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Original Article

Cyclin D1 expression and endocrine therapy are correlated with the prognosis of breast cancer

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Abstract: Aims: The present study is to investigate the relationship between the expression of cyclin D1 and clinicopathological indices of breast cancer. The relationship between cyclin D1 expression and breast cancer prognosis is also studied. Methods: A total of 226 patients with breast invasive ductal carcinoma were included in the study. The expression of cyclin D1 in breast cancer tissues was detected by immunohistochemical staining. Pearson Chi-square test was used to analyze the expression of cyclin D1 at various clinical indicators of breast cancer patients. Kaplan-Meier survival curve analysis was performed to examine how different levels of cyclin D1 expression and the use of endocrine therapy affect the prognosis of breast cancer. Proportional hazard model was employed to carry out COX regression analysis of cyclin D1 and clinicopathological indices. Results: Expression of cyclin D1 was correlated with tumor size, estrogen receptor-α and prognosis in breast cancer patients. The number of affected lymph nodes, endocrine therapy, and cyclin D1 expression were factors that affect the prognosis of breast cancer. Patients with higher expression of cyclin D1 had longer tumor-free survival time. Patients with endocrine therapy had prolonged cumulative tumor-free survival time. Endocrine therapy increased the cumulative tumor-free survival time for breast cancer patients with positive cyclin D1 expression. In addition, endocrine therapy prolonged the cumulative tumor-free survival time for breast cancer patients with negative cyclin D1 expression. Conclusions: The present study demonstrates that cyclin D1 expression in breast cancer tissues is correlated with tumor size, estrogen receptor-α, recurrence and metastasis. Positive expression of cyclin D1 indicates that endocrine therapy can be effective and have a good prognosis for breast cancer.

Keywords: Breast cancer, cyclin D1, clinicopathological indices, endocrine therapy, prognosis

Introduction

The occurrence, development and metastasis of tumors are processes that are participated by changes of multiple genes. The intrinsic mechanism is characterized by uncontrolled proliferation and malignant transformation of cells caused by abnormal activation, overexpression, deletion and mutation of genes [1]. Dysregulation of cell cycles is a key reason for the uncontrolled proliferation of cells, and cyclins play important roles in this process [2]. Sustained high expression of cyclin D1, a member of the cyclin family, reduces the G1 phase of cell cycle, shrinks cell sizes, and facilitates the entrance of the cells into S phase, resulting in uncontrolled growth, transformation and canceration of the cells [3]. It is demonstrated that cyclin D1 is an oncogene in cell cycle that is most directly related to tumor. In various tumor tissues, overexpression of cyclin D1 is required by cell transformation and the maintenance of transformation phenotype [4]. In recent years, cyclin D1 has attracted more and more concerns as an oncogene for breast cancer. Cyclin D1 is a key target gene in Wnt signaling pathway. Regulation by cyclin D1 has important impact on the division cycles of breast cancer cells [5, 6]. Excessive proliferation of breast cancer cells, abnormal cell cycle, and carcinogenesis are closely related to the positive expression of cyclin D1. Cyclin D1 can form complexes with CDK4/6, phosphorylate Rb protein, and help cells enter S phase from G1 phase [7]. In the presence of cyclin D1 overexpression, G1 phase is shortened, and cell cycle progression is accelerated, leading to excessive cell proliferation and canceration. However,

discrepancies exist in researches on the relationship between cyclin D1 and the clinicopathological index of breast cancer. In the present study, we investigate how cyclin D1 expression in breast cancer tissues is correlated to the clinicopathological index of breast cancer, endocrine therapy, and prognosis.

Materials and methods

Patients

A total of 241 patients with breast invasive ductal carcinoma were hospitalized at The First Affiliated Hospital of Xinjiang Medical University between January 2000 and December 2010. All these patients had complete clinical data, and were at 0-II clinical stages. After surgery, the patients were followed up for the duration of 2-12 years until 31 December 2012. During this period, 15 patients died or lost contact, and were thus excluded from the study. As a result, the remaining 226 breast cancer patients were included in the present study regarding cyclin D1. All procedures were approved by the Ethics Committee of Xinjiang Medical University. Written informed consents were obtained from all patients or their families.

Immunohistochemistry

Tissue samples were fixed by formalin and embedded with paraffin, and sections (3 μm) were cut and mounted on glass slides, followed by incubation at 70°C overnight. The sections were deparaffinized by soaking in xylene for 20 min and then soaked in 100% ethanol for 1 min. Then, the sections were preincubated with 3% H_2O_2 for 10 min, and then soaked into gradient concentrations of ethanol (90-70%) for 3 min each, followed by washing with distilled water. Subsequently, the sections were boiled in EDTA repair solution for 20 min, followed by cooling to room temperature before washing with phosphate-buffered saline (PBS). Concentrated human/rabbit polyclonal primary antibody of cyclin D1 (Fuzhou Maixin Biotech. Co., Ltd., Fuzhou, China) was added onto the sections, followed by incubation at 37°C for 1 h in dark. After washing with PBS, horseradish peroxidase-labelled anti-rabbit/mouse secondary antibody (Fuzhou Maixin Biotech. Co., Ltd., Fuzhou, China) was added, followed by incubation at 37°C for 30 min in dark. For control, PBS was used instead of secondary antibody. After washing again with PBS, 3,3'-diaminobenzidine was added and the sections were left still for 5 min, followed by washing with distilled water. The sections were soaked in hematoxylin for staining, and then hydrochloric acid and alcohol. After washing with distilled water, the sections were soaked in hot water, and then dehydrated by 75%, 80%, 95%, 100% and 100% ethanol for 3 min each. Finally, the sections were dried and mounted.

Brown granules in cell nucleus indicate positive cyclin D1 expression. Immune staining is scored according to the intensity of the staining and the number of positive cells [8]. Under the light microscope, ten high-power fields were randomly selected, and 1,000 cells were counted to evaluate the ratio of positive cells and the intensity of staining. To evaluate the intensity of staining, samples with 0% stained cells had negative expression (-), samples with 1-10% light yellow cells had weak positive expression (+), samples with 11-50% yellow cells had positive expression (++), and samples with 50-100% dark yellow cells had strong positive expression (+++).

Statistical analysis

All results were analyzed using SPSS17.0 statistical software (IBM, Armonk, NY, USA). Pearson Chi-square test was used to analyze the expression of cyclin D1 at various clinical indicators of breast cancer patients. Kaplan-Meier survival curve analysis was performed to examine how different levels of cyclin D1 expression and the use of endocrine therapy affect the prognosis of breast cancer. Proportional hazard model was employed to carry out COX regression analysis of cyclin D1 and clinicopathological indices.

Results

Expression of cyclin D1 is correlated with tumor size, estrogen receptor (ER)-α and prognosis in breast cancer patients

To investigate how cyclin D1 is correlated to clinical indices, we calculated the percentages of patients with positive and negative cyclin D1 expression among the 226 patients with breast cancer. The data showed that the percentages of patients with positive cyclin D1 expression

Table 1. Relationship between abnormal cyclin D1 protein expression and clinical indices of breast cancer

Clinical indices	n	Percentage of patients with negative cyclin D1 expression (%)	Percentage of patients with positive cyclin D1 expression (%)	χ^2	P
Menstruation					
Amenorrhoea	114	38 (33.3)	76 (66.7)	0.112	0.738
Non-amenorrhea	112	35 (31.3)	77 (68.8)		
Tumor diameter					
≤ 2 (cm)	140	38 (27.1)	102 (72.9)	4.476	0.034
2-3 (cm)	86	35 (40.7)	51 (59.3)		
Histological grades					
Grade I	56	21 (37.5)	35 (62.5)	1.869	0.393
Grade II	120	34 (28.3)	86 (71.7)		
Grade III	50	18 (36.0)	32 (64.0)		
Lymphatic metastasis					
L (-)	169	50 (29.6)	119 (70.4)	2.259	0.133
L (+)	57	23 (40.4)	34 (59.6)		
ER-α					
(+)	151	42 (27.8)	109 (72.2)	4.188	0.041
(-)	75	31 (41.3)	44 (58.7)		
Chemotherapy					
Yes	199	68 (34.2)	131 (65.8)	2.664	0.103
No	27	5 (18.5)	22 (81.5)		
Radiotherapy					
Yes	159	55 (34.6)	104 (65.4)	1.673	0.196
No	66	17 (25.8)	49 (74.2)		
Endocrine therapy					
Yes	126	41 (32.5)	85 (67.5)	0.007	0.931
No	100	32 (32.0)	68 (68.0)		
Prognosis					
Tumor-free survival	202	60 (29.7)	142 (70.3)	5.871	0.015
Recurrence and metastasis	24	13 (54.2)	11 (45.8)		

were not different between the two groups of patients with and without amenorrhoea, among patients with different histological grades of tumors, between the two groups of patients with and without lymphatic metastasis, between the two groups of patients with and without chemotherapy or radiotherapy, or between the two groups of patients with and without endocrine therapy ($P > 0.05$). By contrast, the percentages of patients with positive cyclin D1 expression were significantly different between the two groups of patients with different tumor diameters, between the two groups of patients with and without ER-α, or between the two groups of patients with and without tumor recurrence and metastasis ($P < 0.05$) (**Table 1**). These results suggest that the expression of cyclin D1 is correlated with tumor size, ER-α and prognosis in breast cancer patients.

The number of affected lymph nodes, endocrine therapy, and cyclin D1 expression are factors that affect the prognosis of breast cancer

To examine the correlation of clinicopathological indices with breast cancer prognosis, we performed COX multivariate regression analysis. The data showed that the number of affected lymph nodes, endocrine therapy, and cyclin D1 expression were independent prognostic factors for breast cancer ($P < 0.05$). Of note, the number of affected lymph nodes was a risk factor ($OR > 1$), while endocrine therapy and cyclin D1 expression were protective factors

Table 2. COX multivariate regression analysis of clinicopathological indices of breast cancer

Variables	β	Standard error	Wald value	P	OR	95% confidence interval	
Menstrual status	-0.692	0.485	2.030	0.154	0.501	0.193	1.297
No. of affected lymph nodes			12.250	0.002			
0-4	1.800	0.517	12.147	0.000	6.050	2.199	16.651
> 4	1.329	0.849	2.448	0.118	3.776	0.715	19.952
Cyclin D1 expression	-1.015	0.491	4.267	0.039	0.362	0.138	0.949
Chemotherapy	-12.198	418.260	0.001	0.977	0.000	0.000	.
Radiotherapy	-0.578	0.574	1.016	0.314	0.561	0.182	1.727
Endocrine therapy	1.144	0.520	4.833	0.028	3.140	1.132	8.710

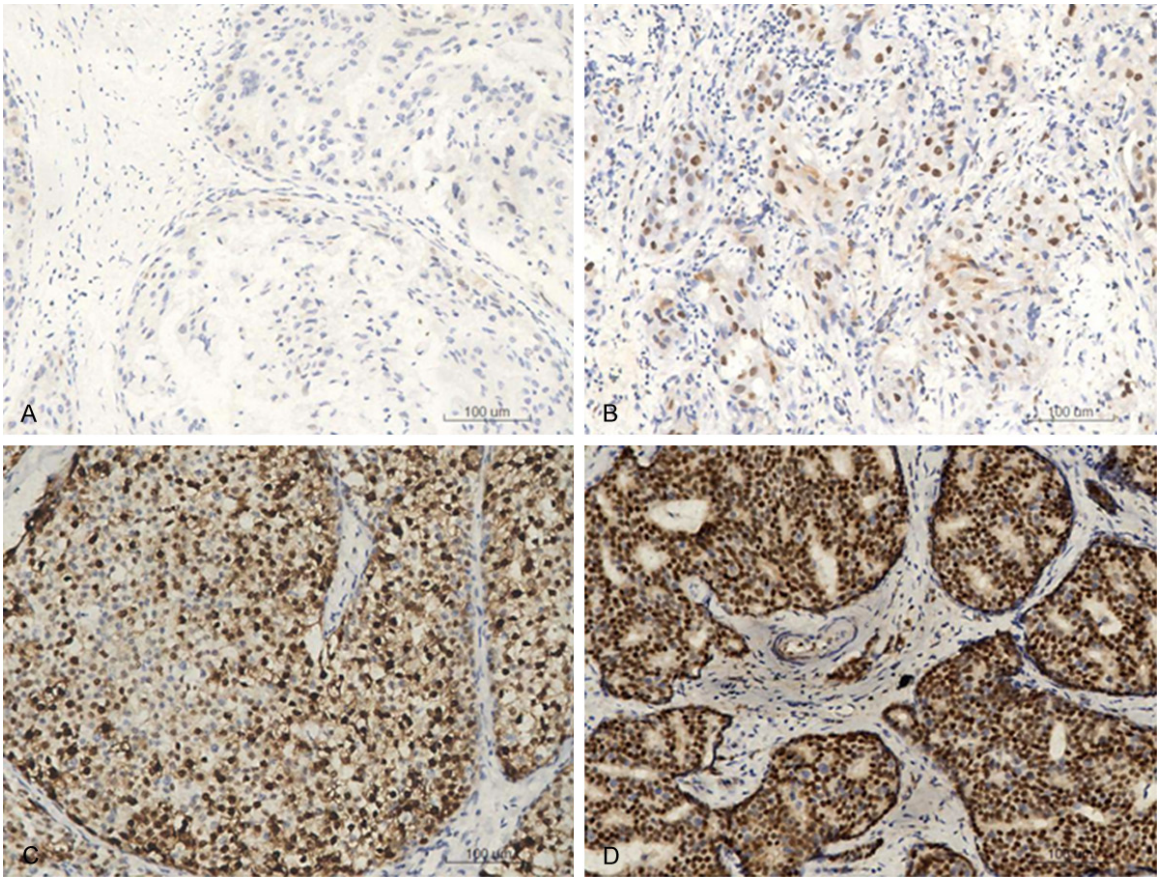

Figure 1. Expression of cycin D1 in breast cancer tissues with (A) grade (-), (B) grade (+), (C) grade (++), and (D) grade (+++). Immunohistochemical analysis was performed.

(OR < 1) (**Table 2**). The result indicates that the number of affected lymph nodes, endocrine therapy, and cyclin D1 expression are factors that affect the prognosis of breast cancer.

Patients with higher expression of cyclin D1 have longer tumor-free survival time

To study the effect of cyclin D1 expression levels in breast cancer tissues on the survival of patients, we divided the patients into negative expression, low expression and high expression groups. Immunohistochemical analysis showed the expression of cycin D1 in breast cancer tissues with grade (-), grade (+), grade (++), and grade (+++) (**Figure 1**). Kaplan-Meier analysis showed that the tumor-free survival time of negative expression group was 8.985 years, that of low expression group was 9.997

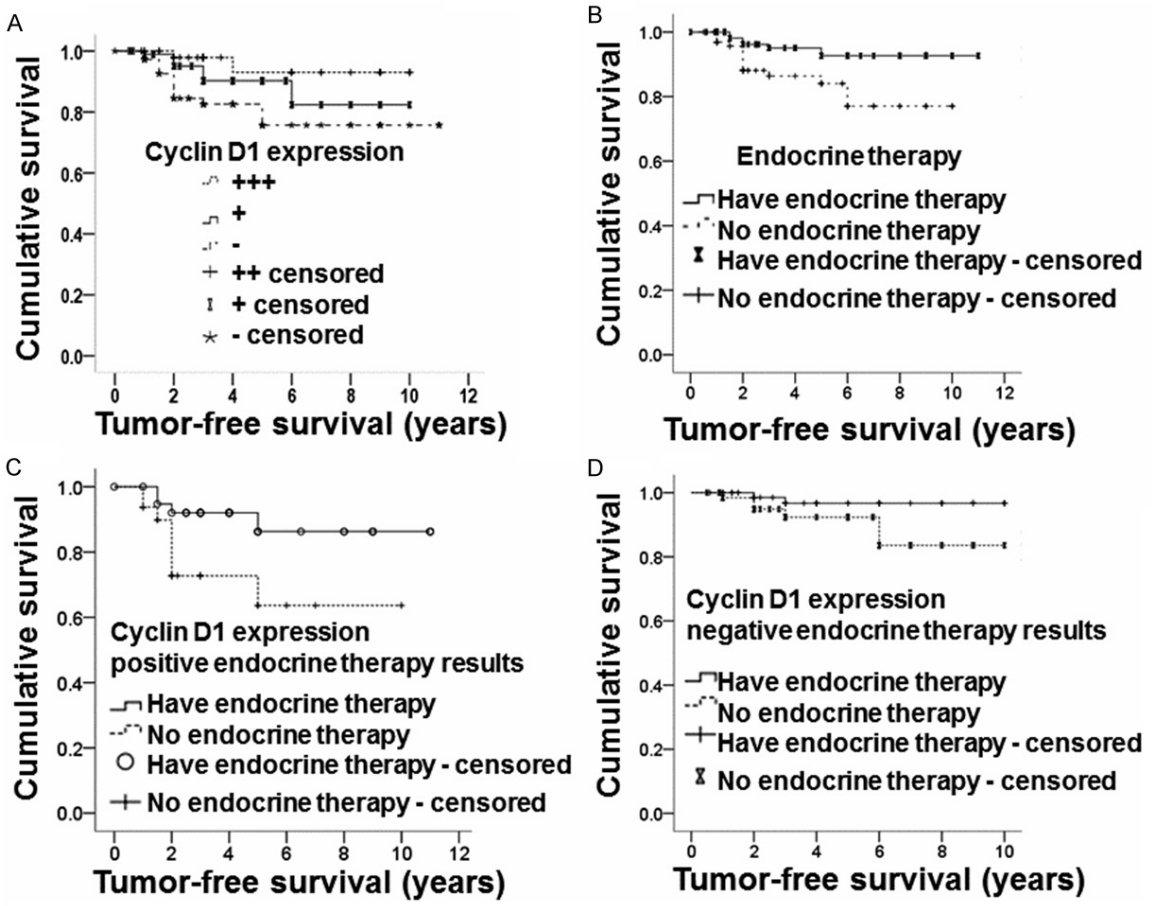

Figure 2. Cumulative tumor-free survival curves (A) at different expression levels of cyclin D1 (Log-rank test: χ^2 = 7.255, P = 0.027), (B) with and without endocrine therapy (Log-rank test: χ^2 = 6.076, P = 0.014), (C) with and without endocrine therapy in the presence of positive cyclin D1 expression (Log-rank test: χ^2 = 4.289, P = 0.038), and (D) with and without endocrine therapy in the presence of negative cyclin D1 expression (Log-rank test: χ^2 = 2.909, P = 0.088). Kaplan-Meier survival curve analysis was performed.

years, and that of high expression group was 9.536 years (Log-rank test: χ^2 = 7.255, P < 0.05) (**Figure 2A**). The result suggests that patients with higher expression of cyclin D1 have longer cumulative tumor-free survival time.

Patients with endocrine therapy have prolonged cumulative tumor-free survival time

To test the effect of endocrine therapy on the survival of breast cancer patients, we divided the patients into endocrine therapy group and non-endocrine therapy group. Kaplan-Meier analysis showed that the tumor-free survival time of endocrine therapy group was 10.414 years, while that of non-endocrine therapy group was 8.493 years (Log-rank test: χ^2 = 6.076, P < 0.05) (**Figure 2B**). The result indicates that patients with endocrine therapy have prolonged cumulative tumor-free survival time.

Endocrine therapy increases the cumulative tumor-free survival time for breast cancer patients with positive cyclin D1 expression

To evaluate the effect of endocrine therapy on breast cancer patients with positive cyclin D1 expression, the patients with positive cyclin D1 expression were divided into endocrine therapy subgroup and non-endocrine therapy subgroup. Kaplan-Meier analysis showed that the tumor-free survival time of these patients with endocrine therapy was 9.911 years, while that without endocrine therapy was 7.282 years (Log-rank test: χ^2 = 4.289, P < 0.05) (**Figure 2C**). The result suggests that endocrine therapy increases the cumulative tumor-free survival time for

breast cancer patients with positive cyclin D1 expression.

Endocrine therapy prolongs the cumulative tumor-free survival time for breast cancer patients with negative cyclin D1 expression

To evaluate the effect of endocrine therapy on breast cancer patients with negative cyclin D1 expression, the patients with negative cyclin D1 expression were divided into endocrine therapy subgroup and non-endocrine therapy subgroup. Kaplan-Meier analysis showed that the tumor-free survival time of these patients with endocrine therapy was 9.753 years, while that without endocrine therapy was 9.046 years (Log-rank test: $\chi^2 = 2.909$, $P > 0.05$) (**Figure 2D**). The result suggests that endocrine therapy prolongs the cumulative tumor-free survival time for breast cancer patients with negative cyclin D1 expression.

Discussion

It is reported that the expression of cyclin D1 in preinvasive carcinoma and invasive ductal carcinoma tissues is significantly higher than those in other tissues [9]. Therefore, it is believed that cyclin D1 plays important roles in the process of cancer development. In the present study, the positive expression rate of cyclin D1 in 140 cases with tumor diameter ≤ 2 cm was 102/140 (72.9%), being significantly higher than that in 86 cases with tumors diameter between 2 and 3 cm was 51/86 (59.3%) ($\chi^2 = 4.476$, $P < 0.05$). This suggests that cyclin D1 expression in breast cancer is related to tumor size, and that overexpression of cyclin D1 usually occurs at the early stage of tumor development. In addition, cyclin D1 positive rate in patients without metastasis is 142/220 (70.3%), being significantly higher than that in patients with recurrence or metastasis (11/24; 45.8%) ($\chi^2 = 5.871$, $P < 0.05$). This suggests that positive expression of cyclin D1 usually leads to low metastasis rate and good prognosis.

It is also reported that the expression of cyclin D1 is dependent on the existence of estrogen and ER [10]. ER induces the overexpression of cyclin D1, which in turn leads to positive ER expression [11]. A report shows that the 6-10 year survival rate of patients with both positive ER and cyclin D1 expressions is 75.8%, while that of patients with both negative ER and cyclin D1 expressions is 50% [12]. In the present study, cyclin D1 expression is correlated with positive ER, and patients with positive ER have higher cyclin D1 expression than patients with negative ER, suggesting that cyclin D1 overexpression is regulated by estrogen in breast cancer patients with positive ER expression.

There are variable opinions about whether endocrine therapy is effective in breast cancer patients with positive cyclin D1 and ER expressions. Diana et al. find that breast cancer patients with higher expression of cyclin D1 have better sensitivity to endocrine therapy and better prognosis [13]. Another report suggests that use of endocrine therapy on patients with positive cyclin D1 expression may have better effect [14]. However, some patients with positive ER and high expression of cyclin D1 still are not sensitive to endocrine therapy. This may be due to the formation of complexes between cyclin D1 and ER. The complex resembles estrogen but is not dependent on estrogen [15]. It directly acts on estrogen response element, so these patients are not sensitive to tamoxifen [16]. Another study shows that breast cancer patients with both positive cyclin D1 and ER expressions have higher sensitivity to endocrine therapy and higher survival rate than patients with positive expression of either cyclin D1 or ER [17]. Therefore, cyclin D1 expression can be used to determine the sensitivity of patients for endocrine therapy. In the present study, the survival curves show that patients with endocrine therapy have longer tumor-free survival time and better prognosis compared with patients without endocrine therapy. When positive cyclin D1 expression is present, patients who receive endocrine therapy have longer tumor-survival time and better prognosis than those without endocrine therapy. This is due to the fact that overexpression of cyclin D1 results in positive ER expression. Of note, patients with both negative cyclin D1 and ER expressions did not receive endocrine therapy in the present study due to the selection of patients. Therefore, further studies are still needed to test whether breast cancer patients with positive expression of both cyclin D1 and ER are more sensitive to endocrine therapy. COX multivariate regression analysis in the present study shows that lymphatic metasta-

sis, endocrine therapy and cyclin D1 expression are independent prognostic factors for breast cancer, with lymphatic metastasis being a risk factor and endocrine therapy and cyclin D1 being protective factors. This demonstrates that patients with positive expression of cyclin D1 and endocrine therapy have good prognosis, while those with lymphatic metastasis have poor prognosis.

It is still controversial that cyclins are associated with breast cancer prognosis. Most studies show that positive expression of cyclin D1 is predictive for good prognosis [18-21]. Chung et al. report that non-metastatic breast cancer patients with positive expression of cyclin D1 have longer disease free survival and lower recurrence rate compared with those with negative expression of cyclin D1 [22]. In addition, positive expression of cyclin D1 is usually observed in well-differentiated and ER-positive breast cancer tissues, suggesting good prognosis [23]. However, other studies show that high expression of cyclin D1 corresponds to active tumor cell proliferation and strong invasiveness, which may lead to poor prognosis [24-27]. In the present study, Kaplan-Meier analysis shows that the median tumor-free survival time of patients with positive cyclin D1 expression is significantly longer than that with negative cyclin D1 expression, suggesting that breast cancer patients with cyclin D1 overexpression have longer survival time and better prognosis and cyclin D1 can possibly used as an independent prognostic factor for breast cancer patients. The mechanism of action of cyclin D1 may be that it facilitates the proliferation and differentiation of cells, induces the deactivation of cyclin D1-dependent protein kinases, or promotes apoptosis. In conclusion, cyclin D1 expression is correlated with tumor size, ER level, recurrence and metastasis. Higher expression of cyclin D1 corresponds to longer tumor-free survival time. For breast cancer patients with positive cyclin D1 expression, endocrine therapy prolongs tumor-free survival time. Lymphatic metastasis, endocrine therapy and positive cyclin D1 expression are independent prognostic factors for breast cancer patients. Lymphatic metastasis is a risk factor, while endocrine therapy and positive cyclin D1 expression are protective factors. Our results suggest that cyclin D1 expression can provide evidence for the evaluation of breast cancer prognosis, with important clinical significance.

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Disclosure of conflict of interest

None.

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