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The utility of serum tumor markers CEA and CA 15–3 for breast cancer prognosis and their association with clinicopathological parameters

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ABSTRACT

Background: We aimed to evaluate the association of serum carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) levels with clinicopathological parameters in patients with breast cancer (BC) and their efficiency for the prediction of recurrence.

Methods: The records of 482 female patients with breast cancer diagnosis followed in Medical Oncology and Radiation Oncology clinics of Kartal Dr. Lutfu Kirdar Education and Research Hospital were evaluated retrospectively.

Results: The median age of the patients was 49. CEA levels were significantly higher in postmenopausal patients ($p = 0.022$). There was no association between CEA and CA 15–3 levels and nodal involvement ($p = 0.689$, 0.379; respectively). CEA levels were significantly higher in hormone receptor-positive patients ($p = 0.007$). HER2 negative patients had significantly higher levels of CEA and CA 15–3 ($p = 0.017$ and 0.011, respectively). The evaluation of metastatic patients showed that CEA and CA 15–3 levels before metastasis were significantly elevated ($p = 0.016$ ve 0.008, respectively). There was no relation between the metastasis site and CEA, CA 15–3 levels ($p = 0.936$, 0.201, respectively). Receiver operating characteristic (ROC) analysis was performed to determine the role of CEA and CA 15–3 levels in the prediction of metastasis, and cut-off values were 1.39 ng/ml and 14.54 U/ml, respectively. Sensitivities of CA 15–3 and CEA levels were 82.1% and 88.3%; specificities were 47.3% and 46.2%, respectively.

Conclusions: CEA and CA 15–3 are useful as tumor markers for early diagnosis of metastases, and their elevations were associated with unfavorable clinicopathological parameters of breast cancer patients. Since these markers are considered a cheap and accessible way of predicting breast cancer prognosis, there is an increasing interest in the prognostic value of serum levels of tumor markers in recent years. More sensitive cut-off values for each marker are needed to be validated with further studies.

1. Introduction

A tumor marker found in blood, urine, or body tissues is a biomarker that can elevate the cancer occurrence. It is produced either by the tumor per se or by the host to respond to a tumor [1]. The ideal tumor marker should be specific and sensitive to allow early diagnosis of small tumors or help in screening [2]. Few markers are specific for a single tumor. Most markers are produced from the same tissue type of different tumors [2]. Tumor markers are usually useful in screening the disease progression after surgery and/or initial chemotherapy and radiotherapy [3].

Breast cancer (BC) is the second most frequent cancer after lung cancer[4], caused by genetic and environmental factors. Although newly developed comprehensive therapies have reduced the mortality rate [3], regional and distant recurrences persist as a significant threat to breast cancer patients [4,5].

The clinical importance of early detection of primary and recurrent breast cancer is of considerable clinical importance to guide decision-making for breast cancer treatment to improve survival rates [6]. Tumor markers have been considered a noninvasive cost-effective way of monitoring disease course, determining prognosis, and planning treatment by predicting response to treatment [7]. In combination with

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other clinical parameters, tumor markers for breast cancer could have clinical significance [8]. Traditional prognostic factors for breast cancer are tumor size, axillary lymph node status, lymphatic and vascular invasion, hormone receptor status, and human epidermal growth factor receptor 2 (HER2) expression [9]; not fully reflect the breast cancer prognosis. Plasma carcinoembryonic antigen (CEA) and cancer antigen 15–3 (CA 15–3) are the most frequently used tumor markers in breast cancer [8,10]. CA 15–3; a member of the mucin-1 (MUC-1) glycoprotein family is heterogeneously expressed from different epithelial cell types. On the other hand, it is aberrantly overexpressed in 90% of breast cancer [11]. CEA is a type of cell adhesion molecule, and high levels of CEA in the blood are usually associated with subclinical metastasis of breast cancer [12]. After surgery, monitoring breast cancer patients with only tumor markers was thought to be not sufficient [13]. However, in line with the current interest, a recent study highlighted their clinical utility and velocity in breast cancer surveillance. [14].

In recent guidelines, it is mentioned that serum levels of tumor markers may be used as adjunctive evaluation to contribute to therapy decisions [15]. Despite the ongoing interest in this issue, a limited number of data evaluated the correlation between increased CA 15–3 and CEA levels at recurrence and clinicopathological parameters [16].

In this retrospective study, we analyzed the association of serum CA 15–3 and CEA levels with clinicopathological parameters in patients with BC and the recurrence prediction.

2. Patients and methods

We evaluated the medical records of 482 female patients diagnosed with breast cancer in Medical Oncology and Radiation Oncology clinics of Kartal Dr. Lutfu Kirdar Education and Research Hospital retrospectively. The patients in whom with available clinicopathological and demographic data, including age at diagnosis, tumor histology, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status, staging information were included in the study. The American Joint Committee on Cancer (AJCC, 7th edition) TNM staging system for breast cancer was used for staging. We grouped the subjects into three categories; metastasis at the time of diagnosis, the presence of metastasis during follow-up, and non-metastatic. Patients with metastasis at the time of diagnosis were excluded from the study. The sites of distant relapse were categorized as bone or soft tissue and visceral metastasis. Patients were treated with adjuvant chemotherapy, radiotherapy, or hormonotherapy according to tumor stage and grade after surgery. Follow-up controls were performed with physical and laboratory examination, including serum tumor markers CEA and CA 15–3, and radiological evaluation with abdominal ultrasound, chest radiography, mammography, and bone scan to reveal local or distant relapse. Furthermore, computed tomography, magnetic resonance imaging, and other diagnostic procedures were performed if necessary.

The serum concentrations of serum CA 15–3 and CEA levels were measured at 3 to 6 months. The Microparticle enzyme immunoassay (IMX) method was used for the evaluation of CEA levels and the radioimmunoassay (RIA) method (CENTOCOR). The normal upper limits for CA 15–3 and CEA were 21 U/ml and 5 ng/ml, respectively.

Statistical analyses were performed with SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA). The X^2 and Fishers' exact probability tests were used to compare frequencies. The Mann-Whitney U test was used to compare unpaired data, and Kruskal-Wallis' test analyzed multiple comparisons. Receiver operating characteristic (ROC) analysis was used to determine cut-off levels for tumor markers.

3. Results

The medical records of 482 female patients were retrospectively evaluated. The clinicopathological characteristics were summarized in Table-1. The median age was 49. The percentage of premenopausal and postmenopausal patients was 53.5%; and 46.5%, respectively. We categorized the subjects into three groups according to disease status: the first group included non-metastatic patients during follow-up (n:388, 80.5%), the second group included patients with metastasis during follow-up (n:63, 13.1%), and the third group included patients with metastasis at the time of diagnosis (n:31, 6.4%). Patients in the third group were excluded from the analyses and 451 patients were selected for the study. One hundred thirty-seven patients underwent breast-conserving surgery; 345 patients underwent a mastectomy. Regarding hormonal receptor status, 383 (79.5%) patients were positive; 83 (17.2%) patients were negative, and 16 (3.3%) patients had no data. Among all the cases, 139 (28.8%) patients were HER2 positive, 286 (59.3%) patients were HER2 negative. In 57 (11.8%) of patients, there were no data about HER2 status. Considering the metastasis site, 56.4% of patients had bone or soft tissue, and 43.6% had visceral metastasis.

Table 1
The clinicopathological characteristic of total patients.

Disease status	%	number
Non-metastatic patients during follow-up	80.5	388
Metastasis during follow-up	13.1	63
Metastasis at the time of diagnosis	6.4	31
Menopausal status		
Premenopausal	53.3	257
Postmenopausal		
Operation	46.7	225
Breast conserving surgery	28.5	137
Mastectomy	71.5	345
Pathology		
Invasive ductal carcinoma	90.7	437
Invasive lobuler carcinoma	5.2	25
Other	4.1	20
Status of Hormonal Receptor		
Hormone receptor-positive	79.5	383
Hormone receptor-negative	17.2	83
HER2		
Negative	59.3	286
Score 3 Positive	28.8	139
Unknown	11.8	57
Endocrine therapy		
No therapy	20	97
Aromatase inhibitor	23.2	112
Tamoxifen	47	226
Aromatase inhibitor after Tamoxifen	9.8	47
Metastasis		
Negative	80.5	388
Positive	19.5	94
Site of Metastasis		
Bone	56.4	53
Visceral	43.6	41

The association between tumor markers and clinicopathological parameters of patients included in the study was evaluated (Table-2). CEA levels were significantly higher in postmenopausal patients ($p = 0.022$). Although CEA levels were higher in invasive lobular carcinoma patients, they did not reach statistical significance ($p = 0.70$). There was no association between CEA, CA 15–3 levels, and nodal involvement ($p = 0.689$, 0.379; respectively).

Regarding the relationship of hormone status with CEA and CA 15–3 levels, CEA levels were significantly higher in hormone receptor-positive patients ($p = 0.007$). HER2 negative patients had significantly higher levels of CEA and CA 15–3 ($p = 0.017$; 0.011, respectively).

CEA and CA 15–3 levels were significantly higher in metastatic patients ($p = 0.016$; 0.008, respectively). There was no relation between the metastasis site and CEA, CA 15–3 levels ($p = 0.936$; 0.201, respectively). The relationship between tumor marker levels and histopathological features was summarized in Table-2.

ROC analysis was performed to determine the role of CEA and CA 15–3 levels in the prediction of metastasis, and cut-off values were 1.39 ng/ml and 14.54 U/ml, respectively. Sensitivities of CA 15–3 and CEA

Table 2
The relationship between CA 15–3, CEA levels, and clinicopathological characteristics of patients.

Clinicopathological characteristics of patients (n:451)	CA 15–3 mean ± STD	P	CEA mean ± STD	P
Menopausal status		0.997		0.022
Premenopausal (n:241)	17.08±8.88		1.88±1.83	
Postmenopausal (n:210)	16.61±7.39		2.16±1.63	
Pathology		0.671		0.70
Invasive ductal carcinoma (n:409)	16.82±8.17		1.98±1.79	
Invasive lobular carcinoma (n:20)	17.77±10.78		2.52±1.83	
Tumor stage		0.004		0.060
T1 (n:152)	15.68±7.38		1.74±1.12	
T2 (n:243)	16.69±8.23		1.98±1.84	
T3 (n:56)	22.29±9.86		3.05±2.62	
Nodal involvement		0.379		0.689
Negative (n:178)	16.08±7.92		2.14±2.16	
Positive (n:267)	17.11±8.43		1.97±1.51	
Hormone status		0.662		0.007
Hormone receptor-positive (n:365)	16.66±7.85		2.10±1.84	
Hormone receptor-negative (n:86)	17.86±10.22		1.42±0.91	
HER2		0.011		0.017
Negative (n:271)	17.94±6.73		2.24±2.08	
Score 3 Positive (n:127)	16.42±8.99		1.55±0.86	
Metastasis		0.008		0.016
Negative (n:387)	16.39±7.70		1.91±1.64	
Positive (n:64)	21.74±11.63		2.66±2.30	
Metastasis site		0.201		0.936
Bone/soft tissue (n:134)	24.54±13.79		2.84±2.83	
Visceral (n:60)	18.52±7.82		2.42±1.47	

STD: Standard deviation.

levels were found as 82.1%, and 88.3%, respectively (Table-3, Fig.-1). The sensivity of CA-15.3 and CEA together was 75%.

4. Discussion

The aim of monitoring patients after treatment for primary breast cancer is early detection of local recurrence, and distant metastasis, which early intervention can be curable. The traditional prognostic factors include pathological tumor features such as tumor stage, hormone receptors, HER-2, and Ki-67 levels [17,18,19]. İt would be useful if serum markers could predict advanced disease [20]. CA 15–3 and CEA remain the most frequently used biomarkers in breast cancer and are recommended for practical use by the American Society of Clinical Oncology (ASCO) as adjunctive assessments to contribute to therapy decisions [15]. The European Group on Tumor Markers has recommended the serial measurement of CEA and CA 15–3 in the early detection of recurrent disease [20].

Studies evaluating the CA 15–3 and CEAs' association with histopathologic and demographic features of patients with breast cancer and their distinctive role in the metastatic process are relatively rare despite the constant interest and the mentioned necessity by recent guidelines [15, 20].

R.Molina et al. [21] studied the relationship between CEA and CA 15–3 and most important prognostic factors in 2062 patients with

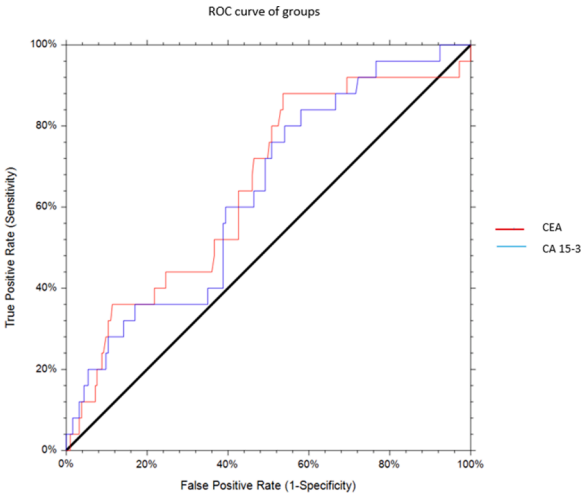

Fig. 1. The ROC curve plot of CEA and CA-15–3.

primary locoregional breast cancer. Elevations of each tumor marker correlated with larger tumor sizes and nodal involvement. CEA levels higher than 7.5 mg/L were associated with a high possibility of subclinical metastases. CEA and CA15–3 levels were significantly higher in stage T2 than T1 ($P = 0.027$ and $P = 0.0001$, respectively) and stage T3 than T2 ($P = 0.013$ and $P = 0.008$, respectively). CEA and CA 15–3 were useful prognostic factors in node-positive and node-negative breast cancer patients. There was no correlation between hormone status and tumor markers in this study. CA 15–3 levels were significantly higher in stage T2 than T1 and stage T3 than T2 in our study. There was a linear association between CA 15–3, CEA levels, and nodal involvement, but it was not statistically significant. Unlike Molina et al. [21], we found significantly higher CEA levels in hormone recptor-positive patients. Also, HER2 negative patients had significantly higher levels of CEA and CA 15–3. Furthermore, CEA and CA 15–3 levels were significantly higher in metastatic patients.

The utility of CEA and CA 15–3 for early diagnosis of recurrence was evaluated in a study including 1023 breast cancer patients [22]. During follow-up, 246 patients developed metastases. The study showed increased levels of CEA and CA 15–3 before diagnosis in 40% and 41% of the patients with local and distant recurrence. Patients with positive hormone receptors had higher levels of both CEA and CA 15–3 at the diagnosis of recurrence.

In another study, 285 breast cancer patients followed postoperatively to determine tumor markers' sensitivity to detect early breast cancer relapses [23]. During postoperative follow-up, distant metastases occurred in 27 (10%) patients. Elevated values of at least one tumor marker were the first pathological sign, and sensitivity of CA 15–3, CEA, tissue polypeptide antigen (TPA) to early diagnosis of metastases were 46%, 7%, and 63%, respectively. İn our study, sensitivities of CA 15–3 and CEA levels were found as 82.1% and 88%; respectively.

Lumachi et al. [24] evaluated the correlation between serum tumor markers CEA and CA 15–3 in 62 breast cancer patients with local or distant metastases. The sensitivity of CEA, CA 15–3, and CEA and CA 15–3, together was reported as 40.3%, 41.9%, and 59.7%, respectively. There was no correlation between tumor markers sensitivity and type of

Table 3
ROC analysis results of CEA ve CA15.3 levels in the prediction of metastasis, hormone status, HER2 status, node involvement.

	CA 15–3			CEA		
	Sensitivity%	Specificity%	P	Sensitivity%	Specificity%	P
Metastasis	82.1	47.3	0.003	88.3	46.2	0.012
Hormone receptor status	88.17	26.92	0.21	54.12	73.08	0.032
HER2 status	58.82	60	0.13	71.15	51.67	0.017
Nodal involvement	53.45	55.56	0.68	87.93	21.92	0.55

recurrence, histologic features, and hormone receptor status. A significant ($p < 0.01$) correlation was found between CEA and the tumor size, node status, and CA 15–3, and patients' age. İn contrast, we showed that elevation of CEA levels in hormone-sensitive patients was statistically significant. Another study also showed a strong correlation between CA 15–3, CEA, and estrogen and progesterone receptor rate ($R = 0.77$) [25]. There was no association between tumor markers and prognostic factors in this study except a mild correlation with CA 15–3 and tumor size. Molina et al. [22] showed that both CEA and CA 15–3 were correlated with tumor size, likewise our findings. İn contrast to our study, they found a significant correlation with nodal involvement.

Consistent with the study that showed elevated CEA levels in older patients at diagnosis [26], CEA levels were significantly higher in postmenopausal patients in our study.

A recent meta-analysis showed that CA 15–3 or CEA had significant prognostic factors in primary or metastatic breast cancer [19]. Furthermore, elevations in CA 15–3 were correlated to advanced histological grade and younger age, while elevated CEA was associated with the non-triple-negative tumor type and older age. These two elevated markers were consistent with a higher tumor burden.

A retrospective study in which the correlation with these two tumor markers and clinicopathological parameters was evaluated showed that elevations in CA 15–3 and CEA levels at diagnosis of recurrence were found in 163 (57.4%) and 97 (34.2%) patients, respectively. Elevated CA 15–3 and CEA levels were found to be related to the molecular subtypes ($P<0.001$ and $P = 0.032$, respectively), similar to our results. Unlike our outcome considering the relation between tumor markers and metastatic site, they showed that an elevated CA 15–3 level was significantly associated with bone metastasis [16].

The results of another study showed that the elevation in CEA levels was significantly higher in patients with HER2 positive tumors, and the elevation in CA 15–3 levels was significantly higher in ER-negative breast patients [27]. Vice versa, we found that HER2 negative and hormone receptor-positive patients had significantly higher levels of CEA and CA 15–3.

A study in which young patients were recruited; was identified that CEA was a predictor for the prognosis. The cut-off values were 3.38 ng/ml and 12.32 U/ml for CEA and CA 15–3 [28]. In contrast, we showed elevated CEA levels in postmenopausal patients, and the cut-off values were 1.39 ng/ml and 14.54 U/ml for CEA and CA 15–3.

5. Conclusions

CEA and CA 15–3 are useful as tumor markers for early diagnosis of metastases, and their elevations were associated with clinicopathological parameters of breast cancer patients. Since these markers are considered a cheap and accessible way of predicting breast cancer prognosis, there is an increasing interest in the prognostic value of serum levels of tumor markers in recent years. More sensitive cut-off values for each marker are needed to be validated with further studies.

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CRediT authorship contribution statement

Meliha Melin Uygur: Investigation, Formal analysis, Writing – original draft. **Mahmut Gümüş:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2021.100402.

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