RESEARCH COMMUNICATION

The Lady with Raised Prostate Specific Antigen: Do We Need To Worry?

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Abstract

Background: Prostate specific antigen (PSA) is generally considered a biological marker of prostate cancer although raised values may also be observed in benign prostatic diseases. PSA can be secreted in females from skeine's periurethral gland but at low levels. This case - control study aimed at the evaluation of relation of PSA with different diseases in women. Method: A total of 297 patients were included, 107 with breast cancer, 90 with benign breast disease (BBD) and 100 controls (patients attending our surgery department for non-breast diseases). PSA was measured in the serum of all and a statistical analysis was conducted. Result: An association of raised PSA with breast diseases was observed. Total PSA was more sensitive for benign breast diseases, whereas breast cancer showed a predilection towards increase in free PSA. PSA decreased after surgery. Conclusion: PSA can be used as a diagnostic and prognostic marker of breast cancer in women, therefore helping secondary prevention of breast cancer.

Keywords: Prostate specific antigen - women - breast cancer

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Introduction

Prostate-specific antigen (PSA) is a serine protease expressed at high levels in prostate epithelium. Elevated PSA in serum is a well-established marker of prostate cancer (Papotti et al., 1989). However, studies have demonstrated that PSA can also be secreted in females, especially from prostate equivalent Skene's peri-urethral gland and other hormonally regulated tissue like breast and ovary (Papotti et al., 1989). But data on relationship of PSA and breast diseases is limited (Diamandis et al ., 1994). Breast cancer (BC) is the commonest cancer of women worldwide with high fatality rate (Bray et al., 2004). Despite modern instrumentation and radiological advancement need exists for more practical and sensitive labo¬ratory method to diagnose and to know the prognosis of BC (Hudis, 2003). A wide variety of morphology-based and molecular-based prognostic factors and tumor markers have been studied as to their potential to predict disease outcome in breast cancer (Goldhirsch et al., 2003). Still, there is a need to find definite biological factors which could help to prognosticate the disease and to plan the future therapy for breast BC. The present work proposes to determine the relation of PSA with breast diseases with special reference to BC and to check the correlation of PSA values with prognostic factors of BC like age, tumour size, lymph node status and hormone receptor status.

Materials and Methods

This prospective case-control study was conducted in the Department of Surgery, Medical College, Kolkata, from 1st March 2009 to 31 August 2010. A total of 297 patients were included in the study. 107 patients with breast cancer, 90 patients with benign breast disease (BBD) and 100 control (patients attending surgery department for non-breast diseases). BC patient who already received any form of treatment for BC (Surgery/ Chemotherapy/ Radiotherapy/ Hormone Therapy), patients receiving oral contraceptive pills, hormone replacement therapy and women with any co-morbid conditions (HIV, diabetes, tuberculosis) were excluded. Sandwich-type ELISAs were used for PSA estimation. The detection limit of immunoassays was 0.001 mg/liter (1 ng/liter).

All the patients with breast lump attending general surgery outpatient department were subjected to thorough history taking, clinical examination. Fine needle aspiration cytology (FNAC) was performed in those who fulfilled all inclusion criteria. Based on FNAC patients were grouped into Breast cancer (BC) group and noncancerous (benign) breast disease (BBD) group. In both the groups an initial PSA measurement was done. In the cancer group, another PSA measurement was done after one month of surgery (modified radical mastectomy). Operative specimen was sent for histopathological examination and Estrogen/

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progesterone receptor (ER/PR) assessment. Controls were the patient volunteers attending aforementioned department for non-breast complaints.

Statistical analyses were performed with SPSS software version 11.0.1 for Windows (SPSS, Inc., Chicago, IL, USA). The Chi-square test was used to examine the categorical variables and the association between PSA status and other clinicopathological variables. Both univariate and multivariate analysis was done to examine the relation of each prognostic factor with PSA status, p values less than 0.05 were considered significant.

Results

The mean age of the study population was 46.6 years ± 9.55 [standard deviation (S.D.)]. The range was from 25 years to 66 years. The correlation between age of the patients and elevated PSA levels were found to be highly but negatively co-related as correlation co-efficient, R= -0.91716 and P<.001 at 98 degree of freedom. Higher age was associated with low PSA value. The total PSA was increased both in BBD (86%) and BC (70%) group in comparison to control group (33%). Serum free PSA was also increased in both BBD (28%) and BC (38%). However, free PSA as the predominant form (that is when free PSA constituted more than 50% of total PSA) was specifically increased in BC group (94%) in comparison with BBD group (24%). It was also found that total PSA had good sensitivity (70%) but low specificity (67and 25 %). Free PSA was specific (90% and 72 %) but not that sensitive (40%), where as free PSA, as the predominant form was both sensitive (94.84%) and specific (97 and 96%) .

The size of tumours and elevated PSA were highly but negatively correlated as the correlation Co-efficient, R= - 0.92942 and P < 0.001 at 98 degree of freedom . It pointed to the fact that smaller tumours were associated with higher PSA value.

Positive PR was found in 93.3% patients with elevated PSA and rest 6.7 % was found with negative PR. Here 1-P (mean±2 s.d) = 0.01 (s.d= standard deviation), that is p < 0.05. Hence, expression of PSA was statistically highly correlated with PR. The correlation was such strong that it ca be hypothesized that PR could be replaced by PSA. A zigzag trend in the graph of PSA level with the behavior of ER was found and 1-P (mode <mean±2 s.d) = 0.43 that means p> 0.05. Thus the behavior of ER does not have any correlation with expression of PSA.

HER2 neu was negative in 93.3% and positive in 6.7 % of patients. Here 1-P (mode <mean ± 2 s.d) =0.03, p value of <0.05. Hence, expression of PSA was statistically inversely correlated with HER 2- neu.

Assuming the distribution is a normal distribution a Z-test was conducted which gave a Z-value as 3.09 (p=0.2) with p value < 0.5. This established that PSA decreases statistically after surgery at 95% confidence interval.

Serum PSA was found to be decreased after surgery. A significant decrease (> 90 % of the pre-surgery value) was seen in 78% cases. Moderate decrease (50-90% of the pre-surgery value) was found in 12 % cases. Minimal decrease (< 50% of pre-surgery value) was seen only in 7% cases. Very few cases (3%) showed no decrease after surgery. Interestingly this small percentage of cases showed a positive microscopic margin in postoperative histopathology report indicating inadequate excision. This data supports the possibility of PSA being used as an indicator of adequate clearance.

The patients were followed-up with serial PSA estimation to note correlation of PSA resurge and recurrence of BC. Table 2 shows that PSA resurge positively correlated with recurrence. Considering PSA as an indicator of adequate surgery, its reappearance can be correctly indicated to recurrence of breast cancer.

Table 1. Sensitivity and Specificity of Total PSA, Free PSA, Free PSA as the Predominant Form in the Diagnosis of Breast Cancer.

Parameter	Sensitivity (%)	Specificity (%)
Total PSA		
BC vs. Control	70	67
BC vs. BBD	70	25
Free PSA		
BC vs. Control	40	90
BC vs. BBD	40	72
Free PSA >50%		
BC vs. Control	94.84	97
BC vs. BBD	94.84	96

Table 2. Follow up and comparison of PSA Resurge & Recurrence of Breast Cancer

Time	PSA Resurge	Recurrence
6 month	Nil	3 %
1 year	5 %	8 %
2 years	20 %	28 %

Discussion

This study demonstrates that the total PSA is increased both in BBD (86%) and BC (70%) in comparison to control group (33%). Serum free PSA is also increased in both BBD (28%) and BC (38%). However, free PSA as the predominant form (that is when free PSA constitutes > 50% of total PSA) is specifically increased in BC group (94%) in comparison with BBD group (24%). This indicates that total PSA has a good sensitivity (70%) but low specificity (67and 25 %), free PSA is specific (90% and 72 %) but not that sensitive (40%), where as free PSA as the predominant form is both sensitive (94.84%) and specific (97 and 96%) (Table 1). This observation points towards the selective secretion of free PSA by the BC cells. This can be explained by production an endopeptidase by tumour cell, which causes a posttranslational modification (internal cleavage) of PSA produced by the breast, thus preventing complex formation with anti-chymotrypsin and increasing the proportion of free PSA (Black et al., 2000).

Total PSA levels in serum were lower in older women. This is probably because of postmenopausal hormonal changes. PSA levels in serum were associated with smaller tumour size. This could be explained by the distorted architecture in larger tumours, which loses hormone secretion ability (Romppanen et al., 1999).

PSA positively correlated with progesterone receptor

expression ($p < 0.05$). Moreover, the correlation is such strong that progesterone receptor assessment can be replaced by PSA, which is cost effective and less time-consuming procedure. Estrogen receptor does not have any correlation with expression of PSA. Expression of HER-2 neu was statistically inversely correlated with PSA (<0.05). These data designates PSA as a good prognostic indicator of BC.

Serum PSA decreases significantly after surgery. A significant decrease (> 90 % of the pre-surgery value) was seen in 78% cases. Moderate decrease (50-90% of the pre-surgery value) was found in 12 % cases. Minimal decrease (< 50% of pre-surgery value) was seen only in 7% cases. Very few cases (3%) showed no decrease after surgery. Interestingly this small percentage of cases showed a positive microscopic margin in postoperative histopathology report indicating inadequate excision. This data supports the possibility of PSA being used as an indicator of adequate clearance. Moreover, PSA resurge positively correlates with recurrence. Since PSA is an indicator of adequate surgery, its reappearance can correctly indicate recurrence of breast cancer.

To conclude, PSA can be used as a prognostic indicator of BC. It can also be used as an indicator of completion of surgery and recurrence. However therapy targeting PSA in BC patients needs further evaluation for validation.

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