Prostate-specific antigen density: correlation with histological diagnosis of prostate cancer, benign prostatic hyperplasia and prostatitis


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Objective To assess the additional value of prostate-specific antigen density in the diagnosis of prostate cancer in patients who undergo prostate biopsies.

Patients and methods The study comprised 376 patients with symptoms of prostatism who were undergoing prostate biopsy. Digital rectal examination (DRE) and transrectal ultrasonography (TRUS) were performed and the prostate specific antigen level (PSA) and density (PSAD) were determined for each patient.

Results Both PSA and PSAD significantly differentiated (P<0.001) between benign and malignant histology. Of the 376 patients, 91 (24%) had a PSA level in the intermediate range (4.0-10.0 ng/mL). In these patients PSAD was significantly better than PSA in differentiating between benign and malignant histology (P=0.027 vs 0.316). With a PSAD limit of 0.15 ng/mL/cm³ in these patients, the sensitivity was 92% and the specificity was 54% for the diagnosis of prostate cancer. No patient with a positive biopsy had a PSAD <0.11 ng/mL/cm³. No limiting value could be found for PSAD that combined both an acceptable sensitivity and specificity. Of the patients with a malignancy detected by the biopsy, 9.2% also had a suspect DRE.

Conclusion In patients with intermediate PSA levels, PSAD is of limited additional value when compared to DRE in correctly diagnosing prostate cancer. Acute prostatitis is also a possible cause of elevated PSA. Both PSA and PSAD had no additional value in differentiating between benign prostatic hyperplasia (BPH) and histologically proven extensive prostatitis.

Keywords Prostate cancer, benign prostatic hyperplasia, prostate-specific antigen, prostate-specific antigen density, prostatitis

Introduction

Digital rectal examination (DRE), transrectal ultrasonography (TRUS) and prostate-specific antigen (PSA) are commonly used as diagnostic tools in the early detection of prostate cancer. None of these tests has sufficient accuracy to justify its use alone as a screening test. The combination of DRE, TRUS and PSA enhances the ability to predict the presence of carcinoma [1].

Although PSA is the most accurate marker for cancer in the prostate, its sensitivity and specificity are insufficient. Consensus exists that for a PSA value <4 ng/mL, where the incidence of prostate cancer is 1.4% [2], biopsies are not indicated if there is no further suspicion for malignancy. At a PSA level >10 ng/mL, the incidence of prostate cancer is 53.3% [3] and most authors [4,5] agree that biopsies have to be taken in these cases. In the range between 4 and 10 ng/mL PSA (intermediate PSA levels, iPSA) diagnosis is difficult as benign prostatic hyperplasia (BPH) or prostate cancer frequently occur in patients with iPSA. An increase in PSA may be found in patients with BPH or after prostatic manipulations such as cystoscopy and prostate biopsy [6]. Because the half-life of PSA is estimated to be 2.2 [7] to 3.2 days [8] it may, depending on the rise in PSA level, take 2-3 weeks after prostatic manipulation before the PSA serum level has decreased to its base-line value.

Because prostatic volume may influence the PSA level it is prudent to make a correction for prostatic volume (PSA/prostatic volume = PSA-density, PSAD) as proposed by Benson et al. [9]. An overview of the results of several studies is shown in Table 1; there is still much debate about the clinical value of PSAD.

According to Benson et al. [5], patients with iPSA, a PSAD <0.15 ng/mL/cm³ and a normal DRE may be treated by watchful waiting, as there is only an 18% chance of them having a positive biopsy. Bazinet et al. [10] also used a limit for PSAD of 0.15 ng/mL/cm³, below which only 3% of patients had a positive biopsy. Ramon et al. [11] used the polyclonal Yang assay in their study but, converting their values to those of the Hybritech assay, and for a PSAD equal to 0.15 ng/mL/cm³, they found a 42% incidence of prostate cancer in the PSA range of 1.7-6.7 ng/mL and a 51%
incidence in the PSA range of 6.7–13.3 ng/mL. In contrast, Brawer et al. [12] found that PSAD was not able to discriminate between patients with prostate cancer and those with BPH in this range. Several other studies [13–18] confirmed that PSAD was superior to PSA in differentiating prostate cancer from BPH. These studies are not listed in Table 1 because they do not provide enough data in the iPSA range.

To evaluate the clinical value of PSAD in the iPSA range, the correlations of PSAD, PSA, DRE and TRUS with the results of histopathological examination of patients who underwent transrectal biopsies were retrospectively investigated. Increases in PSA also occur during acute prostatitis [19–21]. A histologically distinct feature of acute prostatitis is the invasion of white blood cells into the prostatic ducts. These are predominantly polymorphic, rather than mononuclear, white blood cells. This invasion may cause a leakage of PSA from the ductal lumina, as the integrity of the prostatic ducts is disturbed. Therefore, we investigated whether PSAD or PSA was significantly higher in patients for whom we had histological proof of extensive acute inflammation of the prostate.

**Patients and methods**

Between January 1991 and December 1993, transrectal biopsy of the prostate was performed in 376 men (mean age 69.1 years, range 48.4–97.5), all of whom had micturition complaints.

Indications for biopsy were a suspect nodule on DRE, a hypoechoic lesion on TRUS or a PSA value >10 ng/mL. All patients underwent TRUS, DRE and had their serum PSA level determined using the Tandem-E PSA assay (Hybritech, San Diego, CA, USA). No blood samples were used if they were taken within 2 weeks of acute urinary retention, within 3 weeks of prostatic or urethral manipulation (e.g., cystoscopy) or within 4 weeks of acute prostatitis. DRE was considered not to influence the PSA level, according to recent studies [22–24].

TRUS examinations were performed using a Kretz Combison 330 scanner with a 7.5 MHz probe (Multiplane 3-D VRW 77AK) and were carried out by one urologist experienced in performing TRUS. Prostatic volume was calculated using a planimetric method incorporated in the scanner. Biopsies were taken with the Bipty gun (C.R. Bard, Covington, USA), using 18 G 'Tru-cut' biopsy needles. If a hypoechoic lesion was seen, a core was taken from that region. In 76% of the patients, three cores were taken from the right and left sides, equidistant from the base and apex, in 20% two cores were taken from each side of the prostate and in 4% only ultrasound-guided biopsies were taken. The cores were sectioned and stained with haematoxylin and eosin. On the basis of these sections patients were then assigned to either a benign or a malignant group. Analyses were performed on data from the whole group and separately on the patients with histologically proven extensive prostatitis.

Significance was evaluated using the Mann–Whitney U-test and the χ²-tests. Receiver operator characteristic (ROC) curves, graphically representing the correlation between sensitivity and the false positive fraction, were constructed to determine the optimal limits for PSA and PSAD. A perfect test would have a 100% sensitivity and a 0% false positive rate with an area under the curve of one. The usefulness of a diagnostic test is assessed by calculating the fractional area under the ROC curve. A multivariate analysis was also performed to assess the individual value of DRE, TRUS, PSA and PSAD in the detection of prostate cancer.
Table 2 PSA levels, prostatic volume and PSAD in 376 patients who underwent prostate biopsies

<table>
<thead>
<tr>
<th>Number (%)</th>
<th>Median PSA (ng/mL [range])</th>
<th>Median volume (cm³ [range])</th>
<th>Median PSAD (ng/mL/cm³ [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>376</td>
<td>12.0 (5.5–3100)</td>
<td>47.5 (11–202)</td>
</tr>
<tr>
<td>Benign</td>
<td>263 (69.9)</td>
<td>9.60 (0.5–190)</td>
<td>51.0 (11–202)</td>
</tr>
<tr>
<td>Malignant</td>
<td>113 (30.1)</td>
<td>33.0 (1.6–3100)</td>
<td>39.3 (16–145)</td>
</tr>
<tr>
<td>2-tailed P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Results

Total group

A mean of 6.1 cores per patient was taken for biopsy and in 71.6% of the patients at least six cores were taken. The histological examination revealed prostate cancer in 113 patients (Table 2).

Five patients with an initial benign histology were biopsied again within 1 year and were proved to have prostate cancer. The second biopsy was performed because the initial histological diagnosis was suspect (two patients) or there was a rise in PSA level (three patients). These patients were reclassified as having a malignant tumour.

The mean PSA level was 9.6 ng/mL in the patients with a benign diagnosis and 33.0 ng/mL in those with malignancies. Although 95.6% of the patients in the benign group had a PSA <78 ng/mL, there were two patients with BPH and a PSA level >78 ng/mL. One patient with a PSA level of 190 ng/mL underwent transurethral resection of the prostate and 150 g of tissue was resected. Histological examination showed focal abscesses. The mean PSAD was 0.17 ng/mL/cm³ in the benign group and 0.91 ng/mL/cm³ in the malignant group. The PSA level, prostate volume and PSAD were significantly different between the benign and the malignant group (P<0.001). The area under the ROC curves for PSA (0.816) and PSAD (0.858) in the whole group were not significantly different (Fig. 1).

DRE and TRUS

In the group with a negative DRE, 22 (12%) had prostate cancer compared to 91 (47%) with a suspect DRE (Table 3, P<0.001). For patients with a negative DRE, TRUS was of no additional value (Table 3, P=0.131). However, when TRUS showed no abnormality, DRE was able to differentiate between malignant and benign biopsies (P=0.011). In the group with a normal DRE, both PSAD and the PSA level could differentiate between malignant and benign biopsies (Table 4).

Fig. 1. Receiver operator characteristic curve for PSAD and PSA in the whole group (376 patients). — PSAD, - - - PSA.

Table 3 Reliability of DRE and TRUS when DRE was normal, in the detection of prostate cancer

<table>
<thead>
<tr>
<th></th>
<th>Benign n (% of group)</th>
<th>Malignant n (% of group)</th>
<th>Total in group</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE normal</td>
<td>169 (88)</td>
<td>22 (12)</td>
<td>191</td>
</tr>
<tr>
<td>DRE abnormal</td>
<td>94 (51)</td>
<td>91 (47)</td>
<td>185</td>
</tr>
<tr>
<td>Total</td>
<td>263</td>
<td>113</td>
<td>376</td>
</tr>
<tr>
<td>TRUS normal</td>
<td>119 (91)</td>
<td>12 (9)</td>
<td>131</td>
</tr>
<tr>
<td>TRUS abnormal</td>
<td>50 (83)</td>
<td>10 (17)</td>
<td>60</td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>22</td>
<td>191</td>
</tr>
</tbody>
</table>

Prostatitis

In the benign group, 13 patients (3.5%) had biopsies but with moderate to extensive invasion of polymorphic white blood cells and the biopsies were histologically classified as prostatitis. There was no significant difference between the prostatitis group and the benign group but with no prostate inflammation in PSA level, prostate volume or PSAD (P=0.06, P=0.06 and P=0.47, respectively). DRE findings were more often classified as malignant in the prostatitis group than in the benign group.
Table 4 PSA, prostate volume, and PSAD in patients with no abnormal findings on DRE and in the patients with a PSA between 4.0 ng/mL and 10.0 ng/mL (iPSA)

<table>
<thead>
<tr>
<th></th>
<th>Number (%</th>
<th>Median PSA (ng/mL [range])</th>
<th>Median volume (cm³ [range])</th>
<th>Median PSAD (ng/mL/cm³ [range])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative DRE</td>
<td>191</td>
<td>12.0 (0.5-260)</td>
<td>53.6 (13-202)</td>
<td>0.20 (0.01-8.67)</td>
</tr>
<tr>
<td>Benign</td>
<td>169 (88.5)</td>
<td>11.0 (0.5-190)</td>
<td>54.0 (13-202)</td>
<td>0.19 (0.01-3.0)</td>
</tr>
<tr>
<td>Malignant</td>
<td>22 (11.5)</td>
<td>16.5 (8.0-260)</td>
<td>43.8 (20-145)</td>
<td>0.34 (0.12-8.67)</td>
</tr>
<tr>
<td>2-tailed P</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>iPSA</td>
<td>91</td>
<td>6.9 (4.1-9.9)</td>
<td>49.0 (20.3-180)</td>
<td>0.15 (0.03-0.35)</td>
</tr>
<tr>
<td>Benign</td>
<td>79 (86.8)</td>
<td>6.8 (4.1-9.9)</td>
<td>50.0 (20.3-180)</td>
<td>0.13 (0.03-0.35)</td>
</tr>
<tr>
<td>Malignant</td>
<td>12 (13.2)</td>
<td>7.5 (5.8-9.9)</td>
<td>40.0 (29.0-81.0)</td>
<td>0.19 (0.11-0.25)</td>
</tr>
<tr>
<td>2-tailed P</td>
<td></td>
<td></td>
<td></td>
<td>0.0815</td>
</tr>
</tbody>
</table>

(P=0.009), whereas TRUS did not differ between these groups (P=0.536).

iPSA

Ninety-one patients had iPSA levels. A mean of 6.2 cores per patient were taken during biopsy and in 74.7% of these patients six or more cores were taken. In 12 patients the biopsies appeared malignant and in 79 they were benign (Table 4). PSAD was significantly different (P=0.027) between the patients with a benign or a malignant histology but PSA level did not differ significantly (P=0.316). ROC curves were plotted for PSA and PSAD (Fig. 2) giving an area under the curve of 0.59 for PSA and 0.70 for PSAD, which was significantly different, indicating that PSAD was superior to PSA in differentiating between benign and malignant prostatism.

Following the recommendation of Benson et al. [5], a PSAD limit of 0.15 ng/mL/cm³ was used for diagnosis.

One biopsy from a patient with a PSAD below this limit appeared to be malignant. Of the 79 benign biopsies 43 (54%) had a PSAD <0.15 ng/mL/cm³. None of the 12 patients with a malignant biopsy had a PSAD <0.11 ng/mL/cm³ compared with 27 of the 79 benign biopsies (34%). The performance for different values of PSAD is given in Table 5. For some PSAD limits, sensitivity and specificity are given if these values were taken as the upper limit, below which the PSAD was a predictor of benign histology and above which malignant histology could be predicted.

Table 6 gives the performance of DRE and TRUS in this group. DRE findings correlated well with the histological outcome (P=0.004) while TRUS could not discriminate significantly between malignant and benign tissue (P=0.300).

Discussion

The detection of early prostate cancer depends on the accuracy of DRE, TRUS and serum PSA, which are currently considered to be the best tools for the diagnosis.
of prostate cancer [3]. However, the accuracy of PSA in differentiating patients with prostate cancer from those with benign disease is insufficient, according to some authors [7,25]. In the iPSA range there is an overlap of PSA levels in patients with prostate cancer and those with benign disease.

PSAD promised to be a better tool in differentiating between patients with BPH and prostate cancer [13]. All but one of the studies mentioned in Table 1 confirmed the findings of Benson [5] that PSAD is superior to PSA in differentiating between benign and malignant prostates in the iPSA range. A limit of 0.15 ng/mL/cm³ was chosen by these authors, but the choice of a threshold value of PSAD depends on the desired sensitivity for the detection of prostate cancer. A balance must be found between an acceptable proportion of undetected prostate cancers and the lowest possible proportion of unnecessary biopsies.

The reliability of PSAD is a product of the reliability of its constituents; the accuracy of PSAD obviously depends on the accuracy with which the PSA and prostatic volume are assessed. The production of PSA per volume of prostatic tissue is not only related to the presence of BPH and prostate cancer but also to the proportion of epithelial cells and to the histological grade of the carcinoma. Hormonal status and other factors may also play a role. Assessment of the prostatic volume depends on many factors and can be calculated by the ellipsoid or planimetric methods. The calculation of the prostatic volume in the first three articles listed in Table 1 was made using the ellipsoid method (i.e. \(0.52 \times \text{length} \times \text{width} \times \text{height}\)). Stone et al. [26] found that step-section 3D-planimetry gave a variability of 5% compared with 30% for a three-axis method. According to Holmang et al. [27] the ellipsoid method underestimates the volume by 20% compared with the planimetry of several sections, but they are well correlated with each other. The planimetric method, as used in the present study, seems the most accurate.

Moreover, one would expect that PSAD, calculated as serum PSA divided by the prostatic volume measured by TRUS, is consistent with values of PSAD calculated as the change in serum PSA divided by the weight of resected tissue after TURP. However, PSAD values obtained by PSA measurement before and after TURP vary among different authors. Stamey et al. [7], calculated a value of 0.5 (±0.4) ng/mL/cm³ while Lee et al. [15] found a value of 0.12 ng/mL/cm³.

Some authors think that PSAD is of little or no value in discriminating between prostate cancer and BPH and suggest that age-specific PSA values are more useful than PSAD [28]. As prostatic volume increases with age, a higher limit for the lower threshold of the normal PSA range in older men in itself implies a correction for higher prostatic volumes in older men.

The aim of this retrospective analysis was to investigate whether PSAD-based clinical guidelines could help in the diagnosis of prostate cancer and assist in avoiding a significant number of biopsies. In the study, most TRUS was performed immediately after DRE. The subsequent interpretation of TRUS can be biased, because the outcome of DRE (and PSA) may influence the interpretation of the TRUS image. However, TRUS had no significant extra value when combined with DRE in the detection of prostate cancer (\(P=0.131\)). Because all patients were referred for micturition complaints many in the benign group inevitably presented with a high prostate volume. This could explain the significantly higher prostate volume in this group compared to the group with prostate cancer (Table 2), an effect which was also seen by Benson et al. [5].

Overall, PSAD made no significantly better distinction between patients with prostate cancer and those with BPH (Fig. 1). In the iPSA range only 12.1% of the patients appeared to have prostate cancer, which is the lowest rate of the studies quoted in Table 1, possibly because the present study was comprised of patients with micturition complaints. In this group, the mean prostate volume was higher when compared to a screening population which may explain why these patients more often had a PSA value > 4.0 ng/mL.

In the iPSA range, the sensitivity was 100% and the specificity 32% for the diagnosis of prostate cancer when a PSAD limit of 0.11 ng/mL/cm³ was used. If a limit of 0.15 ng/mL/cm³ was used the values were 92 and 54%, respectively. No limit could be found that combined with DRE in differentiating between prostate cancer and benign disease.

| Table 6 | Reliability of DRE and TRUS in patients with a PSA between 4.0 and 10.0 ng/mL. |
|-----------------|------------------|-----------------|
|                | Benign (% of group) | Malignant (% of group) | Total in group |
| DRE normal      | 42 (98)           | 1 (2)             | 43              |
| DRE abnormal    | 37 (77)           | 11 (23)           | 48              |
| Total           | 79                | 12                | 91              |
| TRUS normal     | 39 (91)           | 4 (9)             | 43              |
| TRUS abnormal   | 40 (83)           | 8 (17)            | 48              |
| Total           | 79                | 12                | 91              |

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range. This might be explained by the selection of patients, as patients with an iPSA level, a normal TRUS and a normal DRE were not biopsied.

Conclusions
The PSAD limit chosen is not an absolute value as it depends on the population examined, the reliability of the measurement of prostatic volume and the desired sensitivity. In patients with micturition complaints and an iPSA level, a PSAD <0.15 ng/mL/cm³ indicates a high probability (97.7%) of benign histology, but the PSAD is of limited additional value to DRE. Both PSA and PSAD had no significant value in differentiating between histologically proven extensive prostatitis and BPH.

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