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Assessing the clinical utility of CEA, CA 125 and CA 15.3 in human breast carcinoma: A study among Tamil women

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Abstract

Carcinoma of breast is a common disease that kills more number of women worldwide. A sensitive and specific serum marker would be of great help in early diagnosis of malignancy as well as in monitoring the response of cancer patients to therapy. The alterations in the serum level of 3 tumour markers namely, CEA, CA 125 and CA 15-3 at various stages of the disease were investigated in breast cancer patients of Tamil Nadu using Chemi Luminescence Immuno Assay (CLIA) method. The diagnostic significance of the markers were also analysed in three stages of disease namely, non-metastatic, metastatic and post-treatment levels. The results indicated increased levels of all the 3 tumour markers in breast cancer patients. Furthermore, marked elevation was found in patients with metastatic breast disease. Significant reduction was also observed in the post treatment level of CA 15.3. The findings suggest that among the 3 markers analysed, CA 15.3 is indeed helpful for early diagnosis and for predicting the disease response to therapy in breast cancer patients.

INTRODUCTION

Breast carcinoma is one of the most common neoplasms in women and is the leading cause of cancer related deaths worldwide [1]. For optimum management of these patients, assay of certain biochemical markers is necessary. Carcinoembryonic antigen (CEA), an oncofetal glycoprotein, is expressed in normal mucosal cells and over expressed in adenocarcinoma [2]. Cancer Antigen 125 (CA 125) is a glycoprotein normally expressed in coelomic epithelium during fetal development. Elevated levels are associated with epithelial ovarian cancer and in other malignancies [3]. Cancer Antigen 15.3 (CA 15.3) is a large transmembrane glycoprotein which is frequently over expressed and aberrantly glycosylated in cancer [4]. The above mentioned tumour markers are endogenous products that are produced at a greater rate in cancer cells [5]. There is no single, ideal tumour marker for breast cancer. Combination of tumour markers has been investigated to increase the sensitivity of detecting metastasis by biological markers [6]. Hence the present study was undertaken to compare the clinical usefulness of the 3 conventional serum markers CEA, CA 125 and CA 15.3 in breast cancer patients of Tamil Nadu, at various stages of the disease.

MATERIALS AND METHODS

Patients

In this prospective study, female breast cancer patients belonging to the age group 30-70, from various hospitals of Tamil Nadu were included. Patients were excluded if any other malignancy was known from their past history. They were divided into 4 groups

Control (Group I): consisted of members of the public with no prior history of breast cancer or other cancer related disorders (n=25).

Experimental groups:

Group III: non- metastatic group comprising of breast cancer patients with no evidence of metastasis (n=25).

Group II: metastatic group consisted of breast cancer patients who at the time of diagnosis revealed evidence of distant metastases (n=25).

Group IV: Post treatment group comprising of patients who had undergone either chemotherapy/ radiotherapy or hormone therapy for their disease (n=25).

Clinical details of patients were given in Table 1. Informed consent was obtained from every patient.

Sample collection

Blood samples were collected by venous arm puncture into heparinised tubes and serum was separated by centrifugation at 3000 rpm for 15 minutes. It was stored at 4ºC for further use.

Marker assay

CEA, CA 125 and CA 15-3 were all assayed using the commercially available Acculite™ Chemi Luminescence Immuno Assay (CLIA) Kit (Monobind Inc. USA). The antigen contents were determined by comparing the result with a standard curve generated by standard solutions provided in the kit.

Statistical analysis

The data obtained in the present study was subjected to statistical analysis by SPSS version 14. Standard deviation was done to obtain accuracy. Student's t test was used to compare the significance of means, between control and experimental groups at 5% level.

RESULTS

The results of the 3 tumour markers namely CAE, CA 15.3 and CA 125 in breast cancer patients, healthy subjects and post treatment groups were shown Figures 1 and 2. The level of CEA was found to be significantly elevated in breast cancer patients than that of the healthy subjects (23.20±5.59 ng/ml). Among the breast cancer patients, the level was significantly elevated in metastatic group (45.27±7.53 ng/ml) than the non-metastatic group (35.97± 6.38ng/ml). In post-treatment group (38.37±4.88

Table 1. Clinical details of the study population of breast carcinoma patients

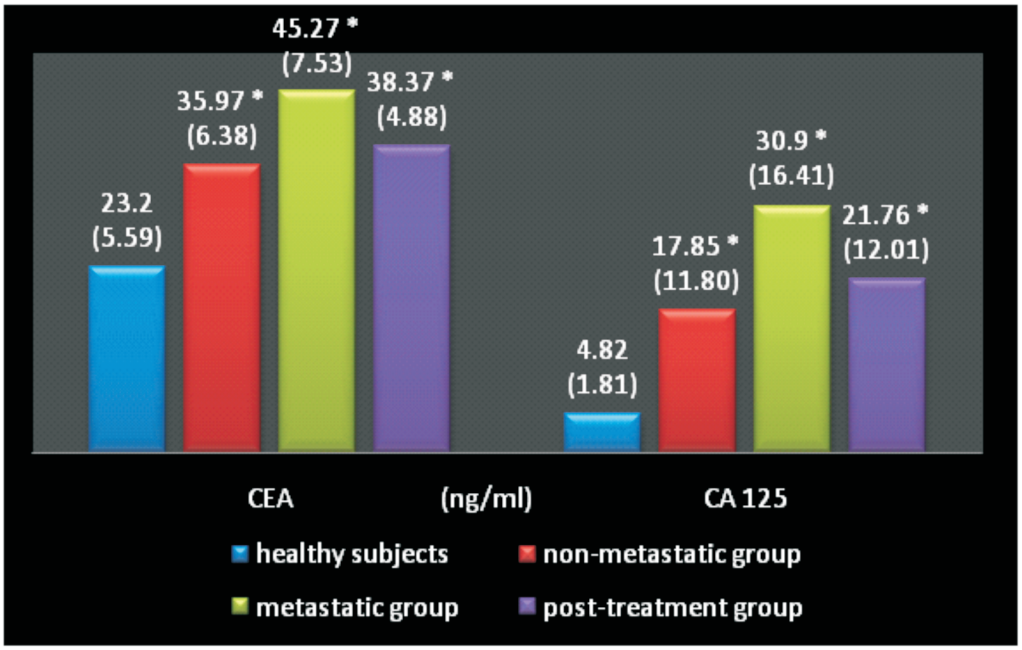
S. No.	Parameter	Numbers
1.	Age range in patients	30-70 yrs
2.	Age at menarche	12-16 yrs
3.	Menopausal status of patients	
	Pre menopausal	45 Nos
	Post menopausal	30 ,,
4.	Clinical status of patients	
	Non- metastatic breast carcinoma	25 ,,
	Metastatic breast carcinoma	25 ,,
	Post-treatment group	25 ,,

Table 2. Distribution of tumour marker levels of CEA, CA 125 and CA 15.3 in healthy subjects and breast carcinoma patients

Tumour markers / Study groups	CEA (ng/ml)			CA125 (ng/ml)			CA 15.3 (U/l)		
	< 35	35-50	>50	< 10	10-40	>40	<20	20-50	>50
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Healthy subjects	25 (100)	NIL	NIL	25 (100)	NIL	NIL	25 (100)	NIL	NIL
Non-metastatic group	9 (36)	16 (64)	NIL	9 (36)	16 (64)	NIL	6 (24)	19 (76)	NIL
Metastatic group	4 (16)	13 (52)	8 (32)	6 (24)	9 (36)	10 (40)	2 (8)	11 (44)	12 (48)
Post-treatment group	5 (20)	20 (80)	NIL	6 (24)	19 (76)	NIL	18 (72)	7 (28)	NIL

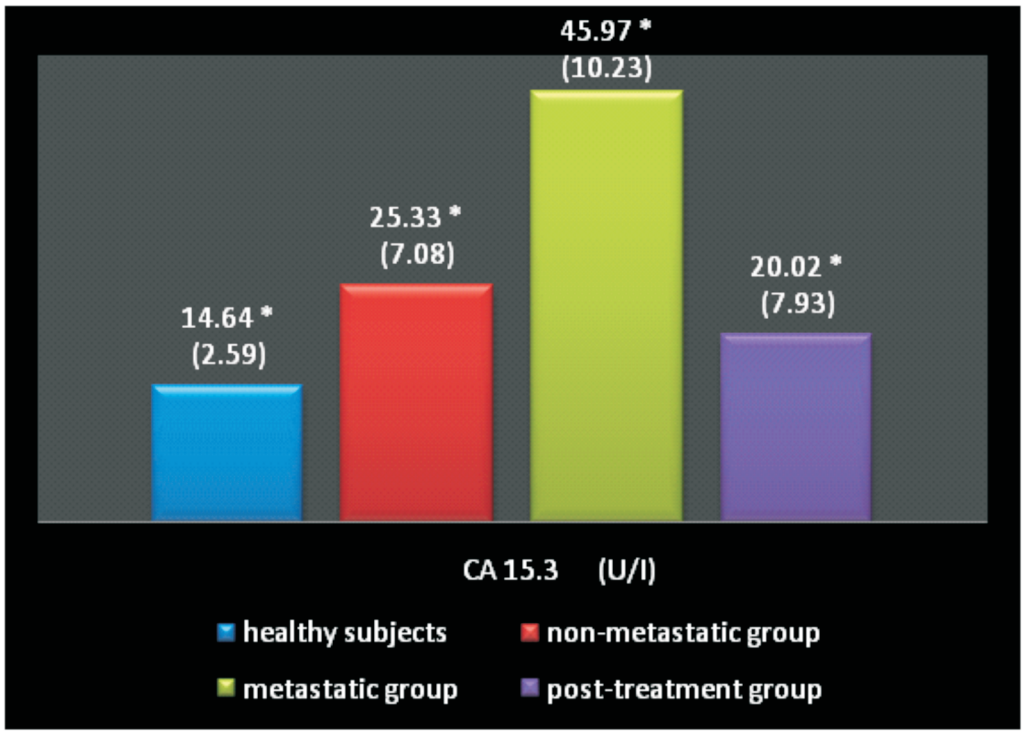
ng/ml) the level was significantly lower when compared with the metastatic group but higher than the normal subjects. The same trend was also observed in CA125 and CA15.3. Significantly increased levels of CA125 were seen in non-metastatic group (17.85±11.80 ng/ml), metastatic group (30.90±16.41ng/ml) and post-treatment group (21.76±12.01) than that of the healthy subjects (4.82±1.81ng/ml). In case of CA 15.3, increased levels of tumour marker were seen in non-metastatic group (25.33±7.08U/l) and metastatic group (45.97±10.23 U/l) than that of the healthy subjects (14.64±2.59 U/l). However in post-treatment group (20.02±7.93 U/l) the level was significantly higher than the control but lower than the breast cancer patients.

Table 2 gives the distribution of 3 tumour markers in healthy and breast cancer patients. In case of CEA, in control group, all 25 subjects (100%) have cut-off values <35ng/ml. In non-metastatic and metastatic group, the percentage of subjects having marker values in the range of 35-50 ng/ml were 16% and 13% respectively. 8% of subjects in metastatic group have values >50 ng/ml. In post treatment group 80% was seen in 35-50ng/ml range and the rest 20% with >35ng/ml of CEA. In case of CA125, the percentage of subjects with <10 ng/ml of tumour marker in control, non-metastatic , metastatic and post-treatment groups were 100, 36, 24 and 24% respectively.16% of non-metastatic, 36% of metastatic and 76% of post-treatment subjects were seen



Values are expressed as mean * Values are significant at 5% level S.D. in brackets

Fig. 1 Serum levels of tumour markers- CEA, CA 125 in healthy subjects and breast carcinoma patients



Values are expressed as mean * Values are significant at 5% level S.D. in brackets

Fig. 2 Serum levels of tumour marker- CA 15.3 in healthy subjects and breast carcinoma patients

to have CA125 level in the range of 10-40 ng/ml. In addition, metastatic group have 40% of subjects with cut-off value >50ng/ml. In case of CA15.3, 100% of control, 24% of non-metastatic group, 8% of metastatic group and 72 % of post treatment group have cut off value >20U/l. 19% of non-metastatic group, 11% of metastatic group and 7% of post-treatment group have CA15.3 values in the range 20-50 U/l. 48% of metastatic group was seen with cut-off value >50 U/l

DISCUSSION

In the present study 3 tumor markers were analyzed namely, CEA, CA 15.3 and CA 125 among 75 breast cancer patients divided into 3 groups namely, non-metastatic, metastatic and post-treatment groups with 25 patients in each group. The same were also analyzed in control group comprising of 25 healthy subjects. CA 125 was found to be significantly elevated in breast

cancer patients than that of healthy subjects (Figure 1 and 2). Patients with advanced breast carcinoma were found to have increased levels of serum CA 125 than that of non- metastatic disease. Previous studies have shown elevated CA 125 in patients with advanced breast cancer [7, 8]. CA 125 levels also correlated with disease activity as it was found to be more associated with metastatic breast disease. Out of the 25 patients with metastatic disease, 19 have shown increased serum concentration of CA 125 (76% sensitivity) whereas in patients with early stage of disease only 64% was found to be CA 125 positive (Table 2). This suggests that CA 125 may be a useful marker in patients with advanced breast cancer.

Similar pattern of variation was observed in case of the serum levels of CEA. In case of CEA as shown in Table 2, values >35 were found in 64% and 52 % of patients in non metastatic and metastatic breast cancer patients respectively, with 32% > 50 in metastatic group. The problem with CEA however, is the fact that it is not often abnormal. In this study only 64% (16 out of 25 samples) had values higher than the normal. Hence this marker seems to be less sensitive and not appropriate for screening as supported by Safi *et al.* [9].

CA15.3 was found to be significantly elevated in breast cancer patients than that of the control. Patients with metastatic disease seem to express higher level of CA15.3 in their serum than that of non- metastatic disease. Sensitivity of CA 15.3 was found to be 76 % in non-metastatic disease and 92% in metastatic disease. This clearly indicates that metastasising breast cancers are associated unequivocally with increased levels of this antigen. This is in accordance with the finding of Safi *et al.* [9]. American Society of Clinical Oncology [10] have reported a positive correlation between CA 15-3 concentrations and disease stage as evidenced by this study. Pathologic values > 20U/ml for CA 15-3 was determined in 76% and 44% of non metastatic disease and metastatic group respectively. Values above 50 U/ml were found in 48% of patients with metastatic disease. Even in CEA/ CA 125 negative samples CA15-3 has proved to be positive. Hence this marker was found to be sensitive than the other two markers.

In the present study, after therapy (group VI), the level of CEA and CA 125 were found to be significantly elevated than the normal subjects whereas in case of CA 15.3 significant reduction has been observed. In 72 % of cases the serum level of CA 15.3 was well within the normal pathological range of < 20 U/l whereas only in 28% elevated values were found. Thus it can be used for monitoring the disease to therapy. This positive correlation of clinical presentation and marker behaviour was mentioned by Ertl [11]. Thus, this marker can be used for early diagnosis of breast cancer, for monitoring the course of disease and for tumour follow up.

CONCLUSION

The summary of the findings of the present study revealed that all the three serum tumour markers CAE, CA 15.3 and CA 125 were significantly elevated in non-metastatic and metastatic breast cancer patients of Tamil women. CA 15.3 was more sensitive than the other 2 markers because it was found to be positive even in CEA/ CA 125 negative samples. CA 15. 3 may be used as a clinically useful indicator of breast cancer metastases and can also be used for monitoring the response of patients to therapy.

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