Original Article

A Comparative Study Of Free Psa In Women With Malignant Breast Disease And Normal Women At A Tertiary Care Centre

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DOI: 10.47750/pnr.2022.13.S03.300

Abstract

Measurement of PSA has potential uses for the treatment of breast cancer in women. Total and free PSA levels in women with breast cysts, uterine fibroids, and breast cancer be fore and six months after surgery are significantly higher versus a control group of healthy women. Women with breast cancer have significantly higher detectable total PSA before surgery than after and serum-free PSA was associated with a higher histologic grade of breast cancer.

As the PSA level detected in a woman's saliva equaled serum PSA levels throughout a woman's menstrual cycle, thus, PSA may be used as a tool for detection and play a role in monitoring treatment response and surveillance for tumour progression and metastasis. Therefore, PSA values may eventually help clinicians detect breast disease and differentiate higher-and lower-risk cancers.

Key Words: Breast cancer, uterine fibroids, menstrual cycle, surveillance, progression, metastasis

Introduction

Although its physiologic function in women has not been determined, PSA has been found in the periurethral gland, normal and hyperplastic breast tissue, breast tumour and cysts, breast secretions (like nipple aspirate fluid), the milk of lactating women, breast cystic fluid, the placenta, and amniotic fluid. PSA also has been found in cancerous and health yovarian, endometrial, adrenal, skin, lung, colon, liver, kidney, and salivary issue. Asinmen, PSA in women is affected by hormones, therefore, PSA levels fluctuate during a woman's menstrual cycle. PSA levels peak in the mid- to late follicular phase of a woman's cycle and are higher in pregnant women than in healthy non-pregnant women.

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Aim

To study whether the increase in PSA levels is associated with breast cancer & clinical applicability of PSA in breast cancer diagnosis. Also to study the correlation of raised PSA levels in breast cancer patients.

Objective

To compare the free prostate-specific antigen in normal women and women with malignant breast disease.

The Normal Breast

Microscopically, the breast is composed of three principal tissue types: glandular epithelium, fibrous stroma and

fat. Functionally, the breast is composed of15 to 20 lobes which contain the glandular tissue in a connective tissue stroma. The glandular apparatus is composed of a branching system of ducts, roughly organized in a radial pattern spreading outward from the nipple-areola complex. After progressive generations of branching, the ducts end blindly in clusters of spaces called terminal ductules or acini. The acini together with their small efferent ducts or ductules are known as lobules and form the functional milk secretory component of the breast.

Blood Supply and Lymphatics

The breast skin receives its blood supply from the sub-dermal plexus; these tiny blood vessels, in turn, communicate with deep underlying arterioles which supply the breast parenchyma. Bloodis supplied to the breast from the following vessels:

- The thoraco-acromial artery
- Internal mammary perforators (second to fifth)
- Lateral thoracic artery
- Thoracodorsalartery
- Terminal branches of the inter costal perforators (third to eighth)

Overall, at least 60% of the blood supply is from the superomedial perforators which come off the internal mammary artery. The breast also has profuse venous drainage divided into the superficial and deep veins.The superficial veins are found along the anterior surface of the fascia; these veins follow the areola path under the nipple-areolar complex, often referred to as the venous plexus of Haller. Deep inside the breast are many large veins which drain into the chest wall veins.

The serratus anterior is another fan-shaped muscle that runs along the lateral wall of the chest wall. The serratus anterior is supplied by branches of the thoraco dorsal and lateral thoracic arteries.The muscle is innervated by the long thoracic nerve.If the long thoracic nerve is damaged during axillary dissection, it can result in winging of the scapula.The rectus abdominis demarcates the inferior border of the breast. The muscle is supplied by the inferior and superior epigastric vessels. In women who have surgery for breast cancer, the rectus abdominis muscle flap (TRAM) based on the superior epigastric flap is sometimes utilized.

The external oblique is a fan-shaped muscle found on the antero-lateral aspect of the thoracic wall. The muscle has a segmental blood supply which originates from the inferior intercostal vessels. The muscle borders the infero-lateral wall of the breast.

Breast Cancer in Women Epidemiology

Breast cancer is the most common site-specific cancer in women worldwide and is the leading cause of death from cancer for women aged 40 to 49 years. It accounts for 33% of all female cancers and is responsible for 20% of the cancer-related deaths in women. In 2010, approximately one and three quarter million new cases werediagnosedworldwide.

The overall incidence of breast cancer has been rising because of increases in the average life span, lifestyle changes that increase the risk for breast cancer and improved survival from other diseases. Despite an increasing incidence, mortality from breast cancer has continued to fall, thought to be the result of both earlier detection via screening and improvements in therapy. There is a tenfold variation in breast cancer incidence among different countries worldwide. The incidence rates of breast cancer are high in North America, Northern and Western Europe, intermediate in South America and Southern Europe and low in Africa and Asia.

In India, breast cancer is the second most common cancer in women next only to cervical cancer. In urban areas, breast cancer is the most common cancer in women. According to the latest population-based cancer registry report (PBCR 2009-2011), breast cancer is the leading malignancy in women in Bangalore and accounts

for 27.3% of all cancers in women in Bangalore.

Pathology of Breast Cancer

Cancer of the breast affects the left breast slightly more often than the right.The upper outer quadrant of the breast is the most common location. Breast cancer may arise from the epithelium of the duct system anywhere from the nipple end of the major lactiferous ducts to the terminal duct unit, which is in the breast lobule. Breast cancers are classified into those that have not penetrated the basement membrane (noninvasive) and those that have (invasive). The chief forms of carcinoma of the breast are classified as follows:

Metastatic spread occurs through lymphatics and hematogenous channels. Lymphatic metastasis occurs primarily to the axillary and the internal mammary lymph nodes. Involvement of supra clavicula rnodes and of any contra-lateral lymph nodes represents advanced disease. More distant hematogenous dissemination eventually ensues, with the involvement of almost any organ or tissue in the body. Favoured locations are the lungs, skeleton, liver and adrenals and (less commonly) the brain, spleen and pituitary. However, no site is exempt. Grading of breast cancer evaluates tubule formation, nuclear grade and mito-ticrate to divide carcinomas into three groups well-differentiated ,moderately differentiated and poorly differentiated carcinomas.

Clinical Presentation

Breast cancer is often discovered by the woman or her physician as a deceptively discrete, solitary, painless and movable mass. At this time, the carcinoma is typically 2 to 3 cm in size, and involvement of the regional lymph nodes (most of ten axillary) is already present in about half the patients. With mammographic screening, carcinomas are frequently detected before they become palpable.

Other less frequent signs and symptoms include : Breast enlargement or asymmetry; Nipple changes, retraction or discharge; Ulceration or erythema of the skin of the breast; Axillary mass; Musculo-skeletal discomfort

Breast Cancer Follow up

Following initial treatment of breast cancer, patients require surveillance for loco-regional tumour recurrence, contra lateral breast cancer, and the development of the distant metastatic disease. In addition, medical follow-up allows clinicians to monitor for late effects of chemotherapy, radiotherapy, or surgery, to gauge ongoing side effects from cancer treatment s such as anti estrogen therapies, and to facilitate opportunities to update patients on new developments that may affect their treatment plan. The American Society of Clinical Oncology (ASCO) has issued surveillance guidelines for women with early-stage breast cancer.

Tumour Markers

A tumour marker is a protein expressed by a tumour or by the host in response to a tumour that is used to differentiate a tumour from normal tissue or to determine the presence of a tumour based on measurements in the blood or secretions. Such substances are found in cells, tissues, or body fluids and are measured qualitatively or quantitatively by chemical, immunological, or molecular biological methods. Some tumour markers are specific for one type of cancer, and others are seen in several cancer types. Many of the well-known markers are seen in non cancerous conditions and cancer. However, it is thought that the blood levels of tumour markers reflect tumour activity and volume.

Clinically an ideal tumour marker should be both specific for a given type of cancer and sensitive enough to detect small tumour for early diagnosis or during screening. In practice, tumour markers are most useful in evaluating the progression of disease status after the initial therapy and monitoring subsequent treatment modalities.

The potential uses of tumour markers are:

1. Screening for cancer
2. Diagnosing cancer
3. Evaluating cancer prognosis
4. Prediction of therapeutic response
5. Tumour staging
6. Detecting tumour recurrence or remission
7. Localising tumour and directing radiotherapeutic agents
8. Monitoring the effectiveness of cancer therapy

A number of international groups have released guidelines on the selection and use of tumour markers in the clinic.These groups include:

1. National Academy of Clinical Biochemistry (NACB)
2. European Group on Tumour-markers (EGTM)
3. American Cancer Society(ACS)
4. American Society for Clinical Oncology (ASCO)

Tumour Markers for Breast Cancer

A number of tumour markers are found to be useful in breast cancer and some of them are undertrial.They include estrogen and progesterone receptors, Hydroxyproline, Ferritin, Mucin like carcinoma-associated antigen (MCA), CA 27.29,CA 549, CA 72-4, Tissue polypeptide antigen, Human placental lactogen, parathyroid hormone, Telomerase, Cathepsins B & D, urokinase-plasminogen activator system (uPA), PSA, ER, PR, CEA, CA 15.3, Arylsulfatase B, Creatine kinase-BB, Esterase, Sialyl transferase,etc.

About Hormone Therapy

Learning whether a tumour has estrogen and/or progesterone receptors helps doctors determine a patient's risk of recurrence (return of cancer after treatment) and whether cancer can be treated with hormone therapy. Hormone therapy blocks the tumour from using estrogen and/or progesterone for cancers that are ER and/or PR positive, slowing or stopping tumour growth. Two types of drugs may be used; one type called tamoxifen (Nolvadex) can be used for women of all ages, while other types of drugs called aromatase inhibitors (AIs) stop tissues and organs other than the ovaries from producing estrogen. AIs must never be used alone for women who have not gonethroughmenopause.

During the 1980s, Tamoxifen became the first anti-estrogenic therapy targeted to ER for adjuvant therapy. The antagonist effects of this drug in breast tissue may result from its ability to bind to the ligand-binding domain of the ER,effectively blocking the potential for estrogen stimulation. Tamoxifen binding further prevents critical ER conformational changes that are required for the association of co-activators.This therapy produced clinical remission in patients with breast cancer positive for ER, differently from tumour with low or undetectable levels of these receptors. Additionally,tumour cells expressing hormone receptors presented a better response to

hormone therapy and patients demonstrated higher survival, both disease-free as overall, and better prognosis. Although hormone therapy has revolutionized the management of breast cancer and results have improved substantially in these patients, the optimal management remains a significant challenge.

Type of Study: Ananalytical study

Source of Data: Patients at a tertiary care centre who were referred there from the department of surgery.

Duration of Study: Over a period of eighteen months
Study Subjects: Patients diagnosed with breast cancer with the necessary approval from the ethical committee of concerned institutes.

Inclusion Criteria:

- Women within the age of 30-80 years diagnosed with breast cancer.
- Women who were free of malignancy from the control group

Exclusion Criteria:

1. Cases who had been operated for breast lesions.
2. Cases of benign breast lumps
3. Cases having any other form of malignancy

Results

Demographic Characteristics:

In the present study, the majority of the controls belonged to the age group of fewer than 40 years (41.66%), followed by 61-70 years (26.66%). The mean age of the controls in the present study was 50.88 ± 14.94years. In the present study, we classified the study cases according to the type of breast carcinoma diagnosed. Majority of the cases had invasive ductal carcinoma (78.33%), followed by invasive lobular type of carcinoma (13.33%) and 8.33% cases had mixed type of breast carcinoma.

Nodal Status

In the current study, majority of cases presented with N1-level nodal status i.e. metastases to the movable ipsi lateral level I, II axillary lymph node(s) among 65% of the cases, followed by N0 level nodal status i.e. no regional lymph node metastases among 31.66% cases. 3.33% of cases presented with N2 level Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted;

Staging

In the current study, when we staged the cases of breast cancer, we observed that the majority of the cases presented with stage III (50%), followed by stage II (45%). 3.33% of cases presented with stage IV and only one case (1.66%) presented with stage I.

Diagnostic Accuracy of Serum Total PSA

In the present study, we evaluated the diagnostic accuracy of the serum total PSA levels as a prognostic marker among the cases. It was observed that its sensitivity was 61.66%, Specificity was 83.33%, Positive predictive value was found to be 78.72%, Negative predictive value was found to be 68.49% and finally the total diagnostic accuracy was found to be72.5%.

ER/PR Status of Cases

In the present study, we evaluated the ER/PR status of the study subjects. We observed that 61.66% of cases were found ER-positive,whereas 53.33% of cases were found PR positive.

Discussion

Serum PSA Levels And Its Association With The Cases Serum Free PSA Vs Serum Total PSA

Immunofluoro metric and immuno histochemical studies, west ernblotting, chromato-graphic analysis and molecular analysis have shown that PSA is expressed in breast milk,breast cyst fluid and in benign and malignant breast tumour.Emerging new diagnostic and prognostic markers may help greatly in the early detection of malignancy as well as in developing newer therapeutic protocols that may reduce morbidity and mortality in breast carcinoma patients. The presence of PSA in some breast cancer cells has prompted investigations into the clinical applications of this marker as an adjunctive tool in the prognostic assessment and management of breast carcinoma.

In the current study, we measured the serum PSA levels among cases and controls.We observed that the mean serum total PSA levels among cases was 0.0105
± 0.007, while the mean serum total PSA level among controls was 0.0048 ± 0.0036.We compared the same levels with the help of student's t-test, we observed that the difference was statistically significant (The t-value is 5.53853. The p-value is < 0.00001).

61.66% of cases found to be positive for serum total PSA marker, while16.66% control found positive for serum total PSA. We analyzed the observed difference between the findings using the chi-square test, and it was found statistically significant (Chi-square statisticis 25.4969. The p-value is **<0.0001**).

In the current study, we could not measure free PSA levels. Only total PSA levels were measured.

Diagnostic Accuracy of Serum Total PSA

In the present study, we evaluated the diagnostic accuracy of the serum total PSA levels as a prognostic marker among the cases. It was observed that its sensitivity was 61.66%, Specificity was 83.33%, Positive predictive value was found to be 78.72%, Negative predictive value was found to be 68.49% and finally the total diagnostic accuracy was found to be72.5%.

In a study conducted by **Kavitha S et al,** PSA was positive in 13.8% of cases without metastasis and absent in all cases with metastasis and was positive in 23.5% of patients with stage II disease and absent in cases with Stage III/IV disease. Though not statistically significant, PSA positivity was associated with the absence of metastasis and earlier stage of breast cancer and hence a favourable prognostic factor. Yu et al showed that PSA positive breast carcinoma cases differed significantly with PSA negative cases with regard to tumour stage–PSA positivity was associated with earlier-stage disease.

Whereas, **Razavi et al** found 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)[67]

SUMMARY

The present study was conducted to study the association of PSA levels with breast cancer & clinical applicability of PSA in breast cancer diagnosis & correlation between raised PSA levels in breast cancer patients and ER/PR positivity.

We found that the mean age of the cases in the present study was 54.11±12.84 years and the mean age of the controls in the present study was 50.88 ± 14.94 years. Majority of the cases had invasive ductal carcinoma (78.33%), followed by invasive lobular type of carcinoma (13.33%) and 8.33% cases had mixed type of breast

carcinoma.

61.66% of cases found to be positive for serum total PSA marker, while16.66% control found positive for serum total PSA. We analyzed the observed difference between the findings using the chi-square test, and it was found statistically significant. Hence we evaluated the diagnostic accuracy of the serum total PSA levels as a prognostic marker among the cases. It was observed that its sensitivity was 61.66%, Specificity was 83.33%, Positive predictive value was found to be 78.72%, Negative predictive value was found to be 68.49% and finally the total diagnostic accuracy was found to be 72.5%.

CONCLUSION

The current study concludes that:

1. In the present study, we found 61.66% of cases found to be positive for serum total PSA marker, while16.66% control found positive for serum total PSA.

2. In this study,we could not measure free PSA levels among any cases.

3. It was observed that its sensitivity was 61.66%, Specificity was 83.33%, Positive predictive value was found to be 78.72%, Negative predictive value was found to be 68.49% and finally the total diagnostic accuracy was found to be72.5%.

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