The Clinical Significance and Biological Function of *PCDH7* in Cervical Cancer

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Research

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Abstract

Background: Cervical cancer is a common malignant tumor in women that is prone to recurrence and metastasis. Recently, many people have explored the role of protocadherin 7 (*PCDH7*) in cancer, and found that *PCDH7* is abnormally expressed in many cancers. The purpose of this study is to investigate the expression and mechanism of *PCDH7* in cervical cancer and evaluate its clinical prognostic significance.

Methods: The expression of *PCDH7* in cervical cancer and cells was detected by qRT-PCR. The relationship between *PCDH7* expression and clinical prognosis was calculated by the Kaplan-Meier method and Cox regression analyses. The effects of *PCDH7* on cancer cell proliferation, migration, and invasion were studied by MTT assay and transwell assays.

Results: The expression of *PCDH7* in cervical cancer tissues and cell lines was significantly down-regulated compared with the control. Low *PCDH7* expression was associated with low survival rate. *PCDH7* expression was significantly correlated with lymph node metastasis, cell differentiation, and FIGO staging. *PCDH7* can be used as an independent prognostic factor for cervical cancer. Up-regulation of *PCDH7* significantly inhibited the proliferation, migration, and invasion of cancer cells.

Conclusions: *PCDH7* may be used as a biomarker for the prognosis of cervical cancer.

Introduction

Cervical cancer is one of the most common malignant tumors in women and ranks second in developing countries(1, 2). With the development of cervical cancer screening and the widespread application of HPV vaccines, great progress has been made in reducing mortality, especially in developed countries(3, 4). Although great progress has been made in early prevention, the rate of cervical cancer metastasis and recurrence is still high, the prognosis is poor, and the patient population becomes younger and younger(5, 6). At present, there are few accurate and specific markers in the prognosis of cervical cancer.(7, 8). Therefore, in order to assess the prognosis of cervical cancer, it is necessary to explore new prognostic biomarkers to predict the risk or prognosis of cervical cancer(9, 10).

Protocadherin (*PCDH*) is the largest subfamily of the cadherin family, which can strengthen nerve synapses and play a certain role in signal transduction(11, 12). The *PCDH* family is divided into clustered *PCDH* and non-clustered *PCDH* according to its gene structure(13). The protein encoded by *PCDH7* has an extracellular domain containing 7 cadherin repeats, which plays a role in cell recognition and adhesion, and is concentrated in the brain and heart(14, 15). Previous studies have found that a variety of genes are abnormally expressed in cervical cancer(16, 17). There have been many studies showings that *PCDH* is abnormally expressed in various cancers and has a carcinogenic or anti-tumor effect(18–20). However, there are few studies on the expression and role of individual *PCDHs* in cancer. Previous studies have found that the expression of *PCDH7* was significantly up-regulated in human non-small cell lung cancer (NSCLC)(21). *PCDH7* was significantly down-regulated in non-muscle invasive bladder cancer (NMIBC)

and Cox analysis found that *PCDH7* can be used as an independent predictor of NMIBC(22). The above results indicate that *PCDH7* plays a role in a variety of cancers, but the role and mechanism of *PCDH7* in cervical cancer have not yet been studied.

In this study, we first determined the abnormal expression of *PCDH7* in cervical cancer tissues and cells. Then we analyzed the relationship between *PCDH7* and clinicopathological characteristics and survival status to understand its role in prognosis. In addition, we studied the role of *PCDH7* expression in cell proliferation, migration and invasion to understand its mechanism of action in cervical cancer. Through the entire study, we will explore whether *PCDH7* can be used as a prognostic biomarker for cervical cancer.

Methods And Materials

Patients and tissue samples collection

We selected 106 patients with cervical cancer who underwent surgery from July 2013 to June 2015 in Ningbo Women and Children's Hospital and ensured that they have not received other treatment before surgery. The patient's tumor tissues and the corresponding surrounding non-tumor tissues are obtained after surgery and then quickly froze in liquid nitrogen. Each patient signed an informed consent form before the operation and agreed to use the tissues for this research. The clinical case characteristics of each patient were recorded in Table 1, and each patient was followed up by telephone for five years to understand his survival status. This study has been approved by the Ningbo Women and Children's Hospital ethics committee.

Table 1
Association of *PCDH7* expression with clinical features of cervical cancer patients

Features	Total No.	*PCDH7* expression		*P* values
	N = 106	High (n = 48)	Low (n = 58)	
Age (Years)				0.595
≤ 50	50	24	26	
> 50	56	24	32	
Tumor size (cm)				0.947
≤ 4	46	21	25	
> 4	60	27	33	
HPV status				0.887
Negative	28	13	15	
Positive	78	35	43	
Lymph node metastasis				0.007
Negative	67	37	30	
Positive	39	11	28	
Differentiation				0.039
Well	48	27	21	
Moderately/Poorly	58	21	37	
FIGO stage				0.001
I-IIA	56	33	23	
IIB-IV	50	15	35	

Cell lines and transfection

Human cervical cancer cell lines HeLa, SiHa, C33A and CaSki and normal human cervical cell lines Ect1/E6E7 were purchased from Cell Bank of Chinese Academy of Sciences (Shanghai, China). Cells were cultured in RPMI 1640 medium supplemented with 10% fetal bovine serum (FBS, Invitrogen, USA), and stored in a humidified incubator at 37 °C with 5% CO_2. Effectene transfection reagent (QIAGEN Companies) was used for cell transfection of pcDNA3.1- *PCDH7* according to the manufacturer's instructions. Cells transfected with pcDNA3.1-control and cells without any transfection were used as controls. All experiments were repeated at least three times.

RNA extraction and quantitative real-time polymerase chain reaction (qRT-PCR)

According to the manufacturer's instructions, TRIzol reagent (Invitrogen, Carlsbad, California, USA) was used to extract total RNA from tissues and cell lines. Reverse transcription was performed by transcriptor first strand cDNA symthesis kit (Roche, Vilvoord, Brussels, Belgium) to synthesize complementary DNA (cDNA). SYBR green I Master Mix kit (Invitrogen) was used for qRT-PCR and then run it on 7300 Real-Time PCR System (Applied Biosystems, USA) to study the expression of *PCDH7*. The $2^{-\Delta\Delta Ct}$ method was used to calculate the relative expression of *PCDH7*.

Cell proliferation

Colorimetric 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to analyze the effect of *PCDH7* on the proliferation of cervical cancer cells. First, the cells were seeded in a 96-well plate (4×10^3/well). We added MTT reagent (Sigma-Aldrich, USA, 5 mg/mL) at 0, 1, 2, 3, and 4 days, and then incubated at 37 °C for 4 hours. After that, we added 100 μl DMSO (Sigma-Aldrich, USA) into the plate and used a microplate reader (Bio-Rad, Inc., Hercules, CA, USA) to measure its absorbance value at 490 nm. The assay should be repeated at least three times for each sample.

Cell migration and invasion

The effects of *PCDH7* on cell migration and invasion were analyzed by transwell (24-well; Corning Life Sciences, New York, USA) assays. The invasion assay required Matrigel (Bedford, Massachusetts, USA) to be pre-coated on the bottom membrane of the upper chamber, while the migration assay did not. The transfected cells were cultured in serum-free RPMI-1640 medium, and then the cell suspension was placed in the upper chamber of the transwell (2×10^4/well), while 600 μl of RPMI-1640 medium containing 10% FBS was added to the lower chamber as a chemokine. After removing the cells that have not migrated or invaded the upper layer of the bottom membrane, the bottom membrane was fixed in 4% paraformaldehyde for 30 minutes and stained with 0.1% crystal violet for 20 minutes. The cells were counted using an optical microscope.

Statistical analysis

The statistical analysis of the data was performed by SPSS 23.0 (SPSS Inc., Chicago, IL) and Graphpad 7.0 (GraphPad Software, Inc., La Jolla, CA, USA). The differences between the groups were analyzed by Student's t-test or one-way ANOVA. The Kaplan-Meier method and Cox regression analyses were used to evaluate the relationship between *PCDH7* and the clinicopathological characteristics and prognosis of patients. All data are expressed as mean ± SD, and the data is statistically significant when $P < 0.05$.

Results

PCDH7 expression in tissue specimens and cells

The expression of *PCDH7* in cervical cancer tissues and cells was studied by qRT-PCR. It can be seen from the results that the expression of *PCDH7* in cancer tissues was significantly down-regulated compared with non-tumor tissues ($P < 0.001$, Fig. 1A). Then we chose to verify this result in cervical cancer cell lines (HeLa, SiHa, C33A and CaSki). It can be seen from the results that the expression of *PCDH7* in cervical cancer cells was significantly lower than that in normal human cervical cells (all $P < 0.01$, Fig. 1B). At the same time, HeLa and SiHa cells had relatively lower expression among the four cell lines, so these two cell lines were selected for subsequent assays.

The relationship between the expression of PCDH7 and the characteristics of cervical cancer clinical cases

Table 1 shows the relationship between *PCDH7* expression and clinicopathological parameters in patients with cervical cancer. Using the average value of *PCDH7* expression in cancer tissues as a critical point, patients were divided into high expression groups (n = 48) and low expression groups (n = 58). As can be seen from Table 1, the expression of *PCDH7* was significantly related to lymph node metastasis ($P = 0.025$), cell differentiation ($P = 0.039$) and FIGO staging ($P = 0.001$). However, there was no correlation between the expression of *PCDH7* and age, tumor size, and HPV status (all $P > 0.05$).

Significance of PCDH7 expression in the prognosis of cervical cancer

Through Kaplan-Meier method and Cox regression model, the relationship between the survival information of cervical cancer patients and the expression of *PCDH7* was analyzed to determine the potential prognostic value of *PCDH7* expression. It can be seen from the figure that the five-year survival rate of patients with high PCDH7 expression is significantly higher than that of patients with low expression (log-rank $P = 0.011$, Fig. 2). Table 2 showed the correlation analysis between patient clinical information and *PCDH7* expression. It can be seen from the table that *PCDH7* expression (HR = 0.245, 95% CI = 0.072–0.838 and $P = 0.025$), lymph node metastasis (HR = 0.424, 95% CI = 00.184–0.976 and $P = 0.044$), cell differentiation (HR = 0.289, 95% CI = 0.093–0.897 and $P = 0.032$) and FIGO staging (HR = 0.264, 95% CI = 0.074–0.943 and $P = 0.040$) can be used as independent factors for the prognosis of cervical cancer patients.

Table 2
Multivariate Cox regression analysis for risk prognostic factors to the overall survival of patients

Parameters	Multivariate analysis		
	HR	95% CI	*P*
PCDH7 expression	0.245	0.072–0.838	0.025
Age	2.276	0.815–6.353	0.117
Tumor size	0.428	0.131–1.396	0.160
HPV status	0.277	0.074–1.036	0.057
Lymph node metastasis	0.424	0.184–0.976	0.044
Differentiation	0.289	0.093–0.897	0.032
FIGO stage	0.264	0.074–0.943	0.040

The up-regulation of PCDH7 inhibited the proliferation, migration and invasion of cervical cancer cells

In order to further determine the biological role of *PCDH7* in cervical cancer, we conducted proliferation, migration and invasion assays on cervical cancer cells. Firstly, it was found that the expression of *PCDH7* in the cells was increased after the transfection of pcDNA3.1-*PCDH7* by qRT-PCR ($P < 0.001$, Fig. 3A). The effect of *PCDH7* on cell proliferation was studied by MTT assay. It can be seen from the figure that the high expression of *PCDH7* significantly inhibited the proliferation of HeLa and SiHa cells ($P < 0.01$, Fig. 3B and 3C). After that, we evaluated the effect of *PCDH7* on cell migration and invasion through transwell assays. It can be seen from the figure that overexpression of *PCDH7* significantly reduced the migratory ability of HeLa and SiHa cells, and suppressed the invasion of these two groups of cells ($P < 0.001$, Fig. 4A and 4B).

Discussion

Cervical cancer is a cancer with a high incidence rate in women(23). It has a high rate of metastasis and recurrence after operation, and it is difficult to cure and control(24). It is necessary to explore more sensitive biomarkers to monitor its prognosis for suppressing its metastasis and recurrence at the earliest possible time. *PCDH* is a cadherin that has been found to be abnormally expressed in cancer and can affect its mechanism of action in recent studies, and *PCDH7* is a subfamily among them(13, 25, 26). Previous studies have found that it is abnormally expressed in cancers such as NSCLC, NMIBC, and gastric cancer(21, 22, 27). So, we studied the abnormal expression and mechanism of *PCDH7* in cervical cancer.

First, we explored the expression differences of *PCDH7* in cervical cancer tissues and cells. It can be seen from the results that the expression of *PCDH7* in cervical cancer tissues is significantly lower than that in surrounding non-tumor tissues. Compared with normal human cervical cells, the expression of *PCDH7* in cervical cancer cell lines was significantly down-regulated. Previous studies have obtained similar results to this study. For example, Bujko et al. have confirmed that *PCDH7* expression was significantly down-regulated in colorectal cancer tissues(28). However, Shishodia et al. have found that *PCDH7* was overexpressed in castration-resistant prostate cancer (CRPC) cells and tissues, and Zhou et al. have discovered that *PCDH7* was overexpressed in NSCLC tumors(21, 29). The different results may be due to the different roles of *PCDH7* in different tumor tissues, but the abnormal expression of *PCDH7* in cancer tissues can be obtained. Other genes also have this phenomenon. For example, *FOXO1* was down-regulated in cervical cancer tissues and significantly up-regulated in epithelial ovarian cancer (EOC) tissues(30, 31).

Then we verified the relationship between *PCDH7* expression and prognosis through Kaplan-Meier survival curve and Cox regression model. It can be found that the five-year survival rate of patients with low *PCDH7* expression is significantly lower than that with high expression. At the same time, it was found that the expression of *PCDH7* was significantly related to the characteristics of clinical cases such as lymph node metastasis, cell differentiation and FIGO staging, and *PCDH7* expression can be used as an independent clinical prognostic factor for cervical cancer. Lin et al. have proved that low expression of *PCDH7* was associated with lower survival rate and can be used as an independent predictor of NMIBC(22). Chen et al. have demonstrated that low *PCDH7* expression was significantly associated with poor prognosis of gastric cancer(27). Combined with the above results, it is indicated that the low expression of *PCDH7* can be used as an independent predictor of cervical cancer prognosis.

We have further studied the effects of *PCDH7* on the proliferation, migration and invasion of cervical cancer cells. First, we transfected pcDNA3.1-*PCDH7* into cervical cancer cells to up-regulate the expression of *PCDH7*. Through MTT assay, it was found that the up-regulated *PCDH7* significantly inhibited the proliferation of cancer cells. Through the transwell assays, the overexpression of *PCDH7* reduced the migration and invasion ability of cancer cells. These assays show that the high expression of *PCDH7* can suppress cell proliferation, migration and invasion. Chen et al. have confirmed that down-regulation of *PCDH7* inhibited the migration and invasion of gastric cancer cells by inhibiting E-cadherin(27). Li et al. have found that overexpression of *PCDH7* promoted the proliferation and invasion of breast cancer cells in vitro(32). Therefore, the expression of *PCDH7* can affect the biological behaviors of cells to affect the development of cancer. Although in vitro cell assays have been carried out in this research, the exploration on its mechanism is not deep enough. The next step should be to deepen the research on its mechanism.

In conclusion, *PCDH7* is down-regulated in cervical cancer tissues and cell lines. The down-regulation of *PCDH7* was related to the poor prognosis of patients. At the same time, the down-regulation of *PCDH7* promoted the proliferation, migration and invasion of cervical cancer cells. All in all, *PCDH7* can be used as a prognostic biomarker for cervical cancer.

Abbreviations

cDNA: complementary DNA

CRPC: castration-resistant prostate cancer

EOC: epithelial ovarian cancer

FBS: fetal bovine serum

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NMIBC: non-muscle invasive bladder cancer

NSCLC: non-small cell lung cancer

PCDH: protocadherin

qRT-PCR: quantitative real-time polymerase chain reaction

SPSS: Statistical Product and Service Solutions

Declarations

Ethics approval and consent to participate

This study has been approved by the Ningbo Women and Children's Hospital ethics committee, and a written informed consent was obtained from each participant.

Consent for publication

All materials had been obtained for medical care of the patients.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SZ and XF designed and performed the experiments and analyzed data. SZ wrote the manuscript. All authors read and approved the final manuscript.

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Not applicable.

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Figures

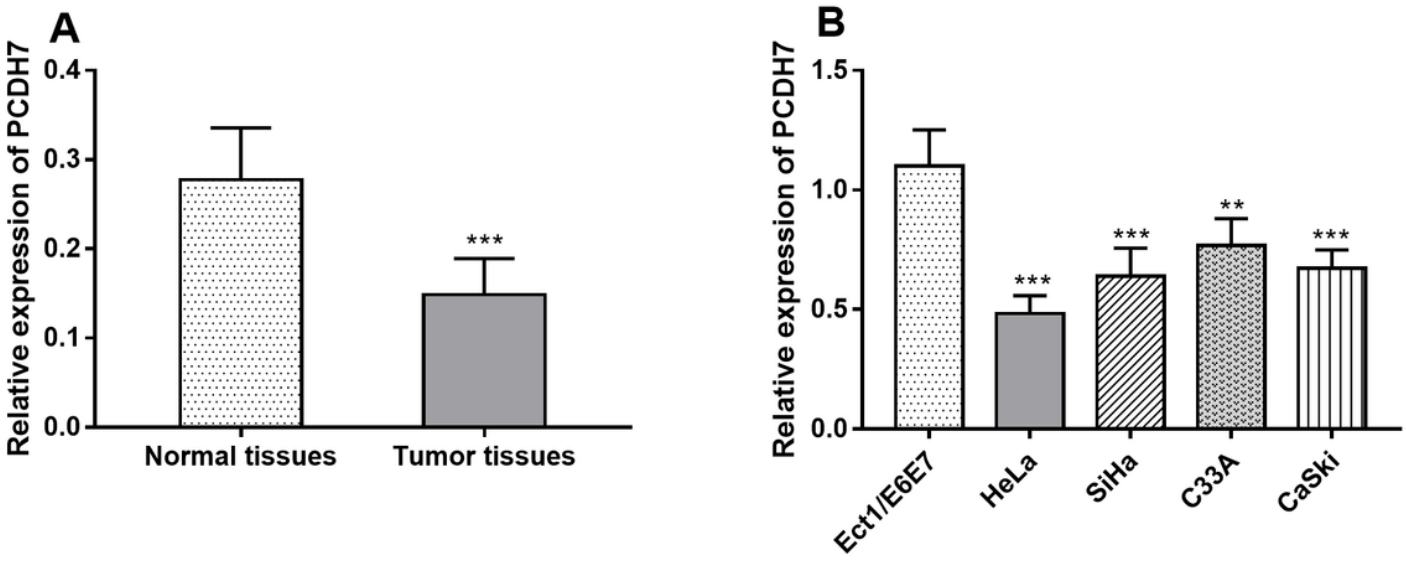

Figure 1

The relative expression level of PCDH7 in cervical cancer tissues and cells. (A) Compared with surrounding non-tumor tissues, the expression of PCDH7 in cervical cancer tissues was significantly down-regulated (***P < 0.001). (B) The expression of PCDH7 in cervical cancer cell lines is significantly lower than in normal human cervical cells (** P < 0.01, *** P < 0.001).

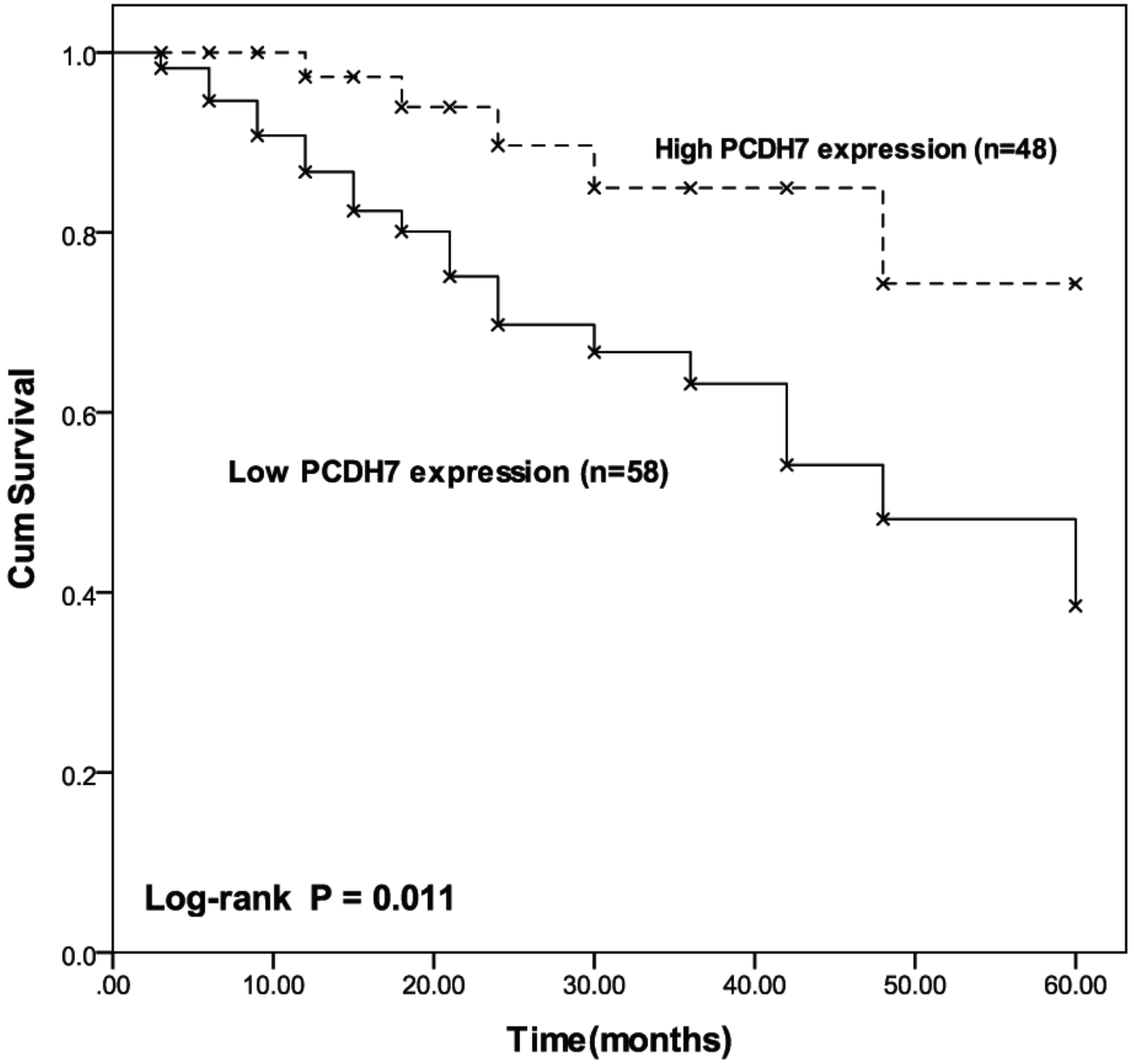

Figure 2

Survival curve of cervical cancer patients based on PCDH7 expression. The five-year survival rate of patients with low PCDH7 expression is lower (P = 0.011).

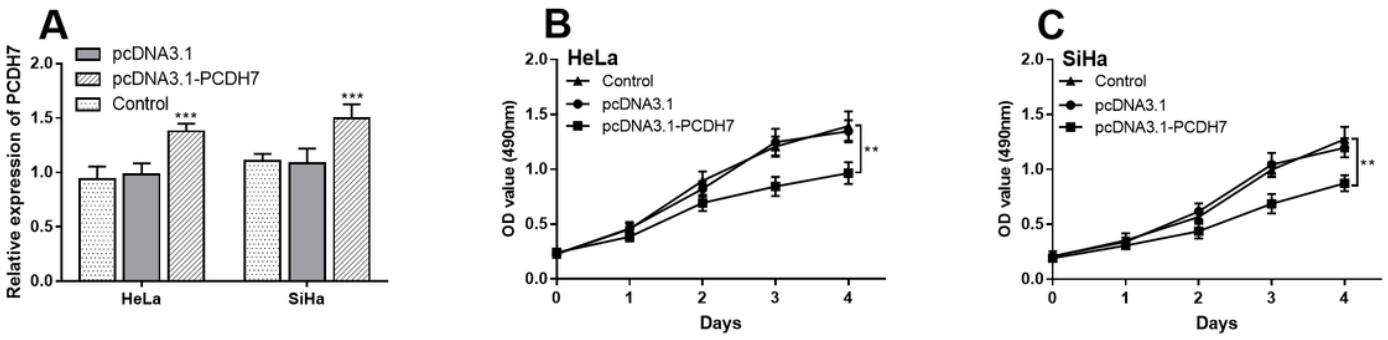

Figure 3

The upregulation of PCDH7 affects cell proliferation. (A) The expression of PCDH7 in cancer cells transfected with pcDNA3.1-PCDH7 was significantly up-regulated, achieving the expected effect (***P < 0.001). (B) Up-regulation of PCDH7 inhibited the proliferation of HeLa cells (**P < 0.01). (C) Up-regulation of PCDH7 inhibited the proliferation of SiHa cells (**P < 0.01).

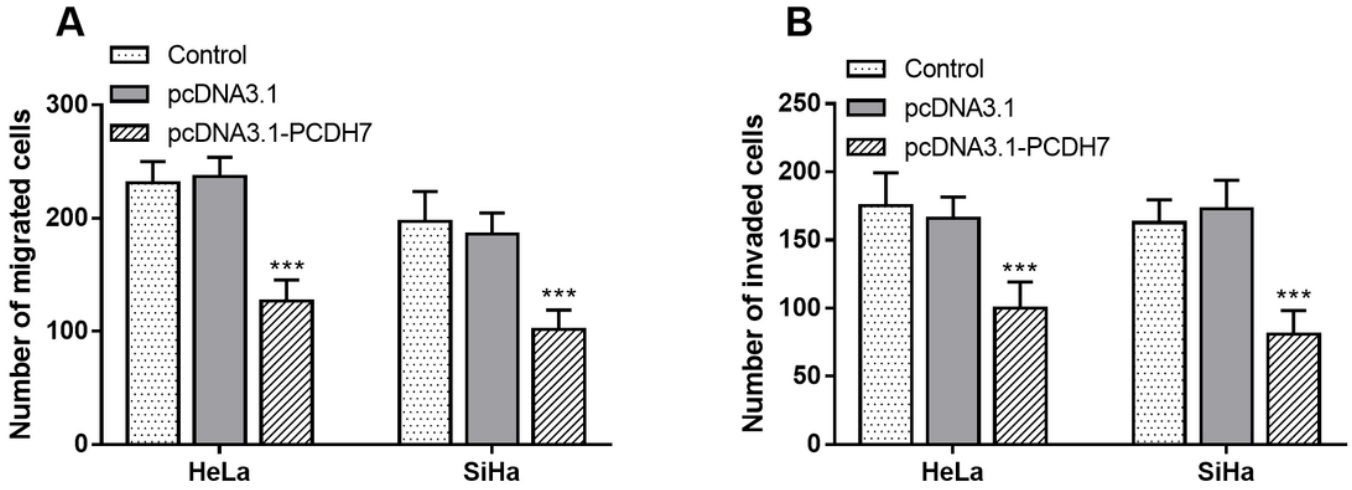

Figure 4

The up-regulation of PCDH7 affects cell migration and invasion. (A) Up-regulation of PCDH7 significantly inhibited the migration of HeLa cells and SiHa cells (***P < 0.001). (B) Overexpression of PCDH7 significantly reduced the invasive ability of HeLa cells and SiHa cells (***P < 0.001).