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PSA Levels and the Probability of Prostate Cancer on Biopsy

Matthew B. Gretzer*, Alan W. Partin

Department of Urology, The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, USA

Abstract

Objectives: Approaches to screening for prostate cancer have continued to be refined since the introduction of prostate-specific antigen (PSA). Since the introduction of PSA, increasing numbers of patients are presenting solely with an elevated PSA, and palpably normal prostate gland. As newer understanding emerges regarding the meaning of an isolated PSA elevation, urologists are becoming more enabled to counsel their patients and project a more accurate prediction of the likelihood of cancer on biopsy. The following will be a review of PSA in determining the presence of cancer on biopsy.

Methods: PubMed and Medline literature searches as well as bibliographic reviews of published peer reviewed journals were performed to select articles regarding PSA and screening for prostate cancer. Relevant articles were reviewed and the data summarized as they pertain to interpreting PSA levels and predicting the presence of prostate cancer.

Results: Widespread use of PSA for early detection has resulted in clinical stage T1c becoming the most prevalent presenting stage. For values of PSA between 4.0 and 10.0 ng/ml, there exist a 22–27% likelihood of cancer, while those above 10 ng/ml yield up to a 67% chance of cancer. It must be stressed that DRE must be combined with interpretation of PSA as up to 25% of men with prostate cancer have PSA levels within the normal range 0–4 ng/ml.

Conclusions: Evaluation of PSA in the context of prostate volume (PSAD), velocity (PSAV), and age-specific reference ranges, percent-free PSA, and predictive nomograms combining values have allowed for more accurate prediction of the likelihood of prostate cancer prior to biopsy.

Keywords: PSA; BPH; DRE; PSAD; PSAV; Percent-free PSA; Age-specific PSA

1. Introduction

As we enter the 21st Century, prostate cancer continues to be the most commonly diagnosed malignancy in men, and the second most common cause of death among men due to non-cutaneous cancer [1]. Recent data revealed that up to 180,400 new diagnoses, and approximately 30,400 deaths due to prostate cancer occurred in 2000 [1]. Thus, early detection of clinically significant cancer remains important. The use of prostate-specific antigen (PSA) coupled with digital rectal examination (DRE) has led to improved detection of prostate cancer and has resulted in earlier diagnosis and treatment [2,3]. These improvements have evolved from both clinical and basic science research, and have greatly impacted routine clinical urology practice today. In the case of PSA, urologists are now being faced with more referrals for isolated PSA elevations. This is illustrated by the 25 million men who underwent PSA testing worldwide in 1998, and the resulting 15% who were identified with an elevated PSA (>4 ng/ml) [1,4]. Of those men who went to transrectal ultrasound guided (TRUS) biopsy 25% ultimately had a diagnosis of prostate cancer [1]. In the face of these overwhelming statistics is the individual man with an elevated PSA asking the urologist *his* likelihood of having prostate cancer. The following will be an overview of the use of PSA in determining the presence of prostate cancer on biopsy. While vast amounts of new information continue to be discovered, this paper will focus on PSA, and due to space constraints will not

* Corresponding author. Tel. +1-410-614-4494; Fax: +1-410-614-8096.
E-mail address: gudoc@axs.net (M.B. Gretzer).

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address the affects multivariate analysis of neural networks or the use of molecular forms of PSA and their ability to augment PSA's utility.

2. PSA

Prostate-specific antigen is a 33 kD serine protease of the Kallikrein family that is produced primarily by prostatic luminal epithelial cells [5]. The function of this enzyme, after it is secreted in high concentrations into the prostatic ductal system, is to serve as a liquifactant of the seminal coagulum. While PSA is primarily produced by prostatic epithelial cells, PSA has also been noted to be detected in trace amounts in the periurethral glands, endometrium, normal breast tissue, breast tumors, breast milk, female serum, adrenal neoplasms, and renal cell carcinomas [6–12]. However, quantifiable levels used in clinical practice essentially make PSA organ-specific leading to its use as an important marker of prostatic disease. A limiting factor of PSA is its organ specificity, and the fact that it is not prostate cancer-specific. As a functional product of normal prostatic epithelial tissue, PSA levels will not only reflect changes due to cancer, but also changes due inflammation, trauma, or benign proliferation. Because PSA is usually found in low concentrations in serum, measured elevations of PSA in serum have allowed it to become an important marker for prostate cancer [13]. While controversy exists regarding the mode of transport into the serum, elevations of PSA during disease processes are believed to be a product of the disruption of the normal cellular architecture within the normal prostate gland [5,14]. The loss of the barrier afforded by the basal layer and basement membranes within the normal gland are described as a likely site for the egress of PSA into the circulation during prostatic disease [14].

3. Understanding serum levels of PSA

Early studies performed by Myrtle and Ivor in 1989 established a reference range of 0–4.0 ng/ml to define normal PSA levels [13]. This level was obtained using the Tandem-R assay (Hybritech) in 860 healthy men. Their analysis revealed that values in all men under age 40, and 97% of men over 40 were less than or equal to 4.0 ng/ml. Results from large screening studies have further supported these values in determining "normal" levels. While further studies have attempted to refine the sensitivity and specificity of these levels, to date, these values remain the standard from which elevations are compared [2,15–17].

Information regarding the clinical presentation is paramount to the interpretation of an elevated serum PSA. As noted earlier, other prostatic disease processes may affect PSA. Elevations due to instrumentation, such as from biopsy or urethral procedures require up to 4 weeks before accurate levels may be obtained; as the half-life of PSA is up to 2.2–3.2 days [18–20]. Other types of manipulation such as that from DRE have been found not to be associated with a significant elevation on PSA, and thus, rarely produce false-positive results [18]. While PSA elevations are suggested to occur following catheterization or cystoscopy, studies evaluating this have failed to confirm a strong association [19]. In either event, it has been commonly recommended to evaluate PSA prior to any prostatic manipulation in order to eliminate potential confounding factors that may lead to a "false-positive" interpretation of elevations [21]. Inflammation due to infection has been found to produce significant elevations in PSA [22]. In this circumstance, it is suggested that PSA evaluation occur after appropriate medical therapy, and that a time interval up to 6–8 weeks may be required for PSA to return to baseline [22,23]. Early controversy regarding the use of PSA was born from suspicion that the contributions to serum PSA from prostate cancer and benign hyperplasia overlap [5,14,22]. However, the degree to which BPH contributes to serum PSA has since been questioned as prostate cancer has been found to produce PSA concentrations up to ten times higher per gram of tissue than BPH [5,14,22]. Thus, further evaluation is warranted when confronted with an elevated PSA level.

4. Use in screening

Since its discovery in the early 1970s, and then introduction into clinical use in 1988, PSA has become one of the most important tumor makers in cancer detection today. While the long-term benefits of early detection of this cancer remain to be determined from ongoing longitudinal trials, current use of this marker has increased. Recent data from the SEER project have revealed that the widespread use of PSA for early detection has resulted in stage T1c becoming the most prevalent clinical stage [24]. This large stage migration has resulted in an earlier stage at presentation for 75% of men, and an earlier age at diagnosis. Through earlier detection it is believed that more cancers may be localized and potentially curable. When evaluated in the context of DRE in large scale screening populations, PSA was found to be effective in determining

significant prostate cancers [2]. Efforts to focus the ability of PSA to detect these curable cancers have continued to yield encouraging results.

5. Refining the meaning of PSA levels

Initial examinations of PSA as a screening tool revealed somewhat mediocre sensitivity and specificity results for PSA alone [25,26]. With values of 67.5–80% sensitivity and 70% specificity, many cancers would be missed and too many unnecessary biopsies would be performed [15,16,21,27]. Methods to improve these values, and ultimately the positive predictive value of PSA in early detection have evolved with the goal of detecting more cancer earlier in life while limiting the number of unneeded biopsies. The evaluation of PSA in the context of prostate volume (PSAD), PSA velocity (PSAV), age-specific reference ranges, and percent-free PSA have assisted in achieving this goal [3,21,28–32].

Prostate-specific antigen density has been evaluated to correlate the degree to which cancer contributes to the serum PSA as determined from transrectal ultrasound determined volume. While a value of 0.15 ng/ml has been shown in a large study to be consistent with the presence of cancer in those men with a PSA between 4 and 10 ng/ml (Fig. 1) [28], other studies have debated whether this value might miss significant cancers, or is a significant value all together [29,33,34]. Debate regarding TRUS technique and the variation of epithelium to stroma has questioned the accuracy of this method. Nonetheless, given these limitations, PSAD has become an additional tool in the evaluation of an elevated PSA in predicting the likelihood of cancer.

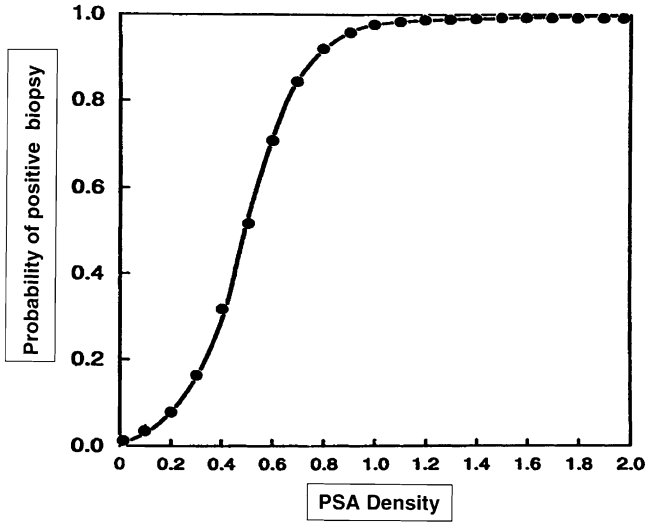

Fig. 1. PSA density values for detecting prostate cancer. Logistic regression demonstrating PSAD for detecting cancer in men with PSA values 4.0–10.0 ng/ml and palpably normal prostate. Adapted with permission from Seamen and Whang [28] (Saunders, Mosby).

The rate of change of PSA has been found to be quite specific in predicting the presence of cancer. Initial studies found that a velocity of >0.75 ng/ml per year was 72% sensitive and 95% specific in predicating prostate cancer in men with PSAs under 10 ng/ml [30,35,36]. Follow-up studies by other investigators confirmed that elevated rate of change of PSA can be used to aid in the detection of cancer [37]. Among the limitations regarding the use of PSAV are the difficulty with the equation, establishing the appropriate time frame for evaluation, and the variation of PSA between laboratories. However, from review of the research regarding PSAV, a value of 0.75 mg/ml year has been found to aid in the detection of cancer when performed with a minimum of three serial PSA values over at least 2 years. Examining the velocity of PSA change with time has further aided in detecting cancer among not only those men with an elevated PSA, but also among men with a PSA within the accepted normal range of 0–4 ng/ml [21,28].

Interpretation of PSA within age-specific time intervals has been advocated to increase the sensitivity of PSA [27,39]. The measurement of PSA is affected by changes in production and secretion as well as prostate volume that occur during the aging process, and is not accurately represented in the standard single reference levels (4.0 ng/ml) as mentioned above [25]. In attempts to increase the sensitivity of identifying cancer in younger men and the specificity (spare biopsy) in older men, age-specific references ranges have been established (Table 1) [39]. The benefit of using these reference ranges is to more accurately identify potentially localized tumors amendable to therapy while sparing older men with clinically insignificant tumors the associated morbidity of unnecessary treatment. These ranges have been found to increase the specificity of PSA in detecting cancer in men less than 60 years of age [27,39,40]. However, it has been argued that this is achieved at the cost of more negative TRUS biopsies [41]. Large multicenter screenings have evaluated this topic and debate the existence of any significant advantages of these reference ranges, and favor the use of the established standard assay range of 0–4.0 ng/ml as they apply to all ages [2,16]. This controversy has limited wide-spread use of these age-specific levels, and it is recommended that these additional reference ranges be used with discretion in case-by-case situations as an adjunct to interpretation of PSA and cancer risk [21].

Table 1
Comparison of free PSA in detecting prostate cancer

Reference	PSA assay	Total PSA range (ng/ml)	Cancer/no cancer	Percent-free PSA cutoff	Sensitivity	Specificity
Luderer et al. [53]	Immunocorp free + TOSOH total	4.0–10.0	25/32	25	100	31
Catalona et al. [44]	Hybriecth free + tandem total	4.0–10.0	63/50	20	90	38
Bangma et al. [54]	Delfina free + total	4.0–10.0	33/107	28	91	19
Chen et al. [55]	Immunocorp sciences free + TOSOH total	2.5–20.0	165/263	25	95	26
Prestigiacomo et al. [56]	Hybritech tandem free + total	4.0–10.0	20/28	14	95	64
Elgamal et al. [57]	Centocor free + total	3.0–15.0	37/48	18	95	40
Van Cangh et al. [58]	Hybritech tandem free + total	2.0–10.0	90/205	25	90	38
Catalona et al. [16]	Hybritech tandem free + total	2.6–4.0	52/232	26	90	24
Partin et al. [32]	Hybrietech free + tandem total	4.0–10	139/78	20	95	29

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6. Free PSA

The discovery of bound and unbound molecular forms of PSA have also contributed to the detection of cancer by PSA. Men with prostate cancer have a lower percentage of total PSA that is unbound and ''free'' within the serum. Thus, the probability of having cancer increases as the percentage of free PSA diminishes [42,43]. Recent studies evaluating free PSA have illustrated enhanced sensitivity for PSA less than 4.0 ng/ml and specificity of PSAs between 4.0 and 10.0 ng/ml [16,32,44–46]. The values of 14–27% free PSA have shown enhancement for PSA to detect cancer within the range of 4.0–10.0 ng/ml. This discrepancy in percent-free PSA value is a product of the various assays used to investigate this claim (Table 2). Catalona's data suggest that using a 27% cutoff for percent-free PSA will allow the detection of up to 22% more cancer for PSAs 2.6–4.0 ng/ml [16,45]. The application of free PSA to clinical practice continues to be investigated. However, percent-free PSA exhibits promise in the early detection of prostate cancer, and no doubt may aid the urologist in counseling a patient during the work-up of an elevated PSA.

Table 2
Age-specific reference ranges for serum PSA

Age range	Reference range (ng/ml)		
	Caucasian	African American	Asian
40–49	0.0–2.5	0.0–2.0	0.0–2.0
50–59	0.0–3.5	0.0–4.0	0.0–3.0
60–69	0.0–4.5	0.0–4.5	0.0–4.0
70–79	0.0–6.5	0.0–5.5	0.0–5.0

Reprinted with permission from Oesterling et al. [31].

7. Predicting cancer on biopsy

The individual patient comes with one question in hand, ''what is the likelihood that I have cancer?'' The aforementioned methods have been shown to enhance the positive predictive value of PSA in detecting prostate cancer. While there is debate over the exact degree of increased risk, most investigators agree that PSA is an objective measure of cancer risk, and that this risk is directly related the PSA level (Fig. 2). These studies of screened populations have shown that levels of PSA between 4 and 10 ng/ml yield a 22–27% likelihood of cancer, while those above 10 ng/ml produce

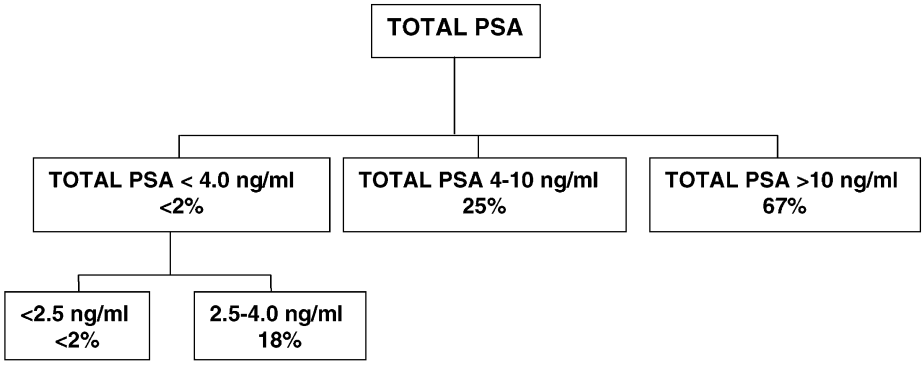

Fig. 2. Probability of prostate cancer by total PSA level. Flow chart of probability of prostate cancer based on presenting PSA level.

Table 3
Probability of detecting prostate cancer on biopsy as a function of age, PSA, and DRE

PSA (ng/ml)	Age <50		Age 51–60		Age 61–70		Age 71–80	
	DRE−	DRE+	DRE−	DRE+	DRE−	DRE+	DRE−	DRE+
<2.5	9	37	12	39	15	42	20	44
2.6–4.0	9	41	12	42	16	44	20	47
4.1–6.0	10	41	14	44	17	47	22	48
6.1–10.0	11	–	15	48	19	50	25	42
10.1–20.0	13	55	19	54	25	58	31	60
>20.0	22	82	45	74	43	81	59	8

95% CI within 2–12%, reproduced with permission from Potter et al. [49].

up to a 67% chance of cancer [5,15,16,38,47]. Although these studies illustrate the increased PPV of PSA in detecting cancer, it has been shown that DRE must be combined with PSA during screening as 11–25% of men with prostate cancer have PSAs within the normal range 0–4.0 ng/ml [2,47,48].

A recent study has created a predictive nomogram using age, DRE status and PSA level to establish likelihood percentages of cancer prior to TRUS biopsy [49]. This study concluded that after appropriate multivariate analysis, patient age, serum PSA, and DRE findings were significant variables in predicting the probability of prostate cancer detected on biopsy [49]. When stratifying for age, men with palpably normal prostate gland and PSAs between 4.1 and 10.0 ng/ml, the probability of detecting cancer on biopsy was 10–25%, and for values above 10.1 ng/ml the probability ranged from 13 to 59%. While limitations in sample selection exist within this study, it presents further support to previous studies that information about patient age and DRE status further enhance the predictive value of PSA in determining the presence of cancer. This data will no doubt be useful in counseling patients (Table 3) who present for evaluation of an elevated PSA.

Eastham et al. evaluated the operational characteristics of PSA between 0 and 4.0 ng/dl as an initial test for prostate cancer. These investigators suggest that because many men avoid screening secondary to DRE, a nomogram that determines the worst case probability of a positive biopsy as a function of PSA level may assist men

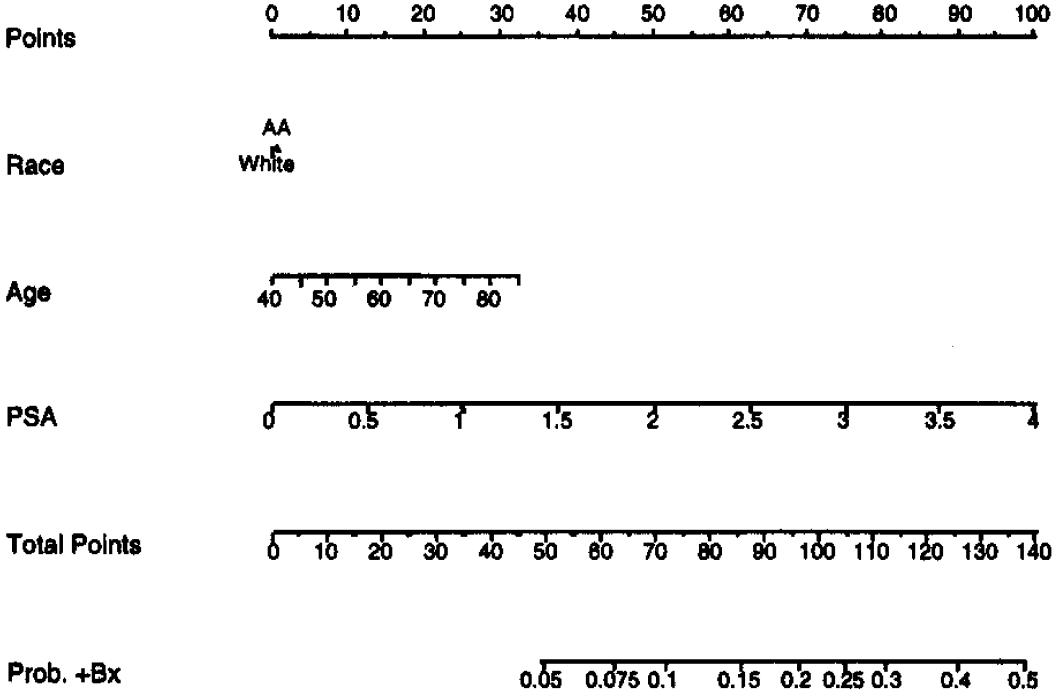

Fig. 3. Nomogram predicting the probability of a positive prostate biopsy. *Directions*: Locate the patients age on the age axis. Draw a straight line upward to the points axis to determine how many points toward the probability of a positive prostate biopsy the receives for age. Repeat the process for PSA. Sum the points. If the patient is African American, add an additional two points. Locate the final sum for age, PSA, and race on the total points axis. Draw a straight line down to find the patient's probability of having a positive prostate biopsy. Adapted with permission from Eastham et al. [50] (Elsevier, Amsterdam).

in arriving at more informed decisions regarding further evaluation for diagnosis of prostate cancer. Evaluating 700 men with serum PSA less than 4.0 ng/dl and suspicious DRE, this study developed a nomogram using race, age, and serum PSA to predict the probability of a positive prostate biopsy in men with a PSA less than 4.0 ng/dl and a suspicious DRE (Fig. 3) [50].

8. Conclusion

It has been established that DRE and PSA are the most useful front-line methods for assessing an individual's risk of prostate cancer [51,52]. In addition to an elevated PSA above 4.0 ng/ml, and an abnormal DRE, the decision to proceed with TRUS biopsy may also be supported by other factors. Determining the presence of a significant rise between PSA testing, whether the degree of PSA is concordant to the size of the prostate, and age appropriate PSA may aid in the interpretation of this risk. Also, with the use of predictive nomograms, the urologist has an array of resources from which to counsel the patient who presents with an elevated PSA. With continued discovery, more specific methods of interpretation will contribute to the evaluation of risk.

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