Preliminary Evaluation of Measurement of Serum Prostate-Specific Antigen Level in Detection of Prostate Cancer*

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ABSTRACT

The measurement was evaluated of serum prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) levels for early detection of prostate cancer on a potentially high-risk group. A PSA level at 5.0 ng per ml and PAP at 4.0 ng per ml were chosen as the cut-off levels. Results obtained for PSA and PAP can be divided into three groups: Group I, with normal levels of PSA and PAP; Group II, with elevated PSA but normal PAP level; and Group III, with elevated levels of both PSA and PAP. Forty-five of 46 patients in Group I were diagnosed as normal, while 70 out of 99 patients in Group II were categorized as having prostatic carcinoma with stages ranging from A1 to D, and nine of nine patients in Group III had stage D carcinoma. Our results also indicated that the measurement of PSA had a greater sensitivity than that of PAP and that PSA measurement could be a valuable adjunct to the diagnosis of prostate cancer.

Introduction

In 1985, the estimated number of new cases of prostate cancer in the United States was 86,000 with estimated deaths of 25,000. It is, indeed, an insidious cancer in men over the age of 45 years. The onset and early progression of this cancer is relatively asymptomatic; once it metastasizes, the prognosis is grave. Therefore, it is important to find a sensitive tumor maker for the detection of the disease.

Acid phosphatase, specifically the L-tartrate sensitive isoenzyme, prostatic acid phosphatase (PAP), has been advocated as an assay for the detection of prostate carcinoma. Difficulties have been frequently encountered in measuring PAP, either by the enzyme activity assay or by the radioimmunoassay (RIA), for the diagnosis and monitoring of prostate cancer. The great instability of the enzyme activity observed in the activity assay resulted in many sporadic errors, such as a high coefficient of variation (CV) of 20 to 30 percent and an unusually high false-negative rate. When PAP by RIA became available, it was initially hoped that both sensitivity and specific-
ity of the measurement would be improved, because the assay involves a more stable and specific antigen-antibody reaction instead of a labile enzymatic reaction. Investigators soon found that despite the improved CV, PAP by RIA also yielded a high false-negative rate and gave no notably improved sensitivity. However, some investigators claimed a greater sensitivity by RIA as compared to the enzyme activity assay. Another expected advantage of the PAP-RIA is that it requires no special treatment of the serum samples, since the immuno-reactivity of the prostatic acid phosphatase protein can still be measured by RIA even if the enzyme activity is completely lost. Nevertheless, lower PAP values were occasionally observed by us that can be attributed to aging of the specimens.

Recently, another prostate tumor marker protein, prostatic-specific antigen (PSA), which is distinct from PAP, has been introduced. The PSA has been purified and characterized as a glycoprotein, with an apparent molecular weight of approximately 34,000. The marker protein was found to be localized only within the prostatic ductal epithelial cells. It has no known biological function and is only present in low concentration in the sera of normal men.

The purpose of this study is to present a correlation of serum PSA and PAP levels, with prostate cancer and benign prostatic hypertrophy (BPH) and to discuss the potential usefulness of measuring PSA in conjunction with PAP among subjects at high risk.

Materials and Methods

A total of 156 potentially at-risk patients were studied for whom PAP by RIA was requested by the physicians. All patients were over 45 years of age. In addition, PSA by RIA was measured on each patient. Diagnoses were provided by the physicians based on needle biopsy, transurethral resection (TUR), and other surgical procedure, or clinical impression in some instances of BPH. Also provided were the clinical stages of carcinoma of the prostate following the modified Whitmore-Jewett protocol. Both PSA and PAP were assayed with the pros-check-PSA kit and pros-check-PAP kit, both being double antibody radioimmunoassays, according to the manufacturer's directions. Precisely 0.2 ml of each of the standards, controls, and samples were incubated with the respective antibody and tracer, followed by precipitation with a second antibody and then counting the bound radioisotope.

In the present study, PSA values greater than 5.0 ng per ml and PAP value greater than 4.0 ng per ml were considered as the abnormal levels, as suggested by the manufacturer.

Results

Specimen stability for the measurement of PSA and PAP was studied and compared. A significantly lower value was observed for PAP than PSA after 24 to 48 hour periods of sample storage at 4°C (table I).

<table>
<thead>
<tr>
<th>Hours of Storage at 4°C</th>
<th>PSA, Percent</th>
<th>PAP, Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>24</td>
<td>66-98</td>
<td>66-85</td>
</tr>
<tr>
<td>(M=92, SD=2.9)</td>
<td>(M=75, SD=6.6)</td>
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<tr>
<td>48</td>
<td>76-89</td>
<td>55-75</td>
</tr>
<tr>
<td>(M=84, SD=4.1)</td>
<td>(M=65, SD=6.8)</td>
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</tbody>
</table>

Stability was expressed as percentage of the initial value. Subsequent analysis was performed on the same specimens after being refrigerated for 24 and 48 hours, respectively. The ranges were the results of 10 specimens at different PSA and PAP levels (M=mean, SD=standard deviation).
A cut-off value of 5.0 ng per ml for PSA was chosen from our study of 720 specimens from which PAP was initially requested as a routine screen for asymptomatic patients or on patients owing to prostate irregularity, including those of the 156 patients that were followed (figure 1) (all patients were men over 45 years of age). The solid and hatched bars in the histogram were used to illustrate the distributions of patients with PSA values smaller and greater than 5.0 ng per ml, respectively. A similar pattern was observed on PAP and a cut-off value of 4.0 ng per ml was chosen (not shown). Thus, a cut-off of 5.0 ng PSA per ml and 4.0 ng PAP per ml were used to define the patient population into three groups.

Defining Group I

This group of patients had PSA less than 5.0 ng per ml and PAP less than 4.0 ng per ml, and was assumed to be least likely to have prostate cancer. Seventy-one percent of the 720 patients belonged to this group. Among 46 patients studied, only one was ultimately diagnosed as having cancer. The one exception who was found to have prostate cancer, stage B2, had PSA of 4.2 ng per ml and PAP of 1.9 ng per ml. However, five out of five patients who had PSA values between 4.0 and 5.0 ng per ml were diagnosed as having benign prostatic hypertrophy (BPH) by clinical impression only (no biopsy).

Defining Group II

This group of patients had PSA greater than 5.0 ng per ml and PAP less than 4.0 ng per ml. Twenty-two percent of 720 patients belonged to this group in which 99 patients were studied. Since all PAP values were still less than 4.0 ng per ml, any prostate cancer found in this group would be an indication of improved sensitivity of PSA. Seventy of 99 patients (70 percent) were found to have cancer ranging from stages A1 to D (table II). Twenty-five patients (25 percent) had only BPH or prostatitis. From 22 patients who were diagnosed as having BPH, 10 were diagnosed by needle biopsy, nine transurethral resection (TUR) and three by clinical impression.

![Figure 1. Prostate specific antigen (PSA) distribution of the high risk patients. All of the values were from 720 specimens requested for PAP and from patients over 45 years old. The solid bars represented patient distribution below and hatched bars above the cut-off value.](image)
TABLE II
Findings in 99 Group II Patients

<table>
<thead>
<tr>
<th># of Patients with Prostate Cancer</th>
<th># of Patients with BPH/Prostatitis</th>
<th># of Patients Found Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 70 (71%)</td>
<td>N = 25 (25%)</td>
<td>N = 4 (4%)</td>
</tr>
</tbody>
</table>

2 stage A1
(6.2, 16.1) 22 BPH 4 normals
(5.1-22.7, m=8.3) 25.2, 28.8)
(5.1-34.0, m=12.8) (5.3, 9.8,
15 stage C 19.9)
(5.0-81.0, m=16.6)
9 stage D
(7.6-74.0, m=56)
21 stage unknown
(6.2-44.2, m=15.7)

All patients had PSA greater than 5.0 ng per ml and PAP less than 4.0 ng per ml. A parenthesis indicates the value or range of PSA and the median (m) in ng per ml.

only. Four patients were diagnosed as normal.

DEFINING GROUP III

This group of patients had PSA greater than 5.0 ng per ml and PAP greater than 4.0 ng per ml. Seven percent of at-risk patients belonged to this group in which nine out of nine patients were diagnosed as having prostate cancer, stage D.

ISOLATED CASES NOT BELONGING TO THE PREVIOUS GROUP

Two patients who had PSA below and PAP above the cut-off values did not belong to any aforementioned group. The clinical significance of this pattern is not clear. Patient 1 who had PAP of 14.7 ng per ml and PSA of 4.8 ng per ml had radical prostatectomy and is currently under treatment of bone metastases. Patient 2 had a PAP of 4.1 ng per ml and a PSA of 0.8 ng per ml on two occasions. This patient is being followed clinically and, at this time, no biopsy is planned.

SENSITIVITY, SPECIFICITY, AND THE PREDICTIVE VALUES

Our results indicated that sensitivity of a positive test result for PSA for detecting prostate cancer was 97 percent (79 of 81 patients), but the specificity was only 61 percent (46 of 75 patients); the predictive value of a positive test result was 73 percent (79 of 108 patients) and the predictive value of a negative test result was 96 percent (46 of 48 patients). If PSA was used to detect either prostate cancer or BPH/prostatitis, then the specificity and the predictive value of a positive test result increased: specificity, 92 percent (46 of 50 patients); predictive value of a positive test result, 96 percent (46 of 48 patients). But the sensitivity and the predictive value of a negative result decreased owing to the five unverified BPH with PSA values between 4.0 and 5.0 ng per ml: sensitivity, 94 percent (104 of 121 patients); predictive value of a negative result, 87 percent (46 of 53 patients).

Discussion

The difficulties clinicians encounter with laboratory as well as other tests are frequently related to the lack of sensitivity and specificity. At present, the digital rectal examination is still considered the most reliable and practical method for screening for prostate cancer before metastases or PAP elevation occurs. However, digital rectal examination is not very sensitive. One study shows that in 22 patients with bone metastases, the gland was digitally negative in six patients. Therefore, a blood test can be a useful adjunct to the conventional methods for the early detection of prostate cancer.

In this study, PSA demonstrated a greater sensitivity than PAP. In addition, PSA in serum specimen has been found...
to be more stable than PAP (table I). The combination of PSA and PAP enhances the usefulness of either test alone, since the probability of metastasis is increased if both the PSA and PAP are elevated (Group III patients).

The potential usefulness of measuring PSA can be dramatized in the case of patient H.F. (table III). Patient H.F. had an elevated PSA without any symptoms, and subsequent biopsy confirmed prostatic carcinoma. In addition to early detection of prostate cancer on potentially at-risk patients, PSA is also useful in monitoring recurrence. Other investigators have noted that PSA became elevated well before clinical recurrence of prostate cancer, thus providing a good laboratory tool to monitor cancer patients. If one considers that the 25 percent of the patients in Group II who had BPH represent false positives, the PSA may not be a good test. Whether or not there is undetected cancer among these patients can only be resolved by long-term follow-up, which is our intent, because the prevalence of prostate cancer in men over 45 years of age is believed to be high.10 But, if one considers that the PSA detects prostatic diseases as a whole, including carcinoma and BPH, it becomes useful. After PSA is found abnormal, then other means can further differentiate prostate cancer from BPH. It appears that an elevated PSA should alert the clinician to the need for further investigation. In addition, serum PSA appears to increase concurrently with tumor growth, therefore, serial determinations at three to six month intervals can be a meaningful, non-invasive monitoring approach. If the PSA level doubles in the three to six month period, the probability of cancer over BPH rises.

Perhaps the cut-off value for PSA should be set at 4.0 ng per ml instead of 5.0 ng per ml. This would increase the sensitivity and the predictive value of a negative result. Since none of the five patients who had PSA values between 4.0 and 5.0 ng per ml had a biopsy, the original 5.0 ng per ml was chosen as the cut-off value for PSA in this study.

In summary, it is believed by the present authors that the assay of serum PSA level is a valuable laboratory adjunct to the diagnosis of prostate cancer, as well as monitoring for recurrence.

Acknowledgments

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References


### TABLE III

<table>
<thead>
<tr>
<th>Date</th>
<th>PSA/PAP, ng per ml</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/14/85</td>
<td>15.7/1.8</td>
<td>Initial testing, no symptom</td>
</tr>
<tr>
<td>6/08/85</td>
<td>20.9/1.9</td>
<td>Follow-up testing</td>
</tr>
<tr>
<td>7/18/85</td>
<td>Radical prostatectomy</td>
<td>Stage C, Gleason IV/V</td>
</tr>
<tr>
<td>7/22/85</td>
<td>4.9/less than 0.5</td>
<td>4 days post prostatectomy</td>
</tr>
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