Clinical significance of syndecan-1 and versican expression in human epithelial ovarian cancer

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Abstract. Proteoglycans are ubiquitous components of the extracellular matrix and cell surface, and may mediate tumor progression and metastasis. The aim of this study was to evaluate the expression of syndecan-1 and versican in epithelial ovarian cancer. We immunohistochemically evaluated the expression of syndecan-1 and versican in 111 patients with epithelial ovarian cancer, and analyzed the correlation of this expression with various observed clinicopathological features, including patient outcome. There is a significant correlation between primary and metastatic sites with respect to syndecan-1 and versican expression. Epithelial syndecan-1 expression was significantly lower in patients with advanced disease. Epithelial versican expression was significantly higher in patients with early disease, especially in clear cell adenocarcinoma patients. Stromal syndecan-1 and versican expression was significantly higher in patients with advanced disease. Multivariate analysis showed that negative epithelial syndecan-1 expression was an independent prognostic factor for progression-free survival. Stromal syndecan-1 and versican co-expression was of borderline significance for progression-free and overall survival. Loss of epithelial syndecan-1 expression and induction of stromal syndecan-1 and versican expression may be associated with tumor progression in epithelial ovarian cancer. Syndecan-1 and versican expression status can serve as an indicator of prognosis in patients with epithelial ovarian cancer.

Introduction

It is well known that the tumor environment is one of the major factors that determines the behavior of malignant cells. Proteoglycans are ubiquitous components of the extracellular matrix (ECM) and cell surface. Remodeling of the ECM through altered expression of molecules involved in cell-to-cell and cell-to-matrix interactions is essential for local tumor invasion and metastasis (1).

Heparan sulfate proteoglycans (HSPGs) consist of a core protein to which heparan sulfate glycosaminoglycan (HS-GAG) chains are covalently attached. These molecules are classified into several families according to the amino acid sequence of the core protein, and examples include syndecans and perlecans (2,3). Syndecans, which are cell-surface HSPGs, participate in cell-cell and cell-ECM interactions (2,4). To date, 4 members of the syndecan family have been identified, all having homologous transmembrane and cytoplasmic domains but differing extracellular domains (5). Syndecan-1 (CD138) is the most well characterized member of the family and its expression is localized entirely in epithelial cells, with stratified squamous epithelia showing the most abundant expression (6). Decreased expression of syndecan-1 has been reported to be correlated with increased tumorigenicity and tumor invasion (7-9). Syndecan-1 binds to various ECM components, such as collagen, fibronectin, thrombospondin, and tenascin, via the HS-GAG chains and most of its biological functions are considered to be associated with this process (2-4). It also binds to members of the heparin-binding growth factor family such as the basic fibroblast growth factor (bFGF), which is the best-studied example; hepatocyte growth factor (HGF); a splice variant of platelet-derived growth factor (PDGF); heparin-binding epidermal growth factor (EGF); vascular endothelial growth factor (VEGF); neuregulins; and others (4). The loss of epithelial syndecan-1 expression has been associated with poor prognosis in some forms of cancer (10-17). Recently, stromal syndecan-1 expression was found to be correlated with a devastating clinical course in several kinds of cancers (11,17-19).

Versican is a member of the large aggregating chondroitin sulfate proteoglycan (CSPG) family (20). Structurally, versican is composed of an N-terminal G1 domain, a GAG attachment region, and a C-terminal G3 domain. Alternative splicing generates at least 4 isoforms of versican, named V0, V1, V2 and V3 (21-23). V0, the largest isoform, contains 2 GAG-binding regions called the CSα and CSß domains. The V1 isoform contains a CSß domain, and the V2 isoform

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contains a CSα domain. The V3 isoform is composed solely of the G1 and G3 domains, lacking any potential GAG attachment sites. Versican is highly expressed in the early stages of tissue development, and its expression decreases after tissue maturation. Its expression is also elevated during wound repair and tumor growth (24-26). An increase in versican expression in the ECM facilitates local tumor invasion and metastasis by decreasing the cell-ECM adhesion (27). In fact, it has been demonstrated that versican expression is related to tumor progression in some types of malignant tumors (28-32).

A few studies have investigated syndecan-1 and versican expression in epithelial ovarian cancers. Here, we investigated the expression of syndecan-1 and versican in 111 patients with epithelial ovarian cancer. We then analyzed the correlation of this expression with various clinicopathological features, including patient outcome.

Patients and methods

Patients and tissue samples. In this study, we examined 111 patients with epithelial ovarian cancer. These patients underwent laparotomy at the Department of Obstetrics and Gynecology of Okayama University Hospital from 1992 to 2003. Tumor specimens were obtained at the time of surgery and were immediately fixed in 10% neutral-buffered formalin and embedded in paraffin. In 12 of the 111 patients, tumor specimens were only available at the peritoneal metastatic site. Informed consent was obtained from each patient before sample collection. Histological cell typing was performed, and on the basis of the World Health Organization (WHO) classification, 66 tumors were identified as serous adenocarcinoma, 23 as endometrioid adenocarcinoma, 15 as clear cell adenocarcinoma, 6 as mucinous adenocarcinoma, and 1 as other epithelial adenocarcinoma. Surgical staging was assessed by the International Federation of Gynecology and Obstetrics (FIGO) system and it was found that 35 patients had stage I; 12, stage II; 55, stage III; and 9, stage IV cancer. The median age at the time of surgery was 54 years (range, 28-84 years). All patients underwent primary debulking surgery and received postoperative platinum-based chemotherapy. Interval debulking surgery was performed for 37 patients. Progression-free and overall survival rates were defined as the interval from the initial surgery to clinically or radiologically proven recurrence and death, respectively. The median duration of follow-up was 35 months (range, 2-160 months).

Immunohistochemical and staining evaluation. We placed 4-μm-thick sections obtained from several representative areas of the tumor specimens on glass slides and immunostained them according to the labeled streptavidin-biotin (LSAB) method by using the Dako LSAB kit (Dako North America, Inc., CA, USA). Briefly, the slides were dewaxed in xylene and rehydrated in an alcohol series. Subsequently, antigen retrieval was performed in a microwave oven in 10 mM citric acid buffer (pH 6.0) for 3x10 min. The sections were incubated with 0.3% hydrogen peroxide to block endogenous peroxidase activity, followed by incubation with normal horse serum for 5 min at room temperature. The sections were immunostained by incubating with 1:100 diluted mouse monoclonal anti-human syndecan-1 core protein (clone, B-B4; Immunotech, Marseille, France) and 1:500 diluted mouse monoclonal anti-human versican (clone, 2B1; Seikagaku Corp., Ltd., Tokyo, Japan) for 2 h at room temperature. Next, the sections were incubated with biotinylated goat anti-mouse immunoglobulin for 20 min followed by incubation with peroxidase-conjugated streptavidin for 20 min and with 0.05% 3,3'-diaminobenzidine tetrahydrochloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan) containing hydrogen peroxide for 10 min. Finally, the slides were counterstained with Mayer's hematoxylin and mounted in an aqueous mounting medium. At each step, the slides were washed carefully in phosphate-buffered saline (pH 7.4). For the negative control, we incubated the sections with normal mouse serum at a concentration of 10 μg/ml. For the positive control, we used normal cervical squamous epithelium for syndecan-1 analysis and the walls of the blood vessels in the myometrium for versican analysis.

Staining evaluation. Syndecan-1 immunoreactivity in stromal cells was expressed as a score on the basis of the percentage of syndecan-1-positive cells as follows: strong (2), >50% of the cells stained; moderate (1), 10-50% of the cells stained; and weak (0), <10% of the cells stained. Versican immunoreactivity in the stroma was expressed as a score on the basis of the percentage area of versican-positive stroma in the peri- and intra-tumoral regions as follows: strong (2), >50% of the stroma stained; moderate (1), 10-50% of the stroma stained; and weak (0), <10% of the stroma stained. Any specimen showing cancer cell-associated syndecan-1 or versican staining was considered as positive (score, 1). Microscopic analyses were independently conducted by two of the authors who had no prior knowledge of the clinical data. In questionable cases, we made the final decision by using a conference microscope.

Statistical analyses. Mann-Whitney U-test was used to examine the association between the clinicopathological factors and syndecan-1 or versican expression. The survival rates were calculated by the Kaplan-Meier method, and the differences between the survival curves were examined using the log-rank test. The factors that were found to be significant were then analyzed by the stepwise Cox's multivariate proportional hazard model to determine their prognostic value. These analyses were performed by utilizing the StatView 5.0 software (Abacus Concepts, Inc., CA, USA). P-values <0.05 were considered to be statistically significant.

Results

Syndecan-1 and versican expression in epithelial ovarian cancer. Figs. 1 and 2 illustrate the representative immunostaining patterns of syndecan-1 and versican, respectively, in epithelial ovarian cancer. In 16 cases, we analyzed the correlation of syndecan-1 and versican expression at the primary and peritoneal metastatic sites. A significant correlation was found between the primary and metastatic sites for syndecan-1 and versican expression both in the epithelium and in the tumor stroma (Table I).

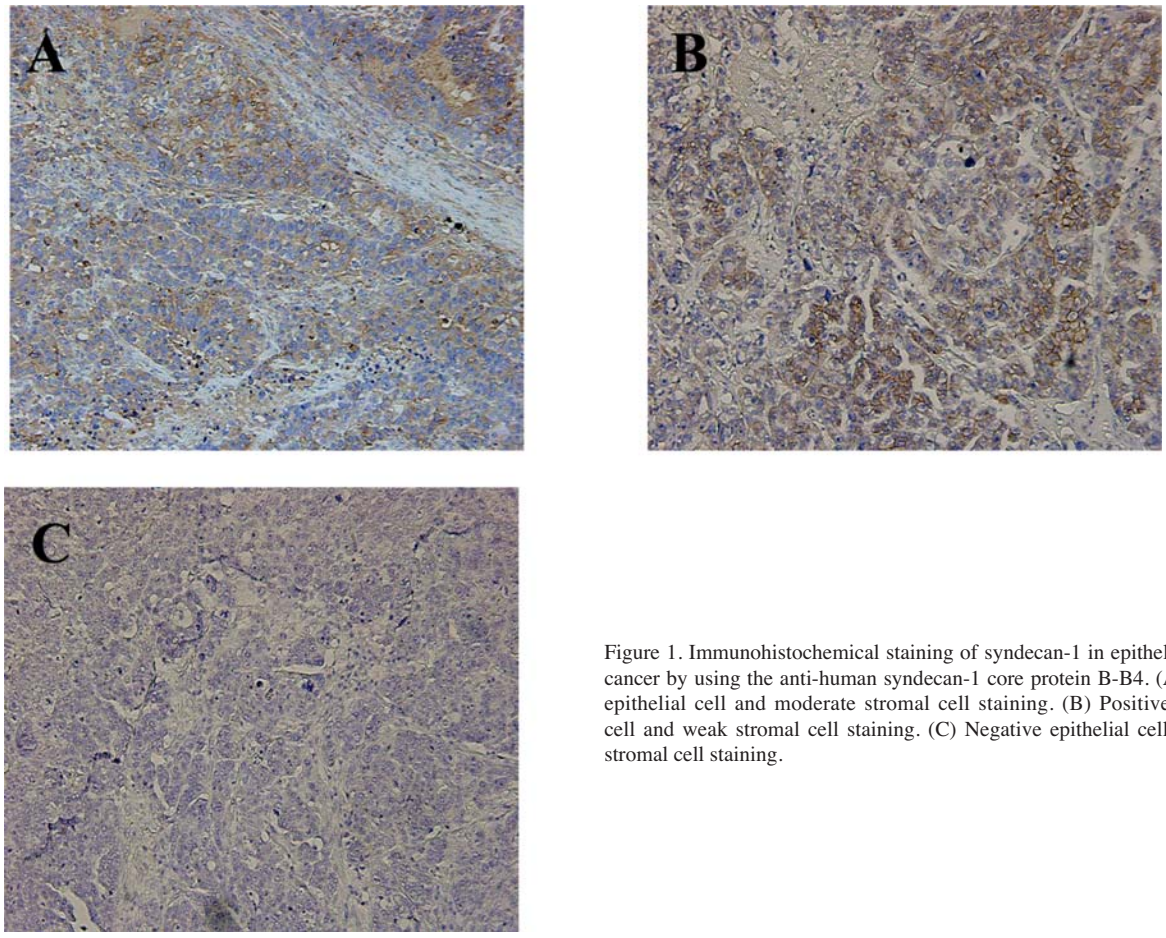

Figure 1. Immunohistochemical staining of syndecan-1 in epithelial ovarian cancer by using the anti-human syndecan-1 core protein B-B4. (A) Positive epithelial cell and moderate stromal cell staining. (B) Positive epithelial cell and weak stromal cell staining. (C) Negative epithelial cell and weak stromal cell staining.

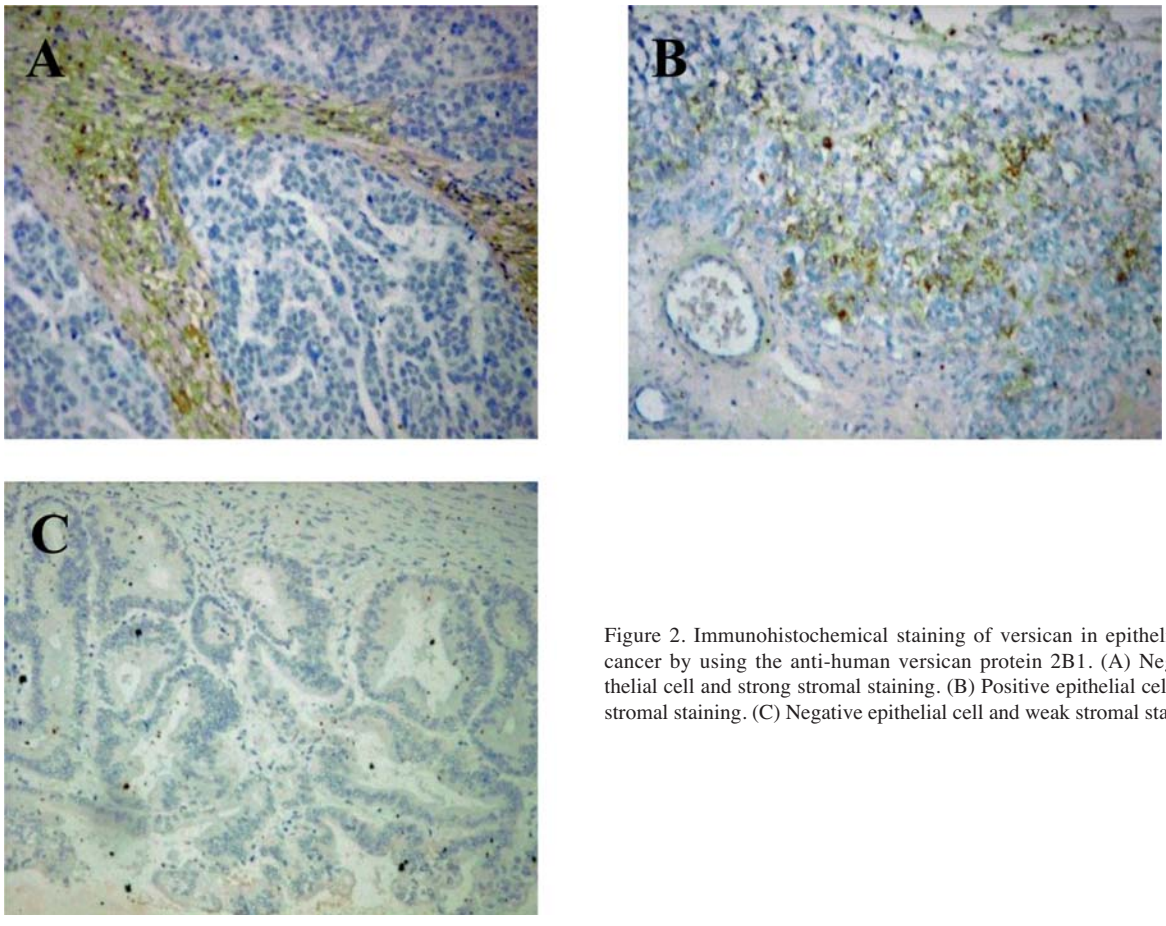

Figure 2. Immunohistochemical staining of versican in epithelial ovarian cancer by using the anti-human versican protein 2B1. (A) Negative epithelial cell and strong stromal staining. (B) Positive epithelial cell and weak stromal staining. (C) Negative epithelial cell and weak stromal staining.

Table I. Correlation of syndecan-1 and versican expression in primary and metastatic sites.

Epithelial Syndecan-1 expression index

Metastatic site \ Primary site	0	1
0	8	1
1	0	7

r = 0.88 ($p < 0.0001$)

Epithelial Versican expression index

Metastatic site \ Primary site	0	1
0	15	0
1	0	1

r = 1.00 ($p < 0.0001$)

Stromal Syndecan-1 expression index

Metastatic site \ Primary site	0	1	2
0	4	0	0
1	0	9	0
2	0	0	3

r = 1.00 ($p < 0.0001$)

Stromal Versican expression index

Metastatic site \ Primary site	0	1	2
0	3	0	0
1	0	3	1
2	0	1	8

r = 0.90 ($p < 0.0001$)

Epithelial and stromal syndecan-1 expression. The association between syndecan-1 expression and clinicopathological factors is shown in Table II. Epithelial syndecan-1 was expressed in 58 tumors (52%) and not expressed in 53 tumors (48%). The score for epithelial syndecan-1 expression was significantly lower in patients with advanced stage cancer (p=0.01), cancer of the serous histological subtype (p=0.03), and positive lymph node metastasis (p=0.002). Strong stromal syndecan-1 staining was seen in 18 tumors (16%), moderate staining in 41 tumors (37%) and weak staining in 52 tumors (47%). The score for stromal syndecan-1 expression was significantly higher in patients with advanced stage cancer (p<0.0001), cancer of the serous histological subtype (p<0.0001), massive ascites (p=0.02), positive peritoneal cytology (p=0.0002), suboptimal cytoreduction (p<0.0001) and lymph node metastasis (p=0.01). There was no significant association between epithelial and stromal syndecan-1 expression (data not shown).

Epithelial and stromal versican expression. The association between versican expression and clinicopathological factors is shown in Table II. Epithelial versican was expressed in 19 tumors (17%) and not expressed in 92 tumors (83%). The score for epithelial versican expression was significantly lower in the elderly (p=0.04), and in patients with advanced stage cancer (p=0.0004), cancer of the serous histological subtype (p=0.0002), massive ascites (p=0.03), positive peritoneal cytology (p=0.01), suboptimal cytoreduction (p=0.01), and lymph node metastasis (p=0.01). It is noteworthy that in 11 of the 15 (73%) cases of clear cell adenocarcinoma, epithelial versican was expressed. The score for stromal versican expression was significantly higher in patients with advanced stage cancer (p=0.0003), cancer of the serous histological subtype (p=0.002), massive ascites (p=0.02), positive peritoneal cytology (p=0.002), and suboptimal cytoreduction (p=0.0003). No significant association was noted between epithelial and stromal versican expression (data not shown).

Univariate survival analysis. Figs. 3 and 4 present the effect of the syndecan-1 expression status on the progression-free and overall survival curves for 111 patients with epithelial ovarian cancer. The progression-free survival rates of patients with epithelial syndecan-1 expression were significantly higher than those of patients with negative epithelial syndecan-1 expression (p=0.025). The progression-free and overall survival rates of patients with high stromal syndecan-1 expression were significantly lower than those of patients with low stromal syndecan-1 expression (p=0.001 and p=0.022, respectively). Figs. 5 and 6 present the effect of the versican expression status on the progression-free and overall survival curves. The progression-free and overall survival rates of patients with epithelial versican expression were significantly higher than those of patients with negative epithelial versican expression (p=0.010 and p=0.028, respectively). The progression-free and overall survival rates of patients with high stromal versican expression were significantly lower than those of patients with low stromal versican expression (p=0.0004 and p=0.043, respectively). The results of the univariate survival analyses of the other variables are shown in Table III.

Multivariate survival analysis. Multivariate analysis showed that massive ascites was the strongest independent prognostic factor for progression-free survival; this was followed by the FIGO stage and negative epithelial syndecan-1 expression

Table II. Association between syndecan-1 and versican expression and clinicopathological factors in epithelial ovarian cancer.

Variables	No. of cases	E-syndecan-1 (mean ± SE)	P-value[a]	S-syndecan-1 (mean ± SE)	P-value[a]	E-versican (mean ± SE)	P-value[a]	S-versican (mean ± SE)	P-value[a]
Age (years)			0.12		0.74		0.04		0.30
<60	71	0.58±0.06		0.68±0.09		0.23±0.05		0.85±0.10	
≥60	40	0.43±0.08		0.73±0.12		0.08±0.04		1.03±0.14	
FIGO stage			0.01		<0.0001		0.0004		0.0003
I+II	47	0.66±0.07		0.34±0.09		0.32±0.07		0.55±0.10	
III+IV		0.43±0.06		0.95±0.09		0.06±0.03		1.17±0.11	
Histological subtype			0.03		<0.0001		0.0002		0.002
Serous	66	0.44±0.06		0.92±0.09		0.06±0.03		1.12±0.11	
Non-serous	45	0.64±0.07		0.36±0.09		0.33±0.07		0.60±0.12	
Amount of ascites			0.76		0.02		0.03		0.02
<1000 ml	84	0.54±0.05		0.61±0.08		0.21±0.05		0.80±0.09	
≥1000 ml	27	0.48±0.10		0.96±0.14		0.04±0.04		1.26±0.17	
Peritoneal cytology			0.88		0.0002		0.01		0.002
Negative	39	0.51±0.08		0.36±0.10		0.31±0.07		0.56±0.12	
Positive	72	0.53±0.06		0.88±0.09		0.10±0.04		1.10±0.10	
Diameter of residual tumor			0.43		<0.0001		0.01		0.0003
<1 cm	65	0.55±0.06		0.45±0.08		0.28±0.06		0.69±0.10	
≥1 cm	46	0.48±0.07		1.04±0.11		0.02±0.02		1.22±0.12	
Lymph node status[b]			0.002		0.01		0.01		0.21
Negative	75	0.63±0.10		0.57±0.08		0.24±0.05		0.84±0.14	
Positive	36	0.31±0.14		0.94±0.12		0.03±0.03		1.06±0.19	

[a]Mann-Whitney U-test; E, epithelial; S, stromal; [b]Lymph node status was assessed by CT imaging in 47 patients.

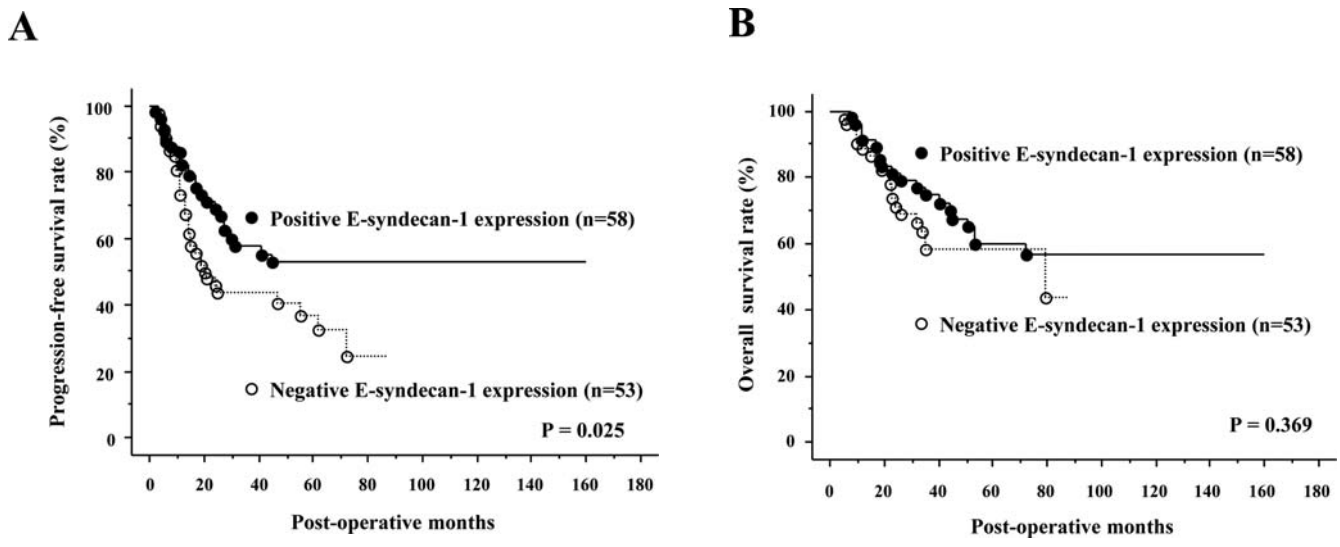

Figure 3. Effect of epithelial (E) syndecan-1 expression status on the (A) progression-free and (B) overall survival curves of 111 patients with epithelial ovarian cancer.

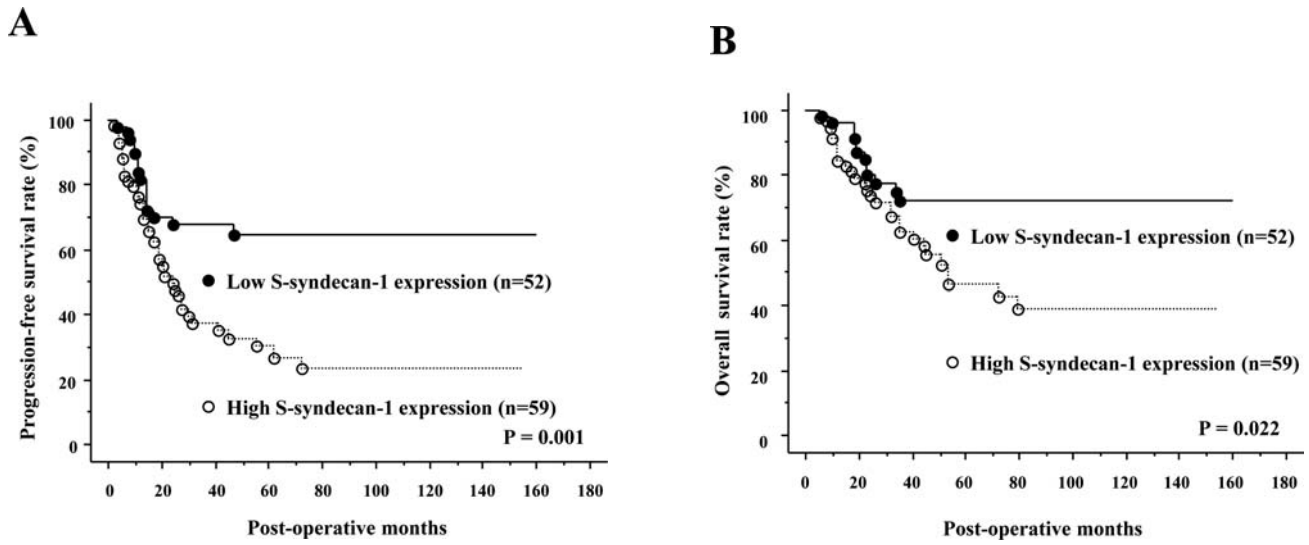

Figure 4. Effect of stromal (S) syndecan-1 expression status on (A) progression-free and (B) overall survival curves of 111 patients with epithelial ovarian cancer. Score 0, low stromal expression; score 1-2, high stromal expression.

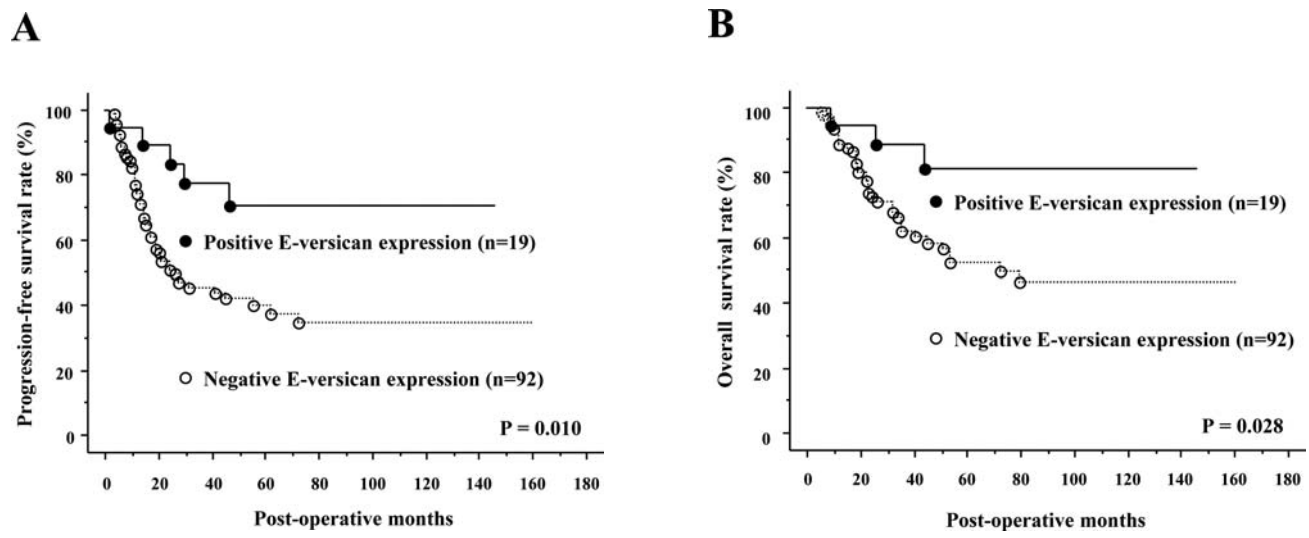

Figure 5. Effect of epithelial (E) versican expression status on (A) progression-free and (B) overall survival curves of 111 patients with epithelial ovarian cancer.

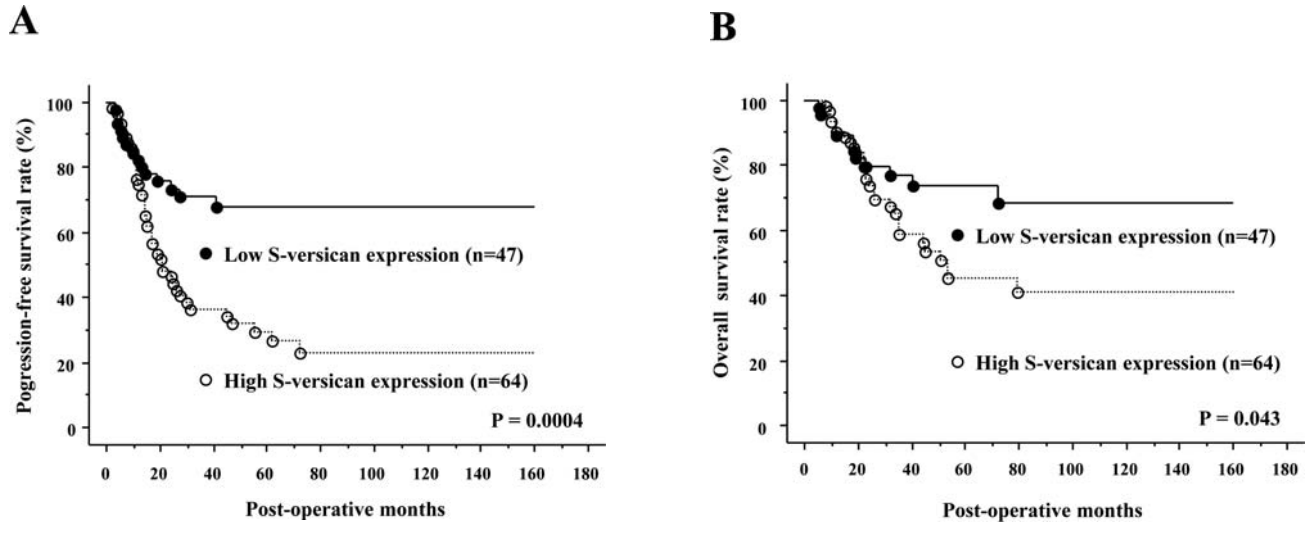

Figure 6. Effect of stromal (S) versican expression status on (A) progression-free and (B) overall survival curves of 111 patients with epithelial ovarian cancer. Score 0, low stromal expression; score 1-2, high stromal expression.

Table III. Progression-free and overall survival analyses of prognostic factors using the log-rank test.

Variables	No.	Estimated 5-year PFS (%)	P-value[a]	Estimated 5-year OS (%)	P-value[a]
Age (years)					
<60	71	59.4	0.0001	67.3	0.013
≥60	40	22.8		42.5	
FIGO stage					
I+II	47	88.2	<0.0001	95.3	<0.0001
III+IV	64	17.6		33.1	
Histological subtype					
Serous	66	27.8	<0.0001	44.6	<0.003
Non-serous	45	73.8		79.2	
Amount of ascites					
<1000 ml	84	56.9	<0.0001	73.8	<0.0001
≥1000 ml	27	9.3		13.2	
Peritoneal cytology					
Negative	39	79.0	<0.0001	95.7	<0.0001
Positive	72	29.4		40.0	
Diameter of residual tumor					
<1 cm	65	63.9	<0.0001	76.8	<0.0001
≥1 cm	46	21.1		32.7	
Lymph node status					
negative	75	53.9	0.002	67.8	0.002
positive	36	28.4		39.7	
Epithelial syndecan-1					
Negative	53	37.0	0.025	58.4	0.369
Positive	58	52.7		59.8	
Stromal syndecan-1					
Low (0)	52	64.5	0.001	72.2	0.022
High (1 or 2)	59	30.4		46.7	
Epithelial versican					
Negative	92	40.0	0.010	52.5	0.028
Positive	19	70.5		81.4	
Stromal versican					
Low (0)	47	67.8	0.0004	74.0	0.043
High (1 or 2)	64	29.2		45.6	

[a]Kaplan-Meier test; PFS, progression-free survival; OS, overall survival; FIGO, International Federation of Gynecology and Obstetrics.

(Table IV). In addition, massive ascites was also the strongest independent prognostic factor for overall survival, followed by the FIGO stage and positive peritoneal cytology (Table IV). Stromal syndecan-1 and versican co-expression was of borderline significance for progression-free and overall survival rates (p=0.076 and p=0.059, respectively).

Discussion

Invasion and metastasis are characteristics of malignant solid tumors, and many mechanisms are involved in these processes. Cell adhesion molecules, such as integrins, cadherins, and cell-surface HSPGs, and ECM components are particularly

Table IV. Prognostic factors for progression-free and overall survival selected by Cox's multivariate proportional hazard model analysis.

	Hazard ratio	95% CI	Cox's test P-value
Progression-free survival			
Massive ascites	2.65	1.43-4.85	0.002
FIGO stage	5.85	1.68-20.41	0.005
Negative epithelial Syndecan-1	1.81	1.00-3.25	0.049
Overall survival			
Massive ascites	2.72	1.29-5.75	0.009
FIGO stage	8.20	1.45-45.45	0.017
Peritoneal cytology	9.01	11.3-71.43	0.038

important in the regulation of cell differentiation, morphology and migration (33-35). In this study, we analyzed syndecan-1 and versican expression in a series of human epithelial ovarian cancer specimens.

Epithelial syndecan-1 expression was observed in 52% of the patients with epithelial ovarian cancer, and it decreased with advanced stage cancer, serous histology and lymph node metastasis. Davies *et al* also reported that epithelial syndecan-1 was expressed in 40% of the cases of epithelial ovarian cancer, although they did not mention the association between epithelial syndecan-1 expression and clinicopathological factors (36). Reduced expression of epithelial syndecan-1 in colorectal, gastric and laryngeal cancers; hepatocellular carcinoma; head and neck carcinoma; cholangiocarcinoma; malignant mesothelioma; and endometrial cancer has been reported to be associated with dedifferentiation of cancer cells or increasing metastatic potential (10-13,15-17). These results suggest that epithelial syndecan-1 is an important molecule in the regulation of cell proliferation and differentiation in a wide range of tumors. Indeed, it has been shown that the suppression of endogenous syndecan-1 expression in epithelial cells by transfection with syndecan-1 antisense cDNA results in a loss of the epithelial characteristics of the parental cells. Further, the parental cells elongate and become fusiform, they can invade and migrate within collagen gels, and become capable of anchorage-independent growth. The transformed fusiform cells show a rearrangement of ß1-integrins, markedly reduced E-cadherin expression, and altered disposition of the actin cytoskeleton (37).

Stromal syndecan-1 expression was first demonstrated by Stanley *et al* in infiltrating breast carcinoma (38). They speculated that because syndecan-1 interacts with heparin-binding growth factors such as FGF-2, accumulation of syndecan-1 within the tumor stroma may contribute to the extensive angiogenesis and stromal proliferation characteristic of infiltrating breast carcinoma. In the present study, we have demonstrated that stromal expression of syndecan-1 is present in advanced tumors. Maeda *et al* have reported that syndecan-1 expression in stromal cells promotes carcinoma cell growth (39). They speculated that syndecan-1 expression in stromal fibroblasts creates a favorable microenvironment for accelerated tumor cell growth by storing and presenting growth factors to the carcinoma cells as many epithelial mitogens, including FGFs, HGF and heparin-binding EGF, bind to syndecan-1 HS-GAG chains.

We demonstrated that the overexpression of stromal versican was associated with advanced stage cancer, cancer of the serous histological subtype, massive ascites, positive peritoneal cytology, and large residual tumors. Our previous studies showed that the overexpression of stromal versican in endometrial and cervical cancer is associated with tumor progression (32,40). These results suggest that stromal versican is an important molecule in the progression of gynecological malignant tumors. Indeed, it has been shown that the versican G1 domain can enhance cell proliferation and reduce cell adhesion in different cell types (41,42), and the versican G3 domain enhances tumor growth and angiogenesis (43).

In the present study, versican was mainly present in the peri-tumoral stroma; however, tumor cell-associated versican was also observed in 17% of the tumors. In fact, Casey *et al* reported that versican mRNA was detected in lower amounts in the ovarian carcinoma cells NIH:OVCAR5 (44). Although versican is probably synthesized mostly in tumor stroma by fibroblasts, malignant cells can also synthesize versican. The occurrence of versican-positive tumor cells was significantly higher in patients with early stage cancer and cancer with the non-serous histology, especially clear cell histology. This is in accordance with the results reported by Voutilainen *et al* (45). Interestingly, our previous studies showed that epithelial versican is significantly associated with lymph node metastasis in endometrial and cervical cancer (32,40). The role of cancer cell-associated versican appears to be specific to the type of cancer. Further studies are required to clarify the mechanism and functional role of epithelial versican expression.

Our study shows that loss of epithelial syndecan-1 expression and stromal syndecan-1 and versican expression is associated with reduced survival in patients with epithelial ovarian cancer. In our previous study, we showed that stromal syndecan-1 and versican expression are independent prognostic factors in endometrial cancer (17,32). However, stromal syndecan-1 and versican expression was not a statistically significant prognostic factor for survival of epithelial ovarian cancer patients, although negative syndecan-1 expression was an independent prognostic factor for progression-free survival.

In conclusion, loss of epithelial syndecan-1 expression and induction of stromal syndecan-1 and versican expression may be associated with tumor progression in epithelial ovarian cancer. Our findings also provide evidence that syndecan-1 and versican expression status can serve as an indicator of prognosis in patients with epithelial ovarian cancer.

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