Are CA 15-3, CEA and CA 125 Predictors for Lymphatic and Vascular Spread In Breast Cancer?

Meme Kanserinde CA 15-3, CEA ve CA 125 Lenfovasküler Yayılım için Belirleyici midir?

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Abstract
Purpose: Tumor markers can be used to predict the prognostic factors in patients with breast cancer and, in this study, correlation between CA 15-3, CEA, and CA 125 and the prognostic factors in breast cancer is evaluated.
Material and Methods: Patients treated for breast cancer between 2002 - 2004 were prospectively included in the study. Serum levels of CA 15-3, CEA, and CA 125 were evaluated in patient groups formed according to various clinical and histopathologic prognostic factors.
Results: 233 patients with breast cancer were included in the study. Higher serum levels of CA 15-3 and CEA were detected in patients with larger tumors (p=0.01 for CA 15-3; p=0.005 for CEA) and serum CA 15-3 and CA 125 levels increased in patients with axillary involvement (p=0.033 for CA 15-3; p=0.036 for CA 125). Besides, serum CA 125 levels increased in patients with extracapsular tumor extension in axillary lymph nodes (p=0.007) and with vascular and lymphatic invasion by tumor cells (p=0.015).
Conclusion: This study has shown that CA 15-3, CEA, and CA 125 could be helpful in predicting well-known prognostic factors such as axillary metastases and tumor size as well as extracapsular tumor extension and lymphovascular invasion in breast cancer.

Key words: **Breast Neoplasms; CA-15-3 Antigen; CA-125 Antigen; Carcinoembryonic Antigen Binding Protein, human.**

Özet
Amaç: Tümör belirteçleri meme kanserli hastalarda prognostik faktörleri tahmin etmede kullanılabilir. Bu çalışmada CA 15-3, CEA, ve CA 125 ile meme kanserinde bilinen prognostik faktörler arasındaki ilişkinin değerlendirilmesi amaçlandı.
Grereç ve Yöntemler: 2002 – 2004 yılları arasında meme kanseri tanısıyla tedavi edilen hastalar prospektif olarak çalışmaya alındı. Klinik ve histopatolojik prognostik faktörlere göre oluşturulan gruplardaki hastaların serum CA 15-3, CEA, ve CA 125 düzeyleri karşılaştırıldı.
Bulgular: Meme kanseri olan 233 hasta çalışmaya alındı. Tümör boyutu daha fazla olan hastalarda serum CA 15-3 ve CEA düzeyleri daha yüksek bulundu (p=0.01 CA 15-3 için; p=0.005 CEA için). Aksillada lenf bezi tutulumu olan hastalarda serum CA 15-3 ve CA 125 düzeylerinde artış saptandı (p=0.033 CA 15-3 için; p=0.036 CA 125 için). Ayrıca, serum CA 125 düzeyinde aksiller lenf bezlerinde ekstrakapsüler yayılım olan (p=0.007) ve lenfovasküler invazyon saptanan (p=0.015) hastalarda artış görüldü.
Sonuç: Bu çalışmada, serum CA 15-3, CEA, ve CA 125 düzeylerinin meme kanserinde aksilla metastazı, tümör boyutu, aksiller lenf bezlerinde ekstrakapsüler yayılım ve lenfovasküler invazyon gibi iyi bilinen prognostik faktörleri tahmin etmede yararlı olabileceği gösterildi.

Anahtar kelimeler: **CA-15-3 Antijen; CA-125 Antijen; Karsinoembryonik Antijen Bağlayan Protein, İnsan; Meme Kanserleri.**

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Introduction

Tumor markers are generally used for early diagnosis of cancer or detection of recurrent disease during follow-up. Various cancer types have specific markers with proven benefits. CA 15-3 and carcinoembryonic antigen (CEA) are the most frequently used tumor markers in breast cancer. CA 15-3 is a mucin encoded by *muc1* gene. Although mucins including CA 15-3 are secreted physiologically by the glandular epithelia, the amount of secretion is usually increased in patients with breast cancer. Elevated serum levels of CA 15-3 are found mostly in patients with metastatic disease and this is a less frequent event in primary breast cancer.

CEA is a glycoprotein with a molecular weight of 180 kDa and it is primarily used for the diagnosis and especially the detection of loco-regional or distant recurrences in colorectal cancer. In addition, CEA was frequently investigated in patients with breast cancer as it is known to be produced by breast cancer cells and released into the circulation. Although elevated serum levels of both CA 15-3 and CEA can be used to detect recurrences after primary treatment, present data are insufficient to support their use for screening, diagnosis, staging or surveillance following primary treatment (1).

On the other hand, CA 125 is a glycoprotein produced by coelemic epithelium lining the pleura, peritoneum, and pericardium. Serum CA 125 level is primarily used in the monitoring of epithelial ovarian cancer. Previously, the significance of CA 125 in the detection of metastatic breast cancer, especially in case of pleural metastases, was reported (2).

Previous studies have investigated the role of CA 15-3, CEA, and CA 125 in the prediction of well-known prognostic factors in breast cancer with contradictory results. There are various pitfalls in these studies such as small number of patients or lack of proper statistical analysis. In this study, correlation between CA 15-3, CEA, and CA 125 and the prognostic factors in breast cancer is evaluated.

Patients and Methods

Patients with breast cancer treated between 1 August 2002 - 31 July 2004 were prospectively included in this study. Patients with distant metastases, with previous history or clinical evidence of malignancies in other organs, or treated with neoadjuvant chemo- or radiotherapy for breast cancer were excluded from the study. The procedures followed in this study are in accordance with the Helsinki Declaration.

Clinical and histopathologic data were recorded from the patients' files. Tumor markers CEA, CA 15-3, and CA 125 were studied from the patients' preoperative serum samples. Chemiluminescent immunometric assay was used to measure the related tumor antigens using monoclonal antibodies according to the manufacturer's manual (BR-MA Immulite 2000, CEA Immulite 2000, OM-MA Immulite 2000, Diagnostic Products Corp., Gwynedd, United Kingdom). Serum values accepted as positive for CEA, CA 15-3, and CA 125 were >2 µg/ml, >25 U/ml, and >21 U/ml, respectively, since patients with benign diseases rarely showed higher values than these values as stated in the manufacturer's manual.

The frequency of CA 15-3, CEA, and CA 125 positivity was evaluated in patient groups formed according to various clinical and histopathologic prognostic factors. Patients were grouped according to tumor size as T1 (<2 cm), T2 (2-5 cm), and T3 (>5 cm) and according to axillary lymph node involvement as positive vs. negative and as N1 (1-3 +), N2 (4-9 +), and N3 (>9 +). In addition, patients were divided according to estrogen (ER) and progesterone receptor (PR), c-erb-B2, and p53 status as positive vs. negative. Tumor characteristics such as grade (I vs. II vs. III), vascular, lymphatic, and neural invasion with tumor cells and extracapsular tumor extension in axillary lymph nodes were evaluated as well. Patients were divided according to age as <50 vs. ≥50 years.

Chi-square and Fisher exact tests were used for statistical analyses as appropriate. Statistical analyses were performed with SPSS 10.0 statistical software package (SPSS Inc., Chicago, IL). $p<0.05$ value was accepted as significant.

Results

In the current study, 233 patients with breast cancer were included. All patients were female with a median age of 50 (range, 27-84). Clinical and histopathologic characteristics of the patients are shown in Table I. Almost half of the patients had T2 tumors (49.3%) and 60.9% showed axillary lymph node metastases. ER and PR positivity were detected in almost two thirds of the patients. c-erb-B2 and p53 were studied in 179 patients. c-erb-B2 and p53 positivity were detected in 60.9% and 39.1% of the patients, respectively. Grade II and III tumors comprised 90% of all tumors. Although lymphatic and vascular invasion by tumor cells were present in 16.3% and 18.9% of the patients, respectively, both lymphatic and vascular invasion was found in 26.6% of the patients.

CA 15-3 was studied in all patients whereas CEA and CA 125 were studied in 209 (90%) and 72 patients (31%), respectively. CEA, CA 15-3, and CA 125 results of the patients are shown in Table II. CA 15-3, CEA, and CA 125 were positive in 13.7% (32/233), 13.4% (28/209), and 29.2% (21/72) of the patients, respectively. When the results of tumor markers were combined, the positivity rate increased compared to the results of individual markers. Either CA 15-3 or CEA was positive in 19.1% of the patients whereas this increased to 32% when CA 15-3 or CA 125 was positive. In contrast, positivity was only 28% in the combination of CEA and CA 125. In addition, positivity increased to 30% when any one of the three tumor markers was positive in patients.

Sensitivity and specificity of CA 15-3, CEA, and CA 125 in detecting the axillary status of the patients are shown in Table III. Histopathologic diagnosis was accepted as the gold standart for the calculation of sensitivity and specificity values. Sensitivity of tumor markers to detect axillary lymph node metastasis (range 17.0-40.0 vs. 84.4-92.5), extracapsular tumor extension in axillary lymph nodes (range 14.5-55.6 vs. 79.6-87.5), and vascular and lymphatic invasion (range 19.4-48.0 vs. 80.9-89.1) is lower compared to their specificity.

The relationship between tumor marker positivity and clinical and histopathologic characteristics of the patients is shown in Table IV. CA 15-3 and CEA positivity were detected more frequently in patients with larger tumors ($p=0.01$ for CA 15-3; $p=0.005$ for CEA) and CA 15-3 and CA 125 positivity increased in patients with axillary involvement ($p=0.033$ for CA 15-3; $p=0.036$ for CA 125). Although a tendency for increased positivity in patients with axillary metastases was also observed for CEA, this difference did not reach statistical significance ($p=0.06$). Besides, CA 125 positivity increased in patients with extracapsular tumor extension in axillary lymph nodes ($p=0.007$) and with vascular and lymphatic invasion with tumor cells ($p=0.015$). On the other hand, when tumor cells invaded blood and lymphatic vessels, CA 15-3 and CEA positivity increased, but the difference was statistically insignificant ($p=0.07$ for CA 15-3; $p=0.058$ for CEA). In addition, CEA positivity correlated with an increase in tumor grade ($p=0.017$). In contrast, CA 15-3, CEA, and CA 125 had no significant correlation with age, ER or PR status, c-erb-B2 or p53 positivity, and neural invasion with tumor cells.

Table I. Clinical and histopathologic characteristics of the patients

Parameter		N	%
Age		median 50 (27-84)	
	< 50	122	52.4
	> 50	111	47.6
Tumor size			
	pT1	47	20.2
	pT2	115	49.3
	pT3	71	30.5
Axillary status			
	pN0	91	39.1
	pN+	142	60.9
	pN1	71	30.5
	pN2	25	10.7
	pN3	46	19.7
Extracapsular tumor extension			
	Present	55	23.6
	Absent	178	76.4
Tumor grade			
	I	22	9.4
	II	96	41.2
	III	101	43.3
	Unknown	14	6.1
Estrogen receptor			
	Positive	150	64.4
	Negative	83	35.6
Progesterone receptor			
	Positive	149	63.9
	Negative	84	36.1
p53			
	Positive	70	30
	Negative	109	46.8
	Unknown	54	23.2
c-erb-B2			
	Positive	109	46.8
	Negative	70	30
	Unknown	54	23.2
Vascular/lymphatic invasion			
	Present	62	26.6
	Absent	171	73.4
Neural invasion			
	Present	34	14.6
	Absent	199	85.4

Table II. CA 15-3, CEA, and CA 125 results of the patients.

		N	%
CA 15.3			
	Positive	32	13.7
	Negative	201	86.3
CEA			
	Positive	28	13.4
	Negative	181	86.6
CA 125			
	Positive	21	29.2
	Negative	51	70.8
CA 15.3 + CEA			
	Positive	40	19.1
	Negative	169	80.9
CA 15.3 + CA 125			
	Positive	23	32
	Negative	49	68
CEA + CA 125			
	Positive	14	28
	Negative	36	72
CA 15.3 + CEA + CA 125			
	Positive	15	30
	Negative	35	70

Table III. Sensitivity and specificity of CA 15-3, CEA, and CA 125 in detecting the axillary status of the patients.

	ALNM Positive/Negative		**ECTE** Positive/Negative		**VLI** Positive/Negative	
CA 15.3						
Positive	25	7	8	24	12	20
Negative	117	84	47	154	50	151
Sensitivity (%)		17.6		14.5		19.4
Specificity (%)		92.3		86.5		88.3
CEA						
Positive	22	6	8	20	11	17
Negative	107	74	41	140	42	139
Sensitivity (%)		17.0		16.3		20.8
Specificity (%)		92.5		87.5		89.1
CA 125						
Positive	16	5	10	11	12	9
Negative	24	27	8	43	13	38
Sensitivity (%)		40.0		55.6		48.0
Specificity (%)		84.4		79.6		80.9

ALNM: axillary lymph node metastasis; ECTE: extracapsular tumor extension; VLI: vascular/lymphatic invasion

Table IV. Distribution of tumor marker positive patients due to various clinical and histopathologic prognostic factors

	CA 15.3			CEA			CA 125		
	Positive n (%)	Negative n (%)	P	Positive n (%)	Negative n (%)	p	Positive n (%)	Negative n (%)	p
Age									
< 50	16 (50)	106 (53)		15 (54)	91 (51)		14 (67)	28 (55)	
> 50	16 (50)	95 (47)	0.85	13 (46)	90 (49	0.84	7 (33)	23 (45)	0.44
Tumor size									
pT1	6 (19)	41 (20)		1 (4)	40 (22)		5 (24)	20 (39)	
pT2	9 (28)	106 (53)		12 (43)	93 (51)		7 (33)	21 (41)	
pT3	17 (53)	54 (27)	0.01	15 (53)	48 (27)	0.005	9 (43)	10 (20)	0.12
Axillary status									
pN0	7 (22)	84 (42)		6 (21)	74 (41)		5 (24)	27 (53)	
pN1	25 (78)	117 (58)	0.033	22 (79)	107 (59)	0.06	16 (76)	24 (47)	0.036
Number of axillary metastases									
pN0	7 (22)	84 (42)		6 (21)	74 (41)		5 (24)	27 (53)	
pN1	11 (34)	60 (30)		9 (32)	56 (31)		5 (24)	11 (21)	
pN2	3 (10)	22 (11)		3 (11)	18 (10)		5 (24)	5 (10)	
pN3	11 (34)	35 (17)	0.07	10 (36)	33 (18)	0.11	6 (28)	8 (16)	0.10
Extracapsular tumor extension									
Present	8 (25)	47 (23)		8 (29)	41 (23)		10 (48)	8 (16)	
Absent	24 (75)	154 (77)	0.82	20 (71)	140 (77)	0.48	11 (52)	43 (84)	0.007
Tumor grade									
I	1 (3)	21 (11)		2 (8)	19 (11)		1 (5)	8 (16)	
II	11 (34)	85 (46)		6 (22)	80 (48)		6 (28)	18 (35)	
III	20 (63)	81 (43)	0.08	19 (70)	69 (41)	0.017	14 (67)	25 (49)	0.29
ER									
Positive	20 (63)	130 (65)		18 (64)	121 (67)		10 (48)	33 (65)	
Negative	12 (37)	71 (35)	0.84	10 (36)	60 (33)	0.83	11 (52)	18 (35)	0.20
PR									
Positive	20 (63)	129 (64)		16 (57)	117 (65)		17 (81)	36 (71)	
Negative	12 (37)	72 (36)	0.84	12 (43)	64 (35)	0.53	4 (19)	15 (29)	0.56
p53									
Positive	8 (31)	62 (41)		11 (44)	52 (40)		10 (48)	17 (33)	
Negative	18 (69)	91 (59)	0.4	14 (56)	78 (60)	0.83	11 (52)	34 (67)	0.29
c-erb-B2									
Positive	15 (58)	94 (61)		16 (64)	84 (65)		9 (43)	17 (33)	
Negative	11 (42)	59 (39)	0.83	9 (36)	46 (35)	1.0	12 (57)	34 (67)	0.59
Vascular/lymphatic invasion									
Present	12 (37)	50 (25)		11 (39)	42 (23)		12 (57)	13 (25)	
Absent	20 (63)	151 (75)	0.14	17 (61)	139 (77)	0.1	9 (43)	38 (75)	0.015
Neural invasion									
Present	7 (22)	27 (13)		5 (18)	23 (13)		7 (33)	9 (18)	
Absent	25 (78)	174 (87)	0.28	23 (82)	158 (87)	0.55	14 (67)	42 (82)	0.21

ER: estrogen receptor; PR: progesterone receptor; n: number

Discussion

In this study, a correlation between tumor markers CA 15-3, CEA, and CA 125 and various histopathologic prognostic factors was detected in breast cancer. Mainly, these tumor markers are related to tumor size and grade, axillary lymph node metastases and extracapsular extension in axillary lymph nodes, and vascular and lymphatic invasion with tumor cells. Tumor markers evaluated in this study frequently increased in the presence of prognostic factors indicating a worse outcome in breast cancer. Since the serum levels of these markers increase parallel to the tumor burden, worse prognosis is an expected outcome in patients with marker positivity.

CA 15-3 positivity was more frequently detected in patients with axillary metastases. In addition, a tendency for increased CA 15-3 values was observed as the number of metastatic lymph nodes increased in the axillary region. A correlation between CA 15-3 and axillary metastases was reported in the previous studies (3-7). Seker et al. detected a higher positivity rate of CA 15-3 in level I and II axillary metastases whereas metastases in all three levels increased with CA 15-3 positivity in this study (3). In other previous studies, CA 15-3 positivity increased as the number of metastatic axillary lymph nodes increased in contrast to the current study (4-6). The reason for showing a tendency but not a significant correlation between CA 15-3 positivity and the number of metastatic lymph nodes might be the relatively small number of patients included in this study compared to those reporting a correlation (4,5). In accordance with this, studies with fewer patients reported no significant correlation between CA 15-3 and axillary metastases (8).

Although a tendency was observed, CEA positivity did not significantly correlate with metastatic lymph nodes in the axillary region. In addition, the number of metastatic axillary lymph nodes was not related to CEA positivity. Similarly, no correlation between CEA and either the presence or the number of axillary lymph node metastases was reported previously (3,4,9). However, there are other studies reporting a correlation between CEA positivity and axillary lymph node involvement either during the treatment of primary tumor or in case of disease recurrence (10).

An increase in tumor size resulted in higher rates of both CA 15-3 and CEA positivity. Previous studies reported contradictory results regarding this issue. CA 15-3 positivity was found to be related to tumor size in studies including higher number of breast cancer patients (4-6) whereas this was not detected when the patient number decreased (8). Current study with a moderate sample size was able to detect this correlation. Similar controversy was also present for CEA and tumor size. In addition, taking into consideration the pathologic rather than clinical tumor size will be more accurate to identify the correlation between tumor size and tumor markers as in this study.

In the previous studies, CA 125 was not frequently evaluated as a marker in primary breast cancer and was reported to increase in case of distant metastases (1,11). However, in this study, CA 125 positivity increased with vascular and lymphatic invasion with tumor cells, axillary metastases, and extracapsular tumor extension in the axillary lymph nodes, all of which is related to lymphovascular spread of the tumor. Thus, there is a possibility of predicting lymphovascular spread of breast cancer using CA 125 as a marker in primary breast cancer. Vascular and lymphatic invasion with tumor cells were reported to be unrelated to both CA 15-3 and CEA in the vast majority of the previous studies (3,4). In the current study, although CA 15-3 and CEA showed a tendency to be more positive in patients with vascular and lymphatic invasion, a significant correlation could not be shown. However, Canizares et al. previously reported a positive correlation between CA 15-3 and vascular invasion (4). In addition, tumor grade correlated with CEA positivity and showed a tendency for a relation with CA 15-3 positivity. Previously, tumor grade and CEA levels were studied in a few studies and none of them reported a significant correlation (3,4).

Hormon receptor status is another histopathologic parameter evaluated for a correlation with tumor markers (4-6). Previously, no significant correlation was reported both with CA 15-3 and CEA. Only Gion et al. found a higher number of patients with CA 15-3 positivity in a group with ER+/PR- tumors compared to those with ER-/PR+ tumors (5). In the current study, CA 15-3 positivity was detected in 11.8% and 12.1% of the patients with ER+/PR- and ER-/PR+ tumors, respectively. Even the difference in CA 15-3 positivity rates between ER+/PR+ and ER-/PR- patients was not significant (13.8% vs. 16%).

In addition to the above mentioned histopathologic parameters, c-erb-B2 and p53 status of tumor and neural invasion with tumor cells were also evaluated in the current

study. No correlation was found between these parameters and all of the tumor markers studied and this is the first study to report on this issue.

In conclusion, this study has shown that tumor markers could be helpful in predicting important prognostic factors such as lymphovascular tumor spread in breast cancer. Among these factors, status of the lymph nodes in the axillary region is of vital importance and predicting this without performing surgery will have profound effects in the management of breast cancer patients. In recent years, sentinel lymph node biopsy was popularized to replace axillary dissection with well-known complications such as lymphedema and motion restrictions in the involved arm and shoulder. Elevated serum levels of CA 15-3 and CA 125 may give valuable information about axillary involvement in adjunct to sentinel lymph node biopsy if these results are verified in similar studies. However, the results should be interpreted cautiously due to low sensitivity and moderate specificity rates. As the number of studies reporting a correlation between preoperative elevation of CA 15-3, CA 125, and CEA levels and the prognostic factors increased, these markers will probably take place in future guidelines for breast cancer.

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