Int J Clin Exp Pathol 2016;9(7):7451-7457
www.ijcep.com /ISSN:1936-2625/IJCEP0025815

Original Article

Overexpression of VCAM-1 is correlated with poor survival of patients with breast cancer

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Received February 10, 2015; Accepted April 28, 2016; Epub July 1, 2016; Published July 15, 2016

Abstract: Vascular cell adhesion molecule-1 (VCAM-1), a transmembrane sialoglycoprotein and member of the immunoglobulin gene family, is suspected to be involved in inflammation-mediated cancer cell migration and tumor invasion; the activity of VCAM-1 is increased in cancer cells. To determine the relationship between VCAM-1 and breast cancer prognosis, we analyzed VCAM-1 expression in tissue microarrays of tumors from 261 breast cancer patients via immunohistochemistry. On a multivariate Cox regression analysis, a high expression of VCAM-1 in the tumor cells was significantly correlated with a short overall survival ($P = 0.035$, hazard ratio = 1.65; 95% confidence interval, 1.037-2.624), as well as the Ki-67 status, human epidermal growth factor receptor 2 and epidermal growth factor receptor statuses, and molecular subtype ($P = 0.018$, $P = 0.004$, $P = 0.047$, and $P = 0.016$, respectively). VCAM-1 expression was not correlated with age, estrogen or progesterone receptor status, lymph node status, or Nottingham histologic grade. VCAM-1 overexpression was significantly correlated with poor prognosis of breast cancer ($P = 0.019$), thereby suggesting that VCAM-1 is a potential prognostic factor for breast cancer.

Keywords: Breast cancer, survival, prognosis, VCAM-1

Introduction

Breast cancer is the second leading cause of cancer-related mortality in women worldwide [1]. In clinical studies, more than 90% of breast cancer-related deaths were determined to be caused by distant metastases, such as lung, liver, and brain metastases [2, 3]. Metastasis is a complex process that involves a series of sequential steps: invasion and intravasation of tumor cells from the primary tumor sites to the circulation, extravasation of these circulating tumor cells into distant tissues, and final colonization of the seeded organ [4, 5]. These steps of metastasis depend on the complex interactions between tumor cells and the unique microenvironments of different organs [6, 7].

Vascular cell adhesion molecule-1 (VCAM-1), also known as cluster of differentiation 106 (CD106), is a 110-kDa transmembrane sialoglycoprotein and member of the immunoglobulin gene family [8, 9]. VCAM-1 is constitutively expressed on many different types of endothelial and stromal cells and mediates cellular adhesion [9]. VCAM-1 mediates the process of cancer cell migration: it acts by binding to leukocyte integrins with α4β1 (VLA4) and circulating monocytes, granulocytes, lymphocytes, and leukocytes with integrin α4β7, thereby resulting in the movement of leukocytes in the blood [10, 11]. After mediating leukocytes in the blood, VCAM-1 mediates the adhesion of leukocytes on endothelial cells and activates signaling pathways to facilitate leukocyte passage from the blood to the tissue. In endothelial cells, VCAM-1 clustering can trigger the activation of Rac1, a Rho-like GTPase, via antibody cross-linking or integrin binding [12]. The activation of Rac1 results in the rearrangement of the cytoskeletal network; this process is thought to alter the tight junctions between vascular endo-

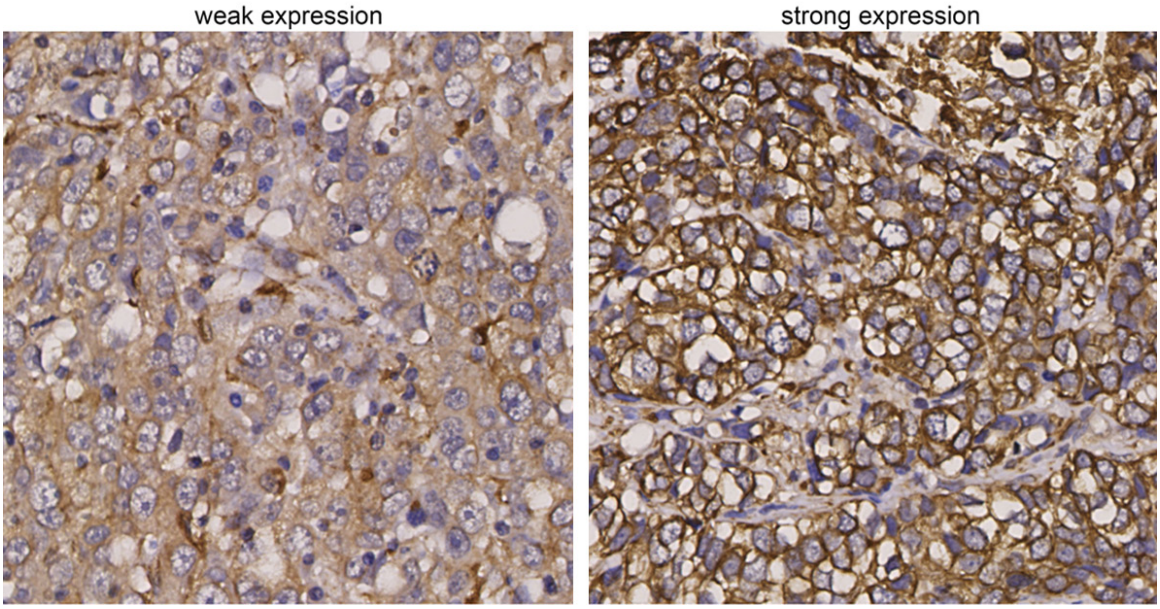

Figure 1. Examples of scoring of IHC staining of VCAM-1 expression in breast cancer tissue (200×).

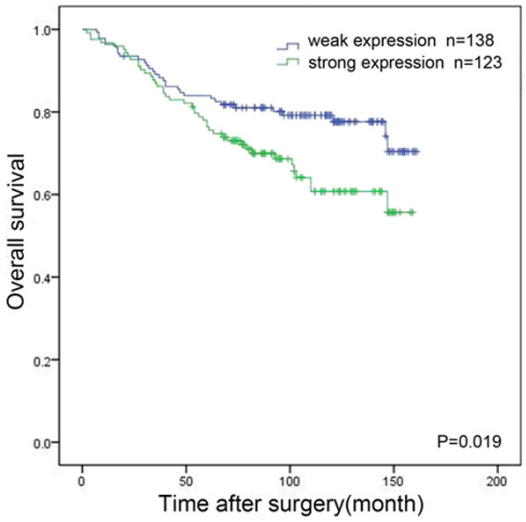

Figure 2. Kaplan-Meier estimates of survival for weak versus strong VCAM-1 expression in tumor tissue shows that strong expression of VCAM-1 in tumor tissue was significantly associated with shorter overall survival.

thelial cells, thus facilitating transendothelial migration of cancer cells [13, 14]. All these interactions play important roles in the process of metastasis to distant organs and growth of the metastatic tumor [15].

High expression of VCAM-1 has been identified in breast cancer, gastric cancer, renal cell cancer, and melanoma [16]. The results of previous animal studies have shown that VCAM-1 expression is significantly correlated with the occurrence of bone and lung metastasis; decreased VCAM-1 expression reduces the incidence of metastasis [15, 17, 18]. However, there is no sufficient direct evidence that indicates the correlation between VCAM-1 expression and the prognosis of breast cancer. Therefore, we performed this study to determine the correlation between VCAM-1 expression in tissue and breast cancer prognosis.

Materials and methods

Patient data

A breast cancer tissue microarray (TMA) containing samples of primary invasive breast tumors from 261 patients were obtained from the National Engineering Center for BioChips in Shanghai, China. To prepare the arrays, a 1.5-mm core of tumor tissue was removed from each tumor; in general, cores were taken from the peripheral aspect of the tumor, and necrotic tissue was avoided. All 261 patients had undergone mastectomy and/or axillary dissection (based on their clinical examination findings: ultrasonography, magnetic resonance imaging, and mammography) between 2001 and 2008; we excluded patients who had received preoperative hormone therapy or chemotherapy.

Table 1. Univariate and multivariate COX regression analyses of the impact on overall survival for different patient and characteristics

Variable	Univariate			
	n	HR[a]	95% CI[a]	*P* value
VCAM-1 (weak vs. strong)	261	1.73	1.088-2.749	0.020
ER[a] (negative vs. positive)	261	0.63	0.399-0.995	0.047
PR[a] (negative vs. positive)	261	0.47	0.289-0.772	0.003
Her2 (weak vs. strong)	261	1.18	0.704-1.966	0.535
Ki67 (negative vs. positive)	261	1.21	0.757-1.941	0.422
NHG[a] (1, 2, 3)	261	1.13	0.695-1.832	0.624
N category (N0, N1, N2, N3)	261	1.37	1.094-1.724	0.006
T category (T1 vs T2 vs T3[b])	261	1.61	1.077-2.392	0.020
CK5/6 (negative vs. positive)	261	1.14	0.676-1.924	0.623
EGFR[a] (negative vs. positive)	261	0.82	0.503-1.331	0.419
	Multivariate			
	n	HR[a]	95% CI[a]	*P* value
VCAM-1 (weak vs. strong)	261	1.65	1.037-2.624	0.035
ER[a] (negative vs. positive)	261	1.19	0.660-2.156	0.560
PR[a] (negative vs. positive)	261	0.45	0.240-0.842	0.012
N category (N0, N1, N2, N3)	261	1.29	1.024-1.620	0.030
T category (T1 vs T2 vs T3[b])	261	1.44	0.941-2.192	0.094

[a]: *HR* hazard ratio, *CI* confidence interval, *ER* estrogen receptor, *PR* progesterone receptor, *NHG* Nottingham histological grade, EGFR epidermal growth factor receptor; [b]: No patient have T4 tumor.

Tissue immunohistochemistry staining

The expression of VCAM-1, ER, PR, Her2, and Ki-67 was measured in the arrays via immunohistochemistry (IHC). VCAM-1 expression was determined by using a VCAM-1 special antibody (Abcam, ab106777), at a dilution as 1:200. Membrane ERFR expression was determined by using a EGFR special antibody (CST, #2085), at a dilution as 1:100, with >10% immunostained membrane being considered positive and ≤10% immunostained membrane considered negative. ER and PR negativity were defined according to current Swedish clinical guidelines (<5% positive nuclei). Ki-67 expression was determined using a cutoff value of 14%, with >14% immunostained nuclei being considered positive and ≤14% immunostained nuclei considered negative. Her2 expression was assessed semiquantitatively by using a standard protocol (HercepTest; DakoCytomation, Shanghai, China) [19], and fluorescence in situ hybridization (FISH) analysis was performed in Her2-positive samples with scores of 2+. Her2 expression was designated as weak (IHC grade 0-1+ or FISH-) or strong (IHC grade 3+ or FISH+). Lymph node metastasis was staged according to the American Joint Committee on Cancer TNM system. This study was approved by the Human Research Ethics Committee of the Wuhan Union Hospital.

Scoring and evaluation

IHC staining was evaluated by two experienced pathologists blinded to the clinical information. VCAM-1 staining intensity was evaluated in the tumor cell membrane. The total score was the product of the scores for the intensity and positive rate of staining: 0 points for <10%; 1 point for 11%-20%; 2 points for 21-75%; and 3 points for >75% of cells stained; the intensity of staining was graded on the following scale: 0, negative; 1, low; 2, moderate; and 3, strong intensity. In this study, a final total score of <3 and ≥3 for VCAM expression was divided into low or high expression, respectively (**Figure 1**). An Aperio ScanScope slide scanner was used to scan the slides; Image Scope software (Aperio), followed by Illustrator (Adobe), were used when representative areas were obtained.

Statistical analysis

The Cox regression proportional hazards models were used to estimate hazard ratios (HRs) for death from breast cancer according to VCAM-1 expression in univariate and multivariate analyses. The covariates with a *P*-value less than 0.05 were used in the multivariate analysis. ANOVA and the Pearson chi-square test were used to analyze the different distributions between VCAM-1 expression levels and other pathological and clinical parameters (age, histological grade, lymph node status, and the ER, PR, Her2, and Ki-67 status). The effect of high VCAM-1 expression on overall survival was assessed by using Kaplan-Meier analysis and the log-rank test.

All statistical tests were two-sided, and *P*-values <0.05 were considered statistically significant. All calculations were performed using SPSS Statistics version 22 software (International Business Machines Corporation).

Table 2. Associations between VCAM1 expression and clinicopathologic features in breast cancer

Factor		Vcam1 staining intensity		*P* Value
	n	0	1	
All n (%)	261	138 (52.9%)	123 (47.1%)	
Age				0.931[a]
Median (range)	55 (31-88)	56 (31-86)	57 (31-88)	
NHG				0.825[b]
I (%)	32 (12.3)	18 (13.0)	14 (11.3)	
II (%)	204 (78.2)	108 (78.3)	96 (78.0)	
III (%)	25 (9.6)	12 (8.7)	13 (10.6)	
Missing (%)	0 (0)			
Nodal status				0.679[b]
N0 (%)	120 (46.0)	61 (44.2)	59 (48.0)	
N1 (%)	74 (28.4)	43 (31.2)	31 (25.2)	
N2 (%)	47 (18.0)	25 (18.1)	22 (17.9)	
N3 (%)	20 (7.7)	9 (6.5)	11 (8.9)	
Missing (%)	0 (0)			
ER status				0.624[b]
Negative (%)	102 (39.1)	52 (37.7)	50 (40.7)	
Positive (%)	159 (60.9)	86 (62.3)	73 (59.3)	
Missing (%)	0 (0)			
PR status				0.443[b]
Negative (%)	142 (54.4)	72 (52.2)	70 (56.9)	
Positive (%)	119 (45.6)	66 (47.8)	53 (43.1)	
Missing (%)	0 (0)			
Ki67 status				0.018[b]
≤14% (%)	170 (65.1)	99 (71.7)	71 (57.7)	
>15% (%)	91 (34.9)	39 (28.3)	52 (42.3)	
Missing (%)	0 (0)			
HER2 status[c]				0.003[b]
Weak (%)	194 (74.3)	113 (81.9)	81 (65.9)	
Strong (%)	67 (25.7)	25 (18.1)	42 (34.1)	
Missing (%)	0 (0)			
EGFR status				0.047[b]
Negative (%)	169 (64.8)	97 (70.3)	72 (58.5)	
Positive (%)	92 (35.2)	41 (29.7)	51 (41.5)	
Missing (%)	0 (0)			

[a]One-factor ANOVA. [b]Pearson chi-square test, 2-tailed *p* value. [c]Weak (score 0-1, or FISH-), strong (score 3, or FISH+).

Results

Strong VCAM-1 expression is associated with poor prognosis of breast cancer patients

Kaplan-Meier analysis demonstrated a significant correlation between VCAM-1 expression (strong vs. weak) and the overall survival of breast cancer patients (*P* = 0.019; **Figure 2**). The results of Cox analysis showed that strong VCAM-1 expression was an independent indicator of poor prognosis of breast cancer patients (*P* = 0.035, HR = 1.65; 95% confidence interval, 1.037-2.624) when the variables described in **Table 1** were included (ER, PR, N category, and T category). Other detailed results of the Cox analyses are demonstrated in **Table 1**.

VCAM-1 expression level is associated with clinicopathogical parameters

The association between VCAM-1 staining intensity and several clinical parameters (age, tumor size, Nottingham histological grade [NHG], lymph node metastasis, and ER, PR, Ki-67, and Her2 expression) was determined, as demonstrated in **Table 2**. The VCAM-1 staining intensity was significantly correlated with the Ki-67 status (*P* = 0.018) and Her2 status (*P* = 0.003). A similar correlation was also observed between VCAM-1 expression and the epidermal growth factor receptor (EGFR) status (*P* = 0.047).

VCAM-1 expression was not significantly associated with age, NHG, lymph node metastasis (*P* = 0.931, *P* = 0.825, and *P* = 0.679, respectively) nor with the ER or PR status (*P* = 0.624 and *P* = 0.443, respectively).

Discussion

VCAM-1 plays an important role in recruiting leukocytes to sites of inflammation [11, 20], and this essential process for carcinogenesis includes enhanced cell proliferation, alterations in epigenetic events, and, subsequently, inappropriate gene expression, thereby increasing resistance to apoptosis and promoting tumor neovascularization, invasion, and metastasis [21, 22]. Previous animal studies have

revealed that aberrant VCAM-1 expression contributes to metastasis of breast cancer to the lungs and bones [15, 23]. Previous clinical studies evaluating VCAM-1 expression focused mostly on circulating VCAM-1 levels and cancer prognosis in breast cancer [24, 25], lung cancer [26], ovarian cancer [27], head and neck cancer [28], colorectal cancer [29], and pancreatic carcinoma [30], among other cancer types. Our study is the first one to evaluate VCAM-1 expression levels in solid tumor tissue. VCAM-1 expression in solid tumor tissue is a more reliable marker, compared to circulating VCAM-1 levels, in elucidating the relationship between VCAM-1 expression and prognosis.

In our study, strong VCAM-1 expression in solid tumor tissue correlated significantly with shorter overall survival. This correlation remained significant even when other clinicopathogical factors were included in the COX regression analysis, suggesting that VCAM-1 is a potential independent prognostic factor for breast cancer.

Positive Ki-67 expression and strong Her2 expression are associated with high tumor proliferation and aggressive phenotypes [31-33]. In our study, samples with weak VCAM-1 expression tended to have lower Her2 expression and Ki-67 expression, indicating that weak VCAM-1 expression could be a protective factor against tumor proliferation and differentiation.

Moreover, in our study, VCAM-1 expression was significantly correlated with the EGFR status. A previous study suggested that EGFR activation could result in the up-regulation of VCAM-1 expression, which subsequently promoted the interaction between macrophages and cancer cells, as well as cancer cell invasion [34]. This could be one of the mechanisms by which VCAM-1 expression affects the prognosis of patients with malignant breast carcinoma.

VEGF-C/PI3Kα-driven remodeling of the lymph nodes promotes tumor metastasis by activating integrin α4β1 on the lymph node lymphatic endothelium. The activated integrin α4β1 then promotes expansion of the lymphatic endothelium in the lymph nodes and serves as an adhesive ligand that captures VCAM-1 metastatic tumor cells, thereby promoting lymph node metastasis [35]. Therefore, a higher VCAM-1 expression can lead to more lymph node metastasis and higher nodular stage. However, we did not observe any correlation between VCAM-1 expression and the nodular stage nor between VCAM-1 expression and the number of metastasized lymph nodes. The following may be the reasons for not observing any correlation: First, the count of metastatic nodes might not be accurate because this number depends greatly on the degree of completeness of the axillary lymph node dissection [36]. Second, the time gap between tumor initiation and surgery may have influenced the nodular stage [37]. Hence, the nodular stage that was classified may not be the actual lymph node metastasis status. To clarify these issues, further research is required. Furthermore, although VCAM-1 expression was not correlated with the nodular status, many patients with strong VCAM-1 expression died of recurrence and metastasis. This suggests that strong VCAM-1 expression indicates higher invasion and metastasis abilities of the cancer cells.

Our study had some limitations. Total VCAM-1 expression in the membrane was measured, not functional VCAM-1 expression, because functional VCAM-1 is more difficult to assess. In addition, as all the tumors were resected samples, it is difficult to make a distinction between functional and nonfunctional expression. Furthermore, VCAM-1 expression was measured only in the samples that were included in the TMA, not the whole tumor. Moreover, although this was a retrospective study, our study demonstrated the correlation between VCAM-1 expression and breast cancer prognosis and other clinicopathogical parameters.

In summary, our results suggest that VCAM-1 expression is significantly correlated with breast cancer prognosis, where higher expression levels tend to be associated with worse prognosis. This suggests that VCAM-1 is a potential independent prognostic factor of breast cancer and could be a suitable treatment target.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (grant no. 81001171) and the Key Technologies R&D Program of Hubei Province (grant no. 2007AA302B07).

We would like to thank editage (http://www.editage.com) for English editing.

Disclosure of conflict of interest

None.

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