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The potential use of prostatic secretory protein of 94 amino acid residues (PSP_{94}) as a serum marker for prostatic tumor

H. von der Kammer[1], C. Jurincic-Winkler[2], R. Horlbeck[2], K.-F. Klippel[2], H. U. Pixberg[3], K.-H. Scheit[1]

[1] MPI für Biophysikalische Chemie, Abteilung für Molekularbiologie, Göttingen, Germany
[2] Urologische Klinik, Allgemeines Krankenhaus, Siemensplatz 4, W-3100 Celle, Germany
[3] Abteilung für Nuklearmedizin, Allgemeines Krankenhaus, Siemensplatz 4, W-3100 Celle, Germany

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Summary. The serum concentrations of prostatic secretory protein of 94 amino acid residues (PSP_{94}) as well as those of prostate-specific antigen (PSA) were determined in 40 patients with established prostatic carcinoma, prior to transurethral resection of the prostate. In a comparison with a control group of healthy men ($n=40$) and a group of patients with histologically established benign prostatic hyperplasia ($n=40$) no significant differences in PSP_{94} serum concentrations between the groups were observed. Similarly, correlations of PSP_{94} serum concentrations with prostatic carcinoma stages or grades were not detected. In contrast, and as expected, PSA behaved as a prostate tumor marker of known sensitivity and specificity. A correlation of PSP_{94} and PSA concentrations in sera of patients with benign prostatic hyperplasia and/or prostatic carcinoma could not be verified. PSP_{94} apparently does not fulfill the criteria of a serum marker for monitoring adenomas and/or carcinomas of the prostate.

Key words: Prostatic cancer markers – Prostatic secretory protein – PSP_{94} – Prostate-specific antigen

As demonstrated by Lilja and Abrahamsson [17] the human prostate secretes three main proteins: prostatic acid phosphatase (PAP), prostate-specific antigen (PSA) and a protein of 10.7 kDa which is known as β-microseminoprotein, β-inhibin or prostatic secretory protein of 94 amino acid residues (PSP_{94}). The molecular and biochemical properties of these proteins have been reviewed recently [24]. Results of Ulvsbäck et al. [28] and Weiber et al. [30] indicated that PSP_{94} cannot be considered as a prostate-specific protein, since it has been demonstrated in tissues other than prostate.

The usefulness of PAP and PSA as markers of adenocarcinoma of the prostate has been amply demonstrated [7]. In recent years, PSA was established as an important parameter for monitoring of prostatic carcinoma in patients under therapy [19]. Our interest was raised by reports that PSP_{94} appears to possess a putative potential as a serum marker for prostatic carcinoma as revealed by PSP_{94}-specific radioimmunoassays [2, 8, 27]. We have developed a highly sensitive PSP_{94}-specific enzyme-linked immunosorbent assay (ELISA) by means of a monoclonal antibody against PSP_{94} [14]. We describe here the results of a study in which this PSP_{94} ELISA was used to measure PSP_{94} concentrations in sera of three different groups of individuals: healthy men, men with benign prostatic hyperplasia, and men suffering from prostatic carcinoma. The results of our study indicate that PSP_{94} does not possess the potential to function as a serum marker for prostatic carcinoma.

Materials and methods

Sera

All sera were taken in morning between 07:30 hours and 09:00 hours and at least 7 days after rectal palpations had been performed. These measures appeared to be necessary to avoid possible influences on serum levels of PSA or PSP_{94} respectively [26]. The sera were stored in aliquots at −80°C and, after thawing, an aliquot was assayed immediately in order to minimize decomposition of PSA [25].

Subjects

Forty men, aged 37–87 years, comprised a group which suffered from histologically established benign hyperplasia of the prostate. All patients in this group had disorders with respect to voiding of the bladder (stage II) with residual urine volumes of > 100 ml.

Another group of 40 men, aged 40–90 years, had developed prostatic carcinomas which were independently diagnosed histologically by two investigators. The American (Jewett-Marshall) classification was used for staging [29]. The staging of prostatic carcinoma done by abdominal sonography, bone scintigraphy with technetium −99 m and computed tomography. All patients underwent transurethral resection; sera for measurement of prostate markers were taken before treatment. Tissue from prostatic carcinomas was graded

Correspondence to: Dr. C. Jurincic-Winkler

Table 1. PSP_{94} serum concentrations in the three patient groups

	Control	PA	PCA
n	40	40	40
Range (ng/ml)	1.5–17.7	0.9–17.4	0.5–195.6
Median (ng/ml)	6.8	5.2	11.4
95% confidence interval of median (ng/ml)	5.3–8.1	4.5–5.7	8.2–12.1
99% confidence interval of median (ng/ml)	4.6–8.6	4.2–6.4	6.8–12.7

PA, Prostatic adenoma (benign prostatic hyperplasia); *PCA*, prostatic carcinoma

Table 2. Prostate-specific (PSA) serum concentrations in the three patient groups

	Control	PA	PCA
n	40	40	40
Range (ng/ml)	0.5–4.5	0.8–18.7	2.9–900.0
Median (ng/ml)	1.8	4.5	12.8
95% confidence interval of median (ng/ml)	1.4–2.0	3.6–5.8	9.0–22.6
99% confidence interval of median (ng/ml)	1.4–2.2	3.0–7.0	6.7–26.5

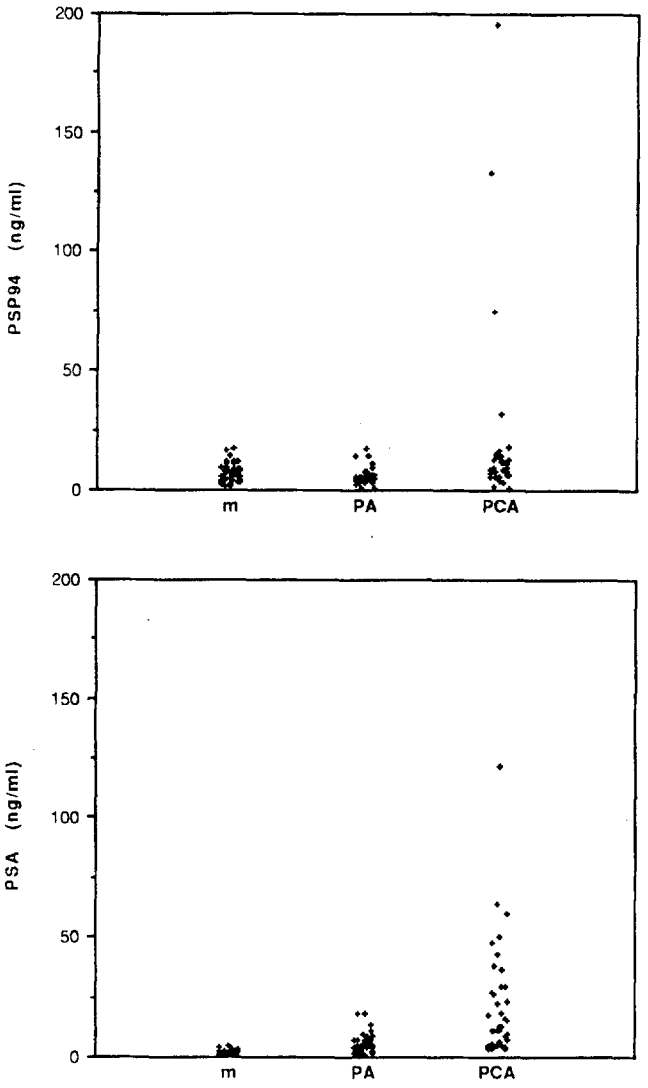


Fig. 1. Distribution of the experimental PSP_{94} and prostate-specific antigen (PSA) values between the three groups. *m*, Normal male group; *PCA*, group of patients with established prostatic carcinoma; *PA*, group of patients with established prostatic adenoma (benign prostatic hyperplasia)

employing the system of the Union International Contre le Cancer (UICC) [12]. The following groups were differentiated: grade 1, well differentiated with slight anaplasia; grade 2, moderately differentiated with moderate anaplasia; grade 3/4, ranging from poorly differentiated to undifferentiated with marked anaplasia.

A group of 40 men, aged 37–81 years, with no signs of disorders of the urinary tract and a healthy status of the prostate, testis, epididymis and accessory glands served as control. This group showed no signs of prostatic hyperplasia by digital rectal examination.

Assays

PSA serum concentrations were measured using the PSA ELISA (Isotopen Diagnostik CIS, Dreieich, Germany). Determinations of PSP_{94} in serum were carried out with the PSP_{94} ELISA [14], which is commercially available (Seratec Gesellschaft für Biotechnologie, Göttingen, Germany). The intra-assay variation in ELISA measurements was $\leq 8\%$. All determinations for PSA and PSP_{94} were carried out in duplicate.

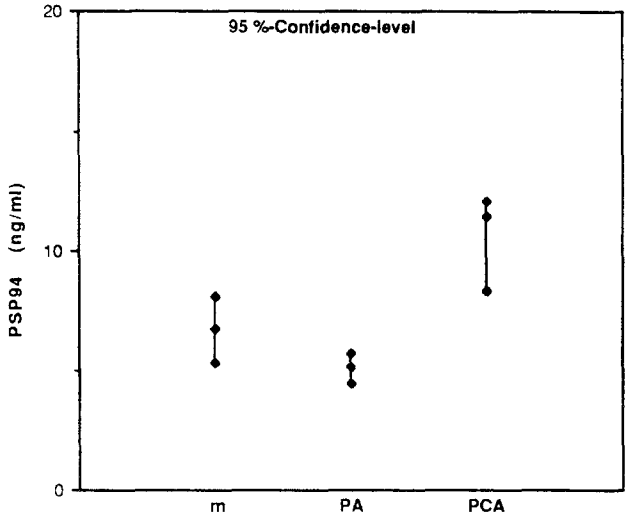
Statistical analysis

Close inspection of the data revealed that they did not follow a Gaussian distribution. Therefore for a comparison of the concentrations of PSA and PSP_{94} in the sera of the three groups, the corresponding median and the respective 95% and 99% confidence intervals were introduced in accordance with a previously published procedure [22]. Confidence ranges of median values for disease groups that did not overlap with those of the control group were considered to be significantly different. Calculations were performed using the programms StatView and CricketGraph on a Macintosh IIcx computer.

Results

Data, medians and confidence intervals of medians are detailed in Tables 1 and 2. The experimental data are also depicted in Fig. 1. The 95% and 99% confidence intervals for the median values of the PSP_{94} data and similarly for the PSA data are graphically represented in Figs. 2 and 3.

Although apparently higher PSP_{94} values are observed in the group of patients with prostatic carcinoma, even the 95% confidence interval of the median partially overlaps with that of the control group. For PSP_{94} the overlap



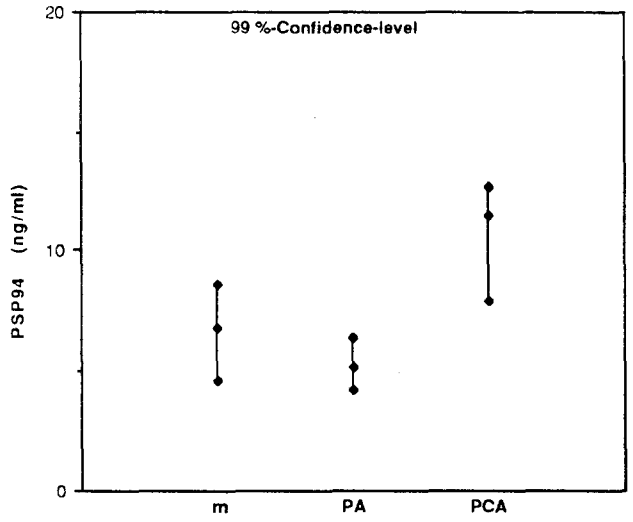
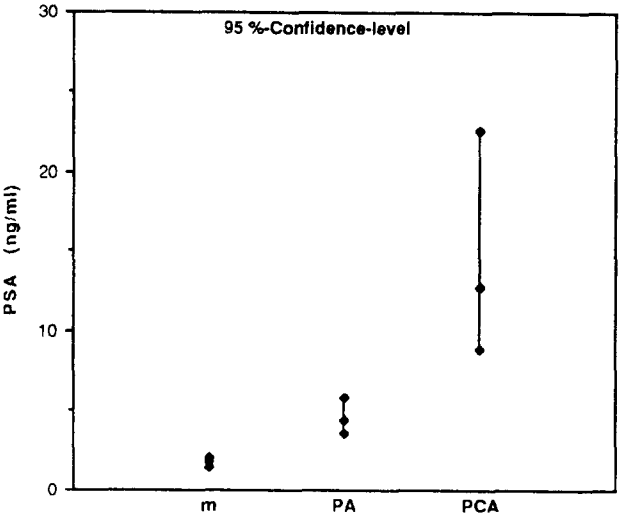


Fig. 2. Serum concentrations of PSP_{94}. Intervals of medians at confidence levels of 95% and 99%. *m*, Normal male group; *PCA*, group of patients with established prostatic carcinomas; *PA*, collective of group with established prostatic adenomas



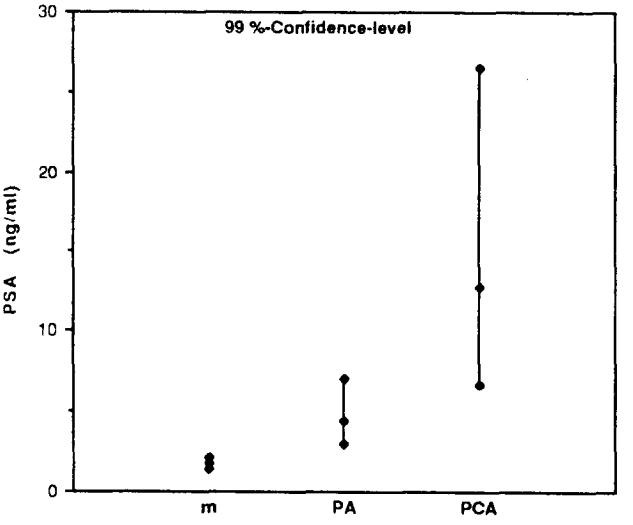


Fig. 3. Serum concentrations of PSA. Intervals of medians at confidence levels of 95% and 99%. *m*, Normal male group; *PCA*, group of patients with established prostatic carcinomas; *PA*, group of patients with established prostatic adenomas

between medians at confidence levels of 95% and 99% for the control group and the group of patients with benign prostatic hyperplasia is excessive.

As expected, a significant increase in PSA concentration was evident in the sera of patients with prostatic carcinoma compared with the control group and with the group of patients with benign prostatic hyperplasia. However, at the 99% confidence level of median values, an overlap at low concentrations (6.7–7.0 ng/ml) was noticed. This is the concentration range which contains the threshold value between a normal and pathological serum level as recommended by various laboratories.

The serum concentrations of PSA and PSP_{94} in the group of patients suffering from prostatic carcinoma were subdivided with respect to staging and/or grading of the carcinoma (Tables 3, 4). The median at different confidence levels of PSP_{94} concentrations in sera did not depend significantly on the stage of a patient's prostatic carcinoma (Fig. 4), although slightly higher values of PSP_{94} concentrations were seen in stage D_2 ($\mu = 12.6$ ng/ml) compared with stage C ($\mu = 11.9$ ng/ml). However, a significant correlation between the stage of prostatic carcinoma and PSA concentrations in sera was found (Fig. 4); this is in agreement with published observations [7]. In the case of stage A and B prostatic carcinomas no statistical analysis was performed due to the low number of cases available.

We were able to verify the finding [3] that the PSA concentrations in sera of patients with prostatic carcinoma correlates positively with the grade of the disease (Fig. 5); the same does not hold for the PSP_{94} concentrations in sera of the same group of patients (Fig. 5). As expected from the above mentioned observations, a statistical analysis yielded no correlation between serum

Table 3. PSP_{94} serum concentrations of patients with prostate carcinoma differing with respect to staging and grading

	Stage				Grade		
	A[a]	B[a]	C	D_2	G1	G2	G3/4
n	4	6	13	17	15	10	15
Range (ng/ml)	5.4–6.6	1.4–14.1	0.5–74.9	3.3–195.6	0.5–74.9	3.3–15.4	5.4–195.6
Median (ng/ml)			11.9	12.6	8.9	10.2	12.6
95% confidence interval of median (ng/ml)			6.5–13.5	8.9–14.6	5.6–12.1	3.9–11.9	8.4–15.0
99% confidence interval of median (ng/ml)			5.4–15.4	7.9–16.7	5.4–13.5	3.3–12.8	8.2–16.7

[a] Due to an insufficient number of cases, statistical analysis was not performed

Table 4. PSA serum concentrations of patients with prostate carcinoma differing with respect to staging and grading

	Stage				Grade		
	A[a]	B[a]	C	D_2	G1	G2	G3/4
n	4	6	13	17	15	10	15
Range (ng/ml)	2.9–4.2	3.5–18.4	4.2–26.5	3.9–900.0	2.9–18.4	4.5–36.7	3.9–900.0
Median (ng/ml)			10.9	36.7	5.3	15.8	38.4
95% confidence interval of median (ng/ml)			6.7–11.4	23.2–47.6	3.5–9.2	6.7–23.2	17.3–50.5
99% confidence interval of median (ng/ml)			4.5–13.0	17.3–60.0	3.3–10.9	4.5–26.5	10.9–60.0

[a] Due to an insufficient number of cases, statistical analysis was not performed

concentrations of PSP_{94} and PSA in patients suffering from either benign prostatic hyperplasia or prostatic carcinoma (data not shown).

Discussion

This study clearly demonstrated the usefulness of PSA as an indicator of prostatic carcinoma, although the specificity of PSA as a tumor marker, as amply pointed out by various investigators, depends on definitions of the threshold concentration of PSA which differentiates normal from pathological values.

The first measurements of PSP_{94} in serum fo healthy men in comparison with men with prostatic cancer were reported by Dubé et al. [8]. A radioimmunoassay gave a mean value of 19 ± 2 ng/ml for asymptomatic men and 115 ± 36 ng/ml for eight patients with stage D2 prostatic carcinoma. The paucity of the data reported parents their statistical evaluation. A more thorough attempt to measure PSP_{94} in sera of both men and women by means of a radioimmunoassay is described by Abrahamsson et al. [2]. The authors also determined the concentration of PSP_{94} in sera from 28 patients with prostatic carcinomas of stages T3 to T4. Half of the cancer patients had serum concentrations of PSP_{94} exceeding the upper reference limit. In this report a range of 1–14.7 ng/ml with a median of 6.2 ng/ml was given as a reference. It is, however, difficult to identify the exact value of the upper reference limit used by the authors in the classification of their data. Furthermore, the reader cannot judge the distribution of the measured concentrations. However, the results indicate, similar to our findings, that elevated serum levels of PSP_{94} were measured in patients with advanced disease status and, furthermore, that tumor progression shifts the distribution of PSP_{94} concentrations to higher levels. The authors do not actually present these data, but only mention them in the text. Most regrettably, Abrahamsson et al. [2] did not include comparative measurements of another established parameter, such as PSA, in their study.

PSP_{94}, PAP and PSA, in that order, are the major secretory proteins of the human prostate [15, 17]. The latter two are widely employed as serum markers for the detection of prostatic carcinoma. The molecular weights of the proteins are: PSP_{94}, 10.7 kDa; PSA, 34 kDa; and PAP, 82 kDa. Their ultrastructural locations have been identified, all three being localized mainly in the epithelium of normal prostatic acini and ducts; extreme concentrations are also found in acinar lumen [5, 9, 17]. Release occurs by exocytosis. PAP was localized, at high levels, in lysosomes and secretory vacuoles [4]. Ito et al. [13] have shown that PSA, like PAP, is localized in the lysosomes of the cells, whereas PSP_{94} is localized primarily in the secretory granules. The question of the tissue specificity of PAP, PSA and PSP_{94} has no simple answer. The main source for these proteins is the prostate. Expression of PAP and PSA in other tissues, although to a lesser extent, has been reported [10, 16]; PSP_{94} has been shown to be produced in substantial amounts by various other tissues [28, 30].

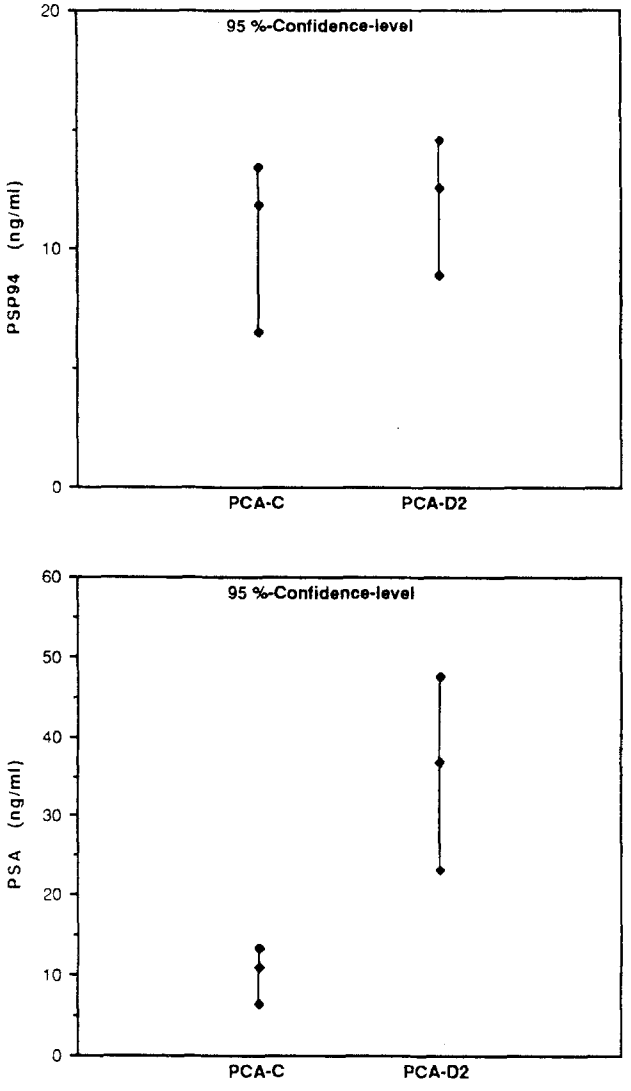


Fig. 4. Serum concentrations of PSP_{94} and PSA at different stages of prostatic carcinoma. Intervals of medians at confidence level of 95%. *PCA-C*, Prostatic carcinoma stage C; *PCA-D_2*, prostatic carcinoma stage D_2

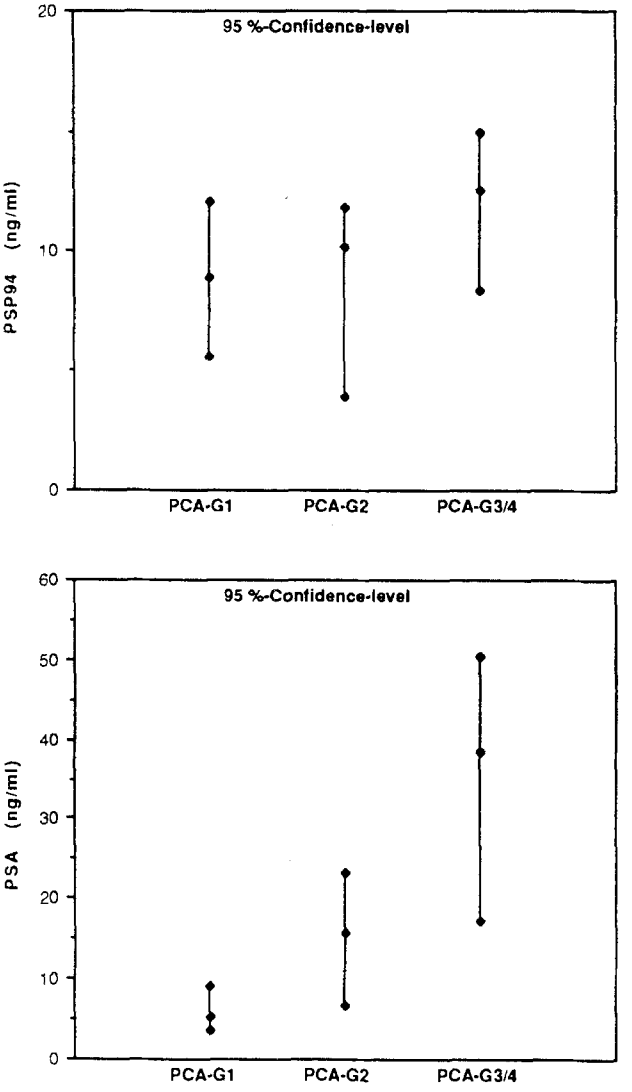


Fig. 5. Serum concentrations of PSP_{94} and PSA at different grades of prostatic carcinoma. Intervals of medians at confidence level of 95%. *PCA-G1*, Prostatic carcinoma grade 1; *PCA-G2*, prostatic carcinoma grade 2; *PCA-G3/4*, prostatic carcinoma grade 3/4

To understand why secretory proteins of the prostate function principally as serum markers of prostatic tumors, and why differences exist with respect to sensitivity and specificity between these markers, the following experimental results need to be reconcited:

(1) Normal sera contain very low concentrations of PSA and PAP, whereas PSP_{94} serum concentrations are higher, very probably because PSP_{94} is not produced exclusively in the prostate.

(2) Levels of PSA and PAP, but less generally of PSP_{94}, are increased in serum in cases of benign prostatic hyperplasia, but especially in cases of prostatic carcinoma.

(3) The increases in PSA and PAP as well as PSP_{94} levels differ between the individual markers. Whereas PAP levels generally increase in a moderate fashion, PSA serum concentrations increase considerably. Serum levels of PSP_{94} in patients with prostatic carcinoma, on the other hand, are distributed over a wide range.

(4) A correlation between the increase in serum concentration and tumor progression exists between PSA and PAP, but not between these markers and PSP_{94}.

(5) The mode of expression of PAP, PSA and PSP_{94} in benign prostatic hyperplasia and in adenocarcinoma of the prostate is perplexing. Immunohistochemical studies revealed that expression of PSA, PAP and PSP_{94} in cases of benign prostatic hyperplasia as well as in cases of highly differentiated (grade I) carcinomas occurred to a similar extent with a high incidence of immunoreactive cells [1].

In moderately and poorly differentiated (grade II and III) tumors, expression of PSA, PAP and PSP_{94} was observed at lower levels with greater variability between the individual protein species. This was confirmed by a quantitative study by Pretlow et al. [20], which convincingly demonstrated that PSA is expressed at lower levels in prostatic adenocarcinoma than in benign prostatic hyperplasia; this has also been observed by in situ hybridization experiments [21]. Expression of PSP_{94} was observed in 89.3% of cases of benign prostatic hyperplasia but in only 50.0–57.3% of prostatic adenocarcinomas and 28% of metastases [11].

(6) As stated by Pretlow et al. [20], "Little is known about the mechanism of the secretion, clearance and excretion of these markers."An attempt to contribute to the understanding of this problem with respect to PSA was provided by Brawer et al. [6]. Serum levels of PSA in patients exhibiting prostatic intraepithelial neoplasia (PIN) were found to be elevated. PIN is believed to represent a premalignant prostatic lesion and is characterized by proliferation and anaplasia of the cells lining prostatic ducts and acini. These lesions are morphologically indistinguishable from invasive carcinoma. A correlation of PIN grade and disruption of the basal cell layer was demonstrated. The observation that PIN may be associated with basal cell layer disruption suggests a possible mechanism of the higher serum PSA levels in patients exhibiting PIN. At least one barrier between the PSA-producing luminal prostatic cells and the circulation is breached.

(7) In view of the findings that the overwhelming majority of prostatic carcinomas produce both PAP and PSA and that there is little convincing evidence that either PSA or PAP is made in lesser amounts or by a smaller proportion of tumors than the other, why have so many investigators found PSA to be a more sensitive marker than PAP in sera of patients with prostatic carcinoma? One attempt to resolve this problem was based on serum stability. The different serum stabilities of PAP and PSA have been said to be responsible for the difference in magnitude by which their concentrations are elevated in sera of patients with prostatic carcinoma. PSA, a serine-type protease, was shown to exist in serum predominantly complexed to α_1-antichymotrypsin [18]. Thus PSA might be protected from proteolytic degradation, whereas the high molecular weight PAP is not. This is supported by the half-life of 1.5 days for PSA [23] and the dramatically shorter half-life for PAP in blood circulation [19]. The results of our studies show, however, that the stability argument can only partially unravel the dilemma. PSP_{94} is a small protein of 94 amino acid residues with a rigid structure provided by four disulfide bridges; it is highly stable in serum [24]. If there are patients with prostatic carcinoma who have elevated serum levels of PSA and PAP (i.e. there is a correlation between the two parameters) but normal (and hence uncorrelated) PSP_{94} serum concentrations, then in addition to the serum stability at least two other mechanisms operate: one which controls the excretion of PSA and PAP into the circulation from prostatic carcinomas and another which controls the excretion of PSP_{94} (and possibly other secretory proteins of the prostate) into the circulation.

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