ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

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

Nikhil Gupta[1], Binita Goswami[2], Shyamveer S. Khangarot[3], Niladhar S. Hadke[4]

[1]Department of Surgery, University College of Medical Sciences, Delhi, [2]Department of Biochemistry, Lady Hardinge Medical College, Delhi, [3]Department of Surgery, Maulana Azad Medical College, Delhi, [4]Department of Surgery, Maulana Azad Medical College, Delhi

Submitted: 17-07-2013 Revised: 20-02-2014 Published: 30-05-2014

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.

Access this article online

Website:
http://nepjol.info/index.php/AJMS

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

Address for Correspondence:
Nikhil Gupta, Assistant Professor, Department of Surgery, University College of Medical Sciences, Delhi.
E-mail: nikhil_ms26@yahoo.co.in; **Tel:** +91-9810592084.

and prognostic implications.[7] 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.[8] The hormonal influence on both prostatic and breast carcinogenesis has prompted studies to evaluate the role of PSA as a biomarker in breast carcinoma.[9]

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).[10,11] 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.

DISCUSSION

The hormonal receptors that are present in the breast include estrogen, progesterone and androgen receptors. The expression of PSA is inhibited by estrogens but stimulated by androgens. Estrogen plays an essential role

Table 1: Staging of breast carcinoma in the patient population

Stage	Distribution No. (%)
Stage I	3 (6%)
Stage II	16 (32%)
Stage III	28 (56%)
Stage IV	3 (6%)

Table 2: ER/PR status in the patient population

Status	Distribution No. (%)
ER+/PR+	6 (12%)
ER-/PR+	9 (18%)
ER+/PR-	7 (14%)
ER-/PR-	28 (56%)

Table 3: Demographic features of the study population

	Breast carcinoma	Benign breast disease	Normal controls
n	50	50	50
Mean age	49.2±12.7	45.6±10.6	47.7±11.9
PSA in ng/litre [mean±S.D (range)]	68.6±13.4 (4-125)	57.8 (5-119)	35.4 (2-68)

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.[12, 13] 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.[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.[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, 10^9; male serum, 1000-2000; normal breast discharge fluid, 5 x 10^6; milk of lactating women, 10^5; female serum, 2-4. It is clear that the serum level in females is 10^6-fold lower as compared to prostatic or breast secretion.[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.[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.[18,19] PSA may play a role in tumor progression and metastasis as it may degrade the extra cellular matrix proteins- fibronectin and laminin.[20,21] PSA may activate latent transforming growth factor - ß (TGF-ß), stimulate cell detachment, and facilitate tumor spread.[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.[14,23] PSA also proteolytically cleaves parathyroid hormone related protein (PTHrP) which stimulates breast cancer cell proliferation thereby abolishes its biological function.[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.[25] PSA also stimulates the conversion of the more potent estradiol to the less potent estrone thus diminishing the pro carcinogenic effect of estrogens.[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.[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.[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.[28,29] But other studies fail to prove it.[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.[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

1. Oktem O and Oktay K. Fertility Preservation for Breast Cancer Patients. Semin Reprod Med 2009; 27(6): 486-492.
2. Porter-Jordan K and Lippman ME. Overview of the biologic markers of breast cancer. Hematol Oncol Clin N Am 1994; 8: 73-100.

3. Duffy MJ. Clinical uses of tumor markers: a critical review. Crit Rev Clin Lab Sci 2001; 38: 225-262.
4. National Institutes of Health consensus development conference statement: breast cancer screening for women ages 40-49. J Natl Cancer Inst 1997; 89: 1015-1026.
5. Eskelinen M, Kataja V, Hämäläinen E, Kosma VM, Penttilä I and Alhava E. Serum tumour markers CEA, AFP, CA 15-3, TPS, and Neu in diagnosis of breast cancer. Anticancer Res 1997; 17: 1231-1234.
6. Heinze T, Schürenkämper P, Minguillon C and Lichtenegger W. Mammary serum antigen (MSA), Ca 549, CA 15-3 and CEA in breast cancer preoperative sensitivity and correlation to prognostic factors. Anticancer Res 1997; 17: 2953-2954.
7. Giai M, Yu H, Roagna R, Ponzone R, Katsaros D, Levesque MA, et al. Prostate-specific antigen in serum of women with breast cancer. Br J Cancer 1995; 72: 728-731.
8. Nariţa D, Raica M, Anghel A, Suciu C and Cîmpean A. Immunohistochemical localization of prostate-specific antigen in benign and malignant breast conditions. Romanian J Morphol Embryol 2005, 46(1): 41-45.
9. Poh BH, Jayaram G, Sthaneshwar P and Yip CH. Prostate-specific antigen in breast disease. Malays J Pathol 2008; 30(1): 43-51.
10. Ogawa Y, Moriya T, Kato Y, Oguma M, Ikeda K, Takashima T, et al. Immunohistochemical assessment for estrogen receptor and progesterone receptor status in breast cancer: Analysis for a cut-off point as the predictor for endocrine therapy. Breast Cancer 2004; 11(3): 267-275.
11. Talman ML, Rasmussen BB, Andersen J and Christensen IJ. Estrogen receptor analyses in the Danish Breast cancer cooperative group. History, methods, prognosis and clinical implications. Acta Oncol 2008; 47(4): 789-794.
12. Dauvois S, Geng SC, Levesque C, Merand Y and Labrie F. Additive inhibitory effects of an androgen and the antiestrogen EM-170 on estradiol-stimulated growth of human ZR-75-1 breast tumors in athymic mice. Cancer Res 1991; 5: 3131-3135.
13. Zarghami N, Grass L, Sauter ER and Diamandis EP .Prostate-specific antigen in serum during the menstrual cycle. Clin Chem 1997; 43: 1862-1867.
14. Yu H, Giai M, Diamandis EP, Katsaros D, Sutherland DJ, Levesque MA, et al. Prostate-specific Antigen is a New Favorable Prognostic Indicator for Women with Breast Cancer. Cancer Res 1995; 55(10): 2104-2110.
15. Lilja H. A kallikrein-like serine protease in prostatic fluid cleaves the predominant seminal vesicle protein. J Clin Invest 1985; 76: 1899-1903.
16. Diamandis EP. Prostate-specific Antigen: A Cancer Fighter and a Valuable Messenger? Clin Chem 2000; 46: 896-900.
17. Borgoño CA, Michael IP and Diamandis EP. Human Tissue Kallikreins: Physiologic Roles and Applications in Cancer. Mol Cancer Res 2004; 2(5): 257-280.
18. Pollak M, Beamer W and Zhang JC. Insulin-like growth factors and prostate cancer. Cancer Metastasis Rev 1998; 17: 383-390.
19. Cohen P, Peehl DM, Lamson G and Rosenfeld RG. Insulin-like growth factors (IGFs), IGF receptors, and IGF-binding proteins in primary cultures of prostate epithelial cells. J Clin Endocrinol Metab 1991; 73: 401-407.
20. Clements JA and Mukhtar A. Glandular kallikreins and prostate-specific antigen are expressed in the human endometrium. J Clin Endocrinol Metab 1994; 78: 1536-1539.
21. Mannello F, Malatesta M, Luchetti F, Papa S, Battistelli S and Gazzanelli G. Immunoreactivity, ultrastructural localization, and transcript expression of prostate-specific antigen in human neuroblastoma cell lines. Clin Chem. 1999; 45(1): 78-84.
22. Killian CS, Corral DA, Kawinski E and Constantine RI. Mitogenic response of osteoblast cells to prostate-specific antigen suggests an activation of latent TGF-ß and a proteolytic modulation of cell adhesion receptor. Biochem Biophys Res Commun 1993; 192: 940-947.
23. Zarghami N, Onsori H and Alani B. Association between steroid hormone receptors and PSA gene expression in breast cancer cell lines. African Biotechnol 2005; 4 (12): 1415-1420.
24. Cramer SD, Chen Z and Peehl DM. Prostate specific antigen cleaves parathyroid hormone-related protein in the PTH-like domain: inactivation of PTHrP-stimulated cAMP accumulation in mouse osteoblasts. J Urol 1996; 156: 526-531.
25. Fortier AH, Nelson BJ, Grella DK and Holaday JW. Antiangiogenic activity of prostate-specific antigen. J Natl Cancer Inst 1999; 91: 1635-1640.
26. Lai LC, Erbas H, Lennard TW and Peaston RT. Prostate-specific antigen in breast cyst fluid: possible role of prostate-specific antigen in hormone-dependent breast cancer. Int J Cancer 1996; 66: 743-746.
27. Nariţa D, Anghel A and Motoc M. Prostate-specific antigen may serve as a pathological predictor in breast cancer. Romanian J Morphol Embryol 2008, 49(2): 173-180.
28. Black MH, Giai M, Ponzone R, Sismondi P, Yu H and Diamandis EP. Serum Total and Free Prostate-specific Antigen for Breast Cancer Diagnosis in Women. Clinical Cancer Research 2000; 6: 467-473.
29. Kaulsay KK, Ng EH, Ji CY, Ho GH, Aw TC and Lee KO. Serum IGF- binding protein- 6 and prostate specific antigen in breast cancer. Eur J Endocrinol 1999; 140: 164-168.
30. Borchert GH, Melegos DN, Tomlinson G, Giai M, Roagna R, Ponzone R, et al. Molecular forms of prostate-specific antigen in the serum of women with benign and malignant breast diseases. Br J Cancer 1997; 76(8): 1087-1094.
31. Yu H, Levesque MA, Clark GM and Diamandis EP. Prognostic Value of Prostate-specific Antigen for Women with Breast Cancer: A Large United States Cohort Study. Clin Cancer Res 1998; 4: 1489-1497.
32. Black MH and Diamandis EP. The diagnostic and prognostic utility of prostate-specific antigen for diseases of the breast. Breast Cancer Res Treat. 2000; 59:1-14.

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

Source of Support: Nil, **Conflict of Interest:** None declared.