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DATABASE ANALYSIS

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Correlation Between High Expression of *FOXA2* and Improved Overall Survival in Ovarian Cancer Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

FG 1 **Hui Shang**
BC 2 **Lingyun Shi**
CF 3 **Xuena Jiang**
CD 4 **Peng Zhou**
AB 1 **Yongqing Wei**

1 Department of Obstetrics, Jinan Central Hospital Affiliated with Shandong First Medical University, Jinan, Shandong, P.R. China
2 Department of Obstetrics and Gynecology, The West District of Qingdao Municipal Hospital (Group), Qingdao, Shandong, P.R. China
3 Department of Obstetrics and Gynecology, Qingdao Longtian Jinqiu Women's and Children's Hospital, Qingdao, Shandong, P.R. China
4 Department of Radiology, Jinan Central Hospital Affiliated with Shandong First Medical University, Jinan, Shandong, P.R. China

Corresponding Author: Yongqing Wei, e-mail: weiyongqing52188@163.com
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Background: The aim of the present work was to evaluate *FOXA2* expression in ovarian cancer and to use integrated bioinformatics analysis to correlate it with patient prognosis.

Material/Methods: *FOXA2* expression was evaluated in multiple cancers in The Cancer Genome Atlas database. A protein–protein interaction (PPI) network relevant to *FOXA2* was constructed using the Search Tool for Retrieval of Interacting Genes/Proteins (STRIN). Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed of *FOXA2* and relevant genes. Correlations between overall survival (OS), disease-free survival, and *FOXA2* expression were evaluated. An immunohistochemical assay (IHC) was used to test for *FOXA2* protein expression in 79 ovarian cancer specimens.

Results: *FOXA2* mRNA was upregulated in colorectal, stomach, liver, and endometrial cancers. In the PPI network, 21 protein nodes and 533 edges were constructed with a local clustering coefficient of 0.698, which indicated significant PPI enrichment ($P<0.01$). *FOXA2* and relevant genes were mainly enriched in the signaling pathways regulating pluripotency of stem cells, cancer, and AMPK. A survival analysis indicated that OS was significantly longer in patients with higher versus lower *FOXA2* protein expression (HR=0.73, $P<0.01$). The IHC assay showed that the *FOXA2* protein was mainly positively expressed in the nucleoplasm of tumor cells with brown-yellow staining. Of the 79 ovarian cancer samples, 31 (39.2%) highly expressed *FOXA2*. The *FOXA2* gene was correlated with International Federation of Gynecology and Obstetrics staging and with lymph node metastasis (both $P<0.05$).

Conclusions: Upregulation of the *FOXA2* gene was correlated with improved OS in patients with ovarian cancer and it can be used as a prognostic biomarker and potential treatment target.

MeSH Keywords: **Diagnosis • Ovarian Neoplasms • Prognosis**

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Background

Ovarian cancer is a commonly diagnosed carcinoma of the female reproductive system. Estimates indicate that in 2019, 1390 patients with ovarian cancer in the United States died of the disease [1]. Ovarian cancer is the most common cause of cancer-related deaths in women, ranking fourth in cancer-associated mortality among women in developed countries. Cancer epidemiology data from China show that the mortality rate in patients with ovarian cancer increased by 21.6% and 1.7% from 2000 to 2003 and 2003 to 2011, respectively, ranking the disease first among carcinomas in terms of deadliness [2]. The development of ovarian cancer is occult and about 75% of cases are diagnosed when the disease is advanced (International Federation of Gynecology and Obstetrics [FIGO] stages III and IV), resulting in a poor prognosis for these patients and an extremely low 5-year survival rate [3]. Therefore, it is of great importance to identify effective biological markers that can facilitate early diagnosis of ovarian cancer and improve patient prognosis [4].

FOX proteins are characterized by a conserved DNA domain that is 110 amino acids long and similar in structure and appearance to the forkhead box [5]. Both fungi and animals have been found to contain a large number of FOX family proteins, which play an important role in embryo development, cell differentiation, energy metabolism, and immune regulation [6]. The FOX family consists of 19 subfamilies, named after FOXA and FOXS, and consists of more than 100 members [7]. The most widely used and studied of them is the FOXA subfamily, which is composed of 3 members: *FOXA1*, *FOXA2*, and *FOXA3*. *FOXA1* is located on human chromosome 14, with a total length of 5300 bp and consists of 2 exons and 1 intron. Its structure is composed of an N-terminal transcriptional activation region, middle DNA binding region, and C-terminal histone binding region. The N-terminal, which is the core region, is mainly composed of 3 α helices and 3 reverse parallel β folds [8,9]. The C-terminal histone binding region can break the compressed chromosome by binding with histone H3/H4, so as to increase the chance of transcription factor binding with it and initiate transcription and translation, regulating the transcription and expression of downstream genes.

FOXA2 is a member of the FOX family and can be dysregulated in multiple cancers, such as those of the colorectum [10], lung [11], and breast [12]. However, the level of expression of the gene in ovarian cancer has rarely been reported in the literature and its biological function is elusive.

Material and Methods

FOXA2 expression analysis

FOXA2 expression was investigated using the database from The Cancer Genome Atlas (TCGA) (*https://portal.gdc.cancer.gov/*). We searched the database by using the words "ovarian cancer" and "*FOXA2*." The relative level of *FOXA2* gene mRNA in multiple carcinomas was identified. The rate of positive expression of the *FOXA2* protein also was evaluated in different cancers.

Protein–protein interaction network construction

A protein–protein interaction (PPI) network related to *FOXA2* was constructed using the Search Tool for Retrieval of Interacting Genes/Proteins (STRIN) database (*http://string-db.org/cgi/input.pl*) [13]. The conditions for the PPI network were: (1) confidence >0.7; and (2) source of interaction limited to co-expression, gene function, and neighborhood relationship.

FOXA2 protein expression and clinical features of ovarian cancer

Seventy-nine patients with ovarian cancer who underwent surgery in our hospital were included in the present study. Written informed consent was obtained from all of the individuals and the research was approved by the Ethics Committee of our hospital. Tumor tissue and corresponding normal ovarian tissue were collected intraoperatively, immediately quick frozen in liquid nitrogen, and then transferred to and stored in a freezer at –80°C until the next use. The mean age of the 79 patients was 52.6±11.3 years. The FIGO stage of ovarian cancer was I/II in 32 cases and II/IV in 47 cases. The pathologic type was mucinous, serous, and endometrioid carcinoma in 52, 21, and 6 cases, respectively.

FOXA2 protein expression was tested with an immunohistochemical assay (IHC) according to the manufacturer's instructions. The correlation between *FOXA2* protein expression and patient clinicopathological features was assessed. Tumor and normal ovarian tissues were fixed with 10% formaldehyde solution and then embedded in paraffin. The specimens were cut into 4-μm slices. Anti-human *FOXA2* antibody was added and the slices were incubated overnight at 4°C. Then they were incubated in a second antibody at room temperature for 30 minutes. A phosphate buffer was used instead of the second antibody as the negative control. After the slices were washed with phosphate- buffered solution, they were stained with DAB solution and examined under a microscope (magnification ×400).

FOXA2 was mainly localized in the nucleoplasm of tumor cells with brown-yellow staining. Five visual fields were randomly

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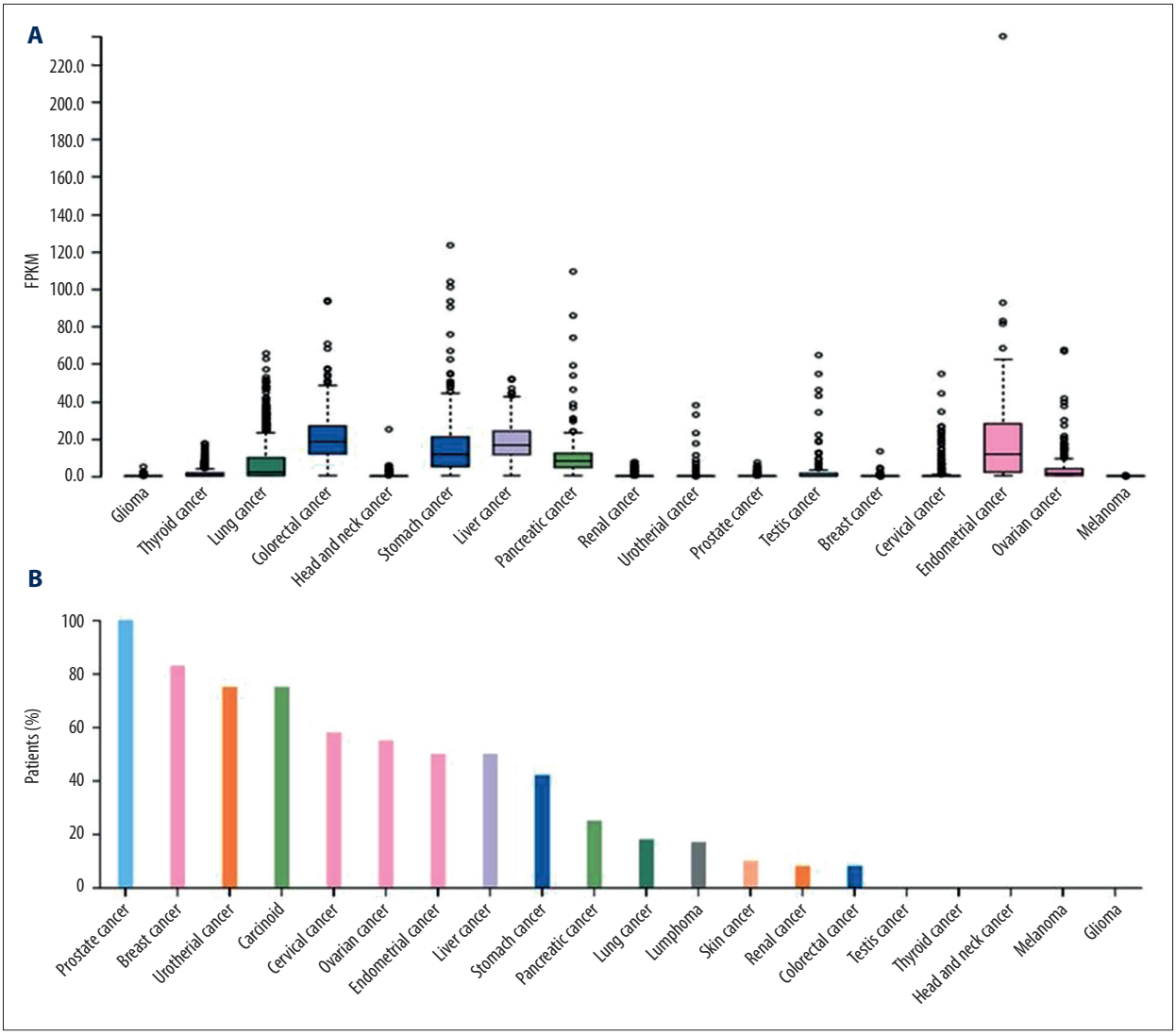

Figure 1. Bar and box plot of *FOXA2* mRNA expression in tissue from multiple types of cancer. (**A**) Box plot expression in multiple cancer tissues. (**B**) Bar plot of *FOXA2* protein positive expression rates in multiple cancers.

selected for counting of the cells and the percentage of cells that were positive was calculated. Expression was considered negative if <5% of cell stained positive; weak positive if 5% to 30% of cells stained positive; positive if 31% to 70% of cells stained positive; and strong positive if >70% of cells stained positive. The positive and strong positive categories were considered high expression of the *FOXA2* protein.

Survival analysis

Patients in the TCGA databases with ovarian cancer were divided into 2 groups, based on the relative level of expression of *FOXA2* mRNA in their tumors: high (>median expression level) and low (≤median expression level). A log-rank test was used to compare overall survival (OS) and disease-free survival (DFS) in the 2 groups.

Statistical analysis

STATA statistical software, version 11.0, was used for data evaluation. Data were expressed as numbers (n) and percentages (%) and compared with a chi-square or Fisher's exact test. Survival data were expressed as medians and compared using a log-rank test. The correlation between *FOXA2* expression and the clinical features of ovarian cancer in the patients was analyzed with a chi-square or Fisher exact test. Logistic regression was performed to analyze independent factors. A 2-tailed $P<0.05$ was considered statistically significant.

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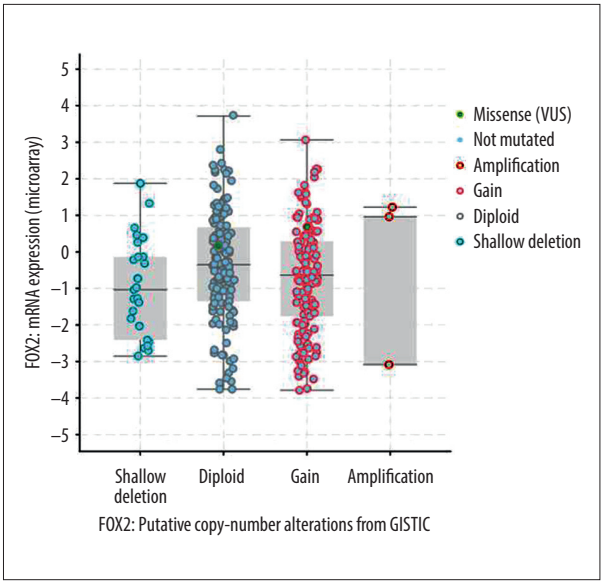

Figure 2. Scatter plot of *FOXA2* mRNA expression in different types of mutations.

Results

FOXA2 mRNA expression

FOXA2 mRNA expression was quite different among the cancers (**Figure 1A**). *FOXA2* mRNA was upregulated in colorectal, stomach, liver, and endometrial cancers. The highest rate of *FOXA2* protein expression was in prostate, breast, and urothelial cancers (**Figure 1B**). No statistically significant differences were seen in *FOXA2* mRNA expression in patients whose ovarian cancer had different types of mutations (**Figure 2**).

PPI network analysis

A PPI network for *FOXA2* and proteins related to it was constructed using the Search Tool for Retrieval of Interacting Genes/Proteins (STRIN) database. Twenty-one protein nodes and 533 edges were identified that had a local clustering coefficient of 0.698, which indicated significant PPI enrichment ($P<0.01$) (**Figure 3**).

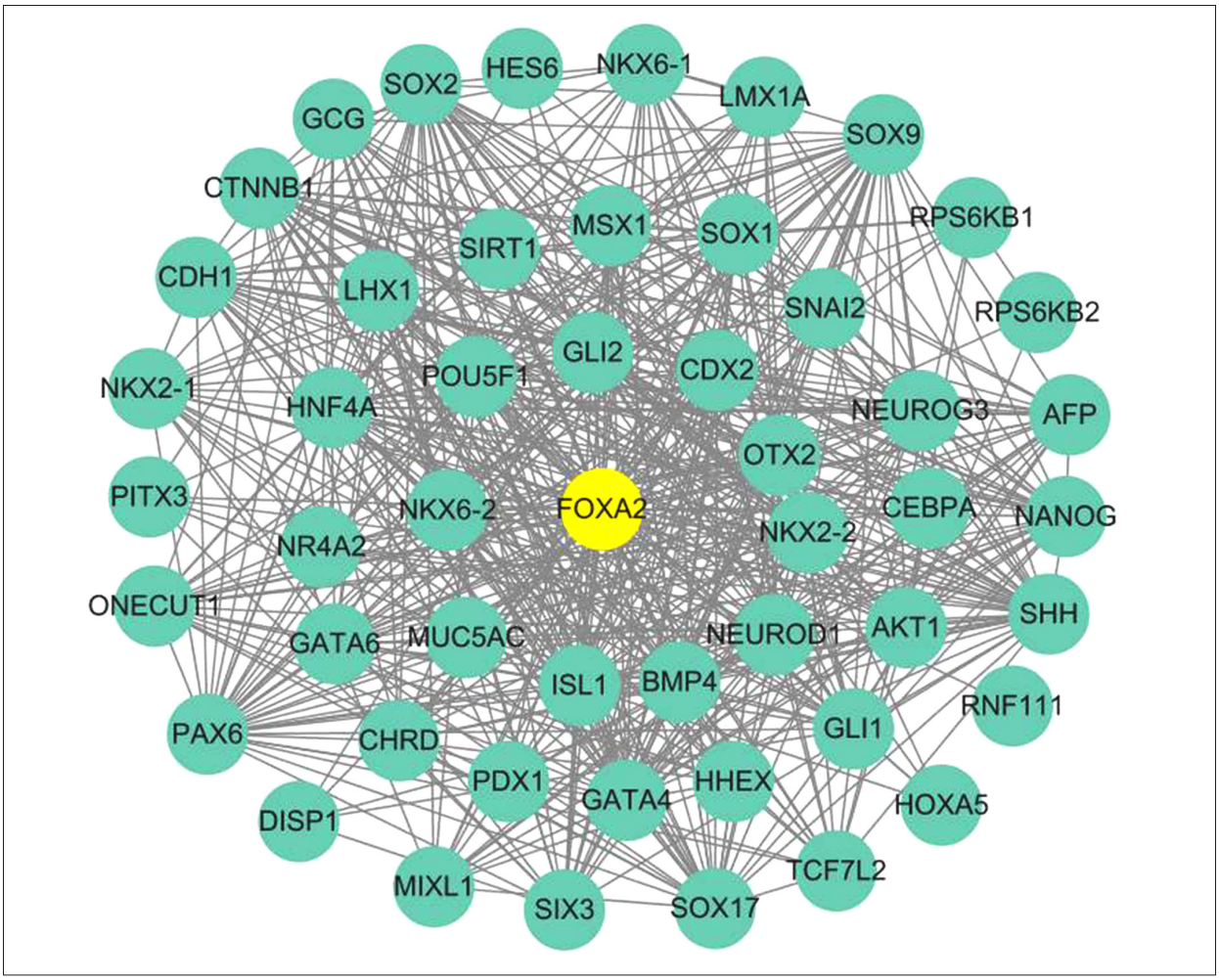

Figure 3. Protein–protein interaction network (PPI) for *FOXA2* and correlated proteins.

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Table 1. Gene Ontology (GO) enrichment of FOXA2 and relevant genes.

Description	Count	Q value	Gene ratio
Biological process			
Endocrine system development	24	1.75E-35	0.2
Positive regulation of transcription, DNA-templated	42	1.75E-35	0.029268293
Positive regulation of macromolecule biosynthetic process	44	1.75E-35	0.025028441
Positive regulation of transcription by RNA polymerase II	39	2.23E-35	0.035326087
Positive regulation of gene expression	44	2.64E-35	0.024096386
Positive regulation of cellular biosynthetic process	44	3.02E-35	0.02383532
Positive regulation of RNA metabolic process	42	1.32E-34	0.026315789
Regulation of transcription by RNA polymerase II	45	1.64E-30	0.017090771
Regionalization	25	1.22E-28	0.079872204
Pancreas development	18	6.81E-28	0.25
Cellular component			
Nucleus	43	1.41E-10	0.006239
Intracellular membrane-bounded organelle	49	8.56E-10	0.004727
Transcription factor complex	12	2.99E-09	0.03681
Nucleoplasm	29	1.72E-08	0.008416
Intracellular organelle lumen	35	1.72E-08	0.00678
Nuclear lumen	30	6.12E-08	0.007444
Nuclear transcription factor complex	7	4.32E-06	0.042169
RNA polymerase II transcription factor complex	5	0.00041	0.035971
beta-catenin-TCF7L2 complex	2	0.00071	0.666667
Nuclear chromatin	6	0.0023	0.018018
Molecular function			
Transcription regulatory region sequence-specific DNA binding	34	4.06E-34	0.047887
Sequence-specific DNA binding	37	7.06E-34	0.035339
Transcription regulatory region DNA binding	35	7.06E-34	0.04222
RNA polymerase II regulatory region sequence-specific DNA binding	31	3.21E-31	0.047913
DNA-binding transcription factor activity	39	2.38E-29	0.022298
DNA-binding transcription factor activity, RNA polymerase II-specific	38	5.07E-29	0.023299
DNA-binding transcription activator activity, RNA polymerase II-specific	24	2.17E-25	0.058824
Proximal promoter sequence-specific DNA binding	24	5.92E-24	0.050526
RNA polymerase II proximal promoter sequence-specific DNA binding	23	7.84E-23	0.050328
DNA binding	38	8.70E-23	0.015466

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Table 2. KEGG enrichment of FOXA2 and relevant genes.

Description	Count	Q value	Gene ratio
Signaling pathways regulating pluripotency of stem cells	9	7.32E-09	0.065217391
Hippo signaling pathway	8	2.18E-07	0.052631579
Gastric cancer	8	2.18E-07	0.054421769
Basal cell carcinoma	6	5.21E-07	0.095238095
Pathways in cancer	11	1.51E-06	0.021359223
Longevity regulating pathway – multiple species	5	1.19E-05	0.081967213
Acute myeloid leukemia	5	1.50E-05	0.075757576
Colorectal cancer	5	4.34E-05	0.058823529
Proteoglycans in cancer	6	0.00014	0.030769231
AMPK signaling pathway	5	0.00018	0.041666667
Endometrial cancer	4	0.00018	0.068965517
Adherens junction	4	0.00036	0.056338028
Breast cancer	5	0.00036	0.034013605
TGF-beta signaling pathway	4	0.00053	0.048192771

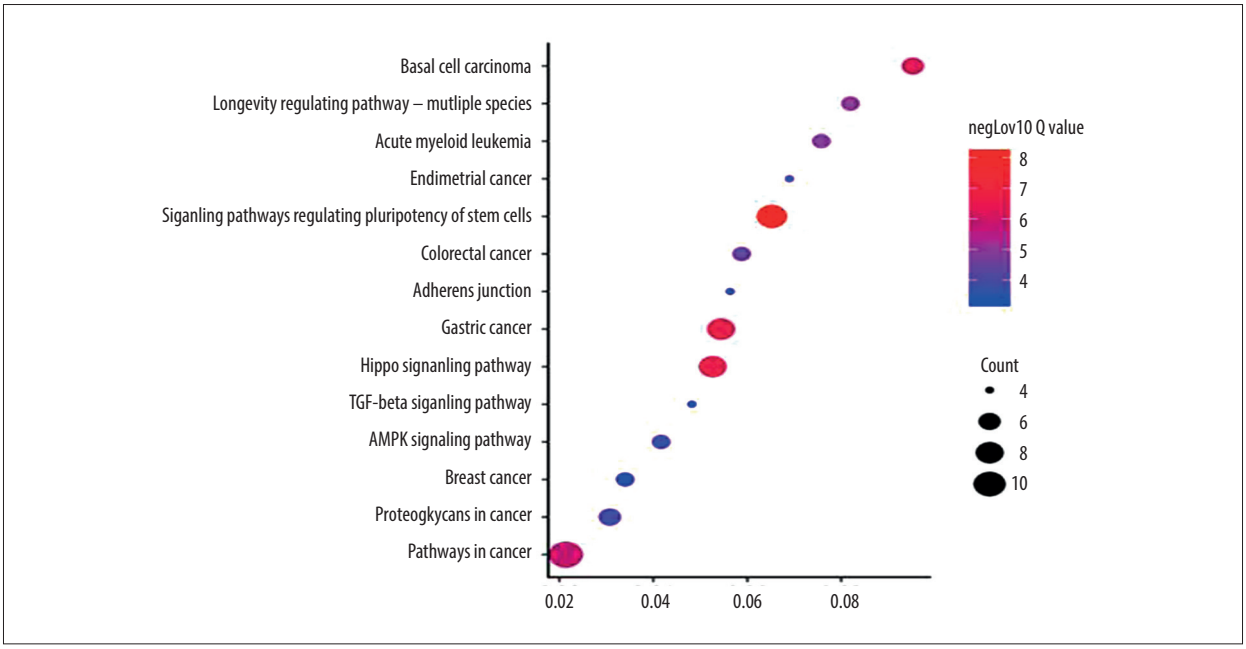

Figure 4. Bubble plot of Kyoto Encyclopedia of Genes and Genomes enrichment of *FOXA2* and relevant genes.

Gene ontology enrichment

In terms of biological processes, *FOXA2* and genes related to it were mainly found to be enriched in development of the endocrine system, positive regulation of cellular biosynthetic processes, and development of the pancreas. Enrichment in cellular components occurred largely in the nucleus, intracellular membrane-bounded organelle, and transcription factor complex. Regarding molecular function, *FOXA2* and genes related to it were concentrated in transcription regulatory-region sequence-specific DNA binding, proximal promoter sequence-specific DNA binding, and RNA polymerase II regulatory-region sequence-specific DNA binding (**Table 1**).

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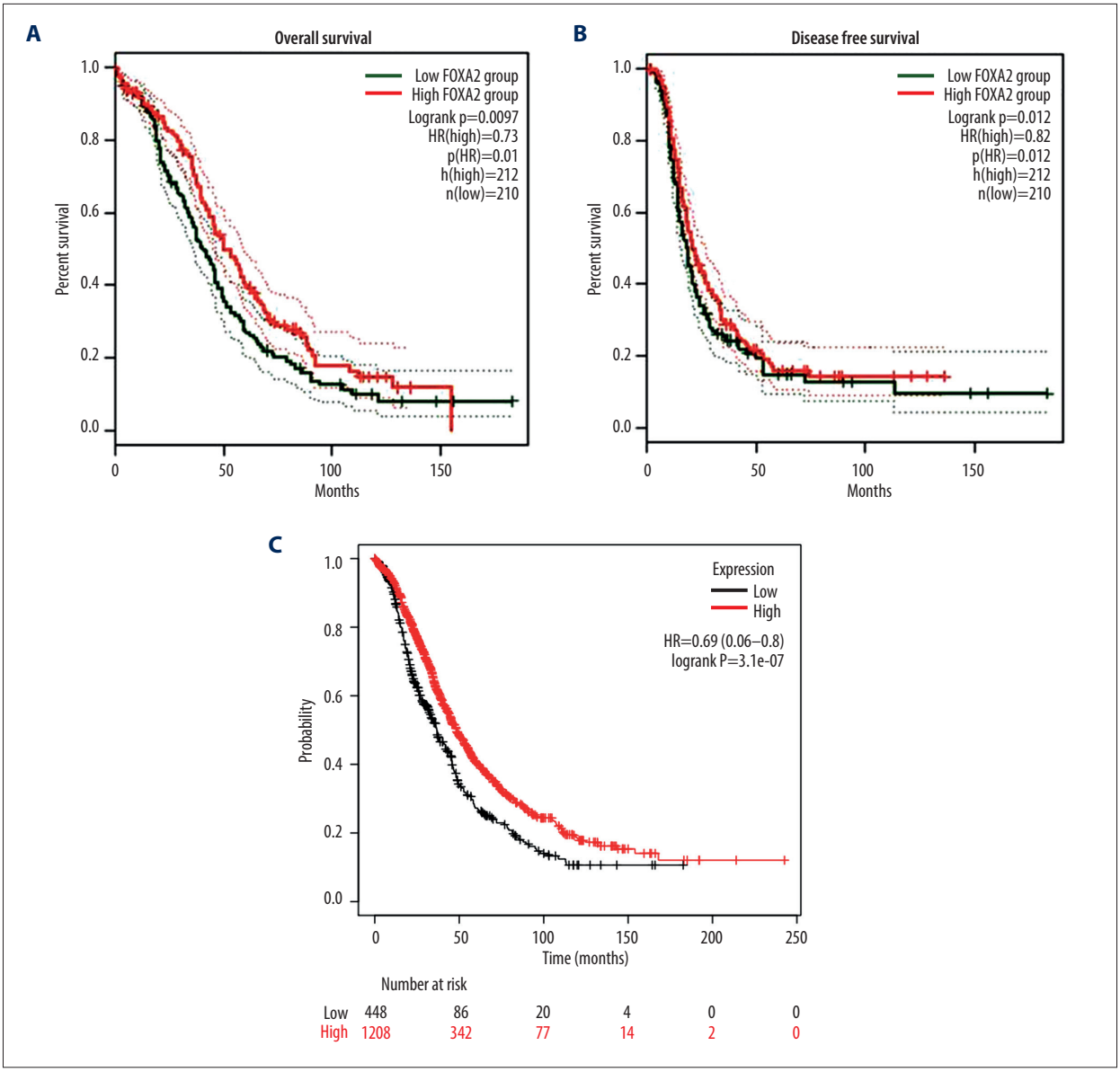

Figure 5. Overall survival (OS) and disease-free survival curve for patients with ovarian cancer who had high and low expression of *FOXA2*. (**A**) Overall survival. (**B**) Disease-free survival. (**C**) OS curve created using data in the Kaplan-Meier plotter database from patients with ovarian cancer who had high and low expression of *FOXA2*.

Kyoto Encyclopedia of Genes and Genomes pathway enrichment

FOXA2 and genes related to it were mainly enriched in the signaling pathways regulating pluripotency of stem cells, pathways in cancer, and the AMP-activated protein kinase (AMPK) signaling pathway (**Table 2, Figure 4**).

Survival analysis

Log-rank analysis indicated that OS was significantly longer in patients with high *FOXA2* expression than in those with low expression (HR=0.73, $P<0.01$). However, DFS (HR=0.82, $P>0.05$) was not statistically different between the groups with high and low expression of *FOXA2* (**Figure 5**). In the Kaplan-Meier plotter database, we also found that OS in patients with high *FOXA2* expression was significantly longer than in those with low expression (HR=0.69, $P<0.01$) (**Figure 5**).

FOXA2 protein expression detected by IHC assay

An IHC assay showed that the *FOXA2* protein was mainly positively expressed in the nucleoplasm of tumor cells that stained brown-yellow (**Figure 6**). Of the 79 ovarian cancer samples

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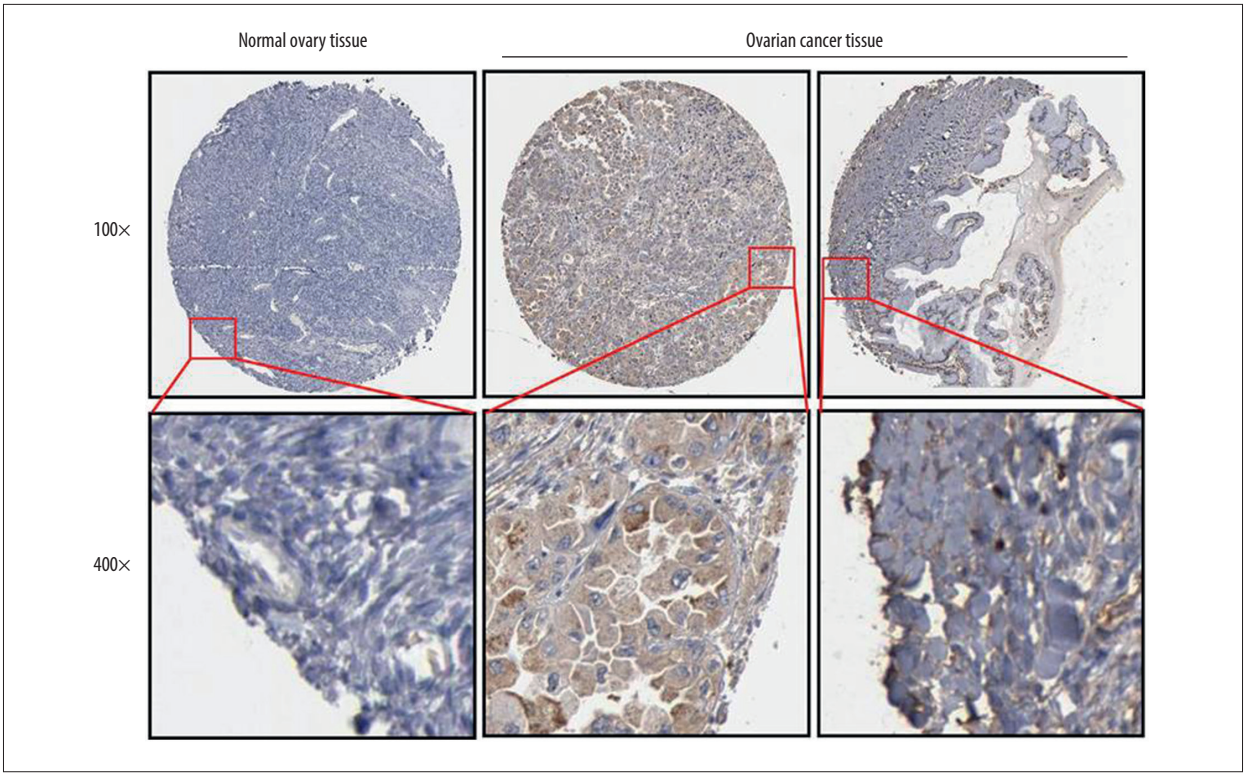

Figure 6. *FOXA2* protein expression detected with an immunohistochemistry assay in normal and cancerous ovarian tissue.

that were included, 31 (39.2%) showed increased expression of the *FOXA2* protein. The *FOXA2* protein was correlated with FIGO stage and lymph node metastasis (both $P<0.05$) (**Table 3**). Multivariate logistic regression of *FOXA2* protein expression and clinical features of ovarian cancer indicated that increased expression of the protein was an independent factor for lymph node metastasis in patients with ovarian cancer (OR=0.36, $P<0.05$) (**Figure 7**).

Discussion

The *FOXA2* gene is located on human chromosome 20. It has a total length of 45 kb and consists of 3 exons and 2 introns. The gene's structure is composed of 2 transcriptional activation regions, conservative cross head frame, inhibition, and phosphorylation regions [14]. *FOXA2* has been confirmed to play an important role in regulating embryo development [15]. *FOXA2* gene expression can be detected in many organs and tissues, such as the breast, liver and pancreas, and adipose tissue [16]. It has been reported that *FOXA2* plays an important role in energy metabolism and tumor development [17]. Abnormal expression of *FOXA2* in tumor tissue has been found to be closely related to the development of various tumors, such as those of the lung [18], gastrointestinal tract [19], and liver [20]. Downregulation of *FOXA2* expression in gastric cancer is related to lymph node metastasis, tumor stage, and 3-year mortality. A previous publication has shown that *FOXA2* downregulation is closely related to vascular invasion, the number of tumors, and the stage of liver cancer [20]. Ren et al. [21] found that relative expression of *FOXA2* mRNA in ovarian cancer tissues was significantly lower than that in benign and normal tissues, and the rate of positive expression of the *FOXA2* protein in normal tissues was 82.14%, while that in ovarian cancer tissues was 23.21%. Clearly, expression of the *FOXA2* protein was lacking in ovarian cancer tissues. In ovarian cancer, a significant correlation has been found between *FOXA2* expression and tumor differentiation and FIGO stage, suggesting that the gene may be closely related to development of the disease. Further analysis showed that the 5-year mortality rate in patients with ovarian cancer who did not express *FOXA2* was much higher than that in individuals with positive expression of *FOXA2*. Multivariate analysis showed that negative expression of *FOXA2* was an independent risk factor for poor prognosis in patients with ovarian cancer.

In the present study, we found that *FOXA2* mRNA expression was quite varied among different cancers. In ovarian cancer, no statistically significant differences were found in *FOXA2* mRNA expression depending on mutation type. This indicates that *FOXA2* may participate in ovarian cancer development. A survival analysis indicated that OS was significantly longer in patients with high *FOXA2* expression than in those with low expression (HR=0.73, $P<0.01$), which was in accordance with previous relevant publications [21].

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Table 3. Correlation between FOXA2 protein expression and ovarian cancer patients clinical features.

Features	n=79	*FOXA2*		Chi-square	*P*
		High (n=31)	Low (n=48)		
Age (year)				1.12	0.29
≤60	49	24	25		
>60	30	7	13		
FIGO				4.35	0.04
I/II	32	17	15		
III/IV	47	14	33		
Tumor diameter (cm)				1.13	0.29
≤7	40	18	22		
>7	39	13	26		
Pathology type				0.60	0.74
Mucinous carcinoma	52	22	30		
Serous Carcinoma	21	7	14		
Endometrioid carcinoma	6	2	4		
Ascites				2.07	0.15
Negative	58	20	38		
Positive	21	11	10		
Lymph node metastasis				6.36	0.01
Negative	23	14	9		
Positive	56	17	39		

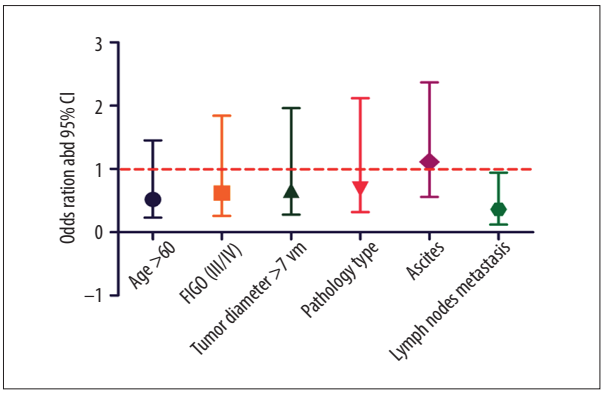

Figure 7. Logistic regression analysis of *FOXA2* protein expression and clinical features in patients with ovarian cancer showed that high expression of *FOXA2* protein was independently associated with lymph node metastasis.

Multivariate analysis of logistic regression for *FOXA2* protein expression and clinical features of patients with ovarian cancer indicated that high expression of *FOXA2* protein was an independent factor for lymph node metastasis in patients with ovarian cancer. Therefore, overexpression of *FOXA2* can be used as an indicator of good prognosis for ovarian cancer.

The molecular mechanism through which *FOXA2* is involved in ovarian cancer prognosis has not yet been elucidated. Basseres [11] evaluated the mechanisms of downregulation of *FOXA2* in lung cancer. The authors found that loss of expression of *FOXA2* is common in multiple lung cancer cell lines and cancer tissues. The molecular mechanism for downregulation of *FOXA2* in cancer cells is GpG island methylation in the promoter region, which is a common mechanism of epigenetic regulation. Another mechanism of *FOXA2* cancer inhibition is weakening of the epithelial-to-mesenchymal transition (EMT) through regulation of transcription of E-cadherin and *ZEB2* in human breast cancer cells [12]. However, Wang et al. reported that in colon cancer, *FOXA2* promotes proliferation, migration, invasion, and the EMT [10].

Conclusions

In the present study, *FOXA2* was found to be dysregulated in ovarian cancer and high expression of it was correlated with longer OS in patients with the disease. High expression of *FOXA2* protein was an independent risk factor for lymph node metastasis in patients with ovarian cancer. The molecular function of *FOXA2* was mainly enriched in the pathway

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of cancer and AMPK and correlated with cell growth and autophagy. Continuous detection of *FOXA2* expression may provide useful information for predicting prognosis in patients with ovarian cancer.

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Conflicts of interest

None

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