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CLINICAL TRIAL

The prognostic significance of preoperative tumor marker (CEA, CA15-3) elevation in breast cancer patients: data from the Korean Breast Cancer Society Registry

Sang eun Nam[1] · Woosung Lim[2] · Joon Jeong[3] · Seeyoun Lee[4] · Jungeun Choi[5] · HeungKyu Park[6] · Yong Sik Jung[7] · Seung Pil Jung[8] · Soo Youn Bae[8]

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Abstract

Purpose Tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) are widely used for monitoring breast cancer. However, the prognostic efficacy of preoperative elevations of CEA and CA15-3 levels in breast cancer patients remains controversial.

Methods We retrospectively analyzed the clinicopathological parameters of 149,238 patients in the Korean Breast Cancer Society Registry Database who underwent surgery between January 2000 and December 2015.

Results The patients with elevated CA15-3/CEA levels had worse overall survival (OS) than the patients with normal CA15-3/CEA levels. For the luminal A subtype, the CA15-3- and CEA-elevated group had a hazard ratio (HR) of 2.14 (95% CI 1.01–4.55). The CA15-3-elevated group had an HR of 2.38 (95% CI 1.58–3.58) and the CEA-elevated group had an HR of 1.79 (95% CI 1.20–2.68) compared to the normal group. For the luminal B subtype, the CA15-3- and CEA-elevated group had an HR of 3.99 (95% CI 2.23–7.16), whereas the CA15-3-elevated group had an HR of 2.38 (95% CI 1.58–3.58) and the CEA-elevated group had an HR of 1.79 (95% CI 1.20–2.68). For the HER2 subtype, elevated CEA level was the only independent prognostic factor. However, for the triple-negative breast cancer (TNBC) subtype, elevated preoperative CEA and CA15-3 levels were not significant prognostic factors for OS.

Conclusion Preoperative CEA and CA15-3 levels showed varying prognostic ability according to breast cancer subtype. Preoperative CA15-3 and CEA elevation are significant prognostic factors for luminal breast cancer, but they were not significant factors for TNBC.

Keywords Breast cancer · Tumor marker · CA15-3 · CEA · Prognosis · Subtypes · Overall survival

✉ Soo Youn Bae
baessu@gmail.com

[1] Department of Surgery, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Republic of Korea

[2] Department of Surgery, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea

[3] Department of Surgery, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

[4] Department of Surgery, Center for Breast Cancer, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea

[5] Division of Breast Surgical Oncology, Department of Surgery, Yeungnam University College of Medicine, Daegu, Republic of Korea

[6] Department of Surgery, Gachon University, Gil Medical Center, Incheon, Republic of Korea

[7] Department of Surgery, Ajou University School of Medicine, Suwon, Republic of Korea

[8] Division of Breast and Endocrine Surgery, Department of Surgery, Korea University Anam Hospital, Korea University College of Medicine, 73 Inchon-ro, Seongbuk-gu, Seoul, Republic of Korea

Introduction

Breast cancer is the most common cancer overall and the second most common cause of cancer deaths in women. According to Korean National Cancer Registration data, the incidence rate of breast cancer is increasing annually [1]. Despite the increased incidence rate, earlier diagnosis and effective treatment are reducing the breast cancer mortality rate. Furthermore, the consideration of reliable prognostic factors is very important for guiding decision-making and proper treatment. In clinical practice, the traditional prognostic factors for breast cancer are patient age, axillary lymph node status, tumor size, histological features (especially histological grade and lymphovascular invasion), and molecular subtype including hormone receptor status and human epidermal growth factor receptor 2 (HER2) expression [2].

Using serum tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) as prognostic factors for breast cancer has been discussed for more than 30 years. CEA was first identified as a tumor-specific antigen found in tumor tissue extracts [3]. CEA is a member of a family of cell-surface glycoproteins and is one of the tumor markers that are clinically useful in a variety of adenocarcinomas [4]. CA15-3 is a member of the mucin-1 (MUC-1) family of glycoproteins that are aberrantly overexpressed in cancers [5, 6]. CA15-3 and CEA have been approved as tumor markers for monitoring breast cancer by the Food and Drug Administration (FDA) [7, 8]. However, the prognostic efficacy of preoperative elevations of CEA and CA15-3 levels in breast cancer remains controversial.

The American Society of Clinical Oncology (ASCO) guidelines do not currently recommend the use of serum CA15-3 and CEA for screening, diagnosis, staging, and treatment monitoring after primary therapy [9]. The National Comprehensive Cancer Network (NCCN) guidelines do not recommend the use of CEA or CA15-3 as markers for clinical evaluation before treatment [10]. In contrast, the European Group on Tumor Markers has recommended the use of CEA and CA15-3 levels for assessing prognosis, early detection of disease progression, and treatment monitoring in breast cancer [11]. In addition, several studies have reported that the elevation of preoperative CA15-3 and CEA levels may reflect tumor burden and exhibit independent prognostic parameters [8, 12, 13].

To evaluate the prognostic efficacy of preoperative tumor markers in breast cancer patients, we retrospectively analyzed the clinicopathological parameters of the Korean Breast Cancer Society Registry (KBCSR) Database. In addition, based on the heterogeneous nature of breast cancer, a subgroup analysis was performed to evaluate the prognostic significance of these markers according to breast cancer subtype.

Materials and methods

Patient selection

We conducted a retrospective analysis of 149,238 patients who underwent surgery between January 2000 and December 2015 in Korea and whose serum CEA and CA15-3 levels were measured prior to surgery. All data were obtained from the KBCSR, which investigates the status of breast cancer in Korea using data from the nationwide hospital-based breast cancer registry containing various clinicopathological and treatment data. Of these patients, 19,530 were excluded for meeting one of the following criteria: (1) stage IV disease with distant metastases at diagnosis, (2) unknown critical information including TNM stage and carcinoma in situ, and (3) history of receiving neoadjuvant chemotherapy. A total of 129,708 patients met all the inclusion criteria, which included (1) female sex, (2) history of unilateral invasive breast cancer, (3) treatment with either modified radical mastectomy or breast conserving surgery, and (4) tumors completely removed by surgery based on pathologic evaluation. After completion of surgery, adjuvant treatment with radiotherapy, chemotherapy, and/or hormone therapy was administered based on international guidelines. TNM staging was based on the Seventh American Joint Committee on Cancer Criteria. The study was approved by the Institutional Review Board committee of Konkuk University Medical Center (Approval number: KUH1020092).

Tumor marker analysis

The levels of serum tumor markers CEA and CA15-3 were determined based on the standard values for each institution. The values were considered positive or negative for the tumor marker if the level was above or below the cut-off value of each institution, respectively.

Stratification of molecular subtypes

The patients were classified into four molecular subtypes, as follows: luminal A: estrogen receptor (ER)-positive (ER+) and/or progesterone receptor (PR)-positive (PR+), human epidermal growth factor receptor 2 (HER2)-negative (HER2−) and low Ki67 level (< 14.0%); luminal B: ER+ and/or PR+, Ki67 ≥ 14.0%, HER2− or HER2-positive (HER2+); HER2: ER-negative (ER−) and PR-negative (PR−), HER2+; and triple-negative breast cancer (TNBC): ER−, PR−, and HER2−.

Statistical analysis

The χ^2 test was used to analyze the differences between proportions. Overall survival (OS) was defined as the time from surgery until the time of death. OS was estimated using the Kaplan–Meier method and compared using the log-rank test. Independent prognostic factors for OS were identified by multivariate Cox proportional hazards analysis. All significant parameters in the univariate analysis were included in a multivariate model. A P value < 0.05 was considered statistically significant. SPSS (ver. 20.0, IBM Corp, Armonk, NY, USA) software was used for all statistical analyses.

Results

The clinicopathological characteristics of the patients according to CA15-3 and CEA are shown in Table 1. Patients with elevated CA15-3 levels exhibited a higher rate of mastectomy (64% vs. 44.6%, $P < 0.001$) and axillary lymph node dissection (61.9% vs. 43.5%, $P < 0.001$) compared to the patients with normal CA15-3 levels. The elevated-CA15-3 group had a more advanced stage (stage III, 36.1% vs. 12.5%, $P < 0.001$), T-stage, and N-stage compared to the normal group. The elevated-CA15-3 group also had an association with ER negativity (40.0% vs. 31.3%, $P < 0.001$), PR negativity (51.1% vs. 40.3%, $P < 0.001$), and HER2 positivity (31.9% vs. 22.7%, $P < 0.001$). The elevated-CA15-3 group also showed a significantly higher rate of luminal B (32.1% vs. 23.9%) and TNBC (22.1% vs. 17.4%, $P < 0.001$). These differences in clinicopathologic characteristics were also observed between the elevated CEA group and the normal CEA group, except for the difference in subtypes. The elevated CEA group exhibited a higher rate of the HER2 subtype (18.9% vs. 10.2%, $P < 0.001$) and a lower rate of the TNBC subtype (13.6% vs. 17.6%, $P < 0.001$).

Patients with elevated levels of both CA15-3 and CEA had a more advanced cancer stage, T-stage, and N-stage, and underwent a higher rate of mastectomy and axillary lymph node dissection. This CA15-3- and CEA-elevated group also exhibited the highest rates of ER positivity, PR negativity, and HER2 positivity. Moreover, the group had the lowest rate of luminal A and highest rate of luminal B subtypes compared with patients with normal CA15-3/CEA levels.

Survival analysis

Patients with elevated CA15-3 levels had worse OS than patients with normal CA15-3 levels. In addition, patients with elevated CEA levels had worse OS compared to patients with normal CEA levels. According to subgroup analysis, the elevated CA15-3 group had worse OS than the normal group in all subtypes. Patients with elevated CEA levels had worse OS than the normal CEA groups for the luminal A, luminal B, and HER2 subtypes. There was no difference in OS between the elevated CEA group and normal group for the TNBC subtype (Fig. 1, Table 2).

Kaplan–Meier analysis showed that both the CA15-3- and CEA-elevated groups had worse prognoses than the normal group. In subgroup analysis, both the CA15-3-elevated and CEA-elevated groups exhibited worse OS for all subtypes (Fig. 2). After adjusting for age, stage, and chemotherapy treatment, it was shown that elevated serum CEA and CA15-3 levels were independent prognostic factors for OS (Fig. 2, Table 3). For the luminal A subtype, the CA15-3- and CEA-elevated group had a hazard ratio (HR) of 2.14 (95% CI 1.01–4.55). The CA15-3-elevated group had an HR of 2.38 (95% CI 1.58–3.58) and the CEA-elevated group had an HR of 1.79 (95% CI 1.20–2.68) compared to the normal group. For the luminal B subtype, the CA15-3- and CEA-elevated group had a HR of 3.99 (95% CI 2.23–7.16), whereas the CA15-3-elevated group had a HR of 2.38 (95% CI 1.58–3.58) and the CEA-elevated group had a HR of 1.79 (95% CI 1.20–2.68) compared to the normal group. Multivariate analysis revealed that elevated CEA level was the only independent prognostic factor for the HER2 subtype. However, for the TNBC subtype, elevated preoperative CEA and CA15-3 levels were not significant prognostic factors for OS.

Discussion

Tumor markers are widely used for screening and monitoring cancers. Two such markers, CA15-3 and CEA, are FDA-approved for monitoring breast cancer [7, 8]. In metastatic breast cancer, the levels of CEA and CA15-3 can predict patient treatment response and prognosis. Unfortunately, they are not often used for screening because of their low sensitivity and specificity for breast cancer [14]. Tumor markers are higher in advanced or metastatic breast cancers than in early-stage breast cancer [15]. Persistently elevated tumor markers are associated with recurrence or treatment resistance, which may be useful in monitoring treatment effects [16].

Many studies have investigated the significance of preoperative tumor marker elevation, but a consensus has not yet been achieved. However, many previous reports show consistent results. The levels of preoperative serum CA15-3 and CEA have been shown to be higher in advanced breast cancer patients with large tumor size, LN metastasis, or higher histological grades. This suggests that elevated tumor markers are related to an increased tumor burden [7, 13, 17–19].

In this study, the preoperative levels of tumor markers were associated with clinical pathologic characteristics and prognosis in patients with breast cancer who had no

Table 1 Clinicopathologic characteristics of patients according to preoperative level of tumor marker

		CEA			CA15-3			CEA and CA15-3				
		Elevated (*N* = 831)	Normal (*N* = 30,667)		Elevated (*N* = 643)	Normal (*N* = 30,885)		Both elevated (*N* = 128)	Only CA15-3 elevated (*N* = 515)	Only CEA elevated (*N* = 703)	Both normal (*N* = 30,152)	
OP	Mastectomy	550 (66.2%)	13631 (44.4%)	< 0.001	415 (64.5%)	13,766 (44.6%)	< 0.001	95 (74.2%)	320 (62.1%)	455 (64.7%)	13311 (44.1%)	< 0.001
	BCS	281 (33.8%)	17036 (55.6%)		228 (35.5%)	17089 (55.4%)		33 (25.8%)	195 (37.9%)	248 (35.3%)	16841(55.9%)	
Axillary OP	ALND	427 (51.4%)	13396 (43.7%)	< 0.001	398 (61.9%)	13425 (43.5%)	< 0.001	79 (61.7%)	319 (61.9%)	348 (49.5%)	13077 (43.4%)	< 0.001
	SLNBx	404 (48.6%)	17271 (56.3%)		245 (38.1%)	17430 (56.5%)		49 (38.3%)	196 (38.1%)	355 (50.5%)	17075 (56.6%)	
pT	T0	1 (0.1%)	37 (0.1%)	< 0.001	2 (0.3%)	36 (0.1%)	< 0.001	0	2 (0.4%)	1 (0.1%)	35 (0.1%)	< 0.001
	Tis	1 (0.1%)	17 (0.1%)		0	18 (0.1%)		0	0	1 (0.1%)	17 (0.1%)	
	T1	302 (36.4%)	18294 (59.6%)		204 (31.7%)	18392 (59.6%)		32 (25.0%)	172 (33.04%)	270 (38.4%)	18122 (60.1%)	
	T2	402 (48.4%)	11210 (36.6%)		307 (47.7%)	11305(36.6%)		57 (44.5%)	250 (48.5%)	345 (49.1%)	10960 (36.3%)	
	T3	100 (12.0%)	935 (3.0%)		99(15.4%)	936 (3.0%)		33 (25.8%)	66 (12.8%)	67 (9.5%)	869 (2.9%)	
	T4	25 (3.0%)	174 (0.6%)		31 (4.8%)	168 (0.6%)		6 (4.7%)	25 (4.9%)	19 (2.7%)	149 (0.5%)	
pN	N0	397 (47.8%)	19789 (64.5%)	< 0.001	265 (41.2%)	19921 (64.6%)	< 0.001	38 (29.7%)	227 (44.1%)	359 (51.1%)	19562 (64.9%)	< 0.001
	Nmi	40 (4.8%)	820 (2.7%)		30 (4.7%)	830 (2.7%)		7 (5.5%)	23 (4.5%)	33 (4.7%)	797 (2.6%)	
	N1	229 (27.6%)	7098 (23.2%)		182 (28.3%)	7145 (23.2%)		48 (37.5%)	134 (26.0%)	181 (25.7%)	6964 (23.1%)	
	N2	101 (12.1%)	2066 (6.7%)		103 (16.0%)	2064 (6.7%)		21 (16.4%)	82 (15.9%)	80 (11.4%)	1984 (6.6%)	
	N3	64 (7.7%)	894 (2.9%)		63 (9.8%)	895 (2.9%)		14 (10.9%)	49 (9.5%)	50 (7.1%)	845 (2.8%)	
Stage	Stage I	212 (25.5%)	14006 (45.7%)	< 0.001	125(19.4%)	14093 (45.7%)	< 0.001	18 (14.1%)	107 (20.8%)	194 (27.6%)	13899 (46.1%)	< 0.001
	Stage II	375 (45.1%)	12803 (41.7%)		286 (44.5%)	12892 (41.8%)		52 (40.6%)	234 (45.4%)	323 (45.9%)	12569 (41.7%)	
	Stage III	244 (29.4%)	3858 (12.6%)		232 (36.1%)	3870 (12.5%)		58 (45.3%)	174 (33.8%)	186 (26.5%)	3684 (12.2%)	
ER	Positive	520 (63.9%)	20617 (68.7%)	0.004	378 (60.0%)	20759 (68.7%)	< 0.001	88 (69.3%)	290 (57.7%)	432 (62.9%)	20327 (68.9%)	< 0.001
	Negative	294 (36.1%)	9395 (31.3%)		252 (40.0%)	9437 (31.3%)		39 (30.7%)	213 (42.3%)	255 (37.1%)	9182 (31.1%)	
	Unknown	17	652		13	689		1	12	16	643	
PR	Positive	390 (48.0%)	17913 (59.8%)	< 0.001	306 (48.9%)	17997 (59.7%)	< 0.001	59 (46.8%)	247 (49.4%)	331 (48.3%)	17666 (59.9%)	< 0.001
	Negative	422 (52.0%)	12064 (40.2%)		320 (51.1%)	12166 (40.3%)		67 (53.2%)	253 (50.6%)	355 (51.7%)	11811 (40.1%)	
	Unknown	19	690		17	722		2	15	17	675	
HER2	Positive	265 (36.9%)	5993 (22.5%)	< 0.001	170 (31.9%)	6088 (22.7%)	< 0.001	42 (38.5%)	128 (30.2%)	223 (36.6%)	5865 (22.3%)	< 0.001
	Negative	454 (63.1%)	20684 (77.5%)		363 (68.1%)	20775 (77.3%)		67 (61.5%)	296 (69.8%)	387 (63.4%)	20388 (77.7%)	
	Unknown	112	3990		110	4022		19	85	93	3899	
Ki_67	≥ 14	271 (56.0%)	8607 (49.3%)	0.004	237 (58.1%)	8641(49.3%)	< 0.001	50 (58.1%)	187 (58.1%)	221 (55.5%)	8420 (49.2%)	< 0.001
	< 14%	213 (44.0%)	8846 (50.7%)		171 (41.9%)	8888 (50.7%)		36 (41.9%)	135 (41.9%)	177 (44.5%)	8711 (50.8%)	
	Unknown	347	13214		234	13356		42	193	5	13021	
Subtype	LumA	278 (38.9%)	12835 (48.2%)	< 0.001	179 (33.8%)	12934 (48.3%)	< 0.001	36 (33.3%)	143 (34.0%)	242 (39.9%)	12692 (48.5%)	< 0.001
	Lum B	204 (28.6%)	6374 (24.0%)		170 (32.1%)	6408 (23.9%)		40 (37.0%)	130 (30.9%)	164 (27.1%)	6244 (23.8%)	

Table 1 (continued)

		CEA			CA15-3			CEA and CA15-3				
		Elevated (N=831)	Normal (N=30,667)		Elevated (N=643)	Normal (N=30,885)		Both elevated (N=128)	Only CA15-3 elevated (N=515)	Only CEA elevated (N=703)	Both normal (N=30,152)	
	TNBC	97 (13.6%)	4694 (17.6%)		117 (22.1%)	4674 (17.4%)		18 (16.7%)	99 (23.5%)	79 (13.0%)	4595 (17.6%)	
	HER2+	135 (18.9%)	2706 (10.2%)		63 (11.9%)	2778 (10.4%)		14 (13.0%)	49 (11.6%)	121 (20.0%)	2657 (10.1%)	
	Unknown	117	4058		114	4091		20	94	97	3964	
Chemotherapy	Yes	643 (77.5%)	22985 (75.1%)	0.123	547 (85.2%)	23081(75.0%)	<0.001	104 (81.2%)	443 (86.2%)	539 (76.8%)	22542 (74.9%)	<0.001
	No	187 (22.5%)	7619 (24.9%)		95 (14.8%)	7711 (25.0%)		24 (18.8%)	71 (13.8%)	163 (23.2%)	7548 (25.1%)	
	Unknown	1	63		1	93			1	1	62	
Radiotherapy	Yes	406 (52.9%)	18313 (63.1%)	<0.001	354 (59.0%)	18365 (62.9%)	0.054	60 (50.8%)	294 (61.0%)	346 (53.2%)	18019 (63.1%)	<0.001
	No	362 (47.1%)	10729 (36.9%)		246 (41.0%)	10845 (37.1%)		58 (49.2%)	188 (39.0%)	304 (46.8%)	10541 (36.9%)	
	Unknown	63	1625		43	1675		10	33	53	1592	
Hormonal therapy	Yes	509 (69.6^)	20120	<0.001	336 (63.8%)	20293 (72.0%)	<0.001	74 (70.5%)	262 (62.1%)	435 (69.5%)	19858 (72.1%)	<0.001
	No	69.60%	71.90%		191 (36.2%)	7893 (28.0%)		31 (29.5%)	160 (37.9%)	191 (30.5%)	7702 (27.9%)	
	Unknown	100	2685		116	2699		23	93	77	2592	

preoperative distant metastasis. CA15-3 and CEA were associated with aggressive factors such as advanced stage and higher grades. Furthermore, there was a significant difference according to subtype in relation to ER and PR negativity and HER2 positivity.

Preoperative tumor marker levels are a significant prognostic factor of OS, and patients exhibiting elevated preoperative tumor markers have poorer prognoses. Several studies have found that elevated tumor markers are associated with poorer disease-free survival (DFS) and OS compared to patients with levels within the normal range [8, 20]. It is believed that tumor markers may be associated with metastatic potential, i.e., micrometastasis or vascularization of the tumor.

There are few studies on the significance of tumor markers according to breast cancer subtypes, which is why we chose to include this in our analysis. For the luminal A subtype, CA15-3 and CEA were significant prognostic factors. The HRs of patients with elevated levels of both tumor markers were the highest in all subtypes. For the luminal B subtype, the elevation of CA15-3 appeared to be a more significant factor than CEA elevation. For the TNBC subtype, neither CA15-3 nor CEA was a prognostic factor, whereas CEA elevation was a significant prognostic factor for the HER2 subtype.

Some previous studies have shown elevated CA15-3 and CEA to be prognostic for all breast cancer subtypes, whereas others have shown differences in prognostic ability according to subtype. Yerushalmi et al. reported that elevated CA15-3 and CEA are more frequently observed in the luminal subtypes than in the non-luminal subtypes [21]. Li et al. showed that preoperative CA15-3 elevation is more common in the luminal A subtype, and that those patients have a poorer prognosis [22]. Shao et al. reported that CEA elevation was more common in HER2+ tumors and that the elevation of CA15-3 was more common in ER− breast cancers. Another study showed that the elevation of CEA and CA15-3 was a significant prognostic factor for luminal B breast cancer [15]. Molina et al. also reported that CEA elevation was associated with poor prognosis in HER2+ tumors [23]. There was also a report indicating that the elevation of tumor markers in TNBC is associated with poor prognosis [24]. However, that study also included stage IV patients. The conflicting results of these studies may be dependent on the stages of patients that were examined. However, in many studies, the elevation of preoperative tumor markers was an important prognostic factor for luminal A breast cancer.

The prognostic differences between CA15-3 and CEA elevation may be related to the characteristics of these tumor markers. Human CEA is a member of a family of cell-surface glycoproteins that represent a subset of the immunoglobulin superfamily [25]. The human CEA family is composed of 29 genes arranged on chromosome

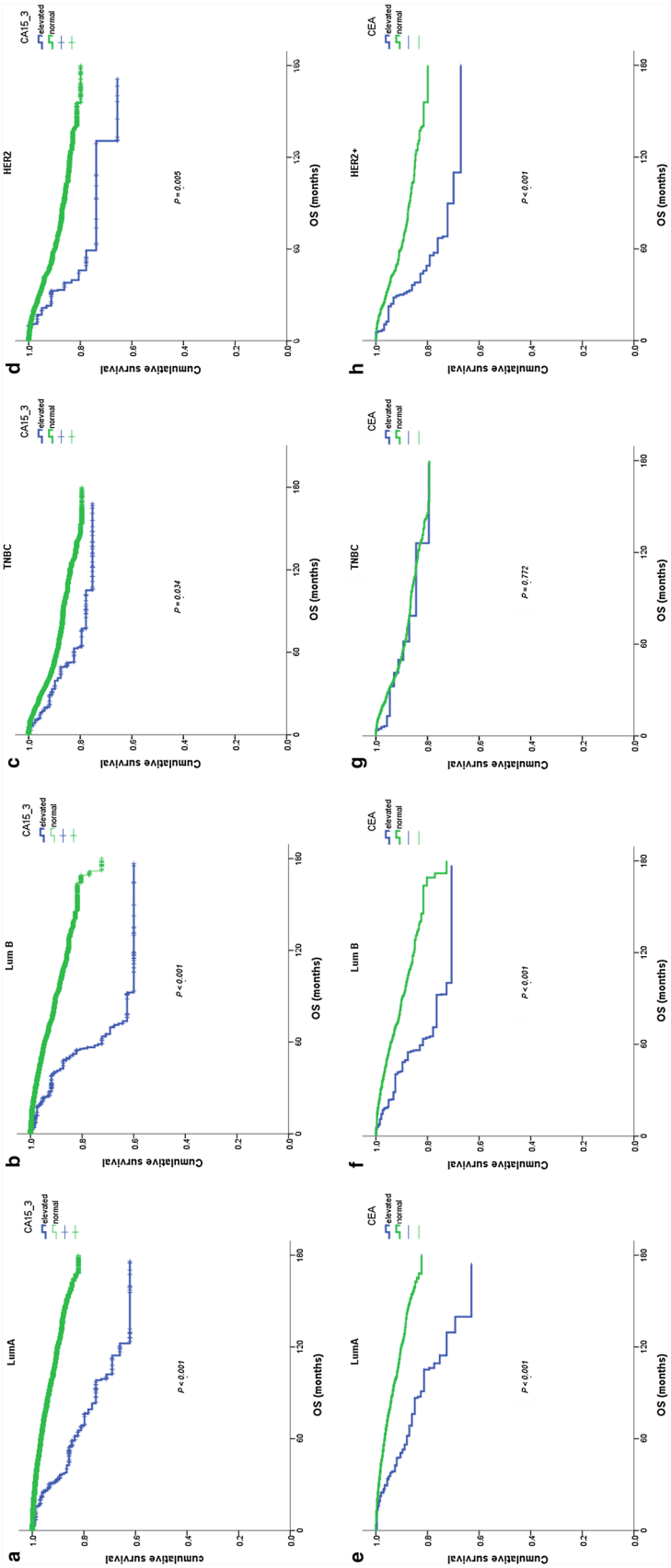

Fig. 1 Overall survival according to tumor markers: (1) CA15-3 and (2) CEA. **a**, **e** Luminal A subtype; **b**, **f** luminal B subtype; **c**, **g** triple-negative breast cancer subtype; **d**, **h** HER2 subtype

Table 2 Univariate analysis of overall survival of patients according to tumor marker

	Tumor marker		HR	95.0% CI		*P*
				Lower	Upper	
Total patients	CA15-3	Normal	1.000			
		Elevated	3.250	2.724	3.877	< 0.001
	CEA	Normal	1.000			
		Elevated	2.459	2.058	2.938	< 0.001
	CA15-3/CEA	Both normal	1			
		Both elevated	4.262	2.972	6.113	< 0.001
		Only CA15-3 elevated	3.137	2.569	3.832	< 0.001
		Only CEA elevated	2.267	1.852	2.774	< 0.001
<subtype>						
Luminal A	CA15-3	Normal	1.000			
		Elevated	4.292	3.005	6.131	< 0.001
	CEA	Normal	1.000			
		Elevated	3.115	2.192	4.425	< 0.001
	CA15-3/CEA	Both normal	1			
		Both elevated	5.812	2.756	12.256	< 0.001
		Only CA15-3 elevated	4.147	2.776	6.194	< 0.001
		Only CEA elevated	2.877	1.941	4.265	< 0.001
Luminal B	CA15-3	Normal	1.000			
		Elevated	3.772	2.640	5.390	< 0.001
	CEA	Normal	1.000			
		Elevated	2.530	1.744	3.671	< 0.001
	CA15-3/CEA	Both normal				
		Both elevated	6.514	3.655	11.610	< 0.001
		Only CA15-3 elevated	3.135	2.018	4.871	< 0.001
		Only CEA elevated	1.884	1.173	3.027	0.009
TNBC	CA15-3	Normal	1.000			
		Elevated	1.598	1.032	2.472	0.035
	CEA	Normal	1.000			
		Elevated	1.092	0.601	1.985	0.772
	CA15-3/CEA	Both normal	1			
		Both elevated	0.473	0.067	3.368	0.455
		Only CA15-3 elevated	1.822	1.165	2.850	0.009
		Only CEA elevated	1.285	0.687	2.404	0.431
HER2+	CA15-3	Normal	1.000			
		Elevated	2.231	1.250	3.982	0.006
	CEA	Normal	1.000			
		Elevated	2.418	1.624	3.599	< 0.001
	CA15-3/CEA	Both normal	1			
		Both elevated	2.558	0.818	7.998	0.106
		Only CA15-3 elevated	2.305	1.184	4.487	0.014
		Only CEA elevated	2.459	1.616	3.744	< 0.001

19q13.2. These genes are classified into two major subfamilies, the CEA cellular adhesion molecule (CEACAM) and the pregnancy-specific glycoprotein subgroups [4]. CEACAM proteins can interact with CEA or non-CEA molecules. This shows that CEA affects cell adhesion. Changes in cell adhesion are involved in the invasion and metastasis of cancer [5, 26]. CEA can inhibit natural killer cell killing through homophilic interactions with CEA-related cell adhesion molecules [27].

CA15-3 has been shown to be a more sensitive prognostic marker for breast cancer than CEA. CA15-3 is a glycoprotein member of the mucin-1 (MUC1) family, and the MUC1 gene is located on human chromosome locus 1q22 [28]. MUC1 is found on nearly all epithelial cells [29,

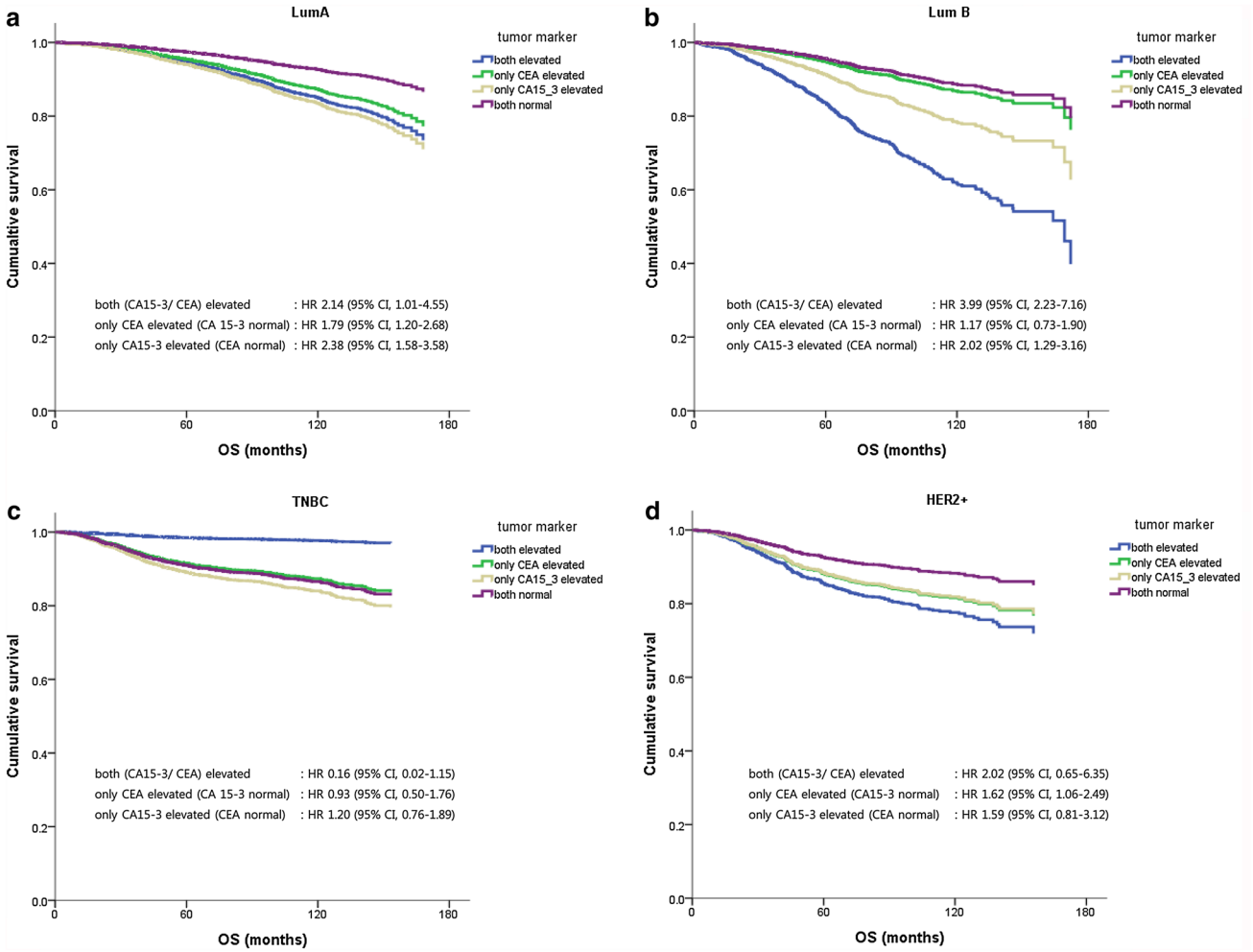

Fig. 2 Multivariate analysis for OS according to tumor markers CA15-3 and CEA. **a** Luminal A subtype, **b** luminal B subtype, **c** triple-negative breast cancer subtype, **d** HER2 subtype

30] and is associated with approximately 80% of human cancers [28].

Alterations in mucin expression or glycosylation affect the development of cancer and influence tumor cell invasion, metastasis, survival, proliferation, and immune surveillance [6, 31, 34]. The cytoplasmic domain of MUC1 has several phosphorylation sites, whereas the cytoplasmic tail of MUC1 (MUC1CT) is associated with several signaling pathways, including Ras, β-catenin, p120 catenin, p53, and ERα. In breast cancer, MUC1 enhances estrogen-dependent growth and survival by binding to and stabilizing ERα [32]. MUC1CT enhances the ERα occupancy of estrogen response elements and activates signaling pathways, including steroid receptor coactivator 1 (SRC-1) [33, 34]. Merikhian et al. suggested that the overexpression of MUC1 in ER + breast cancer is associated with the development of tamoxifen resistance [35].

Conclusions

In breast cancer patients without distant metastasis, the preoperative elevation of CA15-3 and CEA was associated with aggressive characteristics and worse OS. Preoperative tumor markers predicted the prognosis of the patients and showed differences according to breast cancer subtype. In luminal breast cancer, CA15-3 elevation demonstrated a higher HR than CEA elevation, and patients with both tumor markers exhibited the worst prognosis overall. In luminal breast cancer, careful surveillance is required for patients with high preoperative tumor markers.

Table 3 Multivariate analysis for overall survival of patients (adjusted with T-stage, N-stage, age at diagnosis, chemotherapy)

	Hazard ratio	95.0% CI		*P*
		Lower	Upper	
Total patient				
CEA & CA15-3 normal	(ref)			
CEA & CA15-3 elevated	1.822	1.266	2.622	< 0.001
Only CEA elevated	1.427	1.164	1.75	0.001
Only CA15-3 elevated	1.948	1.591	2.386	< 0.001
pT	1.655	1.558	1.757	< 0.001
pN	1.758	1.684	1.836	< 0.001
Age	1.024	1.02	1.028	< 0.001
Chemotherapy	0.938	0.821	1.072	0.35
Luminal A				
CEA & CA15-3 normal	(ref)			
CEA & CA15-3 elevated	2.141	1.008	4.547	0.048
Only CEA elevated	1.793	1.201	2.677	0.004
Only CA15-3 elevated	2.377	1.579	3.577	< 0.001
pT	1.48	1.314	1.667	< 0.001
pN	1.934	1.768	2.115	< 0.001
Age	1.031	1.023	1.039	< 0.001
Chemotherapy	0.85	0.674	1.072	0.171
Luminal B				
CEA & CA15-3 normal	(ref)			
CEA & CA15-3 elevated	3.994	2.229	7.155	< 0.001
Only CEA elevated	1.175	0.726	1.902	0.51
Only CA15-3 elevated	2.022	1.292	3.165	0.002
pT	1.517	1.312	1.753	< 0.001
pN	1.707	1.546	1.885	< 0.001
Age	1.024	1.014	1.034	< 0.001
Chemotherapy	0.967	0.684	1.368	0.85
TNBC				
CEA & CA15-3 normal	(ref)			
CEA & CA15-3 elevated	0.161	0.023	1.153	0.069
Only CEA elevated	0.938	0.5	1.76	0.843
Only CA15-3 elevated	1.208	0.769	1.898	0.412
pT	1.694	1.494	1.92	< 0.001
pN	1.776	1.628	1.937	< 0.001
Age	1.009	1.001	1.017	0.02
Chemotherapy	0.651	0.479	0.885	0.006
HER2+				
CEA & CA15-3 normal	(ref)			
CEA & CA15-3 elevated	2.029	0.648	6.353	0.224
Only CEA elevated	1.628	1.062	2.495	0.025
Only CA15-3 elevated	1.598	0.817	3.126	0.171
pT	1.641	1.38	1.951	< 0.001
pN	1.828	1.629	2.052	< 0.001
Age	1.017	1.005	1.029	0.004
Chemotherapy	0.794	0.508	1.239	0.309

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, informed consent was not required.

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