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ORIGINAL ARTICLE

Diagnostic value of total prostate specific antigen (TPSA) in women with breast cancer in the molecular subtyping era

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Summary

Purpose: *The purpose of this study was to identify the diagnostic value of serum levels of total prostate-specific antigen (TPSA) in female patients under different clinical or pathological conditions of the breast.*

Methods: *Blood samples from 73 women with breast cancer were prospectively analyzed for serum levels of TPSA, carcinoembryonie antigen (CEA), and carbohydrate antigen 15.3 (CA15.3) before surgery, and compared with the levels of a control group of 78 women with benign breast disease and 22 women with breast cancer metastasis.*

Results: *The serum levels of TPSA, CEA, and CA15.3 were significantly higher in women with breast cancer than in women with benign breast diseases (0.018±0.027 vs 0.007±0.008, p=0.001; 2.338±1.681 vs 1.699±1.164, p=0.008; 13.929±7.679 vs 10.415±5.295, p=0.001, respectively). Serum CEA and CA15.3 levels were significantly higher in patients with cancer metastasis compared with patients with benign breast disease (3.405±2.131 vs 1.699±1.164, p=0.001; 20.255±21.120 vs 10.415±5.295, p=0.042, respectively). Moreover, TPSA levels were significantly associated with menstruation status in breast cancer patients (p=0.030), whereas no significant association was found between TPSA levels and four molecular subtypes (luminal A , luminal B , triple-negative and HER2). TPSA serum levels were positively associated with both CEA (p=0.040, R=0.045) and CA15.3 (p=0.032, R=0.049) levels when diagnosing breast cancer.*

Conclusion: *This study indicated the clinical significance for TPSA levels in breast cancer diagnosis. TPSA may act as a useful serologic indicator of future cancer recurrence.*

Key words: *breast cancer, diagnosis, molecular subtypes, total prostate specific antigen*

Introduction

Biochemically, PSA is a 33 kDa single-chain glycoprotein with chymotrypsin-like activity that requires post-translational processing for its full proteolytic activity [1]. The glandular kallikrein gene family is composed of three genes, localized on chromosome 19q13.3-q13.4, and the KLK-3 gene locus encodes the extracellular serine protease PSA, which has also been named human glandular kallikrein 3 (hK3) [2].

Since the discovery of PSA in the 1970s, this molecule has been the focus of extensive investigation. It was used as a marker for diagnosis of prostate carcinoma [3,4], and has also been identified as the most useful biomarker for evaluating disease progression and assessing therapeutic responses, as well as identifying tumor recurrence [5]. However, in recent years, numerous researchers have showed that PSA is not specific to the male prostate [6]. These studies showed beyond doubt that PSA is produced in female hormonally regulated tissues such as the breast, or Skene glands, the so-called female prostate. PSA was also found in other tumors

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involving the lung, ovaries, and salivary glands [7], as well as in nipple aspirate fluids, ascitic fluids, and cerebrospinal fluids, if sufficiently sensitive analytical methods were conducted [8,9]. However, the serum concentration of PSA in females is approximately 1000-fold less than that in males [10].

Most PSA in the blood is bound to serum proteins. TPSA includes all forms of PSA that can be detected as free PSA (FPSA), which is not bound to serum proteins.

Breast carcinoma is by far the most commonly found cancer in women worldwide. It is a heterogeneous disease that can be classified into several types by immunohistochemical (IHC) staining of three receptors: estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor-2 (ERBB2/HER2), along with the presence of proliferating cell nuclear antigen (PCNA/Ki-67) [11]. Thus we can divide breast cancer into four molecular types: luminal A, luminal B, triple-negative breast cancer (TNBC), and HER2-type breast cancer [12].

The prognostic parameters of breast cancer include age, menstruation status, tumor grade, lymph node status, pathological type, molecular-subtyping status such as hormone receptor status, and expression of ERBB2 and Ki-67. Previous studies have shown that PSA is associated with better tumor differentiation or histological type [13], while others have reported no significant association for these factors [14].

However, we still lack any uniform results regarding the relationship between serum concentration of TPSA and different clinical or pathological parameters, especially with regards to molecular subtypes of breast cancer, during diagnosis and prognosis. It is well established that the combined detection of tumor markers can improve the accuracy of tumor diagnosis, thereby prompting this research investigation.

The aim of the current study was to assess serum concentrations of TPSA in invasive breast carcinoma to evaluate its relationship with routine clinicopathological parameters including age, menstruation status, tumor grade, and molecular subtype status, and thus determine its diagnostic value in breast carcinoma. We also assessed the diagnostic value of other markers such as CEA and CA15.3.

Methods

Patients

TPSA was measured in 73 serum samples from female patients, aged 18-80 years, with newly confirmed breast cancer through histology and no other malignancy or history of surgery at the first affiliated hospital of Chongqing University during the period of the study. None of them had received preoperative chemotherapy or radiotherapy before sampling. In addition, 78 women free from cancer and diagnosed with benign breast disease such as breast hyperplasia, cysts, and fibroids, were also analyzed for serum levels of TPSA. We also collected the serum levels of TPSA in 22 patients, who had recognized tumor metastasis by imageological or pathological examination, regardless of the metastatic sites, such as the lung, liver, spine, contralateral or ipsilateral breast. Most of these patients had undergone or were undergoing chemotherapy, radiotherapy, or endocrine therapy.

Data collection

The protocol of this study was approved by the Ethics and Protocol Review Committee of the Chongqing Medical University, Chongqing, China.

Informed consent was obtained from the subjects or the patient's next of kin. Patient confidentiality was preserved according to the guidelines for studies of human subjects. All groups were interviewed using questionnaires designed for the purpose of the study, covering aspects related to socio-demographic characteristics and medical history (past and present).

Biochemical analysis

Blood samples (5 mL) were collected by venipuncture using a sterile disposable syringe in a plain plastic tube. The blood samples were centrifuged at 3000 rpm for 6 min, and the sera were stored at 2-8 °C until analysis. In women with newly diagnosed breast cancer or benign disease, blood samples were obtained preoperatively (prior to any surgical or other therapeutic procedures). Serum TPSA levels were measured using chemiluminescence immunoassay techniques with an analytical sensitivity of 0.003 ng/mL by the Cabas e602 system (Roche Company, Germany). The detection of serum levels for CA15.3 and CEA were performed using similar methods, with sensitivity concentrations of 1.00 U/mL and 0.200 ng/mL, respectively.

Statistics

The correlations between TPSA and age, menopausal status, tumor stage, molecular-subtyping status, and other clinical parameters were examined. In this analysis, TPSA, CEA, and CA15.3 concentrations were used as continuous variables, which were expressed as mean and standard deviation. Associations between TPSA status and other variables were analyzed using t-test, x^2 test, or ANOVA where applicable. SPSS (version 21.0) was used for statistical analyses. The graphics program of Graphpad Prism (version 5) was used to draw diagrams.

The cutoff values for tumor size were 2 and 5 cm. Lymph node status was either positive (any positive number of nodes) or negative. Patients were also categorized with respect to childbearing status (yes vs no), menopausal status (yes vs no), and pathological type (carcinoma *in situ*, noninvasive carcinoma, nonspecific invasive carcinoma, specific invasive carcinoma).

Molecular subtypes were defined as follows: luminal A type was defined as both ER and PR positive, with high expression of PR, ERBB2 negative, and low expression of Ki-67; luminal B type was classified into two subtypes, one was ER and PR positive, ERBB2 negative, and high expression of Ki-67 or low expression of PR, while the other was ER and PR positive, ERBB2 positive, and any status of Ki-67; HER2 type was defined as ERBB2 positive, both ER and PR negative, and any status of Ki-67; and TNBC was ER negative, PR negative, and ERBB2 negative. The critical limit of Ki-67 was at 14% of expression through immunohistochemical analysis, and was 20% for ER/PR expression.

Results

TPSA distribution and relationships with clinical or pathological factors

As shown in Table 1, a total of 73 patients with breast cancer were recruited with mean age 49.48 ± 11.86 years, while that of patients with

Table 1. Association between TPSA concentrations and clinical or pathological factors in patients with breast cancer

	TPSA (ng/ml)		
Variables	*mean± SD*	*n (%)*	*p value*
Age (years)			0.365
≤50	0.015±0.019	44(60)	
>50	0.022±0.036	29(40)	
Menstruation status			0.030
Premenopausal	0.011±0.011	42(58)	
Postmenopausal	0.027±0.038	31(42)	
Fertility condition			0.842
Yes	0.018±0.028	71(97)	
No	0.014±0.016	2(3)	
Tumor size (cm)			0.222
<2	0.016±0.019	20(27)	
2-5	0.017±0.026	50(68)	
>5	0.045±0.072	3(5)	
Nodal status			0.703
Negative	0.017±0.028	64(88)	
Positive	0.021±0.027	9(12)	
Tumor stage			0.899
I	0.015±0.020	18(25)	
II	0.019±0.030	52(71)	
III-IV	0.017±0.025	3(4)	
Pathological type			0.978
Carcinoma *in situ*	0.012±0.013	5(7)	
Noninvasive carcinoma	0.017±0.015	6(8)	
Nonspecific invasive carcinoma	0.018±0.030	58(79)	
Specific invasive carcinoma	0.018±0.019	4(6)	
ER status*			0.670
Negative	0.021±0.041	19(26)	
Positive	0.017±0.021	54(74)	
PR status*			0.950
Negative	0.018±0.034	29(40)	
Positive	0.018±0.022	44(60)	
Molecsular subtyping			0.401
Luminal A	0.014±0.015	8(11)	
Luminal B	0.017±0.021	46(63)	
Ttriple-negtive breast cancer	0.021±0.050	13(18)	
HER2+ breast cancer	0.006±0.005	6(8)	

ER: estrogen receptor, PR: progesterone receptor. *Determined by immunohistochemistry. TPSA levels were significantly higher in postmenopausal than in premenopausal patients ($p<0.05$).

benign breast disease was 42.76±10.73 years. Serological concentration of TPSA was significantly higher in postmenopausal breast cancer patients than in premenopausal patients (0.011±0.011 vs 0.027±0.038, p=0.030). There was positive correlation between the level of TPSA and increased tumor size, since the highest TPSA level was observed when the tumor was larger than 5 cm, However, this finding was not statistically significant (p=0.222).

In addition, we found that the invasive carcinoma, involving both nonspecific invasive carcinoma, such as infiltrating lobular carcinoma and infiltrating ductal carcinoma, and specific invasive carcinoma, like papillocarcinoma, squamous cell carcinoma, and mucinous adenocarcinoma, exhibited higher TPSA levels than noninvasive carcinoma. These levels of invasive and noninvasive carcinoma were also higher than those of carcinoma *in situ*, but this comparison was not statistically significant (p=0.978) (Table 1).

As shown in Table 1, there was no significant relationship between TPSA levels and fertility status or nodal status (0.018±0.028 vs 0.014±0.016, p=0.842; 0.017±0.028 vs 0.021±0.027, p=0.703, respectively). We also found that the serum level of TPSA was highest in stage II tumors, then stage III-IV, with the lowest levels seen in stage I tumors (Figure 1). However no significant difference was observed (p=0.899).

Furthermore, TPSA levels were higher in patients with molecular HER2 type disease than in other types, and were lowest in cases of TNBC. However, the distribution of TPSA was indiscriminate among the four molecular subtypes of breast cancer (p=0.401) (Figure 2). No significant difference was noted for ER and PR status, where the p values were 0.670 and 0.950, respectively.

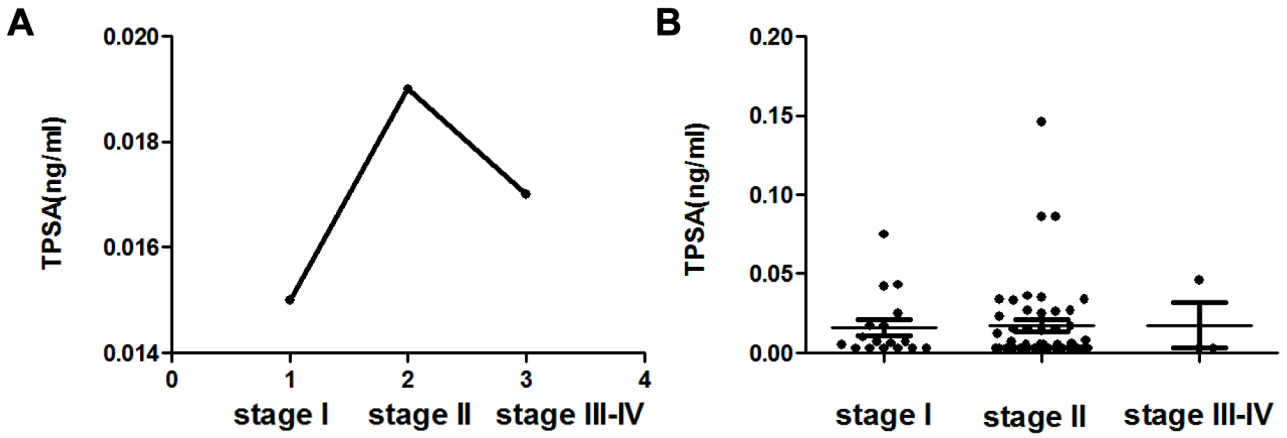

Figure 1. Serum level of TPSA at different tumor stages. The serum level of TPSA was highest in stage II tumors **(A)**, then in stage III-IV **(B)**, with the lowest levels seen in stage I tumors **(A,B)**.

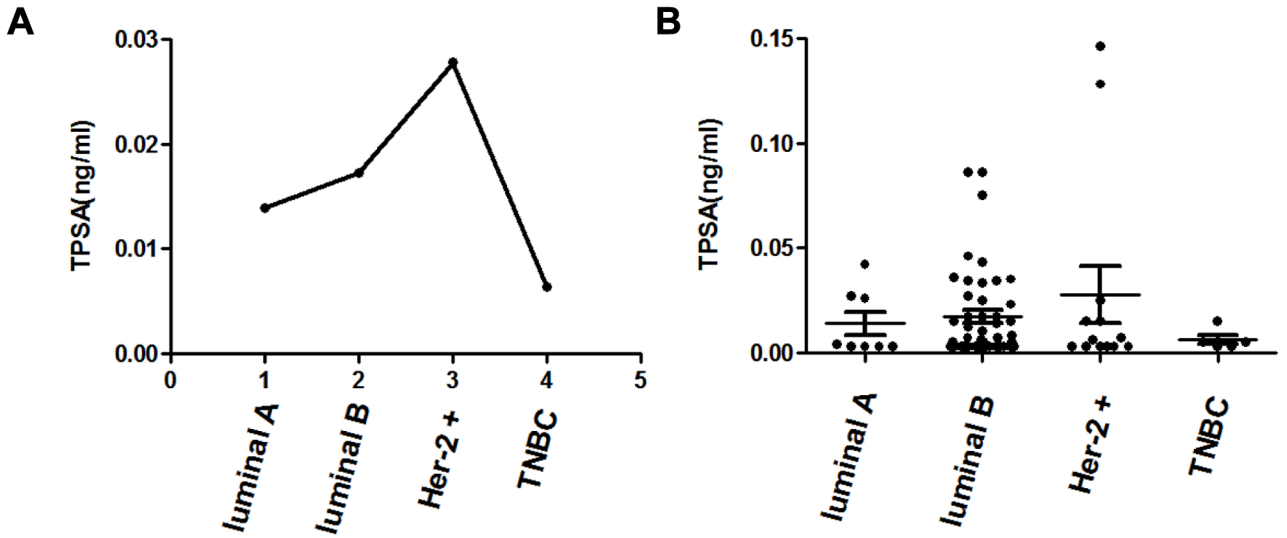

Figure 2. Serum level of TPSA in four molecular subtypes. TPSA levels were higher in patients with molecular HER2 type disease **(A)** than in other types, and were lowest in cases of TNBC **(A,B)**.

Association between TPSA concentration and other variables in patients with benign breast disease

As seen in Table 2, in women with benign breast disease, the serum level of TPSA was significantly higher in patients with history of childbearing (0.003±0.001 vs 0.006±0.008; p=0.001). However, there was no association between TPSA and age, menstruation status, or tumor size (breast fibroids), among benign breast disease patients.

The diagnostic value of TPSA in breast cancer and benign disease

As shown in Figure 3, the serum levels of TPSA, CEA, and CA15.3 were significantly higher in patients with breast cancer than in patients with benign breast disease (0.018±0.027 vs 0.007±0.008, p=0.001.

The diagnostic value of TPSA in breast cancer metastasis

Patients with breast cancer metastasis had higher levels of TPSA, CA15.3, and CEA. There was no meaningful association for TPSA levels between patients with tumor metastasis and patients with malignant breast tumors (0.018 ± 0.027 vs 0.027 ± 0.050, p=0.438) (Figure 3). Both serum CEA and CA15.3 levels were significantly increased in women with cancer metastasis when compared to patients with benign breast disease (3.405 ± 2.131 vs 1.699 ± 1.164, p=0.001; 20.255 ± 21.120 vs 10.415 ± 5.295, p=0.042, respectively) (Figures 4, 5). CEA levels also showed a meaningful increase in breast cancer metastasis compared with breast cancer (3.405 ± 2.131 vs 2.338 ± 1.681, p=0.016) (Figure 4).

Table 2. Association between TPSA concentration and other variables in patients with benign breast disease

	TPSA (ng/ml)		
Variables	*mean± SD*	*n (%)*	*p value*
Age (years)			0.737
≤45	0.006±0.007	42 (54)	
>45	0.007±0.008	36 (46)	
Menstruation status			0.176
Premenopausal	0.007±0.008	64 (82)	
Postmenopausal	0.005±0.004	14 (18)	
Fertility condition			0.001**
Yes	0.003±0.000	75 (96)	
No	0.006±0.008	3 (4)	
Tumor size (cm)			0.549
<2	0.007±0.009	30 (38)	
≥2	0.006±0.007	48 (62)	

**TPSA levels were significantly higher in patients with a history of childbearing in women with benign breast disease (p<0.01).

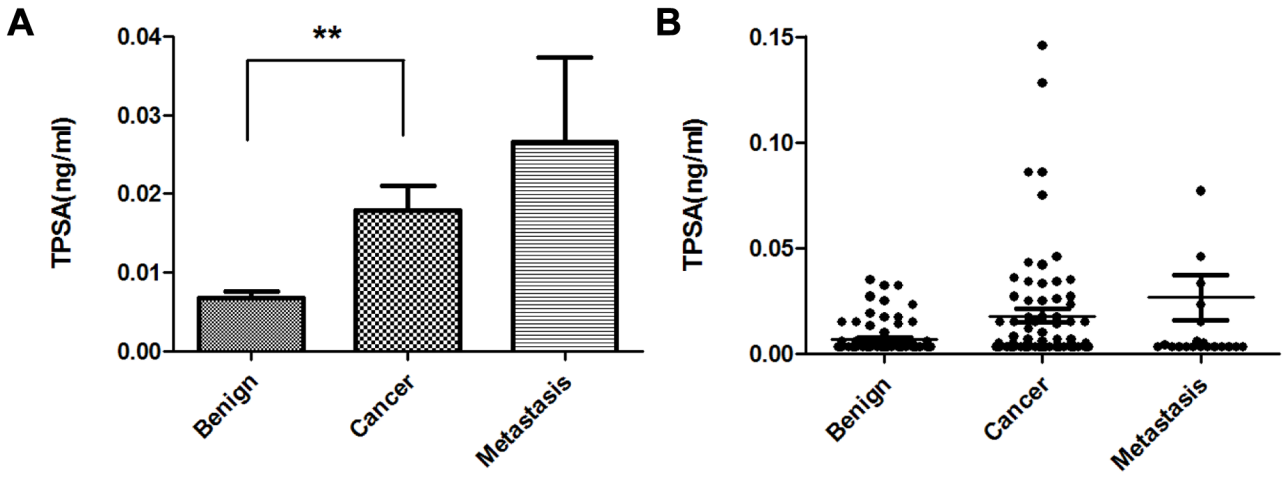

Figure 3. Serum levels of TPSA in breast cancer and benign disease. TPSA levels were significantly higher in patients with breast cancer **(A)** than in patients with benign breast disease **(A,B)**. **p<0.01.

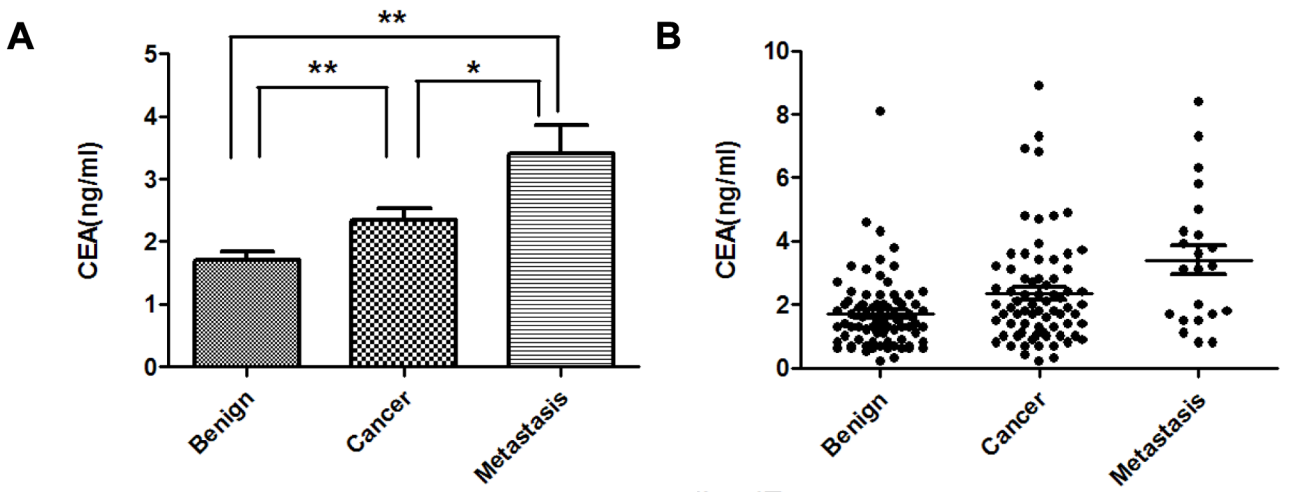

Figure 4. Serum levels of CEA in breast cancer and benign disease **(A,B)**. CEA levels were significantly increased in women with breast cancer when compared to patients with benign breast disease, **p<0.01. And CEA levels were significantly higher in women with breast cancer metastasis when compared to patients with benign breast disease, **p<0.01. CEA levels also showed a meaningful increase in breast cancer metastasis compared with breast cancer, *p<0.05.

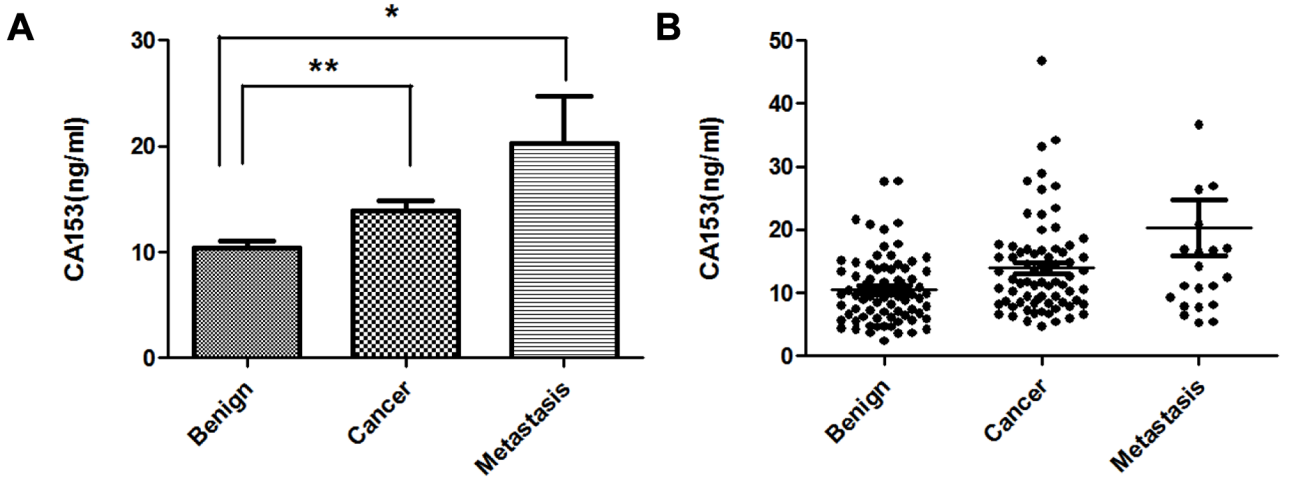

Figure 5. Serum levels of CA15.3 in breast cancer and benign disease **(A,B)**. CA15.3 levels were significantly increased in women with breast cancer compared to benign breast disease, **p<0.01. And CA15.3 levels showed a meaningful increase in breast cancer metastasis compared with breast cancer, *p<0.05.

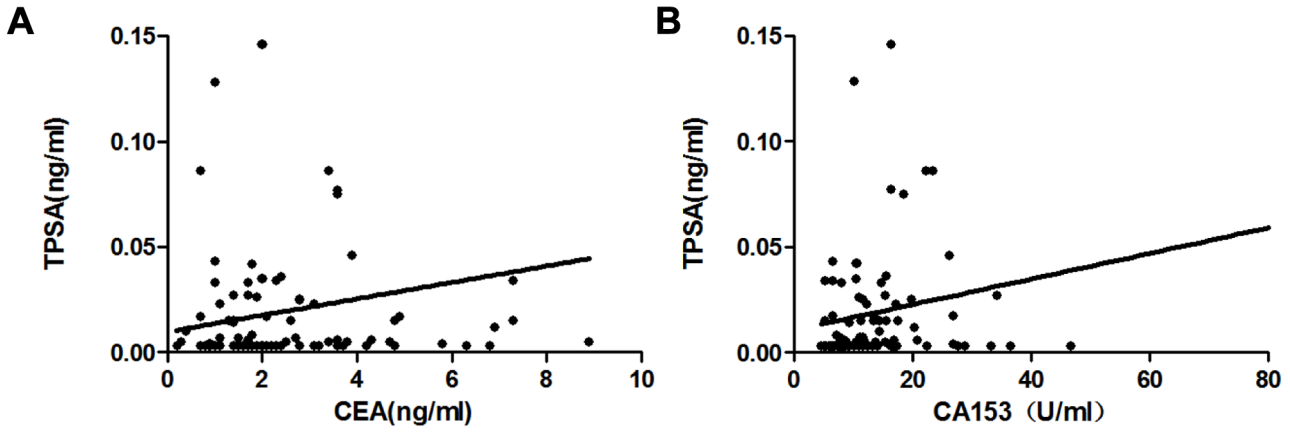

Figure 6. Correlation of serum levels of TPSA and CA15.3, CEA when diagnosing malignant breast tumors and benign disease **(A,B)**. Serum levels for TPSA and CEA had positive association (p=0.040, R=0.045), and TPSA levels and CEA also had positive association (p=0.032, R=0.049).

Correlation of markers in diagnosis of breast cancer

Serum levels of TPSA, CA15.3 and CEA were significantly higher among breast malignant tumor cases when compared with benign disease patients. As shown in Figure 6A, serum levels of TPSA and CA15.3 had positive association when diagnosing malignant breast tumors and benign disease (p=0.032, R=0.049). In addition, it was noticed that serum levels for TPSA and CEA had positive association (p=0.040, R=0.045) (Figure 6B).

Discussion

As long ago as 2001, the United States medical community raised the concept of "Precision Medicine" for the first time, while on January 20, 2015, President Obama put forward the "Program of Precision Medicine". These events not only prompted the development of molecular typing, but also triggered the search for more molecular markers of breast carcinoma [15]. Currently, we classify breast cancer into four types based on ER, PR, and the human ERBB2/HER2, along with proliferating cell nuclear antigen (PCNA/Ki-67) [16]. Although several studies have strongly suggested that the molecular forms of PSA may represent a potential tool for the risk assessment of breast cancer [17].

To date, little has been done to explore the association between molecular types of breast cancer and serum levels of PSA, as well as tumor markers such as CEA and CA15.3. We therefore designed this study to investigate the relationship between serum concentrations of TPSA and different clinical or pathological parameters, especially with regards to different molecular subtypes of breast cancer, and evaluated the diagnostic value of TPSA in breast cancer, when combined with other tumor markers like CEA and CA15.3.

In this study, TPSA levels were higher in patients with the HER2 molecular subtype than in other types, and were lowest in the triple-negative breast cancer (TNBC) subtype. This may be attributed to disrupted hormonal balances in women, leading to aberrant expression of hormone-dependent genes like PSA, which is normally under hormonal control and up-regulated by androgen and progesterone [18]. However, the distribution of TPSA is indiscriminate among the four molecular types of breast cancer.

The role of estrogen receptors (ERs) and progesterone receptors (PRs) in breast carcinomas is well established. There is also prior research data to suggest that PSA gene expression in breast tumors appears to be under hormonal control in the breast cell lines T-47D and BT-474, and can be induced by androgen, progesterone, mineral corticoids, and glucocorticoids [18]. However, in this study, we noticed that the concentration of TPSA was not significantly associated with ERs and PRs, which is also in accordance with other findings [13,19]. Although questions remain about the association of PSA and hormone receptors, other authors believe that the expression of PSA and androgen receptor (AR) is highly correlated [19]. Some researchers found that most of the lobular carcinomas and the majority of medullary carcinomas, as well as ER-negative carcinomas, co-expressed PSA [20]. However, we did not find any association of TPSA with HER2 status.

The purpose of this study was to evaluate the diagnostic value of TPSA in women with breast cancer. It was shown that the serum concentration of TPSA was significantly higher in breast cancer patients than in the group with benign breast disease. We speculate that meaningful increases in TPSA levels in women with breast cancer is the result of a disrupted hormonal balance, triggering the PSA gene, which is hormone-dependent. Moreover, the marked rise in serum TPSA is consistent with previous reports [21,22]. In addition, some researchers have suggested that the major component of total PSA is PSA-ACT, a protein and serine protease inhibitor , which is not produced by tumor cells but more likely by normal breast tissue. This hypothesis may explain why the decline in TPSA levels after breast cancer surgery is less than that of free prostate specific antigen (FPSA) [23].

PSA was shown to stimulate cell detachment, suggesting a role for PSA in tumor progression or metastasis [24]. It has been reported to degrade the extracellular matrix proteins fibronectin and laminin, and also induce uncontrollable proliferation in osteoblast and fibroblast cell lines [25]. We naturally imagined therefore that the serum levels of PSA could be affiliated with tumor metastasis. However, after analysis of 22 women with tumor metastasis in our study, the patients with breast cancer metastasis exhibited higher levels of TPSA than newly diagnosed breast cancer patients and benign disease patients. This could be the result of increased tumor burden stimulating the production of PSA, or the metastatic tumor could have produced the protein by itself [26]. There was no meaningful association however between TPSA and tumor metastasis. Since the concentration of PSA is very low in serum in women, which is incapable of binding to proteinase inhibitors, this does not always permit a distinction between cancer metastasis or non-metastatic conditions, even in healthy and benign disease patients [27].

Early diagnosis of breast cancer remains the key to improving the cure rate and reducing mortality. Prior studies have shown that circulating tumor markers may display abnormal levels before clinical manifestation of cancer symptoms [28]. In this case, it will be crucial to detect levels of circulating tumor markers for timely recognition of the disease. CA15.3 antigen is a mucin glycoprotein immobilized on the membrane, and is currently widely used in breast cancer diagnosis, along with CEA, which is mainly used as a tumor marker to monitor gastrointestinal carcinomas treatment, as well as breast carcinoma, lung carcinoma, and medullary thyroid carcinoma [29]. However, there are currently no tumor markers that can be used with high sensitivity and specificity when diagnosing breast carcinoma. It is therefore necessary to use a combination of existing tumor markers that can be detected, in order to improve the sensitivity and specificity of tumor diagnosis. In this study, the serum levels of TPSA, CA15.3, and CEA in breast cancer patients were significantly higher compared to the control group with benign breast disease, which is in agreement with results from previous studies [29]. In addition, this study also showed that TPSA levels had positive association with both CEA and CA15.3 levels when diagnosing breast cancer.

This study had several strengths. First, in addition to enrolling patients with breast cancer and benign breast disease, breast cancer cases with tumor metastasis were also included, thus broadening the applicability of the results to these populations. Then, based on the simultaneous detection of TPSA, CEA, and CA15.3 levels, we have investigated the value of three tumor markers in the diagnosis of breast cancer and their consistency therein. This study also had several limitations. First, it lacked a larger sample size for statistical analysis, which could explain why there were no significant differences in some results. Second, FPSA levels were even lower than TPSA levels, and could not be sensitively detected using commercially available equipment in our laboratory. Thus in this study, we could not evaluate the diagnostic value of FPSA. Third, due to the inclusion in the study of hospitalized patients, there was lack of normal people as another negative control.

The prominent increase of serum TPSA levels in breast carcinoma patients, as well as the uptrend in patients with tumor metastasis, may establish their diagnostic value in tumors and tumor recrudescence. Discrepancies among results from different studies with regards to the diagnostic value of PSA still remain. This warrants further investigation to finally clarify the significance of PSA in breast cancer according to molecular subtypes . Studies involving larger cohorts and the application of advanced techniques are needed to validate our knowledge over the diagnostic value of PSA levels in breast carcinoma.

Acknowledgements

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Conflict of interests

The authors declare no conflict of interests.

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