**Original Article**

# Can Prostate Specific Antigen Be Used as New Biomarker for Early Diagnosis of Breast Cancer?

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**Received:** 2015/3/26 **Accepted:** 2015/8/14

**Abstract**

**Introduction:** As a glycoprotein, Plasma Prostate-Specific Antigen (PSA) is mainly produced by prostate epithelial cells and is used as a major diagnostic tool for prostate cancer. A group of researchers relate the elevated number of estrogen receptors in breast cancer samples to the over-production of PSA in this type of cancer. The study aimed to determine the plasma PSA level of the participants of the study as a new biomarker for the primary diagnosis of breast cancer.

**Materials & Methods:** Employing a historical cohort design, the study was conducted on 95 patients with breast masses. The participants were assigned to malignant (n=43) and benign (n=40) groups. Male participants and those undergoing a recent hormone therapy were excluded from the study. Independent-samples t-test and Fishers exact test were used to analyze the data using SPSS (Version 20).

**Resuls:** Findings of the study indicated the sensitivity and specificity of the plasma PSA level in patients with breast cancer was 63.15% and 53.48 %, respectively. Also, it was found that the average plasma PSA levels for the benign and malignant groups were 0.047 ± 0.024 and 0.065 ± 0.054, respectively. There was no statistically significant relationship between the two groups. Moreover, no significant difference was observed (P>0.05) between the two groups when background factors were taken into consideration.

**Conclusion:** Plasma PSA level is not a reliable biomarker to diagnose breast cancer although more comprehensive research evidence is required to consider other features of malignant samples and tumor sizes so as to evaluate the role of PSA in differentiating breast neoplastic lesions in a more meticulous way.

**Keywords:** Prostate-Specific Antigen (PSA), Breast Cancer, Biomarker, Early Diagnosis

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## Introduction

Breast cancer is regarded as the second leading cause of cancer mortality within women worldwide [1]. Advances in molecular cancer biology have led to an increased understanding of the biologic factors that contribute to breast cancer pathogenesis and progression, and have also yielded improvements in the cancer diagnosis through molecular pathology and molecular imaging [2]. As a glycoprotein, Plasma Prostate-Specific Antigen (PSA) is mainly produced by prostate epithelial cells., which involves a main diagnostic Prostate cancer indicator [3].

Although in rare cases the PSA level has been reported to be high in the Immunohistochemistry (IHC) samples of other cancer types [4] some researchers assert that the biomarker is a powerful tool to diagnose the breast cancer. In other words, the high number of estrogen receptors in breast cancer can be related to the over-production of the biomarker in this type of cancer. Mohajeri et al hold that MCF-7 and T-47D cell lines in breast cancer samples with positive estrogen receptors (ER+) involve the major source of PSA in the breast cancer. All the hypotheses referred to above have been formulated based on a limited number of studies carried out so far [5] which are remained defendable merely at the theory level. Moreover, no perfectly satisfying evidence has been detected to suggest the relation of breast cancer and plasma level of PSA neither in the clinical settings nor in the literature review [6].

Therefore, the present study sought to explore the potentials of PSA as an inexpensive, meticulous, and non-invasive clinical method to diagnose breast cancer as a highly reported cancer in the context of the study. Results of the present study can contribute to an early clinical diagnosis of breast cancer, as well.

## Materials and Methods

The current study applied a historical cohort design, in which 95 participants were selected out of all benign and malignant breast cancer sufferers referring to Shahid Sadoughi Hospital using convenience sampling method. Moreover, iterative sampling was employed to achieve the intended sample size. Within a time span of three months (April 2013 to December 2014), all candidates of breast mass resection surgery were included in the study, whereas those undergoing hormone therapy as well as the males were excluded.

The participants of the study took either mammography or Fine Needle Aspiration (FNA) diagnostic tests and accordingly, were assigned to malignant and benign groups. Furthermore, at the outset of the study, the participants took PSA test, and Monobind kits were applied to perform ELISA tests using a wave length of 450-630 nm. The study data were analyzed utilizing independent-samples t-test and Fishers exact test via SPSS software (Version 20).



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## Results

Findings of the present study indicated that the PSA plasma level was 0.024 ± 0.047 mg/dg and 0.054 ± 0.065 mg/dg for the benign and malignant groups respectively, which was not proved to be statistically significant (P= 0.712). Analysis of the ROC diagram (Diag. 1) showed the maximum sensitivity and specificity for the plasma PSA level at cutoff 0.045. As diagram 1 represents, the biomarker's sensitivity level, specificity, and negative predictive value were 63.15%, 53.48%, and 45.45% respectively in distinguishing the benign and malignant breast samples. No statistically significant difference was observed between the benign and malignant groups in regard with quantitative background risk factors (Table 1), whereas only history of benign breast diseases demonstrated a significant difference (P:0.024) with respect to qualitative background risk factors (Table 2),. In addition, results of the independent-samples t-test showed no significant difference (p:0.307) between the plasma PSA level of the ER+ group (0.035 ± 0.0623 mg/dl) and PR+ group (0.0307 ± 0.0623) (diagram 2 and 3). As Table 3 demonstrates, the plasma PSA levels of the ER+ and PR+ groups were evaluated using the cutoff 0.045, in none of which the plasma PSA level was revealed to be significantly different.

**Table 1.** Probable quantitative risk factors of the malignant and benign groups

| Probable Risk factors | Benign N:48 | Malignant N:47 | P.value* |
|---|---|---|---|
| **Age (year)** | 36.08 ± 11.87 | 38.69 ± 15.87 | **0.09** |
| **BMI**(kg/m2)** | 24.64 ± 4.67 | 26.1 ± 3.77 | **0.102** |
| **Menstruation age** | 36.5 ± 22.05 | 46.3 ± 10.47 | **0.103** |
| **Menopause age** | 13.52 ± 1.63 | 13.62 ± 2.26 | **0.998** |
| **Number of pregnancy** | 3.23 ± 2.61 | 4.15 ± 2.81 | **0.131** |
| **Duration of OCP usage** | 3.57 ± 2.84 | 3.76 ± 2.43 | **0.839** |

* Independent sample- t-test

** Body Mass Index

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**Table 2**. Probable qualitative risk factors of the malignant and benign groups

| Probable Risk factors | | Benign N:48 | Malignant N:47 | P.value* |
|---|---|---|---|---|
| **History of OCP usage** | Positive | 14(35) | 26(65) | **0.124** |
| | Negative | 21(39.6) | 32(60.4) | |
| **History of benign breast tumors** | Positive | 29(60.4) | 17(35.4) | **0.024** |
| | Negative | 19(39.6) | 31(64.6) | |
| **History of breast cancer in first degree family** | Positive | 12(48) | 34(47.9) | **0.998** |
| | Negative | 13(52) | 37(52.1) | |

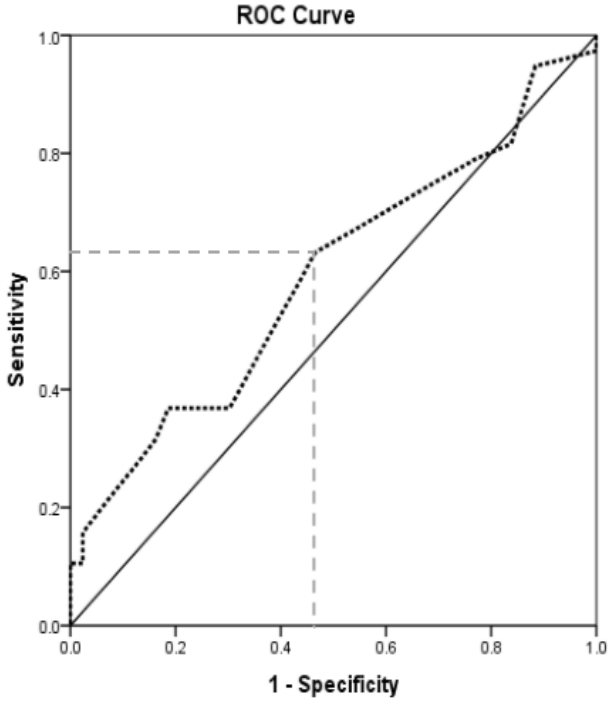
* Fisher's exact Test

**Table 3**. Plasma PSA level of the studied population based on estrogen and progesterone receptors

| Estrogen and Progestrone Receptors status | | PSA<0.045 | PSA≥0.045 | P.value* |
|---|---|---|---|---|
| **Estrogen receptor** | Positive | 7(33.3) | 2(20) | **0.577** |
| | Negative | 14(66.7) | 8(80) | |
| **Progesterone receptor** | Positive | 9(75) | 3(30) | **0.697** |
| | Negative | 3(25) | 7(70) | |

* Fisher's exact Test

**Diagram 1.** Sensitivity and Specificity of different plasma PSA levels in the studied population




Test Result Variable(s): PSA

| Positive if Greater Than or Equal To[a] | Sensitivity | 1 - Specificity |
|---|---|---|
| -1.0000 | 1.000 | 1.000 |
| .0050 | .974 | 1.000 |
| .0150 | .947 | .884 |
| .0250 | .816 | .837 |
| .0350 | .789 | .767 |
| .0450 | .632 | .465 |
| .0550 | .368 | .302 |
| .0650 | .368 | .186 |
| .0750 | .316 | .163 |
| .0850 | .211 | .070 |
| .0950 | .158 | .023 |
| .1100 | .105 | .023 |
| .1300 | .105 | .000 |
| .1550 | .053 | .000 |
| .2400 | .026 | .000 |
| 1.3100 | .000 | .000 |



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**Diagram 2**. Plasma PSA level based on the status of estrogen receptors

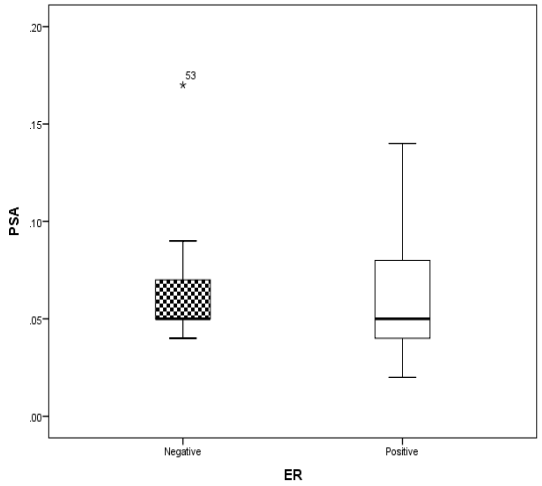
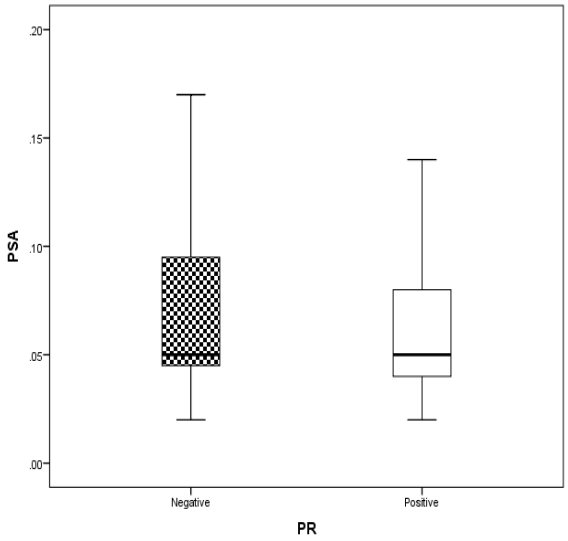



**Diagram 3**. Plasma PSA level based on the status of progesterone receptors




## Discussion

As a new biomarker, plasma PSA level is utilized to diagnose breast cancer in its primary stages. Therefore, the present study sought to determine as well as to compare the plasma PSA level of two malignant and benign breast mass groups. According to the study results, the sensitivity and specificity of a PSA cutoff of 0.045 were reported respectively 63.15% and 53.48% as compared to the pathological findings. Moreover, positive (above the cutoff) and negative (lower than the cutoff) PSA levels were not significantly ($P<0.05$) related to the background variables and breast cancer risk



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factors investigated in the study although in similar studies, a strong relationship was detected between ER+/PR+ subgroup and plasma PSA level [7, 8]. Sensitivity and specificity obtained for plasma PSA level in the current study was not clinically important and thus cannot be considered as an appropriate biomarker to differentiate malignant and benign breast cancer samples. Although the value of PSA as a tool to predict malignancy of breast cancer samples has been rejected [9], Mashkoor *et al.* [10] reported a strong relationship between PSA tissue in IHC breast samples and their malignant diagnosis (P:0.000).

In addition, other studies have related elevated plasma PSA level to the small size of tumors and involvement of lymph nodes [11]. However, it seems that the literature reviewed above proposes three rather paradoxical hypotheses with regard to the relationship between malignancy of breast masses and PSA production. The first hypothesis, considered as the main hypothesis up to 2002, takes a relationship into account between the differentiation of cancerous cells and PSA level in such a way that highly differentiated cells have higher levels of PSA, as well. Furthermore, steroid hormones induce cell differentiation and cellular-molecular findings indicate that PSA is among the last lines of steroid hormone productions [11]. As a matter of fact, malignant samples have a higher tissue PSA in IHC samples.

The second hypothesis posits that androgens mediate the estrogens performance which play an important role in histological differentiation of breast cancer cells [12]. Since PSA is resulted from androgen metabolisms in neoplastic prostate tissues as well as MCF-7 and T-47D cell lines, which is observed in breast cancer samples with positive estrogen receptors [13], less differentiated breast cancer samples are more related to higher tissue PSA levels than benign breast samples [14]. Ultimately, the third hypothesis is concerned with the association between PSA and growth hormone level.

Recently published studies have revealed that PSA can produce IGFBP-3 regarded as one of the six binding proteins to IGF. The protein facilitates the bioavailability and IGFe binding to the membrane receptors of different cells and leaves a strong mitogenic effect on a variety of cells in general and breast cancer cells in particular [14, 15]. Hence, PSA can be considered as a stimulant with respect to mitosis and differentiation in neoplastic tissues by the function of growth hormone. However, no reliable hypothesis has been proposed concerning the relationship between PSA and the features of malignant breast tumors in the relevant clinical studies, which has made it to a controversial issue.

## Conclusion

Regarding the findings of the present study, it can be concluded that PSA cannot be considered



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as a reliable biomarker to diagnose the breast cancer. Although more comprehensive studies confirm that the plasma PSA levels found in low differentiated cancerous samples are comparably higher than those observed in benign breast samples, no significant difference was detected between plasma PSA levels of low differentiated cancerous samples and those of benign breast samples not taking tissue differentiation of neo-plastic samples into consideration.

Having reviewed the literature, it seems that an evaluation of the plasma PSA level of low differentiated breast cancer samples as compared to that of the benign breast cancer samples can be beneficial to determining the role of PSA as a reliable tool for a primary diagnosis of breast cancer. Moreover, future research is recommended to be conducted concerning the PSA role in breast cancer samples in comparison with benign samples based on other features of tumors as size, involvement of lymph nodes, and hormone disorders.

**Limitation of the study**

Incomplete information of medical records and insufficient cooperation of some cases in following their certain diagnosis lead to their exclusion which can be mentioned as the limitations of the study. It should be noted that inadequate sample of fine needle aspiration made unexpected difficulties in making definitive diagnosis.

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