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Is Serum Prostate-specific Antigen a Diagnostic Marker for Benign and Malignant Breast Tumors in Women?

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ABSTRACT

Background: Breast cancer is the most common cancer in women. Prostate-specific antigen (PSA) is a marker of prostate gland malignancy, which has been considered in cases with breast cancer in recent years. The goal of this study was to determine total and free PSA levels in cases with malignant and benign breast lesions.

Methods: In this case–control study, ninety women with histological proved malignant breast masses and 90 with benign breast masses were enrolled. Total and free PSA levels along with Histological grade and conditions of vascular and perinural invasion, status of hormonal tumor receptors, immune-histo-chemistry markers recorded for all cases. Total and free PSA levels were assessed after treatment in cases with malignant masses.

Results: Total and free PSA levels were significantly higher in cases with malignant masses. The best cut-off point for total PSA to differentiate benign and malignant masses was 0.31 with sensitivity and specificity of 100%, 100% (area under the curve [AUC] =1, $P < 0.001$) and the best cut-off point for free PSA to differentiate benign and malignant masses was 0.19 with sensitivity and specificity of 100% and 100% (AUC = 1, $P < 0.001$). After treatment, mean free PSA level was significantly lower than free PSA before treatment (0.23 ± 0.1 vs. 0.3 ± 0.08, $P < 0.001$).

Conclusions: Serum PSA level could be applied for differentiating benign and malignant breast masses.

Keywords: Breast, diagnosis, prostrate-specific antigen

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INTRODUCTION

Breast cancer is the most common cancer in women equally in developing and developed countries.[1] Different factors such as high body mass index, advanced age, family history of breast cancer, a long menstrual history, use of oral contraceptives, exposure to radiation, no childbearing or giving birth to the first child after age 30

are among possible risk factors for breast cancer.[2] Death due to breast cancer has been reduced according to screening approaches like mamography.[3] To differentiate benign and malignant lesions, lesion biopsies, ultrasound assessment, and mammography evaluation are diagnostic methods.[4]

Prostrate-specific antigen (PSA) is a marker of prostate gland malignancy screening test.[5] It is a member of the kallikrein family that is known as human kallikrein 3.[5] Except prostate gland, previous studies showed that it could be present in breast, lung, ovary, uterus, and pancreas tissues.[6,7]

In a previous study conducted by Black *et al*., they investigated that sensitivities and specificities of total and free PSA levels for differentiating benign and malignant breast lesions are 57% and 36%, 25% and 72%.[8] However, there limited number of studies evaluating serum PSA level in cases with breast cancer. The goal of this study was to determine total and free PSA levels in cases with malignant and benign breast lesions.

METHODS

Study design and participants

In this case–control study, 90 women with histological proved malignant breast masses and 90 with benign breast masses were enrolled. The study conducted in Imam Hospital (affiliated hospital of the Tehran University of Medical Sciences) in 2012. Project number 88-03-30-8920.

Histological grade and conditions of vascular and perinural invasion, status of hormonal tumor receptors, immune-histo-chemistry markers including p53, Ki67 and Her2 were determined and registered prior to any treatment. Total and free PSA levels were assessed after treatment in cases with malignant masses. Pregnant women, those with autoimmune diseases and women who had taken corticosteroids during the last month were excluded.

All cases asked to fill informed consent form before study entrance. The study had been approved by local ethics committee.

Procedure and measurements and variables assessment

For each case, 5 cc venous blood was taken, centrifuged at 3,000 g for 10–15 min. Total and free PSA levels were assessed by sandwich chemiluminescence immunoassay technique.

Diasorin Deutschland GmbH (LIAISON) kit was used for total PSA while Diasorin S.P.A, Italy (LIAISON) kit was applied for free PSA analysis.

A method for the quantitative determination of PSA was a sandwich chemiluminescence immunoassay. A specific mouse monoclonal antibody was coated on the magnetic particles (solid phase). Another monoclonal antibody was linked to an isoluminol derivative (isoluminol-antibody conjugate). Free and antichymotrypsin-complex-bound PSA were detected equimolarly. During the first incubation, PSA present in the calibrators, samples or controls bounded to the solid phase monoclonal antibody, and subsequently after a washing step in the second incubation the antibody conjugate reacted with the PSA already bound to the solid phase. After incubation, the unbound material was removed with a wash cycle. Subsequently, the starter reagents were added and a flash chemiluminescence reaction was thus induced, the light signal, and hence the amount of isoluminol-antibody conjugate, was measured by a photomultiplier as relative light units, indicative of PSA concentration present in calibrators samples or controls.

Analytical sensitivity for t-PSA is defined as the minimum detectable dose distinguishable from zero by two standard deviations (SDs). The detection limit is <0.04 ng/ml. The assay trueness was checked by the dilution and recovery tests. Analytical sensitivity for f-PSA is defined as the minimum detectable dose distinguishable from zero by two SDs. The detection limit is <0.09 ng/ml. The functional sensitivity (defined as the lowest analyte concentration that can be determined with an inter-assay coefficient of variation <20%) is <0.15 ng/ml.

Six months after treatment, total and free PSA levels evaluated in cases with malignant masses.

Statistical analysis

All data were analyzed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± SD for continuous or frequencies for categorical variables. Independent sample *t*-test and paired sample *t*-test were used to compare continuous variables. Receiver operating characteristic curve was used to determine optimal cut-off values of total and free PSA. Area under the curve (AUC) calculated.

$P < 0.05$ was considered as significant.

RESULTS

A total of 180 women with breast tumors were enrolled in this study, 90 patients with malignant breast cancers and 90 patients with benign breast masses. Women with benign tumors aged between 28 years and 63 years with an average age of 38 ± 4 years while women with breast cancer were aged between 36 years and 84 years with an average age of 61 ± 3 years old. Forty-seven of the

patients (53.2%) had positive family history for breast cancer. Table 1 shows histological types of benign masses.

Total and free PSA levels were significantly higher in cases with malignant masses [Table 2].

The best cut-off point for total PSA to differentiate benign and malignant masses was 0.31 with sensitivity and specificity of 100%, 100% (AUC = 1, $P < 0.001$) [Figure 1].

The best cut-off point for free PSA to differentiate benign and malignant masses was 0.19 with sensitivity and specificity of 100% and 100% (AUC = 1, $P < 0.001$) [Figure 2].

After treatment mean total PSA level was significantly higher than total PSA level was significantly higher than total PSA level before treatment (0.88 ± 0.3 vs. 0.77 ± 0.25, $P < 0.001$) while mean free PSA level was significantly lower than free PSA before treatment (0.23 ± 0.1 vs. 0.3 ± 0.08, $P < 0.001$).

Table 1: Demographic and pathologic findings in patients

	Number	Percentage
Inflammatory lesion		
Mammary duct ectasia	7	7.7
Fat necrosis	5	5.5
Other inflammatory diseases	4	4.4
Benign proliferative breast disease		
Fibroadenoma	16	17.7
Intraductal papilloma	4	4.4
Nipple adenoma	1	1.1
Adenosis	7	7.7
Fibrocystic diseases	46	51.1
Age (years)		
<50	15	16.6
≥50	75	83.3
ER*		
Positive	57	63.3
Negative	33	36.6
PR**		
Positive	53	58.8
Negative	37	41.1
HER-2		
1+	1	1.1
2+	3	3.3
3+	18	20
p53		
Positive	34	37.7
Negative	56	62.2
Histology grade		
I	20	22.2
II	49	54.4
III	21	23.3
Vascular invasion		
Positive	37	41.1
Negative	53	58.8
Perineural invasion		
Positive	17	18.8
Negative	73	81.1

*ER=Estrogen receptor, **PR=Progestron receptor, HER-2=Human epidermal receptor 2

DISCUSSION

The result of the current study showed that total and free PSA levels are significantly higher in women with malignant breast masses compared with women who had benign breast masses. We also found that free PSA level was significantly higher before surgery than postsurgery in cases with breast masses. These findings are against the findings of Black *et al*.[8]

They evaluated total and free PSA levels in women with breast cancer, breast cysts and also healthy controls. They

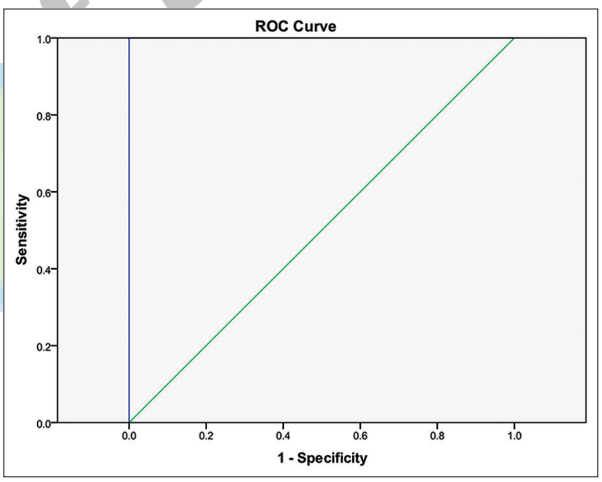

Figure 2: ROC curve for free PSA measure

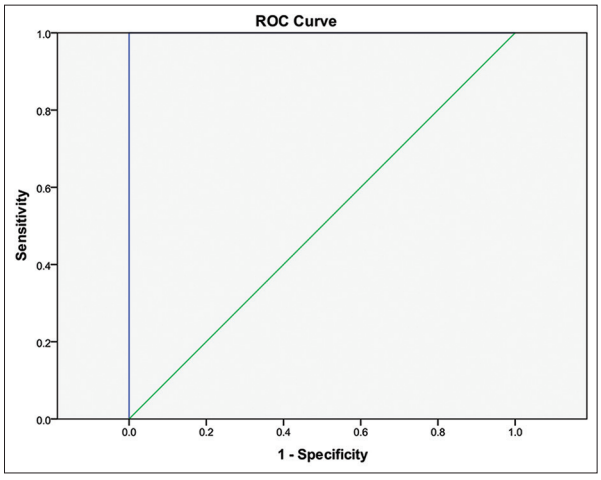

Figure 1: ROC curve for PSA measure

Table 2: Comparison of total PSA and free PSA serum levels in women with benign masses and malignant tumors before surgery and 6 months after treatment

	Benign masses	Malignant masses	P
Total PSA	0.17±0.016	0.77±0.1	<0.001
Free PSA	0.39±0.12	0.09±0.03	<0.001

PSA=Prostrate-specific antigen

investigated that patients with breast cancer had higher total PSA levels before surgery than after surgery and patients with breast cysts had significantly higher levels of total PSA than presurgical breast cancer patients.

In a recent study, Mashkoor *et al*. evaluated total and free PSA levels in women with breast cancer and healthy subjects.[9] They found that both forms of PSA were significantly higher in patients with breast cancer. Furthermore, after surgery both markers decreased significantly which is against our finding and compatible with Dash *et al*. finding. Dash *et al*. measured serum total and free PSA levels in cases with malignant and benign masses and healthy subjects.[10] Their results showed that total and free PSA levels were significantly different between cases either benign or malignant masses versus controls, but total and free PSA levels were not significantly different between patients with benign and malignant masses.

Prostrate-specific antigen is a well-established serum tumor marker for diagnosis and postsurgery follow-up for prostate cancer. Normally, it liquefies the sperm-entrapping seminal coagulum after ejaculation.[11] The name PSA reflects the idea that the expression of this protein is restricted to prostate a gland. Recently, it has been showed that PSA could be present in breast, lung, ovary, uterus, and pancreas tissues.[6,7] Previous studies showed rise in total and free PSA levels in women with breast masses in comparison with healthy subjects. This could suggest hormonal imbalance in these cases which leads to the expression of genes that are normally controlled by hormones and up-regulated by androgens and progesterone.[12,13] Literatures show that there is a positive correlation between PSA and testosterone levels in patients with breast cancer confirms the role of androgens on expression of PSA gene.[10,13,14]

In postsurgical assessment, we only found that free PSA level decreased and total PSA level increased. This is against findings of previous studies. In prior studies, both total and PSA levels decreased significantly after breast tumor removal, which shows the role of breast tumors in PSA production.[8,15]

Our study had some limitation. First, we did not assess testosterone in enrolled cases, and we did not include healthy subjects. Multicentric studies with a comprehensive evaluation of patients with benign and malignant masses along with healthy subjects are recommended.

CONCLUSIONS

Serum PSA level could be applied for differentiating benign and malignant breast masses.

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