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Complexed PSA: A First-Line Aid in Prostate Cancer Detection and Management

By Tricia A. Bal, MD

Answers for life.

Complexed PSA: A First-Line Aid in Prostate Cancer Detection and Management

Prostate cancer is one of the leading types of cancer in men, and complexed PSA has been shown to be valuable as a first-line test, aiding in its early detection.

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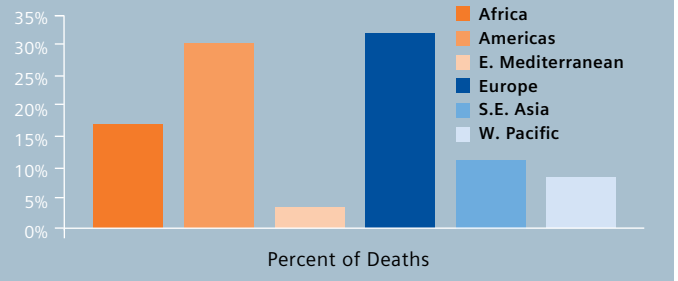

1 World Health Organization estimated percentage of prostate cancer deaths by region for 2008[14]

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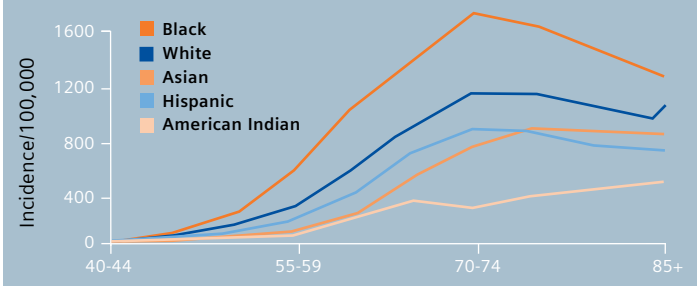


2 Prostate cancer incidence varies with age and ethnicity (USA data).[15]

Introduction

Complexed prostate specific antigen (cPSA) is a first-line test used in the detection of prostate cancer and has been endorsed in the National Comprehensive Cancer Network (NCCN) guidelines.[1] cPSA is a single test that offers the advantage of higher specificity than total PSA for the detection of prostate cancer.[2,10] Use of cPSA, instead of total PSA, has been shown to reduce the number of unnecessary biopsies.[3, 6, 11, 12] cPSA is also a valuable aid in prostate cancer management.[1]

Epidemiology of Prostate Cancer

Prostate cancer is one of the leading types of cancer in men. About 680,000 men are diagnosed yearly worldwide.[13] The World Health Organization (WHO) projected that in 2008 prostate cancer would have accounted for 0.6 percent of deaths (347,000) worldwide. Over 60 percent of these deaths were projected to occur in the Americas and Europe (Figure 1).[14] Prostate cancer incidence has been shown to vary with ethnicity and age, with certain ethnic groups having a much higher incidence of disease at every age (Figure 2).[15]

Prostate Cancer Detection and Management

While the diagnosis of prostate cancer can only be made definitively by biopsy, PSA tests are used by clinicians in conjunction with digital rectal examinations (DRE) as aids in prostate cancer detection.[1] Tumor grade (a measure of tumor aggressiveness) is quantitated by Gleason scores, which evaluate the microscopic pattern of cancer cells.

The Gleason system assigns a grade from 1 (least aggressive) to 5 (most aggressive) based on the amount of architectural differentiation of the tumor. The Gleason score is obtained by adding the most predominant grade (the grade that occurs most often in the biopsy) to the highest grade for a total score between 2 and 10. Aggressive tumors include those with Gleason scores of 7 to 10, and the most aggressive tumors have scores of 8 to 10.[16] cPSA and total PSA assays play crucial roles in prostate cancer management. An increase in cPSA or total PSA levels during treatment indicates disease progression; increasing PSA values in a patient who is being managed by active surveillance may trigger the initiation of therapy.[1]

3

System	Assay	Analytical Sensitivity (ng/mL)	Upper Limit (ng/mL)
ADVIA Centaur CP®/ADVIA Centaur XP®	PSA	0.01	100
	Complexed PSA	0.03	100
	Free PSA[c,d]	0.01[b]	25
IMMULITE® 1000/2000/2500	PSA	0.04	150
	Free PSA	0.02	25
	Third-Generation PSA	0.005	20
Dimension® Vista[a]	PSA	0.010[b]	100
	Free PSA	0.015[b]	20
Dimension EXL™	PSA	In development	In development
	Free PSA	In development	In development
Dimension® RxL Max/Dimension® Xpand Plus	PSA	0.05	100
	Free PSA	0.05	45

a. Not currently FDA approved; b. Limit of detection; c. Not available in the U.S.; d. Not available on the ADVIA Centaur CP

3 **Siemens Healthcare Diagnostics PSA menu**

Types of PSA

PSA (human kallikrein 3) is primarily produced by prostatic epithelium and is thus a prostate-specific marker.[17, 18] PSA is a product of the human glandular kallikrein gene locus on chromosome 19 and is one of the dominating prostate-derived proteins found in seminal fluid. The mature form of PSA, a single chain glycoprotein of 237 amino acids, is a serine protease with restricted chymotrypsin-like activity. PSA is mainly responsible for gel dissolution in freshly ejaculated semen by proteolysis of the major gel-forming proteins, semenogelin I and II, and fibronectin. In semen, approximately two-thirds of PSA is enzymatically active. The remaining 30 to 40 percent is inactive due to internal cleavage(s).[18] PSA elevations are associated with cancer, but are also associated with noncancerous conditions such as prostatitis (infection or inflammation of the prostate), trauma, or benign prostatic hyperplasia (a non-cancerous enlargement of the prostate due to tissue hyperplasia that can lead to obstruction of urine flow).[1] PSA exists bound to protease inhibitors, primarily alpha-1-antichymotrypsin (ACT) (up to 95 percent of PSA) or in a free, unbound form in serum.[19] PSA complexed to ACT constitutes the predominant molecular form of serum PSA. PSA also forms stable complexes with alpha-2-macroglobulin in vitro, but since PSA epitopes are completely masked in these complexes, specific immunodetection would be quite difficult.[18] PSA also forms complexes with alpha-1-antitrypsin.[20] Free PSA constitutes a minor fraction of the serum PSA but the major fraction of intracellular PSA. PSA in semen is also bound to protein C inhibitor.[18, 21]

Siemens PSA Testing Portfolio

The Siemens portfolio consists of total PSA assays (including the Third-Generation PSA assay) that detect both free and bound PSA, free PSA assays that detect only free PSA, and a cPSA assay that detects PSA bound to ACT (Figures 3 and 4). While free PSA must be used in conjunction with a total PSA assay, cPSA and total PSA assays are first-line assays used for aiding prostate cancer detection.

The Value of cPSA

cPSA is included in NCCN guidelines for use as an aid in the detection of prostate cancer in conjunction with DRE. cPSA is also used to monitor/manage prostate cancer. cPSA testing offers certain advantages when compared to total PSA testing.[1, 9] Interestingly, cPSA values have been shown to be lower than comparable total PSA values (Figure 5).[10]

4

4 **Schematic illustrating the forms of PSA detected in cPSA, free PSA, and total PSA assays.**

5

tPSA (ng/mL)	cPSA (ng/mL)
0–2.0	0–1.5
2.0–4.0	1.5–3.2
4.0–6.0	3.2–5.1
6.0–8.0	5.1–6.3
8.0–10.0	6.8–8.3
>10.0	>8.3

5 **cPSA and total PSA (tPSA) comparable levels[10]**

PSA Assays–At-a-Glance

Total PSA

- First-line test
- Aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years or older
- Management (monitoring) of prostate cancer

Free PSA

- Used in conjunction with total PSA
- Aid in distinguishing prostate cancer from benign prostate conditions in men aged 50 years or older with total PSA of 4-10 ng/mL and DRE not suspicious for cancer

Complexed PSA

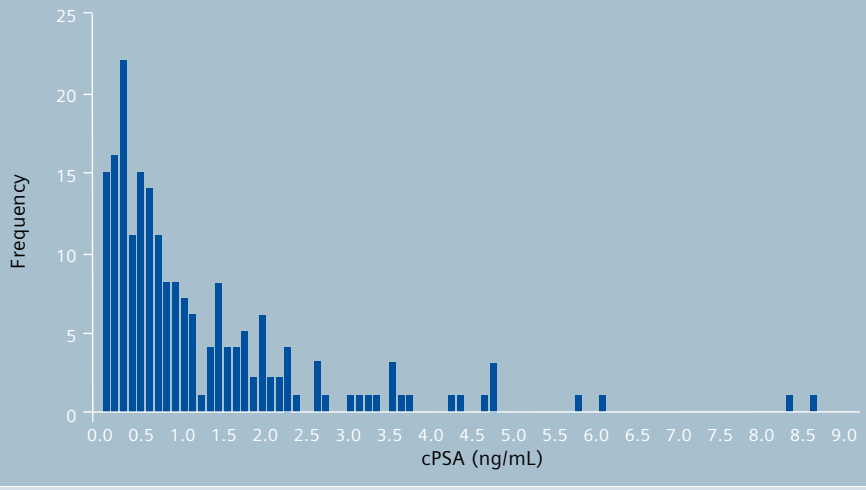
- First-line test
- Aid in the detection of prostate cancer in conjunction with DRE in men aged 50 years or older
- Management (monitoring) of prostate cancer

6

Study	Total PSA Range (ng/mL)	ROC Analysis (AUC) Complexed PSA	Total PSA
Parsons 2004	2–4	0.63	0.56
Babaian 2006	2.5–6	0.689	0.632
Bratslavsky 2008	2–10	0.52	0.53
Fillella 2004	0.18–55	0.672	0.633
Okihara 2006	1–100	0.741	0.721

6 **ROC analysis showing the diagnostic performance of complexed PSA compared with total PSA over a wide range of total PSA values.** [2, 3, 8, 22, 23]

7



7 **The distribution of cPSA in 199 apparently healthy males with ages ranging from 42 to 92 years.**[24]

8

cPSA (ng/mL)	N	Cancers (N)	Risk (%)	95% Confidence Interval
< 3.6	147	40	27.2	20.8–35.1
3.6 to 5.0	89	35	39.3	30.2–50.2
> 5.0	119	61	51.3	42.7–60.5

Probability of positive biopsy results for DRE alone negative is 38.3% (136/355; 95% CI 33.5% – 43.6%).

8 **cPSA levels and probability of a positive biopsy result with a normal DRE.**[24]

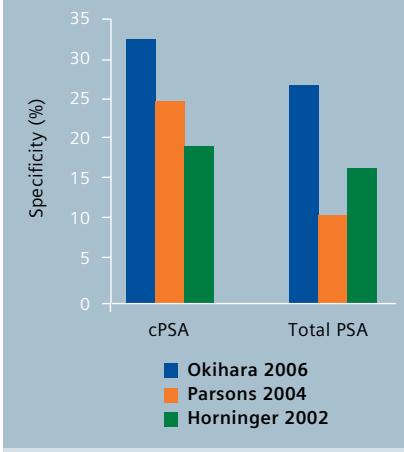
9

cPSA (ng/mL)	N	Cancers (N)	Risk (%)	95% Confidence Interval
< 3.6	70	37	52.9	41.9–64.9
3.6 to 5.0	29	17	58.6	42.3–76.5
> 5.0	50	39	78.0	66.3–88.5

Probability of positive biopsy results for DRE alone positive is 62.4% (93/149; 95% CI 54.8% – 70.2%).

9 **cPSA levels and probability of a positive biopsy result with a DRE suspicious for cancer.**[24]

10



10 **cPSA has a higher specificity than total PSA for the detection of prostate cancer (specificity at 90% sensitivity).** [8, 11, 23]

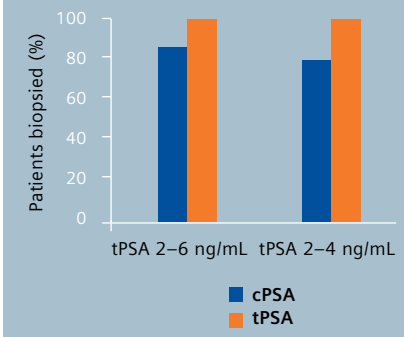
11

Total PSA between 4.0–10.0 ng/mL

Sensitivity (%)	Total PSA	cPSA
80	30	37
85	21	31
90	21	25
95	7	18

11 **Comparison of cPSA specificity and total PSA specificity over a range of sensitivities among patients with total PSA values between 4–10 ng/mL. cPSA showed higher specificity over a range of sensitivities.** [25]

12



12 **cPSA has been shown to reduce the number of unnecessary biopsies by 11 percent (total PSA 2–6 ng/mL) and by 20 percent (total PSA 2–4 ng/mL).** [2]

cPSA Is a First-Line Aid in Detection

Several studies have demonstrated the utility of cPSA as an aid in the detection of prostate cancer and have shown that cPSA performs as well as or better than total PSA (evaluated by receiver operating characteristics [ROC] analysis) (Figure 6).[2,5, 22, 23]

In a study of apparently healthy males, most cPSA values were below 3.5 ng/mL (Figure 7). Similar to total PSA, cPSA values tend to increase with age.[24] As cPSA levels increase, the probability of a positive biopsy result increases (Figures 8 and 9). If the patient has a suspicious DRE, the probability of a positive biopsy result is higher than the probability of a positive biopsy result in a patient with a negative DRE (Figures 8 and 9).[24]

cPSA Has Higher Specificity

cPSA, in addition to performing as well as or better than total PSA for detection of prostate cancer by ROC analysis, has also been shown to be more specific than total PSA for detection of prostate cancer (Figure 10).[8, 11, 23] This higher specificity has resulted in fewer false positives (positive by PSA test but negative by biopsy).

The increased specificity of cPSA compared with total PSA is consistent across a range of sensitivities (Figure 11) and across a range of total PSA values including the gray zone (4–10 ng/mL range) where total PSA is less effective at discriminating between prostate cancer and benign prostatic hyperplasia.[25]

cPSA Means Fewer Tests, Fewer Biopsies

Percent-free PSA was developed to address the low specificity of total PSA particularly in the 4–10-ng/mL range. cPSA is a single test that offers the advantage of higher specificity than total PSA. Because cPSA is a single first-line test, it may offer the lab certain operational efficiencies over running both a total PSA and a free PSA test.[1]

Consistent with its higher specificity, cPSA was shown in one study to reduce the number of unnecessary biopsies by 11 percent in the total PSA range of 2–6 ng/mL, and by 20 percent in the total PSA range of 2–4 ng/mL compared with total PSA (Figure 12).[2] Other studies have also shown that compared with total PSA, cPSA reduced the number of unnecessary biopsies by 10–20 percent.[6, 12]

cPSA and Prostate Cancer Management

There are several management options for prostate cancer. Options for local disease include watchful waiting (monitoring without the intent to actively treat), active surveillance (monitoring with the intent to treat if needed), surgery, and radiation (external beam and brachytherapy). Management options for metastatic disease include hormonal (androgen deprivation therapy) and chemotherapy.[1]

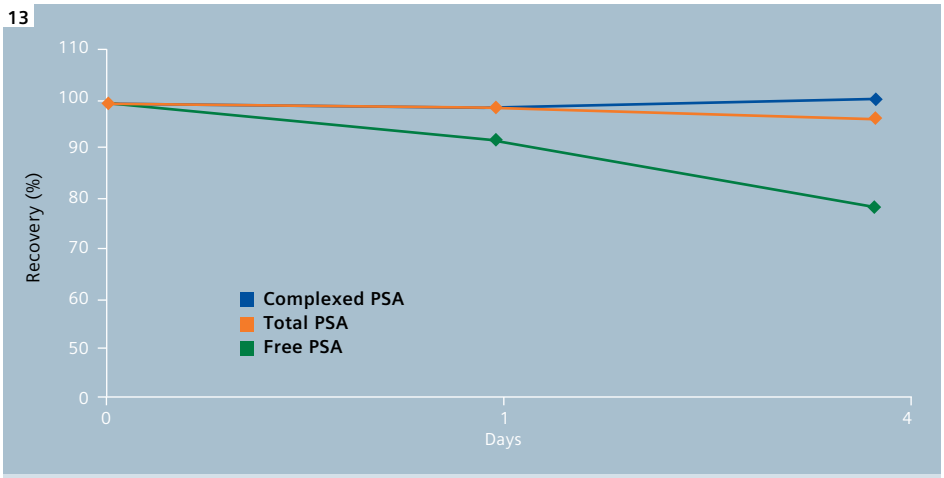
Because prostate cancer is a slowly-growing cancer, early detection and treatment of local disease has a high success rate.[26, 27] Metastatic disease, however, is much harder to treat, especially if it is hormone insensitive.

cPSA, like total PSA, is an integral aid for managing/monitoring prostate cancer. Trends in cPSA levels provide information regarding disease status and response to therapy. Increasing levels are associated with residual disease, poor response to therapy, progressive disease, and recurrent disease, while persistently elevated levels after therapy are associated with residual disease. In contrast, decreasing levels after therapy are associated with response to therapy.[1, 15, 16, 28, 29]

cPSA Is More Stable Than Total PSA and Free PSA

In terms of analyte stability, cPSA is more stable than both total PSA and free PSA in serum (Figure 13).[30] This is important for samples that are stored for extended periods prior to measurement. Serum samples should be stored at 4°C when the analysis will be performed within 8 hours of sample collection. Samples should be stored at -80°C if analysis will occur after 8 hours.[30]

13



13 **Complexed PSA is more stable than total PSA and free PSA at 4°C.**

Conclusion

The cPSA test offers the advantage of higher specificity for the detection of prostate cancer than total PSA,[8, 11, 23, 25] making cPSA a preferred first-line test. It has also been shown to perform as well as or better than total PSA as an aid in prostate cancer detection.[2, 3, 8, 22, 23] Using cPSA instead of total PSA has resulted in a reduction in the number of unnecessary biopsies by as much as 20 percent.[2, 6] cPSA is also an important tool in prostate cancer management.[9] Overall cPSA is a valuable test that can assist clinicians and patients through the prostate cancer care continuum, from early detection to disease management.

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