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Increased expression of plakophilin 3 is associated with poor prognosis in ovarian cancer

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Abstract

Considering the essential role of plakophilin 3 (*PKP3*) in the maintenance cell-cell adhesion, dysregulation of *PKP3* is involved in human diseases. This study aimed to explore the clinical significance of *PKP3* in ovarian cancer. Immunohistochemistry was performed to examine the *PKP3* expression in 157 cancer specimens from primary ovarian cancer patients. *PKP3* was expressed in both the cytoplasm and nucleus. Eighty-one (51.6%) out of 157 ovarian cancer tissues showed *PKP3* expression, while absent expression was observed in normal ovarian tissues. High *PKP3* expression was associated with lymph node metastasis (LNM, $P = .004$) and advanced International Federation of Gynecology and Obstetrics (FIGO) stage ($P = .013$). Patients with high *PKP3* expression had shorter overall survival (OS) than those with low *PKP3* expression (60.2 months vs 74.2 months, $P = .021$). However, no association between *PKP3* expression and progression-free survival (PFS) was observed ($P = .790$). Cox regression analysis indicated that *PKP3* expression was an independently predictive factor for the OS of patient with ovarian cancer (adjusted HR = 1.601, 95%CI: 1.014-2.528, $P = .043$), especially those with FIGO stages III and IV disease (adjusted HR = 1.607, 95%CI: 1.006–2.567, $P = .047$). The gene expression profiling interactive analysis (GEPIA) databases also showed that *PKP3* was upregulated in ovarian cancer ($P < .001$) and patients with high *PKP3* expression had shorter OS ($P = .004$). In conclusion, our findings suggest that *PKP3* is upregulated in ovarian cancer and is likely involved in the progression of ovarian cancer. *PKP3* might therefore serve as a prognostic biomarker for patients with ovarian cancer.

Abbreviations: 95% CI = 95% confidence interval, CDH17 = cadherin 17, CDH3 = cadherin 3, CTNNB1 = catenin beta 1, DCHS2 = dachsous cadherin-related 2, FAT4 = FAT atypical cadherin 4, FBXO7 = F-box protein 7, FFPE = formalin-fixed paraffin-embedded, FIGO = International Federation of Gynecology and Obstetrics, GEPIA = gene expression profiling interactive analysis, H&E = haematoxylin and eosin, HR = hazard ratio, IHC = immunohistochemistry, LNM = lymph node metastasis, OR = odds ratio, OS = overall survival, PFS = progression-free survival, *PKP3* = plakophilin 3, TMA = tissue microarray, ZEB1 = zinc finger E-box binding homeobox 1.

Keywords: cell adhesion, desmosome, ovarian cancer, plakophilin 3, prognosis

1. Introduction

With the progression in the early detection and treatment, the incidence and mortality of ovarian cancer is declining in China.[1,2] Ovarian cancer is the 11th most common cancer and the 10th leading cause of death from cancer in women, with an estimated 51,000 (3.0%) new cases diagnosed and 23,000 (2.7%) deaths in 2014.[2] Most patients with ovarian cancer are diagnosed at late stages due to vague associated symptoms, and thus the overall prognosis of ovarian cancer remains poor, with an overall 5-year survival rate of less than 50%.[3] Since ovarian cancer exhibits highly invasive and metastatic properties and existing therapeutic strategies have limited efficacy for advanced disease, it is critical to understand the underlying molecular mechanism of the progression of ovarian cancer.

Epithelial cells are joined to each other by tight junctions, adherens junctions, and desmosomes.[4] Desmosomes are important cell-cell junctional protein complex that tethers intermediate filaments cytoskeleton to the plasma membrane–spanning desmosomal cadherins via the armadillo (i.e., plakoglobin and plakophilin) and plakin (i.e., desmoplakin, periplakin, and envoplakin) proteins. Disruption of desmosomal adhesion caused by mutations in desmosomal genes, and autoantibodies or bacterial toxins targeting desmosomal cadherins has been linked to human diseases such as skin diseases and cardiomyopathies.[5] It is not surprising that desmosomes play an important role in cancer progression since cancer invasion and metastasis require breaking down the junctions that hold cells together in a tissue.[6] Substantial evidence supports a tumor-inhibitory function of desmosomes that loss of desmosome proteins and desmosomal adhesion is involved in cancer development and progression. However, this may not be the case in all circumstances because

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some desmosome proteins exhibit oncogenic potential in some types of human cancer.[6]

Plakophilin 3 (*PKP3*) is a member of the p120^{ctn}/plakophilin subfamily of armadillo proteins that mediate the cytoplasmic associations with the cadherins. Unlike *PKP1* and *PKP2*, *PKP3* is ubiquitously expressed in all the layers of the stratified epithelia except hepatocytes.[7,8] In addition to desmosomal functions, *PKP3* also plays an important role in the regulation of protein synthesis, growth control, and transcription.[8–10] Dysregulation of *PKP3* is observed in various types of cancer including colon, lung, and bladder cancers, which is associated with the cancer progression.[11–15] Knockdown of *PKP3* leads to a decrease in desmosome size and cell-cell adhesion, and enhanced cancer cell metastasis and growth.[16] However, upregulation of *PKP3* is associated with the progression of breast and lung cancers.[9,14]*PKP3* seems to play a different role in different types of cancer. To date, there is little knowledge about the role of *PKP3* in ovarian cancer. Considering its critical role in the progression of aforementioned cancers, this study aimed to investigate *PKP3* expression in ovarian cancer as well as its clinical significance.

2. Materials and methods

2.1. Clinical tissue sample collection

This study was approved by the Ethics Committee of Taizhou people's Hospital. The methods and experimental protocols of the present study were carried out in accordance with the approved guidelines of Taizhou people's Hospital. Written informed consent was obtained from all patients. We used 157 formalin-fixed paraffin-embedded (FFPE) ovarian cancer tissues from 157 patients who underwent radical surgery between 2007 and 2010 at Taizhou people's Hospital. The histological cell-type was defined according to the criteria of the World Health Organization classification. All patients were pathologically confirmed with epithelial ovarian cancer. No patients had received any anticancer therapy such as neoadjuvant chemotherapy, radiation therapy and immunotherapy prior to surgery. Progression-free survival (PFS) was defined as the time from the surgery until relapse, progressive disease, or last follow-up. Overall survival (OS) was defined as the time from the surgery until death from any cause or the last follow-up.

2.2. Immunohistochemistry (IHC)

Core tissues with a 1.5 mm diameter were taken from individual paraffin embedded block and then embedded in the prepared hole in the acceptor block as described previously.[17] Subsequently, sections with 4 μm thickness were cut from the array blocks to make a tissue microarray (TMA). TMA was stained with haematoxylin and eosin (H&E) and validated by two pathologists. TMA sections was deparaffinized by sequential washings with xylene, 100% ethanol, 95% ethanol, 80% ethanol, and PBS. After antigen retrieval, endogenous peroxidase activity was blocked with 3% hydrogen peroxide. Nonspecific epitopes were blocked through incubating the sections with 10% goat serum in PBS at room temperature for 1 hour. TMA section was incubated with a primary monoclonal rabbit anti-*PKP3* antibody (dilution 1:100; Abcam, Cambridge, MA, USA) overnight at 4°C and then incubated with horseradish peroxidase-conjugated goat anti-rabbit secondary antibody at room temperature for 1 hour. Known positive ovarian cancer was used as a positive control, whereas negative control was obtained by replacing primary antibody with PBS. Immunostained section was evaluated by two independent pathologists, who were blinded to each other's scores as well as the clinical and pathological data.

2.3. Statistical analyses

Statistical analyses were performed using IBM SPSS software version 25.0 (SPSS Inc., IL) and GraphPad Prism 7 (GraphPad Software, CA). Two-sided P values $< .05$ were considered to be statistically significant for all statistical procedure. Continuous data were compared with the Mann-Whitney test. Fisher exact test was used to evaluated the association between clinicopathologic variables and *PKP3* protein expression. Survival curves were estimated with the Kaplan–Meier method and compared by log-rank test. Factors with a value of $P < .05$ in the univariate analysis were further analyzed using a multivariate Cox proportional hazard model.

3. Results

3.1. Clinicopathological characteristics of patients with ovarian cancer

The retrospective analysis included medical records of 157 patients with ovarian cancer who underwent radical surgery between 2007 and 2010. Clinicopathological characteristics of patients were described in Table 1. Briefly, the median age at the diagnosis was 52.0 years (range from 20.0–75.0 years). The histological type of 157 patients was epithelial ovarian cancer with 129 (82.2%) patients with serous and 28 (17.8%) with non-serous type. Forty-two (26.8%) patients had lymph node metastasis (LNM) and 33 (21.0%) had distant metastasis at the time of diagnosis. The majority of cases were poor differentiated (72.5%). The vast majority of patients (71.3%)

Table 1

Clinical characteristics of patients with ovarian cancer.

General characteristics	All (n = 157)
Age at primary diagnosis (years)	50.9 ± 11.6
Follow-up period (month)	Median: 64.0 (4.0–110.0)
Diameter of the tumor (cm)	Median: 12.5 (1.9–25.5)
Status	
Survival	72 (45.9)
Death	85 (54.1)
Histological type	
Serous	129 (82.2)
Others	28 (17.8)
Histologic grade	
1	15 (9.6)
2	15 (9.6)
3	127 (80.9)
Lymph node status	
Negative	115 (73.2)
Positive	42 (26.8)
Distant metastasis	
Negative	124 (79.0)
Positive	33 (21.0)
FIGO stage	
I	9 (5.7)
II	36 (22.9)
III	79 (50.3)
IV	33 (21.0)

FIGO = International Federation of Gynecology and Obstetrics.

were classified as International Federation of Gynecology and Obstetrics (FIGO) stage III and IV. The median PFS and OS survival time were 41.0 months (95%CI: 30.9–51.1) and 75.0 months (95%CI: 51.5–98.5), respectively.

3.2. Upregulation of PKP3 in ovarian cancer

IHC was used to evaluated the expression levels of *PKP3* in 157 ovarian cancer specimens. *PKP3* protein expression showed both nuclear and/or cytoplasmic staining in ovarian cancer. *PKP3*

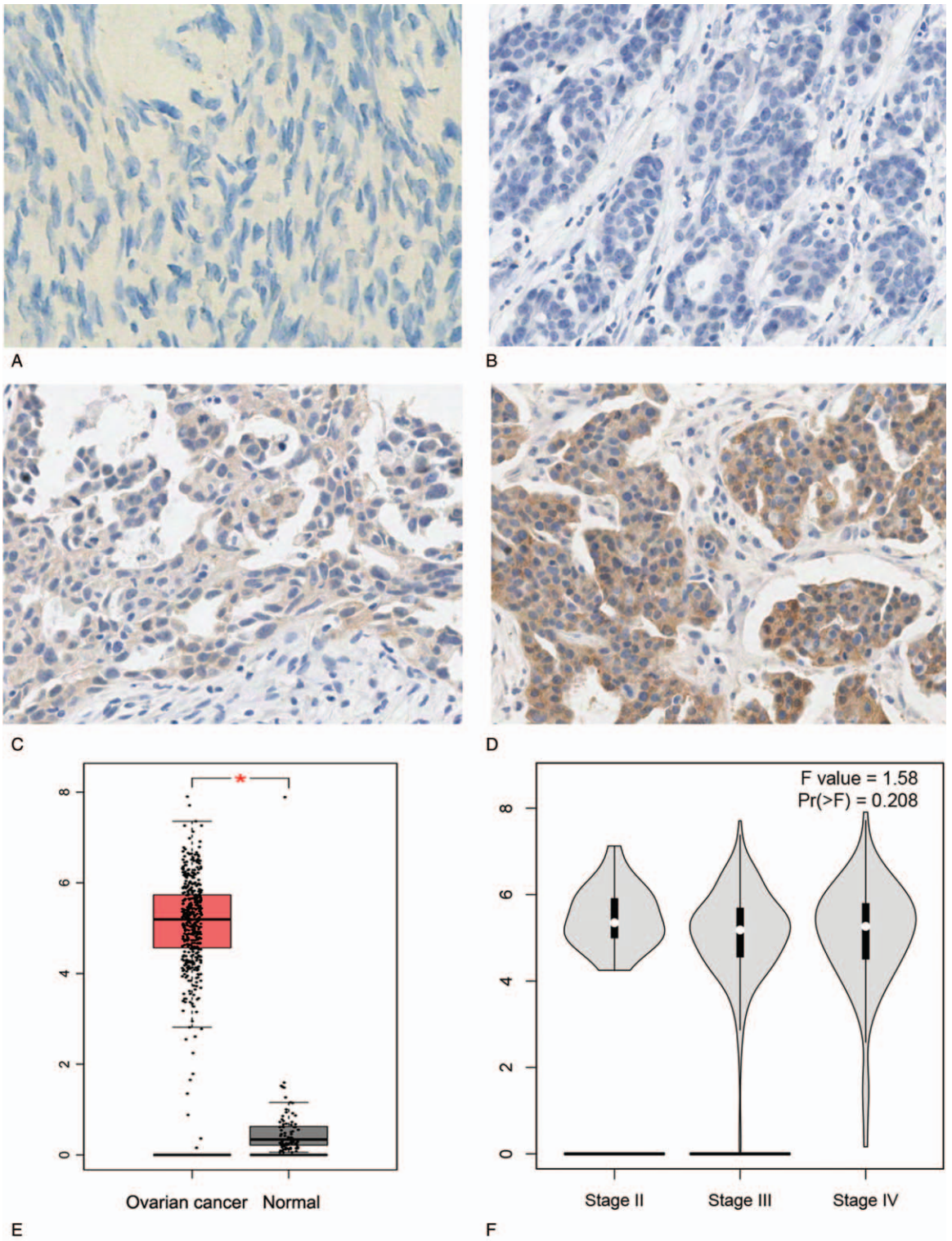

Figure 1. *PKP3* was upregulated in ovarian cancer. A, negative staining of *PKP3* in normal ovarian tissue. B, negative staining of *PKP3* in ovarian cancer tissue. C, weak cytoplasmic staining of *PKP3* in ovarian cancer tissue. D, strong cytoplasmic and weak nuclear staining of *PKP3* in ovarian cancer tissue. E, the GEPIA database revealed that *PKP3* expression was significantly upregulated in ovarian cancer tissues (n = 426) compared with normal ovarian tissues (n = 88). *$P < .05$. F, there was no significant difference in *PKP3* between different pathologic stage of ovarian cancer based on the GEPIA database. GEPIA = gene expression profiling interactive analysis, *PKP3* = plakophilin 3.

protein expression was negative in normal ovarian tissues, whereas ovarian cancer tissues displayed significantly increased expression of *PKP3* (Fig. 1). Positive cytoplasmic staining of *PKP3* was observed in 81 (51.6%) cases, among which 6 (7.4%) cases showed strong *PKP3* expression. In addition, 14 cases with cytoplasmic staining of *PKP3* also showed nuclear staining of *PKP3*. The expression levels of *PKP3* in ovarian cancer tissues were higher than those in normal ovarian tissues ($P < .001$). We further evaluated *PKP3* expression using the gene expression profiling interactive analysis (GEPIA) database.[18] The results revealed that the expression levels of *PKP3* in 426 ovarian cancer tissues were higher than those in 88 normal ovarian tissues (Fig. 1), which was consistent with the IHC results. There was no correlation between pathological stage and the *PKP3* expression level ($P > .05$).

3.3. Association between PKP3 expression and clinicopathological features of ovarian cancer

To explore the role of *PKP3* in the progression of ovarian cancer, we further analyzed the associations between *PKP3* expression and clinicopathological features of ovarian cancer. As shown in Table 2, high *PKP3* expression was associated with LNM ($P = .004$), and advanced FIGO stage ($P = .013$). No association between *PKP3* expression and age, tumor size, pathologic type, histologic grade and distant metastasis was observed ($P > .05$).

3.4. Survival analyses

We also evaluated the effect of *PKP3* on the survival of patients with ovarian cancer. The median OS time in patients with high *PKP3* expression was 60.2 months, which was significantly lower than that in patients with low *PKP3* expression (74.2 months, $P = .009$, Fig. 2). There was no significant association between *PKP3* expression and PFS ($P = .709$). The prognostic role of *PKP3* in ovarian cancer was then assessed using the GEPIA database. High *PKP3* expression was significantly associated with shorter OS ($P = .004$) but not PFS ($P = .69$), which were in an agreement with our results.

Furthermore, univariate analysis using Cox proportional hazard model showed that larger tumor size (hazard ratio [HR] = 3.459, 95%CI: 2.124–5.929, $P < .001$), LNM (HR = 5.541, 95%CI: 3.560–8.625, $P < .001$), distant metastasis (HR = 5.687, 95%CI: 3.563–9.078, $P < .001$), advanced FIGO stage (HR = 2.338, 95%CI: 1.672–3.270, $P < .001$), and high *PKP3* expression (HR = 2.128, 95%CI: 1.366–3.314, $P = .001$) were associated with poor OS (Table 3). In the multivariate analysis, larger tumor size (adjusted HR = 2.797, 95%CI: 1.624–4.815, $P < .001$), LNM (adjusted HR = 2.237, 95%CI: 1.175–4.257, $P = .014$), advanced FIGO stage (adjusted HR = 1.987, 95%CI: 1.409–2.802, $P < .001$), and high *PKP3* expression (adjusted HR = 1.601, 95%CI: 1.014–2.528, $P = .043$) were independent unfavorable prognostic factors for OS in patients with ovarian cancer. Further analysis revealed that this effect was existed in patients with FIGO stages III and IV disease (adjusted HR = 1.607, 95%CI: 1.006–2.567, $P = .047$) (Table 4).

3.5. Prediction of interaction networks of PKP3

To identify the genes that could interact with *PKP3*, we conducted an interaction network prediction using STRING v10.5,[19] which were further validated using GEPIA to increase the credibility of the conclusion.[18] The genes with the top 20 scores were listed in Table S1, http://links.lww.com/MD/C848. The protein-protein interaction (PPI) network of the top 20 genes was shown in Figure 3. Subsequently, these PPIs were further examined using GEPIA based on the result in the STRING protein query from public databases. The results revealed that PPIs predicted using STRING and GEPIA were consistent except for catenin beta 1 (CTNNB1), F-box protein 7 (FBXO7),

Table 2

Association of *PKP3* expression with clinicopathologic parameters.

Variables	*PKP3* expression		*P* value
	High	Low	
Age (years)			
< 55	50 (53.8)	43 (46.2)	.515
≥ 55	30 (47.6)	33 (52.4)	
Histological type			
Serous	71 (55.0)	58 (45.0)	.094
Non-serous	10 (35.7)	18 (64.3)	
Histologic grade			
1	7 (46.7)	8 (13.3)	.789
2 + 3	74 (52.1)	68 (47.9)	
Tumor size (cm)			
< 10	29 (46.0)	34 (46.0)	.260
≥ 10	52 (55.3)	42 (44.7)	
LNM			
non-LNM	51 (44.3)	64 (55.7)	.004
LNM	30 (71.4)	12 (28.6)	
Distant metastasis			
Negative	61 (49.2)	63 (50.8)	.327
Positive	20 (60.6)	13 (39.4)	
FIGO stage			
I + II	16 (35.6)	29 (64.4)	.013
III + IV	65 (58.0)	47 (42.0)	

FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, *PKP3* = plakophilin 3.

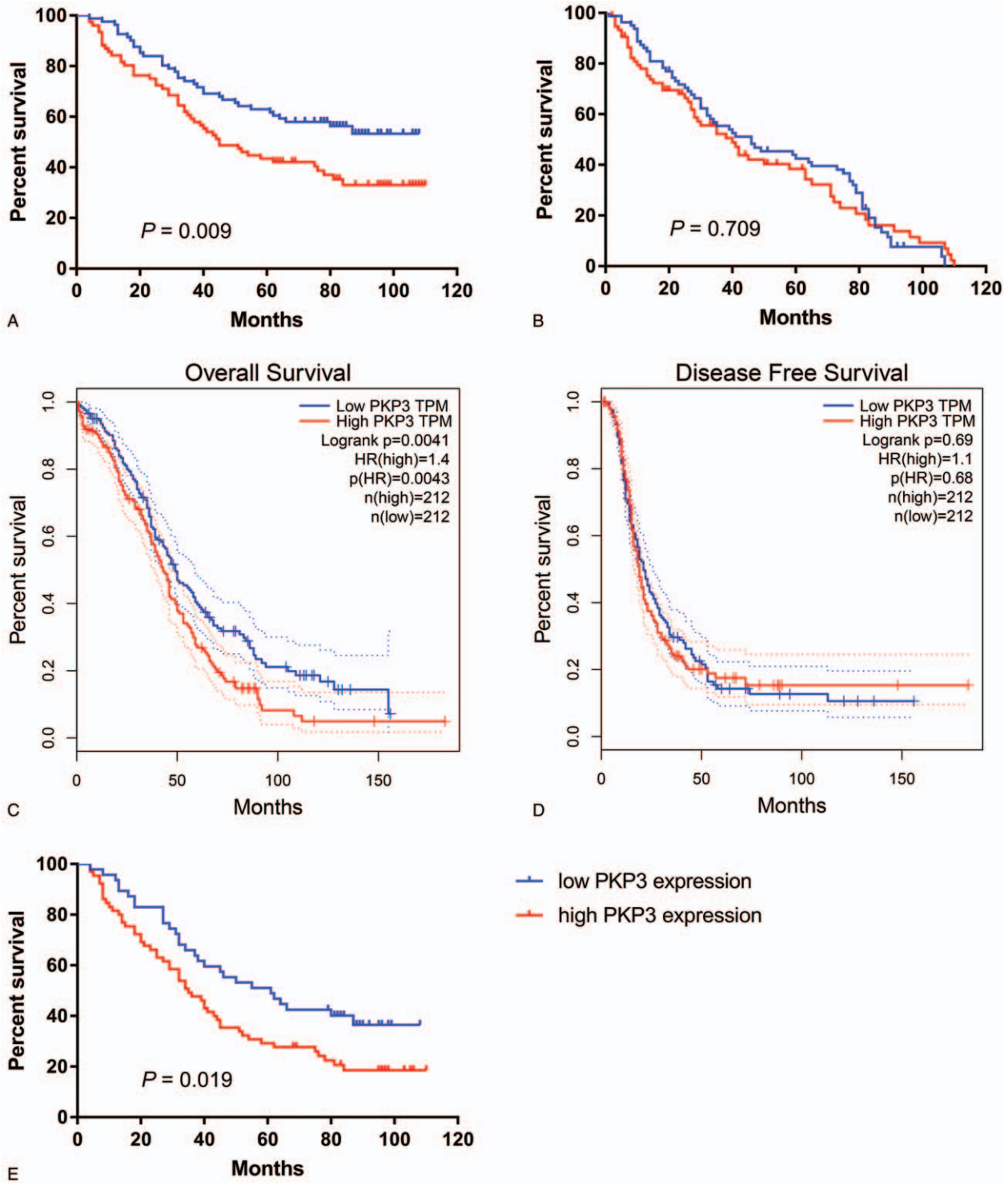

Figure 2. Kaplan-Meier curves for OS and PFS. A, OS curves stratified by *PKP3* expression in 157 patients with ovarian cancer. B, PFS curves stratified by *PKP3* expression in 157 patients with ovarian cancer. C, OS curves stratified by *PKP3* expression based on the GEPIA database. D, PFS curves stratified by *PKP3* expression based on the GEPIA database. E, OS curves stratified by *PKP3* expression in patients with FIGO stages III and IV. FIGO = International Federation of Gynecology and Obstetrics, GEPIA = gene expression profiling interactive analysis, OR = odds ratio, OS = overall survival, PFS = progression-free survival, *PKP3* = plakophilin 3.

cadherin 3 (CDH3), cadherin 17 (CDH17), and dachsous cadherin-related 2 (DCHS2). Thirteen genes were positively correlated with *PKP3*, whereas FAT atypical cadherin 4 (FAT4) and Zinc finger E-box binding homeobox 1 (ZEB1) were negative correlated with *PKP3*.

4. Discussion

Recurrence and metastasis are critical causes of cancer-related death. It is important to understand the underlying molecular and cellular processes involved in the regulation of ovarian cancer metastasis. Cell-cell adhesion and interactions mediated by

Table 3

Univariate and multivariate Cox regression analysis of overall survival in 157 ovarian cancer cases.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years), < 55 *vs* ≥ 55	1.459 (0.950–2.241)	.085		
Histological type, serous vs non-serous	0.532 (0.275–1.030)	.061		
Histologic grade, 2 + 3 vs 1	1.253 (0.827–1.899)	.287		
Tumor size (cm), v ≥ 10 vs < 10	3.549 (2.124–5.929)	< .001	2.797 (1.624–4.815)	< .001
LNM, positive vs negative	5.541 (3.560–8.625)	< .001	2.237 (1.175–4.257)	.014
Distant metastasis, positive *vs* negative	5.687 (3.563–9.078)	< .001	1.494 (0.755–2.956)	.248
FIGO stage, III + IV vs I + II	2.338 (1.672–3.270)	< .001	1.987 (1.409–2.802)	< .001
PKP3 expression, positive vs negative	2.128 (1.366–3.314)	.001	1.601 (1.014–2.528)	.043

FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, *PKP3* = plakophilin 3.

adhesive junction components are essential for the maintenance of the structural integrity of tissues. Disruption of adhesive junctional complexes plays a causal role in the promotion of invasion and metastasis. Loss of cell adhesion contacts confer a highly motile and invasive phenotype on cancer cells and thus enables them to dissociate from the primary mass. As a result, cancer cells eventually invade and spread to adjacent or distal organs.

PKPs that are characteristic plaque proteins of desmosomes assist in assembling and stabilizing cadherins at the plasma membrane and bridge them to the intermediate filament cytoskeleton.[20–23] Dual nuclear and cytoplasmic localization of PKPs suggests that they have diverse nondesmosomal functions such as regulation of transcription and translation, growth control, and the trafficking of desmosomal cadherins,[8–10,24] but not fully understood. Loss or reduction of *PKP1* and *PKP3* is frequently observed in various types of human cancer including colon, prostate, and gastric cancers, associated with their malignant behavior,[11,16,24–26] whereas *PKP2* seems likely to have a potentially oncogenic role in human cancer.[27,28] In addition, *PKP3* also exhibits oncogenic potential in breast and lung cancers.[9,14] Therefore, *PKP3* might have tumor-suppressor and oncogenic potentials in different types of cancer depending on the cellular context. In the present study, *PKP3* was expressed in 51.6% of ovarian cancer tissues but was not expressed in normal ovarian tissues. High *PKP3* expression was associated with LNM and advanced FIGO stage. Survival analysis revealed that high *PKP3* expression was associated with a higher probability of mortality. This result indicates the prognostic potential of *PKP3* in ovarian cancer. To further confirm these results, we assessed *PKP3* expression in the GEPIA database. We found that the expression levels of *PKP3* in ovarian cancer tissues were dramatically higher than those in normal ovarian tissues, and high *PKP3* expression was associated with poor prognosis, which was consistent with our findings. These results imply that *PKP3* might serve as a novel potential biomarker for ovarian cancer and is involved in the progression of ovarian cancer. This study, to the best of our knowledge, was the first to evaluate the clinical significance of *PKP3* in ovarian cancer. Combined with IHC assay and GEPIA data, we confirmed that *PKP3* was upregulated in ovarian cancer tissues, and high *PKP3* expression may play an important role in ovarian cancer.

Table 4

***PKP3* expression and OS of patients with ovarian cancer by clinicopathologic parameters.**

Variables	HR (95% CI)*	*P* value
Age (years)		
< 55	1.479 (0.800–2.735)	.212
≥ 55	1.677 (0.810–3.471)	.164
Histological type		
Serous	1.569 (0.959–2.568)	.073
Non-serous	1.322 (0.311–5.622)	.706
Histologic grade		
1	1.530 (0.307–7.628)	.604
2 + 3	1.555 (0.964–2.508)	.071
Tumor size (cm)		
< 10	1.736 (0.719–4.196)	.220
≥ 10	1.471 (0.868–2.493)	.151
LNM		
Non-LNM	1.560 (0.854–2.850)	.148
LNM	1.706 (0.806–3.610)	.163
FIGO stage		
I + II	1.492 (0.210–10.611)	.690
III + IV	1.429 (0.919–2.224)	.113

FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, OS = overall survival, *PKP3* = plakophilin 3.

* Adjusted for age, tumor size, grade, pathologic type, LNM, and FIGO stage, as appropriate.

To identify the genes that might have an interaction with *PKP3*, we conducted PPI analysis using the STRING database and further validated using the GEPIA database. The top 20 genes interacting with *PKP3* were enriched in cell-cell junction pathways. Only 15 interaction nodes further reach statistical significance in the GEPIA database. Among these genes, FAT4 and ZEB1 exhibited the negative correlations with *PKP3*. ZEB1 can bind directly to the *PKP3* promoter and represses its transcription.[13] Therefore, downregulation of ZEB1 in ovarian cancer leads to the upregulation of *PKP3*.[13,29] In addition, 14 (8.9%) cases showed nuclear staining of *PKP3*, which indicated that nuclear *PKP3* might participate in transcription regulation through interacting with transcription factor. Further studies are necessary in order to elucidate the role of nuclear *PKP3* in ovarian cancer.

In conclusion, our findings provided the first evidence that *PKP3* is upregulated n ovarian cancer and may serve as a novel prognostic biomarker for ovarian cancer. However, the underlying molecular mechanism by which *PKP3* contributed to malignant behavior of ovarian cancer requires further research.

Author contributions

Conception and design: HQ and HY; provision of study materials or patients: HQ, DY, HS, and HY; collection and assembly of data: DY, JB, FL, WZ, and XY; data analysis and interpretation: GH, JH, and HS; manuscript writing: HQ, DY, and HY; final approval of manuscript: all authors.

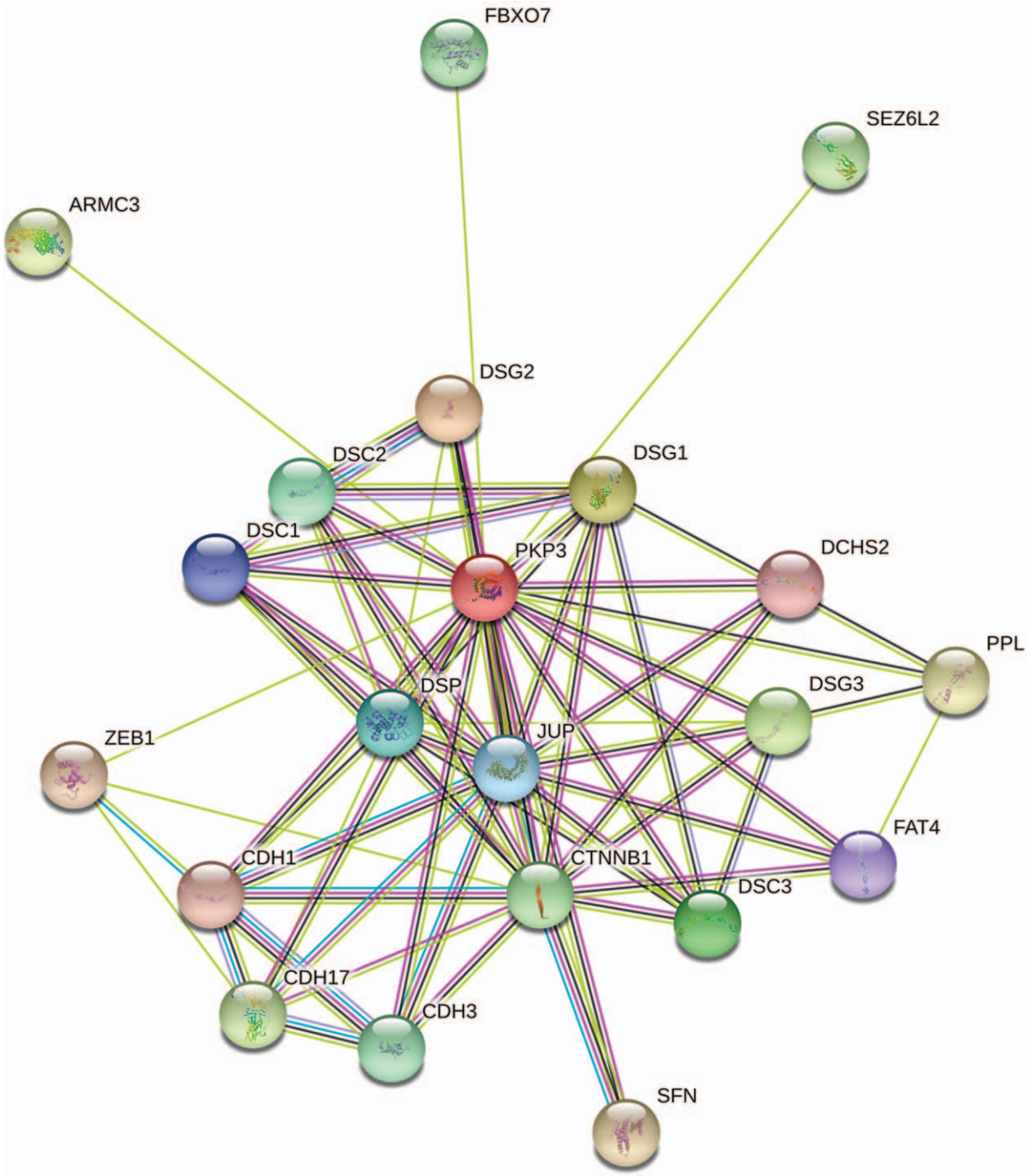

Figure 3. PPI network analysis of *PKP3* with other genes. Top 20 candidate genes might have an interaction with *PKP3*. *PKP3* = plakophilin 3.

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Writing – original draft: Hua Qian, Donglan Yuan, Hong Yu.
Writing – review & editing: Hua Qian, Hong Yu.

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