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Original Article

Combined expression of E-cadherin and KAI1 is associated withlymph node metastasis and poor prognosis in breast cancer

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Abstract: *Background:* Metastasis, and not the primary tumor, is the main cause of breast cancer-related mortality. E-cadherin (E-cad) and KAI1 have been shown to play crucial roles in tumor invasion and metastasis, however, the association between the expression of E-cad and KAI1 in breast cancer patients remains unclear. *Methods:* 96 cases were diagnosed as invasive ductal breast cancer, and forty cases as benign hyperplasia. The immunohistochemical was used to detect E-cad and KAI1 expression in cases of invasive ductal carcinomas of the breast, and benign hyperplasia. The relationship between E-cad and KAI1 was analyzed as well as the relationship between two tumor markers and potential metastasis of invasive ductal breast cancer. *Results:* The expression of both E-cad and KAI1 protein in breast cancer tissue was significantly lower than that in benign breast tissue. The expression rates of E-cad and KAI1 were lower for patients with axillary lymph node metastasis than for normal lymph nodes. And the expression of E-cad and KAI1 was also related to the expression of estrogen and progesterone receptors in breast carcinoma. The loss of E-cad and KAI1 function was also associated with poor prognosis in breast cancer. *Conclusions:* The low expression levels of E-cad and KAI1 were correlated with the malignant progression of breast cancer. E-cad and KAI1 may be considered as valuable markers for staging human breast cancer and predicting cancer prognosis.

Keywords: Metastasis, breast cancer, E-cadherin, KAI1

Introduction

Breast cancer is the most prevalent malignant disease affecting the physical and mental health of women, and it is one of the leading causes of death among women [1, 2]. Metastasis, and not the primary tumor, is the main cause of breast cancer-related mortality [3], andit is estimated that 20%-30% of breast cancer patients develop metastasis [3]. Poor prognosis has been attributed to tumor invasion and metastasis. Therefore, identification of prognostic markers of metastatic risk could identify breast cancer patients with a high risk for developing metastasis, and thus help to improve the clinical management of these patients.

The processes underlying tumor invasion and metastasis involve a cascade of sequential events, that involve the cell adhesion molecules (CAMs) [i.e., E-cadherin (E-cad)], which have been shown to play a crucial role in tumor invasion and metastasis [4]. E-cad is a transmembrane glycoprotein that mediates calcium-dependent intercellular adhesion, and is specifically involved in epithelial cell-to-cell adhesion [4]. Studies have shown that loss of E-cadherin expression is associated with the acquisition of invasiveness and a more advanced tumor stage for many cancers, such as oral squamous cell carcinoma, ovarian cancer, colorectal and hepatocellular carcinoma, and breast cancer [5-10].

The role of KAI1 as a possible metastasis suppressor was first identified in prostate cancer cells [11]. Dong *et al.* identified the location of the *KAI1* (*Kang Ai*in Chinese) gene on chromosome 11p, with ten exons and nine introns

Table 1. Clinicopathological characteristics of breast cancer patients

Characteristics	Cases	
	n	(%)
Ages (years)		
≤50	58	60.42
>50	38	39.58
Tumor size (cm)		
≤2.0	73	76.04
>2.0	23	23.96
TNM stage		
I	20	20.83
II	56	58.33
III	20	20.83
Histological grade		
I	56	58.33
II-III	40	41.67
Lymph node metastasis		
No	42	43.75
Yes	54	56.25

spanning approximately 80 kb [12]. KAI1 plays a role in growth inhibition and invasion, and exists in two isoforms, with 267 residues in isoform-1 and 242 residues in isoform-2 [13]. KAI1 suppresses metastasis by multiple mechanisms regulating inhibition of cell motility, adhesion, fusion, and proliferation. Many studies have shown that decreased KAI1 expression could be a useful marker for metastatic, invasive, and prognostic factor in many human tumors, such as lung, gastric, liver, colorectal, bladder, esophageal, and prostatic cancer [14-21]. Loss or reduced expression of KAI1 has also been reported in the tissues of metastatic breast tumors, when compared to benign and early stage breast tumor samples [22]. Down-regulation, both at the transcription and translational levels, has also been implicated in brain metastasis during breast cancer progression [23].

The objective of the study is to determine the correlation between E-cad, KAI1 expression and metastasis as well as poor prognosis in breast cancer patients, we investigated the expression of E-cad and KAI1 in 96 breast cancer cases. And E-cad and KAI1 may serve as markers of breast cancer metastasis, and may be considered as possible targets of breast cancer therapy.

Materials and methods

Patients and samples

In total, 96 patients who received surgery for primary breast cancer were randomly selected from the Second Xiangya Hospital of Central South University, between April 2007 and April 2009. Forty benign hyperplasia cases were also obtained. The diagnosis of breast cancer and benign hyperplasia was confirmed by pathological staining. Tumor tissue samples were obtained from the patients at the time of surgery, and the patients were followed-up until December 2014. Clinical data were obtained from the medical records and showed in **Table 1**. Prior informed consent was obtained and the study protocol was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University.

Immunohistochemistry

Formaldehyde-fixed, paraffin-embedded tissue sections were cut to 4 μm thickness, then deparaffinized. Immunohistochemistry was performed with a panel of primary antibodies against E-cad, KAI1 (Santa Cruz Biotechnology, Santa Cruz, CA, USA), estrogen receptors (ERs) and progesterone receptors (PRs) by using a streptavidin-biotin complex following relevant antigen retrieval techniques according to standard protocols. Tissues incubated with phosphate-buffered saline instead of primary antibodies were used as negative controls. Slides were independently reviewed by two observers to evaluate the staining pattern of the protein under the light microscope. Ten visual fields were randomly selected from each slide. Expression scores were assigned semiquantitatively according to both the extent and intensity of immunopositivity. The intensity of the positive result was scored as follows: negative (0); weak (1); moderate (2); and strong (3). The extent of positivity was scored according to the percentage of cells that stained positive: <10% (1); 11%-50% (2); 51%-75% (3); and >75% (4). Expression was considered positive when the scores were >1.

Statistical analysis

Pearson's chi-square test or Fisher's exact tests were used to analyze clinicopathological parameters and possible associations between the expression levels of E-cad and KAI1. And a

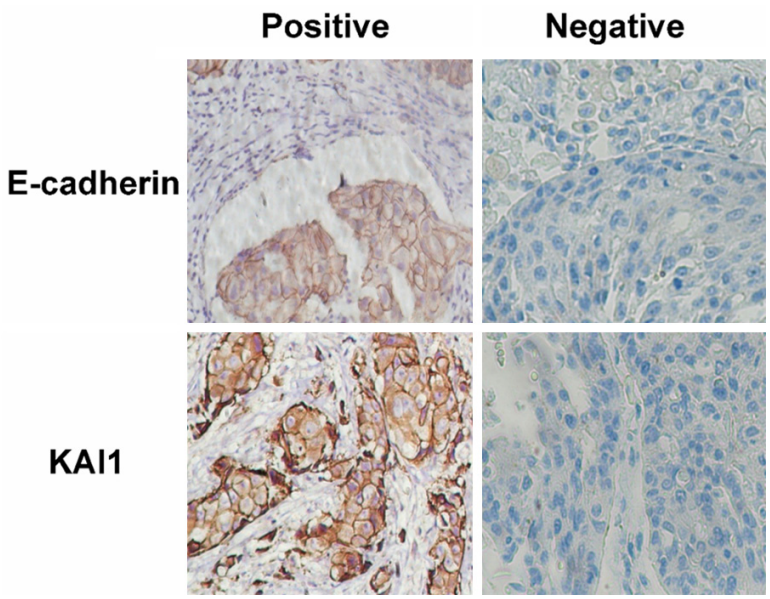

Figure 1. Expression of E-cad and KAI1 in breast cancer. The membranous expression of E-cad and KAI1 was seen in breast cancer tissues. Magnification: ×200.

p-value less than 0.05 was considered statistically significant.

Results

Expression of E-cad and KAI1 in invasive breast ductal carcinomas and benign hyperplasia

The expression levels of E-cad an KAI1 were compared between two groups, comprised of 96 patients with invasive breast ductal carcinoma and 40 subjects with benign hyperplasia (**Figure 1**). A loss of E-cad expression was found in 54 cases with invasive breast ductal carcinoma (54/96), while high E-cad expression was found in the remaining cases (42/96). Regarding the expression levels of E-cad in 40 cases with benign hyperplasia, there was 5 case with a loss of E-cad expression (5/40), and high expression of E-cad was found in the remaining 35 cases (35/40). Expression of E-cad was significantly different between invasive breast ductal carcinomas and benign hyperplasia (P<0.001, **Table 2**).

KAI1 expression was also characterized for these two groups. Based on the results of immunostaining, low KAI1 expression was detected in 58 of 96 patients with invasive breast ductal cancer, and high expression of KAI1 in the remaining 38 cases (38/96). In the benign hyperplasia group, there was low expression of KAI1 in 7/40 patients, and high expression of KAI1 in 33/40 patients. KAI1 expression was also significantly different between these two groups (P<0.001, **Table 2**). The results demonstrated that E-cad and KAI1 expressions were related to the malignancy of breast diseases.

Loss of E-cad and KAI1 expression was correlated with metastasis of breast cancer

In 96 invasive breast ductal cancer cases, there were 54 cases with axillary lymph node metastasis (ALNM), and 42 cases without ALNM. In the ALNM cases, 75.9% (41/54) showed loss of E-cad expression and 24.1% (13/54) showed high expression of E-cad. However, in patients without ALNM, E-cad expression was found at a low expression level in 30.9% (13/42) of patients, and found at a high expression level in 69.0% (29/42) of patients. The loss of E-cad expression in breast cancers with ALNM was higher than in breast cancers without ALNM (P<0.001, **Table 3**).

There were 40/54 (74.1%) cases with low KAI1 expression and 14/54 (25.9%) cases with high KAI1 expression for the ALNM patients. In cases without ALNM, low KAI1 expression occurred at a frequency of 18/42 (42.8%), and high KAI1 expression occurred at a frequency of 24/42 (57.1%). KAI1 immunoreactivity occurred significantly less frequently in breast cancer samples with ALNM than in samples without ALNM (P<0.001, **Table 3**).

The results above showed that E-cad and KAI1 expressions were related to the metastasis of breast cancer.

Association of E-cad and KAI1 expression with estrogen and progesterone receptors

The levels of ERs and PRs were quantitated by immunohistochemistry. ER- and PR-positive expressions were observed in 27 and 29 cases of 42 patients without ALNM, respectively (**Table 4**). EP- and PR-positive expressions were detected in 15 and 19 cases of 54 ALNM

Table 2. Expression of E-cadherin and KAI1 in invasion breast ductal carcinoma and benign breast diseases

Groups	n	E-cadherin		*P* value	KAI1		*P* value
		Low	High		Low	High	
Invasion breast ductal carcinoma	96	54	42	**<0.001**	58	38	**<0.001**
Benign breast diseases	40	5	35		7	33	

P value obtained from Pearson's Chi-Square or Fisher's exact tests. Bold, statistically significant.

Table 3. Association of E-cadherin and KAI1 expression with axillary lymph node metastasis

Groups	n	E-cadherin		*P* value	KAI1		*P* value
		Low	High		Low	High	
Non-axillary lymph node metastasis	42	13	29	**<0.001**	18	24	**<0.001**
Axillary lymph node metastasis	54	41	13		40	14	

P value obtained from Pearson's Chi-Square or Fisher's exact tests. Bold, statistically significant.

Table 4. Expression of ER and PR in breast cancer

Groups	n	ER		*P* value	PR		*P* value
		-	+		-	+	
Non-axillary lymph node metastasis	42	15	27	**<0.001**	13	29	**<0.001**
Axillary lymph node metastasis	54	39	15		35	19	

P-value obtained from Pearson's Chi-Square or Fisher's exact tests. Bold, statistically significant.

Table 5. Association of E-cadherin and KAI1 expression with ER and PR expression

Groups	n	E-cadherin		*P* value	KAI1		*P* value
		Low	High		Low	High	
ER(+)/PR(+)	36	6	30	**<0.001**	14	22	**<0.001**
ER(+)/PR(-)	6	4	2		3	3	
ER(-)/PR(+)	12	5	7		7	5	
ER(-)/PR(-)	42	39	3		34	8	

P-value (ER(+)/PR(+) vs. ER(-)/PR(-)) obtained from Pearson's Chi-Square or Fisher's exact tests. Bold, statistically significant.

patients, respectively (**Table 4**). This suggests that lymph node metastasis occurred more frequently in EP- and PR-negative cases than in positive one ($P<0.001$). We further analyzed the association of E-cadand KAI1 expression with ER and PR. We found that high E-cad expression occurred more frequently in ER(+)/PR(+) cases than in ER(-)/PR(-) cases ($P<0.001$, **Table 5**). KAI1 expression was consistent with E-cad ($P<0.001$, **Table 5**). ER- and PR-negative patients have poor prognosis of breast cancer, therefore loss of E-cad and KAI1 correlated with poor prognosis of breast cancer patients.

Association between E-cad and KAI1 expression in breast cancer

We investigated the association between the expression of E-cad and KAI1 in breast cancer patients (n=96), and found that there were 29 cases with both high E-cad expression and high KAI1 expression (30.2%), while both low E-cad expression and KAI1 expression occurred in 45 (46.9%) of 96 cases. There was a positive correlation between the expression of E-cad and KAI1 in breast cancer ($P<0.001$, **Table 6**).

Because losses of E-cad and KAI1 expression were associated with lymph node metastasis, we further investigated the association of their combined expression with lymph node metastasis (**Table 7**). Compared with cases with E-cad (high) and KAI1 (high) expression, E-cad (low) and KAI1 (low) expression subjects were more inclined to occurred with lymph node metastasis ($P=0.002$, **Table 7**).

Loss of E-cad and KAI1 expression was correlated with poor prognosis of breast cancer

We also examined the association of the expression of E-cad and KAI1 with the overall survival in breast cancer patients. Compared with tumors with and E-cad (high) or KAI1 (high) expression, tumors with E-cad (low) or KAI1 (low) expression were associated with shorter overall survival in breast cancer patients ($P=0.0335$, 0.0308, **Figure 2A** and **2B**). We further investigated the association of their com-

Table 6. Correlation between the expression of E-cadherin and KAI1 in breast cancer

	E-cad (low)	E-cad (high)	
KAI1 (low)	45	13	
KAI1 (high)	9	29	**p<0.001**

P value was obtained from Pearson's Chi-Square. Bold, statistically significant.

Table 7. Association of combination of E-cadherin and KAI1 with lymph-node metastasis of breast cancer

	Lymph-node metastasis		*P* value
	No (n)	Yes (n)	
E-cad (low)/KAI1 (low)	12	33	
E-cad (low)/KAI1 (high)	4	5	0.286[a]
E-cad (high)/KAI1 (low)	8	5	**0.019**[b]
E-cad (high)/KAI1 (high)	18	11	**0.002**[c]

P-value obtained from Pearson's Chi-Square or Fisher's exact tests. [a]E-cad (negative)/KAI (positive) vs. E-cad (negative)/KAI (negative); [b]E-cad (positive)/KAI (negative) vs. E-cad (negative)/KAI (negative); [c]E-cad (positive)/KAI (positive) vs. E-cad (negative)/KAI (negative). Bold, statistically significant.

bined expression with overall survival rate of breast cancer patients. And cases with both low expression of E-cad and KAI have poor prognosis (*P*=0.0178, **Figure 2C**). The results suggested that E-cad and KAI1 would be prognostic factors in breast cancer patients.

Discussion

Ongoing research has indicated the important role of E-cad and KAI1 in the process of cancer development. These components especially influence the stage of metastasis. In the present study, we examined the expression of E-cad and KAI1 in 50 breast cancer cases and 40 control ones with benign hyperplasia, and found that E-cad expression decreased in breast cancer samples compared with the control samples. Low E-cad expression occurred significantly more frequently in breast cancers with ALNM than in breast cancers without ALNM. Our findings are consistent with a previous study showing that E-cad is downregulated in breast cancer and is associated with breast cancer metastasis [4, 24, 25]. Additionally, we found that the expression of KAI1 was also downregulated in breast cancer samples compared with control samples. The expression level of KAI1 was significantly lower in breast cancer with ALNM than in cases without ALNM. Our finding that KAI1 levels were low in breast cancers was consistent with previous studies showing KAI1 downregulation in tumors such as breast cancers [26-28]. And we also found that loss expression of E-cad and KAI1 was also associated with poor prognosis of breast cancer patiens. In addition, previous studies reported that E-cad and KAI1 played important roles in tumor occurrence and progression. Their expression was significantly downregulated in many cancers, including hepatocellular cancer, lung cancer, retinoblastomas, endometrial carcinomas, and gastric cancers, which correlated with malignancy, metastasis, and clinical stages [29-34].

However, it is unclear whether E-cad downregulation is associated with loss of KAI1 expression in breast cancer. In the present study, we found that the expression of KAI1 was positively correlated with the expression of E-cad in breast cancer patients, suggesting that KAI1 may contribute to the downregulation of E-cad. This finding was supported by a previous report showing that KAI1 may stabilize or strengthen E-cad-dependent intercellular adhesion, by regulating β-catenin-mediated signal transduction of cancer cells, and consequently preventing cancer cells from migrating from the primary tumor site [35].

It is well-known that the ERs and PRs contribute to breast cancer progression, ER- and PR-positive breast cancer patients usually receive endocrine treatment [36]. Furthermore, the lack of ERs and PRs has been reported to be associated with higher tumor grade, larger tumor size, higher degree of lymph node involvement, and aggressive histopathological types of tumors [37]. In the present study, we found that there was a significant correlation between E-cad, KAI1 and expression of ERs and PRs. Loss of E-cad and KAI1 expression occurred more frequently in ER- and PR-negative cases than positive cases. It demonstrated that loss of E-cad and KAI1 predicted a poor prognosis for breast cancer.

In summary, we characterized the expression of E-cad and KAI1 in breast cancer, and analyzed the correlation of E-cad and KAI1 expression alone and in combination with metastasis and the prognosis of breast cancer patients.

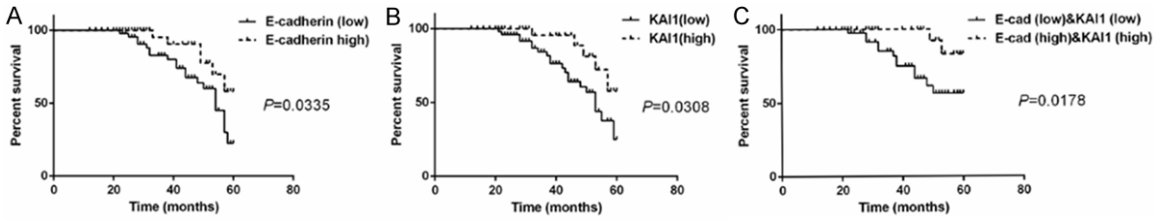

Figure 2. A-C. Overall survival was analyzed in the same cohort of breast cancer patients and the results showed that patients in the low E-cad and KAI1 expression group have poorer overall survival than those in the high E-cad and KAI1 expression group.

We found that low E-cad or low KAI1 expression was associated with lymph node metastasis and poor prognosis for breast cancer. Combined low E-cad and low KAI1 expression was associated with lymph node metastasis and poor prognosis of breast cancer. The present study therefore suggested that E-cad and KAI1 can serve as markers of breast cancer metastasis, and may be possible targets of breast cancer therapy.

Disclosure of conflict of interest

None.

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