RESEARCH COMMUNICATION

Evaluation of Tumor Markers in Southern Indian Breast Cancer Patients

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Abstract

Tumor markers are biochemical substances elaborated by tumor cells either due to the cause or effect of malignant processes. Here we investigated serum levels of cancer antigen (CA15.3) and carcino embryonic antigen (CEA) in 153 pre and post operated southern Indian breast cancer patients (stage-I- 45, stage-II-55, stage-III- 53 samples) and 37 normal controls.Patients with malignant lesions had high frequencies of abnormal CA15.3 in stage-II (46.3%) and stage-III (42.6%) and of CEA in stage-III (64.3%). The mean serum levels of CA 15.3 in all stagesdropped significantly after 9 days of mastectomy, but this was not the case with CEAeven after 27 days. At 27 days after mastectomy, values for CA 15.3 had again significantly increased. Tumor size, node metastases (≥4) and stage of disease (≥III), but not patient's age, were associated with higher preoperative levels. Evaluation of CA15.3 and CEA values showed sensitivities and specificities of 35.3% and 18.3% and 95.6% and 62.7%, respectively. Based on these findings we conclude that correlation with CA 15.3 was superior to CEA in terms of stage of disease, so that this is the more powerful marker for detecting lesions and determining response to treatment.

Key Words: Breast cancer - tumor marker - diagnosis - cancer antigen - carcinoembryonic antigen

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Introduction

Breast cancer has a major impact on the health of women (Winer et al., 2001). Breast cancer is the most common female-related cancer that causes of death among women aged between 40-45 years (Bland et al., 2005). Despite modern instrumentation and radiological scanning techniques to identify a tumor mass, the need exists for more practical and sensitive labo-ratory method, which can indicate the presence of any neoplasm and provide a quantitative estimate of changes associated with growth, spread or dissemination and the-rapy (Muthuswamy and Raste, 2000). Despite intensive efforts to develop improved therapeutic regi-mens like Mammography, Ultra-sound and MRM, the mortality rate for cancer of the breast has remain-ed stable over several decades, ex-cept when diagnosed in early stages (Roisman et al., 1994).

Tumor markers are biochemical substances elaborated by tumor cells either due to the cause or effect of malignant process. These markers can be normal endogenous products that are produced at a greater level in cancer cells or the products of newly switched on genes that remained quiescent in the normal cells. A tumor marker produced by the tumor and, when present in significant amounts indicates the presence of a cancer. They may be present as intracellular substrates in tissues or may be released in to the circulation and appear in serum (Malati, 2007). CEA is one of the first tumor marker to be identified and characterized (Sikorska et al., 1988). Several studies have reported that positive serum CEA levels at the time of primary breast cancer diagnosis may represent a negative prognostic parameter (Molina et al., 1998). The availability of the CA 15.3 tumor marker in the last decade has greatly reduced the value of CEA in breast cancer management. The recent studies discourage the routine use of the CEA assay because of its low sensitivity in both early and advanced diseases, compared with CA 15.3 (Fiorella et al., 2001).

In the last few years, the development of several monoclonal antibodies has made it possible to identify new tumor associated antigens, which have opened new vistas for the use of simple laboratory tests in the diagnosis and follow-up of breast cancer patients. However, these tests differ in terms of sensitivity and specificity. Moreover, although the monoclonal antibodies that detect breast cancer associated antigens seem to react with different epitopes of a common antigen, those antigens associated with breast cancer are not simultaneously expressed in human breast cancer.

Previous studies (Vizacarra et al., 1996; Fiorella et al., 2001) in breast cancer patients suggest that CA 15.3 is clinically more useful than CEA, although the percentage of elevated levels vary from one study to another, fundamentally depending on cut-off value, tumor

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stage and clinical situation of the patient. In the present study we analyzed the serum CA 15.3 and CEA markers in pre and postoperative breast cancer patients, and related levels of both markers to patient's outcome using both univariate and multivariate analysis.

Materials and Methods

A total of 191 females were taken into this study (aged 29-76 years; mean age 44.9 ± 9.06) who underwent breast cancer surgery at Mahatma Gandhi Memorial hospital, Warangal, Andhra Pradesh, India between April 2006-April 2009. All the samples were taken by venous puncture and transferred to ice. After clotting, the blood samples were centrifuged. The serum was transferred to another tube and stored at -20˚C until processed (within one month). CEA and CA 15.3 levels were determined by enzyme immunoassay method (BioCheck, Inc Diagnostic Kit; ELISA, Antuos 2010 Germany). Samples were obtained before and after operations.

The serum levels of CEA below/ equal to 5 ng and level of CA 15.3 below/ equal to 35 U/ml was considered normal. The patients in this study were divided into two groups, including 38 normal controls (healthy individuals), who showed no evidence of disease after a complete physical examination and laboratory work up(chest x-ray, bone scan and sonography) and 153 breast cancer patients, 45 had stage I, 55 had stage II, 53 had stage III disease. Patient characteristics are shown in Table 1. Three more samples were taken after mastectomy from metastatic breast cancer patients. The second sample was drawn 3 days, third sample was drawn 9 days and the fourth sample was drawn 27 days postoperatively. The patients with metastatic breast cancer were further evaluated for their family history, clinical nodal status, tumor size and age. Statistical analysis was performed using ANOVA followed by Newman keuls test. Difference was regarded as statistically significant when p value <0.05. All calculations were performed with statistical package, Graph-Pad Prism, version 4 for Windows (San Diego, CA, USA).

Table 1. Clinical Characteristics of the 153 Patients

Characteristics (n)		No. of patients (%)
Age (mean ± SD)		44.9±9.06 (29-76)
Family history	Yes	37 (24.2%)
	No	116 (75.8%)
Clinical nodal status	N0	72 (47.1%)
	N1	41 (26.8%)
	N2	26 (17.0%)
	N3 and above	14 (9.3%)
Clinical stage	I	45 (29.4%)
	II	55 (36.0%)
	III	53 (34.6%)
CA 15.3 levels (mean ± SD)		16.9±6.45 (4.0 - 98)
Normal	(<35 U/ml)	99 (64.7%)
Abnormal	(>35 U/ml)	54 (35.3%)
CEA levels (mean ± SD)		1.8±1.2 (0.6 - 41)
Normal	(< 5 ng/ml)	125 (81.7%)
Abnormal	(>5 ng/ml)	28 (18.3%)

CA15.3, cancer antigen; CEA, carcinoembryonic antigen

Table 2. Mean ± SD CA 15.3 and CEA Levels in Normal Controls and Patients with Metastatic Breast Cancer

Patients (n)	Preoperative (mean ± SD)	Postoperative(mean) 3days	9days	27days
CA 15.3				
Controls (38)	16.9 ± 6.45			
Breast cancer (153)				
stage I (45)	18.4 ± 7.52	18.3	14.9*	17.4*
stage II (55)	31.9 ± 6.32***	31.2	17.1***	21.63**
stage III (53)	47.2 ± 12.2***	46.9	20.1***	35.3***
CEA				
Controls(38)	1.80 ± 0.98			
Breast cancer (153)				
stage I (45)	1.95 ± 1.17	1.90	1.91	1.70
stage II (55)	2.69 ± 1.70	2.71	2.55	1.92
stage III (53)	5.88 ± 4.96**	5.80	5.63	4.07

CA15.3, cancer antigen; CEA, carcinoembryonic antigen; ***p < 0.001; ** p < 0.01; * p < 0.05

Table 3. Sensitivity of Tumor Markers

Marker	Total samples	Elevated samples	Sensitivity (%)
CA 15.3	153	54	35.3
CEA	153	28	18.3

CA15.3, cancer antigen; CEA, carcinoembryonic antigen

Table 4. Frequency of Elevation of Tumor Markers

Marker	Stage	Frequency of elevation (%)
CA 15.3	Stage- I	11.1
	Stage- II	46.3
	Stage- III	42.6
CEA	Stage- I	7.1
	Stage- II	28.6
	Stage- III	64.3

CA15.3, cancer antigen; CEA, carcinoembryonic antigen

Results and Discussion

The mean ± SD serum levels of CA 15.3 and CEA in healthy individuals were 16.9 ± 6.45 (range 4-35 U/ml) and 1.8 ± 0.98 (range 0.2-5 ng/ml) respectively. Mean ± SD preoperative CA 15.3 and CEA levels were 18.4 ± 7.52 U/ml in stage I; 31.9 ± 6.32 U/ml in stage II; 47.2 ± 12.2 U/ml in stage III (range 4-98 U /ml) and 1.95 ± 1.17 ng/ml in stage I; 2.69 ± 1.70 ng/ml in stage II; 5.88 ± 4.96 ng/ml in stage III- (range 0.6-41), respectively. Elevated CA 15.3 and CEA levels were identified in 54 (35.3 %) and 28 (18.3 %) patients respectively. Patient demographics are presented in Table 1.

After clinical staging was performed, the premastectomy CA15.3 and CEA values were evaluated according to the stage. The increase in CA15.3 with increasing stage of the disease was statistically significant, but no statically significant correlation was observed between the stage of the disease and CEA's (Table 2). The mean ± SD values for tumor for different stages of the disease and characterization of patients according to cut-off values are shown in Table 1. Among the two serum markers, CA 15.3 levels were significantly higher in breast cancer patients than in normal patients (Table 2).

Patients had elevated levels of CA 15.3 and CEA in three stages. However the frequency of preoperative abnormal CA 15.3 and CEA levels were varying from stage-I to stage III. Elevated CA 15.3 levels were noted in 11.11% of stage I, 46.3% of stage II and 42.6% of stage III patients, whereas CEA in 7.14% stage I, 28.6% of stage II and 64.3% of stage III patients had elevated levels respectively (Table 4). The frequency of elevated CA 15.3 levels were higher in stage II and III and in CEA stage III, respectively when compared to stage I samples (Table 4). CA 15.3 and CEA levels, as a diagnostic marker had a sensitivity of 35.3%, 18.3 % (Table 3) and a specificity of 95.6%, 62.7%, respectively. According to the serum levels of CA 15.3 it was more sensitive and specific in breast cancer patients than CEA (Arsalan et al., 2000). These findings support our results.

Following mastectomy, CEA and CA15.3 levels were evaluated thrice. The mean serum levels of CA 15.3 dropped slightly 9 days after mastectomy, however, 27 days later the values were significantly increased (Table 2). The mean serum levels of CEA dropped slightly 27 days after mastectomy.

Serum levels of both CA 15.3 and CEA were associated with host tumor burden such as larger tumor size, more lymph node metastasis (≥4), and advanced stage, on the other hand no association was found with preoperative levels of tumor markers and the patient's age. Same type of findings observed by Park et al (2008). In contrast to this findings, Lumachi et al (2000) reported correlation with the age of patients.

Patients with stage II and III disease having abnormal CA15.3 values and CEA in stage III having abnormal values when compare to those with stage I disease. There is not much difference in CEA levels of stage I and II patients when compared to normal levels. Elevated CA15-3 levels are more common in metastatic breast cancer patients than CEA (James, 2001). We noted a greater frequency of abnormal CA15-3 values in patients with malignant lesions than CEA. This finding is consistent with the report of Fiorella et al. (2001).

Women with a history of invasive breast cancer are at risk of developing metastatic disease. As screening programs identify more patients with early stage of disease and as the number of women diagnosed with invasive ductal carcinoma continuously rises, there will be more women living with a personal history of breast cancer (Winer et al., 2001), but in our study only 37 out of 153 patients (24.2%) have family history.

In this study we observed that CA 15.3 was more sensitive (34.6%) when comparedwith CEA (18.2%) in detecting the disease. We also observed that treatment (surgery) results in reduction in CA 15.3 than CEA levels, which coincides more with the response to the treatment. CA 15.3 was a significantly more powerful marker for determining response to treatment. Similar results also observed by Fiorella et al. (2001).

In conclusion, our study shows the lower sensitivity of serum CEA levels compared with CA 15.3 in detecting breast cancer. The study also provided evidence for recommending the serum CEA should not be used in management of this disease.

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