

## Expression of Free Prostatic Specific Antigen (PSA) In Breast Mass

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### ملخص:

إن الأجسام المستضادة المتخصصة لغدة البروستات تزداد في أورام الثدي وان نسبة الحر منها يقل بصوره ملحوظة في عينة مصل الدم للنساء بعد إجراء العمليات الجراحية لسرطان الثدي. مع إن الأجسام المستضادة المخصصة لغدة البروستات الحرة تكون سائدة متخصصة الى سرطان الثدي فان الاستخدام التشخيصي الطبي محدود في هذا الوقت بسبب قلة التحسس لها لذلك نحتاج الى دراسات أخرى مع أخذ عينات من مرضى أكثر من هذه الدراسة للتشخيص بهذه المستضدات بما يخص عدد المرضى وانتشار السرطان في الجسم وأخيرا الميكانيكية الفيزيولوجية خلف زيادة المستضدات المتخصصة لغدة البروستات في أورام الثدي تحتاج إلى تحاليل ودراسات أكثر.

**الهدف:** ان الهدف من هذه الدراسة هو قياس ومقارنة نسب الأجسام الحرة المستضادة المخصصة لغدة البروستات في المصل الدموي لمرضى النساء الذين يشكون من أورام في الثدي مع قياس نسبه هذه المستضدات قبل وبعد العمليات الجراحية لسرطانات الثدي كمؤشر مصلي تشخيصي .

**طريقة البحث:** في الوقت الحاضر الدراسة أجريت في مدينة الصدر الطبية التعليمية في مدينة النجف الأشرف بين الخامس عشر من شباط ٢٠١٠ الى الأول من تشرين الثاني ٢٠١٠ لستين ٦٠ حاله مرضيه لأورام الثدي أخذت عينات الدم منهم لغرض قياس نسبه المستضدات المخصصة لغدة البروستات.

ثلاثون حاله منهم يشكون من سرطان الثدي والذي تم تشخيصه بالفحص الخلوي والفحوصات الأخرى أخذت عينات منهم قبل إجراء العمليات الجراحية وبعد عشره الى أربعة عشر يوما بعد إجراء العمليات تم أخذ عينات من نفس المرضى ثلاثون حاله يشكون من أورام حميدة بالثدي تم أخذ عينات منهم . تم أخذ عمر المرضى أيضا للمقارنة بين الحالات.

**النتيجة:** نسبة المستضدات الحرة المخصصة لغدة البروستات PSA في عينات المصل الدموي المأخوذ من المرضى الذين يعانون من سرطان الثدي قبل العملية هو 5ng/ml-1.380ng/ml، ولكن بعد العملية نسبة المستضدات الحرة لغدة البروستات لنفس المرضى نقص بصوره ملحوظة ليصبح 0.011ng/ml- 0.222ng/ml. نسبة المستضدات الحرة المخصصة لغدة البروستات للمرضى الذين يشكون من أورام حميدة بالثدي كانت 0.000ng/ml-0.893ng/ml.

### الاستنتاج والتوصيات:

توجد علاقة بين المستضدات الحرة لغدة البروستات قبل وبعد العمليات الجراحية لسرطان الثدي لذلك يعتبر كمؤشر تشخيصي لذلك ننصح لكل مريض لديه ورم في الثدي لذلك ننصح ان تؤخذ عينه من دمه لقياس نسبة المستضدات الحرة المخصصة لغدة البروستات للتشخيص المبكر لسرطان الثدي، وأيضا نوصي ان يستعمل المستضدات الحرة لغدة البروستات كعامل تنبؤي مثل مستضدات البروجسترون والاستروجين كما أظهرت الدراسات الأخرى لذلك نحتاج إلى دراسات أخرى في المستقبل لإثبات ذلك.

**Key Words:** Prostate specific antigen (PSA), breast cancer, Benign breast tumor.

### Abstract

**Background:** Free prostatic specific antigen (PSA) is the predominant molecular form of serological PSA increase in a significant proportion of breast cancer patients and that free PSA levels decrease significantly after surgery. Given the heterogeneity of the population of breast cancer patients, additional studies with larger cohorts of patients are required for the examination of molecular forms of PSA with regard to individual parameters such as risk of relapse or metastasis. Finally, the physiological mechanism behind the free PSA increase in breast cancer and its ramifications with respect to tumor progression should be further investigated.

**Objective: To measure and compare :**

- 1:- free PSA in the serum of women with breast cancer before and after surgery and
- 2:-the serum of women with benign breast mass as a diagnostic tumor marker.

**Patients and Methods:** A prospective study was done in AL Sader teaching Hospital in AL-Najaf city between 15th January 2010 and 1st of November 2010, where 60 cases of breast mass were taken to measure the expression of free PSA in their serum, 30 cases of them have breast carcinoma diagnosed by cytology and other ways of diagnosis, and their serum were taken before the operation and at 10th-14th post-operative day. The other 30 cases have benign breast tumor. We also took the age of all the 60 patients.

**Results:** In the 30 patients with breast carcinoma the level of free serum PSA was between 1.380ng/ml- 5.000 ng/ml before operation, but highly decreased to become 0.011ng/ml – 0.292 ng/ml post-operatively. While in the benign tumor patients the level was 0.000ng/ml – 0.893 ng/ml.

**Conclusion and Recommendation:** There is an association between the serum level of free PSA before and after surgery of ca breast patients, so it is regarded as a marker for diagnosis of breast cancer. We advise to send every patient with breast lump for serum free PSA level for early detection of ca breast. Our study show that the free serum PSA is a diagnostic tumor marker like in the diagnosis of prostate carcinoma and also may be use PSA as a prognostic factor in patients with ca. breast like progesterone and estrogen receptors as showed by other studies, but we need further studies in the future to confirm

**Introduction:**

PSA is a single-chain glycoprotein expressed at high levels in the epithelium of the human prostate gland<sup>(1)</sup>. The prostatic function of PSA is to liquefy the sperm-entrapping seminal coagulum after ejaculation<sup>(2)</sup>. The name "PSA" reflects the initial widespread belief that

expression of the protein was restricted to the prostate gland<sup>(3)</sup>. Over the past 5 years, however, this notion has clearly been dispelled. Numerous studies have shown that PSA is expressed extra prostatic ally<sup>(4)</sup>, suggesting that PSA may be functional outside the prostate gland. The peri urethral (Skene's) gland was the first female tissue that was suggested to be able to produce PSA<sup>(5)</sup>. This tissue has been referred to as the "female prostate because its developmental origin is homologous to that of the male prostate"<sup>(6)</sup>.

Therefore, it may not be surprising that this gland produces PSA in both males and females. It is now clear that hormonally regulated tissues in females, such as the breast, can produce PSA. PSA is detectable in normal and hyperplastic breast tissue<sup>(7,4,2)</sup> and is present in the majority of breast tumors<sup>(8)</sup> and breast cysts<sup>(9, 10)</sup>. PSA is released into breast secretions, such as the milk of lactating women<sup>(11,8,6)</sup> and nipple aspirate fluid<sup>(12)</sup>. PSA gene expression in breast tumors appears to be under hormonal control because the steroid hormone receptor-positive breast cancer cell lines T-47D and BT-474 can be induced by androgens, progesterone's, mineral corticoids, and glucocorticoids to produce PSA<sup>(13,14)</sup> in vitro. Detectable circulating levels of PSA, likely originating from breast tissue, are present in the serum of women<sup>(15,13,10)</sup>. The PSA concentration in female sera is approximately 1000 fold less than that of males (0.004 mg/liter);<sup>(16)</sup>. Many immunoassays have been established for PSA, some of which measure 'total'

PSA, that is PSA whether or not it is bound to an inhibitor, while others measure 'free PSA', that is PSA not bound to an inhibitor which could comprise both enzymatically active PSA and the inactive 'nicked' form<sup>(17,15,8)</sup>. Using chromatographic techniques it is found that the predominant form of PSA in the sera of women without breast cancer is PSA bound to ACT (serine protease inhibitor alfa 1 antichemo trypsin), whereas free PSA constitutes the major form of PSA in the pre surgical serum of breast cancer patients<sup>(18,10,4)</sup>. Level of serum PSA affected by tumor size, lymph nodes involvement and patient received adjuvant therapy<sup>(19)</sup>. Although free PSA as the predominant molecular form appears to be unique to breast carcinoma, an increase in total PSA levels in the serum of all patients was observed in comparison to the control group<sup>(20)</sup>. It is speculated that the slight increase in total PSA in the serum of women with breast cancer<sup>(21)</sup>, benign breast disease, or uterine fibroids is the result of a disrupted hormonal balance in these women, triggering the aberrant expression of hormone-dependent genes such as PSA. The observation that total PSA is only slightly decreased in

breast cancer patients after surgery is an indication that a major<sup>(22,20,5)</sup> component of total PSA (in this case PSA-ACT) is not produced by the tumor cells but more likely by normal breast tissue<sup>(23)</sup>. Alternatively, free PSA decreases more dramatically after surgery, strongly indicating that this fraction is produced by breast tumors<sup>(24)</sup>. It has been reported that the majority of breast tumor, PSA occurs in the free form<sup>(25,8)</sup>, whereas free PSA and PSA-ACT appear to exist in approximately equal proportions in breast cyst fluid<sup>(26,11)</sup>. It has also been observed that PSA added to the hormone-dependent human breast cancer cell line MCF-7 is growth inhibitory and stimulates conversion by the cells of estradiol to the less potent estrogen, estrone (Lai et al. 1996). Since the cells are hormone-dependent this action of PSA could mediate its growth inhibitory effect on the cell line<sup>(27)</sup>.

**In summary,** It is demonstrated that free PSA is the predominant molecular form of serological PSA in a significant proportion of breast cancer patients and that free PSA levels decrease significantly in the serum of women with breast cancer after surgery<sup>(28)</sup>.

#### **Patients and methods:**

A prospective study was done in Al-Sader Teaching Hospital in AL-Najaf city between 15th January 2010 and 1st of November 2010 where 60 cases were taken to measure the level of free PSA in their serum. 30 cases of them have breast carcinoma diagnosed by cytology and other ways for diagnosis and recorded in breast clinic of our hospital, before operation and at 10th -14th day post operatively. The other 30 cases have benign breast tumors. We aspirate 5 cc of blood from each patient and the serum was isolated and the specimens stored at - 20 C until completion of all aspirates. We use international centrifuge of 3000 circle/minute. All specimens were read by ELISA READER 450 nm wavelength absorbance in the laboratory of the same Hospital.

The name of kit free prostate specific antigen PSA immunosorbant assay (Ellisa 96-test kit) from Accutest Laboratories.

Statistical analysis done by: T-test, pairs T-TEST

**Results:** In all the 30 patients with ca breast the level of PSA in their serum before operation was between 1.380ng/ml- 5.000 ng/ml, while the level of PSA measured after

10th-14 th day post operatively was 0.011ng/ml – 0.292 ng/ml, as shown in table 1. The level of free serum PSA in the other 30 benign tumor patients were 0.000ng/ml – 0.893 ng/ml as shown in table 2. The serum level of free PSA post operatively and in benign tumor patients was nearly similar as shown in table 3. Regarding the age of patients the serum level of free PSA were not affected before and after operation and neither in benign cases as shown in figures 2,3 and 4.

**Table No. 1** (Pre and post operative level of free PSA in ca breast patients)  
P Value between pre and postoperative values ,Paired Samples Statistic

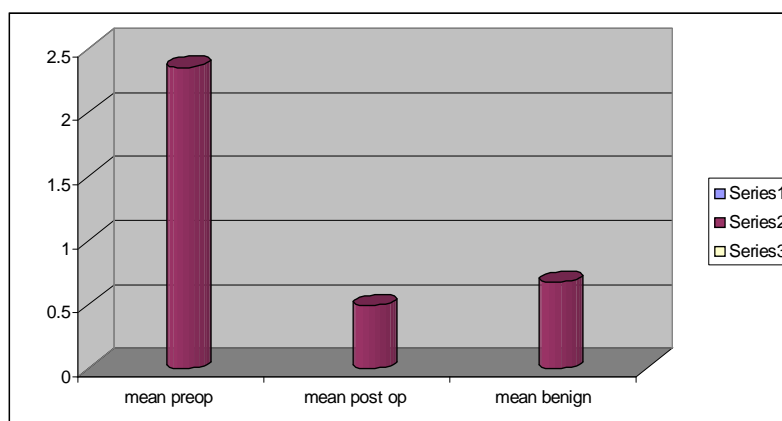
Group	mean	number	Std.deviation	Std.error mean	P value
Pre surgical	2.3493	30	1.3800	0.25195	0.00001 Highly significant
Post surgical	0.4845	30	0.30697	0.5604	

**Table No. 2** (serum free PSA mean in patients with ca breast and benign breast mass)

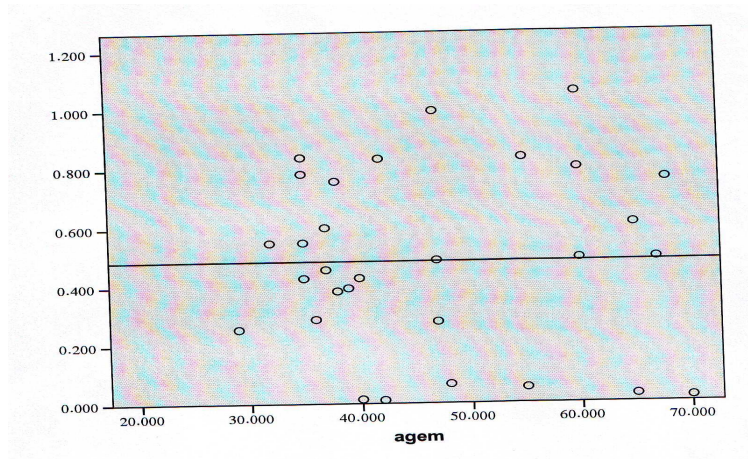
Group	Number	Mean	Std.Deviation	Std.Error mean	P value
PSAPRE 1	30	2.3493	1.3800	.25195	0.00001 significant
BENIGN 2	30	0.6681	0.36806	06720	

**Table No.3** (mean of serum free PSA in post-operative ca breast patients and patients with benign mass)

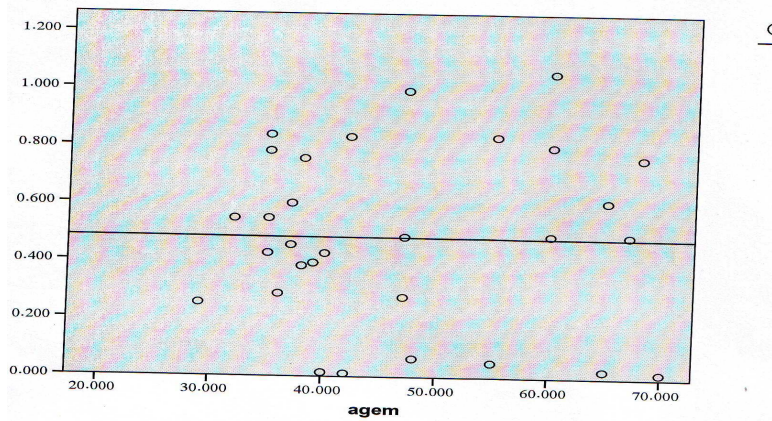
Group	Number	Mean	Std.Deviation	Std.Error mean	P value
PSAPOST OPERATIV	30	0.4845	0.30697	0.05604	0.0400 Not significant
BENIGN	30	0.6681	0.36806	0.6720	



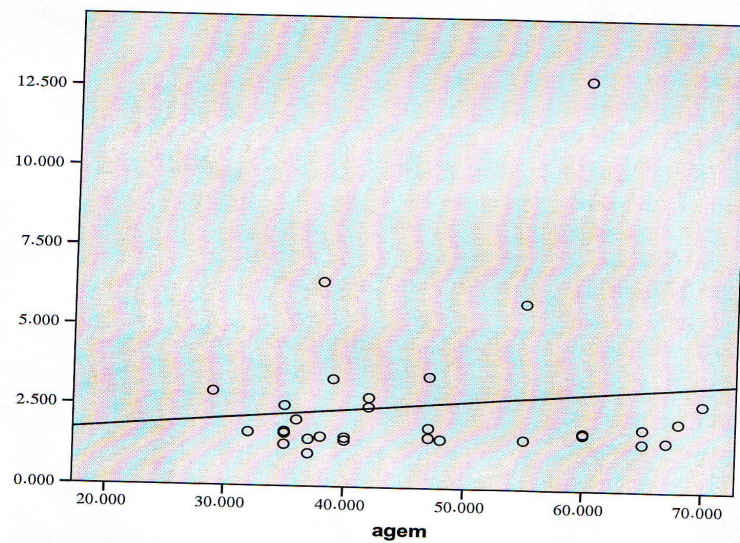
**Figure No. 1 :** (mean level of serum free PSA in pre surgical ,post surgical and benign cases)



**Figure No. 2:** (free PSA serum level in post surgical ca breast patients relation with age groups)



**Figure No 3:** (free PSA serum level in pre surgical ca breast patients relation with age groups).



**Figure No.4:** (free PSA serum level benign breast mass patients relation with age groups).

## **DISCUSSION**

Breast cancer is a leading cause of morbidity and mortality in females of developed countries and is the most common malignancy among North American women<sup>(1)</sup>. It is estimated that by the year 2000, 500,000 women worldwide will die from breast cancer<sup>(2)</sup>. Currently, the most effective way to minimize morbidity and mortality from breast cancer is by early diagnosis and administration of therapy<sup>(3)</sup>. It is thus highly desirable to devise new methods of early diagnosis.<sup>(4,5)</sup> To further improve the effectiveness of distinguishing breast cancer from benign breast lump, measurement of various molecular forms of PSA has been introduced into clinical practice.<sup>(4)</sup> Sera from women with breast cancer, benign breast lump, were analyzed for free PSA and PSA-ACT using an established total PSA immunoassay<sup>(6)</sup>. Like in our study other study has shown that the predominant molecular form of PSA (.50% of total PSA) in a significant proportion of females with breast cancer is the free PSA, and free PSA levels decrease in breast cancer patients after surgery<sup>(7)</sup>.

The vast majority of healthy women or women with other endocrinopathies, including benign breast disease, have free PSA as the minor molecular form and PSA-ACT as the predominant molecular form<sup>(9,10)</sup>. Like in our study although free PSA as the predominant molecular form appears to be unique to breast carcinoma, they observed an increase in total PSA levels in the serum of all patients in comparison to the benign group<sup>(11,10)</sup>,

The observation that total PSA is only slightly decreased in breast cancer patients after surgery is an indication that a major component of total PSA (in this case PSA-ACT) is not produced by the tumor cells but more likely by normal breast tissue.<sup>(12,2,3)</sup>

Like in our study, alternatively, free PSA decreases more dramatically after surgery<sup>(13,2,1)</sup>, strongly indicating that this fraction is produced by breast tumors. It has been reported that the majority of breast tumor PSA occurs in the free form<sup>(14, 10,11)</sup>. Alternatively, breast tumors may produce an endopeptidase which causes a posttranslational modification (internal cleavage) of PSA produced by the breast, thus preventing complex formation with ACT and increasing the proportion of free PSA<sup>(15,8,2)</sup>. The age independence of free PSA may enhance its applicability as a diagnostic tool.<sup>(16,10)</sup>

## **Conclusion and Recommendation:**

There is an association between the serum level of free PSA before and after surgery of ca breast patients, so it is regarded as a marker for diagnosis of breast cancer. We advise to send every patient with breast lump for serum free PSA level for early detection of ca breast. Our study shows that the free serum PSA is a diagnostic tumor marker like in the diagnosis of prostate carcinoma and also may be used as a prognostic factor in patients with ca. breast like progesterone and estrogen receptors as showed by other studies, but we need further studies in the future to confirm that.

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