original article

Annals of Oncology 19: 675–681, 2008
doi:10.1093/annonc/mdm538
Published online 23 November 2007

Preoperative CA 15-3 and CEA serum levels as predictor for breast cancer outcomes

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Received 24 August 2006; revised 4 October 2007; accepted 22 October 2007

Background: To investigate the association between tumor markers [cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA)] and clinicopathological parameters and patient outcomes in breast cancer.
Materials and methods: A total of 740 patients with stages I–III breast cancer had preoperative CA 15-3 and CEA concentrations measured. Univariate and multivariate analyses were used to investigate associations between marker concentration and clinicopathological parameters and patient outcomes.
Results: Among 740 patients, elevated preoperative levels of CA 15-3 and CEA were identified in 92 (12.4%) and 79 (10.7%) patients, respectively. Tumor size (>5 cm), node metastases (≥4), and advanced stage (≥III) were associated with higher preoperative levels. Elevated CA 15-3 and CEA levels were associated with poor disease-free survival (DFS, $P = 0.0014$, $P = 0.0001$, respectively) and overall survival (OS, $P = 0.018$, $P = 0.015$) even in stage-matched analysis. Patients with normal levels of both CA 15-3 and CEA showed better DFS and OS than those with elevated group. In multivariate analysis, age (<35 years), tumor size (>2 cm), node metastases, estrogen receptor expression, and elevated CA 15-3 and CEA preoperative values were independent prognostic factors for DFS.
Conclusion: High preoperative CA 15-3 and CEA levels may reflect tumor burden and are associated with advanced disease and poor outcome. Measuring preoperative levels of CA 15-3 and CEA can be helpful for predicting outcomes.
Key words: breast cancer, CA 15-3, CEA, prognosis, tumor marker

introduction

Axillary lymph node status has been the most important prognostic factor for primary breast cancer; tumor size, histologic grade (HG), and hormone receptors status are also traditional prognostic factors. In addition, circulating tumor markers, such as cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA), have been evaluated for use as predictive parameters in patient outcome and treatment response. Although its usefulness remains uncertain and American Society of Clinical Oncology guidelines do not recommend its use for follow-up [1], measurement of circulating CA 15-3 and CEA levels is widely used for surveillance purposes in clinical field. It is a fast, noninvasive, reproducible, and quantitative serum test.

CA 15-3 is the product of MUC-1 gene, and mucins are aberrantly overexpressed in many adenocarcinomas in an underglycosylated form and then shed into the circulation [2, 3]. Therefore, higher level of CA 15-3 may be associated with larger burden of occult disease and poor outcome. There have been many reports showing worse prognosis in patients with high concentration of CA 15-3 [4–7], and CA 15-3 has been shown to be an independent predictor of first recurrence as well as a powerful prognostic indicator in patients with advanced breast cancer [8].

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 [9, 10]. Several authors have shown that an increase or a decrease in the CEA level may reflect the status of disease progression or regression [11, 12]. CEA may be useful in the postoperative follow-up of the breast cancer patients for an early diagnosis of recurrence [13–15] and for monitoring response to treatment [16, 17].

In the present study, we retrospectively evaluated the relationship between the level of the markers and clinicopathological parameters and then the ability of CEA and CA 15-3 serum levels in predicting breast cancer outcome using univariate and multivariate analyses.

materials and methods

patients

A total of 740 patients treated at Yonsei University Severance Hospital from April 1999 to December 2003 with breast cancer had their preoperative CA 15-3 and CEA concentrations measured. All tumors

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were invasive cancers with stages I–III, and the median age of patients was 47 years (range 20–88 years).

Patients were treated with either modified radical mastectomy or quadrantectomy and axillary lymph node dissection with local radiotherapy. 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 and CA 15-3, liver function test, complete blood count, chest radiography, abdominal and breast ultrasonography, mammography, and bone scan every 6–12 months, for detection of local or distant relapse. Additional computed tomography and radiography were obtained as necessary.

Table 1. General characteristics of study population

Characteristics (*N*)	*n*	%
Age (740)		
≤35 years	75	10.1
>35 years	665	89.9
Tumor size (740)		
T1	411	55.5
T2	308	41.6
≥T3	21	2.8
Nodal status (740)		
N0	431	58.2
N1	183	24.7
N2	84	11.4
N3	42	5.7
TNM stage (740)		
I	284	38.4
II	329	44.4
III	127	17.2
HG (628)		
I	123	19.6
II	316	50.3
III	189	30.1
ER (710)		
Negative	267	37.6
Positive	443	62.4
PR (711)		
Negative	387	54.4
Positive	324	45.6
HER2 (699)		
Negative	434	62.1
Positive	265	37.9
CA 15-3 (740)		
≤20.11	648	87.6
>20.11	92	12.4
CEA (740)		
≤3.88	661	89.3
>3.88	79	10.7

TNM, tumor–node–metastasis; HG, histologic grade; ER, estrogen receptor; PR, progesterone receptor; CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen.

marker analysis

Serum tumor markers were determined by automated immunoanalyzer systems using chemiluminiscent immunoassay for CEA (ADVIA Centaur®, Bayer HealthCare LLC Diagnostic Division, NY) and CA 15-3 (VITROS®

Table 2. Correlation between serum CA 15-3 and CEA level and clinicopathological factors

	CA 15-3			CEA		
	Mean	SD	*P*	Mean	SD	*P*
Age						
≤35 years	13.16	6.37	0.896	1.88	2.31	0.209
>35 years	13.32	10.48		2.47	3.95	
Tumor size						
T1	12.77	10.08	**<0.001**	2.29	4.10	**<0.001**
T2	13.24	7.45		2.28	2.51	
≥T3	24.78	26.88		6.71	8.84	
Nodal status						
N0	12.52	9.84	**0.003**	2.38	4.01	**0.041**
NI	13.16	7.88		1.94	1.35	
N2	16.23	11.44		3.24	6.05	
N3	16.66	16.75		3.16	3.47	
TNM stage						
I	12.37	10.60	**0.001**	2.29	4.17	**0.037**
II	13.01	8.00		2.21	2.66	
III	16.37	13.38		3.22	5.32	
HG						
I	12.01	5.24	0.317	1.93	1.22	0.303
II	13.30	8.80		2.39	3.45	
III	13.03	8.16		2.62	5.42	
ER						
Negative	12.71	8.24	0.284	2.53	4.85	0.418
Positive	13.50	10.07		2.30	2.86	
PR						
Negative	13.31	9.52	0.722	2.48	4.17	0.472
Positive	13.05	9.31		2.27	3.12	
HER2						
Negative	13.39	10.43	0.509	2.37	4.30	0.789
Positive	12.90	7.67		2.45	2.66	

CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; SD, standard deviation; TNM, tumor–node–metastasis; HG, histologic grade; ER, estrogen receptor; PR, progesterone receptor.

Table 3. Adjuvant treatment according to tumor markers levels

	CA 15-3			CEA		
	Normal (%)	Elevated (%)	*P* value	Normal (%)	Elevated (%)	*P* value
Chemotherapy						
Done	427 (66)	66 (72)	0.29	436 (66)	54 (68)	0.71
No	221 (34)	26 (28)		225 (34)	25 (32)	
Endocrine Tx						
Done	509 (79)	76 (83)	0.41	527 (80)	58 (73)	0.19
No	139 (21)	16 (17)		134 (20)	21 (27)	
Radiation Tx						
Done	290 (45)	44 (48)	0.58	297 (45)	37 (46)	0.81
No	358 (55)	48 (52)		364 (55)	42 (54)	

CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen; Tx, treatment.

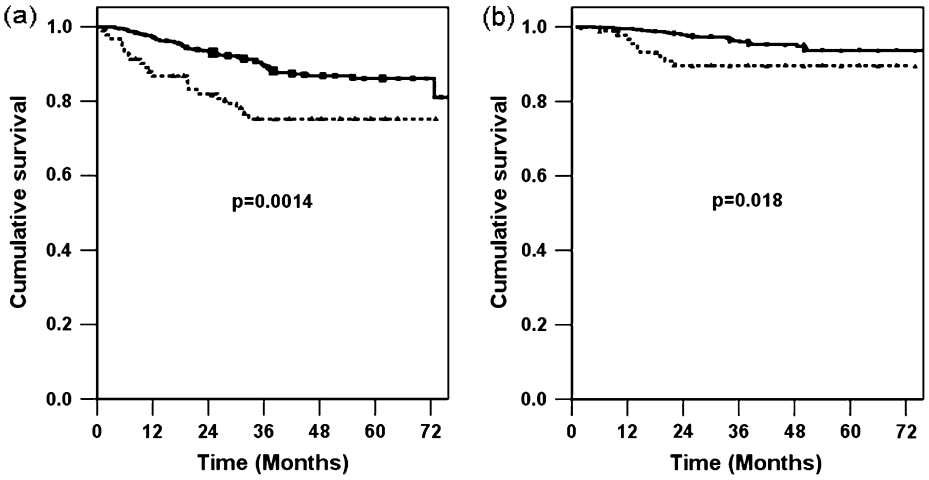

Figure 1. Survival curves according to preoperative cancer antigen 15-3 levels. Disease-free survival (A) and overall survival (B). Bold line represents patients with normal level and dotted line represents patients with elevated levels.

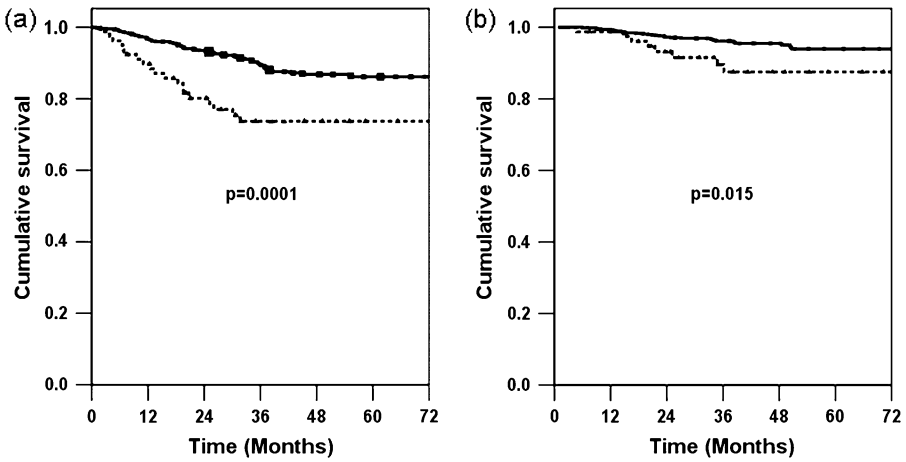

Figure 2. Survival curves according to preoperative carcinoembryonic antigen levels. Disease-free survival (A) and overall survival (B). Bold line represents patients with normal level and dotted line represents patients with elevated levels.

ECi Immunodiagnostic System, Ortho-Clinical Diagnostics, Inc., NY). Range of normality was determined by mean ± 2 standard deviations (SDs) of the marker distribution in healthy females tested in an annual screening program.

statistics

The difference between proportions was evaluated by the chi-square test. Univariate survival curves for disease-free survival (DFS) and death were estimated using the Kaplan–Meier method; group differences in survival time were tested by the log-rank test. Multivariate Cox regression analysis was carried out to compare and identify independent prognostic factors for DFS and death and to calculate hazard ratios. All significant parameters in univariate analyses were entered into a multivariate model and excluded for *P* value >0.05. SPSS for Windows (version 10.0) was used for all statistical analyses.

results

Median follow-up was 37.2 months (mean 38.7, range 1–84 months). Recurrence occurred in 91 patients (first relapse: local recurrence alone $n = 19$, distant metastasis alone $n = 47$, both local and systemic recurrences $n = 25$). There were 35 deaths, including one nonbreast cancer death.

The mean ± SD of CA 15-3 and CEA in healthy individuals were 11.45 ± 4.33 and 1.42 ± 1.23, respectively. To define cut-off values, we chose the 95 percentile of healthy individuals and the calculated upper limit of CA 15-3 and CEA were 20.11 U/l and 3.88 ng/ml, respectively.

Patient demographics are listed in Table 1. Median preoperative CEA and CA 15-3 levels were 1.66 ng/ml (range 0.19–34.37) and 10.6 U/ml (range 2.5–87.5), respectively. Elevated CA 15-3 and CEA levels were identified in 92 (12.4%) and 79 (10.7%) patients, respectively.

As shown in Table 2, both CA 15-3 and CEA were correlated with larger tumor size (>5 cm) and greater lymph node metastases (≥4). Age, HG, hormone receptor status, and HER2 status, however, were not associated with preoperative levels of tumor markers (Table 2).

Adjuvant treatments given after surgery were summarized in Table 3. Because adjuvant treatment was determined not by the tumor marker levels but by the international guidelines,

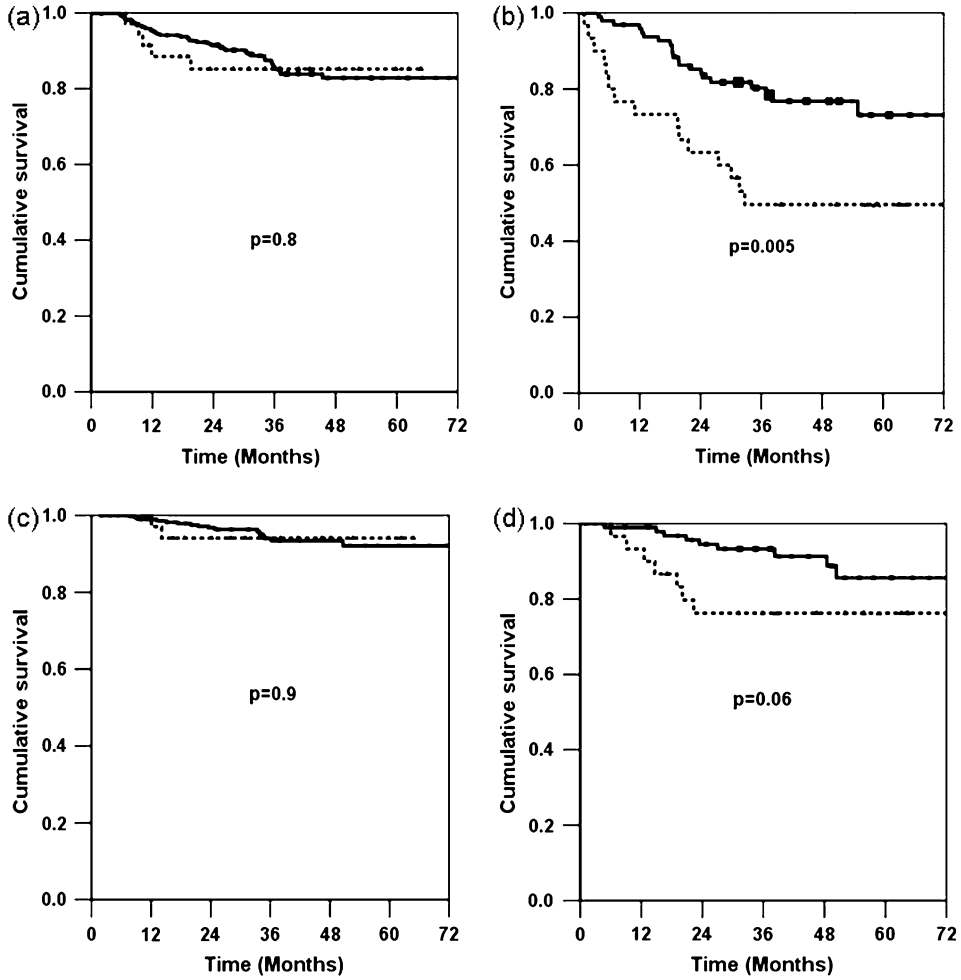

Figure 3. Tumor stage-matched survival curves according to cancer antigen 15-3 levels. Disease-free survival curves of stages II and III (A and B) and overall survival curves of stages II and III (C and D). Bold line represents patients with normal level and dotted line represents patients with elevated levels.

there was no difference between the normal and the elevated groups (Table 3).

Elevated CA 15-3 and CEA values were associated with poor DFS ($P = 0.0014$ and $P = 0.0001$, respectively) and also with overall survival (OS) ($P = 0.018$ and $P = 0.015$, respectively, Figures 1 and 2).

In tumor stage-matched analysis, elevated CA 15-3 group showed significantly poorer DFS ($P = 0.005$) and marginally poor OS ($P = 0.06$) in stage III (Figure 3). In terms of CEA, significantly poorer DFS in stages II and III ($P = 0.026$ and $P = 0.007$, respectively) and marginally poor OS in stage II were seen ($P = 0.06$) (Figure 4).

Nineteen patients had elevated levels of both CA 15-3 and CEA, 133 showed elevated level of either CA 15-3 or CEA, and 588 were normal in both markers. Patients with normal levels of both markers showed significantly better DFS and OS. Either one marker elevated group showed a trend of better DFS and OS than the group with both markers elevated, but not statistically significant (Figure 5).

Young age (<35 years), larger tumor size (>2 cm), axillary node metastases, and negative ER expression were also significant prognostic factors (data not shown). Of these prognostic factors, preoperative values of CA 15-3 and CEA were entered into the Cox's multivariate analysis. Young age (<35 years), larger tumor size (>2 cm), axillary node metastases, negative ER expression, and elevated preoperative values of CA 15-3 and CEA were independent prognostic factors in DFS and distant relapse-free survival; however, patient age, elevated CA 15-3, and CEA were not statistically significant in OS (Table 4).

discussion

In addition to traditional prognostic factors, such as axillary lymph node status, tumor size, HG, hormone receptor expression, and HER2 expression status, multigene assay [18] and gene expression profiling [19, 20] have been recently spotlighted. All these factors require tissue samples. Progressive size reduction of detected tumor can make it difficult to obtain samples. On the other hand, serum is easily accessible and soluble circulating tumor markers, if found to be accurate prognostic factors, would be ideal candidates for predicting outcome and monitoring treatment course [21]. Measuring markers is simple, objective, reproducible, and cost-effective, and serum CA 15-3 and CEA have been the most frequently investigated tumor markers in breast cancer. Due to low

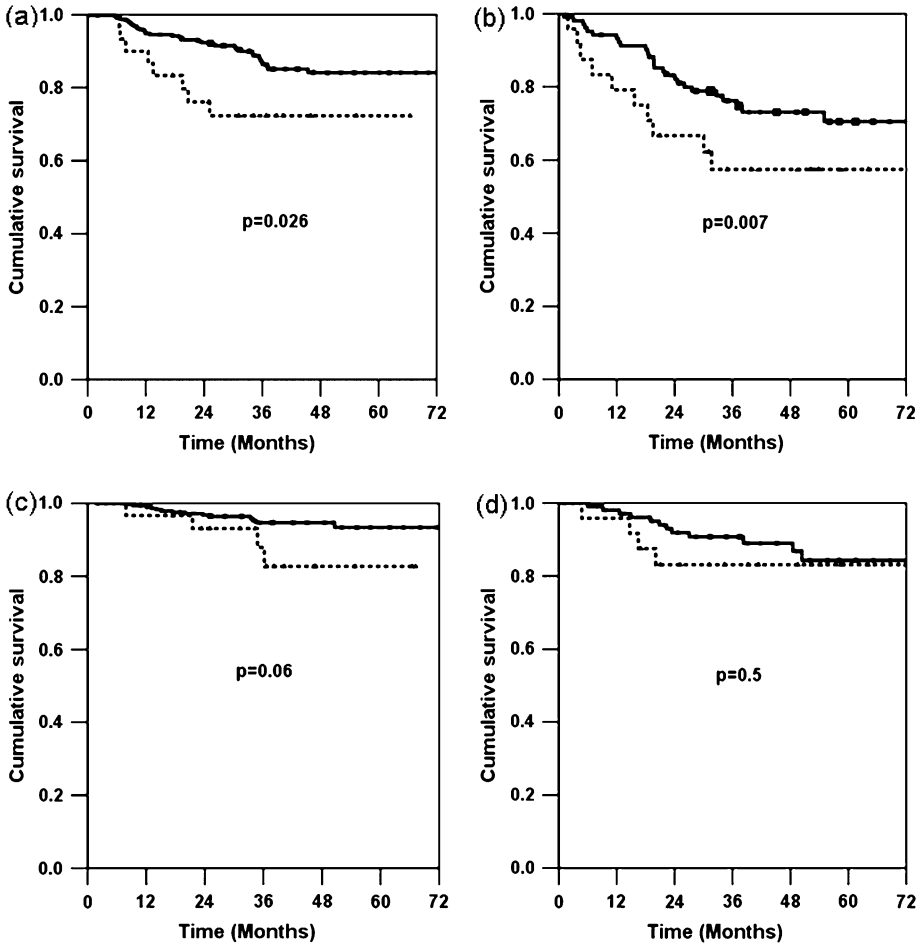

Figure 4. Tumor stage-matched survival curves according to carcinoembryonic antigen levels. Disease-free survival curves of stages II and III (A and B) and overall survival curves of stages II and III (C and D). Bold line represents patients with normal level and dotted line represents patients with elevated levels.

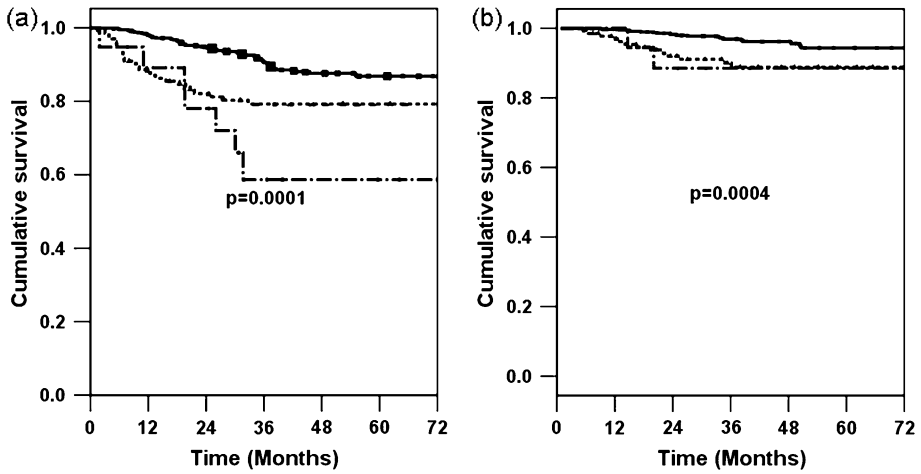

Figure 5. Survival curves by combination of both levels of preoperative cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) concentrations. Disease-free survival (A) and overall survival (B). Bold line represents patients with normal levels in both CA 15-3 and CEA, dotted line represents patients with elevated level in either CA 15-3 or CEA, and chain line represents patients with elevated levels in both CA 15-3 and CEA.

sensitivity and specificity, both CA 15-3 and CEA have no value for early detection of primary breast cancer. They can, however, be useful in predicting prognosis, monitoring treatment response, and surveillance.

Previous studies report variable results on the prognostic value of CA 15-3 and CEA; small sample size, short follow-up, and variable cut-off values contribute to the inconsistency. Duffy et al. [22] reported that a cut-off value of CA 15-3 might

Table 4. Cox proportional hazards regression analysis according to age, stage, hormone receptor status, and serum markers

	DFS			DRFS			OS		
	RR	CI	*P*	RR	CI	*P*	RR	CI	*P*
Age									
<35 years									
≥35 years	0.4008[a]	0.2140–0.7508	0.0043	0.3413[a]	0.1801–0.6471	0.0010	1.0939	0.3273–3.6562	0.8841
Tumor size									
≤2 cm									
>2 cm	3.2468[a]	1.7518–6.0177	0.0002	3.3169[a]	1.7125–6.4245	0.0004	3.6533[a]	1.3345–10.0014	0.0117
Node									
Negative									
Positive	2.9665[a]	1.6796–5.2395	0.0002	3.2277[a]	1.7486–5.9576	0.0002	3.0669[a]	1.2631–7.4466	0.0133
ER									
Negative									
Positive	0.4508[a]	0.2710–0.7499	0.0022	0.4305[a]	0.2504–0.7400	0.0023	0.1994[a]	0.0827–0.4810	0.0003
CA 15-3									
Normal									
Elevated	2.0944[a]	1.1768–3.7274	0.0120	2.1110[a]	1.1333–3.9320	0.0186	2.0924	0.8758–4.9991	0.0966
CEA									
Normal									
Elevated	2.5640[a]	1.4097–4.6635	0.0020	2.0557[a]	1.0556–4.0033	0.0341	1.9539	0.7747–4.9280	0.1559

[a]Significantly different from reference group.

DFS, disease-free survival; DRFS, distant relapse-free survival; OS, overall survival; RR, risk ratio; CI, confidence interval; ER, estrogen receptor; CA 15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen.

influence both the result and prognostic impact. We therefore used reference values of CEA and CA 15-3 measured from healthy women who had an annual health screening at Severance Health Promotion Center. We determined the normal range by mean ± 2 SDs of marker distribution in this population and defined cut-off values by the 95 percentile (20.11 U/ml for CA 15-3 and 3.88 ng/ml for CEA). Among 740 patients, 92 (12.4%) and 79 (10.7%) patients had levels greater than the cut-off values for CA 15-3 and CEA, respectively (Table 1).

As shown in Table 2 and other reports [1, 6, 8, 23], serum levels of both CA 15-3 and CEA were associated with host tumor burden such as larger tumor size (>5 cm), more lymph node metastases (≥4), and advanced stage, but were not associated with HG, hormonal receptor status, and HER2 status. Since CA 15-3 and CEA are directly associated with host tumor burden and presence of serum tumor associated antigens at diagnosis indicates vascularization of the tumor with possibility of micrometastases [24], preoperative levels of serum tumor markers could be related to poor outcome. Taken together with other reports [4–7, 10, 22, 23, 25, 26], the current study showed that elevated values of CA 15-3 or CEA were associated with poor DFS ($P = 0.0014$ and $P = 0.0001$, respectively) and poor OS ($P = 0.018$ and $P = 0.015$, respectively). These results are further supported by the tumor stage-matched analysis (Figures 3 and 4) and multivariate analysis (Table 4). Despite some controversies, both CA 15-3 and CEA levels could provide independent prognostic information to be taken together with conventional markers measured in tumor tissues [27]. Furthermore, Duffy [28] reported that preoperative concentrations could be combined with existing prognostic factors for adjuvant therapy selection. Although study sizes were small, several studies evaluating early treatment based exclusively on increasing marker concentrations showed improved prognosis compared with controls [29–33]. Therefore, breast cancers with elevated CA 15-3 or CEA could be in consideration for determining adjuvant treatments.

As shown in Figure 5, with the combination of both marker levels, the prognostic value is further intensified; patients with both markers in normal level showed significantly better DFS and OS than those with either one or both markers elevated. This result indicates that patients showing elevated levels of both C15-3 and CEA could be included in high-risk group for recurrence. On the basis of the reports using preoperative CA 15-3 and CEA levels in determining adjuvant treatment [29–33] and results shown in Figure 5, breast cancer patients with elevated levels of both CA 15-3 and CEA should be in consideration of early or new combination of adjuvant treatments.

In conclusion, elevated preoperative CA 15-3 and CEA levels are directly related to tumor burden and are independent prognostic factors for breast cancer. Even in stage-matched analysis and multivariate analysis, both markers showed significant prognostic value. Therefore, both markers could be considered for clinical use such as predicting patient outcome and determining adjuvant treatment for better outcome.

funding

Brain Korea 21 Project for Medical Science, Yonsei University; Astra-Zeneca Korea Co.; Dong-A Pharmaceutical Co.; CJ Corporation; Sanofi-Aventis Pharmaceutical Co.; Novartis Korea Co.; Lilly Korea Co.

acknowledgements

A major part of this study was presented at the 2006 American Society of Clinical Oncology poster session in Atlanta, GA, USA.

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