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ORIGINAL RESEARCH

Distinct expression and prognostic value of members of the epidermal growth factor receptor family in ovarian cancer

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Background: Increased aberrant expression or activation of the epidermal growth factor receptor (*EGFR*) family members has been reported in a wide range of cancers, and the *EGFR* family of tyrosine kinases has emerged as an important therapeutic target in malignancies. However, the expression patterns and exact roles of each distinct *EGFR* family member, which contribute to tumorigenesis and progression of ovarian cancer (OC), are yet to be elucidated.

Materials and methods: In the current study, we report the distinct expression and prognostic value of *EGFR* family members in patients with OC by analyzing a series of databases including ONCOMINE, Gene Expression Profiling Interactive Analysis , Kaplan–Meier plotter, cBioPortal, and Database for Annotation, Visualization and Integrated Discovery .

Results: It was found that in patients with OC, mRNA expression levels of *ERBB2/3/4* were significantly upregulated, whereas the transcription levels of *EGFR* were downregulated. Aberrant *EGFR* expression and *ERBB2/3/4* mRNA levels were associated with OC prognosis.

Conclusion: These results suggest that *EGFR* and *ERBB3/4* are distinct prognostic biomarkers and may be potential targets for OC. These results may be beneficial to better understand the molecular underpinning of OC and may be useful to develop tools for more accurate OC prognosis and for promoting the development of EGFR-targeted inhibitors for OC treatment.

Keywords: EGFR, ovarian cancer, database mining, prognostic value, bioinformatics analysis

Introduction

Ovarian cancer (OC) shows the highest cancer-related death rate among gynecological malignancies, with an estimated 204,000 cases and 125,000 deaths annually worldwide.[1,2] Over 75% of patients are not diagnosed until the disease is advanced (stages III and IV). Current prognostic factors do not allow reliable prediction of response to chemotherapy and survival for individual OC patients. The poor rate of survival and the high rate of lethality are partly due to lack of effective biomarkers for prognosis. Therefore, there is a pressing need to find reliable predictive biomarkers for prognosis and to develop novel therapeutic strategies for OC patients.[2,3]

The epidermal growth factor receptor (*EGFR*) tyrosine kinase family consists of four members: *EGFR*, *ERBB2*, *ERBB3*, and *ERBB4*. These receptors are activated when a ligand binds to their extracellular ligand binding domain, which triggers receptor homodimerization or heterodimerization, resulting in the activation of several downstream cell signaling pathways and ultimately in tumor cell proliferation, reduced apoptosis, and tumor migration and invasion.[4–6] In the past three decades, increased aberrant expression or activation of the *EGFR* family members has been reported in a wide range of cancers, and in some studies, has also been associated with poor prog-

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nosis and resistance to therapeutic options.[5,7] Moreover, the *EGFR* family of tyrosine kinases has emerged as an important therapeutic target in malignancies, and to date, numerous antibodies, recombinant proteins, peptide mimetics, and small molecules, such as cetuximab, panitumumab, trastuzumab, gefitinib, erlotinib, and lapatinib, have been developed for targeting *EGFR* family receptors as therapeutic targets for many kinds of solid tumors.[4,7] Recent reports have suggested that the functions of different EGFR members contribute to OC tumorigenesis. However, the clinicopathological and prognostic value and expression patterns of *EGFR* family members in OC remain controversial.[8–10] In addition, the role of *EGFR* family members in OC and the underlying molecular mechanism responsible for its involvement in tumor development and progression are largely unknown.

The development of microarray and RNA-sequencing technology has revolutionized RNA and DNA research, which has become a crucial component of biology and biomedical research.[11,12] In the current study, we extended the knowledge base related to OC based on a variety of large databases, with the purpose of determining the expression patterns, genetic alteration, potential functions, and distinct prognostic values of *EGFR* family members in OC.

Materials and methods

Ethics statement

This study was approved by the Academic Committee of the People's Hospital of China Three Gorges University, and conducted according to the principles expressed in the Declaration of Helsinki. All the datasets were retrieved from the databases, so it was confirmed that written informed consent had been obtained from all patients.

ONCOMINE analysis

The gene expression array datasets of ONCOMINE (www.oncomine.org), which is a publicly accessible, online cancer microarray database helps facilitate research data from genome-wide expression analyses. ONCOMINE was used to analyze the mRNA levels of *EGFR* family members in OC.[13,14] In this study, the Student's *t*-test was used to generate *P*-values for comparison between cancer specimens and normal control datasets. The cutoff *P*-value and fold change were defined as 0.05 and 1, respectively.

Gene Expression Profiling Interactive Analysis (GEPIA) dataset analysis

GEPIA is an interactive web server for estimating mRNA expression data based on 9,736 tumors and 8,587 normal samples in The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression dataset projects. GEPIA provides key interactive and customizable functions including differential expression analysis, profiling plotting, correlation analysis, patient survival analysis, similar gene detection, and dimensionality reduction analysis.[15]

The Kaplan–Meier plotter analysis

The prognostic value of the mRNA expression of *EGFR* family members was evaluated using an online database, Kaplan–Meier Plotter (www.kmplot.com), which contains gene expression data and survival information of 1,816 clinical OC patients. To analyze the overall survival (OS), progression-free survival (PFS), and post-progression survival (PPS) of patients with OC, patient samples were split into two groups by median expression (high vs low expression) and assessed by a Kaplan–Meier survival plot, with a HR with 95% CI and log-rank *P*-value.[16]

TCGA and CBioPortal analysis

Gene alteration frequency of EGFR family member mRNA in OC was performed using CBioPortal for Cancer Genomics (http://www.cbioportal.org). The genomic profiles included mutations, putative copy-number alterations from GISTIC, mRNA expression z scores, and protein expression z scores.[17]

Functional enrichment and bioinformatics analysis

GeneMANIA (http://www.genemania.org) is a flexible, user-friendly web interface for generating hypotheses about gene function, analyzing gene lists, and prioritizing genes for functional assays. GeneMANIA was used to conduct correlation analysis of EGFR family members at the gene level, which revealed relationships in pathways, shared protein domains, co-localization, and co-expression.[18] Finally, enrichment analysis was performed with The Database for Annotation, Visualization and Integrated Discovery (DAVID) (version 6.7) for *EGFR* family members and their neighboring genes. DAVID includes the gene ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.[19,20]

Results

Transcription levels of *EGFR* family members in patients with OC

Using ONCOMINE analysis, four *EGFR* family members have been identified in human cancers, including hematological malignancies and solid tumors (Figure 1). ONCOMINE analysis revealed that the mRNA expression levels of *ERBB3*

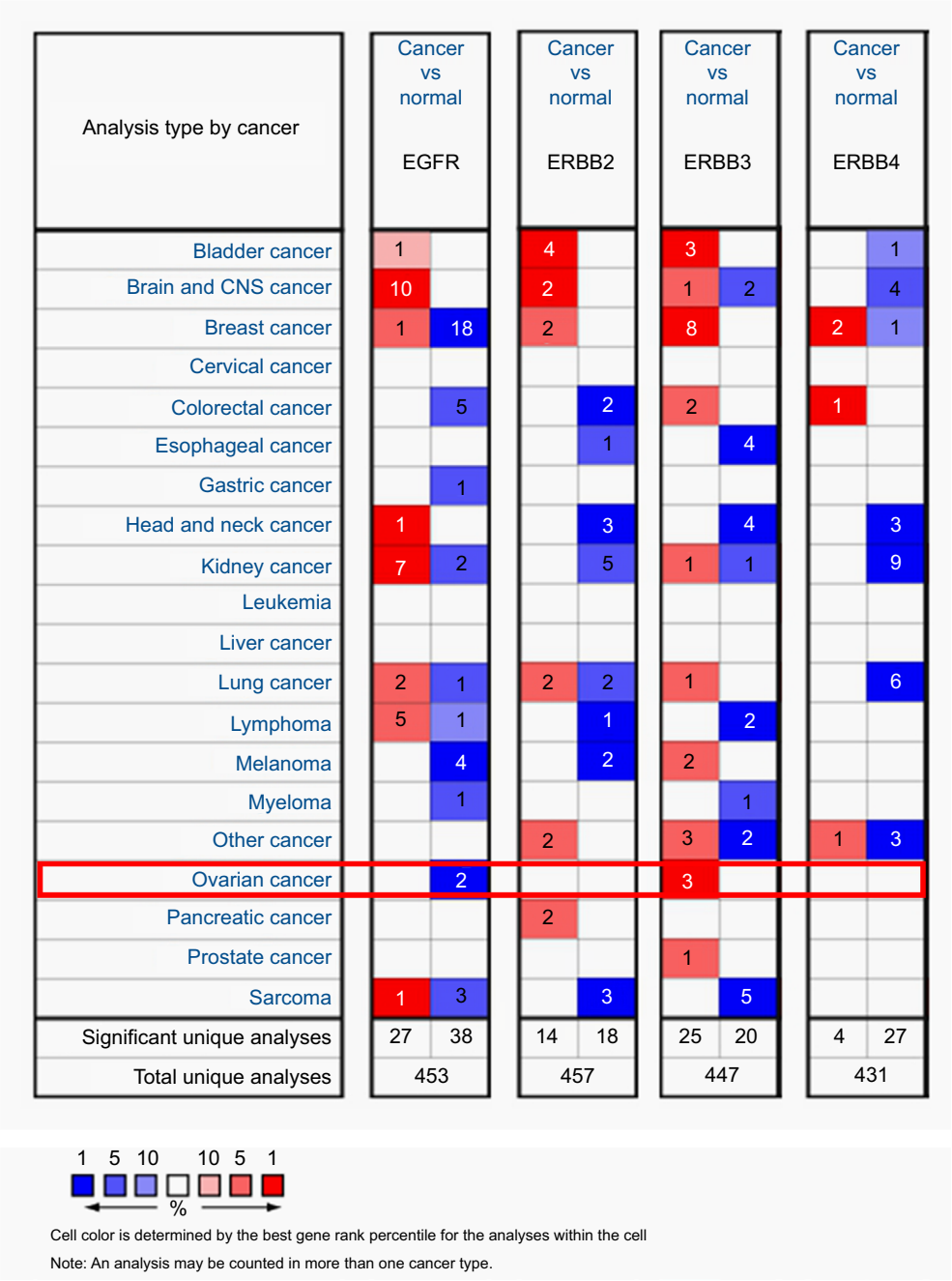


Figure 1 The transcription levels of *EGFR* family members in different types of cancers (ONCOMINE).
Notes: The graphic demonstrated the numbers of datasets with statistically significant mRNA over-expression (red) or down-expression (blue) of the target gene. The threshold was designed with following parameters: *P*-value =0.001; fold-change =1.5 and data type, mRNA.
Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2; ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ErbB4*, receptor tyrosine-protein kinase *erbB-4*.

were significantly upregulated in patients with OC in three datasets. In Hendrix's dataset,[21] *ERBB3* is overexpressed compared with that in the normal samples in all OC types – ovarian mucinous adenocarcinoma with a fold change of 2.355, ovarian clear cell adenocarcinoma with a fold change of 2.308, ovarian endometrioid adenocarcinoma with a fold change of 1.897, and ovarian serous adenocarcinoma with a fold change of 1.857. In Adib's dataset,[22] *ERBB3* is overexpressed in ovarian serous adenocarcinoma with a fold change of 1.807. In Lu's dataset,[23] *ERBB3* is overexpressed in ovarian endometrioid adenocarcinoma with a fold change of 1.635 and in ovarian serous adenocarcinoma with a fold change of 1.947 compared with that in the normal samples. The transcription levels of *EGFR* in ovarian serous adenocarcinoma were

lower than that in normal ovarian tissues in two datasets (fold changes were –1.223 and –1.349, respectively)[22,24] (Table 1).

As shown in Table 1, the transcription levels of *ERBB2* and *ERBB4* in different pathological types of OC (eg, ovarian endometrioid adenocarcinoma, ovarian mucinous adenocarcinoma, ovarian serous adenocarcinoma, ovarian clear cell adenocarcinoma, ovarian serous surface papillary carcinoma, ovarian serous adenocarcinoma, and ovarian carcinoma) were also slightly higher than those in normal ovarian tissues, and their cutoff of *P*-value was >0.05.

In addition, using the GEPIA dataset (http://gepia.cancer-pku.cn/), we compared the mRNA expression of EGFR family members between OC and normal tissues. The results demonstrated that the mRNA expression levels of *ERBB3* and *ERBB4* were significantly higher in OC tissues than in normal ovarian tissues, whereas the expression level of *EGFR* was significantly lower in the former than in the latter. We also analyzed the expression of EGFR family members in different tumor stages of OC. None of the EGFR family members varied in the different tumor stages (Figure 2).

Prognostic values of *EGFR* family members in all patients with OC

Using Kaplan–Meier plotter analysis, we initially assessed the prognostic significance of the *EGFR* family members in all OC patients. The Kaplan–Meier survival curves are demonstrated in Figure 3. The increased *EGFR* mRNA level and the decreased *ERBB2* and *ERBB3* mRNA levels were strongly associated with the poor OS. However, high mRNA levels of *EGFR* or low mRNA levels of *ERBB4* were predicted to have high *PFS*. In addition, the mRNA expression levels of *EGFR*, *ERBB2*, *ERBB3*, and *ERBB4* were not correlated with PPS of all patients with OC.

The prognostic value of EGFR family members was assessed in different pathological histology subtypes of OC, including serous and endometrioid. As shown in Table 2, high *ERBB2* mRNA expression was correlated to longer OS in serous OC patients. The mRNA expression levels of *EGFR* and *ERBB4* were associated with poor OS in serous OC patients. Increased *EGFR*, *ERBB2*, and *ERBB3* mRNA expression levels were associated with poor *PFS*. In endometrioid OC, high *ERBB4* mRNA expression level was associated with better OS. The rest of the EGFR family members were not related with prognosis in endometrioid OC.

Prognostic values of *EGFR* family members in OC patients with different clinicopathological features

To further assess the association of individual EGFR family members with other clinicopathological features, we assessed

Table 1 The transcription levels of *EGFR* family members between different types of OC and normal tissues (ONCOMINE)

EGFR family members	Types of OC vs normal	Fold change	*t*-Test	*P*-value	Ref	PMID
EGFR	Ovarian serous adenocarcinoma vs normal	–1.223	–1.44	0.906	Adib Ovarian	14760385
	Ovarian serous adenocarcinoma vs normal	–1.349	–2.226	0.983	Yoshihara Ovarian	19486012
ERBB2	Ovarian endometrioid adenocarcinoma vs normal	1.402	11.344	**2.35E–12**	Hendrix Ovarian	16452189
	Ovarian mucinous adenocarcinoma vs normal	1.47	9.83	**3.85E–08**	Hendrix Ovarian	16452189
	Ovarian serous adenocarcinoma vs normal	1.408	13.145	**2.76E–12**	Hendrix Ovarian	16452189
	Ovarian clear cell adenocarcinoma vs normal	1.826	7.306	**5.99E–05**	Hendrix Ovarian	16452189
	Ovarian serous surface papillary carcinoma vs normal	1.75	5.939	**8.97E–05**	Welsh Ovarian	11158614
	Ovarian serous adenocarcinoma vs normal	1.984	4.55	**6.53E–06**	Yoshihara Ovarian	19486012
	Ovarian carcinoma vs normal	2.484	8.219	**2.85E–06**	Bonome Ovarian	18593951
	Ovarian clear cell adenocarcinoma vs normal	1.672	4.176	**2.00E–03**	Lu Ovarian	15161682
ERBB3	Ovarian mucinous adenocarcinoma vs normal	2.355	14.003	**2.04E–09**	Hendrix Ovarian	16452189
	Ovarian clear cell adenocarcinoma vs normal	2.308	13.845	**5.07E–08**	Hendrix Ovarian	16452189
	Ovarian endometrioid adenocarcinoma vs normal	1.897	13.296	**3.89E–07**	Hendrix Ovarian	16452189
	Ovarian serous adenocarcinoma vs normal	1.857	13.245	**1.05E–06**	Hendrix Ovarian	16452189
	Ovarian serous adenocarcinoma vs normal	1.807	5.877	**6.89E–04**	Adib Ovarian	14760385
	Ovarian endometrioid adenocarcinoma vs normal	1.635	4.022	**9.14E–04**	Lu Ovarian	15161682
	Ovarian serous adenocarcinoma vs normal	1.947	4.391	**1.07E–04**	Lu Ovarian	15161682
	Ovarian serous adenocarcinoma vs normal	11.326	7.647	**2.03E–06**	Yoshihara Ovarian	19486012
ERBB4	Ovarian serous adenocarcinoma vs normal	1.725	13.668	**1.67E–17**	Hendrix Ovarian	16452189
	Ovarian endometrioid adenocarcinoma vs normal	1.465	9.503	**5.91E–12**	Hendrix Ovarian	16452189
	Ovarian clear cell adenocarcinoma vs normal	1.646	4.866	**8.73E–04**	Hendrix Ovarian	16452189

Notes: *P*-value was analyzed using the *t*-test. The bold font indicates that the difference was statistically significant between the OC and normal tissue group.
Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2; ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB4*, receptor tyrosine-protein kinase *erbB-4*; OC, ovarian cancer; PMID, PubMed unique identifier; Ref, references.

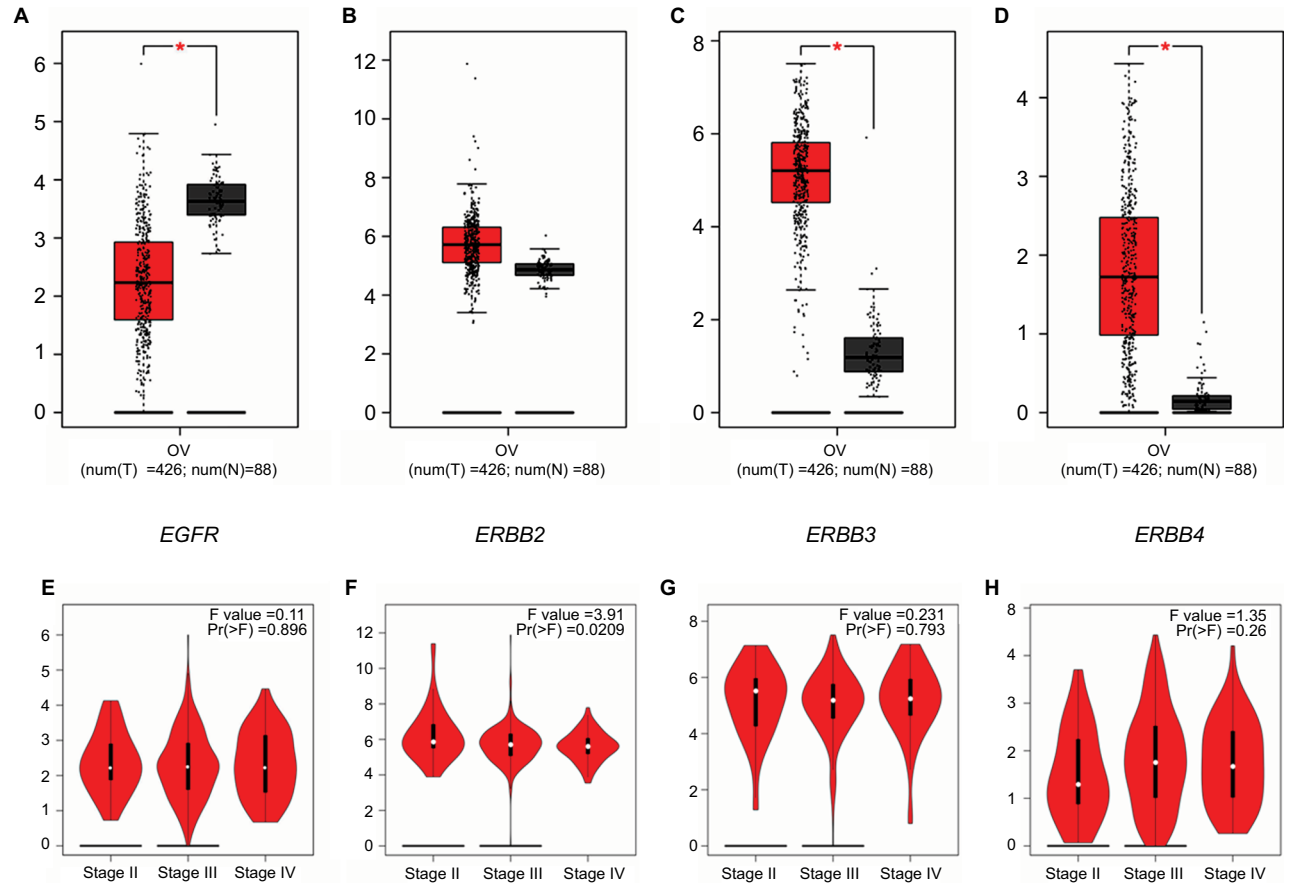


Figure 2 The expression of *EGFR* family members and tumor stage in OC patients (*GEPIA*).

Notes: Box plots derived from gene expression data in GEPIA comparing expression of a specific EGFR family member in OC tissue and normal tissues, the *P*-value was set up at 0.05. (**A**) The distribution of *EGFR* mRNA expression; (**B**) the distribution of *ERBB2* mRNA expression; (**C**) the distribution of *ERBB3* mRNA expression; (**D**) the distribution of *ERBB3* mRNA expression between OC tissue and normal tissues; (**E**) correlation between *EGFR* expression and tumor stage; (**F**) correlation between *ERBB2* expression and tumor stage; (**G**) correlation between *ERBB3* expression and tumor stage; (**H**) correlation between *ERBB4* expression and tumor stage in OC patients.

Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2*; *ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB4*, receptor tyrosine-protein kinase *erbB-4*; OC, ovarian cancer; T, tumor; N, normal.

the correlation between them with pathological grades, clinical grades, and TP53 status of OC patients (Table 3). As shown in Table 3, high mRNA expression of *ERBB4* was associated with better OS and PFS in pathological grade I OC patients. Elevated mRNA expression of *ERBB3* was associated with better OS and PFS in grade II OC patients. In pathological grade III OC patients, high *EGFR* and *ERBB4* mRNA expression was linked to poor OS or PFS, but high *ERBB2* mRNA expression was found to be correlated to longer OS. None of the EGFR family members were related with prognosis in grade IV OC patients. In terms of clinical staging, as we can see from Table 3, increased mRNA expression of *ERBB2* and *ERBB4* was associated with longer PFS, but high mRNA expression of *ERBB2* was linked to poor OS in clinical stage I and II patients. For clinical stage III and IV OC patients, high mRNA expression of *EGFR* and *ERBB2* was associated with poor PFS in this subgroup. Additionally, Table 3 also shows that high mRNA expression levels of *ERBB2* and *ERBB3* were associated with poor OS and PFS, and elevated mRNA expression of *EGFR* was associated with poor PFS in mutated-TP53-type OC. However, high mRNA expression level of *ERBB4* was associated with better PFS in this subgroup.

Genetic alteration and neighbor genes of *EGFR* family members in OC

We analyzed the genetic alterations of *EGFR* family members by using the cBioPortal online tool for OC. A total of 839 patients from three datasets of ovarian serous cystadenocarcinoma and 12 patients from one dataset of small cell carcinoma were analyzed. Among 4°C datasets analyzed, alterations ranging from 10.3% (58/563) to 13.7% (83/606) were found for the gene sets submitted for analysis (Figure 4A). The percentages of genetic alterations in *EGFR* family members for OC varied from 2.7% to 5.0% for individual genes (*EGFR*, 2.7%; *ERBB2*, 4%; *ERBB3*, 5%; and *ERBB4*,

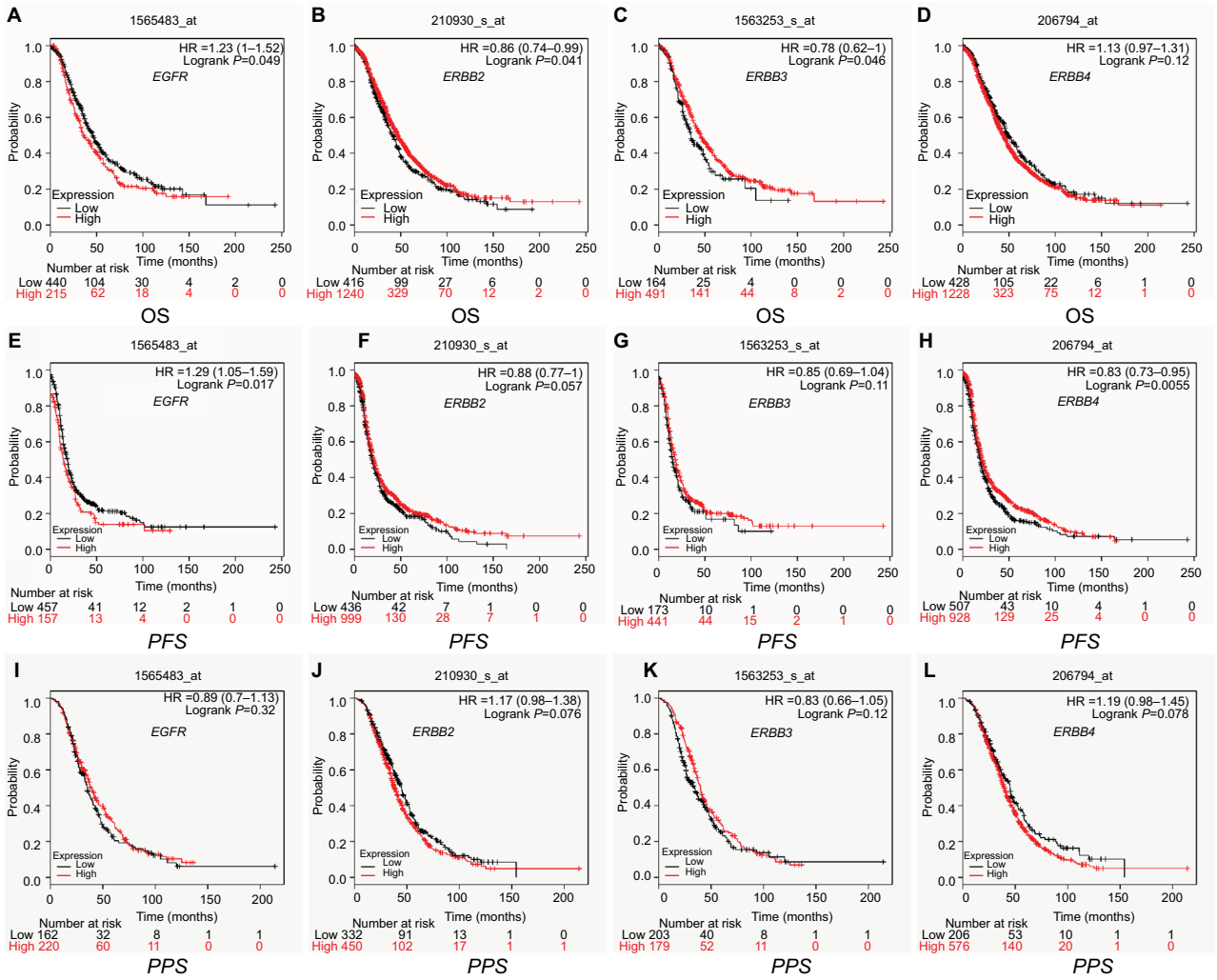


Figure 3 The prognostic value of mRNA level of *EGFR* family members in OC patients (Kaplan–Meier plotter).

Notes: The OS, PFS, and PPS survival curve comparing the patient with high (red) and low (black) EGFR family members' expression in OC were plotted from Kaplan–Meier plotter database as the threshold of *P*-value <0.05, respectively. OS curves of (**A**) *EGFR* (Affymetrix IDs: 1565483_at); (**B**) *ERBB2* (Affymetrix IDs: 210930_s_at); (**C**) *ERBB3* (Affymetrix IDs: 1563253_s_at); (**D**) *ERBB4* (Affymetrix IDs: 206794_at). PFS curves of (**E**) *EGFR* (Affymetrix IDs: 1565483_at); (**F**) *ERBB2* (Affymetrix IDs: 210930_s_at); (**G**) *ERBB3* (Affymetrix IDs: 1563253_s_at); (**H**) *ERBB4* (Affymetrix IDs: 206794_at). PPS curves of (**I**) *EGFR* (Affymetrix IDs: 1565483_at); (**J**) *ERBB2* (Affymetrix IDs: 210930_s_at); (**K**) *ERBB3* (Affymetrix IDs: 1563253_s_at); (**L**) *ERBB4* (Affymetrix IDs: 206794_at).

Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2*; *ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB4*, receptor tyrosine-protein kinase erbB-4; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

5%) (Figure 4B). After cBioPortal, Kaplan–Meier plotter and log-rank test, the results indicated that there are no significant difference in OS and disease-free survival (DFS) in cases with or without alterations in one of the *EFGR* family genes (*P*-values, 0.454 and 0.321, respectively) (Figure 4C, D). We then constructed a network for *EGFR* family members with the structure or function of neighboring genes using GeneMANIA. The results showed that 20 genes – *ABL1*, *ABL2*, *ANKS1A*, *ANKS1B*, *BTC*, *CRK*, *EREG*, *GRAP2*, *GRB2*, *GRB7*, *NRG1*, *NRG2*, *PIK3R2*, *PIK3R3*, *PLCG2*, *PTK6*, *SHC1*, *SHC4*, *TGFA*, and *TNS3* – were closely associated with EGFR family members (Figure 4E). GeneMANIA also was used to conduct correlation analysis of *EGFR* family members at the gene level. There were relationships between *EGFR* and *ERBB2* in co-expression, pathway, physical interactions, and shred protein domains. There were also relationships between *EGFR* and *ERBB3* in pathway, physical interactions, and shred protein domains. There were physical interactions, prediction, and shared protein domains between *EGFR* and *ERBB4*. In addition, there were relationships in co-expression, co-localization, pathway, physical interactions, shared protein domains, and prediction between *ERBB2* and *ERBB3*. There were relationships between EEBB2 and *ERBB4* in pathway, physical interactions, prediction, and

Table 2 The prognostic values of *EGFR* family members in all and different pathological subtypes OC patients (Kaplan–Meier plotter)

EGFR family	Histology	OS				PFS			
		Cases	HR	95% CI	*P*-value	Cases	HR	95% CI	*P*-value
EGFR	Overall	655	1.23	1.00–1.52	**0.049**	617	1.29	1.05–1.59	**0.017**
1565483_at	Serous	523	1.31	1.03–1.66	**0.027**	1,104	1.33	1.06–1.67	**0.013**
	Endometrioid	30	–	–	0.260	44	2.01	0.45–8.97	0.350
ERBB2	Overall	1,656	0.86	0.74–0.99	**0.041**	1,435	0.88	0.70–1.00	0.057
210930_s_at	Serous	1,207	0.80	0.68–0.95	**0.009**	1,104	1.25	1.08–1.45	**0.002**
	Endometrioid	37	0.29	0.03–2.56	0.230	51	0.53	0.19–1.49	0.230
ERBB3	Overall	655	0.78	0.62–1.00	**0.046**	614	0.85	0.69–1.04	0.110
1563253_s_at	Serous	523	1.22	0.97–1.53	0.084	483	1.26	1.01–1.56	**0.004**
	Endometrioid	30	–	–	0.020	44	2.66	0.44–9.57	0.120
ERBB4	Overall	1,656	1.13	0.97–1.31	0.120	1,435	0.83	0.73–0.95	**0.006**
206794_at	Serous	1,207	1.27	1.07–1.51	**0.006**	1,104	0.88	0.75–1.03	0.110
	Endometrioid	37	0.14	0.02–0.24	**0.039**	51	0.53	0.21–1.34	0.170

Notes: *P*-value was analyzed using the survival analysis test. The bold font indicates that the difference was statistically significant.
Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2*; *ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB4*, receptor tyrosine-protein kinase *erbB-4*; OC, ovarian cancer; OS, overall survival; *PFS*, progression-free survival.

shred protein domains. *ERBB3* and *ERBB4* shared physical interactions, prediction, and shred protein domains. Detailed results are presented in Figure 4E.

Significant functions and pathway enrichment analysis of *EGFR* family members in OC

The functions of *EGFR* family members and their neighboring genes were predicted by analyzing GO and KEGG in DAVID. Based on DAVID, a total of 58 GO functions were enriched. The enrichment items were classified into three functional groups: biological process (BP) group (10 items), molecular function (MF) group (41 items), and cellular component (CC) group (7 items). As shown in Table 4, the *EGFR* family members and their neighboring genes were mainly enriched in the following BP: transmembrane receptor protein tyrosine kinase signaling pathway, EGFR signaling pathway, insulin receptor signaling pathway, positive regulation of cell proliferation, and cell differentiation. The MF that these genes were mainly associated with are receptor binding, non-membrane spanning protein tyrosine kinase activity, manganese ion binding, ATP binding, and receptor tyrosine kinase binding; the CC that these genes were associated with are the extrinsic component of the cytoplasmic side of the plasma membrane, extracellular space, and phosphatidylinositol 3-kinase complex, and the focal adhesion and receptor complex.

Next, 51 pathways related to the functions of *EGFR* family members were found through KEGG analysis. The top ten KEGG pathways for EGFR family members are shown in Figure 5. Among these pathways, the ErbB signaling pathway, neurotrophin signaling pathway, Ras signaling pathway, microRNAs in cancer, proteoglycans in cancer, and focal adhesion were found to be involved in OC tumorigenesis and pathogenesis.

Discussion

Accumulative studies have determined that aberrant expression or activation of the *EGFR* family members is a common feature in human cancers, and the functions of different *EGFR* family members are associated with tumorigenesis and progression of solid tumors.[4,5,7,25–27] However, the patterns of expression and the exact roles the distinct EGFR family members play in contributing to OC are yet to be elucidated.[8–10,28] In the current study, we comprehensively explored the expression patterns, prognostic values (OS, PFS, and PPS), genetic alteration, and potential functions of different *EGFR* family members based on a variety of large databases.

Among the *EGFR* family members, *EGFR* is the most studied in OC since it was first identified in the 1970s.[29] Till date, various cancer cells are characterized by *EGFR* hyperactivation, overexpression, or mutants with dysregulated signaling. *EGFR* and its signaling activity have been targets for developing novel therapeutic drugs to treat a variety of cancers.[30–33] Recent studies confirmed that amplification and overexpression of *EGFR* have been reported in several solid cancers, and a growing body of research interests has focused on the prognostic value and therapeutic potential of *EGFR* for OC.[8–10,28] In our study, ONCOMINE and GEPIA datasets revealed that the mRNA expression of *EGFR* was lower in OC than in normal tissues. This inconsistent expression pattern might be because ONCOMINE and GEPIA only represent mRNA data, which only correlate to ~40% of the total protein

Table 3 The prognostic values of *EGFR* family members in OC patients with different clinicopathological features (Kaplan–Meier plotter)

EGFR family	Clinicopathological features	OS				PFS			
		Cases	HR	95% CI	*P*-value	Cases	HR	95% CI	*P*-value
Pathological grade									
EGFR	I	41	2.71	0.60–12.35	**0.180**	28	3.44	0.43–27.54	0.220
1565483_at	II	162	0.78	0.50–1.20	0.250	161	0.78	0.54–1.33	0.190
	III	392	1.38	1.07–1.78	**0.013**	315	1.37	1.04–1.81	**0.026**
	IV	18	–	–	–	18	–	–	–
ERBB2	I	56	0.55	0.19–1.57	0.250	37	0.47	0.15–1.45	0.180
210930_s_at	II	324	1.27	0.94–1.72	0.120	256	1.39	0.99–1.95	0.058
	III	1,015	0.79	0.66–0.95	**0.014**	837	1.18	1.00–1.40	0.520
	IV	20	0.6	0.20–1.75	0.340	19	–	–	–
ERBB3	I	41	0.43	0.14–1.34	0.130	28	2.79	0.35–22.33	0.310
1563253_s_at	II	162	0.52	**0.32–0.85**	**0.008**	161	0.49	0.33–0.71	**0.000**
	III	392	0.8	0.59–1.06	0.120	315	1.19	0.92–1.53	0.180
	IV	18	–	–	–	18	–	–	–
ERBB4	I	56	0.24	0.09–0.65	**0.003**	37	0.33	0.11–1.01	**0.041**
206794_at	II	324	1.38	0.96–1.98	0.078	256	1.15	0.82–1.62	0.420
	III	1,015	1.26	1.04–1.52	**0.018**	837	0.86	0.71–1.03	0.100
	IV	20	0.42	0.15–1.15	0.081	19	–	–	–
Clinical stage									
EGFR	I+II	83	2.7	0.61–11.98	0.170	115	0.50	0.23–1.10	0.080
1565483_at	III + IV	487	0.87	0.69–1.09	0.230	494	1.30	1.05–1.61	**0.016**
ERBB2	I+II	135	2.86	0.98–8.33	**0.043**	163	0.52	0.27–0.99	**0.042**
210930_s_at	III + IV	1,220	0.88	0.75–1.03	0.099	1,081	1.25	1.07–1.46	**0.005**
ERBB3	I+II	83	0.54	0.19–1.54	0.240	115	0.53	0.25–1.14	0.099
1563253_s_at	III + IV	487	1.15	0.91–1.45	0.230	494	1.12	0.91–1.38	0.260
ERBB4	I+II	135	0.53	0.24–1.16	0.110	163	0.48	0.26–0.89	**0.017**
206794_at	III + IV	1,220	0.86	0.74–1.01	0.062	1,081	0.83	0.71–0.97	**0.018**
TP53 mutation									
EGFR	mutated	124	1.33	0.91–1.95	0.130	124	1.59	1.09–2.31	**0.001**
1565483_at	wild type	19	–	–	–	19	–	–	–
ERBB2	mutated	506	1.52	1.21–1.91	**0.000**	483	1.55	1.24–1.95	**0.000**
210930_s_at	wild type	94	1.61	0.92–2.81	0.095	84	0.68	0.38–1.19	0.170
ERBB3	mutated	124	1.63	1.07–2.50	**0.023**	124	1.76	1.17–2.66	**0.006**
1563253_s_at	wild type	19	–	–	–	19	–	–	–
ERBB4	mutated	506	1.16	0.90–1.49	0.240	483	0.78	0.61–1.00	**0.047**
206794_at	wild type	94	1.32	0.73–2.37	0.360	84	0.70	0.42–1.18	0.180

Notes: *P*-value was analyzed using the survival analysis test. The bold font indicates that the difference was statistically significant.
Abbreviations: *EGFR*, epidermal growth factor receptor; PFS, progression-free survival; *ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB2*, receptor tyrosine-protein kinase *erbB-2*; *ERBB4*, receptor tyrosine-protein kinase *erbB-4*; OC, ovarian cancer; OS, overall survival.

levels.[34] Consistent with the results of most previous studies, our results demonstrated that *EGFR* expression was not correlated with the clinical stage of the patients with OC, and an increased *EGFR* expression was significantly associated with poor OS and PPS in the patients with OC, especially in serous and advanced OC. However, several different studies suggest that *EGFR* is not a reliable marker of survival in OC.[29,35,36] The utility of *EGFR* expression as an independent prognostic indicator in OC patients is yet to be confirmed.[37,38]

ERBB2 is a tyrosine kinase receptor in the EGFR family and plays a pivotal role in cell proliferation and tumor cell metastasis.[39,40] Previous studies have demonstrated that *ERBB2* overexpression or mutations in human malignant cancers correlate with poor prognosis and chemo-resistance.[40–42] Until now, the association between *ERBB2* expression and OC has been widely studied, however, its relationship with disease stage, grade, and response to treatment remains controversial.[43–45] A recent meta-analysis study showed that *HER2* expression can be used as a prognostic biomarker in OC patients.[46] Our results demonstrated that the transcription levels of *ERBB2* in different pathological types of OC were not remarkably higher than those in normal tissues, and increased *ERBB2* mRNA levels were significantly associated with the better OS, especially in clinical stage I and II

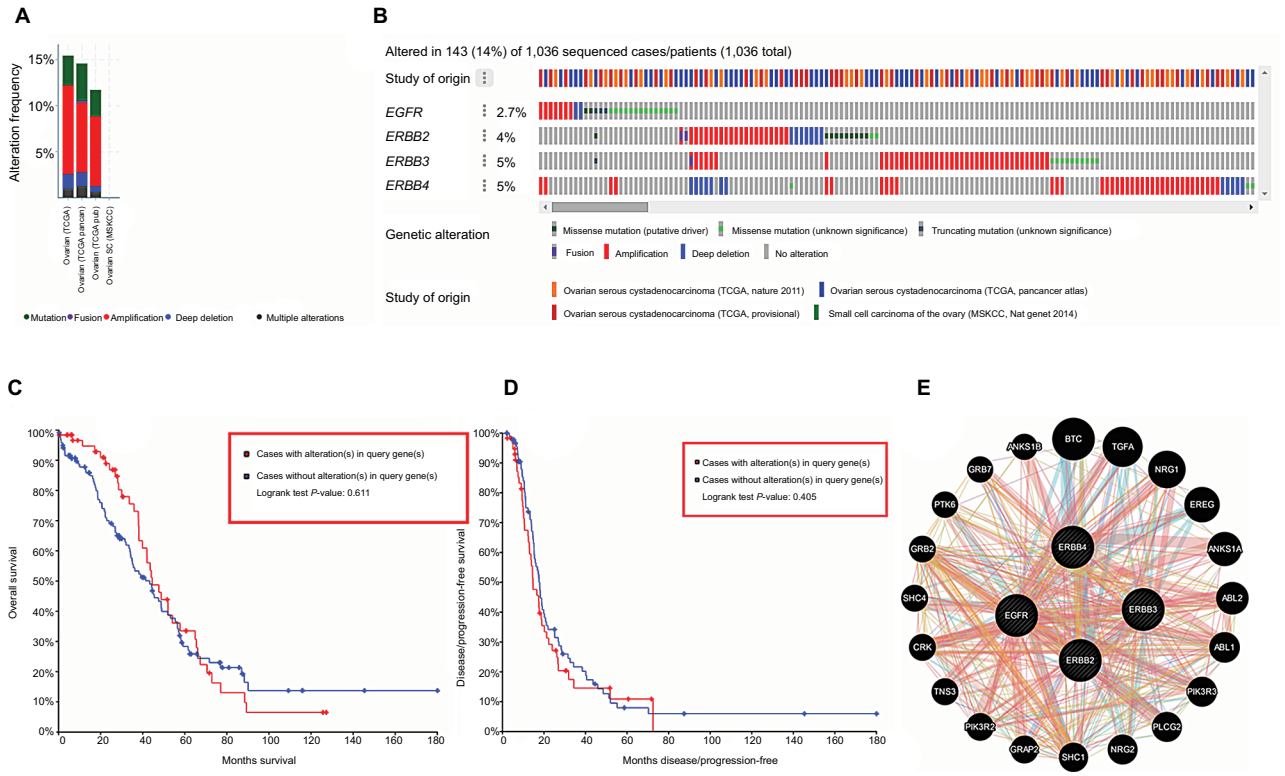


Figure 4 Alteration frequency of *EGFR* familymembers and neighbor genes network in OC (cBioPortal and GeneMANIA).
Notes: (**A**) Summary of alteration in *EGFR* family members. (**B**) OncoPrint visual summary of alteration on a query of *EGFR* family members. (**C**) Kaplan–Meier plots comparing OS in cases with/without *EGFR* family members gene alterations. (**D**) Kaplan–Meier plots comparing disease-free survival (DFS) in cases with/without EGFR family member alterations. (**E**) Gene–gene interaction network among *EGFR* family members.
Abbreviations: *EGFR*, epidermal growth factor receptor; *ERBB2*, receptor tyrosine-protein kinase *erbB-2*; *ERBB3*, receptor tyrosine-protein kinase *erbB-3*; *ERBB4*, receptor tyrosine-protein kinase *erbB-4*; OS, overall survival.

OC patients. Interestingly, high expression of *ERBB2* was associated with poor PFS in clinical stage III and IV OC patients and with poor OS and PFS in mutated-TP53-type OC patients.

The third member of the *EGFR* family, *ERBB3*, unlike the other EGFR family members that are activated through autophosphorylation upon binding with the ligand, lacks an intracellular tyrosine kinase domain.[47] Therefore, *ERBB3* must act as an allosteric activator. It forms heterodimers with other *EGFR* family members, thus stimulating downstream growth and signaling pathways.[48] *ERBB3* has been shown to be overexpressed in several human carcinomas, and somatic mutations have been found scattered throughout the *ERBB3* gene in subsets of breast cancers, gastric cancers, and OC.[49–51] In addition, *ERBB3* has been recently characterized as having a significant role in mediating resistance to *EGFR*- and *ERBB2*-directed therapies in solid malignancies, suggesting that *ERBB3* also has a role in mediating resistance to PI3K/AKT pathway inhibitors.[48,52,53] Our study showed that the mRNA expression levels of *ERBB3* were considerably upregulated in patients with OC in three datasets, and increased *ERBB3* mRNA levels were associated with the better OS, especially in pathological grade II OC patients. High expression of *ERBB2* was associated with poor PFS in serous OC patients and poor OS and PFS in mutated-*TP53*-type OC patients.

ERBB4 is one of the four members in the EGFR subfamily of receptor tyrosine kinases. Unlike *ERBB2*, which cannot directly bind a ligand, and *ERBB3*, which does not have a functional kinase domain, *ERBB4* is a fully functional receptor tyrosine kinase capable of signaling, both as a homodimer and as a heterodimer.[54] Among different EGFR family members, the role of *ERBB4* in cancer is probably the least understood.[55] *ERBB4* is necessary for the development of the heart, mammary gland, and the central nervous system, and mutations in *ERBB4* have been identified in various cancer types including melanoma, lung adenocarcinoma, and medulloblastoma. These results suggest that *ERBB4* can be a potential biomarker for malignant tumors.[54,56] Our results showed that increased expression of *ERBB4* might indicate better PFS in all OC patients and longer OS in endometrioid OC patients; however, increased

Table 4 The GO function enrichment analysis of *EGFR* family members and neighbor genes in OC (DAVID)

Category	Term	Description	Count	*P*-value
GOTERM_BP_DIRECT	GO:0007169	Transmembrane receptor protein tyrosine kinase signaling pathway	6	**4.85E–08**
GOTERM_BP_DIRECT	GO:0007173	EGFR signaling pathway	5	**2.78E–07**
GOTERM_BP_DIRECT	GO:0008286	Insulin receptor signaling pathway	4	**3.15E–05**
GOTERM_BP_DIRECT	GO:0008284	Positive regulation of cell proliferation	6	**4.02E–05**
GOTERM_BP_DIRECT	GO:0030154	Cell differentiation	4	**1.16E–03**
GOTERM_MF_DIRECT	GO:0004716	Receptor signaling protein tyrosine kinase activity	4	**7.99E–08**
GOTERM_MF_DIRECT	GO:0005154	EGFR binding	3	**3.87E–05**
GOTERM_MF_DIRECT	GO:0004714	Transmembrane receptor protein tyrosine kinase activity	3	**2.49E–04**
GOTERM_MF_DIRECT	GO:0008083	Growth factor activity	3	**3.46E–04**
GOTERM_MF_DIRECT	GO:0046935	1-Phosphatidylinositol-3-kinase regulator activity	2	**5.60E–03**
GOTERM_CC_DIRECT	GO:0016323	Basolateral plasma membrane	3	**3.56E–03**
GOTERM_CC_DIRECT	GO:0043235	Receptor complex	3	**3.69E–03**
GOTERM_CC_DIRECT	GO:0005925	Focal adhesion	4	**1.34E–02**
GOTERM_CC_DIRECT	GO:0005942	Phosphatidylinositol 3-kinase complex	2	**2.19E–02**
GOTERM_CC_DIRECT	GO:0005615	Extracellular space	5	**3.03E–02**

Notes: The bold font indicates that the difference was statistically significant.
Abbreviations: GO, gene ontology; BP, biological process; CC, cellular component; DAVID, Database for Annotation, Visualization and Integrated Discovery; MF, molecular function.

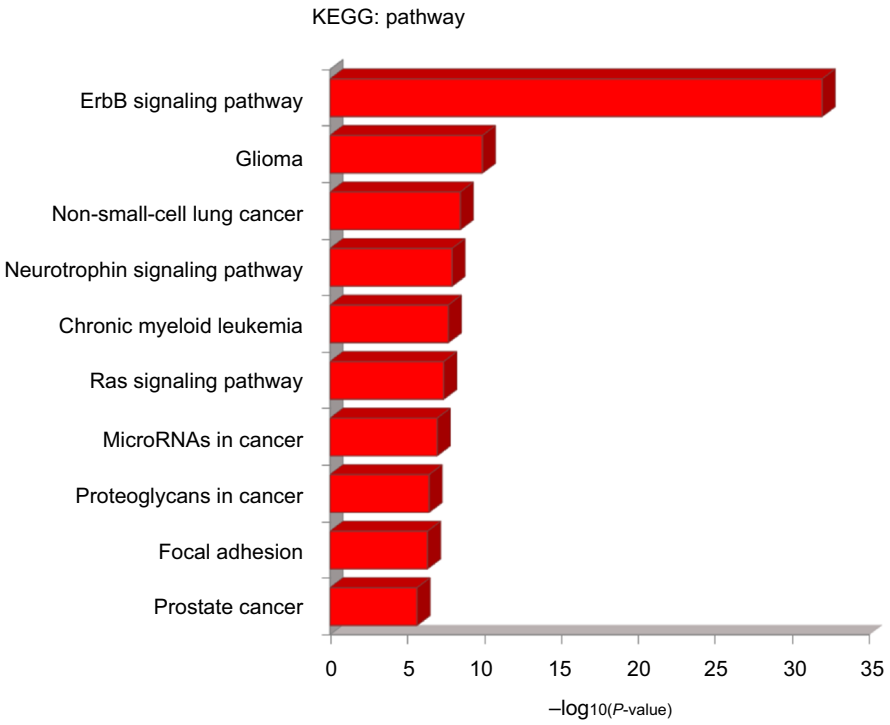


Figure 5 The *KEGG* pathway enrichment analysis of *EGFR* family members and neighbor genes in OC (DAVID).
Notes: The graphic demonstrated the functions of *EGFR* family and genes significantly associated with EGFR family alterations were predicted by analysis of the KEGG. The length of the X-axis represents –log (*P*-value).
Abbreviations: OC, ovarian cancer; EGFR, epidermal growth factor receptor; KEGG, Kyoto Encyclopedia of Genes and Genomes.

ERBB4 expression may correlate with worse OS in serous OC patients.

Mutations, gene amplification, and protein overexpression of *EGFR* family members are all linked to carcinogenesis.[47] Mutant *EGFR* family members cause a gain-of-function phenotype and are involved in tumorigenesis, invasion, and metastasis.[57] In our current analysis, we found that the percentages of alterations in EGFR family members among OC varied from 2.7% to 5.0% for individual genes, but there is no significant difference in OS and DFS in cases with or without alterations in one of the EFGR family genes (*P*-values, 0.454 and 0.321, respectively). To further clarify the carcinogenic

mechanism of the EGFR family members, we constructed a network for *EGFR* family members and 20 neighboring genes. The results of GO and KEGG analysis indicated that these genes are mainly enriched in tumor-related pathways, including the ErbB signaling pathway, neurotrophin signaling pathway, and Rams signaling pathway, and in microRNAs and proteoglycans in cancer, and during focal adhesion. Our study adds to the growing evidence regarding the complexity of the *EGFR* family members and their associated signaling pathways, which offer clues into the rational development of dual targeting with anti-EGFR or HER2 and downstream pathway inhibitors.

To the best of our knowledge, this is the first bioinformatics analysis exploring the distinct expression and prognostic value of EGFR family members in OC. There were some limitations to this study that need to be addressed. First, this is an in silico and bioinformatics analysis based on functional genomics using data from several large databases, which may introduce background heterogeneity. To address these issues, we are planning functional verification studies in well designed in vitro and in vivo models in the near future. In addition, the sample size of the study cohort was limited, and a small fraction of the clinical data was missing. As such, larger studies are needed to clarify these findings. Finally, no multivariable analyses were included; therefore, it is impossible to identify any potential association with other important prognostic factors, such as the FIGO stage, patient age, residual tumor after initial surgery, lymph node metastasis, vascular invasion, cancer antigen 125, and Human epididymis protein 4, BRCA, Risk of Malignancy Index II, and Risk of Malignancy Algorithm. Therefore, future research is still needed to address these issues.

Conclusion

In summary, the mRNA expression levels of *ERBB2/3/4* were significantly upregulated, whereas the transcription levels of EGFR were low in patients with OC. Aberrant *EGFR* expression and *ERBB2/3/4* mRNA levels were all found to be associated with the prognosis of OC. These results suggest that *EGFR* and *ERBB 3/4* may be prognostic biomarkers and potential targets for OC. These results may help us better understand the molecular foundations of OC. They may also be useful for the development of tools that can be used for OC prognosis and may help promote the development of *EGFR*-targeted inhibitors for the treatment of OC.

Disclosure

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