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The role of prostatic specific antigen in monitoring prostatic cancer and its prognostic importance

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Summary. Serum prostatic specific antigen (PA) and prostatic acid phosphatase (PAP) levels were measured in 113 untreated patients with prostatic cancer and in 137 patients with benign prostatic hypertrophy (BPH). Of the 113 cancer patients, 81% and 69%, respectively, were detectable by means of PA or PAP assay alone. PA was a more sensitive indicator, than PAP in all stages, especially localized disease (stages A, B and C). Using the BPH group as a negative control, specificities of PA and PAP were 81% and 94% respectively. In another group of 68 patients with BPH whose blood samples were taken immediately after prostatic manipulation, both PA and PAP levels were elevated significantly. In 87 of the 113 cancer patients the two markers were serially determined, and 22 patients presented disease progression. Concerning the sensitivity within 6 months before progression, PA appears to be more reliable than PAP in early detection of disease progression. According to Kaplan-Meier projections, the patients with normal pretreatment PA levels had significantly longer intervals to progression than did those with moderate to marked PA elevation (more than 100 ng/ml) ($P < 0.05$). This study shows that PA is more reliable than PAP for detection and monitoring of prostatic cancer. Pretreatment PA levels appear to be of a high prognostic value for time to progression, irrespective of stage and treatment regimen.

Key words: Prostatic specific antigen – Tumor marker – Prognostic factor – Prostatic cancer

Prostatic acid phosphatase (PAP) is the serum marker that has been most widely used for prostatic cancer [1, 14]. With many refinements in the assay of PAP, including the application of radioimmunoassay, a more objective assessment of the disease may be possible. PAP is reasonably sensitive in the detection of advanced prostatic cancer, but is less sensitive in cases with a surgically curable stage of disease [4, 14].

A new serum marker, prostatic specific antigen (PA), has given promising results [3, 5, 10]. PA, a 34,000 molecular-weight glycoprotein with a 6.9 isoelectric point, was first identified and purified in 1979 by Wang et al. [18]. It is localized specifically to ductal epithelial cells of the prostate. Clinical studies find PA to be a more sensitive marker for prostatic cancer PAP, and PA may be a more reliable indicator of prognosis [7, 10]. Current evidence indicates that PA is more useful in monitoring of prostatic cancer than any other serum marker [8]. However, the role of PA in the management of patients with prostatic cancer is just beginning to emerge, and numerous questions about PA remain unanswered.

The concentration of PA and PAP in sera from patients with prostatic cancer and benign prostatic hypertrophy was examined in this report. The usefulness of PA in detection and monitoring of prostatic cancer will be discussed. Also, PA was evaluated for reliability as a prognostic indicator of disease progression.

Materials and methods

Patients

The study population consisted of 113 untreated patients with histologically diagnosed prostatic adenocarcinoma: 5 had stage A1, 3 stage A2, 8 stage B1, 8 stage B2, 26 stage C, 14 stage D1, and 49 stage D2 disease. Staging pelvic lymphadenectomy was performed in 1 of 3 patients with stage A2, 5 of 8 with stage B1, 6 of 8 with stage B2, 8 of 26 with stage C and 9 of 14 with stage D1 disease (in 5 patients diagnosis was made by means of CT scan or magnetic resonance imaging). All remaining patients with stage D2 tumor had metastatic disease as confirmed by a bone scan. PA and PAP were serially determined in 87 of 113 patients to evaluate their usefulness as a monitoring tool. Of these 87 patients, 6 underwent radical prostatectomy and 6 definitive radiation therapy, and all of the remaining 75 received hormone therapy.

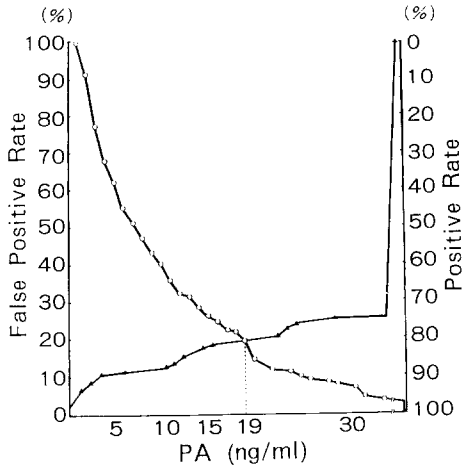

Fig. 1. Positive rate for patients with prostatic cancer (▲—▲) and false-positive rate for group I BPH patients (○—○) according to prostate-specific antigen value

Table 1. Results – (serum levels of prostate-specific antigen (PA) and prostatic acid phosphatose (PAP))

Group	No. of patients	PA (ng/ml)[a]	PAP (ng/ml)[a]
Prostatic Ca:			
A1	5	55.4± 79.0	2.5± 1.3
A2	3	282.1±263.9	6.3± 9.3
B1	8	35.4± 49.9	2.5± 2.7
Stage B2	8	128.6±184.2	2.9± 1.4
C	26	156.4±160.9	19.4±32.4
D1	14	273.0±194.9	17.0±31.7
D2	49	326.6±230.2	55.3±65.3
Totals	113	233.0±217.0	31.2±51.6
Benign prostatic hypertrophy:			
Group I	137	10.1± 10.4	1.1± 1.1
Group II	68	26.8± 50.6	2.9± 4.6

[a] Means ± standard deviation

During the follow-up period of 3–58 months, 22 patients had clinically detectable disease progression, recurrence or objective progression confirmed both by radiographic and radionuclide examination and by laboratory data in accordance with criteria of the NPCP [16].

Serial levels of PA and PAP were plotted for patients with clinically detectable disease progression and for patients whose disease had been clinically well controlled for more than 6 months. The scattergram included all PA and PAP levels recorded within 6 months prior to progression in patients with disease progression, and all PA and PAP levels within 6 months before the last measured PA and PAP levels for patients whose disease was still well controlled.

PA and PAP were also determined in 205 patients with histologically proven benign prostatic hypertrophy (BPH). These 205 patients were divided into two groups based upon the timing of blood samples taken. In group I (137 patients), blood samples were taken before prostatic manipulation, and in group II (68 patients) they were taken immediately after digital palpation of the prostate. Thus, the flucation of serum marker levels caused by prostatic manipulation was evaluated. PA and PAP values in group I BPH patients were used as a negative control

Assays

Sera were stored at −20°C until the measurements were carried out. Serum PA determination was performed with sandwich-type enzyme immunoassay kit (PA-TESTWAKO, Wako Pure Chemical Industries, Osaka, Japan). Purified PA or test samples are reacted with a glass bead (solid phase) coated with antil-PA monoclonal antibody directed toward a unique site on the PA molecule, and simultaneously with a horseradish peroxidase-labeled anti-PA antibody (Fab'). After formation of the solid phase/PA/labeled antibody sandwich, the beads are washed to remove unbound labeled antibody. Bead-bound enzyme activity as a proportional of the amount of PA was measured using substrate (hydrogen peroxide) and chromogen (*o*-phenylenediamine). Absorbance was determined at 492 nm with a spectrophotometer. The quantitative determination of PA was carried out based on the calibration curve provided by reference standards. The standard curve was based on the concurrent testing of the PA calibrators from 1.0 to 640 ng PA per ml. The standard PA was purified seminal plasma prostatic specific antigen. The coefficient of variation for within-assay reproducibility was 3.7–4.5% and that for between-assay reproducibility was 4.3–8.4%. The upper limit of normal for healthy men above 50 years of age was 14.0 ng/ml.

For some information about a correlation with other kits, a total of 96 serum samples with a range of PA values were analyzed with PA-TESTWAKO and Tandem-R-PSA (Hybritech, San Diego, Calif.) assays. Although there was a high linear correlation between the two assays ($r = 0.954$), values obtained with the PA-TESTWAKO assay weren, on average, 3.58 times those yielded by the Tandem-R-PSA assay.

Serum PAP was measured with a radioimmunoassay kit (Eiken Chemical Co., Tokyo, Japan). The upper limit of normal quoted by the manufacturers for PAP was 3.0 ng/ml. This value was used as a cut-off for PAP for analysis purpose.

Statistics

Sensitivity was defined as the percentage of patients with prostatic cancer and elevated marker levels. Using the group I BPH patients as negative controls, specificity was the percentage of patients with BPH and normal marker levels. Efficiency was defined as the percentage of patients classified correctly and was determned according to the formula $[pa + (1-p)b] \times 100$, where a represents sensitivity, b specificity and p prevalence (the percentage of patients who had prostatic cancer in the population studied) [5].

The positive rate in prostatic cancer group and the false-positive rate in group I BPH patients are plotted according to the PA values in Fig. 1. The 19.0 ng/ml at which the two curves intersect each other was defined as a cut-off value for PA for the purpose of analysis.

The prognostic impact of pretreatment PA values was assessed by using the first evidence of disease progression as the end-point of the study. A curve representing the interval to disease progression was generated using the Kaplan-Meier-method [6]. Any differences in the interval to progression were tested for statistical significance by the generalized-Wilcoxon test.

Table 2. Positive rates for PA and PAP

Group		No. of patients	No. with PA > 19.0 ng/ml (%)	No. with PAP > 3.0 ng/ml (%)
Prostatic Ca:				
	A1	5	3 (60)	2 (40)
	A2	3	2 (67)	1 (33)
	B1	8	3 (38)	2 (25)
Stage	B2	8	6 (75)	3 (38)
	C	26	19 (73)	18 (69)
	D1	14	14 (100)	9 (64)
	D2	49	45 (92)	43 (88)
Totals		113	92 (81)	78 (69)
A, B and C		50	33 (66)	25 (50)
D		63	59 (94)	52 (83)
Benign prostatic hypertrophy:				
Group I		137	26 (19)	8 (6)
GroupII		68	29 (43)	19 (28)

Results

PA and PAP in serum of patients with BPH

The mean PA and PAP levels in the 137 group I patients were 10.1 ± 10.4 and 1.1 ± 1.1, respectively. In contrast, in the 68 group II BPH patients were 26.8 ± 50.6 and 2.9 ± 4.6, respectively (Table 1).

Both PA and PAP levels in group II were significantly higher than those in group I according to the Wilcoxon test ($P < 0.01$).

PA and PAP in serum of patients with prostatic cancer

Serum PA and PAP levels in prostatic cancer according to stage are shown in Table 1. There was a progressive rise in PA and PAP levels with advancing stage. The mean PA levels were elevated even in the localized stages (A, B and C). On the other hand, the elevation of PAP was not so prominent in early stages (A1, B1 and B2). The correlation coefficient between PA and PAP was 0.3994; that is to say there was no good correlation between the two markers.

Sensitivity and specificity

Of the 113 patients with prostatic cancer, 92 (81%) had PA levels greater than 19 ng/ml: 3 of 5 (60%) with stage A1, 2 of 3 (67%) with stage A2, 3 of 8 (38%) with stage B1, 6 of 8 (75%) with stage B2, 19 of 26 (73%) with stage C, 14 of 14 (100%) with stage D1, and 45 of 49 (92%) with stage D2 (Table 2). Serum PAP was observed to be elevated in 78 (69%) of 113 cancer patients: 2 of 5 (40%) with stage A1, 1 of 3 (33%) with stage A2, 2 of 8 (25%) with stage B1, 3 of 8 (38%) with stage B2, 18 of 26 (69%) with stage C, 9 of 14 (64%) with stage D1, and 43 of 49 (88%) with stage D2. In all stages the positive rates of PA were higher than those of PAP. Also, in 50 patients with apparently localized disease (stages A, B and C), PA was found to be elevated in 33 patients (66%), and PAP in only 25 patients (50%). In the 137 BPH patients (group I), the positive rates of PA and PAP were 19% (26/137) and 6% (8/137), respectively.

In comparison, the positive rates of PA and PAP were raised in the group II BPH patients to 43% (29/68) and 28% (19/68), respectively. Efficiency was calculated as 81% for PA and 83% for PAP. When the upper limit of normal for PA (14.0 ng/ml) was used as a cut-off, sensitivity, specificity and efficiency were 84%, 72% and 78%, respectively.

Elevation of PA and PAP prior to disease progression

PA and PAP levels in patients with disease progression and those whose disease was well controlled are illustrated in Fig. 2A, B. The data points in Fig. 2 denote all serial levels of PA and PAP within 6 months before clinically detectable progression in 16 patients whose disease had progressed and all serial levels 6 months before and including the last meansurement in 26 patients in whom disease was clinically well controlled. In 16 patients with disease progression, a total of 56 blood samples were taken (2–5, average 3.5, samples per patient) within 6 months before disease progression. The PA levels were positive in 44 of the 56 (79%), as against the PAP levels, which were positive in 36 of the 56 (64%). At the time of clinically detectable progression, sensitivities of PA and PAP were 100% (16/16) and 69% (11/16), respectively. Within the last 6 months before progression, a gradual increase in PA had been seen in 9 of 16 patients, and minor fluctuation in the remaining 7 patients. In 26 patients whose disease was clinically well controlled, almost all levels of PA and PAP were observed to be negative.

Pretreatment PA values and interval to disease progression

In 87 patients with prostatic cancer who were followed up, the serum levels of PA before treatment was compared with the interval to progression, irrespective of stage and treatment regimen. These 87 patients were divided into four groups based upon pretreatment PA levels. As shown in Fig. 3, the lower the pretreatment PA levels, the longer was the interval to progression. The difference of interval to progression between group A and group C or group A and group D were significant ($P < 0.05$). Although no significant difference was found between groups B and C or groups B and D, there was a trend for a longer interval to progression with initial PA, if elevated, less than 100 ng/ml. There was no difference

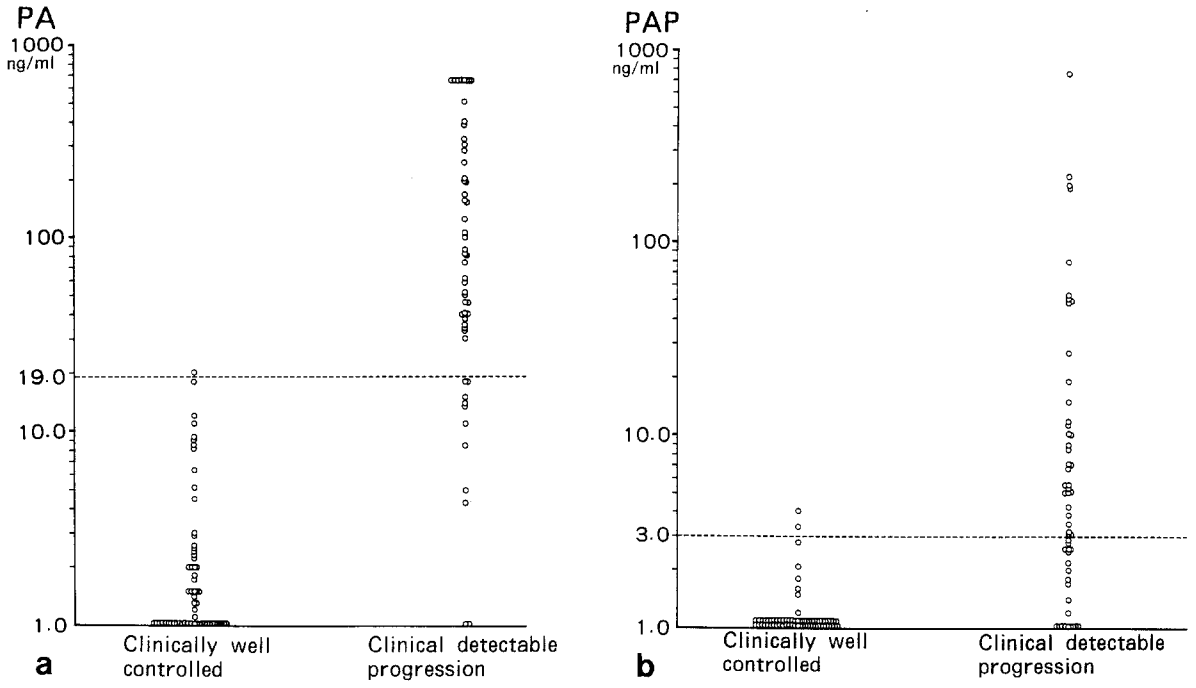

Fig. 2a, b. Serial levels of PA(a) and PAP (b) in patients with and without a clinical disease progression. *Data points* illustrate all serial levels of PA and PAP within 6 months before disease progression (progressing group) or all serial values within 6 months before and including the last serial results (group with well-controlled disease)

between groups C and D. Therefore, the interval to progression was equally short in the groups with an initial PA of more than 100 ng/ml.

Discussion

PA is a chemically and immunologically defined glycoprotein and distinct from PAP, PA has been shown to be more significant than PAP for monitoring patients with prostatic cancer. Guinan et al. [5] reported that, compared with PAP, the PA test is more sensitive by approximately 10% for stage A, 24% for stage B, 53% for stage C and 92% for stage D cancer. Present study shows that PA is more sensitive than PAP for detecting every stage of prostatic cance. The overall increase in sensitivity is not simply due to the better detection of advanced stage, but appears to result from an increase in the detection of prostatic cancer at the curable stage. This study suggests that in localized disease (stages A, B and C) 66% of cases could be detected by PA assay, but only 50% by PAP. Also, there is a progressive rise in the percentage of patients with elevated PA as stage advances. Further, Oesterling et al. [13] reported that the pre-operative concentration of PA correlated statistically with capsular penetration and with seminal vesicle and lymph node involvement at the time of radical prostatectomy. Recently, Csapo et al. [2] reported on a study conducted in nude mice bearing transplantable human prostatic adenocarcinoma. The study revealed that both serum PA and PAP were directly correlated with tumor volume in untreated animals, and that PA was a substantially more sensitive tumor marker than PAP. However, current clinical data do not show that a reliable differentiation between all stages is possible.

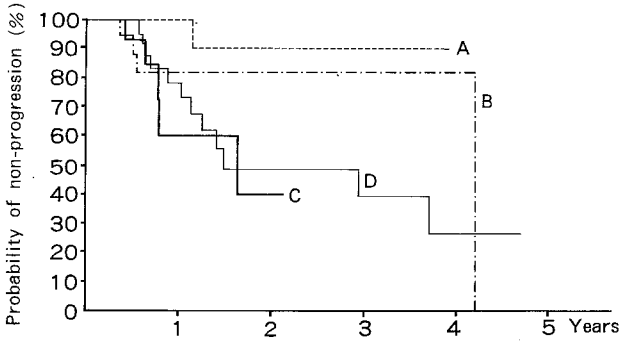

Fig. 3. Probability of non-progression and pretreatment PA levels in 87 patients with prostatic cancer. The pretreatment PA levels were: group A ($n=13$), up to 19.0 ng/ml; group B ($n=20$), 19.1–100 ng/ml; group C ($n=15$), 101–300 ng/ml; group D ($n=29$), over 300 ng/ml

The problem is that with increasing sensitivity there is a loss of specificity and a net decrease in efficiency. Many reports dealing with PA have suggested that PA is more sensitive but less specific for BPH than PAP [3, 5, 10]. Kuriyama et al. [10] reported a sensitivity of 79% but a specificity of only 59%. This study shows that, compared with PAP, there has been a major increase in sensitivity (69% to 81%) and a decrease in specificity (94% to 81%) and a minor net decrease in efficiency (83% to 81%). Considering the prevalence of prostatic cancer in the general population, PA appears to be of little value in general screening for prostatic cancer. Although why the

PA and PAP "leak" into the lymphatics or vessels is not fully understood, it is believed that PA leaks more readily than PAP into the circulation [15]. Notably, patients with recent prostatic manipulation have been shown to have transient elevation of serum PA and PAP [17, 19]. Positive rates of PA have increased to 43% in BPH patients tested immediately after digital examination. Thus, serum assay for PA as well as PAP before prostatic manipulation or repeat assay within 2–3 weeks is needed to clarify false-positive elevations.

At present, PA is considered to be most valuable in detecting residual cancer following ablative therapy of localized disease and in signalling progression following initial therapy of any stage of prostatic cancer. Oestering et al. [13] reported that PA is a sensitive tumor marker for the detection of residual recurrent prostatic cancer after radical prostatectomy. There is also a direct correlation between serial PA levels and the clinical course of the advanced stage patients treated with hormonal therapy [9]. In the present study, at the time of clinical manifestation of progression, serum PA elevation was observed in 100% of the patients (16 of 16), whereas PAP elevation was observed in 69% (11 of 16). Further, a reliable marker should predict increased growth of malignant cells before a tumor has progressed to clinical manifestation. Killian et al. [7] reported that 92% of the patients (24 of 26) who had recurrences after definitive therapy for disease confined to the pelvis had a serum PA elevation at least 12 months before clinically detectable recurrence. Siddall et al. [15] found that serum PA elevation can warn of disease progression well in advance of serum PAP elevation. This study confirmed that PA is superior to PAP in earlier prediction of disease progression.

Although cumulated data have been clarifying the role of PA in detecting disease, its role as a prognostic factor remains ill-defined. In men with stage D2 prostatic cancer Kuriyama et al. [9] found that pretreatment PA levels had a high prognostic value for patient survival, irrespective of the treatment. In other studies of stage B2 to D1 disease, pretreatment PA values are considered more reliable than PAP as a prognostic indicator of survival and disease progression [7]. Using animal models, Csapo et al. [2] revealed a direct correlation between tumor volume and pretreatment serum PA level. McNeal et al. [12] found that loss of differentiation was closely correlated with tumor volume and the capacity to metastasis. Further, Vesey et al. [17] suggest that the elevated serum PA levels found in patients with prostatic carcinoma do not arise from the primary disease itself, but mainly from its metastases.

In the light of these observations it is possible, therefore, that the initial PA levels, if elevated, reflect the extent and malignant potential of tumor. The present study suggests that initial PA levels correlate well with time to treatment failure, irrespective of stage and treatment regimen. The patients with normal PA levels or mild PA elevation before treatment could have fairly good survival without progression. On the other hand, the patients with moderate to marked PA elevation (more than 100 ng/ml) should be considered to have high risk of early disease progression. Actually, the prognostic importance of PA should be studied with reference to survival time, since assessment of the disease status in patients with advanced disease is sometimes difficult. The patients in this study were newly diagnosed and in the follow-up period too few patients have died for practical survival time analysis. Further documentation is required to clarify the ultimate role of PA as a prognostic indicator. In addition, whether the rate of fall in PA levels with treatment or time to attain nadir levels correlates with prognosis is under study.

In summary, the role of PA in monitoring prostatic cancer and its prognostic importance was investigated. PA appears to be a valuable tumor marker for detection of patients with prostatic cancer, especially with apparently localized stages. It is suggested that PA can be used for screening which is not true in view of the 19% false-positive rate in BPH patients. As a monitoring tool, PA may be most useful in early prediction of disease progression. Although long-term survival has not been analyzed, pretreatment PA levels strongly correlate with time to disease progression and may be used as an prognostic indicator. Additional studies with larger patient populations and longer follow-up periods are warranted for further investigation of the role of PA in the management of prostatic cancer.

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