Evaluation of serum PSA levels as a biomarker for breast carcinoma in north Indian females

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ABSTRACT

Objective: Breast cancer has emerged as the most common malignancy among females during the last few years. Early diagnosis is essential for disease management so research is underway to identify potential serological bio markers with acceptable sensitivity and specificity. The current study was undertaken to compare the levels of serum PSA in patients with benign breast diseases, carcinoma breast and normal controls. Methods: The study was conducted jointly by the departments of Biochemistry and Surgery. Fifty patients of breast carcinoma were enrolled in the study, along with 50 cases of benign breast disease and 50 healthy controls. Serum PSA levels were estimated by Roche Elecsys modular Cobas e 411 (electrochemiluminescence immuno assay) (Manheim Germany). Results: We did not find any significant differences in the PSA levels between normal controls, patients with benign breast disease as well as females presenting with breast carcinoma. No correlation was observed between serum PSA levels with clinical staging as well as histopathological grading. Conclusions: According to previous published studies, tumor levels of PSA are valuable for breast cancer patient prognosis, since patients with PSA positive tumors have much longer disease-free and overall survival. PSA levels in the serum of breast cancer patients are not significantly different from the PSA levels in the serum of normal women. Based on these data we conclude that serum PSA levels are not useful for breast cancer patient diagnosis or monitoring.

Key words: Prostate specific antigen, PSA, breast carcinoma

INTRODUCTION

Breast cancer has emerged as the most common malignancy among females during the last few years leaving cervical cancer behind.¹ Breast cancer is a complex disease probably caused due to aberrations in the complex interrelated pathways of apoptosis, hormonal regulations and incurred oxidative stress and inflammatory insults.² The disease can be controlled/ eliminated effectively by surgery along with chemo-radiation if detected at an early stage. Hence, early diagnosis is essential for disease management.

Cancer biomarkers are basic modules that help in evaluating cancer risk, screening, diagnosis, staging, and monitoring response to therapy, prognosis and detecting disease recurrence to improve patient management and outcomes.³ Mammography is the most sensitive and specific screening modality for breast cancer, however it has not been possible to implement mammographic evaluation for routine screening protocols.⁴ Research is underway to identify potential serological bio markers with acceptable sensitivity and specificity. Prospective markers include carcinoembryonic antigen, carbohydrate antigen 15.3, tissue polypeptide-specific antigen, and mammary serum antigen among others. However, the diagnostic sensitivity of these markers is very limited.⁵,⁶ Another addition to this list is that of prostrate specific antigen (PSA) which is being evaluated for its diagnostic and prognostic efficacy. PSA is a 33 kd glycoprotein encoded by a gene localized on chromosome 19. PSA has emerged as an eminent biomarker for prostatic carcinoma with proven diagnostic
and prognostic implications. The demonstration of PSA from extra prostatic sites such as salivary glands, pancreas, breast (healthy breast tissues and breast tumors, breast cystic disease), periurethral (Skene’s) gland, endometrial tissue, amniotic fluid, bronchoalveolar washing, ascitic fluid, pleural effusions, cerebrospinal fluid has caught the attention of researchers for prospective role of PSA in a myriad of other diseases also. The hormonal influence on both prostatic and breast carcinogenesis has prompted studies to evaluate the role of PSA as a biomarker in breast carcinoma.

The current study was undertaken to compare the levels of serum PSA in patients with benign breast diseases, carcinoma breast and normal controls as well as to evaluate any correlation of PSA levels with histopathological grading and clinical staging of breast cancer.

METHODS

The study was conducted jointly by the departments of Biochemistry and Surgery, Maulana Azad Medical College and associated G B Pant Hospital, Delhi. Fifty patients with newly diagnosed, histopathologically confirmed breast carcinoma were enrolled in the study, along with 50 cases of benign breast disease and 50 healthy controls, without history or laboratory evidence of malignancy; after prior informed consent and examination. The staging was done by the TNM staging and the ER/PR status was also determined by immunocytochemistry. The study protocol was approved by the hospital ethics committee and all patients and controls voluntarily gave informed consent. Detailed clinical history was taken for all patients and clinical examination was performed and clinical staging was done. The ER/PR status of the tumours was determined by ER/PR pharmDx™ Kits (Dako, USA) which are semi-quantitative immunohistochemical kit systems. The receptor status was considered to be positive when >10% of the cells are stained (DAB reaction). Single blood samples were taken from patients, before start of any therapy and controls. Serum PSA levels were determined estimated by Roche Elecsys modular Cobas e 411(electrochemiluminescence immuno assay) (Manheim Germany) using commercially available kits supplied by Roche diagnostics.

Statistical analysis

The data were expressed as the mean ± standard deviation. Mann Whitney test was used to compare the values between the patients with breast cancer and controls. Spearman’s correlation analysis was used to find the association between the various parameters of our study. A p value of <0.05 was accepted as statistically significant. All statistical analyses were performed with the program Statistical Package for the Social Science 12.0 (SPSS Inc, Chicago, Illinois).

RESULTS

The mean age of the patients in carcinoma group was 49.2±12.7 years, in benign breast disease group was 45.6±10.6 years and that of the controls was 47.7±11.9 years. Majority of the patients presented with stage III breast carcinoma (Table 1). The ER/PR status of the patients is depicted in Table 2. The incidence of ER-/PR- was 50 % in our study population. We did not find any significant differences in the PSA levels between normal controls, patients with benign breast disease as well as females presenting with breast carcinoma (Table 3). No correlation was observed between serum PSA levels with clinical staging as well as histopathological grading.

Table 1: Staging of breast carcinoma in the patient population

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Stage II</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

Table 2: ER/PR status in the patient population

<table>
<thead>
<tr>
<th>Status</th>
<th>Distribution No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PR+</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>ER-/PR+</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>ER+/PR-</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>ER-/PR-</td>
<td>28 (56%)</td>
</tr>
</tbody>
</table>

Table 3: Demographic features of the study population

<table>
<thead>
<tr>
<th></th>
<th>Breast carcinoma</th>
<th>Benign breast disease</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Mean age</td>
<td>49.2±12.7</td>
<td>45.6±10.6</td>
<td>47.7±11.9</td>
</tr>
<tr>
<td>PSA in ng/litre</td>
<td>68.6±13.4 (4-125)</td>
<td>57.8 (5-119)</td>
<td>35.4 (2-68)</td>
</tr>
</tbody>
</table>
in the development as well as progression of breast cancer. Hence depletion, antagonism or suppression of estrogenic stimuli may prove effective in breast cancer management. It has been demonstrated that androgens exert an anti estrogenic effect and hence inhibit the proliferation of breast cancer cells. In fact androgens have been exploited as an effective treatment modality in breast cancer patients.\textsuperscript{1, 2} As the expression of PSA is steroid mediated, the presence of PSA immunoreactivity in breast cancer cells may be considered to be an indicator of endogenous hormone balance between estrogen and androgen/progestin. Thus, detection of PSA immunoreactivity in breast tumors may be valuable in predicting prognosis of breast cancer patients. In fact PSA expression may indicate a favorable outcome.\textsuperscript{14}

We do not know whether breast tumors can be classified as ‘estrogen dependent’ and ‘androgen dependent’. If this sub classification is applicable then individualized therapy such as anti estrogen regimens for estrogen dependent and anti androgens for androgen dependent tumors respectively will prove to be highly effective. Hu et al concluded from their study that patients with PSA positive tumors presented with early stage disease and smaller tumors with less likelihood of relapse as compared to PSA negative tumors.\textsuperscript{14}

Detection of PSA in serum of females requires highly sensitive assays as the concentration is very low. The approximate concentration (ng/L) in various body fluids is as follows: seminal plasma, $10^6$; male serum, 1000-2000; normal breast discharge fluid, $5 \times 10^6$; milk of lactating women, $10^6$; female serum, 2-4. It is clear that the serum level in females is $10^6$-fold lower as compared to prostatic secretion.\textsuperscript{15}

PSA, which belongs to the kallikrien family, digests the seminogelins and fibronectin present in high concentrations in seminal plasma and hence liquefies the seminal clot shortly after ejaculation. The roles of PSA in cancer is controversial with studies in favour of pro carcinogenic as well as anti carcinogenic properties of PSA have been reported in literature.\textsuperscript{16, 17} PSA being a serine protease can also act as a growth regulator by cleaving insulin like growth factor binding protein-3 (IGFBP-3) to release insulin-like growth factor-I (mitogen) or enzymatically activating latent human transforming growth factor-alpha.\textsuperscript{18, 19} PSA may play a role in tumor progression and metastasis as it may degrade the extra cellular matrix proteins- fibronectin and laminin.\textsuperscript{20, 21} PSA may activate latent transforming growth factor - β (TGF-β), stimulate cell detachment, and facilitate tumor spread.\textsuperscript{22}

The favourable role of PSA in breast cancer can be explained in the following manner: the expression of PSA indicates the existence of androgenic influence which might counteract estrogenic influence- a known procarcinogenic agent. The fact that PSA expression is observed in well differentiated tumors also confers a survival advantage as well differentiated tumors are more treatment responsive and carry a better prognosis than poorly differentiated cancers. The presence of PSA may be regarded as a marker of functional steroid hormone receptor pathway.\textsuperscript{14, 23} PSA also proteolytically cleaves parathyroid hormone related protein (PTHrP) which stimulates breast cancer cell proliferation thereby abolishes its biological function.\textsuperscript{24} It has also been demonstrated that PSA exerts an inhibitory effect on the endothelial response to angiogenic stimulation by fibroblast growth factor-2 and vascular endothelial growth factor. PSA also releases antiangiogenic fragments (angiostatin-like) by digestion of plasminogen.\textsuperscript{25} PSA also stimulates the conversion of the more potent estradiol to the less potent estrone thus diminishing the pro carcinogenic effect of estrogens.\textsuperscript{26} Narita et al have shown that her2 neu expression is associated with PSA negativity thereby substantiating the role of PSA as a favorable prognostic marker.\textsuperscript{27}

Tumor levels of PSA appear to be valuable for breast cancer patient prognosis, since patients with PSA positive tumors have much longer disease-free and overall survival.\textsuperscript{14} As PSA is found in 30% of breast cancer cytosols, it is worthwhile examining if PSA is also present in the serum of breast cancer patients. Few studies have reported higher levels of PSA in breast cancer.\textsuperscript{28, 29} But other studies fail to prove it.\textsuperscript{7, 30} No similar study has been carried out from India, where carcinoma breast is a very frequently encountered malignancy. This study was carried out to see the pattern in Indian patients.

Our study did not demonstrate any significant differences in the PSA levels between patients with benign breast disease and breast cancer patients. Our findings are in accordance with other studies which have proven superior discriminatory role of tissue PSA level or PSA concentration in nipple aspirate fluid for diagnostic and prognostic purposes.\textsuperscript{31, 32} Based on these observations it seems unlikely that the PSA levels in the serum of breast cancer patients are significantly different from the PSA levels in the serum of normal women. Based on these data we conclude that serum PSA levels are not useful for breast cancer patient diagnosis or monitoring.

REFERENCES


Authors Contribution:
NG – Concept, writing and data collection; BG – Writing, data collection and analysis; SSK – Data collection and analysis; NSH – Analysis and review.

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