostate-specific antigen in the early detection of prostate cancer: result of multicenter
199 clinic trial of 6,630 men. J urol 1994; 151: 1283
- 200 **21.** Ellis Wj, Chetner MP, Preston SD Brawer MK. Diagnosis of prostatic carcinoma: the
201 yield of serum prostate-specific antigen. Digital rectal examination and transrectal utral
202 sonography. J urol 1994; 152:1520
- 203 **22.** Brawer M, prostate-specific antigen CA cancer J Clin 1999;49:264
- 204 **23.** Epstein JI, Wash PC, Carmichael M, Brendler CB pathologic and clinical finding to
205 predict tumor extent of non palpable (stage T1c) prostate cancer. JAMA 1994;271:368
- 206 **24.** Carter HB Epstein JI Chan DW, Fozard JL, Person JD Recommended prostate-specific
207 antigen testing intervals for the detection of curable prostate cancer JAMA
208 1997;277:1456
- 209 **25.** Smith DS, Catalona WJ Herschman JD, Longitudinal screening for prostate cancer with
210 prostate-specific antigen JAMA 1996; 276: 1309
- 211 **26.** Thompson IM Pauler DK, Goodman PJ. Prevalence of prostate cancer among men with a
212 prostate-specific antigen level < or = 4.0ng per milliliter N Engl J Med 2004 may 27;350
213 22:2239-2246
- 214 **27.** Sturgeon CM Duffy MJ Stenman UH. National academy of clinical Biochemistry
215 laboratory medicine practice guidelines for use of tumor markers in testicular, prostate,
216 colorectal breast and ovarian cancers. Clin chem. 2008 Dec: 54 12:11-79
- 217 **28.** Brawer MK prostate-specific antigen: current status. CA cancer J clin 1999 sept-oct:
218 49,5: 264-281

- 219 **29.** Christensson A, Bjork T, Nilsson O et al Serum Prostate Specific antigen complexed to
220 apha-antichynotrsin as an indicator of prostate cancer. J. urol 1993; 150:100
- 221 **30.** Catalina WJ, Partin AW Slawin KM use of the percentage of free prostate-specific
222 antigen to enhance differentiation of prostate cancer from benign prostate disease: a
223 prospective multicenter clinical trial JAMA 1998 may 20; 279 19 : 1542-1547
- 224 **31.** Woodrum D French C shamel LB stability of free prostate-specific antigen in serum
225 samples under a variety of sample collection and sample storage conditions. Urology
226 1996 Dec; 48:33-39
- 227 **32.** Paus E, Nilson O, Boroner op. Stability of free and total prostate-specific antigen in
228 serum from patients with prostate carcinoma and benign hyperplasia. J urol 1998 may
229 159 5: 1599-1605
- 230 **33.** Hauchett CL, Schwartz GG. Geographic patterns of prostate cancer mortality. Evidence
231 for a protective effect of ultraviolet radiation. Cancer 1992; 70:2861
- 232 **34.** Partin AW, Catalona WJ Southwick PC, Analysis of percent free prostatic-specific
233 antigen (PSA) for prostate cancer detection: influence of total PSA prostate volume and
234 age. Urology 1996; 48 55-61
- 235 **35.** Carter HB, Pearson JD metter EJ, , Longitudinal evaluation of prostate-specific antigen
236 levels in men with and without prostate disease. JAMA 1992;267:2215-20
- 237 **36.** Person JD Uderer AA, Metter EJ. Longitudinal analysis of serial measurements of free
238 and total PSA among men with and without prostatic cancer urology 1996;48:4-9
- 239 **37.** Loeb S, kettermann A, Ferrucci, L,. PSA doubling time versus PSA velocity to predict
240 high-risk prostate cancers: data from the Baltimore longitudinal study of Aging. Eur urol
241 2008 Nov; 54:5:1073-80
- 242 **38.** Meany DL, Sokoll LJ, Chan DW. Early detection of cancer: Immunoassays for plasma
243 tumor markers. Expert Opin Med Diagn. 2009 Nov 1; 3(6): 597-605
- 244 **39.** Carter HB, Pearson JD. PSA Velocity for the diagnosis of early prostate cancer. A new
245 concept. The urologic clinics of North America 1993 Nov 20 4:665-670
- 246 **40.** Oesterling JE, Cooner WT Jacobsen SJ. Gness H A,Lieber MM. Influence of patient age
247 on the serum PSA concentration. An important clinical observation. Urol Clin North AM
248 1993; 20:671