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Clinicopathological Significance of CEACAM1 Gene Expression in Breast Cancer

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Abstract

Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is a cell adhesion molecule expressed in a variety of cell types. The role of CEACAM1 in breast cancer development and progression is largely unknown. Immunohistochemical analysis was used to examine CEACAM1 expression in breast cancer with long-term follow-up. CEACAM1 expression level in primary breast cancer was low or undetectable. In 65% of the cases, CEACAM1 expression within tumor tissue was lower than that in adjacent tissues. In 20% of the cases, CEACAM1 was negative. In 28.3% of cases, equivalent CEACAM1 expression level was detected in tumor and adjacent tissues. The expression level of CEACAM1 in tumor tissue was negatively correlated with patient mortality, while positively correlated with the expression level of ER+/ PR+. CEACAM1 expression was not related with patients' age, pathological classification, lymphatic involvement and the size of tumor. The down-regulation of CEACAM1 was correlated with negative ER-/PR- and might be attributed to the malignant process of breast cancer. The prognosis of the patients with low CEACAM1 expression and high tumor pathological grade were poorer than those patients with high expression and low pathological grade, $P < 0.05$. Clinically, it is possible to predict the prognosis among the patients of breast cancer by measuring CEACAM1 gene expression in the tumor tissues.

Key Words: CEACAM1, breast cancer, ER, PR, prognosis

Introduction

Breast cancer is the leading cause of cancer in Southeast Asian women, and is second only to gastric cancer in East Asian women. In some areas of China, the incidence of breast cancer is increasing by 3-4% per year, greater than that of the worldwide increasing rate. Recently, molecular abnormality of the carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) was identified in breast cancer, which suggested that CEACAM1 might play an important role in breast carcinogenesis (5). CEACAM1, also known as CD66a and the biliary glycoprotein, is a highly abundant and broadly expressed glycoprotein of the immunoglobulin superfamily. It consists of a single Ig variable domain-like amino terminus, from one to three Ig constant domain-like regions, and a single membrane-spanning segment followed by either a short (CEACAM1-S) or long (CEACAM1-L) cytoplasmic domain. CEACAM1 is expressed on the cells

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of a variety of tissues, and is recognized as a tumor suppressor gene (7). It is involved in the intracellular adhesion activity and mediates intercellular interactions. Clinical studies show that CEACAM1 expression is detected in epithelial and vascular endothelial cells from bladder, prostate gland and oral of human cancers (8, 22-24). And current research indicates that the biological activity of CEACAM1 terminus of cells could down-regulate the growth of tumors and enhance the process of apoptosis of breast, rectum and lung cancer cells (9, 14, 20) suggesting that CEACAM1 may play some roles in the regulation of tumor development. Now, expression of CEACAM1 was found to be down-regulated among cancers originated from breast, rectum and prostate gland (3, 13, 16). However, there are few clinical studies on the role of CEACAM1 function in clinical progression of breast cancer and its correlation with the expression of estrogen recepter (ER) and progestogen receptor (PR) in patients with breast cancer.

In our study, we examined CEACAM1 gene expression in breast tissues from the patients with breast cancer, and analyzed its relationship with malignancy of tumor and survival of the patients. At same time, correlation between CEACAM1 and ER/PR activity in the tumors was investigated.

Materials and Methods

Patients and Tissues

Sixty female breast cancer patients were involved in our study, and the median age was 45 years (range from 20 to 65 years). All the patients were histologically proven with infiltrated ductal carcinoma. All the patients underwent mastectomy to remove the tumors at Qilu Hospital of Shandong University in 1997, and patients were followed up for 12 years. None of the patients received chemotherapy or radiotherapy before the surgery. All patients signed an informed consent form before being included in this study, which was approved by the Research Committee of Shandong University. Paraffin-embedded specimens were prepared by harvesting the tumor and its surrounding breast tissues within 3 cm from the margin of the cancer tissue as adjacent tissue. The surrounding breast tissues were considered as the normal breast tissues which were 5 cm away from the tumor. They were confirmed to be tumor-free by microscopic examination.

Immunohistochemistry (IHC) Staining

Paraffin-embedded specimens were routinely cut at 4 μm thickness. Serial sections were deparaffinized in xylene and rehydrated in a series of graded ethanols to Tris-buffered saline (TBS, 50 mM Tris, 150 mM NaCl, pH 7.5). The slides were microwaved for 15 min in TRIS-EDTA, pH 9.0. After cooling for 20 min, the slides were washed three times in TBS, blocked for 30 min at room temperature with a normal goat serum (Dako, Carpinteria, CA, USA), and incubated overnight at 4°C with monoclonal antibodies directed against ER/PR (Dako) or CEACAM1 (R&D, Minneapolis, MN, USA), respectively. The next morning, the sections were washed three times in TBS for 5 min and then incubated with a second biotinylated rabbit anti-mouse antibody (Dako) for 20 min at room temperature. After further washes in TBS, the sections were incubated with a streptavidin-horseradish peroxidase complex for 30 min followed by additional washes in TBS. Diaminobenzidine and hydrogen peroxide were used for visualization. Negative controls were treated the same way except for incubation with the primary antibody.

The staining results of ER and PR were evaluated by the system of Harvey (9) to estimate cancer cells IHC staining: [1] Staining of the cancer cells was recorded as follows: 0 for 0% cancer cell staining, 1 for 1/100 cancer cell staining, 2 for 1/100 to 1/10 cancer cell staining, 3 for 1/10 to 1/3 cancer cell staining, 4 for 1/3 to 2/3, and 5 for > 2/3 staining; [2] Intensity of positive cancer cells staining was rated on a scale from 0 to 3: 0 indicates no staining, 1 for light yellow staining indicating positive weak staining, 2 for moderate yellow staining indicating relatively strong staining and 3 for brown yellow staining indicating very strong staining. Sum of these two scales defined ER and PR expression in the tissue. On the basis of these results, tumors were defined as ER- and PR-positive if their total IHC score was greater than 2. We had modified immunohistochemical score of R.A.S (18) to estimate cancer cells IHC staining for CEACAM1 expression. Staining of the cancer cells was recorded as follows: 0 for 0% cancer cell staining, 1 for 1-30% cancer cell staining, 2 for 31-70% cancer cell staining, and 3 for > 70% cancer cell staining; intensity of positive cancer cells staining like above ER and PR described, sum of these two scales defined CEACAM1 gene expression in the tissue. Zero (0) indicates negative expression, 1-2 indicates weak, 3-4 moderate, and 5-6 intense staining. For statistical analysis, we combined negative and weak as low expression, moderate and intense as high expression.

Statistical Analysis

Statistical analysis was performed using the SPSS16.0 software package for Windows. *Chi*-square test, Log-rank and Cox proportional hazards were used to analyze the data. Variables with a value of

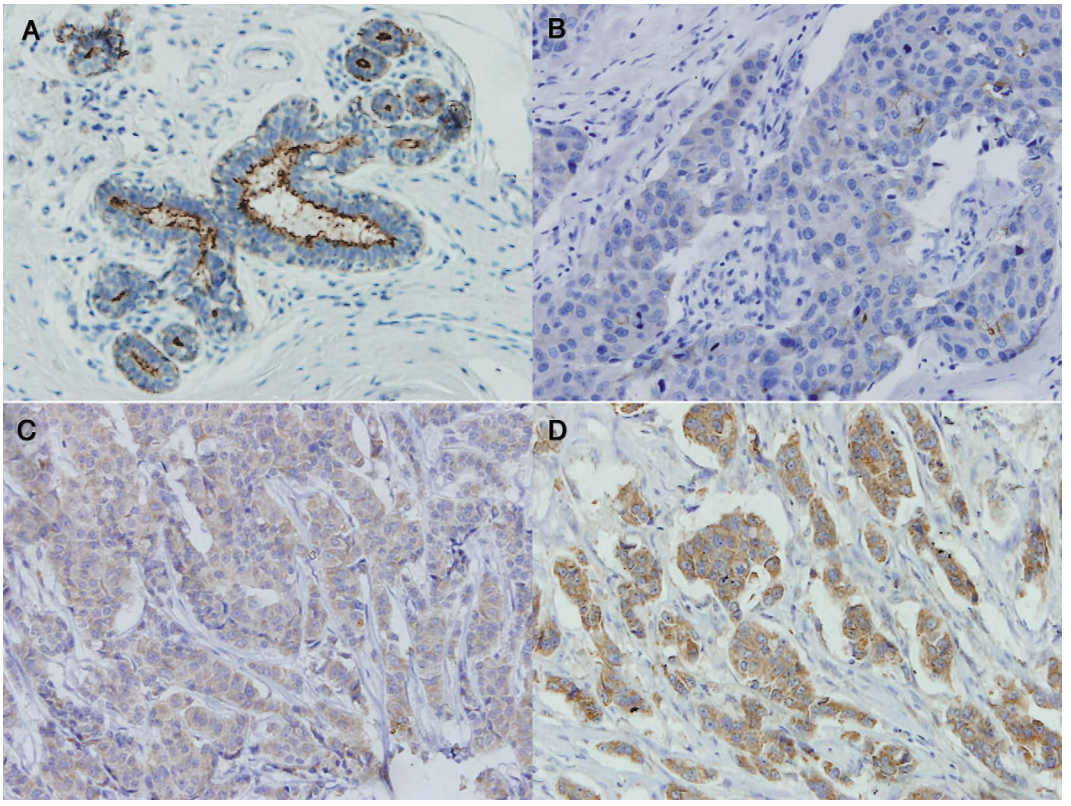

Fig. 1. (A) Intensity staining of CEACAM1 in normal breast tissues. The staining collected at the apical plasma membrane of epithelial cells; 400× magnification. (B) Weak expression of CEACAM1 in cancer tissues. The stain for CEACAM1 is hardly seen on the cancer cells; 400×. (C) CEACAM1 moderate expression in breast cancer cells with cytoplasmic pattern; 400×. (D) CEACAM1 intense expression in cancer tissues. The stain for CEACAM1 is mainly seen in the cytoplasm of breast cancer cells; 400×.

$P < 0.1$ in univariate analysis were used in a subsequent multivariate analysis based on the Cox proportional hazards model. A probability level of 0.05 was chosen for statistical significance. Differences were considered significant at $P < 0.05$.

Results

Characteristics of the Patients

General information of the patients is shown in Table 1. Among the 60 patients with breast cancer, 92.7% were staged clinically as TNM I-II and about 58.3% of the patients were with regional lymph nodes involvement. Thirty-three with both ER- and PR-positive expression were detected among 60 patients. In this group of the patients, age, tumor stage, grade of tumor differentiation and lymph node metastasis had no significant influence on the expression of CEACAM1, $P > 0.05$.

CEACAM1 Gene Expression in Cancer and Adjacent Tissues

CEACAM1 expression was detected in normal breast tissues predominantly at the apical plasma membrane of epithelial cells lining along the luminal surface (Fig. 1A). Epithelial cells of duct and gland lobule showed abundant staining. CEACAM1 staining was even distributed throughout cytoplasm of the cancer cells. We found that 12/60 (20%) cancer tissues appeared no CEACAM1 staining (data not shown) and 13/60 (21.7%) with weak expression of CEACAM1 (Fig. 1B). The adjacent breast tissues around the cancers showed moderate (Fig. 1C) to intense (Fig. 1D) CEACAM1 staining in most cases without negative expression. The expression of CEACAM1 in 65% (39/60) cases of primary tumors was lower than that in adjacent tissues, 28.3% (17/60) cases were equal to the adjacent tissued, and another 6.6% (4/60) cases were stronger than that in adjacent tissue (Table 2), $P < 0.05$.

Correlation between the Expression of CEACAM1 and ER/PR in Tumor Tissues

ER and PR were measured in cancer cells from

Table 1. Relationship between CEACAM1 status and other characteristics

Characteristic	No. of patient	CEACAM1		*P*-values
		Low	High	
Total	60	35	25	
Age				
≤ 50	37	13	14	> 0.05
> 50	23	12	21	
TNM stage				
I	18	4	14	> 0.05
II	39	20	19	
III	3	1	2	
Pathological grade				
I	19	5	14	> 0.05
II	31	17	14	
III	10	3	7	
Lymph node				
Positive	35	17	18	> 0.05
Negative	25	8	17	
ER				
ER-	15	13	2	< 0.05*
ER+	45	12	33	
PR				
PR-	22	14	8	< 0.05*
PR+	38	11	27	
ER and PR				
ER-/PR-	12	10	2	< 0.05*
ER+/PR+	33	8	25	
Survival condition				
Death (5 years)	9	6	3	< 0.05*
Survival (5 years)	51	19	32	
Death (10 years)	21	14	7	< 0.05*
Survival (10 years)	39	11	28	

Low = negative & weak, High = moderate & intense; *Correlation was analyzed by the *Chi*-square test method. Statistical significance between patients of low and high CEACAM1was observed in the incidence of ER, PR, ER/PR, 5 years and 10 years survival condition.

Table 2. Expression of CEACAM1 in primary tumor and adjacent tissues

Adjacent tissue	Cancer				Total
	Negative	Weak	Moderate	Intense	
Weak	4	2	2	0	8
Moderate	7	7	5	2	21
Intense	1	4	16	10	31
Total	12	13	23	12	60

60 cases and there were about 75% of cases with positive ER and 63.3% with positive PR (Table 1). Among tumors with the moderate or intense expression of CEACAM1, positive ER was found in 91.7% (33/35) of the cases. In the cases with weak or absent of expression of CEACAM1, 52% (13/25) of cases were ER-negative. The results indicate that expression of CEACAM1 had a positive relation with ER expression (Table 1), $P < 0.05$. At same time, PR positive cases were found in 27 of 35 cases with moderate or high expression of CEACAM1 (77.1%) of cancer tissues. And 56% (14/25) patients with negative or weak

Table 3. Multivariate analysis for overall survival

Variables	Odds ratio	95% CI	*P*-values
History grade	2.533	(1.311-4.895)	0.006*
CEACAM1 expression	0.215	(0.083-0.560)	0.002*

CI = confidence interval; *The hazard ratio of lower CEACAM1 expression compared to higher expression for cancer death. $P < 0.05$ indicates an independent and significant prognostic factor for overall survival.

activity of CEACAM1 showed no PR staining. The expression of CEACAM1 also had a significant positive relation with PR expression (Table 1), $P < 0.05$. In the ER+/PR+ group, higher CEACAM1 activity was identified (Table 1), $P < 0.05$.

Loss of CEACAM1 Expression Was Correlated with Worse Prognosis

The patients were followed up for a period of 12 years. The 5-year survival rate was 85% (51/60), and 10-year survival rate was 65% (39/60). Among 85% of patients with 5-year survival rate, moderate and high levels of CEACAM1 expression were detected in 62.7% (32/51) cases (Table 1). There were about 71.8% (28/39) cases of moderate or high expression of CEACAM1 in the patients with 10-year survival rate (Table 1). The group of moderate or high expression had 91.4% (32/35) with 5-year survival and 80% (28/35) with 10-year survival rate in comparison with absent or weak expression as 76% (19/25) and 44% (11/25), respectively (Table 1). There was a significant difference on the overall-survival rates between the two groups. The overall-survival rate of the patients with moderate and intense expression of CEACAM1 was significant higher than that of the patients with lower or absent expression of CEACAM1 (Fig. 2). No relationship between patient's age, tumor stage or lymph node status and survival rate was identified except of CEACAM1 expression and tumor pathological grade (OR, 0.215; CI, 0.083-0.560) (Table 3). Multivariate analysis indicated that the negative or weak expression ratio of CEACAM1 was found to be an independent and significant prognostic factor for survival.

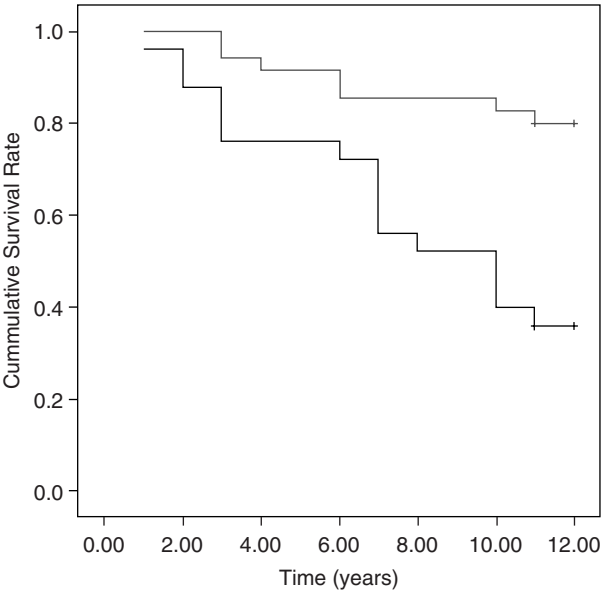

Fig. 2. Overall survival rate of patients with breast cancer grouped according to CEACAM1 expression status of the cancer tissues. Patients whose tumors expressed low (negative and weak) CEACAM1 (black curve) had a significantly poorer survival than patients whose cancer tissues were high (moderate or intense) CEACAM1 (gray curve), $P < 0.05$.

Discussion

CEACAM1 has been found to play a pivotal role in development and progression in cancers of different origins (2, 6, 12, 17, 19). Current researches reported that the expression of CEACAM1 was decreased in tumors of the prostate (3, 8) and rectum (4, 15). Our present study showed that there was about 65% of cases with lower expression of CEACAM1 among breast cancer tissues in comparison with adjacent breast tissues. As an inhibitor of carcinogenesis and a promoter of cancer apoptosis (9, 11, 14), CEACAM1 has an effect on maintaining the formation of normal breast acini and duct, growth progression of normal cells (10) and inhibition of cancer cell growth. Losing polarity and over-proliferation of cells occurred when expression of CEACAM1 decreased in tissues (20). As an adhesion molecule, the high levels of CEACAM1 expression in epithelial cells of normal breast tissues indicated that CEACAM1 may play a key role for cell-cell adhesion. Loss or down-regulation of CEACAM1 can reduce adhesion ability between tumor cells and attachment between cells (12). At same time, CEACAM1 may be involved in the regulation of the gene activities in tissue matrix. Kilic's study showed that expression of CEACAM1 in microvascular endothelial cells of brain hemangioblastoma, renal small cell carcinoma, stimulated proliferation human microvascular endothelial cells and accelerated formation of microvessels (4, 8). CEACAM1was

down-regulated in prostate intraepithelial neoplasia (PIN) compared with its up-regulation in adjacent blood vessels around the lesion (21). These findings indicate that CEACAM1 might be involved in tumor angiogenesis and accelerated metastasis (8, 21). Down-regulation of CEACAM1 has been observed in breast cancer tissues compared with the adjacent nonmalignant epithelia in this study. Expression of CEACAM1 in adjacent tissues was higher than in tumor tissues. Down-regulated CEACAM1 gene expression may affect the development and progression of the cancer cells and dedicates the response to treatment and prognosis of patients with breast cancer.

For analysis of CEACAM1 expression on the survival of the breast cancer patients, the patients were followed-up for more than 10 years according to the level of CEACAM1 activity. The expression of CEACAM1 had close correlation with the overall survival of the patients. The prognosis of the patients with CEACAM1-negative or weak expression was poor than those with moderate or intense expression. Breast cancer is known to be a hormone-regulated tumor. ER and PR affect growth regulation, differentiation of tumor cells (1) and survival of patients with breast cancer. Our current study showed that there was a relationship between positive-staining of ER/PR and the CEACAM1 expression level within the cancer cells. 21.7% (13/60) of primary tumors with ER-negative had CEACAM1-negative or weak staining in cancer cells, and 55% (33/60) primary tumors with ER-positive CEACAM1-moderate or intense ($P < 0.05$). Among the PR-positive group, 45% (27/60) were demonstrated CEACAM1 moderate or intense expression within cancer tissues ($P < 0.05$). Our results suggested that there were possible interactions between expression of the hormone receptors and CEACAM1 activity in breast cancer cells. Whether CEACAM1is regulated by hormones in breast cancer needs further research. Riethdorf *et al*. have demonstrated loss of CEACAM1 expression in breast cancer, but found no correlation to ER status (16). The discrepancy may be due to differences between ethnic groups.

In summary, our study demonstrated that CEACAM1 was down-regulated in breast cancer. CEACAM1 expression was also found to be high among patients with ER or/and PR positivity and better prognosis during the 5- and 10-year follow-up period. Although we have found a highly significant positive correlation between the expression of CEACAM1 and ER or/and PR of the cells of the primary breast cancer, the mechanism is still unclear. The mechanisms of interaction between CEACAM1 and ER or/and PR in primary breast cancer need further studies.

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