



SERUM PROSTATE-SPECIFIC ANTIGEN AS SURROGATE FOR THE HISTOLOGICAL DIAGNOSIS OF PROSTATE CANCER

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Introduction. To determine whether there is a cut-off value of serum prostate-specific antigen (PSA) which can be used confidently to make the diagnosis of prostate cancer, thereby obviating the need for biopsy.

Patients and methods. During the period October 1991 to March 1998 the Department of Chemical Pathology at Tygerberg Hospital performed a total of 6 733 serum PSA assays on 3 960 patients. The histopathological and clinical diagnoses of these patients were obtained from records in the departments of Anatomical Pathology, Urological Oncology and Radiation Oncology. The serum PSA levels were correlated with the histopathology reports, using different PSA cut-off values ranging from 5 to 500 ng/ml, to calculate the sensitivity, specificity, and positive and negative predictive values of each cut-off value of PSA in predicting the presence of prostate cancer.

Results. In total, 3 837 (57%) of the 6 733 serum PSA assays were ≤ 4 ng/ml, 1 045 (15.5%) of the assays were ≥ 50 ng/ml, and 798 (11.9%) were ≥ 100 ng/ml. Of the total of 3 960 individual patients, 531 (13.4%) had a serum PSA ≥ 50 ng/ml and 423 (10.7%) had a PSA ≥ 100 ng/ml. A serum PSA of ≥ 30 ng/ml had a positive predictive value (PPV) of 90% at a specificity of 87% and sensitivity of 78%, while a PSA ≥ 60 ng/ml had a PPV of 98% at a specificity of 98% and sensitivity of 65% for the presence of prostate cancer. The PPV reached 99% at a PSA ≥ 100 ng/ml and 100% at a PSA ≥ 500 ng/ml, with a specificity of 99% and 100%, but sensitivity of only 53% and 19%, respectively.

Conclusions. A serum PSA ≥ 60 ng/ml has a PPV of 98% for the presence of adenocarcinoma of the prostate, and may be used as a surrogate for histological diagnosis where facilities for obtaining prostatic biopsies are not readily available, thus decreasing costs and patient morbidity.

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The diagnosis of prostate cancer can be suspected on abnormal digital rectal examination (DRE) or elevated serum prostate-specific antigen (PSA), but usually histopathological confirmation of malignancy is required before treatment is given.^{1,3} However, prostatic biopsy carries a significant risk of complications, some of which may be life-threatening.^{4,6} Also, in developing countries, especially in rural areas, the human and technical resources to perform prostatic biopsy must be unavailable. The cost of transferring patients to a centre where biopsy can be performed may lead to delayed diagnosis or even non-treatment of the disease. We conducted a retrospective analysis to determine whether a certain PSA cut-off level could be used with confidence to establish the diagnosis of prostate cancer, thereby obviating the need for biopsy.

PATIENTS AND METHODS

The results of serum PSA assays performed during the period October 1991 to March 1998 by the Department of Chemical Pathology at Tygerberg Hospital were obtained (6 733 assays performed on 3 960 patients). The histopathology reports of patients with a serum PSA ≥ 4 ng/ml were obtained, if available, from the Department of Anatomical Pathology. The study cohort represents patients referred to Tygerberg Hospital (a tertiary referral centre) and does not constitute a prostate cancer screening population.

The serum PSA levels were correlated with the histopathology reports, using different PSA cut-off values ranging from 5 to 500 ng/ml, to calculate the sensitivity, specificity, and positive and negative predictive values (PPV and NPV) of each cut-off value of PSA in predicting the presence of prostate cancer. Data analysis was performed using Excel 2000.

In patients with a PSA > 50 ng/ml, where no pathology report was available, the patients' clinical data were obtained from the Urological Oncology Clinic computer database, the Department of Radiation Oncology or the Tygerberg Hospital Records Department. In these patients without prostatic histopathology a clinical diagnosis of prostate cancer was made if there was a DRE suspicious of malignancy plus radiological or bone scan evidence of skeletal metastases, an elevated serum acid phosphatase or serum PSA, clinical response to androgen ablation, or clinical progression and death consistent with a diagnosis of prostate cancer.

RESULTS

In total, 3 837 (57%) of the 6 733 serum PSA assays were ≤ 4 ng/ml, 1 045 (15.5%) of the assays were ≥ 50 ng/ml, and 798 (11.9%) were ≥ 100 ng/ml. Of the total of 3 960 individual patients, 531 (13.4%) had a serum PSA ≥ 50 ng/ml and 423 (10.7%) had a PSA ≥ 100 ng/ml.

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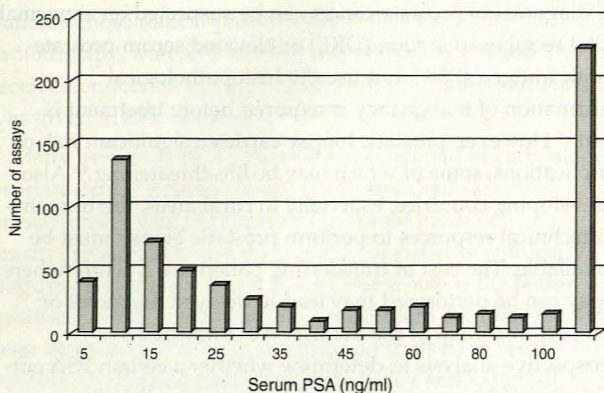


Fig. 1. Frequency distribution of PSA values in 716 patients with PSA ≥ 4 ng/ml ≤ 6 months before prostate biopsy.

In 716 cases with a PSA ≥ 4 ng/ml the date of the serum PSA assay was ≤ 6 months before the date of the prostatic histopathology report. The frequency distribution of PSA values in this group of 716 patients is shown in Fig. 1. The sensitivity, specificity, PPV and NPV of PSA at various cut-off levels were calculated in this group of patients (Table I). A serum PSA of ≥ 30 ng/ml had a PPV of 90% at a specificity of 87% and a sensitivity of 78%, while a PSA ≥ 60 ng/ml had a PPV of 98% at a specificity of 98% and sensitivity of 65% for the presence of prostate cancer. The PPV reached 99% at a PSA ≥ 100 ng/ml and 100% at a PSA ≥ 500 ng/ml, with a specificity of 99% and 100%, but sensitivity of only 53% and 19%, respectively (Table I).

Table I. Value of various cut-off levels of serum PSA in predicting a histological diagnosis of prostate cancer

PSA cut-off (ng/ml)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
5	99	8	60	81
10	93	43	70	81
15	88	65	78	79
20	84	75	82	77
25	80	83	87	75
30	78	87	90	74
35	75	90	91	72
40	75	92	93	72
45	73	95	96	71
50	72	96	96	71
60	65	98	98	67
70	62	98	98	65
80	59	98	98	65
90	56	99	98	62
100	53	99	99	60
200	37	100	99	53
300	27	100	99	48
400	23	100	99	48
500	19	100	100	47

The clinical data for the 15 patients with a serum PSA ≥ 50 ng/ml and prostatic histology showing no evidence of malignancy are shown in Table II. Histological examination revealed only benign prostatic hyperplasia (BPH) in 11 patients, infarction in 2 and prostatitis in 2. However, there was clinical evidence of prostate cancer in 6 of these patients. Follow-up was available in only 3 patients, and all had died of unknown causes.

There were 4 patients with BPH on histological examination whose serum PSAs came down, respectively, from 400 to 18 ng/ml in 6 weeks, from 66.9 to 32 ng/ml in 7 weeks, from 52.8 to 8 ng/ml in 11 weeks (without any surgery) and from 50 to 8 ng/ml in 17 months after transurethral resection of the prostate (TURP) (Table II). All 4 patients had presented with acute retention and were catheterised, but urinary tract infection was proved in only 1 of 3 who had a urine culture.

In 18 patients with a serum PSA ≥ 50 ng/ml and histologically confirmed prostate cancer, prior or subsequent tissue specimens did not show malignancy. Prostatic histology showed BPH in 12, prostatitis in 2, and was inconclusive in 4 patients in whom prior or subsequent prostatic histology (6 and 12 patients, respectively) showed adenocarcinoma. In the patients with a serum PSA ≥ 50 ng/ml and initially non-malignant histology, prostatic cancer was demonstrated histologically within 1 month in 3 patients, within 1 year in 6 patients, and after 22, 57 and 65 months in 3 patients.

DISCUSSION

The accuracy of clinical diagnosis of prostate cancer based on DRE ranges from 21% to 53%, which is clearly insufficient for making treatment decisions.³ The specificity of an elevated serum PSA ranges from 75% to 91%, and the PPV from 32% to 47%.² Therefore, histopathological confirmation of the diagnosis is usually obtained before proceeding to definitive treatment.

Transrectal needle biopsy of the prostate carries inherent risks and morbidity, including anxiety (65%), discomfort or pain during the procedure (86 - 96%), fever (4%), persistent pain for 1 - 2 days (7 - 48%), rectal bleeding (2 - 40%), haematuria (13 - 58%), haematospermia (5 - 51%), sexual impairment or decreased libido (21%), voiding difficulty (25%) or urinary retention (0.4 - 12%) and infection (2.5 - 27%), which may be localised to the urinary tract or systemic (0.3 - 5%) and may lead to septic shock and death.^{4,6}

Serum PSA is the single test with the highest PPV for prostate cancer, and its use improves the predictive value of DRE from 21% to 49%.^{3,7} Although the sensitivity of an elevated serum PSA (≥ 4 ng/ml) in predicting prostate cancer is high (72 - 90%), its specificity is only 75 - 91%). False-positive results are caused by BPH, acute and chronic prostatitis, acute and chronic urinary retention, prostatic infarction, procedural



Table II. Clinical data of patients with prostatic histology showing no malignancy

No.	Age (yrs)	Date	Clinical presentation	Date	PSA (ng/ml)	Date	Histology	Date	Follow-up	
1	80	2/11/88	Prostatitis, MSU culture positive							
		9/1/89	DRE large BPH							
		9/12/96	Acute retention, catheterised, DRE? BPH? T4 CAP, MSU culture negative, bone scan negative	11/12/96	400	17/12/96	Biopsy = BPH			
							27/1/97	18	22/2/97	Died
2	87	7/5/92	Acute retention, catheterised, DRE T2 CAP, MSU negative, acid phosphatase normal	7/5/92	84.5	8/5/92	Biopsy = BPH+ infarction			
						15/5/92	RPP = BPH			
3		26/8/92	Chronic retention, DRE T3 CAP, MSU culture positive, acid phosphatase slightly elevated	30/8/92	74.5	4/8/88	TURP = BPH			
						10/9/92	TURP = prostatitis			
4	87	9/6/93	Chronic retention, DRE BPH, MSU culture negative	6/6/93	93.2	10/6/93	RPP = BPH			
5				12/8/93	149.6	6/9/93	TURP = BPH			
6	75	5/9/94	MSU culture negative	6/7/94	43.7					
		14/3/95	Bone scan negative	13/3/95	77.45					
		15/6/95	DRE T4 CAP			19/6/95	Biopsy = BPH			
						22/6/95	BO			
7	83	8/6/95	Clinically CAP	25/2/92	22	27/2/92	Biopsy = atypia			
						4/3/92	TURP = BPH			
						8/6/95	BO, clinically CAP			
				19/8/97	1 140			23/8/97	Died	
8	69	24/4/95	Acute retention, catheterised, DRE BPH, MSU culture negative	24/4/95	47.4					
		24/6/95	DRE 150 g BPH	23/6/95	66.9					
				16/8/95	32	18/8/95	RPP = BPH			
9	88	26/6/95	DRE T2, MSU culture negative, acid phosphatase elevated, bone scan M1	25/6/95	96.2	27/6/95	Biopsy = BPH			
						5/7/95	Biopsy = BPH			
10	86	18/3/96	Acute retention, catheterised, DRE BPH? T2, MSU culture negative	17/3/96	190	19/3/96	Biopsy = BPH			
		27/3/96	Bone scan? M0			20/3/96	TURP = BPH + infarction			
11	68	26/5/96	DRE ? T3 CAP	25/5/97	110	28/5/97	Biopsy = BPH + prostatitis			
		11/6/97	DRE T3 CAP, bone scan? M0			4/6/97	Biopsy = BPH			
						11/6/97	TURP = BPH + prostatitis			



Table II. Continued

12	76	25/9/96	Chronic retention, catheterised, DRE BPH, MSU culture negative	24/9/96	107	7/11/96	Biopsy = BPH	
		30/10/96	MSU culture positive			14/11/96	Biopsy = BPH	
13	80	9/11/96	Acute retention, DRE 100 g BPH, MSU culture positive	8/11/96	52.8	21/11/96	Biopsy = BPH	
		21/11/96	DRE? T3? T4 CAP	29/1/97	8	6/3/97	Biopsy = BPH	
		3/12/96	Bone scan? M1					1/4/98 Died
14	88			11/11/96	50.6	11/12/96	TURP = BPH	
15	58	16/2/97	Acute retention, catheterised	13/2/97	50	20/2/97	TURP = BPH	
				24/7/98	8			

MSU = midstream urine; DRE = digital rectal examination; BPH = benign prostatic hyperplasia; CAP = cancer of the prostate; T2, T3, T4 = UICC tumour stage 2,3,4, respectively; RPP = retroperitoneal prostatectomy; TURP = transurethral resection of the prostate; BO = bilateral orchidectomy; M0, M1 = skeletal metastases absent or present, respectively; ? = clinician indicates uncertainty.

intervention (biopsy, TURP, transrectal ultrasound (TRUS)), while minor elevations are caused by DRE, ambulation, ejaculation and catheterisation.^{2,8-12}

Serum PSA levels correlate with tumour volume, grade, stage, lymph node status and metastatic spread.^{13,14} A very high PSA level is more likely to be due to prostate cancer than any of the conditions mentioned above, which mostly cause only mild elevations in serum PSA. In a study of 422 men (350 with clinically localised, histologically proven prostate cancer and 72 with histologically proven BPH), Partin *et al.*¹⁴ found that no patients with BPH and only 1% with organ-confined prostate cancer had PSA levels ≥ 50 ng/ml.

In a study of 1 749 patients with histologically proven adenocarcinoma of the prostate seen at our institution between 1976 and 1996, the tumour was locally advanced (stage T3 - T4) in 64% of cases, and 45% of the patients had skeletal metastases demonstrated on a radio-isotope bone scan.¹⁵ Therefore, the high incidence of locally advanced and metastatic prostate cancer in our patient population explains the fact that, in the present study, 13.4% of patients had a serum PSA ≥ 50 ng/ml and 10.7% had a PSA ≥ 100 ng/ml. This is likely to be representative of most developing countries where early prostate cancer detection or screening programmes are non-existent and patients present because of symptoms.

There is very little published information about the predictive value of high levels of serum PSA. Labrie *et al.*¹⁶ reported a screening study of 1 002 men aged 45 - 80 years and calculated the PPV of PSA to be 51% at levels above 10 ng/ml and 90% at levels above 30 ng/ml. Grob *et al.* analysed data on 177 biopsies performed between 1990 and 1997 for PSA ≥ 40 ng/ml. The positive biopsy rate in patients with PSA 40 - 74.9 ng/ml was 84%, with PSA 75 - 99.9 ng/ml, 96%, and with PSA > 100 ng/ml, 98%. They concluded that in men who are not being offered definitive therapy a PSA > 75 ng/ml is adequate to establish the diagnosis of prostate cancer (Grob

B M, Chernoff A, Sherman J, Macchia R J — unpublished abstract, meeting of the New York section of the American Urological Association, October 2000, Cape Town).

The present study indicates that a serum PSA ≥ 30 ng/ml had a PPV of 90% at a specificity of 87% and sensitivity of 78%, while a PSA ≥ 60 ng/ml had a PPV of 98% at a specificity of 98% and sensitivity of 65% for the presence of prostate cancer. The PPV reached 99% at a PSA ≥ 100 ng/ml and 100% at a PSA ≥ 500 ng/ml, with a specificity of 99% and 100%, but sensitivity of only 53% and 19%, respectively.

It is interesting to note that in 12 of 18 patients with a serum PSA ≥ 50 ng/ml initial histological examination failed to show prostate cancer, which was subsequently found in 9 patients within 1 year of follow-up, and in 3 patients only after 22 - 65 months of follow-up. Therefore, patients with a serum PSA ≥ 50 ng/ml should be followed up closely despite initially negative prostatic biopsy, since the possibility of cancer is very high. On the other hand, in 4 of our patients with a serum PSA ≥ 50 ng/ml and prostatic biopsy showing only BPH the serum PSA decreased significantly, although it did not return to normal levels. However, repeat biopsies were not performed in these patients, and further follow-up may have revealed the presence of prostate cancer.

In conclusion, our study shows that a serum PSA ≥ 60 ng/ml has a 98% PPV for prostate cancer. Therefore, in selected patients a very high level of serum PSA may be used as a surrogate for a histological diagnosis of prostate cancer. The advantage of such an approach would be that the costs and morbidity of prostatic biopsy could be avoided in this group of patients.

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COLORECTAL CARCINOMA — A NEW THREAT TO BLACK PATIENTS? A RETROSPECTIVE ANALYSIS OF COLORECTAL CARCINOMA RECEIVED BY THE INSTITUTE FOR PATHOLOGY, UNIVERSITY OF PRETORIA

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Objective. To compare black and white patients with colorectal carcinoma treated at Pretoria Academic and Kalafong hospitals, and to compare pathological trends of our study population with others reported in the literature.

Design. A retrospective study of all cases of resected colorectal carcinomas received by our department during the periods 1986 - 1987 (82 cases) and 1996 - 1997 (91 cases). To investigate variables of age, race and gender distribution in the two study populations.

Methods. Routinely stained histological sections of all relevant cases were examined. Findings regarding age, gender, population group, anatomical location of the tumour and presence of other pathological lesions were recorded. Changes in the referral population and number of surgical specimens received were also considered during statistical analysis of the study findings.

Results. There has been a significant increase in the number of black patients with colorectal carcinoma at our Institute. In addition, adenomatous polyps were found in 9 of our black patients (1996/97). This is significantly higher than expected from reports in the literature. This could be predictive of an increase in incidence of colorectal carcinomas in our black population. Black patients were also found to be considerably younger at age of presentation than their white counterparts. A further significant finding was a considerable increase in the number of black females under the age of 40 years from 1986/87 to 1996/97. On the other hand, the number of white females above 40 years of age decreased considerably over this time. The reason for this finding is uncertain and warrants further study.

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