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Prostate-Specific Antigen and Diagnosing Early Malignancies of the Prostate

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Abstract Prostate-specific antigen is a kallikrein-like serine protease that is produced exclusively by the epithelial cells of all types of prostatic tissue, benign and malignant. Physiologically, it is present in the seminal fluid at high concentration and functions to cleave the high molecular weight protein responsible for the seminal coagulum into smaller polypeptides. This action results in liquefaction of the coagulum. Prostate-specific antigen is also present in the serum and can be measured reliably by several different assays.

Although the protein is prostate-specific, it is not prostate-cancer-specific. As a result, benign conditions such as benign prostatic hyperplasia, prostatitis and infarction, as well as prostatic intraepithelial neoplasia, can be associated with elevated serum levels of prostate-specific antigen. Approximately 25% of men with benign prostatic hyperplasia have an elevated serum value of prostate-specific antigen, whereas 35% to 40% of patients with organ-confined prostate cancer have a level within the reference range. Prostate-specific antigen can identify some cancers not detectable by digital rectal examination; alternatively, this examination can identify cancers not detectable from the serum prostate-specific antigen concentration. Thus, the most complete evaluation of the prostate gland is achieved when both the prostate-specific antigen value and the digital rectal examination are used.

The density and the rate of change of serum prostate-specific antigen are new concepts to improve the ability of prostate-specific antigen to detect early prostate cancer. Preliminary results are encouraging, but additional studies are required to determine the true usefulness of these new variables. Thus, in 1992, determination of the prostate-specific antigen value is a valuable new tool for the practicing physician and will be instrumental in our campaign to diagnose clinically significant prostate cancer at an early, curable stage.

Key Words: PIN, prostate carcinoma, PSA density, PSA velocity, screening, tumor progression

Prostate-specific antigen (PSA) is a glycoprotein that was first identified in seminal plasma by Hara and associates in 1971 [1]. They referred to this newly recognized component of human seminal plasma as γ-seminoprotein. Two years later, Li and Beling [2] were able to isolate and purify this same protein, also from human seminal plasma. They found the protein to have a low molecular weight of approximately 31,000 daltons, a slow β-mobility on electrophoresis, and a high diffusion rate in agar medium. They called this protein E_1 antigen, according to its mobility in conventional electrophoresis. In 1978, Sensabaugh [3] first truly characterized this "semen-specific protein" with immunoelectrophoretic analysis. He determined that this protein was indeed highly immunogenic and had several sugar moieties; the molecular weight was 30,000 daltons, and its isoelectric points ranged from 6.5 to 8.0. He designated it p30 because of its molecular weight.

In 1979, Wang and colleagues [4] isolated an antigen from prostatic tissue, purified it, and demonstrated its specificity with prostatic tissue. Although it was identified in all types of prostatic tissue (normal, benign hyperplastic, and malignant), it could not be found in any other human tissue. With gel filtration and gel electrophoresis, it was demonstrated to have a molecular weight of 33,000 to 34,000 daltons, have a single isoelectric point of 6.9, and to exist as a monomer. This report first described the purification of an antigen that was prostate-specific and distinct from prostatic acid phosphatase. Because of its association with prostatic

tissue only, it was termed "prostate-specific antigen." Subsequently, Wang and associates [5] demonstrated that the PSA found in seminal plasma was immunologically identical and biochemically similar to that isolated from the prostate gland.

Finally, Papsidero and coworkers [6] were able to identify PSA in human serum and verify that this molecule was identical to the one purified directly from prostatic tissue. Thus, from these studies and others [7,8], it became clear that PSA could be measured reliably in the serum and that it was specific for the prostate. Indeed, the *only organ-specific* serum marker in all of cancer biology had been discovered.

BIOMOLECULAR CHARACTERISTICS OF PSA

For assessment of the ability of the serum PSA value to identify premalignant and early malignant lesions of the prostate, it is necessary to have a complete understanding of the biomolecular and physiologic properties of this tumor marker. Biochemically, PSA is a single-chain glycoprotein that contains 93% amino acids and 7% carbohydrates [9]. It is a monomer with 240 amino acid residues and 4 carbohydrate side chains (Fig. 1). Evidence suggests that an N-linked carbohydrate side chain exists at amino acid 45 (asparagine) and that O-linked carbohydrate side chains are attached to amino acid 69 (serine), 70 (threonine), and 71 (serine) [10]. The N-terminal amino acid is isoleucine, and the C-terminal residue is proline. The overall molecular weight is 34,000 daltons, and the isoelectric points range from 6.8 to 7.2 because of various isometric forms [11]. With use of five murine monoclonal antibodies (1A5, 2A4, 3F1, F5, and 3A12) and an antigen-affinity purified goat polyclonal IgG antibody, the prostate-specific antigenic domain of the PSA molecule has been identified and its three-dimensional structure characterized [9]. In addition, the complete gene encoding PSA has been sequenced and localized to chromosome 19. With the use of PSA cyclic deoxyribonucleic acid fragments as hybridization probes, the gene has been found to be approximately 6 kilobases in size and composed of 4 introns and 5 exons; two major transcription initiation sites also have been identified [12]. An 82% homology has been found between the PSA gene and the human kallikrein-1 gene [13]. Other studies have confirmed this extensive homology between PSA and proteases of the kallikrein family [14,15].

PHYSIOLOGIC PROPERTIES OF PSA

Functionally, PSA is a kallikrein-like serine protease that is produced exclusively by the epithelial cells lining the acini and ducts of the prostate gland [8,16]. Using immunoperoxidase staining techniques, Papsidero and associates [17] demonstrated that within the normal prostate gland, PSA was located only in epithelial cells; none of the other cellular components of the prostate, including the stromal and vascular elements, stained for PSA. Subsequently, Nadji and coworkers [18] detected PSA in the epithelial cells of benign prostatic hyperplasia (BPH) tissue, primary prostate cancer tissue, and metastatic prostate cancer tissue.

Normally, PSA is secreted into the lumina of the prostatic ducts and is present in the seminal plasma at high concentrations. In the seminal fluid, PSA is involved directly in the liquefaction of the seminal coagulum that is formed at ejaculation [16]. Lilja and Laurell [16,19] demonstrated that PSA cleaves this protein rapidly into several basic low molecular weight proteins in concurrence with liquefaction of the coagulum. In a subsequent study, McGee and Herr [20] demonstrated that seminal vesicle-specific antigen, a glycoprotein that is produced by the epithelial cells of the seminal vesicle, is the substrate for PSA during semen liquefaction. Akiyama and associates [21] and Ban and colleagues [22] found it to possess chymotrypsin-like and trypsin-like activity. The effect of this proteolytic compound on other body tissues and organs once it is present in the serum in high concentration is unknown.

PSA AND PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia (PIN), also known as atypical hyperplasia and intraductal dysplasia, is characterized by an increased proliferation and dysplasia of the epithelial cells lining the lumina of the acini and ducts [23]. PIN is considered to be a premalignant change in the human prostate and has been demonstrated to be closely related to adenocarcinoma on the basis of immunophenotypic studies [24-28].

Brawer [29] believes that PIN may be responsible for the elevated PSA levels in some patients who have benign prostatic hyperplasia only. To investigate this hypothesis, he and his associates [30] meticulously analyzed the surgical specimens of 81 men undergoing simple prostatectomy (open or transurethral resection) and

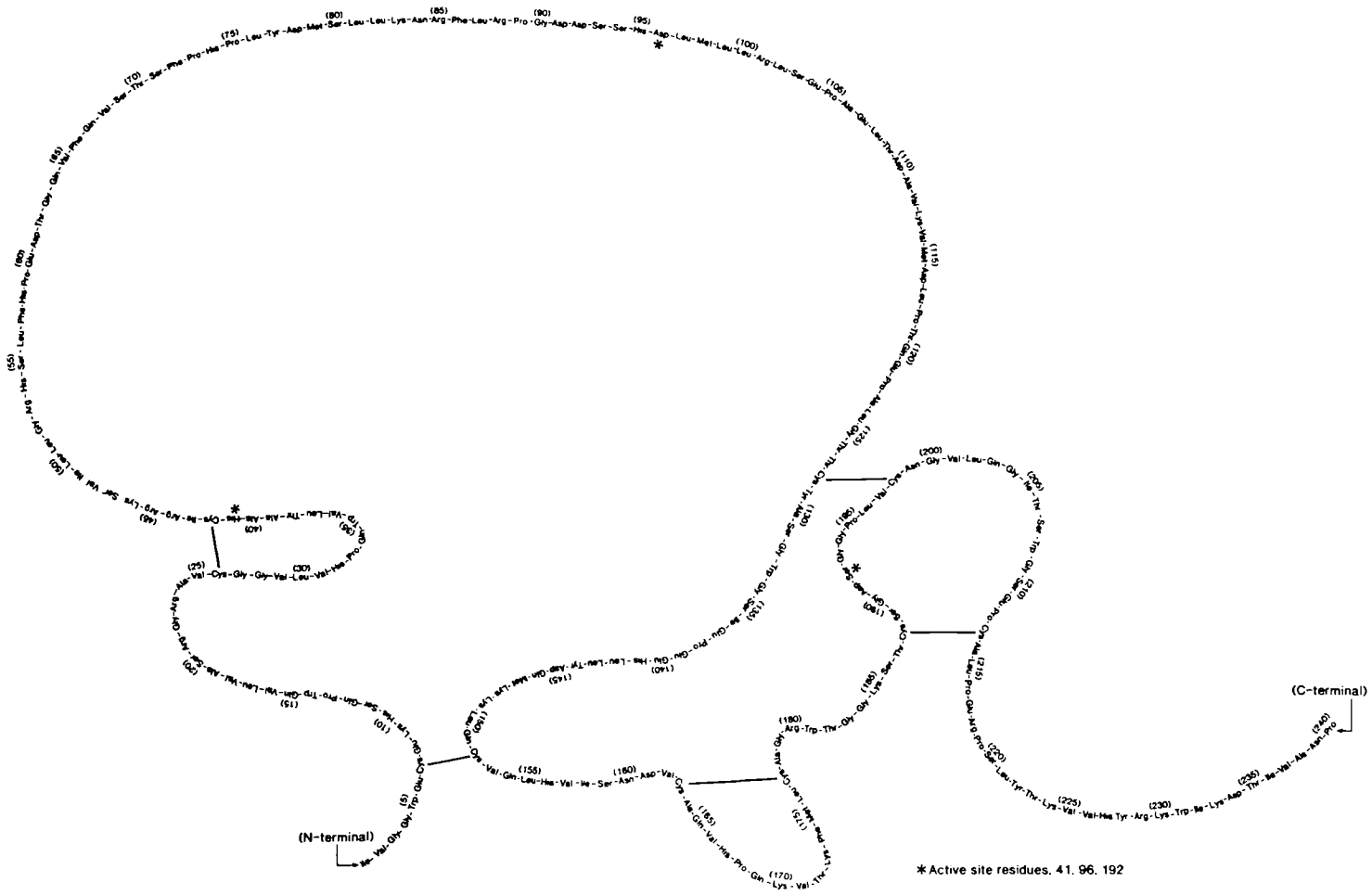


Fig. 1. Molecular structure of prostate-specific antigen. (From Oesterling JE: Prostate-specific antigen: a valuable clinical tool. Oncology [Williston Park] 5 no. 4:107-122, 1991. By permission of Dominus Publishing Company.)

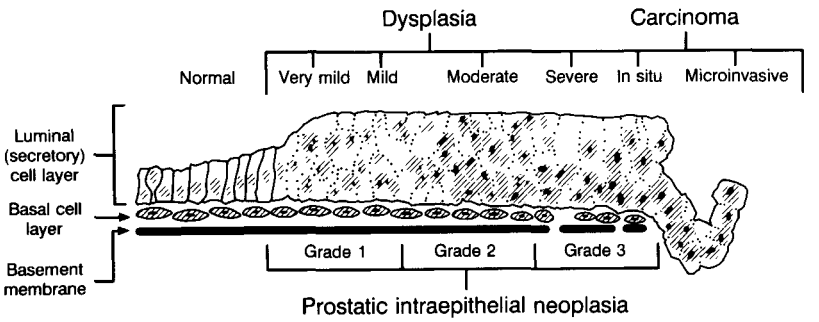


Fig. 2. Salient features of prostatic intraepithelial neoplasia. (From Bostwick DG, Brawer MK: Prostatic intra-epithelial neoplasia and early invasion in prostate cancer. Cancer 59:788-794, 1987. By permission of the American Cancer Society.)

compared the pathologic findings with the preoperative serum PSA level. PIN was identified in 25 patients (31%). The median PSA level for these men was 4.0 ng/mL (range, 0.3 to 22.3 ng/mL) compared with 2.1 ng/mL (range, 0.3 to 4.7 ng/mL) for the 26 men with BPH only and 5.9 ng/mL (range, 0.92 to 34 ng/mL) for the 14 patients with adenocarcinoma in the resected tissue. Lee and colleagues [31] observed similar results for patients undergoing transrectal ultrasound-guided biopsy of hypoechoic peripheral zone lesions. The mean prebiopsy serum PSA level (Pros-Check PSA assay) was 4.0 $\pm$ 4.0 ng/mL (standard deviation) for 91 men who had BPH tissue only, 9.5 $\pm$ 10.4 ng/mL for 27 patients with PIN in the biopsy specimen, and 84.0 $\pm$ 377 ng/mL for 103 patients whose biopsy specimens were positive for adenocarcinoma. Although the standard deviations were large and only 27 patients with PIN were identified, the natural logarithmic PSA values of men with PIN were significantly different from those of men with BPH ($p < 0.05$) and of men with prostate cancer ($p < 0.5$).

Thus, in some patients it seems that PIN can be associated with a serum PSA concentration higher than that observed for BPH alone. This increase is most likely due to a disorganization of the basal cell layer and perhaps disruption of the epithelial basement membrane (Fig. 2), which allows the low molecular weight PSA molecule to diffuse more easily from the lumina of the acini to the lumina of the adjacent capillaries or lymphatics. Another explanation is that there may be a coexisting adenocarcinoma of the prostate that has not yet been identified. Several investigators have shown that PIN frequently is found in prostates with adenocarcinoma. Thus, the association between PIN and a moderately elevated serum PSA level may be of interest with respect to early diagnosis of prostate cancer. However, the true significance of an elevated PSA value in conjunction with the finding of PIN on biopsy of the prostate awaits further investigation.

PSA AND EARLY PROSTATE CANCER

When one contemplates use of the PSA concentration for the early detection of prostate cancer or as a screening tool, several criteria must be imposed: 1) the test being used is safe and inexpensive so that it will have widespread acceptance, 2) the disease being sought is common in the population under investigation, and 3) an effective treatment is available for early-stage disease which will result in a decreased morbidity and mortality from the disease process. On the basis of objective data, PSA determination fulfills criterion 1 and prostate cancer fulfills criterion 2. Despite the lack of prospective, randomized, controlled studies, radical prostatectomy and radiation therapy are presumed to satisfy criterion 3 and, indeed, are effective treatments for organ-confined disease.

If PSA is to be useful in the early detection of clinically significant prostate cancer, the serum value must be able to 1) distinguish curable prostate cancer from BPH (specificity) and 2) identify prostate cancer not detectable by digital rectal examination (sensitivity). The first issue can be addressed by comparing the serum PSA values of patients with organ-confined prostate cancer (patients who have the greatest likelihood of cure with definitive therapy) with those of men who have BPH

TABLE I. Prostate-Specific Antigen Values for Benign Prostatic Hyperplasia and Organ-Confined Prostate Cancer*

Reference	No. of patients, by disease		PSA values in specified range									
			0.0-4.0 ng/mL†				4.1-10.0 ng/mL†				> 10.1 ng/mL†			
			BPH		Organ-confined prostate ca		BPH		Organ-confined prostate ca		BPH		Organ-confined prostate ca	
	BPH	Organ-confined prostate ca	%	No./total	%	No./total	%	No./total	%	No./total	%	No./total	%	No./total
Partin et al. [33]	72	185	47	34/72	45	83/185	46	33/72	44	82/185	7	5/72	11	20/185
Lange et al. [34]	357	31	79	282/357	45	14/31	18	64/357	32	10/32	3	11/357	23	7/31
Hudson et al. [32]	168	103	79	133/168	38	39/103	19	32/168	36	27/103	2	3/168	36	37/103
Totals	597	319	75	449/597	43	136/319	22	129/597	37	119/319	3	19/597	20	64/319
			$p < 0.0001$				$p < 0.0001$				$p < 0.0001$			

*Both diseases were confirmed histologically.

†Tandem-R PSA assay was used to determine values.

Abbreviations: BPH, benign prostatic hyperplasia; ca, cancer; PSA, prostate-specific antigen.

From Oesterling JE: Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol 145:907-923, 1991. By permission of the American Urological Association, Inc.

only. Table I summarizes the PSA values for these two groups of patients as determined from three major investigations [32-34]. Within each PSA range, there is a statistically significant difference between the PSA values for patients with BPH and those for men with organ-confined prostate cancer ($p < 0.0001$). Of note, however, is the fact that 43% (136 of 319) of patients with prostate cancer have a PSA value within the normal range, and 25% (148 of 597) of men with BPH have a PSA value above the reference range (0.0 to 4.0 ng/mL). When these data are evaluated statistically (Table II), PSA has a 64% diagnostic accuracy (efficiency) for organ-confined prostate cancer if the serum PSA concentration is more than 4 ng/mL and a 70% diagnostic accuracy if the serum value is more than 10 ng/mL. The positive predictive values are 49% and 75% for serum PSA values of more than 4 and 10 ng/mL, respectively.

When the patient population as a whole is evaluated, the serum PSA value seems able to distinguish patients with organ-confined prostate cancer from men who have BPH only. However, because of the tremendous overlap in PSA values between the two groups irrespective of the cutoff level chosen, the serum PSA level, by itself, cannot reliably distinguish patients with early, curable prostate cancer from men with BPH on an individual basis. Thus, PSA determination is not a specific test for early prostate cancer.

To determine whether PSA can identify prostate cancers that are not detectable by digital rectal examination, one can review the data of Cooner and associates [35]. These investigators reported on 225 men who presented to their urologic practice for prostatic evaluation and had benign results on digital rectal examination. All men under study also had a serum PSA determin-

TABLE II. Ability of Prostate-Specific Antigen Level to Distinguish Organ-Confined Prostate Cancer From Benign Prostatic Hyperplasia (Both Histologically Confirmed)

Statistical parameter	% patients at PSA cutoff level	
	> 4 ng/mL	> 10 ng/mL
Sensitivity	57	23
Specificity	68	96
False-negative rate	43	77
False-positive rate	32	4
Diagnostic accuracy (efficiency)	64	70
Positive predictive value	49	75
Negative predictive value	75	70

Abbreviation: PSA, prostate-specific antigen.

From Oesterling JE: Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol 145:907-923, 1991. By permission of the American Urological Association, Inc.

ation and transrectal ultrasonography. Irrespective of the serum PSA value, if a hypoechoic area was identified by transrectal ultrasonography, a biopsy of the suspicious area was performed. The results are summarized in Table III. Of the 225 men in whom results of digital rectal examination were negative, 61 (27%) had an elevated serum PSA concentration; of these, 21 (34%) had biopsy-proven prostate cancer. Thus, 9.3% (27% x 34%) of the patients in this series had their prostate cancer diagnosed because of an elevated serum PSA concentration. Without question, these data imply that the serum PSA value can lead to the detection of prostate cancers not identified by digital rectal examination.

Use of the PSA value, however, is not perfect. With a cutoff level of 4.0 ng/mL, the sensitivity and positive predictive value of PSA for this group of men with no evidence of malignancy by digital rectal examination were 75% and 34%, respectively (Table IV). Seven men (4%) had biopsy-proven cancer despite a normal PSA value. Clearly, the serum PSA concentration is not always elevated in the setting of cancer; stated another way, a serum PSA value in the reference range does not guarantee the absence of a prostatic malignancy. Catalona and associates [36] observed similar results. In a group of 235 men who had a serum PSA determination before undergoing prostate biopsy for clinical conditions (induration, asymmetry, or hematospermia), 61 (26%) had cancer. Of these, 13 patients (21%) had a normal serum PSA value. Thus, if PSA had been used to decide who should have biopsy, 21% of the cancers identified would have been missed.

Taken together, these results indicate that the PSA value can identify some prostate cancers not detected by digital rectal examination but that not all cancers are associated with an elevated serum PSA level. Thus, PSA is not an entirely sensitive test for early prostate cancer. Nevertheless, can the routine use of the serum PSA level increase the detection rate of prostate cancer?

Recently, two large-scale studies have been conducted to examine the role of PSA determination as a screening test for prostate cancer [36,37]. At Washington University in St. Louis, Catalona and associates [36] evaluated 1,653 healthy, asymptomatic men with a serum PSA determination; cancer was diagnosed in 37 men, and the overall detection rate was 2.2%. Brawer and colleagues [37] at the University of Washington in Seattle studied 1,249 men; they identified 32 patients with prostate cancer, and the detection rate was 2.6%. These values are somewhat better than the rates of 1.3% to 1.5% reported for digital rectal examination [38]. In the Washington University study, 32% of the cancers identified would have been missed if digital rectal examination alone had been used. The Seattle group found that 38% of the cancers would not have been identified if digital rectal examination had been used to screen

TABLE III. Serum Prostate-Specific Antigen Level and Biopsy Results for 225 Men With Benign Results of Digital Rectal Examination

Serum PSA, ng/mL	No. of patients	Biopsy results			
		Benign		Cancer	
		%	No.	%	No.
0.0-4.0	164	96	157	4	7
4.1-10.0	43	74	32	26	11
> 10.0	18	44	8	56	10
Total	225	88	197	12	28

Abbreviation: PSA, prostate-specific antigen.

Modified from Cooner WH, Mosley BR, Rutherford CL Jr, Beard JH, Pond HS, Bass RB Jr, Terry WJ: Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer. J Urol 139:758-761, 1988.

the population under study. Thus, use of the PSA value in a screening capacity will increase the detection rate of prostate cancer. However, not all the additional cancers identified by the PSA level are low-volume, organ-confined, curable tumors, nor are they found only in men with a minimal life expectancy of 10 years. In the screening study from Seattle, 2 (6%) of the 32 men found to have cancer had clinical stage C disease; 30 (94%), however, were thought to have organ-confined disease. Sixteen (50%) underwent surgical exploration; one (6%) had stage D1 cancer and six (38%) had pathologic stage C disease. Six other patients in the series with newly diagnosed cancer were followed expectantly because of poor health or advanced age. Perhaps only men with a life expectancy of 10 years or more should be included in early detection programs.

These data relating to the ability of the serum PSA value to detect early prostate cancer indicate that 1) patients with early, curable prostate cancer can have serum PSA values similar to those of men with obstructive BPH, 2) the PSA level can identify prostate cancers not detectable by digital rectal examination, 3) digital rectal examination can identify prostate cancers not detectable by the serum PSA value, and 4) overall, the PSA value can identify more prostate cancers than digital rectal examination when both are used in a screening capacity. Neither, however, is sufficiently sensitive nor specific to be used alone as a screening test for prostate cancer. Thus, the PSA value seems to identify some cancers, digital rectal examination identifies some tumors, and the lesions identified are not necessarily the same lesions. In 1992, the most complete, yet cost-effective, evaluation of the prostate gland is achieved when both determination of the PSA value and digital rectal examination are used together.

TABLE IV. Ability of Prostate-Specific Antigen Level to Detect Prostate Cancer in Men With Benign Results of Digital Rectal Examination

	% patients at PSA cutoff level	
Statistical parameter	> 4 ng/mL	> 10 ng/mL
Sensitivity	75	36
Specificity	79	96
False-negative rate	25	64
False-positive rate	21	4
Diagnostic accuracy (efficiency)	79	88
Positive predictive value	34	56
Negative predictive value	96	91

Abbreviation: PSA, prostate-specific antigen.
Data from Cooner WH, Mosley BR, Rutherford CL Jr, Beard JH, Pond HS, Bass RB Jr, Terry WJ: Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer. J Urol 139: 758-761, 1988.

RATE OF CHANGE IN SERUM PSA VALUE

If the ability of PSA to detect early, curable prostate cancer is to be improved, the following capabilities of this tumor marker need to be enhanced: 1) to distinguish organ-confined prostate cancer from BPH because both conditions occur in the same age range and 2) to identify nonpalpable prostate cancer in a reliable manner. To this end, Carter and associates [39] examined the concept of "rate of change in serum PSA." They conducted a retrospective analysis of 54 men who had been followed in the Baltimore Longitudinal Study of Aging for a minimum of 7 years before BPH or prostate cancer was diagnosed or before the exclusion of any prostatic disease was established. The control group consisted of 16 men who had no prostatic disease, the second group had 20 men who underwent a simple prostatectomy and had a histologic diagnosis of BPH, and the third group consisted of 18 patients with biopsy-proven prostate cancer. All men underwent a complete history, physical examination, and laboratory evaluation every 2 to 2.5 years. Stored serum obtained from each visit was used for determining the serum PSA concentration.

In this unique study, the investigators demonstrated that the rate of change was more useful than the actual serum PSA level for detecting prostate cancer. By using rate of change, they found that prostate cancer could be detected years before it was diagnosed by other methods. At 5 years before diagnosis--at a time when the serum PSA levels did not differ significantly between subjects with BPH and those with prostate cancer--the rate of change in PSA was markedly greater in the prostate cancer group as compared with controls ($p < 0.01$) and BPH subjects ($p < 0.01$) (Table V; Fig. 3). With a cutoff of more than 0.75 ng/mL per year for the rate of change, the specificities for distinguishing prostate cancer from BPH and from controls were 90% and 100%, respectively. These are markedly better than what is observed for the serum PSA concentration. The sensitivity for the rate of change, however, was not significantly better than that for the serum PSA concentration.

This important observation involving rate of change in serum PSA value will undoubtedly have valuable implications as more and more patients return annually for a serum PSA determination and digital rectal examination. Thus, an increase in the serum PSA level from 2.1 ng/mL to 3.4 ng/mL in 1 year is significant and may lead to the detection of a clinically significant, but potentially curable, prostate cancer, even though both values are within the reference range. Although these data are preliminary, they do indicate that the rate of change may improve the ability of the PSA value to detect early prostate cancer. More experience with this concept may also identify a percentage change per unit of time that is significant for recognizing prostate cancer and distinguishing prostate cancer from BPH only. Because PSA expression is under hormonal regulation [40], it also may be worthwhile to incorporate the patient's state of androgenic stimulation, perhaps the serum free and total testosterone levels, into these new variables.

PSA DENSITY

Another technique for improving the ability of the PSA value to detect early prostate cancer is to correlate the serum PSA concentration with the prostatic volume. Indeed, a mildly elevated serum PSA level associated with a small prostate gland may be indicative of cancer, whereas the same value in a patient with a large gland may be

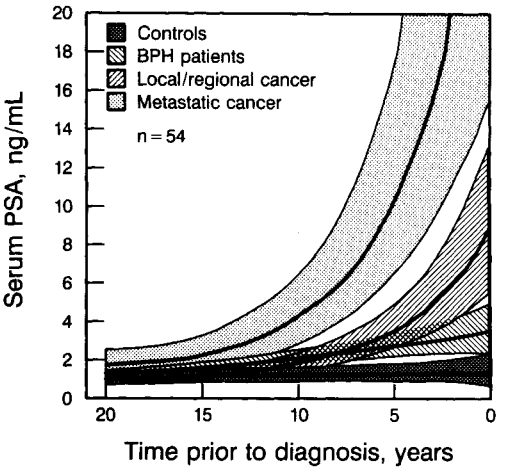


Fig. 3. Serum prostate-specific antigen (PSA) concentration as a function of time before diagnosis of prostatic condition. Note significant increase in serum value years before the diagnosis of either local/regional or metastatic cancer was established. BPH, benign prostatic hyperplasia. (From Carter et al. [39]. By permission of the American Medical Association.)

indicative of BPH only. To investigate this concept, Benson and associates [41,42] defined a new variable--"PSA density." It is the quotient of the serum PSA concentration divided by the volume of the prostate gland as determined by transrectal ultrasonography. In a preliminary study of 61 patients [41], these investigators found this variable useful for distinguishing men with BPH from patients with prostate cancer. The mean PSA density for the 41 patients with clinically localized prostate cancer was 0.58, whereas the mean value for the 20 men with BPH was 0.04 ($p < 0.0001$). In the study, 33 of 33 patients with a PSA density more than 0.12 had prostate cancer; only 2 patients with prostate cancer had a PSA density less than 0.05. In fact, 10 (83%) of the 12 patients with prostate cancer and a normal serum PSA concentration had an elevated PSA density value. With regard to the patients with BPH, 19 (95%) of the 20 had a PSA density less than 0.1. The highest PSA density value for any of the patients with BPH was just 0.117. These same investigators also developed a probability plot that allows the practicing physician to estimate the probability of a patient having prostate cancer given the PSA density (Fig. 4).

This concept of PSA density may have its greatest value for patients with a PSA value that is either in the upper normal range or mildly elevated (between 4.0 and 10.0 ng/mL). Benson and colleagues [42] learned that patients with a serum PSA concentration in the "mildly elevated range" who have an elevated PSA density are at increased risk for having prostate cancer, whereas patients who have a concomitant low PSA density are unlikely to harbor a malignancy in the prostate. In this manner, PSA density may

TABLE V. Rate of Change in Serum Prostate-Specific Antigen Level

Interval before diagnosis, yr	Rate of change by group, ng/mL per year			
	Controls	BPH	Local/ regional	Metastatic
0-5	0.03	0.12	0.88	5.35
5-10	0.01	0.09	0.27	1.33
10-15	0.02	0.09	0.14	0.30

Modified from Carter et al. [39].

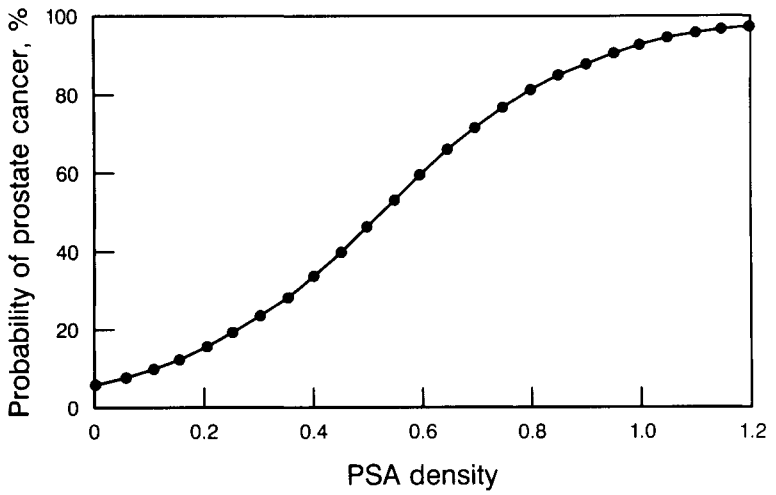


Fig. 4. Probability of prostate cancer as a function of prostate-specific antigen (PSA) density. For a PSA density of 0.15, the risk of prostate cancer is approximately 12%. (From Benson et al. [42]. By permission of the American Urological Association.)

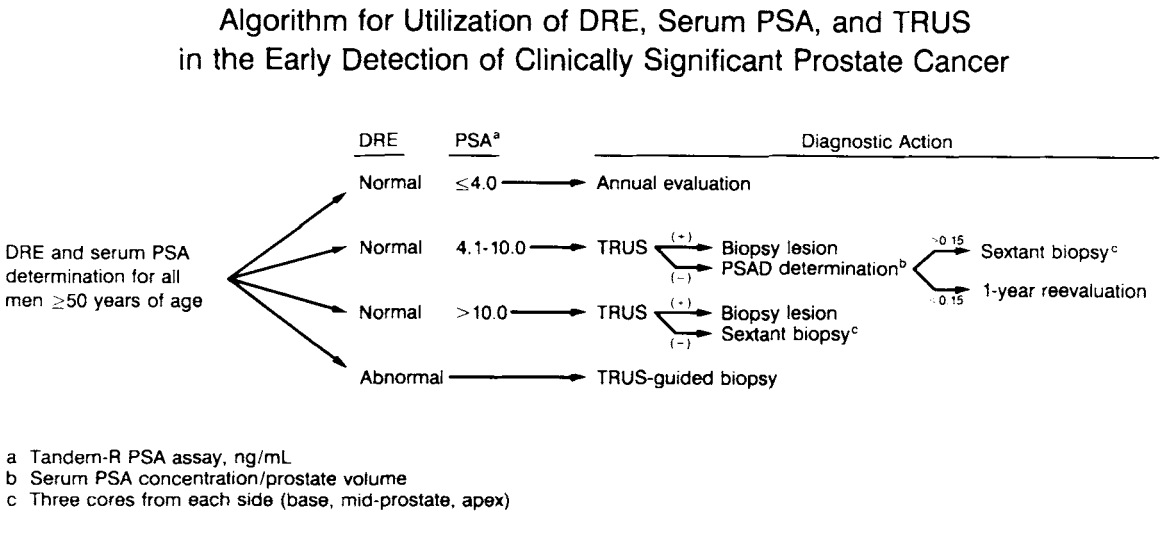
become a useful tool for helping physicians decide which patients with a high normal or mildly elevated serum PSA level to subject to prostate biopsy and which to follow with annual evaluations.

CONCLUSIONS

Without question, PSA determination is a valuable new tool for the clinician and clearly has a role in the early diagnosis of clinically significant prostate cancer. When used in a screening capacity, the PSA value can detect approximately twice as many cancers as digital rectal examination. The PSA level, however, is neither sufficiently specific nor sensitive to be the "perfect" screening test for prostate cancer. It lacks specificity because it is produced by all types of prostatic tissue--normal, hyperplastic (BPH), and cancerous. It is not prostate-cancer-specific. PSA lacks sensitivity because it is produced by epithelial cells and secreted into the prostatic ductal system; very little enters the general circulation. It is only when there has been a significant derangement in the architectural pattern of the prostate gland that PSA can diffuse from acini into the stroma and enter the systemic circulation through the lymphatics and capillaries. Thus, not all prostate cancers produce an elevated serum PSA concentration.

Because of these shortcomings with the serum PSA concentration, it is recommended that PSA determination and digital rectal examination be used together when evaluating the prostate gland for malignancy. In addition, the new concepts of "PSA density" and "rate of change in serum PSA" are being developed to improve further the ability of the PSA value to diagnose early prostate cancer and to distinguish it from BPH. Although the preliminary results are encouraging, additional studies will be necessary to confirm the true usefulness of these two new variables.

In the interim, the most prudent approach when evaluating a man 50 years or older is to both determine the serum PSA concentration and perform a digital rectal examination. If results of both are normal, the patient should be followed up with annual evaluations monitoring palpable changes in the prostate and the rate of change in the serum PSA level. If results of digital rectal examination are unremarkable and the serum PSA level is mildly elevated (4.1 to 10.0 ng/mL), transrectal ultrasonography should be performed. The echogenicity of the gland can be examined, and the volume of the prostate can be determined for calculating the PSA density. If an abnormality cannot be identified by digital rectal examination or transrectal ultrasonography but the PSA density is elevated, the patient should undergo a systematic biopsy of the prostate. If the results of digital rectal examination are normal and the serum PSA level is markedly



a Tandem-R PSA assay, ng/mL
b Serum PSA concentration/prostate volume
c Three cores from each side (base, mid-prostate, apex)

Fig. 5. Algorithm for the early detection of clinically significant prostate cancer with digital rectal examination (DRE), serum prostate-specific antigen (PSA) level, and transrectal ultrasonography (TRUS). PSAD, prostate-specific antigen density. (From Cupp and Oesterling [38]. By permission of the American Urological Association.)

elevated (more than 10.0 ng/mL), the patient should be subjected to transrectal ultrasonography and biopsy of any suspicious lesions. If no discrete, hypoechoic areas are visualized, a systematic biopsy of the prostate should be done. An abnormal result of digital rectal examination, irrespective of the serum PSA level, signals that biopsy should be done on the area in question. This approach for evaluating the prostate gland is summarized by the algorithm in Figure 5.

As we progress through the 1990s and head into the 21st century, PSA is clearly the "standard" tumor marker for prostate cancer. The routine use of PSA determination in the population at risk for the development of prostate cancer should increase the detection rate of early, organ-confined lesions--tumors that are curable with definitive therapy. Indeed, the discovery of PSA is one of the most significant advancements in the field of urology in recent times. Until a "prostate-cancer-specific antigen" is identified (one that appears in the serum as soon as the cancer achieves biologic significance), we will continue to use the only organ-specific tumor marker in all of cancer biology--PSA.

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