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Prostate-specific antigen as a marker of prostate disease

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Abstract Serum prostate markers, in particular prostate-specific antigen (PSA), have truly revolutionised all aspects of the management of men with prostatic carcinoma (PCa), the most important application being related to its early detection and screening. Several studies have shown the clinical utility of PSA levels for staging patients with PCa, especially when associated with other parameters, such as tumour grade, digital rectal examination and transrectal ultrasound findings, to establish the likelihood of disease extension outside the gland and of positive lymph nodes. Also, serum PSA levels are useful in monitoring patients either after the initial diagnosis of PCa or following therapy.

Key words Serum prostate-specific antigen · Prostate carcinoma · Prostatic intraepithelial neoplasia · Benign prostatic hyperplasia

Introduction

The prostate-specific antigen (PSA) gene (*hKLK3*) is located on chromosome 19 [57]. Its androgen-regulated transcription results in the biosynthesis of a 261-amino-acid PSA precursor. This precursor is believed to be activated by the proteolytic liberation of a small amino-terminal fragment. PSA is secreted into the seminal fluid by the luminal epithelial cells of the prostatic ducts and acini. In seminal fluid, about 70% of PSA is enzymatically active. Its physiological role is to liquefy the seminal gel by lysing seminogelin I and II into soluble fragments. Normally, PSA is present in semen in a concentration that is 1 million times that in serum. It has been speculated that the basement membrane of the prostatic ducts and acini and their basal cells, as well as the prostatic stromal cells, act as a barrier to the entry of PSA into the circulation [46].

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Tissue PSA

PSA can be detected immunohistochemically in frozen sections, paraffin-embedded sections, cell smears and cytological preparations of normal and neoplastic epithelium of the prostate. Microwave antigen retrieval is usually not necessary, even in tissues that have been stored in formalin for several years. Formalin fixation is optimal for localisation of PSA, and variations in the intensity of staining are not due to fixation and embedding effects. Immunoreactivity is still present in specimens after decalcification.

Strong immunoreactivity with antibodies to PSA is present in the secretory cells of the normal prostatic ducts and acini as well as those of benign prostatic hyperplasia (BPH) [37, 46]. Basal cells have not been shown to stain with PSA. Normal squamous and transitional epithelium does not stain with PSA. There is less intense expression of PSA in prostatic intraepithelial neoplasia (PIN) than in normal epithelium [16, 46]. McNeal et al. noted a progressive decrease in antibody binding as the grade of dysplasia increased, suggesting progressive cellular de-differentiation [37]. There is a concurrent decrease in immunoreactivity of foci of prostate carcinoma (PCa) found in the same pathological specimens, suggesting a similarity in de-differentiation between PIN and invasive carcinoma [16]. There appears

to be at least a tendency to an inverse correlation of staining intensity and tumour grade.

Some extraprostatic tissues and tumours may show patchy, weak, or equivocal immunoreactivity of PSA. For instance, occasional staining of urachal remnants, cystitis cystica, cystitis glandularis and periurethral glands (including Cowper's glands) has been reported. Rare PSA-positive neoplastic cells are seen in bladder adenocarcinoma. Salivary gland and breast tumours have also been shown to stain with PSA. Most of the paraurethral (Skene's) glands, the female homologue of the prostate, have been shown to stain positively with PSA [58]. Many carcinomas of Skene's gland origin have also been reported to be positive for PSA (Table 1).

PSA in PCa

A serum PSA value equal to 4 ng/ml is a widely accepted trigger point for biopsying [13], but is unsupported by any rigorous science. The negative predictive value of PSA <4 ng/ml is not known and does not denote the absence of cancer. It is estimated that PCa will be detected during the initial systematic biopsy in 28–45% of men whose digital rectal examination (DRE) results are normal but whose serum PSA values range from 4.1 and 10.0 ng/ml (e.g., intermediate PSA values or iPSA; see Table 2). It has been found that PSA correlates well with advancing age in relation to the progressive increase in prostate size [3, 22, 24, 25, 43, 45, 49]. Based on the 95th percentile values in a regression model, white men under 50 years of age had PSA values below 2.5 ng/ml, those under age 60 had PSA values below 3.5 ng/ml, those under age 70 had PSA values below 4.5 ng/ml, and for those under age 80 PSA levels were below 6.5 ng/ml. It has been suggested that these age-related values be used as the upper limit of normal in PSA-related diagnostic strategies. The benefit of age-specific PSA reference ranges has been seen in some studies; in others, while the predictive value has been greater with age-specific PSA the detection rate of PCa has been significantly lower [3, 22, 24, 25, 40, 43, 45, 49].

Table 1 Immunoreactivity of prostate-specific antigen (PSA) in extraprostatic tissues and tumours

Extraprostatic tissues
Urethra, periurethral glands (male and female)
Bladder, cystitis cystica and glandularis
Urachal remnants
Neutrophils
Anus, anal glands (male only)
Extraprostatic tumours
Mature teratoma
Urethra, periurethral gland adenocarcinoma (female)
Bladder, villous adenoma and adenocarcinoma
Penis, extramammary Paget's disease
Salivary gland, pleomorphic adenoma (male only)
Salivary gland, carcinoma (male only)
Breast carcinoma

PSA density

PSA density (PSAD) is the ratio of the serum PSA concentration to the volume of the prostate measured by transrectal ultrasound (TRUS). The PSAD values are divided into three categories: normal (values equal or lower than 0.050 ng/ml per cm^3), intermediate (from 0.051 to 0.099 ng/ml per cm^3) and pathological (equal to or greater than 0.1 ng/ml per cm^3). The production of PSA per volume of prostatic tissue is related to the presence of BPH and PCa and to the proportion of epithelial cells and the histological grade of the carcinoma [31]. Some studies found that PSAD was superior to total PSA in differentiating between benign and malignant prostate lesions in the iPSA range, while others pointed out that PSAD does not enhance the ability of serum PSA to predict the presence of PCa and is therefore no more useful than total PSA [5, 7, 15, 47, 61] (Table 3). These discrepancies probably relate to differences in TRUS techniques, the methods and/or techniques of prostate biopsy, or differences in patient populations [59].

Lepor et al. [31] found that the serum PSA level is most strongly correlated with the volume of epithelium in the transition zone and thought that the adjustment of serum PSA levels according to transition zone epithelial and/or the transition zone volume would probably enhance the sensitivity and specificity of this serum marker for detecting prostate carcinoma. These authors suggested the PSA epithelial density (PSAED, equal to serum

Table 2 Performance of serum PSA

Series	PSA >4.0 ng/ml		PSA >10.0 ng/ml	
	Brawer et al. [14]	Cooner et al. [23]	Brawer et al. [14]	Cooner et al. [23]
Number of patients	188	96	188	96
Number of patients With cancer	77 (41.0%)	28 (29.2%)	77 (41.0%)	28 (29.2%)
Sensitivity[a]	67.5	75.0	41.6	35.7
Specificity[a]	60.3	70.6	82.0	94.1
False positive[a]	39.6	29.4	18.9	5.9
False negative[a]	32.5	25.0	58.4	64.3
Positive predictive value[a]	54.2	51.2	60.4	71.4
Negative predictive value[a]	72.8	87.3	66.7	78.1

[a] Percent values

Table 3 PSA density results

Reference	Biopsy	No. of patients	PSA (ng/ml)[a]	Prostate volume (cc)[a]	PSA density (ng/ml per cm^3)[a]
[6]	Positive	98	7.0 (1.7)*	28.9 (14.6)*	0.30 (0.15)*
	Negative	191	6.8 (1.8)	40.1 (20.2)	0.21 (0.11)
[52]	Positive	115	6.87 (1.70)	29.2 (14.2)*	0.285 (0.147)*
	Negative	311	6.77 (1.71)	42.2 (21.8)	0.199 (0.108)
[17]	Positive	68	10.7 (11.4)*	40.5 (16.6)	0.29 (0.41)
	Negative	159	5.2 (5.0)	42.6 (25.6)	0.14 (0.14)
[5]	Positive	217	21.4 (29.6)*	37.6 (21.4)*	0.63 (0.86)*
	Negative	317	9.1 (8.1)	51.6 (27.3)	0.21 (0.25)
[50]	Positive	612	15.5 (21.6)*	42.7 (27.2)*	0.47 (0.11)*
	Negative	1394	4.9 (4.7)	47.0 (31.6)	0.105 (0.09)
[38]	Positive	171	12.0 (16.0)*	38.9 (16.4)	0.35 (0.5)*
	Negative	650	2.1 (2.3)	33.5 (14.2)	0.08 (0.09)
[44]	Positive	110	9.3 (0.3–1320)[b]	28.1 (15.1–228.7)[b]	0.21 (0.009–39.3)[b]
	Negative	134	4.8 (0.2–64.1)[b]	47.3 (13.3–332.6)[b]	0.09 (0.007–1.82)[b]

* $P<0.05$

[a] Data reported as mean (standard deviation)

[b] Data reported as median (range), $P<0.05$

PSA divided by prostate epithelial volume as determined morphometrically in biopsies) should be superior to PSAD. However, the amount of PSA produced by individual epithelial cells is variable and serum levels of PSA may be related to additional factors such as hormonal milieu, vascularity, presence of inflammation, and other, unrecognised, phenomena [61, 63].

Hammerer et al. [28] showed that most PSA leakage from the prostate into the serum comes from the transition zone. Lloyd et al. [34] pointed out that this prostatic zone is the main determinant of serum PSA levels in patients with BPH. After transurethral resection of the prostate (TURP), mean PSA levels are reduced by 70% [4]. Therefore, it seems logical that the volume of the transition zone rather than total volume should be used in attempts to interpret elevated levels of serum PSA. The ability of PSA density of the transition zone (PSA TZD) to enhance prostate carcinoma detection in patients with intermediate PSA levels was investigated by Zlotta et al. [63], who measured the volume of the transition zone by TURS. They suggested that PSA TZD was more accurate in predicting PCa than PSA density for PSA levels of less than 10 ng/ml.

PSA forms in serum

Different molecular forms of PSA exist in serum [19, 32, 33, 53]. These result from complex formation between free PSA and two major extracellular protease inhibitors that are synthesised in the liver. This is because, being PSA a serine protease, its normal mode of existence in the serum is in complexation with α-1-anti-chymotrypsin (ACT), a 67-kDa single-chain glycoprotein, and α-2-macroglobulin (AMG), a 720-kDa glycoprotein. PSA is also bound, in trace amounts, to two other proteins: α-1-antitrypsin and inter-a trypsin inhibitor. These forms of PSA are not believed to have clinical relevance. Only a small percentage of the PSA found in the serum is consistent with its native form. Because this free form does not bind to ACT or AMG, it is thought to be either the enzymatically inactive precursor (i.e., zymogen) for PSA or an inactive nicked or damaged form of the native molecule.

Measurement of free PSA is of clinical value in distinguishing men with PCa from those with benign prostatic conditions when used in conjunction with total PSA. The free form of PSA occurs to a greater proportion in men without carcinoma [60] and, by contrast, the α-1-chymotrypsin complex PSA comprises a greater proportion of the total PSA in men with malignancy. This has been linked to the fact that α-1-chymotrypsin may be present to a greater degree in neoplastic epithelium than in epithelium in BPH. Complexation could conceivably occur within the prostate itself [8, 9, 21, 33, 53, 54, 62].

The utility of measurement of free and total PSA was reported by Catalona et al. [20]. As for cut-off values, a recent work by Stephan et al. [54] showed that the median values of total PSA and of the free-to-total PSA ratio were 7.8 ng/ml and 10.5% in PCa patients, 4.3 ng/ml and 20.8% in patients with BPH, and 1.4 ng/ml and 23.6% in the control group, thus lending further support to the concept that patients with PCa have a lower proportion of free PSA than those with BPH and healthy men. The same group [54] found that there was a significant difference in free-to-total PSA ratio between PCa and BPH patients with prostate volumes smaller than 40 cm^3, but not between patients in these two groups with prostate volumes exceeding 40 cm^3. A similar result was obtained by Haese et al. in a study in which a threshold of 60 cm^3 was adopted [27].

Free PSA and PSAD are independent predictors of carcinoma after controlling for age, total PSA and rectal examination results. The use of free-to-total PSA ratio is considered more cost effective than PSAD for the early detection of carcinoma, because it does not require the performance of ultrasonography in all patients. Initial results have shown that the complex PSA value offers better specificity than total PSA and the free-to-total PSA ratio [18] (Tables 4, 5).

Table 4 Specificity of the cut-off values of the different prostate specific antigen assays at selected sensitivities [18]

Sensitivity (%)	Total PSA		Complex PSA		Free/total PSA	
	Cut-off (ng/ml)	Specificity (%)	Cut-off (ng/ml)	Specificity (%)	Cut-off (ng/ml)	Specificity (%)
80	4.11	35.6	3.98	51.6	19	46.2
85	3.86	31.1	3.34	38.7	22	32.4
90	3.4	25.3	2.94	33.8	24	26.2
95	3.06	21.8	2.52	26.7	28	15.6
97.5	2.28	12.9	1.67	14.7	32	8.9
100	1.0	3.1	0.89	6.2	67	0

Table 5 Performance of total PSA (tPSA), complex PSA (cPSA) and free-to-total PSA ratio (f/t PSA) in multiple sites [15]

Site	(Entire tPSA range)							
	Sensitivity (%)				Specificity (%)			
	n	tPSA[a]	cPSA[b]	f/t PSA[c]	*n*	tPSA[a]	cPSA[b]	f/t PSA[c]
Seattle	75	85	83	77	225	37	48	48
Johns Hopkins	167	90	85	87	128	20	29	27
Bayer Screening Trial	78	87	81	81	124	26	36	52
Combined	320	88	83	84	477	30	40	37

[a] Cut-off=4.0 ng/ml
[b] Cut-off=3.75 ng/ml
[c] Cut-off=25% when total PSA >4.0 ng/ml

PSA in atypical small acinar proliferation

In the absence of absolute diagnostic criteria for PCa, the phrase "atypical small acinar proliferation (ASAP) suspicious for but not diagnostic for malignancy" is used by some pathologists. In most cases, the suspicion is qualified with "favour benign" or "highly suspicious". The term does not define lesions that are qualitatively different from PCa, but is recommended for prostate glands that "fall short" of cancer. The use of ASAP has been criticised by Murphy [42]. ASAP is identified in 1.5–5% of needle biopsies, as opposed to 2–16.5% of cases of high-grade PIN and 28–45% of cancer cases . On short-term follow-up, 41–60% of patients with ASAP are found to have PCa on repeat biopsy. In particular, a diagnosis of ASAP, favour benign, results in a cancer frequency of 22–23% on follow-up, whereas a diagnosis of ASAP, favour malignant, results in a cancer frequency rate of 60–61% on follow-up. Patients with subsequent cancer on repeat biopsy have higher mean initial PSA concentrations (14.6 ng/ml) than those whose repeat biopsy results are negative (5.4 ng/ml).

PSA in PIN

High-grade PIN is regarded as the direct precursor lesion of prostate carcinoma [10, 11, 36]. High-grade PIN, when found alone in a prostate biopsy, is associated with a 50% risk of detection of PCa of the peripheral zone in a subsequent biopsy [12]. This is because high-grade PIN usually arises in the peripheral zone of the prostate, the area in which the majority (70%) of prostatic cancers occur, and both are frequently multifocal, indicating a "field" effect. The effect of PIN on serum PSA has been investigated in a certain number of studies.

The earliest investigations found that patients with high-grade PIN displayed total PSA values greater than those associated with benign prostates and lower than those indicative of carcinoma. Brawer et al. [16] performed a study on patients with symptoms of bladder outlet obstruction undergoing simple prostatectomy. They found that a total of 26 patients with benign hyperplasia and chronic prostatitis were noted to have a mean PSA value of 2.1 ng/ml. In contrast, 25 men diagnosed with PIN showed a mean PSA level of 5.6 ng/ml, whereas 14 others had invasive carcinoma and a mean PSA value of 35.1 ng/ml. Similar results were reported by Bostwick et al. [12] in a study on the incidence of high-grade PIN in needle biopsies. They found that the median serum PSA concentration in PIN was intermediate (i.e., 5.9 ng/ml) between those in benign conditions (4.0 ng/ml) and in carcinoma (7.2 ng/ml). However, it was also seen that there was a substantial overlap in serum PSA values between the various pathologies, precluding the use of PSA to discriminate between benign, inflamed, dysplastic or malignant prostate tissue. In addition, a sizable number of patients with the initial diagnosis of PIN associated with elevated PSA were found to have carcinoma in the repeat biopsy; this pointed out that the elevation in the PSA concentration might not have been due to PIN itself but to the existence of concomitant carcinoma not sampled in the simple prostatectomy or biopsy specimens. Because PIN occurs in pre-existing ducts and acini, secretory products such as PSA would be expected to empty into the lumens rather than the stroma and blood vessels, so that a strong correlation of PSA and PIN would be surprising [39].

PSA density

Ronnett et al. [51] performed a study to determine whether there was an association between high-grade PIN and serum PSA elevations. To account for all pathological processes that might contribute to PSA elevations they used radical prostatectomy specimens as the source of material. To minimise the contribution of BPH and PCa to PSA levels they chose relatively small glands with minimal tumour volumes. The results of this study showed that there was a poor correlation between high-grade PIN volume and serum PSA values. The correlation of high-grade PIN to PSAD, whose values ranged from 0.03 to 0.14 ng/ml per cm^3, was no better. Therefore, it was concluded that high-grade PIN in and of itself does not account for elevated serum PSA levels, even when PSAD is evaluated. Alexander et al. [2] reached a similar conclusion in a study performed on whole-mounted radical prostatectomy specimens removed for clinically localised PCa. When cases with small cancers (less than 6.0 cc) were considered, PIN volume did not correlate with serum PSA concentration or PSAD. This means that PSAD does not provide information additional to that give by total PSA [48].

PSA velocity

Studies specifically investigating PSA velocity in PIN have not yet been published. However, serial PSA levels were evaluated by Aboseif et al. [1] over a period of 2 years in patients with evidence of PIN on initial biopsy. These authors found that 18 out of 21 patients showed PSA levels that had progressively increased from a mean of 8.4 to 11.6 ng/ml when carcinoma was diagnosed on the repeat biopsy. Fifteen patients continued to demonstrate PIN alone on repeat biopsy. The mean initial PSA in this group of patients was 5.1 ng/ml, and in five patients the PSA level increased from a mean of 4.8 to 5.9 ng/ml; in the remaining 10, the PSA level decreased from a mean of 5.1 to 4.6 ng/ml. According to Aboseif et al. [1], an increase in serial PSA levels in patients with high-grade PIN has a high predictive value for carcinoma. These findings were not confirmed in a study by Krishnamurthi et al. [30].

Free PSA

The effect of high-grade PIN on total and percent free PSA (or free-to-total PSA ratio) has been explored in recent papers. Tarle and Kraljic [57] published an investigation on the value of the serum free-to-total PSA ratio as a clinical tool for discriminating latent from manifest prostatic carcinoma. This study also included PIN lesions of different grades, whose diagnosis was said to be made on cytological material. Even though this is an unusual and suspect way of diagnosing PIN, the authors reported that low-grade PIN and BPH had a mean free-to-total PSA ratio of 27.9%, similar to that found in BPH (29.6%). Patients with high-grade PIN had a mean value very similar to that observed in carcinoma, i.e., 14.7% and 14.1%, respectively. Another study was performed by Kilic et al. [29]. This group confirmed that the ratio of free to total PSA is better for discriminating between patients with PCa (mean value 14%) and those with BPH (mean value 31%). In high-grade PIN, the data related to total PSA were comparable to those reported by Brawer et al. [16], i.e., total PSA values in high-grade PIN intermediate between those of BPH and those of PCa. For the ratio of free to total PSA values, two subgroups were seen, one with a ratio close to that of carcinoma and the other close to that of BPH. Basically only the former subgroup was shown to have carcinoma in the subsequent biopsy. They concluded that the decreased free-to-total PSA ratio obtained at the time of initial diagnosis of PIN without concurrent carcinoma could be used as a predictive factor to distinguish patients in whom carcinoma will be found in the subsequent biopsy and those with PIN not associated with carcinoma in repeat biopsy. Morote et al. [41] performed a study in which radical prostatectomy specimens from patients with T1c carcinoma and PIN were analysed. They affirmed that the changes on total and free serum PSA were not attributable to PIN.

PSA in benign prostatic diseases

BPH is a common cause of serum PSA elevation and probably accounts for approximately 60% of cases with elevated serum PSA. The degree of elevation is usually modest and ranging from 4.1 to 10.0 ng/ml. Additional benign entities that cause an elevated serum PSA include acute and chronic prostatitis, prostatic ischaemia or infarction and acute urinary retention (Table 6).

In needle biopsies, acute inflammation is present in approximately 60% of men with high serum PSA levels, as against 27% of men with normal PSA. Chronic inflammation is found more often in needle biopsies from men with elevated serum PSA (close to 100%), but is also common in prostate biopsies of men with normal PSA (77%). Prostatic infarcts have also been shown to elevate serum PSA, although only a few cases have been reported to date. Prostatic manipulation, including cystoscopy, needle biopsy and TURP are known to elevate PSA levels. In a small percentage of men, DRE (9%),

Table 6 Possible causes of serum PSA elevation

1.	Prostate cancer
2.	Benign prostatic hyperplasia
3.	Prostatitis
4.	Prostatic ischaemia or infarction
5.	Acute urinary retention
6.	Prostatic biopsy
7.	Prostatic massage
8.	Urethral manipulation
9.	Ejaculation

prostatic massage (6%), and transrectal ultrasound scanning (11%) result in elevation of serum PSA.

When examining a biopsy the pathologist has to bear in mind that ejaculation also increases total serum PSA levels by about 0.4–0.8 ng/ml and free PSA, by about 0.2 ng/ml [19]. Free PSA levels, which are preferentially increased after ejaculation, return to baseline by 6 h, while total PSA levels require 24–48 h to return to baseline. Thus, ejaculation produces a perturbation of the free-to-total PSA ratio, increasing the ratio for the first 6 h and then decreasing it for the subsequent 42 h. Similarly, free PSA is preferentially released after biopsy or surgery.

Table 7 Serum and tissue prostate markers

Prostate specific antigen (PSA)
1. Total PSA
2. Age-specific reference ranges
3. PSA density (including PSA epithelial density and PSA density of the transition zone)
4. PSA velocity (including PSA doubling time)
5. PSA forms in serum (free and complex PSA)
Serum prostate markers other than PSA
1. Prostatic acid phosphatase
2. Human glandular kallikrein
3. Prostate-specific membrane antigen
Polymerase chain reaction and reverse transcriptase

PSA after therapy

Men with PCa and treated by radiation therapy or with androgen ablation with LHRH agonists and/or antiandrogens have low PSA levels. It is not uncommon for prostate needle biopsies to be performed in men with BPH who are given the 5-α-reductase inhibitor finasteride for 6 months or longer. In these patients, serum PSA is lowered as a consequence of the treatment that induces atrophy and apoptosis of the secretory cells in the prostate. This means that the serum PSA level might not help the pathologist or the urologist to decide whether or not the patient has carcinoma. However, the distribution of serum PSA levels is affected in a predictable manner [55]. In men with BPH and no evidence of prostate carcinoma the distribution of serum PSA is simply shifted down by approximately 50%. Among men with BPH and prostate carcinoma, the distribution of serum PSA is shifted downward by no greater than 50%. To interpret serum PSA levels in men with PSA treated with finasteride for 6 months or longer, the serum PSA level should be multiplied by 2 and compared with either age-independent or age-specific upper limits of normal for serum PSA in untreated men with BPH [26]. The free-to-total ratio, currently used to help differentiate benign from malignant processes in the prostate, remains valid during treatment with finasteride; it does not affect the free-to-total ratio [35].

Concluding remarks

1. There was no absolute science in the establishment of 4.0 ng/ml as the most widely utilised upper limit of "normal" PSA. However, serum PSA is elevated beyond the arbitrary cut-off point of 4.0 ng/ml in the majority of patients with PCa.
2. PSA may also be greater than 4.0 ng/ml in some benign conditions, such as BPH. Therefore, serum PSA lacks high sensitivity and specificity for PCa. This problem has been partially overcome by calculating several PSA-related indices (such as PSA density, PSA velocity, percent free PSA) and/or evaluating other serum markers (not dealt with in this review) (Table 7).
3. Patients with the initial diagnosis of high-grade PIN associated with an elevated PSA are found to have carcinoma in the repeat biopsy; this pointed out that the elevation in the PSA concentration might be due to the existence of concomitant carcinoma not sampled in the biopsy.
4. Serum PSA is usually affected by radiation therapy as well as hormonal manipulation.

References

1. Aboseif S, Shinohara K, Weidner N, Narayan P, Carroll PR (1995) The significance of prostatic intra-epithelial neoplasia. Br J Urol 76:355–359
2. Alexander EE, Qian J, Wollan PC, Myers RP, Bostwick DG (1996) Prostatic intraepithelial neoplasia does not appear to raise serum prostate-specific antigen concentration. Urology 47: 693–698
3. Anderson JR, Strickland D, Corbin D (1995) Age-specific reference ranges for serum prostate specific antigen. Urology 46: 54–57
4. Aus G, Bergdahl S, Frosing R, Lodding P, Pileblad E, Hugosson J (1996) Reference range of prostate-specific antigen after transurethral resection of the prostate. Urology 47: 529–531
5. Bazinet M, Meshref AW, Trudel C, Aronson S, Peloquin F, Nachabe M, Begin LR (1994) Prospective evaluation of prostate-specific antigen density and systematic biopsies for early detection of prostatic carcinoma. Urology 43:44–52
6. Benson MC, Whang IS, Olsson CA, McMahon DJ, Cooner WH (1992) The use of PSA density to enhance the predictive value of intermediate levels of serum PSA. J Urol 147:817–821
7. Benson MC, McMahon DJ, Cooner WH, Olsson CA (1993) An algorithm for prostate cancer detection in a patient population using prostate-specific antigen and prostate-specific antigen density. World J Urol 11:206–213
8. Bjartell A, Bjork T, Matikainen MT, Abrahamsson PA, di Sant'Agnese A, Lilja H (1993) Production of alpha 1-antichymotrypsin by PSA-containing cell of the human prostate epithelium. Urology 42:502–510
9. Bjork T, Hulkko S, Bjartell A, di Sant'Agnese A, Abrahamsson PA, Lilja H (1994) alpha 1-antichymotrypsin production in PSA-producing cell is common in prostate cancer but rare in benign prostatic hyperplasia. Urology 43:427–434
10. Bostwick DG (1995) High grade prostatic intraepithelial neoplasia: the most likely precursor of prostate cancer. Cancer 75: 1823–1836
11. Bostwick DG, Brawer MG (1987) Prostatic intraepithelial neoplasia and early invasion in prostate cancer. Cancer 59: 788–794

12. Bostwick DG, Qian J, Kenneth F (1995) The incidence of high-grade prostatic intraepithelial neoplasia in needle biopsies. J Urol 154:1791–1794
13. Brawer MK (1995) How to use PSA in the early detection or screening for prostatic carcinoma. CA Cancer J Clin 45:148–164
14. Brawer MK, Lange PH (1989) PSA in the screening, staging and follow up of early-stage prostate cancer: a review of recent developments. World J Urol 7:7–11
15. Brawer MK, Partin A (2000) Prostate cancer serum markers. Contemp Urol 1999 (in press)
16. Brawer MK, Rennels MA, Nagle RB, Schifman R, Gaines JA (1989) Serum prostate-specific antigen and prostate pathology in men having simple prostatectomy. Am J Clin Pathol 92: 760–764
17. Brawer MK, Aramburu EAG, Chen GL, Preston SD, Ellis WJ (1993) The inability of PSA index to enhance the predictive value of PSA in the diagnosis of prostatic carcinoma. J Urol 150:369–373
18. Brawer MK, Meyer GE, Letran JL, et al (1998) Measurement of complexed PSA improves specificity for early detection of prostate cancer. Urology 52:372–378
19. Catalona WJ (1997) Clinical utility of measurements of free and total PSA: a review. In: Murphy G, Denis L, Chatelain C, Griffiths K, Khoury S, Cockett AT (eds) Proceedings of the-First International Consultation on Prostate Cancer, Monaco, 20–22 June. Scientific Communication International, Monaco, pp 104–111
20. Catalona WJ, Partin AW, Slawin KM, Brawer MK, Flanigan RC, Patel A, Richie JP, deKernion JB, Walsh PC, Scardino PT, Lange PH, Subong EN, Parson RE, Gasior GH, Loveland KG, Southwich PC (1998) Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 279:1542–1547
21. Christensson A, Bjork T, Nilsson O, Dahlen U, Matikainen MT, Cockett AT, Abrahamsson PA, Lilja H (1993) Serum prostate specific antigen complexed to α-1-antichymotrypsin as an indicator of prostate cancer. J Urol 150:100–105
22. Collins GN, Lee RJ, McElvie GB (1993) Relationship between prostate specific antigen, prostate volume and age in the benign prostate. Br J Urol 71:445–450
23. Cooner WH, Eggers CW, Lichtenstein P (1987) Prostate cancer: new hope for early diagnosis. Alabama Med 56:13–16
24. Dalkin BL, Ahmann FR, Kopp JB (1993) Prostate specific antigen levels in men older than 50 years without clinical evidence of prostate cancer. J Urol 150:1837–1839
25. De Antoni P, Crawford ED, Oesterling JE, Ross CA, Berger ER, McLeod DG, Staggers F, Stone NN (1996) Age and race specific reference ranges for prostate specific antigen from a large, community-based study. Urology 48:234–239
26. Guess HA, Gormley GJ, Stoner E, Oesterling JE (1996) The effect of finasteride on prostate specific antigen: review of available data. J Urol 155:3–9
27. Haese A, Graefen M, Noldus J, Hammerer P, Huland E, Huland H (1997) Prostatic volume and ratio of free-to-total prostate specific antigen in patients with prostatic cancer or benign prostatic hyperplasia. J Urol 158:2188–2192
28. Hammerer PG, MC Neal JE, Stamey TA (1995) Correlation between serum prostate-specific antigen levels and the volume of the individual glandular zones of the human prostate. J Urol 153:111–116
29. Kilic S, Kukul E, Danisman A, Guntekin E, Sevuk M (1998) Ratio of free to total prostate-specific antigen in patients with prostatic intraepithelial neoplasia. Eur Urol 34:176–180
30. Krishnamurthi V, Klein EA, Levin HS (1997) Probability of prostate cancer detection following diagnosis of prostatic intraepithelial neoplasia. J Urol [A] 157 [Suppl]:232
31. Lepor H, Wang B, Shapiro E (1994) Relationship between prostatic epithelial volume and serum prostate-specific antigen levels. Urology 44:199–205
32. Lilja H (1993) Significance of different molecular forms of serum PSA: the free, noncomplexed form of PSA versus that complexed to alpha-1-antichymotrypsin. Urol Clin North Am 20:681–686
33. Lilja H, Christensson A, Dahlen U, Matikainen MT, Nilsson O, Pettersson K, Lovgren T (1991) Prostate-specific antigen in serum occurs predominantly in complex with α1-antichymotrypsin. Clin Chem 37:1618–1625
34. Lloyd S, Collins GN, McKelvie GB, Hehir M, Rogers ACN (1994) Predicted and actual change in serum PSA following prostatectomy for BPH. Urology 43:472–479
35. Matzkin H, Barak M, Braf Z (1996) Effect of finasteride on free and total serum prostate-specific antigen in men with benign prostatic hyperplasia. Br J Urol 78:405–408
36. McNeal JE, Bostwick DG (1986) Intraductal dysplasia: a premalignant lesion of the prostate. Hum Pathol 17:64–71
37. McNeal JE, Alroy J, Leav Y, Redwine EA, Freiha FS, Stamey TA (1988) Immunohistochemical evidence for impaired cell differentiation in the premalignant phase of prostate carcinogenesis. Am J Clin Pathol 90:23–32
38. Mettlin C, Littrup PJ, Kane RA, et al. (1994) Relative sensitivity and specificity of serum PSA level compared with age-referenced PSA, PSA density and PSA change. Cancer 74: 1615–1620
39. Montironi R, Mazzucchelli R, Marshall JR, Bartels PH (1999) Prostate cancer prevention. Review of target populations, pathological biomarkers, and chemopreventive agents. J Clin Pathol 52:793–803
40. Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW (1996) Age-specific reference ranges for serum prostate-specific antigen in black men. N Engl J Med 335:304–310
41. Morote J, Encabo G, Lopez M, De Torres IM (1999) Influence of high grade prostatic intraepithelial neoplasia on total and percent free serum prostatic specific antigen. Br J Urol [Int] 84:657–660
42. Murphy WM (1999) ASAP as a bad idea. Hum Pathol 30:601
43. Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA (1993) Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. JAMA 270:860–864
44. Ohori M, Dunn JK, Scardino PT (1995) Is prostate-specific antigen density more useful than prostate-specific antigen levels in the diagnosis of prostate cancer. Urology 46:666–671
45. Partin AW, Criley SR, Subong ENP, et al (1996) Standard versus age-specific prostate specific antigen reference ranges among men with clinically localized prostate cancer: a pathological analysis. J Urol 155:1336–1339
46. Porter JR, Brawer MK (1993) Prostatic intraepithelial neoplasia and prostate-specific antigen. World J Urol 11:196–200
47. Ramon J, Boccon-Gibod L, Billebaud T, Astier L, Kobelinsky M, Meulemans A, Dauge MC, Boccon-Gibod L, Villers A (1994) Prostate-specific antigen density: a means to enhance detection of prostate cancer. Eur Urol 25:288–294
48. Ravin G, Zlotta AR, Janssen T, Descamps F, Vanegas JP, Verhest A, Schulman CC (1996) Do prostate-specific antigen and prostate-specific antigen density enhance the detection of prostate carcinoma after initial diagnosis of prostatic intraepithelial neoplasia without concurrent carcinoma? Cancer 77: 2103–2108
49. Richardson TD, Oesterling JE (1997) Age specific reference ranges for serum prostate specific antigen. Urol Clin North Am 24:339–351
50. Rommel FM, Agusta VE, Breslin JA, Breslin JA, Huffnagle HW, Pohl CE, Sieber PR, Stahl CA (1994) The use of prostate specific antigen and prostate specific antigen density in the diagnosis of prostate cancer in a community based urology practice. J Urol 151:88–93
51. Ronnett BM, Carmichael MJ, Ballentine Carter H, Epstein JI (1993) Does high grade prostatic intraepithelial neoplasia result in elevated serum prostate-specific antigen levels? J Urol 150:386–389

52. Seaman E, Whang M, Olsson CA, Katz A, Cooner WH, Benson MC (1993) PSA density (PSAD): role in patient evaluation and management. Urol Clin North Am 20:653–663
53. Stenman UH, Leinonen J, Mfthan H, Ranniko S, Tulikanen K, Alfihan O (1991) A complex between prostate-specific antigen and alpha-1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res 51:222–226
54. Stephan C, Lein M, Jung K, Schnorr D, Loening SA (1997) The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. Cancer 79:104–109
55. Stoner E, Round E, Ferguson D, Gormley GJ and The Finasteride Study Group (1994) Clinical experience of the detection of prostate cancer in patients with benign prostatic hyperplasia treated with finasteride. J Urol 151:1296–1300
56. Takayama TK, Vessella RL, Lange PH (1994) Newer applications of serum prostate-specific antigen in the management of prostate cancer. Semin Oncol 21:542–553
57. Tarle M, Kraljic I (1997) Serum free/total percent PSA value as a clinical tool for discriminating latent from manifest prostatic carcinoma. Acta Clin Croat 36:15–19
58. Tepper S, Jagirdan J, Heath D, Geller SA (1984) Homology between female paraurethral (Skene's) glands and the prostate. Arch Pathol Lab Med 108:423–425
59. Terris MK, Stamey TA (1991) Determination of prostate volume by transrectal ultrasound. J Urol 145:984–987
60. Thiel RP, Oesterling JE, Wojno KJ, Partin AW, Chan DW, Ballentine Carter H, Stamey TA, Prestigiacomo AR, Brawer MK, Petteway JC, Carlson G, Luderer AA (1996) Multicenter comparison of the diagnostic performance of free prostate-specific antigen. Urology 48:45–50
61. Van Iersel MP, Witjes WPJ, De La Rosette JJMGH, Oosterhof GON (1995) Prostate-specific antigen density: correlation with histological diagnosis of prostate cancer, benign prostatic hyperplasia and prostatitis. Br J Urol 76:47–53
62. Wolff JM, Borchers H, Effert PJ, Habib FK, Jakse G (1996) Free-to-total prostate-specific antigen serum concentrations in patients with prostate cancer and benign prostatic hyperplasia. Br J Urol 78:409–413
63. Zlota AR, Djavan B, Marberger M, Schulman CC (1997) Prostate specific antigen density of the transition zone: a new effective parameter for prostate cancer prediction. J Urol 157: 1315–1321