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A PROFILE OF SERUM CARCINOEMBRIONIC ANTIGEN LEVELS IN PATIENTS WITH BREAST CANCER

PROFILI I VLERAVE TË CEA-S NË SERUM NË PACIENTET ME KANCER GJIRI

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PËRMBLEDHJE
Nivelet e larta të CEA-s shoqërohen me prognozë të ulët të kancerit të gjirit. Megjithatë përdorimi i parametrave të ndjekjes është i paqartë. Ne përcaktuam efektin e disa testeve të gjakut në zbulimin e pranisë së metastazave. Ky studim retrospektiv tregon avantazhin e CEA-s për dedektimin e hershëm të rishfaqjes së kancerit të gjirit ku u përfshinë 110 gra me karcinomë invazive të cilat kishin rishfaqje lokale ose metastaza dhe/ose ngritje të nivelit të CEA-s (>3.3 U/ml). Nga 110 pacientë 8(7%) iu rishfaq tumori dhe 20 gra (18.1%) kishin nivele mbinormë të CEA-s. Përqëndrimi i CEA lidhet me përmasat e tumorit, gradën histologjike dhe statusin e nodusit ($p<0.01$) ndërsa mosha, statusi i receptorëve hormonalë (ER/PR) dhe statusi i HER2 nuk shoqërohen me nivelet e CEA-s. CEA mund të përdoret për qëllime monitoruese për ata pacientë me sëmundje të avancuar që nuk i kanë të larta vlerat e markuesve të tjerë.
Fjalë çelës: kancer gjiri, CEA, markues tumori, rishfaqja

SUMMARY
High concentrations of CEA are associated with poor prognosis in breast cancer. However, the usefulness of follow-up parameters remains unclear. We determined the effect of a variety of blood tests used to detect the presence of overt metastatic disease. This retrospective study shows the advantage of the CEA assay for the early detection of relapse in breast cancer. It involved 110 women with invasive carcinoma who had local recurrence or metastasis and/or an elevation of CEA (> 3.3 U/ml). From 110 patients, 8(7%) had a recurrence, before which 20 women (18.1%) had abnormal CEA level. CEA concentration was correlated with tumor size, histological grade and nodus status ($p<0.01$) while age, hormone receptors status (ER/PR) and HER2 status were not associated with levels of CEA. For those patients with advanced disease who do not have increased other markers concentrations, CEA, may be considered for monitoring purposes.
Key-words: breast cancer, CEA, tumor marker, relapse

INTRODUCTION

Carcinoembryonic antigen (CEA) is a well-known, cell-surface 200-kd glycoprotein and widely studied serological tumour marker. Several studies suggested that its evaluation could provide valuable clinical information in patients affected by breast carcinoma (1), but data are still not conclusive (ASCO, 1996). Most of the prognostic indicators for breast cancer currently in use such as tumour size and histology, axillary

lymph nodes, hormonal, receptors and growth factors depend on tumour tissue and thus they may not be available for repeated evaluation (2,3). Therefore, serum carcino-embryonic antigen, an inexpensive tumour marker with proven efficacy, has been used as an indicator of prognosis in breast cancer.

Although the value of CEA has greatly reduced with arising the value of CA 15-3 in breast cancer field, CEA is one of the first tumor markers and there have been many reports related to negative prognostic effect. Several authors have shown that an increase or a decrease in the CEA level may reflect the status of disease progression or regression (4). CEA may be useful in the postoperative follow-up of the breast cancer patients for an early diagnosis of recurrence (5) and for monitoring response to treatment (6).

In the present paper we have evaluated the enzyme-linked immunosorbent assay expression of CEA in a series of 110 breast carcinomas to evaluate its potential prognostic value in relation to conventional clinicopathological parameters and ER status.

MATERIALS AND METHODS

A total of 110 patients treated at Oncologic Hospital "Mother Tereza" from January 2006 to December 2007 with breast cancer had their periodical CEA concentrations measured. The study period ended by November 2011. All tumors were invasive cancers with stages I–III, and the mean age of patients was 51 years (range 28–83 years).

After completion of surgery, radiotherapy and appropriate adjuvant chemotherapy or hormone therapy was not altered according to the marker levels but was administered as indicated based on the international guidelines.

General clinicopathological parameters such as tumor size, axillary node involvement, HG, estrogen receptor (ER), progesterone receptor, HER2 expression, and age are summarized in Table 1. Staging was based on 6th American Joint Committee on Cancer criteria. Clinical follow-up included history taking, physical examination, and laboratory tests, including CEA, liver function test and complete blood count. Values higher than 3.3 U/ ml were considered as elevated values. Progesterone and Estrogen receptors were assayed by DakoCytomation CA (USA). HER 2 analysis were performed only in 25 patients and thus we had evaluated the correlation to CEA refering to this group.

The CEA Quantitative analyse is based on a solid phase enzyme-linked immunosorbent assay. The assay system utilizes one monoclonal anti-CEA antibody for solid phase (microtiter wells) immobilization and another mouse monoclonal anti-CEA antibody in the antibody-enzyme (horseradish peroxidase) conjugate solution. The standards and test specimen (serum) are added to the CEA antibody coated microtiter wells. Then CEA antibody labeled with horseradish peroxidase (conjugate) is added. If human CEA is present in the specimen, it will combine with the antibody on the well and the enzyme conjugate resulting in the CEA molecules being sandwiched between the solid phase and enzyme-linked antibodies. After 1 hour incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies. A solution of chemiluminescent substrate is added and the intensity of the emitting light is proportional to the amount of enzyme present and is directly related to the amount of CEA in the sample. By reference to CEA standards assayed in the same way, the concentration of CEA in the unknown sample is quantified. *Statistical analysis*: The mean serum level of the marker was compared using two-side t-test (Independent Sample T-test) and P value < 0.05 was considered as significant.

Feature	Number of cases	%
Total enrolled	**110**	
Age		
<=35 years	4	4

>35 years	106	96
Tumor size		
T1	14	2.7
T2	82	74.5
T3	14	12.7
Node status		
N0	18	16
N1	58	53
N2	34	31
N3	0	0
Metastase		
M0	106	96
M1	4	4
Histological Grade		
I	9	8
II	89	81
III	12	11
Receptor status		
ER+/PR+	56	50.9
ER-/PR-	42	37
HER 2 (25)		
Negative	8	32
Positive	17	68
Relapse		
No	94	85.4
Yes	16	14.6
CEA		
≤3.4	92	84
>3.4	18	16

Table 1. Pathologic, biochemical, and clinical characteristics of cancers investigated.

RESULTS AND DISCUSSIONS

Although histologic factors such as tumor size, tumor grade, and lymph node status have been the cornerstone of assessing cancer prognosis for decades, data suggest that circulating markers can provide additional or independent data.

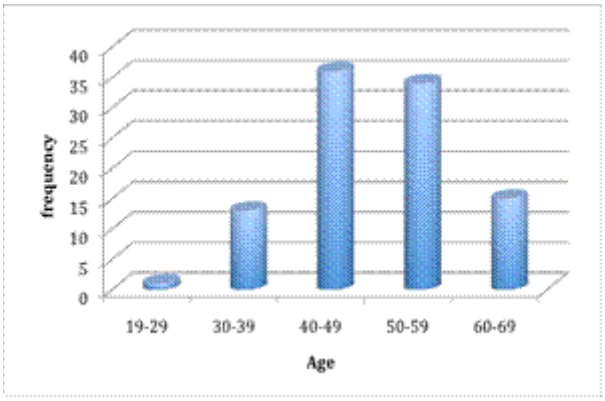

Fig 1. Distribution of women with breast cancer according to age.

On the basis of the preoperative evaluation, the distribution of the patients in different stages was stage 1 (2.7 %), stage II (74.5 %), stage 111(12.7%) according to table 1.

Feature	**CEA**		
Total enrolled	**Mean value**	DS	P
Age			
<=35 years	10.8	16.83	0.06
>35 years	3.2	3.5	
Tumor size			
T1	1.7	2.1	0.01
T2	2.97	4.4	
T3	2.7	1.2	
T4	15.21	5.4	
Node Status			

N0	1.6	8.6	0.01
N1	3.11	5.69	
N2	13.75	16.40	
Metastase			
M0	3.15	6.06	
M1	11.74	16.3	0.3
Histological Grade			
I	1.6	0.37	0.04
II	3.5	5.66	
III	5.36	12.71	
Receptor status			
ER+/PR+	2.88	1.907	0.4
ER-/PR-	3.71	7.532	
HER 2 (25)			
Negative	6.6	0.496	
Positive	1.48	1.232	0.7
Relapse			
No	2.33	4.049	0.016
Yes	10.03	16.80	

Table 2. Mean concentrations in CEA different subgroups

Different stages of tumour produced significantly different serum CEA levels (p = 0.01). Well-differentiated tumour was found in 12 (11%) patients, moderately differentiated in 89 (81%) and poorly differentiated in 9 (8%) of the cases. Histological grading was statistically associated with CEA concentrations with p=0.04 (table 2). A detailed breakdown on the distribution of CEA concentrations in relation to age (fig 1), tumor size, patient age, axillary nodal status, and ER/PR, HER 2 status is shown in Table 2.

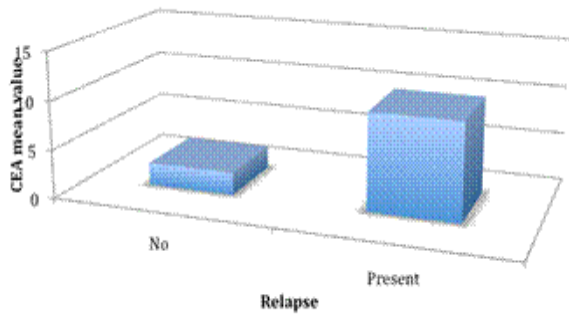

Fig 2. Association of serum CEA value with relapse, in patients with breast cancer**.**

The mean value of CEA was 3.46 U/ml. Elevated CEA levels were identified in 18 (16%) and recurrence occurred in 16 (14.6%) of the patients, during 36-48 months of follow-up.

The difference between the serum CEA score within the modalities of some dichotomous variables considered, was statistically significant, as indicated using the T-test: tumour size (P = 0.01); nodal status (P = 0.01) and histological grading (P = 0.04).

Auxiliary lymph nodes had tumour deposits in 84% of the cases. Node 0 was involved in 16%, node 1 in 53% and node 2 in 31% of the patients. Serum CEA levels differed significantly with the nodal status (p = 0.01). Concentrations were also higher in patients who were axillary node positive compared with those who were axillary node negative as showen in table 2, and the degree of lympho-reticular response to the tumour significantly influenced the serum CEA levels. However, the histological grade of the tumour and the nodal status altered the CEA level significantly, as reported ealier (7).

We could not demonstrate any interaction between the HER 2 and, stratifying patients on the basis of the CEA values (table 2), we could not find any statistically significant prognostic value for CEA.

There was no influence in CEA concentrations in patients who were ER positive and PR positive but concentrations were higher in patients <=35 years compared with those older than 35 years.

While, in other studies (8,9,10) were reported an association between CEA expression and positive ER status.

Forth patients developed metastasis during 36-48 months of follow-up. The difference in serum CEA levels of the patients with metastatic breast cancer (mean 11.74 U/ml) was not significant (p = 0.3).

Patients with relapse	CA 15-3 value	CEA-s value	abnormal tumor marker value
1.	36.77	4.4	
2.	74.7	35.2	
3.	74.97	3.93	
4.	12	1.7	
5.	35.5	3.7	
6.	55	4.5	
7.	45	3.9	
8.	38	5.4	
9.	42.8	1.46	+
10.	45	5.6	
11.	32.6	38	
12.	45	2.1	+
13.	55.4	4.5	
14.	18.73	37.51	+
15.	55.4	4.7	
16.	45	3.9	

Table 3. Concentrations of both tumor marker in patient with relapse.

Serum CEA level was associated with the tumour recurrence (p=0.016) with the mean value of 10.03 U/ml and DS= 16.8 (fig 2). As mentioned above, existing histologic and biological prognostic factors for breast cancer all require tumor tissue. In this study, we confirm and extend findings on the prognostic value of serum CEA in breast cancer. Serum CEA level may be used as the first sign of the tumour recurrence and has been found to be a valuable tool in therapy as seen in other studies (11,12,13,14).

Analysing patients with relapse, we see 3 cases with only one abnormal tumor marker value (Table 3). Therefore, in conclusion, by combining it with another tumour marker such as CA 15-3, the efficacy of CEA can be improved (15).

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