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The Prognostic Value of β-catenin Expression in Endometrial Cancer

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Abstract

Objective: *To investigate the prognostic value of β-catenin expression in endometrial cancer.*

Methods: *Immunohistochemistry was used to evaluate samples from 27 early stage and 39 advanced stage endometrial cancers. Smears were examined for the expression of β-catenin protein in the cell membrane, cytoplasm, and nucleus. The staining patterns were then evaluated for their correlation with several prognostic factors, including 5-year survival.*

Results: *Decreased cell membrane β-catenin expression was significantly associated with advanced stage (stage III–IV), high grade (grade 3), deep (>50%) myoinvasion, and positive lymph node status ($P < 0.05$). Negative membrane staining for β-catenin was associated with a lower 5-year survival rate, compared to that for positive staining (51.7% vs. 86.6%, respectively; $P < 0.05$).*

Conclusions: *Loss of membrane β-catenin expression is a strong and independent predictor of unfavorable outcomes in patients with endometrial carcinoma.*

Keywords: ***endometrial cancer, beta-catenin, immunohistochemistry.***

Introduction

Endometrial cancer currently has one of the highest incidence rates among all gynecological cancers in developed Western countries. However, the incidence in South Korea is much lower than that in Western Europe and North America. Nevertheless, the rapid increase in the incidence of endometrial cancer over the past few years has made it important to develop appropriate management approaches, such as early diagnosis and treatment.[1,2] The prognostic factors for endometrial cancer include histological classification, cell differentiation, myometrial invasion, International Federation of Gynecology and Obstetrics (FIGO) stage, and lymph node metastasis.[3,4]

In recent years, various studies have attempted to establish the molecular and biological prognostic factors for endometrial cancers. For example, several studies have demonstrated that expression of the E-cadherin/catenin complex, which is associated with the coupling between normal epithelial cells, was a significant prognostic factor for endometrial cancer. In this context, β-catenin plays a role in two types of carcinogenesis. The first type involves the loss of E-cadherin/catenin-mediated coupling between cells, and the second type involves the expression of an oncogene through the Wingless-Wnt signaling pathway.[5,6,19] In the first pathway, β-catenin helps form the cadherin-catenin junction complex, and failed adhesion (due to altered β-catenin function) can lead to invasive and metastatic carcinomas. In the second pathway, β-catenin is involved in the signal transduction system and the adenomatous polyposis coli (APC)/β-catenin/T-cell factor (Tcf) cell membrane pathways in the cell.[7] If mutations in the APC or β-catenin genes prevent protein interactions or phosphorylation, β-catenin is stabilized through the Wnt signaling system and accumulates in the cytoplasm. The β-catenin then enters the nucleus and combines with a protein in the Tcf/lymphoid effector factor family, which promotes DNA transcription and the subsequent expression of an oncogene.[8] This step can increase the expression of nuclear β-catenin and cause further cytoplasmic accumulation.

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Decreased expression of the E-cadherin-catenin complex has been reported in various cancers, including breast, stomach, skin, and bladder cancers. In addition, gynecological cancer research has demonstrated that decreased levels of the E-cadherin-catenin complex resulted in less differentiation and unfavorable outcomes.[9,14] These factors have led to increasing South Korean interest regarding the relationship between the E-cadherin-catenin complex and endometrial cancer. However, because the incidence of endometrial cancer is not high in Korea (vs. the incidences of other gynecologic cancers), the related research remains sparse. Therefore, no study has evaluated whether β-catenin expression is an independent prognostic factor for endometrial cancer in South Korea.

This study aimed to identify whether β-catenin expression mediated carcinogenesis, via increased cytoplasmic β-catenin expression and decreased β-catenin expression in cell membranes. Therefore, immunohistochemical staining of endometrial cancer tissue samples was used to investigate the β-catenin expression patterns according to stage, prognostic factors, and survival rates.

Subjects and Methods

Subjects

This study was performed using 66 tissue samples from patients who were diagnosed with endometrial cancer and underwent staging and surgical treatment at the Department of Obstetrics and Gynecology of a general hospital in Seoul, South Korea between January 1993 and December 2006. These samples came from 27 cases with FIGO stage I–II cancer and 39 cases with FIGO stage III–IV cancer; all cases were treated using appropriate stage-dependent surgery. Based on these procedures, the available data included surgical stage, myometrial invasion, histologic differentiation, and lymph node metastasis. The patients' characteristics are shown in Table 1.

Methods

Immunohistochemical staining

Histological evaluation of the samples was performed using hematoxylin and eosin-stained slides at the hospital's Department of Pathology. The slides for early endometrial cancer (stage I–II) and for advanced endometrial cancer (stage III–IV) were prepared via tissue array, using 57 and 40 2-mm spots, respectively; each sample used the same paraffin tissue section as the selected slide. Normal deparaffinization and hydration were performed using 5-μm thick sections of the prepared arrays. For each slide, β-catenin immunohistochemical staining was performed using a 1:100 dilution of β-catenin that was manufactured by Zymed (San Francisco, CA, USA). After 1 h of reaction at 37°C, the slide was washed three times with Tris-buffered saline (TBS). The slide was then reacted with a biotin-coupled secondary antibody (Dako) for 10 min, washed with TBS, and then treated with streptavidin-biotin conjugate for 10 min. The slide was then washed with TBS, reacted with 3-amino-9-ethylcarbazole (Dako), and contrast stained with Mayer's hematoxylin.

Classifying the staining findings

One observer classified all tissue samples. After observation at low power (×40 and ×100), the well-stained parts of the lesions were selected and evaluated at high power (×200 and ×400). For the β-catenin scoring, reddish-brown stains on the nucleus, cytoplasm, and cell membrane of the tumor cells were scored separately, using the sum of the staining intensities and the percentages of positively stained cells, as described by Moreno-Bueno et al.[15] The staining intensities were expressed as scores that ranged from 0 to 4. For the frequency of positively stained cells, scores of 0, 1, 2, 3, 4, and 5 were assigned for 0%, <10%, 10–33%, 34–66%, and >66%, respectively. The results for the intensity and frequency tests were then added together to calculated the final score for each sample (range, 0–7). We used Scholten et al.'s [20] criteria to classify positive and negative results for the cytoplasm and cell membrane, with scores of 1–4 and 5–7 being classified as decreased expression and increased expression, respectively. For staining inside the nucleus, all samples with positive staining (any magnitude) were classified as having increased expression (Figs. 1-3).

Statistical analysis

For the statistical analyses, we tested whether increased expression of β-catenin in the nucleus and cytoplasm, or decreased cytoplasmic expression, were associated with the prognostic factors for endometrial cancer. We used Fisher's exact test to analyze the degree of expression according to endometrial cancer stage, histologic differentiation, myometrial invasion, and lymph node metastasis. We also created survival curves for β-catenin expression using the Kaplan-Meier method. All analyses were performed using SPSS software (version 12.0; SPSS Inc. Chicago, IL), and differences were considered statistically significant at a P-value of <0.05.

Table 1: Patient characteristics

Clinical features	N (%)
Age, years	46.8 ± 12.7
No. of patients	66 (100)
Stage	

DOI: 10.23958/ijirms/vol02-i11/01

Stage I	22 (33.3)
Stage II	5 (7.6)
Stage III	34 (51.5)
Stage IV	5 (7.6)
Histology	
Endometrioid	60 (90.9)
Non-endometrioid	6 (9.1)
Grade	
Grade 1	31 (47.0)
Grade 2	18 (27.3)
Grade 3	17 (25.8)
Positive cytology	9 (13.6)
Myoinvasion, >50%	34 (51.5)
Lymphovascular invasion	24 (36.4)
Lymph node metastasis	27 (40.9)

Table 2: Staining scores for β-catenin and the combined positive and negative results

Stain scores	Membrane	Cytoplasm	Nucleus
7	39 (59.1)	12 (8.2)	
6	14 (21.2)	32 (48.5)	
5	6 (9.1)	12 (10.2)	3 (4.5)
Positive	59 (89.3)	56 (84.8)	
4	2 (3.0)	1 (1.5)	5 (11.6)
3	3 (4.6)		
0	2 (3.0)	9 (13.6)	
Negative	10 (10.6)	10 (15.2)	58 (87.9)
Total no. (%)	**66 (100)**	**66 (100)**	**66 (100)**

Table 3: Relationship between stage and β-catenin expression

	Stage I–II	Stage III–IV	p-value
No. patients	27 (100%)	39 (100%)	
β -catenin expression			
Positive nucleus	4 (14.8%)	4 (10.3%)	0.70
Positive cytoplasm	26 (96.3%)	30 (76.9%)	<0.05
Negative membrane	0 (0%)	7 (17.9%)	<0.05

Table 4: Relationship between histologic grade and β-catenin expression

	Grade 1	Grade 2	Grade 3	p-value
No. patients	31 (100%)	18 (100%)	17 (100%)	
β -catenin expression				
Positive nucleus	4 (12.9%)	3 (16.7%)	1 (5.9%)	0.61
Positive cytoplasm	28 (90.3%)	16 (88.9%)	12 (70.6%)	0.16
Negative membrane	0 (0%)	1 (5.6%)	6 (35.3%)	<0.05

DOI: 10.23958/ijirms/vol02-i11/01

Table 5: Relationship between myoinvasion and β-catenin expression

	≤50% invasion	>50% invasion	p-value
No. patients	32 (100%)	34 (100%)	
β -catenin expression			
Positive nucleus	5 (15.6%)	3 (8.8%)	0.47
Positive cytoplasm	31 (96.9%)	25 (73.5%)	<0.05
Negative membrane	0 (0%)	7 (20.6%)	<0.05

Table 6: Relationship between lymphovascular invasion and β-catenin expression

	Invasion	**No invasion**	**p-value**
No. patients	24 (100%)	42 (100%)	
β -catenin expression			
Positive nucleus	3 (12.5%)	5 (11.9%)	0.90
Positive cytoplasm	17 (70.8%)	39 (92.9%)	<0.05
Negative membrane	7 (29.2%)	0 (0%)	<0.05

Table 7: Relationship between lymph node metastasis and β-catenin expression

	Positive	**Negative**	**p-value**
No. patients	27 (100%)	39 (100%)	
β -catenin expression			
Positive nucleus	2 (7.4%)	6 (15.4%)	0.45
Positive cytoplasm	18 (66.7%)	38 (97.4%)	<0.05
Negative membrane	6 (22.2%)	1 (2.6%)	<0.05

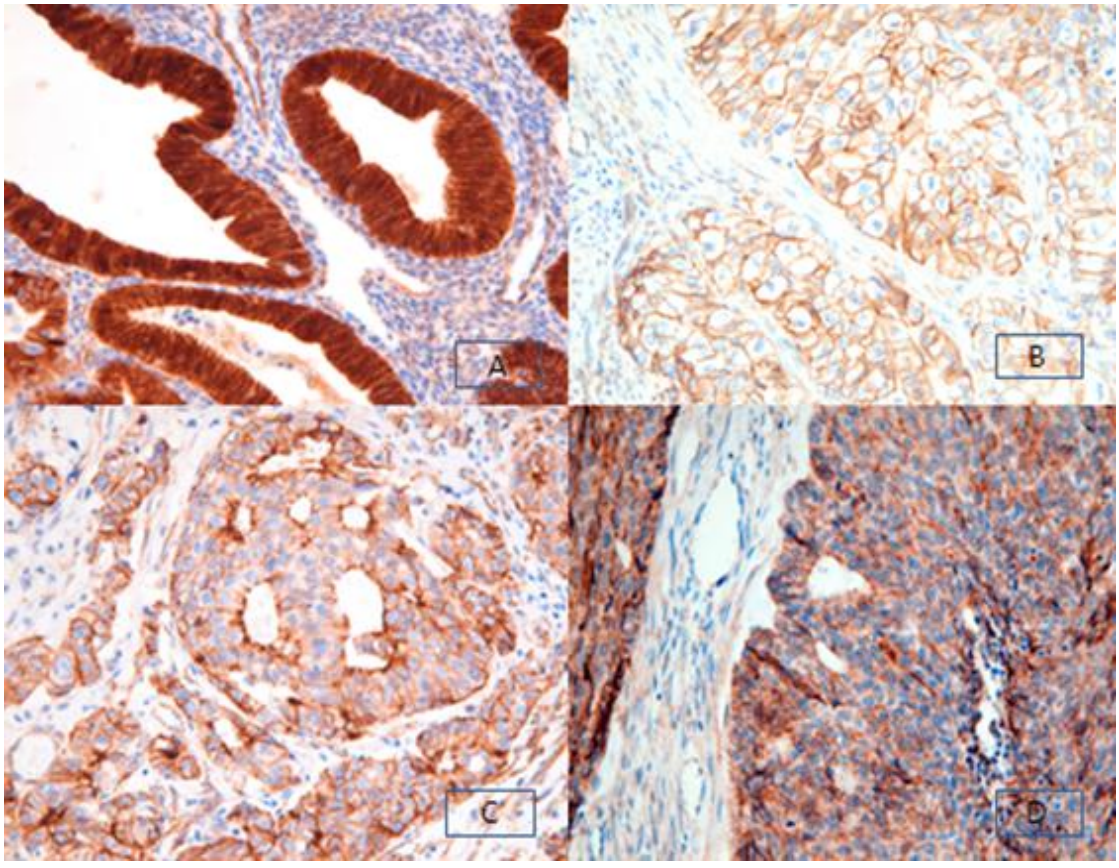

Figure 1: Membrane staining intensity for beta-catenin in endometrial cancer. A) A staining intensity of 3. B) A staining intensity of 2. C) A staining intensity of 1. D) A staining intensity of 0.

DOI: 10.23958/ijirms/vol02-i11/01

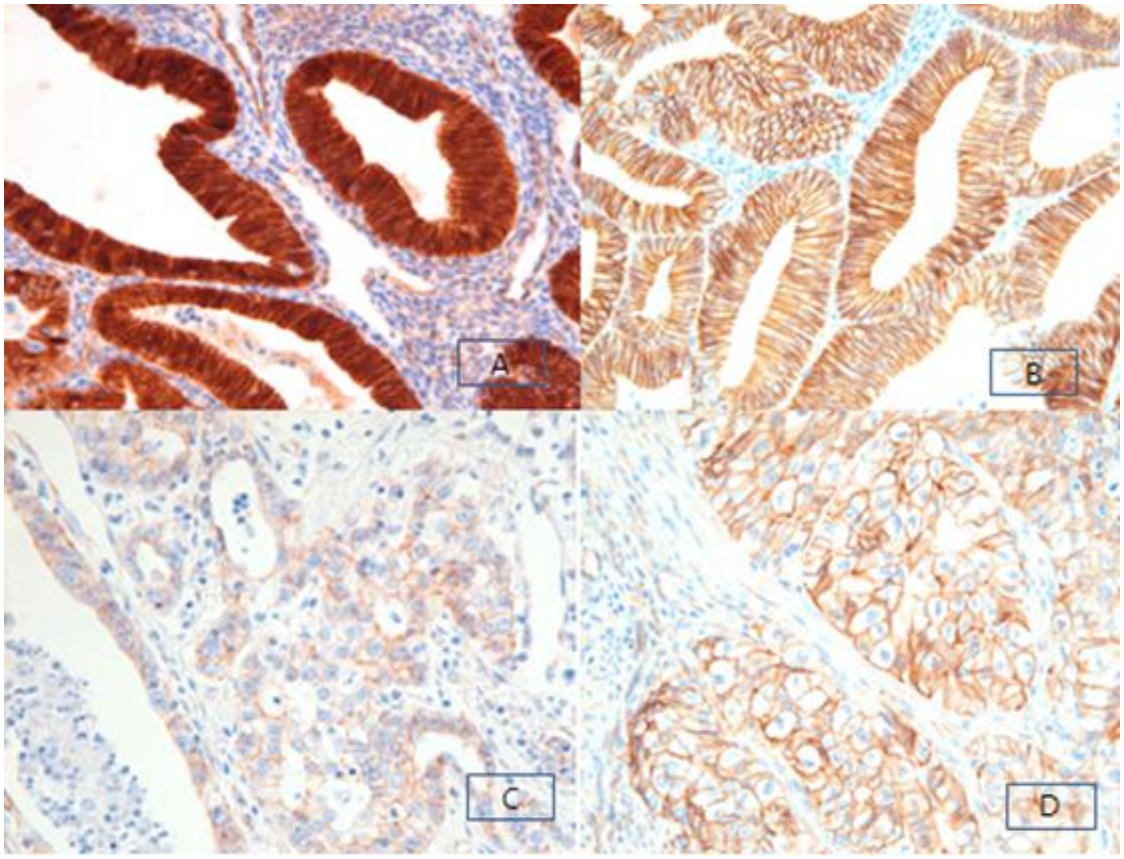

Figure 2: Cytoplasm staining intensity for beta-catenin in endometrial cancer. A) A staining intensity of 3. B) A staining intensity of 2. C) A staining intensity of 1. D) A staining intensity of 0.

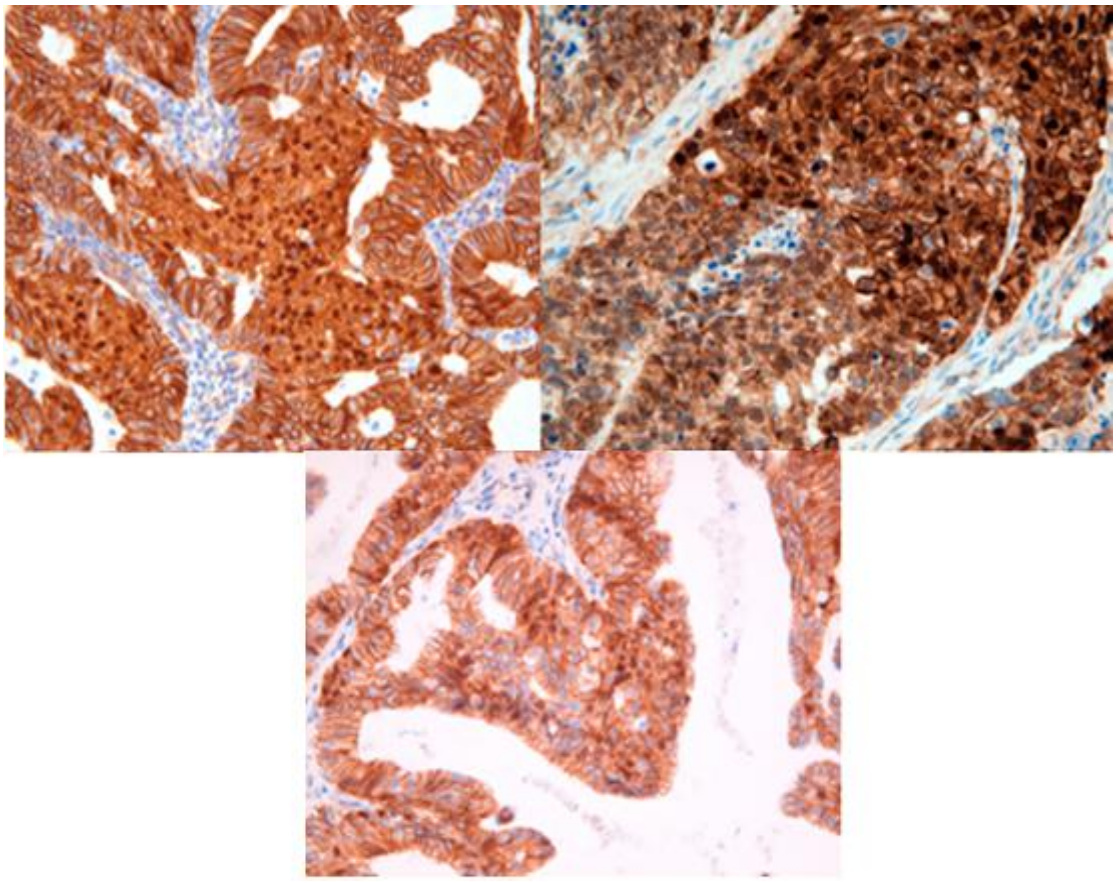

Figure 3: Nuclear staining intensity for beta-catenin in endometrial cancer. A) A staining intensity of 3. B) A staining intensity of 2. C) A staining intensity of 1. D) A staining intensity of 0.

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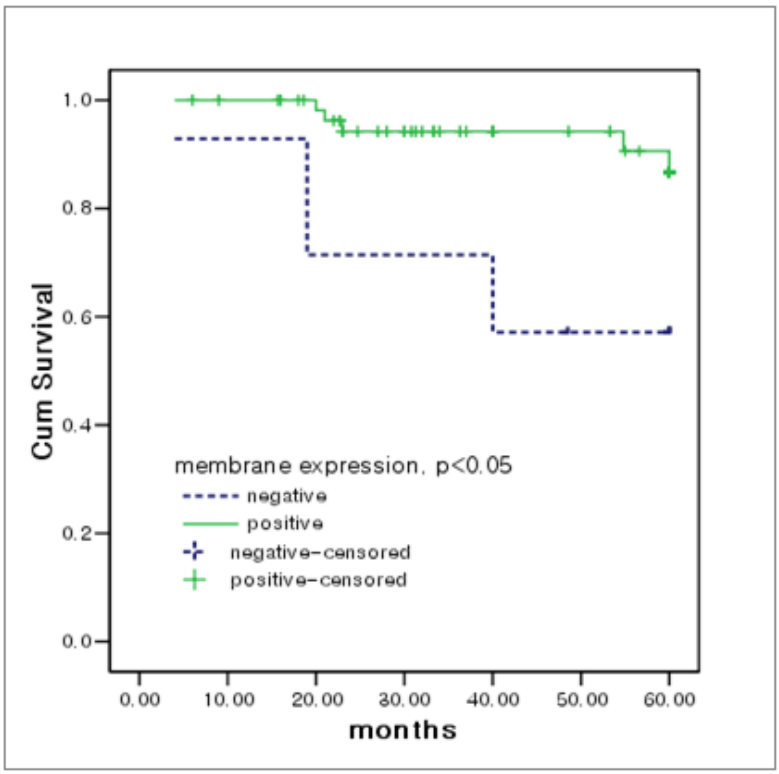

Figure 4: Survival curves for patients with endometrial carcinoma according to membrane beta-catenin staining.

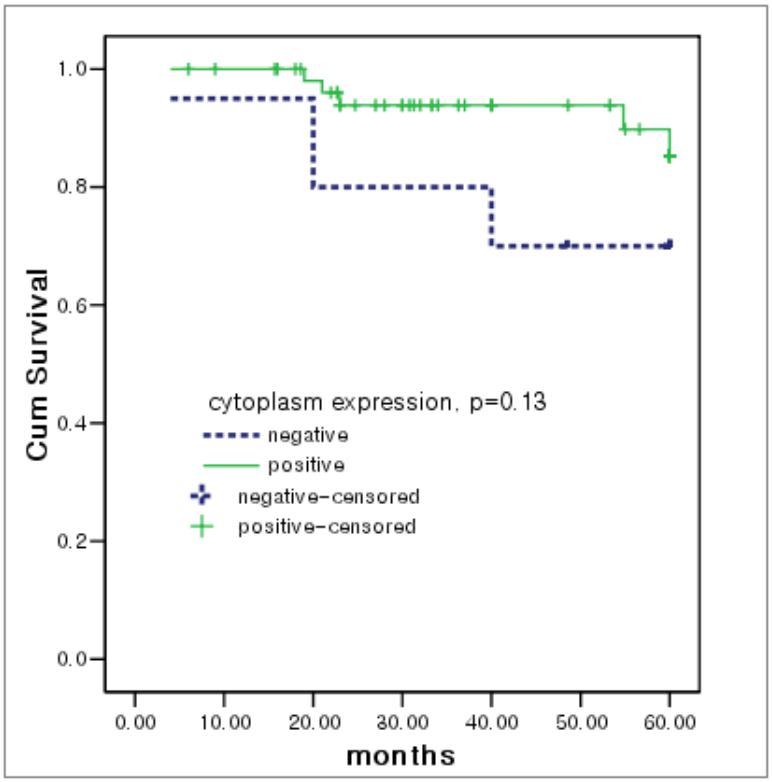

Figure 5: Survival curves for patients with endometrial carcinoma according to cytoplasm beta-catenin staining.

Results

β-catenin expression patterns

Among the 66 included cases, 56 cases exhibited increased β-catenin expression in the cytoplasm (84.8%), 8 cases exhibited decreased β-catenin expression in the cell membrane (10.6%), and 8 cases exhibited increased β-catenin expression in the cell nucleus (12.1%) (Table 2).

The correlation between β-catenin expression and the prognostic factors

The stages of endometrial cancer were divided into early cancer (stage I–II) and advanced cancer (stage III–IV).

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Negative cell membrane β-catenin expression was significantly more common in the advanced cancer samples, compared to the frequency in the early cancer samples (17.9% vs. 0%, respectively; P < 0.05) (Table 3). Overexpression of β-catenin was significantly more common in the cytoplasm of the early cancer samples (96.3% vs. 76.9%, respectively; P < 0.05). Decreasing tissue differentiation was associated with decreased β-catenin expression in the cell membrane (Table 4). When the degree of myometrium invasion was >50%, β-catenin expression in the cell membrane decreased. When the degree of myometrium invasion was <50%, β-catenin expression in the cytoplasm increased (P < 0.05) (Table 5). Samples with metastasis in the blood vessels and lymph nodes were significantly associated with negative β-catenin expression in the cell membrane, compared to the non-metastatic samples (29% vs. 0% and 22.2% vs. 2.6%, respectively; P < 0.05) (Tables 6 and 7).

Survival according to β-catenin expression

The 5-year survival rate was 51.7% for samples with decreased β-catenin expression in the cell membrane, compared to 86.6% for samples with increased β-catenin expression in the membrane (P < 0.05) (Fig. 4). Increased cytoplasmic expression appeared to increase the survival rate, compared to decreased expression, although this difference was not statistically significant (Fig. 5).

Discussion

Endometrial cancer is one of the most common gynecologic cancers in developed countries, with approximately 40,000 patients and 6,600 deaths reported in the United States during 2001. In South Korea, endometrial cancer has the third highest incidence, after cervical and ovarian cancers. Since the gynecologic cancer registry was established during 1991, the reported incidence of endometrial cancer has increased >3-fold, and is expected to increase significantly in the future. The prognostic factors for endometrial cancer include the patient's age at diagnosis, stage, tissue differentiation, myometrial invasion, lymph node metastasis, peritoneal cytology, histologic type, preoperative CA125 tumor size, presence of vascular invasion, hormone receptor status, DNA ploidy, and treatment method.[3,4] In this study, we found that specific β-catenin expression patterns (decreased cell membrane expression and increased cytoplasmic expression) were associated with several prognostic factors for endometrial cancer, including postoperative stage, histological differentiation, myometrial invasion, and lymph node metastasis.

Previous studies have reported that the E-cadherin-catenin complex was expressed in several tumors, and that its expression was inversely related to cell differentiation and metastasis. In this context, various forms of catenin act as E-cadherin binding proteins, including α-catenin (102 kDa), β-catenin (95 kDa), and γ-catenin (82 kDa). Within cells, catenin connects actin fibers (the intracellular backbone), Na+/K+ adenosine triphosphatase (an intracellular membrane protein), and E-cadherin. Therefore, catenin plays an essential role in maintaining the normal inter-cellular function of E-cadherin.[11]

The β-catenin protein also acts a link between E-cadherin and the cytoplasm, and is involved in signal transduction and the regulation of cancer cell invasion.[22] For example, research in gastric cancer cell lines has demonstrated that the loss of β-catenin in the cell membrane reduced the function of E-cadherin, and subsequently increased the invasion of gastric cancer cells. Research in colorectal and bladder cancers has also demonstrated that decreased expression of β-catenin in the cell membrane was involved in cancer invasion.[23-25] In the field of gynecological cancer, Davies et al.[26] have argued that simultaneously decreased expression of α- and β-catenins in the cell membrane of ovarian cancer mediates the interaction with E-cadherin, and plays an important role in cancer invasion. Mun et al.[27] have also demonstrated that decreased β-catenin expression is observed in invasive cervical cancer.

In endometrial cancer, Holcomb et al.[10] have studied the expression of E-cadherin according to endometrial cancer cell type in 76 cases, and reported that cell types with poor prognoses appeared alongside decreasing expression of E-cadherin. Choi et al.[14] also studied the expression of E-cadherin and catenin (α-, β-, and γ-catenin) in 33 cases, and reported that E-cadherin was associated with endometrial cancer cell type and lymph node metastasis; γ-catenin was associated with myometrial invasion. However, they did not find any statistical associations between FIGO stage prognostic factors and the expression of E-cadherin or catenin. Furthermore, they reported that only E-cadherin expression was related to the survival rate. In contrast, Moreno-Bueno et al.[15] studied 149 patients with either endometrial cancer or atypical endometrial hyperplasia, and reported that the cell membrane expression of E-cadherin and β-catenin was lower in endometrial cancer, compared to that in endometrial hyperplasia. In addition, they found that the cell membrane expressions of E-cadherin and β-catenin were lower in endometrioid endometrial cancer, compared to those in non-endometrioid endometrial cancer. Moreover, they reported that the expression of E-cadherin and β-catenin decreased with advancing stage. Stefansson et al.[16] have also argued that E-cadherin expression was associated with cell type, stage, myometrial invasion, vascular invasion, and survival rate, and that β-catenin was related to myometrial invasion and the survival rate. Yang et al.[9] have also recently demonstrated that the frequency of abnormal β-catenin expression increases with advancing stage. In addition, histologic differentiation was correlated

DOI: 10.23958/ijirms/vol02-i11/01

with abnormal B-catenin expression, although this association was not statistically significant. In the present study, we found that decreased cell membrane expression of β-catenin was significantly associated with cancer stage, high differentiation, and high myometrial invasion. We also observed poor prognoses and a lower survival rate among patients with decreased β-catenin expression in the cell membrane. These findings are in agreement with Steffanson et al.'s[16] finding that poor survival was related to decreased β-catenin expression. Despite these findings, the prognostic value of β-catenin remains debatable, as a South Korean study failed to identify β-catenin expression as a significant prognostic factor.[3] However, that study only included a small number of patients with endometrial cancer, which may explain the lack of statistically significant findings. Therefore, the expression of β-catenin may be associated with survival rate, as a recent study has demonstrated that reduced membrane expression of β-catenin was an independent prognostic factor for endometrial cancer.[29]

Unlike cadherin, β-catenin is associated with the intracellular signal transduction system,[17] and plays an important role in the intracellular Wnt signaling pathway that controls gene expression, cell shape, cell-cell adhesion, and polarity.[18] Because β-catenin is normally degraded in the cytoplasm, cytoplasmic levels of β-catenin are normally low. However, if the degradation process is altered (e.g., due to an abnormality in the Wnt signaling pathway), this state increases the cytoplasmic levels of β-catenin. Overexpression of β-catenin in the cytoplasm is also associated with overexpression in the cell nucleus.[18] In this context, the overexpression of β-catenin in the nucleus may induce the expression of oncogenes, such as c-myc, or may be associated with cancer-related gene mutations.[12,13]

Deregulation of β-catenin activity is associated with the progression of various cancers, including colon cancer, hepatocellular carcinoma, skin melanoma, and gastric cancer.[32-36] Mutations in APC, axin, or β-catenin can also deregulate β-catenin activity via activation of Wnt signaling.[37,38] In addition, β-catenin in the nucleus induces the p53-p21 WAF-1 pathway and causes overexpression of cyclin-D, which leads to inhibition of cell proliferation and cellular aging.[19] Furthermore, overexpression of β-catenin in the nucleus is related to progression from atypical endometrial hyperplasia to endometrial cancer.[18,19] Moreover, overexpression of β-catenin in the nucleus is associated with high or ongoing differentiation of squamous cells.[30,31] However, in the present study, we did not find any specific risk or prognostic factors that were associated with nuclear β-catenin overexpression, despite the proposed relationship between the differentiation of squamous cells and nuclear β-catenin overexpression.

In this study, we found that cytosolic β-catenin overexpression was associated with a lower survival rate. However, this relationship was mainly observed in cases with no risk factors for early cancer or a good prognosis. Athanassiadou et al.[29] have recently reported that cytoplasmic β-catenin expression decreased in advanced endometrial cancer cells, which is similar to our findings. Those authors speculated that cytoplasmic expression may occur more frequently during the early initiation or progression stages. Other studies have reported that cytoplasmic β-catenin expression increased in gastric adenoma (the stage before gastric cancer), which suggests that β-catenin is involved in the early stages of cancer.[36,37] Therefore, additional research is needed to resolve the ongoing debate regarding the relationship between cytoplasmic β-catenin overexpression and endometrial hyperplasia (a pre-cancer stage).

In the present study, we evaluated β-catenin expression patterns, and evaluated the associations between the expression patterns and various prognostic factors. Our results indicate that decreased β-catenin in the cell membrane may be a significant prognostic factor for endometrial cancer. However, the prognostic value of β-catenin expression should be confirmed in future studies.

Competing interests

The authors have declared that no competing interests exist.

Abbreviations

FIGO: International Federation of Gynecology and Obstetrics; APC: adenomatous polyposis coli; Tcf: T-cell factor.

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