Yonsei Medical Journal
Vol. 43, No. 6, pp. 701 - 711, 2002

Expression of E-Cadherin and α-, β-, γ-Catenin Proteins in Endometrial Carcinoma

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Loss of the cell adhesion molecule E-cadherin is suggested to promote tumor invasion and distant metastasis in tumor development. Recently, it has been proposed that E-cadherin function requires its linkage to the cytoskeleton through catenins. We evaluated the expression of E-cadherin and α-, β-, and γ-catenins in tissues of human endometrial carcinoma, analyzed the patterns of cell adhesion molecules' expression in endometrial carcinoma and investigated the relationship between the statuses of cell adhesion molecules and various clinicopathological factors. This study investigated the immunohistochemical expression of E-cadherin and α-, β-, and γ-catenins in 33 paraffin embedded formalin fixed tissues of endometrial carcinomas. Aberrant E-cadherin, and α-, β-, and γ-catenin expression was observed in 33.3 (11 of 33), 27.3 (9 of 33), 18.2 (6 of 33), and 51.5 (17 of 33) % of the specimens, respectively. Statistically significant correlation was found between aberrant expression of E-cadherin and lymph node metastasis and cell types other than endometrioid adenocarcinoma. Aberrant pattern of γ-catenin expression was also correlated with deep myometrial invasion. However, α-, and β-catenin expression was not correlated with any clinicopathological parameters. Using the Kaplan-Meier method and log-rank comparison test, abnormal expression of E-cadherin was correlated closely with poor survival ($p<0.05$), but cases with loss of both E-cadherin and catenin expression predicted even poorer survival than cases with only one or no aberrant expression in E-cadherin and catenins. We revealed aberrant expression of these cell adhesion molecules among patients with endometrial carcinoma. Aberrant expression of E-cadherin was correlated with lymph node metastasis and cell types other than endometrioid adenocarcinoma, while aberrant expression of γ-catenin was related with deep myometrial invasion. The expression of E-cadherin might be a possible prognostic factor for endometrial cancer while the expression of catenins may help predict patient's survival.

Key Words: E-cadherin, catenin, endometrial cancer

INTRODUCTION

Invasion is the hallmark of malignancy. Half of all cancer deaths are either directly or indirectly due to local invasion and the other half are due to metastasis in distant organs, a process necessitating invasion. Transition from noninvasive towards invasive state is a critical event in cancer development and reversion of this process is one of the possible targets in cancer therapy.[1]

The first step in invasion and metastasis is the detachment of cancer cells from the primary tumor, followed by suppression in cell-to-cell adhesive function in the tumor. The detachment of cancer cells is mainly dependent upon function of the adherens junction,[2] which consists of transmembrane E-cadherin, intracellular actin filament-attachment proteins, and actin cytoskeleton filament.[3] The adherens junction forms a cell-to-cell junction complex and conserves tyrosine kinases of the src oncogene family (c-yes, c-src, c-lyn kinases)[4] which contribute to the regulation of cell growth.

E-cadherin is a 120 kD transmembrane glycoprotein and is localized mainly in the zonula adherens junctions, mediated by its extracellular

Received September 4, 2002

This study was supported by Brain Korea 21 Project for Medical Science, Yonsei University.

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domain, cell-to-cell adhesion through calcium-dependent, homotypic interactions. Its carboxy cytoplasmic domain is associated with a group of closely related but distinct undercoat proteins, termed catenins (α-, β- and γ-catenins).[3-6] Both β (92 kD protein) and γ-catenin β (96 kD protein) bind directly to the cytoplasmic domain of E-cadherin, whereas α-catenin(102 kD protein) links the bound β- or γ-catenin to the actin microfilament network of the cellular cytoskeleton. This binding is essential for the establishment of tight, physical, cell-to-cell adhesion, and several integrities of the components of this complex necessary for the adhesive function of E-cadherin.[5-11]

Immunohistochemical studies have shown that all normal epithelial tissues strongly express E-cadherin at the cell membrane.[11] However, alterations of E-cadherin expression with reduced or heterogeneous staining have been noted in a number of tumors. Some positively staining tumors have an abnormal distribution of protein, with cytoplasmic rather than membranous localization, suggesting an abnormally functioning protein.[12] Loss of E-cadherin expression has been correlated with high grade and advanced stage in a number of tumors including breast, gastric, colorectal, pancreatic, bladder, and prostate cancers.[13-19]

However, it is not only E-cadherin but also other members of the junctional complex that have been shown to play an important role in tumorigenesis. In several tumor cell lines showing impaired cell-to-cell adhesion, mutations in catenin proteins were found, although E-cadherin expression was normal. Since catenins play a critical role in the regulation of cadherin-mediated adhesion, these results might indicate that E-cadherin immunoreactivity does not always imply the presence of a functionally normal cadherin-catenin complex.[20] In this study, we evaluated the simultaneous expression of E-cadherin and α-, β-, and γ-catenins in tissues of endometrial carcinoma. We also examined the relationship between the results of the statuses of these adhesion molecules and various prognostic parameters including stage, tumor cell type, myometrial invasion, grade and lymph node involvement.

MATERIALS AND METHODS

Patients and tumor specimens

Formalin-fixed, paraffin-embedded endometrial carcinoma tissue samples were selected from the archival tissue bank of pathology at Yonsei University College of Medicine, Seoul, Korea. A total of 33 specimens of endometrial carcinoma were obtained. The mean age of patients at diagnosis was 48.4 years (range 27 - 67 years). These patients had undergone staging laparotomy including total abdominal hysterectomy and bilateral salpingo-oophorectomy, bilateral pelvic lymph node dissection and para-aortic lymph node sampling, from Jan. 1989 to Dec. 1998. Surgical staging by findings at operation, and pathological reports and outcome, including lengths of survival after surgery, were obtained from patient medical records. The patients' characteristics are detailed in Table 1. A section from each specimen block was stained with H & E for histological evaluation and representative blocks were chosen for immunostaining. The quality of preservation was generally good with no significant autolysis. The tumors were graded as well, moderate, and poorly differentiated according to FIGO definition for grading of endometrial carcinoma. Surgical staging of the primary tumor was performed according to the criteria of the FIGO (International Federation of Gynecology and Obstetrics) staging system for endometrial carcinoma.

Monoclonal antibodies

Mouse monoclonal immunoglobulin(Ig)G antibodies to E-cadherin and α-, β-, and γ-catenins were purchased from Zymed Ltd (San Francisco, CA, USA). Appropriate antibody dilutions were determined by serial titration in the presence of positive and negative controls. Final dilutions were as follows: anti-E-cadherin, 1 : 10; anti-α-catenin, 1 : 150; anti-β-catenin, 1 : 200; anti-γ-catenin, 1:200.

Immunostaining

Formalin-fixed, paraffin-embedded tissue blocks

Table 1. Patients Characteristics

	No. of patients	Percent(%)
Age (years)		
21-30	4	12.1
31-40	4	12.1
41-50	9	27.3
51-60	9	27.3
61-70	7	21.2
Menopausal status		
Premenopause	17	51.5
Postmenopause	16	48.5
Stage		
I-II	26	78.8
III-IV	7	21.2
Lymph node status		
No metastasis	28	84.8
Pelvic lymph node (+) 4	12.1	
Inguinal lymph node (+)	1	3.0
Cell type		
Endometrioid	28	84.8
Non-endometrioid*	5	15.2

*includes adenosquamous carcinoma(n=3) and serous carcinoma(n=2).

were cut to 4-μm-thick sections for H & E and immunostaining. The streptavidin-biotin indirect immunoperoxidase method was employed for immunostaining. Sections were dewaxed, rehydrated, and incubated with 0.3% hydrogen peroxide for 30 minutes to block endogenous peroxidase activity. To enhance antigen retrieval, sections were microwave treated at this stage. Briefly, sections were immersed in 0.01 mol/L citrated buffer (pH 6.0) and heated four times in a microwave oven at 75W for 5 minutes each. After rinsing in 0.01 mol/L phosphate-buffered saline (PBS), normal goat serum diluted at 1 : 20 was applied for 20 minutes to block nonspecific antibody binding. Subsequently, sections were incubated overnight at 4℃ with the primary antibodies. After additional rinsing in PBS, sections were incubated with biotinylated goat anti-mouse IgG (Dako, High Wycombe, UK) for 60 minutes. The peroxidase reaction was developed with 0.01% hydrogen peroxide in 0.05% diaminobenzidine tetrahydrochloride (Sigma Chemical Co., Poole, UK) solution in PBS.

Interpretation of immunostaining

Staining was scored in a semiquantitative fashion from 0 to 3, with 0 defining absent staining, 1 cytoplasmic distribution, 2 heterogeneous staining (i.e. when tumors were composed of both normal and abnormally stained areas), and 3 normal membranous pattern of staining.

For purposes of data analysis, all tumors with loss of normal distribution of staining were classified as aberrant staining. This included those with absent, heterogeneous, or cytoplasmic patterns of staining (i.e. scores 0,1,2). Staining results were correlated with tumor characteristics and prognostic factors including histological type, grade, myometrial invasion, lymph node metastasis, and stage.

Statistical analysis

The relationship between the expression of E-cadherin and catenin proteins and various clinicopathological factors was analyzed with the multiple linear regression method. Additionally,

the X^2 linear trend in proportion test was applied to those variables for which statistically significant correlations had emerged. Differences were considered significant when the probability of error was below 5% ($p<0.05$). The following variables were studied: age, menopausal status, FIGO stage, tumor size, cell type, histological subtype, and lymph node status. The prognosis of patients was determined by overall survival (OS) after treatment. Patient overall survival was calculated from the time of pathological diagnosis to the time of death of last event. Estimates of survival probability were obtained using the Kaplan-Meier non-parametric method. Cox proportional hazards regression model was used to detect the impact of variables on OS. Differences in survival duration between subgroups were analyzed using a two-sided log-rank test. Statistical analyses were carried out using SPSS software (version 9.0, SPSS Inc., Chicago, Illinois, USA)

RESULTS

A total of 33 specimens were examined for E-cadherin and α-, β-, and γ-catenins (Fig. 1 and 2). Aberrant E-cadherin, and α-, β-, and γ-catenin expression was observed in 33.3 (11 of 33), 27.3 (9 of 33), 18.2 (6 of 33), and 51.5 (17 of 33) % of the specimens, respectively (Table 2). Aberrant expressions of E-cadherin, and α-, β-, and γ-catenins were correlated well with each other (Table 3). Especially, the correlation between the

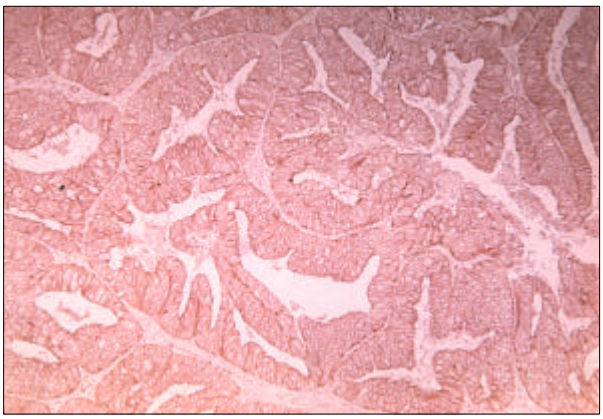

Fig. 1. Immunohistochemical staining of E-cadherin showing normal membranous expression. Strong expression of E-cadherin well outlined the intercellular borders and there was no demonstrable cytoplasmic distribution or decreased expression (× 400).

Table 2. The Expression Patterns of Each Components of E-cadherin/catenin Complex

	E-cadherin	α-catenin	β-catenin	γ-catenin
Normal	22 (66.7%)	24 (72.7%)	27 (81.8%)	16 (48.5%)
Aberrant	11 (33.3%)	9 (27.3%)	6 (18.2%)	17 (51.5%)

Table 3. The Correlation between the Components of E-cadherin/catenin Complex

		E-cadherin		α-catenin		β-catenin		γ-catenin	
		+	-	+	-	+	-	+	-
E-cadherin	+	-		21	1	21	1	14	8
	-			3	8	6	5	2	9
		-		$p<0.001$		$p=0.003$		$p=0.013$	
α-catenin	+	21	1	-		23	1	15	1
	-	3	8			4	5	9	8
		$p<0.001$		-		$p<0.001$		$p=0.007$	
β-catenin	+	21	1	23	1	-		16	11
	-	6	5	4	5			0	6
		$p=0.003$		$p<0.001$		-		$p=0.007$	
γ-catenin	+	14	8	15	1	16	11	-	
	-	2	9	9	8	0	6		
		$p=0.013$		$p=0.007$		$p=0.007$		-	

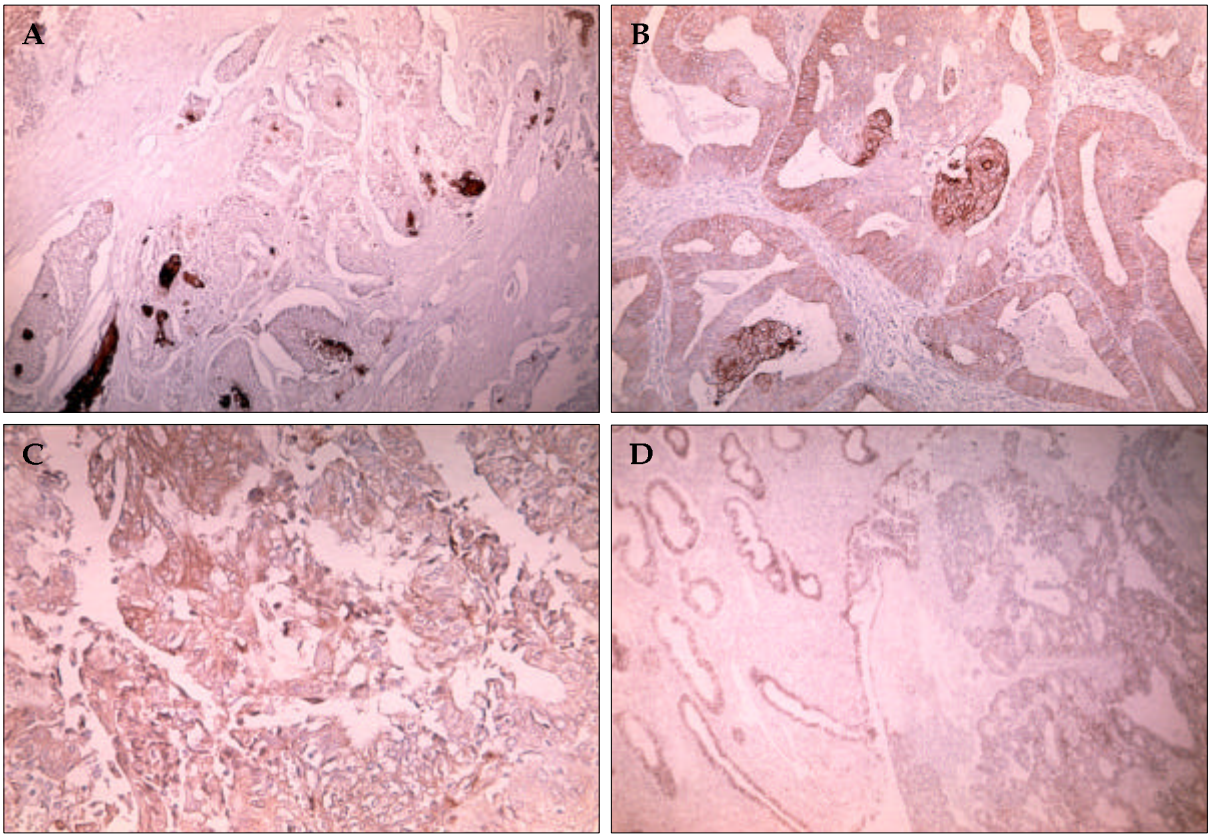

Fig. 2. Aberrant expression of E-cadherin and catenin proteins by immunohistochemical staining. A) Immunohistochemical staining of E-cadherin showing negative expression. Expression of E-cadherin almost disappeared in whole tumor cells in the field (× 400). B) Immunohistochemical staining of α-catenin showing heterogeneous expression. Some tumor cells showed distinct expression of α-catenin at intercellular borders, whereas the other areas did not (× 400). C) Immunohistochemical staining of β-catenin showing cytoplasmic distribution. β-catenin that normally localized at cell to cell boundary was now localized in cytoplasm(×400). D) Immunohistochemical staining of γ-catenin showing negative expression. Nearly all tumor cells lost its expression of γ-catenin (× 400).

expression of E-cadherin and α-catenin was so close that α-catenin showed a different pattern of expression with that of E-cadherin in only 2 cases (6.06%).

The relationships between the clinicopathological factors and expression of E-cadherin, and α-, β-, and γ-catenins were evaluated with X^2 test and multivariate analysis, respectively. The results of X^2 test are summarized in Table 4: When E-cadherin protein expression was compared with histopathological and clinical parameters, a statistically significant correlation ($p<0.05$) was found between aberrant E-cadherin expression and lymph node metastasis and cell types other than endometrioid adenocarcinoma. Aberrant pattern of γ-catenin expression was also correlated with deep myometrial invasion. However, α-, and β-catenin expressions were not correlated with any clinicopathological parameters. Multivariate analysis confirmed the above findings obtained from X^2 test (Table 5).

Survival analysis

Using the Kaplan-Meier method, abnormal expression of E-cadherin was correlated closely with poor survival ($p<0.05$). The survival curves according to expression of E-cadherin and catenins are illustrated in Fig. 3. Mean survival was significantly shorter for patients with tumors showing aberrant expression of e-cadherin (mean, 34 months) than those with normal expression (mean, 61 months). Aberrant expression of α-catenin also showed a trend toward worse survival,

Table 4. The Statistical Correlation between Expressions of E-cadherin/catenin Complex and Clinicopathological Prognostic Factors in Endometrial Carcinoma

	E-cadherin		α-catenin		β-catenin		γ-catenin	
	N	A	N	A	N	A	N	A
Grade								
1	11	8	12	7	13	6	9	10
2	10	1	10	1	11	0	6	5
3	1	2	2	1	3	0	1	2
	NS		NS		NS		NS	
Myometrial invasion								
0	7	3	7	3	10	0	8	2
≤1/2	10	3	10	3	9	4	5	8
>1/2	5	5	7	3	8	2	3	7
	NS		NS		NS		p=0.046*	
Stage								
I-II	19	3	19	7	20	6	11	15
III-IV	3	4	5	2	7	0	5	2
	NS		NS		NS		NS	
Lymph node								
negative	21	7	21	7	22	6	13	15
positive	1	4	3	2	5	0	3	2
	p=0.049*		NS		NS		NS	
Cell type								
endometrioid	21	7	21	7	23	5	13	15
adenosqua.†	1	2	2	1	2	1	1	2
serous	0	2	1	1	2	0	2	0
	p=0.041*		NS		NS		NS	

*statistically significant ($p<0.05$), N; normal expression.
†adenosquamous cell carcinoma, A; Aberrant expression.

Table 5. The Statistical Correlation between Expressions of E-cadherin/catenin Complex and Clinicopathological Prognostic Factors in Endometrial Carcinoma

	E-cadherin	α-catenin	β-catenin	γ-catenin
Grade	0.718	0.346	0.034	0.902
Myometrial invasion	0.358	1.000	0.260	0.025*
Stage	0.073	0.671	0.332	0.291
Lymph node metastasis	0.031*	0.145	0.391	0.333
Cell type	0.011*	0.443	0.825	0.312

*statistically significant ($p<0.05$).

but this was not statistically significant ($p>0.05$). Aberrant expression of β- and γ-catenin expression showed no correlation with survival. Patients with aberrant expression of both E-cadherin and catenins showed statistically significant, poorer survival than patients with normal expression in both E-cadherin and catenins, or than patients with one abnormality in E-cadherin or catenin (Fig. 4).

DISCUSSION

Cell-to-cell junctions are specialized macromolecular structures that are essential for both intercellular adhesion and communication. Several dis-

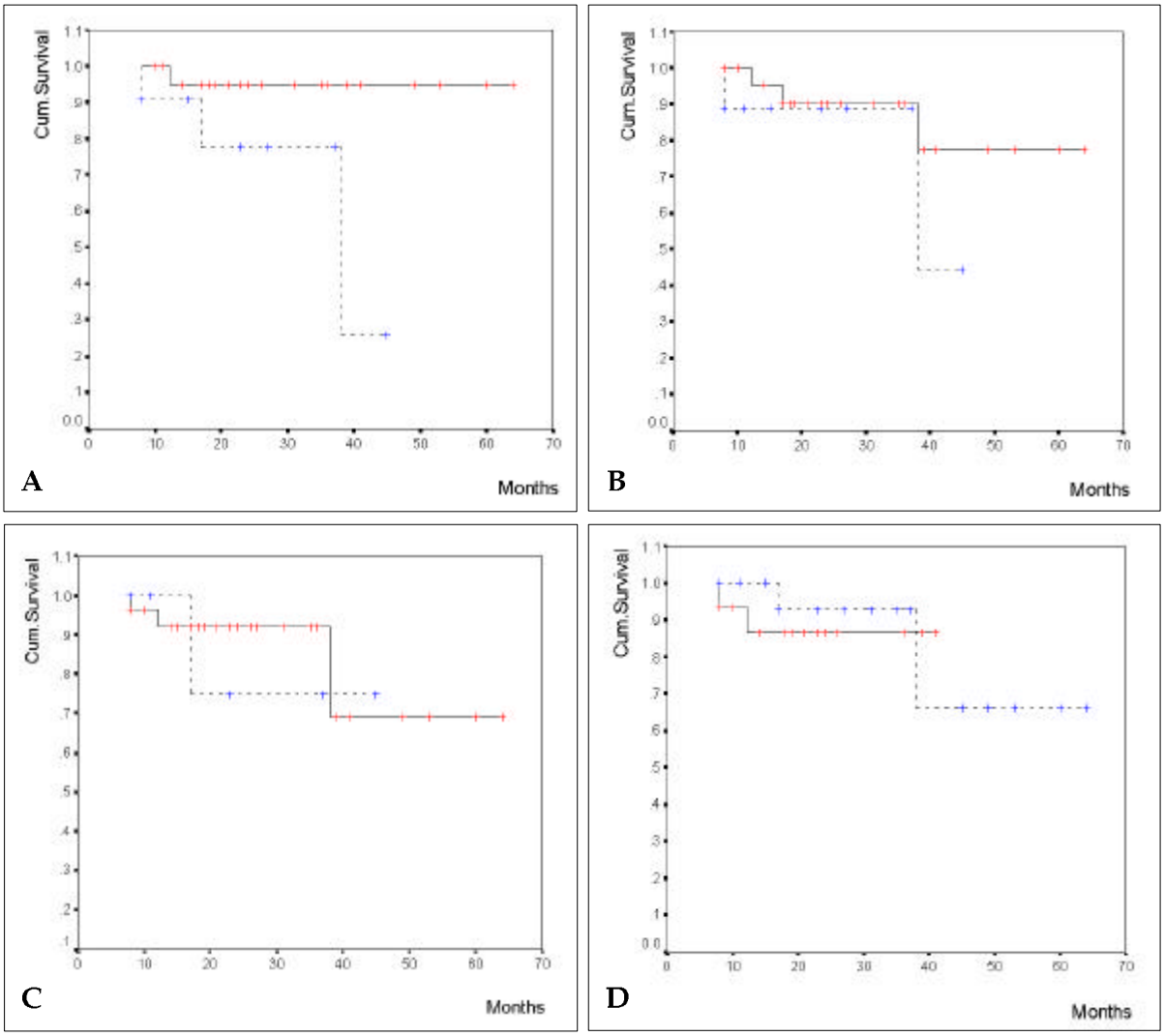

Fig. 3. The Kaplan-Meier survival curves according to patterns of E-cadherin (A), α-catenin (B), β-catenin (C), γ-catenin (D) expression. The survival curves between patients with normal E-cadherin expression and aberrant expression showed statistically significant difference by log-rank test ($p<0.05$).
—— : normal expression, ------ : aberrant expression.

tinct types of junction are present in vertebrate cells: tight junctions, adherence junctions, desmosomes, and gap junctions. Each possesses a different array of protein components with unique functional characteristics. Tight junctions form seals that prevent solutes from freely passing across epithelial tissue, whereas gap junctions allow for the transport of ions and small molecules between cells. Adherens junctions and desmosomes play an adhesive, as well as architectural, role in the epithelium by providing a link between cell-surface adhesion molecules and the cytoskeleton.[21-23]

One of the proteins from the cadherin superfamily that is functionally important for the maintenance of epithelial architecture is E-cadherin, which is expressed on the basolateral surfaces of the epithelial cells at points of cell-to-cell contact.[24,25] E-cadherin is known to form a complex with several cytoplasmic proteins, including α-, β-, and γ-catenins, and to be connected finally to the actin filaments.[26] In the intercellular adherence junction, the cytoplasmic domain of cadherin is bound to β-catenin, which is also bounded to the amino terminal of α-catenin at another site. The carboxyl terminal of α-catenin

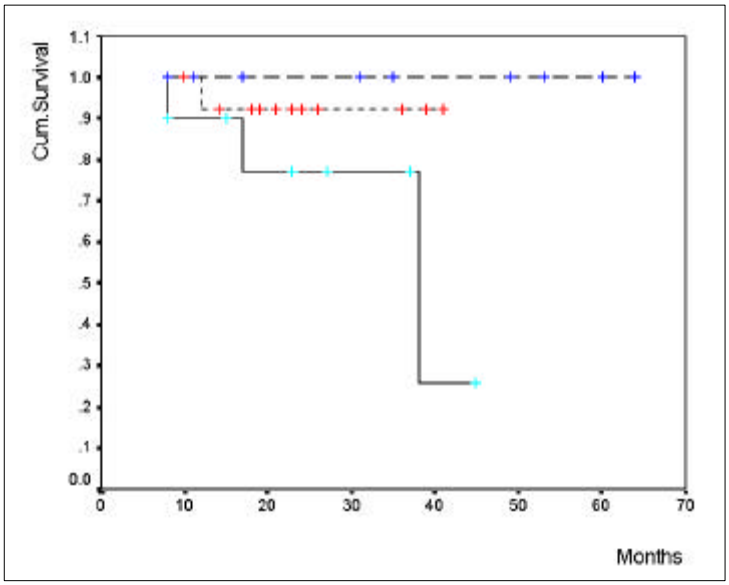

Fig. 4. The Kaplan-Meier survival curves according to expression of components of cadherin-catenin complex. Patients with aberrant expression in both E-cadherin and catenins showed statistically significantly poorer survival ($p<0.05$) than patients with normal expression of cadherin and catenins or patients with one aberrant expression either cadherin or catenins.

– – – – – : Both E-cadherin and catenin showed normal expression.
- - - - - - - : Either E-cadherin or catenin showed aberrant expression.
——— : Both E-cadherin and catenin showed aberrant expression.

is directly bound to the actin filament or is indirectly bound to actin through α-actinin.[27,28] γ-catenin is structurally related to β-catenin and is thought to play a similar role to that of β-catenin in regulating cadherin adhesive junctions, as well as in modulating the activity of desmosomal cadherins.[29]

Down-regulation or abnormal expression of E-cadherin is correlated with a high invasive capacity and poor differentiation of several different types of epithelium-derived carcinomas.[30] Transfection of tumor cells with E-cadherin cDNA prevents invasive growth and E-cadherin has therefore been suggested to act as a tumor suppressor.[31] Moreover, the dependence on both functional E-cadherin and/or catenins has been demonstrated *in vivo* and *in vitro*.[32,33] Thus, deletions in the E-cadherin gene or the catenins result in a loss of cell-cell adhesion in tumor cells,[30] and mutations in Ca^{2+}-binding sites have been observed in a limited number of poorly differentiated tumors.[34,35]

Modulation of the expression of E-cadherin and catenins is less well explored but it seems that the E-cadherin/catenin invasion-suppressor complex is regulated multifactorially, at multiple levels and sometimes in reversible ways. Mutations in the E-cadherin gene combined with loss of the wild type allele, causing irreversible downregulation, have been demonstrated only in a minority of human cancers. Post-translational and reversible downregulation that has been ascribed to tyrosine phosphorylation is also implicated in transmembrane receptor signal transduction through the E-cadherin/catenin complex. E-cadherin interacts with E-cadherin on another cell through a dimeric adhesion zipper, involving the histidine-alanine-valine (HAV) sequence of the first extracellular domains.[36] This is the major extracellular link of the E-cadherin/catenin complex, though not the only one. Vandenbossche et al.[37] reported recently a host regulation of E-cadherin expression by as yet unidentified factors; it was found that when non-invasive cells that express normal levels of E-cadherin are injected into the body, they undergo a reversible loss of expression of E-cadherin and gain invasiveness. This may be due to their contact with host cells or to regulation by host factors. Expression of wild-type APC gene caused a pronounced reduction of β-catenin concentration, particularly its intracellular pool, at a post-translational level, presumably increased degradation of β-catenin.[38] In contrast, transfection with the Wnt-1 oncogene increased the accumulation of β- and γ-catenins, increased the binding of β-catenin to cadherin, and strengthened calcium-dependent cell adhesion.[39] The E-cadherin promoter is not active in non-expressing cells; this may result from binding of a repressor protein to the promoter.[40] Studies on the regula-

tion of expression of the complex are accumulating and more mechanisms are being identified; some of them may have clinical importance.

In previous studies, decreased E-cadherin expression or nuclear localization of β-catenin was observed in endometrial cancer tissues.[21,41] However, no prior study has examined simultaneously the expression of E-cadherin and α-, β-, and γ-catenins. In order to investigate the expression of cell adhesion molecules and its correlation with clinicopathological factors and survival, we evaluated the expression of E-cadherin and α-, β-, and γ-catenin proteins by immunohistochemistry in a series of human endometrial carcinomas. The results from this study indicated that aberrations of the immunoreactivity of not only cadherin but also of catenin proteins are shown in endometrial carcinoma. Of the 33 tumors stained for E-cadherin and α-, β-, and γ-catenins, 57.6% (19/33) stained abnormally for one or more components of the cadherin-catenin complex and a significant correlation between normal expression of E-cadherin and normal expression of catenin was shown in 42.4% of the cases studied. This number of tumors expressing aberrant expression is compatible with the results of other carcinomas.[42-45] Sakuragi et al.[21] also reported aberrant expression of 60% in 30 endometrial carcinomas. The pattern of E-cadherin and catenin expression in our case showed a strong correlation between the individual components of the complex. Loss of E-cadherin was associated with loss or disruption of catenins ($p<0.05$). These observations suggest that catenin expression is at least partly dependent on the normal expression of E-cadherin. Because α-catenin is normally found bound to β-catenin and E-cadherin, their loss may render α-catenin unstable due to enzymatic digestion in the cytoplasm; the same may apply to γ-catenin. Matsui et al.,[43] and Jawhari et al.[44] have made the same observations in their reports about the expression of E-cadherin and catenin proteins. Maybe immunostaining of E-cadherin is a more accurate indicator of dysfunction of cell adhesion molecules than of catenin.

Many investigators have demonstrated that the decline of the E-cadherin cell adhesion molecule directly resulted in tumor invasion *in vivo*, and that this has a strong correlation with tumor invasion and metastasis in human cancer tissues.[11-21] Since the E-cadherin-catenin complex is known to be the prime mediator of intercellular cohesion and epithelial tissue integrity, these alterations may allow cells to detach from the primary site, invade surrounding tissues and metastasize to lymph nodes and distant organs. Acquisition of cell dissociation and motility introduced by aberrations of the E-cadherin-catenin complex could enhance cancer cell release from the primary site and affect the initial steps in the metastatic process. We found statistically significant correlations between aberrant expression of γ-catenin and deep myometrial invasion, and between aberrant expression of E-cadherin and lymph node metastasis. These findings suggest that disturbance in E-cadherin-catenin complex expression and function might play an important role in the progression of endometrial cancer.

In addition to correlations with metastasis or tumor invasion, there are several reports indicating that abnormal expression of the cadherin-catenin complex is more frequent in poorly differentiated tumors, and advanced stage and advanced tumor progression. Sakuragi et al.[21] reported that decreased E-cadherin expression in endometrial carcinoma is associated with tumor dedifferentiation. In contrast, our study found no statistically significant relationship between components of cadherin-catenin complex and tumor grade or advanced stage. However, reduced or cytoplasmic expression of E-cadherin seemed to be related with cell types other than endometrioid adenocarcinoma.

Among the four parameters examined, only E-cadherin expression was correlated with survival. Tumors with aberrant E-cadherin expression showed much shorter survival (mean: 34 months) than those with normal E-cadherin expression (mean: 61 months). This finding was in agreement with a report of Sakuragi et al.[21] that demonstrated a prognostic value for E-cadherin. Aberrant expression of catenin alone cannot show any predictive power for patient's survival, but the patients with aberrant expression in both E-cadherin and catenin showed poorer survival than those with aberrant expression in only one of E-cadherin or catenin. Hence, expression of catenin might be a factor, additional to that of E-cadherin,

in predicting the survival of endometrial cancer.

In conclusion, we have demonstrated that aberrant expression of E-cadherin-catenin complex immunoreactivity occurred in 57.6% of endometrial cancers and was correlated with myometrial invasion, lymph node metastasis, cell types other than endometrioid carcinoma and poorer survival. Nevertheless, the clinical use of E-cadherin-catenin complex as an additional stratification indicator in multi-institutional prospective studies involving patients with endometrial carcinoma remains to be determined.

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