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Correlation of cancer antigen 15-3 (CA15-3) serum level and bony metastases in breast cancer patients

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Abstract

Background: Cancer antigen 15-3 (CA15-3) is a common tumor marker and the serum level of this tumor marker is evaluated during the treatment period (periodically) in breast cancer patients. Assuming that the elevated serum levels of this tumor marker can be a potential risk, this study was conducted to determine the association between CA15-3 and bone metastasis and CA15-3 and metastasis spreading rate in breast cancer patients.

Methods: In this study, 70 women with the mean of age 51.69 (10.77) years who suffered from breast cancer were studied by performing both bone scintigraphy and measuring CA15-3. Independent sample t test, Fisher's exact test, Spearman rho correlation, and logistic regression were used for inferential section. To determine the new cross section, Roc curve and coordinates of the curve were applied. Also, significance level was set at $p<0.05$. Data were analyzed by SPSS 16 software.

Results: There was no difference among patients in age ($p=0.123$). Assuming the CA15-3 (≥ 30 U/mL) as a potential risk, there was no association between CA15-3 and bone metastases ($p=0.167$). Based on Spearman's rank correlation coefficient, there was no significant correlation between CA15-3 and metastasis spreading rate ($r=-0.07$, $p=0.851$). Based on ROC curve and Youden's J statistic index, the new cutoff was pointed at CA15-3 ≥21.76 Unit/mL, which correlated with bone metastases ($p<0.001$).

Conclusion: This study found a decreased cutoff point at CA15-3 (≥21.76) against 30 (routine value). Based on CA15-3 (≥21.76), there was a correlation between bone metastases and CA15-3, indicating that patients with CA15-3 (≥21.76) were most likely to experience bone metastases.

Keywords: Breast cancer, Bone scintigraphy, CA15-3, Bone metastases

Conflicts of Interest: None declared
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Introduction

Breast cancer is the most common malignancy in women worldwide (One every 9 women is statistically involved.). About 13% of American women are afflicted with breast cancer, with the mortality rate of 3% (1). Despite the increased prevalence of breast cancer, statistics show a descending mortality pattern due to screening and treatment developments in the last 2 decades (2). Invasive ductal carcinoma is the most common type of breast malignancy

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↑What is "already known" in this topic:
Tumor marker CA15-3 is considered as an important concern in realm of breast cancer oncology. Generally, CA15-3 serum level ≥30 ([CA15-3] ≥30) is deemed as a risk. Due to ascending statistics on breast cancer, it seems that the high-risk threshold of CA15-3 should be deeply taken under consideration.

→What this article adds:
In this study, the relationship between CA15-3 and bone metastases was investigated in patients with breast cancer, and it was suggested that patients with CA15-3 ≥21.76 U/mL are at risk of bone metastases compared to those with CA15-3 (≥30 U/mL).

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which includes 75% of all cancerous cases. The rate of lymphatic metastasis is considerable in this type of tumor (3). Spreading of initial breast tumor by lymphatic or blood vessels would lead to distant metastasis, especially bone metastases (73% in general) that associates with pain, motion problems, neurogenic disorders, hypercalcemia, and pathologic fractures (4-7). Usually, the more delayed the diagnosis, the more probability of metastasis, including brain, bone marrow, liver, lymph nodes, and lungs metastases) (7). The structure of skeletal system is more attractive to metastasis homing because of hematopoietic activity due to high perfusion and growth factors (8). Generally, lymphatic system plays an important role in distribution of malignant cells, but the tumor marker is helpful in determining the extent of the spread of breast cancer, especially spinal metastases (9, 10). The bone scintigraphy by ^{99m}Tc-bisphosphonates is a well-known method to diagnose bone metastasis (11). To avoid false positive results, a comprehensive patient's history should be taken (12, 13). The CA15-3 tumor marker has been widely considered for the prognosis of bone metastases in patients with breast cancer. CA15-3, a high molecular weight glycoprotein (300-450 kDa), is synthesized by apical surface of epithelial ducts and acinic breast cells and is then secreted in milk normally. In cancerous statue, CA15-3 drains into the blood perfusion because of disrupted breast morphology (14). CA15-3 may be helpful in determining the extent of the spread of breast cancer. A high CA15-3 would be a symptom of metastasis, especially bone metastases. It seems that CA15-3 could be considered as a useful factor in prognosis of bone metastases in related patients (5). Based on bone scintigraphy, patients with breast cancer in stages 1, 2, and 3 will statistically be involved with bone metastasis of 2%, 10%, and 20%, respectively (5). In this study, a survey was developed on CA15-3 in patients with breast cancer to find a correlation between serum level of CA15-3 and bone metastases by either measuring CA15-3 or bone scintigraphy in the same patient.

In this study, the followings were done: (1) measuring CA15-3; (2) performing bone scintigraphy; (3) studying the correlation of CA15-3 and results of bone scintigraphy; (4) studying the correlation of CA15-3 with bone metastases spreading rate in patients suffering from certain metastases; (5) surveying CA15-3 in patients with no metastatic lesions; and (6) measuring CA15-3 in patients with certain bone metastases. The aim of this study was to investigate whether CA15-3 could be used in the prognosis of bone metastases as an available, more economical, and easy to perform method.

Methods

In this study, 70 patients with breast cancer were studied by bone scintigraphy. In all patients, the serum level of CA15-3 tumor marker ([CA15-3]) had previously been measured using chemiluminescence method (ECLIA). Because both procedures (bone scan & serum test) had been requested by related physicians (oncologists) with long treatment, there was no need to obtain the contest of patients. Moreover, patients were notified that their documents were used in this study surreptitiously. Bone scintigraphy is an objective diagnostic method just for visualization of bony metastases. Routinely, whole body bone scintigraphy was performed by ^{99m}Tc-MDP through dual head gamma camera. The evacuated MDP kits (methylene diphosphonate) were purchased from Pars Isotope Co. and bone scintigraphy was performed by Siemens SPECT dual head gamma camera and low energy-high resolution collimator. The results of scintigraphy were interpreted by 2 nuclear medicine physicians who were blind to CA15-3. The results from both bone scan and CA15-3 was extracted from patients' documents to find whether there was a correlation between the serum level of CA15-3 and bone metastasis.

Inclusion criteria were as follow: (1) being female; (2) all patients were pathologically confirmed to have breast cancer; (3) all patients suffered only from breast cancer; and (4) CA15-3 was measured in all patients.

Exclusion criteria were as follow: (1) patients with more than one malignancy; (2) patients who underwent chemo/radiotherapy prior to the study; (3) patients with confusing documents.

For the descriptive section, data were presented as mean (SD) for qualitative variables and frequencies (percent) for qualitative variables. Independent sample t test, Fisher's exact test, Spearman rho correlation, and logistic regression with Hosmer-Lemeshow test were used for inferential section. To determine the new cross section, Roc curve and coordinates of the curve were used. P values less than 0.05 ($p<0.05$) was considered as significant. Data were analyzed by SPSS 16 (SPSS Inc., Chicago, IL) software.

Results

The patients were classified into 2 groups: (1) 22 patients with no bone metastasis (N); (2) 48 patients with bone metastasis (Y). Both groups were assayed based on age, CA15-3, metastases spreading rate, and CA15-3 ≥30 U/mL. Moreover, the cutoff point for CA15-3 was routinely considered at ≥30, which is available in https://emedicine.medscape.com/article/2087491-overview.

Also, the mean number of metastases sites was 2.96 (1.81), with minimum of 1 and maximum of 7. The mean age of the 2 groups are presented in Table 1. Based on independent sample t test, there was no difference between the 2 groups in age (p=0.123).

Considering the cutoff point at ≥30, 8.6% of all patients experienced bony metastases (abnormal) and the rest were

Table 1. Descriptive statistics for age (years) of patients in the 2 groups

Group	Number*	Mean (SD)	Min-Max	p*
(N)	22	48.73(8.87)	34-67	0.123
(Y)	48	53.04(11.45)	35-81	
All patients	70	51.69(10.77)	34-81	

* Based on independent sample t test

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normal (without bony metastases). Also, 6% of group Y were abnormal and 42% were normal; and all patients (100%) in group N were normal (Table 2, Diagram 1).

Distribution of patients with/without bony metastases based on CA15-3 is demonstrated in Graph 1. The area under the curve (AUC) for patients with bony metastases was clearly more than that of patients without bony metastases, but more patients had less than CA15-3 ≥30 U/mL. According to (p=0.167) and Graph 1, serum levels above 30 (for tumor markers) are not considered as appropriate risk factors.

There were no statistically significant differences between the 2 groups at cutoff point ≥30 based on the results of Fisher's exact and t test, indicating that there was no considerable association between CA15-3 and bone metastases (p=0.167).

Based on Spearman's rank correlation coefficient, there was a weak and inverse correlation between CA15-3 and metastasis spreading rate (r=-0.07, p=0.851) (Graph 2).

Introducing a new cutoff could cover the possibility of bone metastasis in patients with breast cancer, which was determined at 21.76 based on Table 3 (coordinates of the curve), with sensitivity of 91.70 and specificity of 91.90, based on ROC curve (Graph 3) and Youden's J statistic index.

The average of CA15-3 for groups N-new and P-new was calculated to be 18.94 (2.01) and 27.05 (4.33), respectively, which should be descripted in abbreviation of N/P-new, the word "new" was used for each group after applying a new cutoff point. Independent sample t test results have shown a significant difference between the 2 groups (p<0.001) (Table 4, Diagram 2). According to p>0.05 for Hosmer-Lemeshow test, logistic regression adjusted for age showed that odds of CA15-3 ≥21.76 in group Y was obviously more than in group N (OR=11.0, p<0.001).

Table 2. Frequency (percent) of [CA15-3]≥30unit/mL(abnormal) in the 2 groups

Group	Abnormal [CA15-3]≥30	Normal [CA15-3]<30	p*
(N)	0 (0.0)	22 (100.0)	0.167
(Y)	6 (12.5)	42 (87.5)	
All patients	6 (8.6)	64 (91.4)	

* Based on Fisher's exact t test

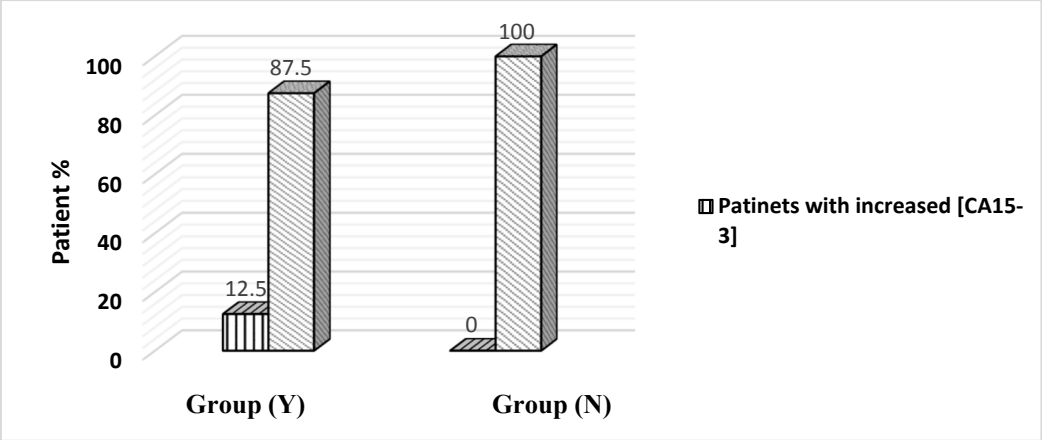
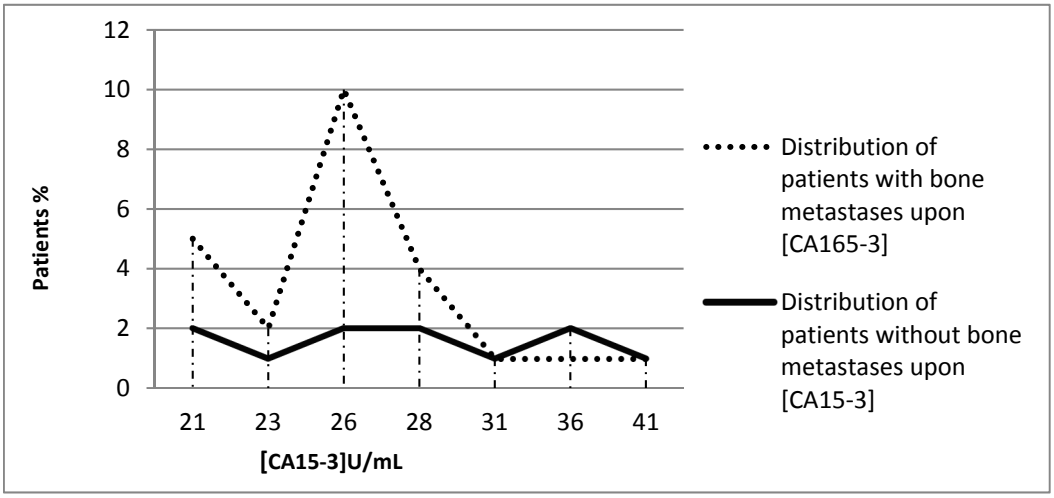


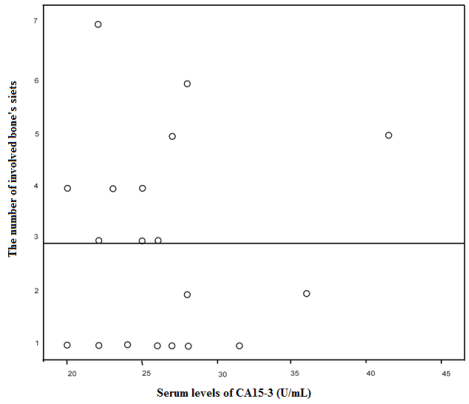
Diagram 1. Percentage of increased (abnormal) and normal levels of CA15-3 in patients with/without bony metastasis based on CA15-3 ≥30



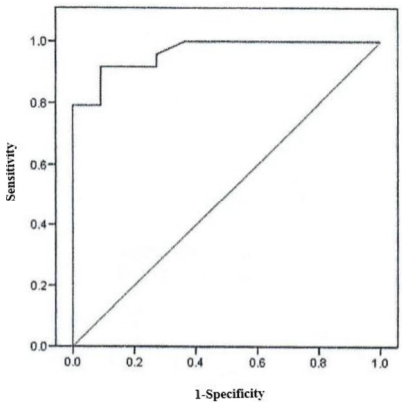
Graph 1. Distribution of patients with/without bony metastases based on serum level of CA15-3 (U/mL)

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Graph 2. Asscociation between CA15-3 and spreading rate of bone metastases (r = -0.07, p = 0.851)



Graph 3. Plotting ROC curve of [CA15-3] to evaluate bone metastases

Table 3. Sensitivity & specificity for different cutoff points in the diagnosis of breast cancer bone metastases

Specificity	Sensitivity	<(U/mL) CA15-3	Specificity	Sensitivity	<(U/mL) CA15-3
0.00%	100%	15.50	100%	79.20%	22.25
9.10%	100%	16.70	100%	79.20%	22.75
18.20%	100%	19.95	100%	75.00%	23.50
27.30%	100%	17.50	100%	70.80%	24.50
36.40%	100%	18.25	100%	54.20%	25.50
45.50%	100%	18.75	100%	41.70%	26.50
36.60%	100%	19.50	100%	29.20%	27.50
72.80%	95.80%	20.05	100%	12.50%	29.75
72.80%	91.70%	20.55	100%	8.30%	33.75
81.80%	91.70%	21.30	100%	4.20%	33.65
91.90%	91.70%	21.76	100%	0.00%	42.30

Table 4. Descriptive statistics for CA15-3 of patients in the 2 groups based on new cutoff points

Group	Mean (SD)	Min-Max	p*
(N-new)	18.94 (2.01)	16.5-22.5	<0.001
(Y-new)	27.05(4.33)	20-41	
All patients	23.01(3.17)	16.5-22.5	

* Based on independent sample t-test

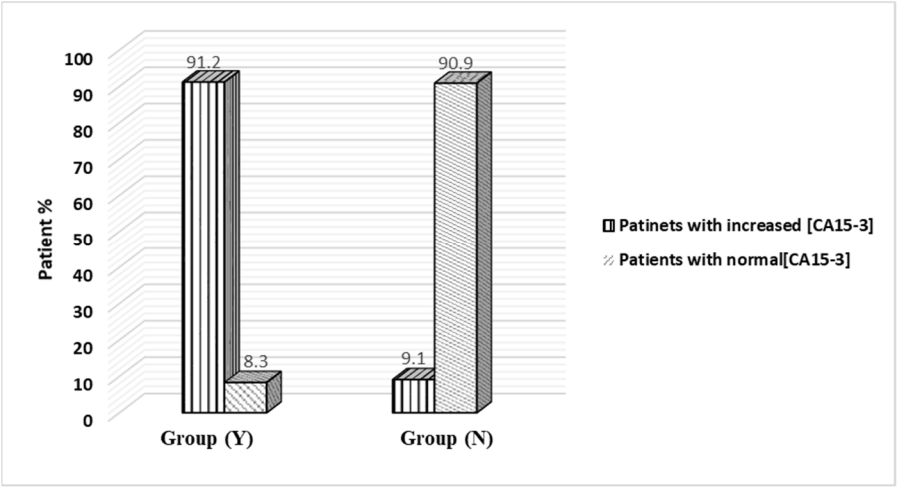


Diagram 2. Percentage of increased and normal levels of CA15-3 in patients with/without bony metastasis based on new cutoff points

Discussion

In this study, the relationship between CA15-3 and results of bone scintigraphy was investigated in the enrolled patients (14). The bone scan was assumed as a gold standard. However, in suspicious bone lesions, MRI is routinely recommended (15). Patients with bone metastases had elevated serum tumor markers (27.05) compared to patients without bone metastases who had a serum level of 18.94. Geng et al reported that elevated serum level of CA15-3 was associated with bone metastases (p=0.017) (16). Also, they found that although elevated [CA15-3] resulted from skeletal metastases, it was not correlated with bone scan findings (17). Zhen-Yu He et al investigated whether there was a correlation between CA15-3 and the risk of site-specific metastases in metastatic breast cancer patients. They reported that increased CA15-3 is a principle predictive

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factor for bone metastases (OR 1.688; 95% CI, 0.992–2.874; p=0.054) (18). Carsten Nieder et al studied different serum levels of CA15-3 to assay their prognostic impact in patients with breast cancer. They found that among all their participants (patients with breast cancer), only 16% had normal level of CA15-3 and abnormal levels caused sporadic metastases, especially bone metastases (19). Biao Geng et al pointed out that CA15-3 is correlated with expansion of metastasis. Also, CA15-3 was more elevated in patients with multiple metastatic site than in patients with a single metastasis (p = 0.001) (20). Contrary to Reference 17, Hoor Fatima et al have shown that not only is serum concentration of tumor marker dependent on bone metastases but is also consistent with bone scan results (In fact, the higher the serum concentration, the greater the number of metastases; multiple metastases were also evident in bone scan) (21). In several studies, different increased amounts of CA15-3 were reported in patients with bony metastases (22-25). Ali HQ et al had assayed CA15-3 with early diagnosis and treatment in patients with breast cancer. They placed great importance on the significant association of CA15-3 and size of primary tumor ($p<0.05$) (26). Another study investigated whether the presurgical CA15-3 could predict the short-term disease-free survival (DFS) in patients with breast cancer. They reported that patients with [CA15-3] (≤30 U/mL) had better DFS than patients with CA15-3 (≥30 U/mL). Moreover, they demonstrated that CA15-3 was positively correlated with the initial tumor size (27). Incoronato et al studied the association between CA15-3 and PET/CT (hybrid positron emission tomography and computed tomography) findings. They reported that increased CA15-3 could be positively associated with PET/CT findings in patients with breast cancer. They also suggested that patients who are in the next phase of treatment with elevated serum marker tumor levels and negative PET/CT results should be seriously considered. Because high serum levels of the tumor marker indicate malignant metabolically active lesions; and as a result, there is a chance of cancer recurrence (28). The correlation between bone scan and CA15-3 found by Younsi et al suggested that in patients with related bone metastases but normal CA15-3, the CA15-3 will increase to reach abnormal levels (29). During the present study, [CA15-3] (≥30) unit/mL did not result in meaningful differences between (N) and (Y) groups. Thus, a new cross section was introduced at the [CA15-3] ≥21.76 unit/mL and led to meaningful and significant differences between (N) and (Y), which was associated with 91.70% and 91.90% sensitivity and specificity, respectively.

Conclusion

In this study, the amount of CA15-3 was significantly more in group Y than in group N. Moreover, there was no meaningful statistic correlation between CA15-3 and bone spreading rate. Also, there was not any meaningful difference between the 2 groups with regards to CA15-3 (>30 U/mL). By introducing a new cross section at CA15-3 (>21.76 U/mL), significant differences were developed, suggesting that CA15-3 could be useful in early prognosis of bone metastases if an effective cross section is considered, specifically in advanced. Furthermore, based on ascending statistics of breast cancer, it seems that the decreased threshold of CA15-3 should be considered instead of ≥30. For instance, CA15-3 (≥21.76 U/mL) seems to be appropriate for the patients in this study despite CA15-3 (≥30 U/mL). In general, in this study and similar surveys, it has been suggested that CA15-3 is a contributory parameter in estimating occurrence of metastases. By an appropriate cutoff point, CA15-3 could be a warning sign for bone metastases in involved patients during the treatment process. In this study, it was found that patients with CA15-3 (≥21.76 U/mL) were most likely to be involved with bone metastases.

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Conflict of Interests

The authors declare that they have no competing interests.

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