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Assessment of Elevated Serum Tumor Markers Carcinoembryonic Antigen (CEA) and Cancer Antigen 15-3 (CA15-3) among Patients with Different Subtypes of Metastatic Breast Cancer

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Abstract

Background: Cancer antigen 15-3 and carcinoembryonic antigen are used in clinical and laboratory diagnosis of metastatic breast cancer. Previous studies have noted conflicting results about the association between carcinoembryonic antigen and cancer antigen 15-3 in metastatic breast cancer. The present study examined serum tumor marker levels of carcinoembryonic antigen and cancer antigen 15-3 among patients with different subtypes of metastatic breast cancer.

Methods: In this cross-sectional study, we assessed metastatic breast cancer patients diagnosed between 2005 and 2012 who referred to academic Hospitals affiliated with Mashhad University of Medical Sciences. The patients were selected by systematic randomization sampling. Demographic, clinical, pathological, and therapeutic data were collected from patients' hospital records. Statistical analyses were performed by Statistical Package for the Social Sciences version 16.0 software.

Results: A total of 298 eligible patients enrolled in the study. Patients' median age was 48.39±12.57 years. Elevated serum levels of carcinoembryonic antigen were identified in 65.17% of patients and cancer antigen 15-3 in 57.29% of patients. Based on molecular subtype categorization, 109 (39.5%) patients were human epidermal growth factor receptor 2 negative and 105 (38.0%) patients were in the luminal group. There was no significant correlation between serum carcinoembryonic antigen and cancer antigen 15-3 with subtypes of the tumor. The most common sites for metastasis were bones and liver, respectively. However, there was no significant correlation between serum carcinoembryonic antigen and cancer antigen 15-3 with the site of metastasis. There was a significant association between serum carcinoembryonic antigen level and stages IIA and IV.

Conclusion: One of the most significant findings of the current study was the increased serum carcinoembryonic antigen and cancer antigen 15-3 levels in most metastatic breast cancer participants. We postulate that regular measurement of serum cancer antigen 15-3 and carcinoembryonic antigen could be useful for earlier detection and prediction of outcomes.

Keywords: Breast cancer, Metastasis, Cancer antigen 15-3 (CA15-3), Carcinoembryonic antigen (CEA)

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Introduction

Breast cancer is the most common malignancy in women and is one of the leading cause of cancer related mortality. In addition, breast cancer related death is the second cause of cancer mortality after lung cancer.[1] However, in Iranian women, breast cancer is a leading cause of cancer related mortality.[2] Breast cancer is composed of many biologic subtypes that have distinct behaviors and responses to therapy, which predict their clinical outcomes.[3,4] Genetic studies have shown several distinct breast cancer subtypes that differ markedly in prognosis and the therapeutic targets they express. These include triple negative (TN), human epidermal growth factor receptor 2 (Her2) positive, and luminal subtypes.[5-7] Several different tumor-specific antigens are usually generated by tumor cells or by host cells in response to tumor genesis. These unique antigens are termed tumor markers and can be used for cancer screening and monitoring.[8] The sensitivity and specificity of an individual specific tumor marker cannot be efficacious enough; rather, the combination of multiple tumor markers can be more helpful as a clinical prognostic tool in oncology. Cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) are used in clinical and laboratory diagnosis of metastatic breast cancer.[9] Based on gene expression profiling, breast cancer is categorized into 5 subtypes – luminal A, luminal B, human epidermal growth factor receptor 2 (HER2 negative), luminal B (HER2 positive), and TN. Triple negative is also classified into basal-like and null subtypes.[9] Evidence shows that the main cause of mortality in breast cancer is due to metastasis.[9,10]

Although some studies recognize the significance of serum CEA and CA15-3 levels associated with metastatic breast cancer, the diagnostic value of these two tumor markers levels is unclear.[11] Many reports claim that serum CEA and CA15-3 levels are independent of breast cancer stages.[9,12] In contrast, among patients with metastatic breast cancer, serum tumor marker elevation is more efficacious than in individuals with primary breast cancer. Some researchers have stated that there is a significant association between CA15-3 serum level and different stages of metastatic breast cancer. The aim of this study was to investigate the serum levels of CEA and CA15-3 in different subtypes of metastatic breast cancer.

Materials and Methods

Patient selection

This cross-sectional study was performed on 298 metastatic breast cancer patients diagnosed between 2005 and 2012 who were seen at 3 academic Hospitals affiliated with Mashhad University of Medical Sciences (MUMS). Participants were enrolled in the study by systematic randomization sampling. We retrospectively reviewed the patients' hospital-based records and extracted demographic data of age, gender, weight, and height. We also gathered the following clinical, pathological, and therapeutic data from patients' files: hormonal medication, estrogen receptor (ER), progesterone receptor (PR), tumor grade, tumor stage, subtypes of metastatic breast cancer, date of breast cancer diagnosis, site of primary metastasis, and level of serum tumor markers that included CEA and CA15-3 at 3 months before recurrence and after recurrence.

Inclusion and exclusion criteria

Inclusion criteria consisted of the presence of metastatic breast cancer, signed written consent for study participation, and presence of complete and available clinicopathological and demographic data. Data on serum tumor markers CA15-3 and CEA were available at the time of metastatic breast cancer diagnosis. As an important inclusion criteria, we have considered that the CEA and CA15-3 serum levels are often elevated in gastritis, gastric ulcer, bronchitis, cholangitis, liver cirrhosis, tuberculosis, diverticulitis, sarcoidosis, and systemic lupus erythematosus. Therefore, patients with these disorders were not included in this study. Unavailable and incomplete hospital records were considered to be exclusion criteria. World Health Organization defined criteria

Table 1. Correlation between serum CA15-3 and CEA levels and clinicopathological characteristics.

Characteristics	N (%)	CA15-3(ng/ml)			CEA(U/ml)		
		Positive	Negative	*P*-value	Positive	Negative	*P*-value
Age (years)*							
<35		29	12	0.481	21	15	0.893
>35		160	90		136	102	
Tumor markers							
CA15-3	130.55±235.1Ω						
CEA	53.72± 21.41Ω						
Tumor type**							
Primary	204 (69.6)	123	77	0.308	104	86	0.604
Metastatic	86 (29.3)	2	1		2	1	
Recurrent	3 (0.1)	59	24		47	30	
Histological grade**				0.647			0.267
I	14 (9)	10	3		10	3	
II	81 (52.2)	49	28		39	35	
III	60 (38.8)	38	20		31	25	
Molecular subtype**							
Luminal A	105 (38)	64	39		57	38	
Luminal B	14 (5)	8	6	0.871	8	6	0.100
Basal-like	48 (17.5)	31	16		16	29	
HER2−enriched	109 (39.5)	70	36		65	35	
Metastasis*							
Bone		73	37	0.43	54	50	0.168
Liver		45	14	0.47	41	13	0.002
Brain		17	13	0.319	11	17	0.460
Lung		25	26	0.010	25	24	0.343
Metastatic sites*				0.276			0.361
Single		161	92		134	105	
Multiple		28	10		23	12	
Estrogen receptor*				0.049			>0.99
Positive		55	72		72	55	
Negative		50	107		90	67	
Familial history of breast cancer*				0.814			0.651
Positive	22 (7.4)	13	8		11	10	
Negative	276 (92.6)	175	94		146	106	
Menopausal status*				0.006			0.500
Pre-menopause	167 (56)	118	46		79	73	
Post-menopause	131 (44)	71	56		78	44	

CA15-3: Cancer antigen 15-3; CEA: Carcinoembryonic antigen; HER2: Human epidermal growth factor receptor 2; ER: Estrogen receptor; *: Fisher's exact test was used to evaluate the difference between CA15-3 and CEA respectively; **: Chi-square test was used to evaluate the difference between CA15-3 and CEA respectively Ω: Mean±SD

for histopathological diagnosis and breast carcinoma categorization and we used WHO criteria for these purposes. We also used the Nottingham combined histological grading system for tumor grading. Based on the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system, we identified the clinical typing and staging of the malignant tumors.

Tumor analysis marker

We measured the concentration of serum tumor markers with an automated immune-analyzer system and chemiluminescent immunoassay for CEA (ADVIA Centaur, Bayer HealthCare LLC Diagnostic Division, NY, USA) and CA15-3 (VITROS ECi Immunodiagnostic System, Ortho Clinical Diagnostics, Inc., NY, USA). Based on patients' records, we identified 5 subtypes of breast cancer – luminal A (ER+ or PR+, HER2- and Ki67 <14%), luminal B (ER+ or PR +, HER2- and Ki67 >14%), luminal C (ER+ or PR+, and HER2+), HER2- enriched (ER-, PR- and HER2+), and basal-like (HER2+, ER-, and PR-). Serum CA15-3 levels more than 30 U/ml and CEA levels more than 2.5 ng/ml were considered to be

Table 2. Correlation between serum tumor marker levels and molecular subtype.

				CA15-3(U/ml)			CEA(ng/ml)		
Molecular subtype*	**Positive**	**Negative**	***P*- value**	**>100**	**<100**	***P*- value**	**>10**	**<10**	***P*- value**
Luminal A	62	49	0.087	44	67	0.506	33	70	>0.99
Basal-like	21	26	0.524	33	14	0.506	9	36	0.078
HER2−enriched	47	58	0.256	30	57	0.12	37	63	0.172

HER2: Human epidermal growth factor receptor 2; CA15-3: Cancer antigen 15-3; CEA: Carcinoembryonic antigen.; *: Fisher's exact test was used to evaluate the difference between CA15-3 and CEA respectively

positive. We considered those cases which were -1 and +1 as HER2 negative. The fluorescent in situ hybridization (FISH) test was used for individuals with 2+ HER2 results. FISH positive and HER2 more than 2+ patients were considered to be HER2 positive.

Statistical analysis

We used the Statistical Package for the Social Sciences (SPSS) version 16.0 software for statistical analyses. Patients' data were divided into 2 categories, descriptive and analytical. The Kolmogorov–Smirnov test was used to assess for normal distribution of the variables. The student's t-test was used to investigate the relationship between quantitative variables where there was normal distribution of the data. In cases of non-normal data distribution, the Mann-Whitney U test was used. The relationship between qualitative variables was evaluated with chi-square and Fisher's exact tests. $P<0.05$ was considered statistically significant.

Ethics

The Medical Research Ethics Committee of MUMS reviewed and approved this study (ethical code: IR.MUMS.REC.1392.90).

Results

A total of 298 eligible patients enrolled in this study. Patients' median age was 48.39±12.57 years. At the time of diagnosis, 56% of patients were premenopausal. Serum CEA had a mean baseline value of 53.72±21.41 ng/ml and for CA15-3, the mean baseline value was 130.55±235.1 U/Ml , respectively. Patients had a median weight of 65.5±14.2 kilogram (kg) and a median height of 155.3±6.97 centimeter. Table 1 lists the patient and tumor characteristics.

The findings showed positive serum CA15-3 levels in 71.9% of premenopausal patients and in 55.9% of post-menopausal patients. At the time of diagnosis, 44.5% of patients suffered from metastasis (Table 1).

We observed elevated CA15-3 serum levels in 65.17% of patients and elevated CEA serum levels in 57.29% of patients . The most common sites for metastasis were bone and liver metastases, respectively. However, we observed no statistical difference in CA15-3 serum levels among patients with bone metastasis and those without bone metastasis. It was more complicated about liver metastasis. The analyses showed that CEA, as a tumor marker, could play a more specific role for individuals with liver metastases (P=0.002). Based on Fisher's exact test, CA15-3 possessed lower sensitivity for lung metastasis compared to other places of metastases (P=0.01).

There was a significant association between serum CEA level and tumor stages II and IV. In the serum CEA level comparison among different stages, we observed significant correlation between stages II and IV. This comparison was performed based on the Mann-Whitney test between each two stages (P=0.019).

There was no significant correlation between serum CEA and CA15-3 levels with tumor subtypes, hormonal medication, family history, ER, grade of tumor, and menopausal status. A comparison of ER positive and ER negative individuals showed significant differences in tumor markers at serum CA15-3 levels greater than 100 U/ml. This difference could be observed more in the ER positive subtypes compared to the ER negative group (P=0.049).

There was a statistically significant association between ER positive patients and serum CA15-3 levels greater than 100 U/ml (P=0.049). A total of 109 (39.5%) participants ranked as the HER2-

enriched subtype (Table 2). According to the pathology reports, none of the patients had stage IB tumor. Of note, the serum CEA level had a sensitivity of approximately 57.3% for detecting metastasis. We divided the patients into 2 groups: more than 35 years of age and less than 35 years of age. There was no significant correlation between serum CEA and CA15-3 tumor marker levels and age groups. Further analysis showed that the prevalence of ER positive participants with visceral metastasis was statistically higher than another group (The group with bone metastasis) (P=0.049).

Discussion

We found increased serum CEA and CA15-3 levels in most metastatic breast cancer patients, which was similar to the results of other studies.[9-12] The patients with elevated tumor marker serum levels had worse outcomes compared to those with normal serum levels. Patients who had elevated tumor marker serum levels before surgery also showed more frequent elevation at recurrence.[9]

Our finding might indicate that these tumor markers could be used to assess diagnosis and prognosis. A meta-analysis projected that the levels of CEA and CA15-3 in serum could be used to predict breast cancer diagnostic value and provide a prognostic modality for breast cancer detection.[8] The European Group on Tumor Markers has suggested that serum CEA and CA15-3 levels can play an important role in early detection and management of breast cancer.[13] Several studies have shown that these tumor markers are independent factors for prognosis,[8,10,12,14] early diagnosis,[8,10] and screening[8,12] of metastatic breast cancer.

In the current study, we found no significant association between CEA and CA15-3 serum levels and subtypes of metastatic breast cancer. In contrast to our finding, Yerushalmi et al.[15] presented a significant correlation between elevated serum tumor marker levels and different breast cancer subtypes, sites of metastasis, and prognosis; these differences could be due to the larger sample size of their study and different numbers of molecular subtypes.

Prior reports noted controversial results about the association between CEA and CA15-3 and metastatic sites. Given et al.[16] have confirmed that CA15-3 is a significant predictor for recurrence of bone and visceral metastasis. Geng et al.[11] reported elevated serum CA15-3 levels in recurrent bone metastasis. Although the results of current study showed increased CA15-3 levels in patients with bone metastasis, there was no significant association between CA15-3 and metastatic sites. Similar to the Lee et al. study,[9] we found a significant correlation between serum CEA level and liver metastasis. These findings might help clinicians to use CEA as a more specific serum marker for liver metastasis.

In this study, there was a significant association between the serum level of CEA and metastatic breast cancer stages IIA and IV. We observed that the CA15-3 serum level was not associated with different tumor stages. However, in a meta-analysis report, there was a significant association between serum CA15-3 level and all stages.[8] These conflicting outcomes might be due to fewer patients in different stage groups in the current study.

We also assessed the menopausal status and noted a significant association between menopausal status and CA15-3 serum level. A meta-analysis has indicated that menopausal status can affect the serum level of tumor markers.[8] Other studies have considered the effect of menopausal status on tumor marker serum levels, but did not claim any significant association,[10,11] which could be due to the smaller sample sizes of these studies.

Incomplete patients' hospital-based data would be considered one of the limitations of current study. In addition, the cross-sectional study design did not enable follow-up of these patients. We suggest that other study methods, such as cohort studies, should be performed. In the current study, we assessed the effect of CEA and CA15-3 serum levels independently in diagnosis and prognosis. It would be better to assess CEA and CA15-3

serum levels in combination with other tumor markers to achieve more reliable consequences for diagnosis and prognosis of metastatic breast cancer.

Further researches should be undertaken to investigate the effects of age, tumor size, and body mass index (BMI) on metastatic breast cancer patients. In addition, variations in cut-off values for tumor marker evaluations can lead to different results. Thus, it can be suggested that we need to determine certain cut-off value in future studies.

Conclusion

This investigation has identified that the level of CEA and CA15-3 serum tumor markers increased significantly in metastatic breast cancer patients. Because of decreased cost and easy measurement of these tumor markers, assessment of CEA and CA15-3 serum levels can be used as a clinical implication for earlier detection of recurrence and prognosis in metastatic breast cancer patients.

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Conflict of Interest

None declared.

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