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Original Research Article

# A Comparative Study of Serum VEGF (Vascular Endothelial Growth Factor) with Tumor Markers CEA and CA 15-3 in Breast Cancer

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**Abstract**

Angiogenesis is essential for tumor growth. Vascular endothelial growth factor (VEGF) is one of the most potent angiogenic cytokines. In breast cancer, tumor VEGF has been shown to have a good correlation with relapse-free survival. The aim of this study was to determine the relation of serum VEGF levels to the various indices of breast cancer and known tumor markers CEA and CA15.3. Preoperative serum VEGF levels were determined in 110 women with breast lesions in which 67 were diagnosed with benign breast disease while 43 were having malignant lesions. The serum VEGF levels of the patients with malignant lesions as a group were significantly elevated compared with those of the benign group ($P < 0.05$). VEGF levels was seen elevated in patients with metastatic disease, higher histological grade, increased tumor size and higher staging.

**Conclusions:** Preoperative serum VEGF detects breast cancer with a sensitivity of 83.5 % seen in present study it is reasonable to say that high VEGF levels is associated with disease progression, so determination of serum VEGF can predict the aggressiveness of tumor which can further determine the outcome of breast cancer disease. Therefore, from present study it appears that serum VEGF levels could be promisimg prognostic test for tumor activity in breast carcinoma patients.



## Introduction

Cancer breast is the most common malignancy in women worldwide, it accounts for 23% of total new cancer. It is the main cause of death in women due to malignancy. In 2018, it was estimated that 627,000 women died from breast cancer (WHO 2019)

In India it is the most common cancer among women according to National cancer registry programme 2011 report. [1] Worldwide it is the most common non-skin cancer in females. [2] By the year 2030 global burden of breast cancer will be more than two million every year. [3] At present

the mortality rate for breast cancer in India is 11.1per 10,000. [4]

There are many factors that are responsible for the development and amelioration of breast cancer. Cancer development involves proliferative signal changes, suppressor genes inactivation and suppression of apoptosis allowing continuous cell growth and immortality leading to new angiogenesis, invasion and metastasis formation [5].

Angiogenesis, the formation of new blood vessels, is necessary for the growth and metastasis of solid tumors. [6] Vascular endothelial growth factor(VEGF), also referred to as vascular permeability factor, is a multifunctional cytokine that stimulate endothelial growth and angiogenesis, probably by stimulating nitric oxide(NO) activity. [7,8] Recently, it has been suggested that VEGF expression correlates with the degree of angiogenesis and plays a predominant role in breast cancer prognosis. [9,11]

In this study our aim was to evaluate the significance of Serum VEGF as a tumor marker in breast cancer as well as its comparison with already established tumor markers serum CEA and CA 15.3.

## Material and Methods

In the present study we analysed serum samples from 110 female patients with histologically confirmed breast lesions comprising of 43 malignant and 67 benign breast lesions.

Out of total 43 malignant breast tumors 24 cases had metastatic disease while 19 cases were non metastatic.

Patients receiving hormonal therapy or chemotherapy and those with diabetes mellitus, lung diseases, renal failure, infectious diseases and synchronous secondary malignancies were also excluded.

The 10 ml of blood samples for CEA, CA 15-3 & Serum VEGF collected in Plain vials between 9:00 AM and 11:00 AM to minimize possible circadian variations after overnight fasting. The blood samples were collected in sterile plain vacutainers. The samples were allowed to coagulate at $+4^0$ C from 60 to 240 minutes, centrifuged at 2000 g for 10 minutes and then stored at $-20^o$ C. Samples were then analysed for serum VEGF, CEA , CA 15-3.

The VEGF was measured in serum by sandwich ELISA method using commercial reagents (Human VEGFA ELISA Kit-96T, Cat#ELK1129, Lot #203 47215031,Make: ELK Biotechnology), purchased from Clementia Biotech.The test principle applied in this kit was Sandwich enzyme immunoassay.

The serum CEA and CA 15-3 were determined by commercial enzyme immunoassay adapted to an Abbott architect anlyzer.

The levels of CEA, CA 15-3 and Serum VEGF were correlated with lymph node status, presence or absence of metastasis and histological grading.

### Statistical Analysis

The results were presented as mean ± SD. The paired t test were used in statistical analysis. A p value less than 0.05 was considered significant.

## Results

The present study reported two observations, first statistical difference of serum levels of VEGF in benign versus malignant breast lesion was found to be highly significant with statistical analysis of ($p<0.05$). Second, there was a significant difference in levels of serum VEGF of lymph node positive and lymph node negative status of malignant cases ($p<0.05$). These results suggest that progression and dissemination of invasive breast cancer is accompanied by an acclivity of circulating VEGF. The serum levels of VEGF was also seen raised with tumor staging, histological grading and tumor size.

**Serum levels of biomarker according to various clinico-pathological state in breast cancer patients and benign cases**

| Factors | | Number of Cases | VEGF (pg /ml) | CA 15-3 (U/ml) | CEA (ng/ml) |
|---|---|---|---|---|---|
| Benign | | 67 | 96.3±48.2 | 6.8±4.4 | 1.8±0.3 |
| Malignant | | 43 | 234.5±12.8 | 29.6±14 | 10.5±8 |
| | | | p <0.0001 | p<0.0001 | p<0.0001 |
| Menopause Status in malignant group | Premenopausal | 05 | 268.1±24.6 | 33.5±6.4 | 7.7±0.4 |
| | Postmenopausal | 37 | 285.3±20.9 | 35.3±2.2 | 15.1±0.8 |
| | | | p =0.0979 | p=0.2012 | p=0.4292 |
| Tumor size | <2 cm | 13 | 196.6±17.5 | 22.6±6.3 | 9.2±0.9 |
| | >2 cm | 30 | 289.2±16.9 | 39.4±5.7 | 16.8±2.4 |
| | | | p <0.001 | p <0.001 | p <0.001 |
| Nodal status | Negative | 19 | 135.2±50.5 | 17.5±11 | 8.2±1.2 |
| | Positive | 24 | 292.7±10.8 | 35.2±15 | 17.1±2.9 |
| | | | p <0.0001 | p=0.0001 | p<0.0001 |
| Staging | I, II | 18 | 128.5±28.8 | 34.3±8.8 | 7.9±0.7 |
| | III, IV | 25 | 301.3±12.7 | 42.9±6.5 | 16.9±2.6 |
| | | | p <0.001 | p=0.0007 | p <0.001 |
| Histological grading | I | 9 | 136.8±26.7 | 20.1±0.7 | 6.6±1.5 |
| | II | 20 | 211.1±14.6 | 25.4±5.9 | 9.8±0.8 |
| | III | 14 | 310.6±10.6 | 33.3±7.3 | 16.6±4.2 |
| | | | p <0.0001 | p=0.0015 | p=0.0005 |

While there was no significant change in serum VEGF levels in relation to menopausal status. The difference among serum CEA levels of benign and malignant lesions was significant, but showed a higher p value in case of menopausal status. Serum CEA levels were seen with significant raise in case of tumor size, nodal status, tumor staging and histological grading. The serum CA 15-3 levels were also significantly raised in malignant lesions than of benign lesions. Serum CA 15-3 levels were also seen with significant raise in case of tumor size, nodal status, tumor staging and histological grading. While there was no statistically significant correlation with menopausal status.

The obtained cut off point by using ROC curve was 138.25 pg/ml with a sensitivity and specificity of 86.05% and 83.58% respectively. Considering that the AUC indicated a moderate to good diagnostic value with relatively good sensitivity, it is reasonable to say that high VEGF levels is associated with disease progression, so determination of serum VEGF can predict the aggressiveness of tumor which can further determine the outcome of breast cancer disease.

## Discussion

Recent studies have shown that growth of malignant tumors , particularly solid tumors is associated with an increase in vascularization through the process of angiogenesis. Blood vessels in solid malignant tumors arise from two sources. One of these sources is the existing network of the body, morphologically mature and active blood vessels, while the second source is capillaries formed through the process of vascularization.

The basic vascularization of solid tumors is associated with the presence of factors which stimulate tumor growth, and in particular with vascular endothelial growth factor (VEGF).

VEGF increases the permeability of the endothelium of blood vessels, which in turn allows for cancerous cells to penetrate the vessel walls and begin the process of metastasis, even in very distant organs.

VEGF is also involved in metabolic processes such as increasing the activity of phospholipase C, stimulating the secretion of von Willebrand factor from endothelial cells and has an effect on the synthesis of collagenases and on the activity of plasminogen.

VEGF is a potent mitogen that is involved in the process of angiogenesis in many human tumors. It has been suggested that the expression of VEGF in tumor tissue is an independent prognostic indicator for breast cancer patients regardless of the nodal status, elevated serum levels of VEGF have been reported in patients with various types of cancer and found to be associated with worsened prognosis. It has been reported that dissemination of breast cancer may be accompanied by an elevation of serum VEGF levels. This findings in our study were similar we found a higher serum VEGF levels in patients with metastatic disease than in those with non-metastatic disease. Serum VEGF levels were similar in patients who attained complete remission and in control subjects. Elevated serum VEGF levels seem to be linked to the extent of disease in breast cancer.

In the present study , serum VEGF was estimated in over 110 patients with breast lesions, out of which 43 were malignant and 67 were benign breast lesions.

Serum VEGF levels increased significantly in breast cancer patients (234.5± 12.8) as compared to benign cases (96.3± 48.2) ($p<0.0001$)

Our results were in agreement with Heer et al [12] and Nervana et al [13] who stated that tumor induce blood vessels growth by secreting various growth factors & that serum VEGF was increased in breast cancer patients than control, they reported that the main cause of high VEGF level measured in the serum is breast tumor tissue. Out of 43 cases 24 were lymph node positive and 19 were lymph node negative. Significant higher values of VEGF levels were observed in lymph node positive cases than non-metastatic cases ($p<0.001$)

The malignant disease group was further subdivided into groups comprising of malignant disease with lymph node metastasis with serum VEGF levels 292.7±10.2 pg /ml, while other group included patients with malignant disease but no lymph node metastasis with serum VEGF levels 135.2±50.5 pg/ml.

In a study done by Thielmann A et al [14], the serum VEGF levels in malignant lesion group was 154± 124.7, the levels were higher in lymph node positive cases while lower levels were seen in lymph node negative cases. The results of our study are in agreement with these findings. Similar results were also obtained by Salven P et al [15] whose findings associated increased VEGF levels and vascularization of solid, malignant tumors having median level of VEGF 186 pg/ml and 57pg/ml in metastatic and benign lesions respectively. Byrne et al [16] also concluded that VEGF has a crucial role in breast cancer progress as it is increased in early and late stages of cancer when compared to normal. A study done by Ahmed LA et al [17] found promising levels of serum VEGF levels in malignant lesions (496.31±309.09) with node positive (669.22±264.65), node negative (445.07±304.72) and benign group (173.39±165.64).

Kirwan et al [18] suggested that serum VEGF was the major angiogenic factor in breast carcinoma and the most important factor involved in tumor spread and disease progression.

Serum CEA levels in node positive cases were significantly higher than in node negative cases ($p<0.0001$) Ghaffari et al [19] reported that serum CEA is the preferred marker for the detection of metastases in axillary lymph nodes.

Kuhajda et al [20] also found a strong relationship between elevated CEA in tumors more than 3 cm which were associated with axillary metastasis. Bruce et al [21] found elevated plasma CEA in a small percentage of patients with early breast cancer and in about 60% cases with the disease disseminated to regional lymph nodes. Similar findings were reported by Faridi et al [22] and Pathak KA et al [23] where serum CEA levels differed significantly with nodal status and the number involved nodes; also, patients with distant metastasis had significant rise in serum CEA levels.

In the present study a significant correlation between serum VEGF levels and positive lymph nodes. These results are in accordance with Nervana et al [13] and Mohammad et al [24] which showed VEGF was associated with lymph node metastasis in breast cancer as VEGF induced lymphangiogenesis was strongly correlated with dissemination to regional lymph nodes. These results were also in agreement with Enas et al [25] who found that serum VEGF was strongly linked with grade III tumor, large tumor size > 2 cm, ER – ve status, positive lymph node and + ve HER2-neu.Also these findings are similar to Spill et al [26] who stated that in breast cancer, low serum VEGF level was linked with low cancer stage, low grade tumor, and negative lymph node status.

In our present study the elevation of CEA and CA 15-3 are significant in relation to the lymph node status of patients, but no correlation was found between serum VEGF, CEA, CA 15-3.

In malignant group, no significant correlation was found between serum VEGF and menopausal status of patients which was in accordance of Enas et al [25] and Nervana et al [13] which had similar results.

Forteva et al [27] found no significant relationship of serum CEA in patients with breast cancer with the menopausal status of the patient. Luqmani et al [28] also obtained similar results and there was no significant relationship of serum CEA with the menopausal status of the patients with the breast cancer. In our study 5 patients with breast cancer were premenopausal and 37 were postmenopausal, and the menopausal status was not significantly related to the serum CEA levels.

Consistent with other studies Brekelmans et al [29] and Lumachi et al [30] our study shows no significant correlation between menopausal status of breast cancer patients and serum CA15-3 levels, this was in contrast of Dehaghani et al [31] found the relation statistically significant.

In the present study we found the high serum levels of VEGF in relation to tumor size which was in agreement with study by Nervana et al [13] and Sledge et al [32] However , studies carried out by Stimfl et al [33] found no such relationship.

Serum CEA levels were found significantly higher in tumors of more than 2 cm in size which was in consonance with Kuhajda et al [20] who found a strong relation between elevated CEA in tumors more than 3 cm.

On correlating the serum CA 15-3 levels with tumor size a significant correlation was found which concorded with results of Chourin et al [34] who found a significant correlation between CA 15-3 and tumor size.

The current study showed that serum VEGF levels were significantly raised with advanced tumor stages. These results were in agreement with Nervana et al [13] Enas et al [25] and Spill et al [26] who found that serum VEGF was strongly linked with higher stages. Serum CEA and CA 15-3 also showed significant correlation with tumor staging in present study which was in accordance with Hosseini et al [35]

Patients with higher grade of tumor showed a significantly higher levels of VEGF in the serum. This finding was in accordance

with Nervana et al [13] and Xiaowei et al [36]

Serum CEA and CA 15-3 showed significant correlation with histologic grade of tumors but to a lesser degree than serum VEGF. Our findings were in accordance with Spill et al [26] and Enas et al [25] but was not with Park et al [37]

One of the main criteria for assessing the diagnostic value of tumor marker is the sensitivity /specificity chart. The diagnostic value can be assessed by AUC of ROC curve. A tumor marker with AUC= 1 can completely differentiate between patients with breast cancer and one with benign breast disease, meanwhile AUC=0.5 that there was no difference between the level of biomarker in these groups. Current study obtained AUC= 0.845, sensitivity and specificity of 86.05% and 83.58% respectively, and which indicates a good diagnostic value of the studied marker. Similar findings were observed by Ahmed LA et al [17] who reported a sensitivity of 95.71% and specificity of 45.0%. Indra et al [38] in their study, obtained a sensitivity of 83.3% and specificity of 66.7% which further corroborated our findings. Study conducted by Wardhani et al [39] showed sensitivity and specificity for VEGF as 76.6% and 75.0% respectively. All the above findings indicated a good diagnostic value for serum VEGF in breast cancer patients. However, study done by Heer et al [12] found a sensitivity of 62.1% for serum VEGF in detecting breast cancers.

## Conclusion

Our results showed that high VEGF levels are associated with disease progression, so determination of serum VEGF can predict the aggressiveness of tumor which can guess the outcome of the breast cancer disease. Therefore, it seems from the present study that serum VEGF levels could hold promising prognostic value for tumor activity.

Further studies in large population are needed to investigate the underlying biological mechanism, the prognostic value of serum VEGF in various breast cancer types and its significance in assessing the treatment response.

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