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High GNG13 Expression Associated with Poor Survival in Epithelial Ovarian Cancer and Breast Cancer

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Abstract

Background: Change the expression of Guanine nucleotide binding protein 13 (Gng13) resulting in multiple congenital malformations and sexual reversal, and it also found in brain. The aim of this study was to measure protein expression levels in epithelial ovarian cancer (EOC) and breast cancer (BC) tissues and assess their value as a potential prognostic marker.

Methods: We analyzed Gng13 protein expression by immunohistochemistry (IHC) in 119 EOC tissue samples and 125 BC tissues. Assessment of the associations between Gng13 levels and various clinicopathological features was identified, the relationship between Gng13 and prognosis in BC and EOC patients was analyzed using online resources of Oncomine and Kaplan-Meier Plotter.

Results: Protein expression levels of Gng13 were both significantly lower in BC and EOC compared with normal tissues (P<0.0001 and P<0.001, respectively). Among the clinicopathological characteristics of BC, tumor grade (p=0.001) and TNM stage (p=0.001) were significantly associated with low expression of Gng13. While in EOC, low expression of Gng13 was significantly related to FIGO stage (P=0.001), presence of metastasis (P=0.001) and CA125 (P=0.001).

Conclusion: Our data suggest that Gng13 expression maybe as a new inhibitor, which can strongly inhibit metastasis and partially attenuates tumor growth in EOC and BC.

Keywords: Guanine nucleotide binding protein 13(Gng13); Breast cancer (BC); Ovarian cancer; Prognosis

Abbreviations

EOC: Human Epithelial Ovarian Cancer; BC: Breast Cancer

Introduction

Maize Understanding of breast and ovarian cancers has greatly increased over recent decades [1,2]. Ovarian cancer causes the greatest number of cancer deaths among women aged 50-70 years in China, and other countries [3]. In the past 30 years, 30% of patients with EOC live 5 years after their diagnoses [4]. Breast cancer (BC) has the highest morbidity and mortality of diagnosed cancers among women worldwide, but is a heterogeneous disease influenced by natural history, and environmental, genetic, behavioral and other factors [5-8].

The two diseases share some risks, including diet and hormonal factors [9]. The Cancer Genome Atlas (TCGA) also indicates strong gene-based similarities between BC and EOC [7]. The discovery of BRCA1 and BRCA2 genes and their associations with breast and EOC's prompted changes in our understanding of genetic factors in the etiology of cartilage [5]. common cancers, but only 8%-10% of the diseases are caused by BRCA1/2 mutations [10-13]. Other genome-based risk elements are likely to be identified, and their associated proteins may provide new biomarkers to diagnose, monitor BC and EOC.

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Guanine nucleotide-binding protein-13 γ (GNG13), is encoded by the GNG13 gene and is mainly expressed in the ovary and belongs to guanine-nucleotide binding protein (G-protein) subunit [14-16]. Akihiro found that the GNG13 gene is 1.5 genomic kb long with three exons, and an open reading frame of 208 bp [17]. They also found that GNG13 expression is limited to gonads during ovarian differentiation. Erickson found that GNG13 expression can be altered, resulting in multiple congenital malformations and sexual reversal [15].

GNG13 has also been found in brain tissue, taste receptor cells, olfactory epithelium and retinal ON bipolar cells, and early developing ovary [16]. It is reportedly expressed in retinal and neuronal tissues and plays an especially critical role in taste signal transduction [18]. However, the role of GNG13 in tumor tissues has not been widely studied.

As patients with EOC or BC are typically diagnosed at advanced stages with few early warning symptoms, they tend to have poor prognoses. A reliable biomarker for early-stage disease is therefore urgently needed.
We hypothesized that GNG13 expression could be a marker for EOC and BC. Our study used tissue microarray immunohistochemistry (TMA-IHC) to evaluate both diseases. We the analyzed the relationship between GNG13 expression and various clinicopathological features in EOC and BC. Our findings were supported by bioinformatics analysis, the Oncomine and Kaplan-Meier plotter databases.
This interesting case became the cornerstone of the author studies in the field, trying to comprehend how the treatment based on the root of the problem could treat different diseases and symptoms simultaneously and using the same methods [8-13].

Materials and Methods

Patients and tissue samples

Ovarian cancer: We collected specimens from 213 patients who underwent surgery for EOC at the Gynecology Department of the Affiliated Hospital of Nantong University. These tissues were embedded in paraffin while fixed with formalin. All patients underwent standardized surgery and/or chemotherapy for at least 6 cycles after resection. Of the specimens, 119 were ovarian carcinoma (84 serous carcinoma, 18 endometrioid tumors, and 17 other types); 77 showed stage I-II disease and 42 showed stage III-IV disease; 91 were histologically high-grade tumors and 28 were low-grade, based on the International Federation of Obstetrics and Gynecology (FIGO) criteria.

Breast cancer: We used 125 paraffin-embedded BC tissue samples and 127 matched non-cancerous tissue samples from specimens resected at the Affiliated Hospital of Nantong University from January 2008 to May 2012, to construct the Tissue Microarray (TMA). Diagnoses of BC were confirmed according to the latest World Health Organization criteria. All experiments were conducted in accordance with guidelines approved by the Nantong University Affiliated Hospital.

All the patients had undergone mastectomy and/or axillary dissection (radical or functional, based on clinical and surgical findings). None of the patients received preoperative radiotherapy or chemotherapy before surgery. Postoperative histological examination confirmed lymph node metastasis in all patients. The initial clinical data were collected simultaneously from the hospital's medical records, including tumor grade, hormone receptor (ER/PR) status, patient age, tumor size, ERB-B2 receptor tyrosine kinase 2 (HER2) expression, Ki67 status, triple-negative BC (TNBC) status (i.e., PR-/ER-/HER2- tumors), lymph node metastasis and TNM stage [19]. Tissues for the TMA were formalin-fixed and paraffin-embedded and had been obtained between 2005 and 2015. The TMA was made by Tissue Microarray System (Quick-Ray, UT06, UNITMA, Korea).

The study obtained the permission of the Human Research Ethics Committee of the Affiliated Hospital of Nantong University, Jiangsu, China. The study was approved by the Ethics Committee of the Affiliated Hospital of Nantong University and all experiments were performed in accordance with approved guidelines of the Affiliated Hospital of Nantong University.

Immunohistochemistry

The IHC methods were performed as previously described [20]. All tissue samples were fixed in 10% buffered formalin solution overnight and embedded in paraffin at room temperature. Paraffin embedded (5 m) sections were divided into core tissue biopsies (2 mm in diameter) to make TMA. Sections were deparaffinized and then incubated with 3% H2O2, which was methanol for 15 min to quench endogenous peroxidase. Sections were then incubated with primary goat anti-GNG13 antibody (NO.NBP1-91950, 1:200, Novus Biologicals, USA) overnight at 4° C. After washing with phosphate-buffered saline, sections were incubated with horseradish peroxidase-conjugated donkey anti-goat antibody (Abcam) for 15 min, and then washed again.

Two investigators used an Olympus BX53 microscope (Olympus Co, Tokyo, Japan) to quantify GNG13 immunostaining, by scoring staining intensity as 0 (-, no staining), 1 (+, mild staining), 2 (++, medium staining), or 3 (+++, intense staining) and percentages of cells that stained positive.

We used the X-tile software program (The Rimm Lab at Yale University) to identify the optimal cutoff point for GNG13 IHC scores in terms of patients' overall survival (OS). We used the cutoff 120; 0-120 was considered low expression and 121-300 was high expression.

Statistical analysis

Statistical analyses of GNG13 expression were carried out using SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA) and the Stata 12.0 (Stata Corp, College Station, TX, USA) software [21,22]. We used $\chi 2$ tests for correlations between GNG13 and EOC clinicopathological factors. Multivariate Cox regression models were used to determine significant prognostic factors. Kaplan-Meier analysis and log-rank tests were used to evaluate OS. $P<0.05$ was considered significant.

Bioinformatic analysis and Kaplan-Meier Plotter Curves: We used Oncomine, which is a database of RNA and DNA sequencing information intentioned by TCGA, the Gene Expression Omnibus and other literature to evaluate the expression of CCR8 in EOC tissues, using the search terms: "GNG13", "Cancer vs Normal Analysis," Breast Cancer "Ovarian Cancer" and "mRNA" to obtain the expression data for EOC. These data were provided in the Oncomine microarray database as the median center of log2. The Kaplan-Meier Plotter was to identify correlation between GNG13 expression and OS in patients with EOC or BC.

Results

GNG13 expression was greater in non-cancerous tissues than in BC and EOC tissues

We used IHC to determine GNG13 protein expression in the two cancers. GNG13 was detected in different strengths and percentages in BC and EOC (Table 1) and was primarily associated in the cytoplasm. Low GNG13 expression was detected in 63.94% (94/147) of EOC samples and 48% (60/125) of BC samples. Typical GNG13 IHC staining patterns are presented in Figures 1 and 2.

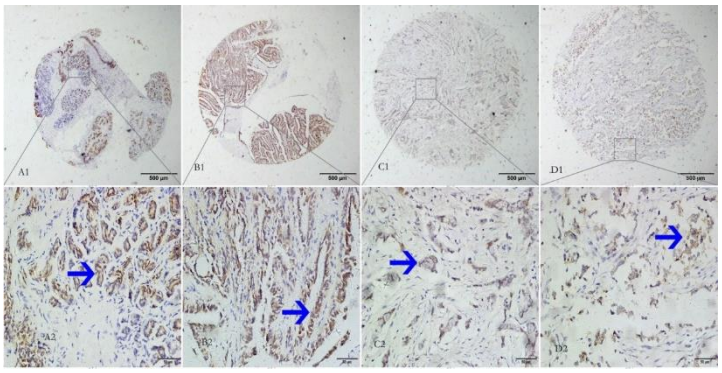

Figure 1: Representative images of Gng13 protein expression in BC and corresponding non-cancerous tissues with tissue microarray (TMA). (A) High IHC staining of Gng13 in the cytoplasm of non-cancerous breast tissue cells. (B) High IHC staining of Gng13 in the breast ductal papilloma cells. (C) Low IHC staining of Gng13 in the poorly differentiated invasive breast cancer cells. (D) Low IHC staining of Gng13 in moderately differentiated invasive ductal carcinoma. (E) Low IHC staining of Gng13 in highly differentiated invasive ductal carcinoma. Original magnification × 40 in (A, B, C, D, E); × 400 in (A1, B1, C1, D1, E1).

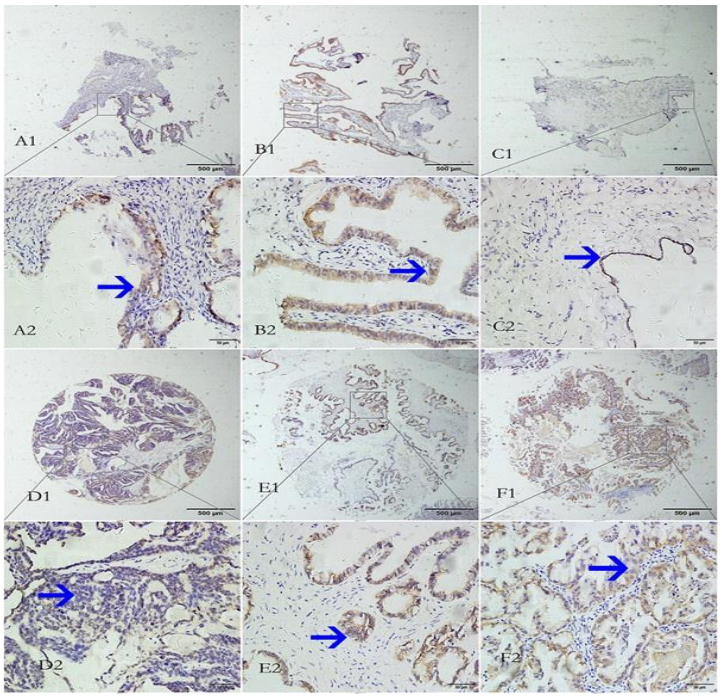

Figure 2: Gng13 protein level in EOC tissues and normal and benign ovarian tissues by IHC. (A) Strong IHC staining of Gng13 in benign ovarian tumour (B) Strong IHC staining of Gng13 in normal fallopian tube tissue; (C) Strong IHC staining of Gng13 in normal ovarian tissue; (D) negative IHC staining of Gng13 in poorly differentiated EOC samples; (E) Low IHC staining of Gng13 in borderline ovarian tumour samples; (F) Weak IHC staining of Gng13 in highly differentiated EOC samples. Original magnification × 40 in (A, B, C, D, E, F); × 400 in (A1, B1, C1, D1, E1, F1).

Tissue sample	n	HMP19 expression			
		Low or none	High	Pearson χ^2	*P*-value
Normal ovarian tissue	30	12 (40.00)	18 (60.00)	16.58	0.002*
Normal fallopian tube tissue	30	10 (33.33)	20 (66.67)	-	-
Benign ovarian tumor	30	11 (36.67)	19 (63.33)	-	-
Borderline ovarian tumor	20	8 (40.00)	12 (60.00)	-	-
EOC	147	94 (63.95)	53 (36.05)	-	-

Table 1: Immunohistochemical staining of Gng13 protein in normal ovarian, normal fallopian tube, benign ovarian tumour, borderline ovarian tumour and EOC tissues.

Relationship between GNG13 expression and clinical parameters of BC/EOC

In EOC, low GNG13 expression was significantly related to FIGO stage (P<0.001), presence of metastasis (P<0.001) and CA125 (P<0.001), but had no significant relationship to patients' age, tumor grade, histological classification, lymph node involvement or CA199 expression (Table 2). In BC, low GNG13 expression was associated with tumor grade (P<0.001) and TNM stage (P<0.001). These data imply that EOC metastasis is related to GNG13 expression (Table 3).

Groups	Gng13				
	n	Low or no 69)	High	Pearson χ^2	P-value
Total	147	94 (63.94)	53 (36.05)	-	-
Age				0.634	0.426
≤ 60 years	88	54 (61.36)	34 (38.64)	-	-
>60 years	59	40 (67.80)	19 (36.20)	-	-
FIGO stage				19.477	0.001*
1 ~ 2	84	41 (48.81)	43 (51.19)	-	-
3 ~ 4	63	53 (84.13)	10 (15.87)	-	-
Grade				7.609	0.006
Low grade	32	14 (43.75)	18 (56.25)	-	-
High grade	114	80 (70.18)	34 (29.82)	-	-
Histological classification				0.573	0.751
Serous carcinoma	111	73 (65.77)	38 (34.23)	-	-
Endometrioid carcinoma	14	9 (64.29)	5 (35.71)	-	-
Other[a]	21	12 (57.14)	9 (42.86)	-	-
Lymph nodes				2.079	0.149
Yes	117	72 (61.54)	45 (38.46)	-	-
No	29	22 (75.86)	7 (24.14)	-	-
Metastasis				14.722	0.001*
Yes	83	42	41	-	-

		(50.60)	(49.40)		
No	64	52 (81.25)	12 (18.75)	-	-
Single or double				2.161	0.142
Single	94	56 (59.57)	38 (40.43)	-	-
double	53	38 (71.70)	15 (28.30)	-	-
CA199				4.477	0.107
Yes	89	62 (69.66)	27 (30.34)	-	-
No	20	13 (65.00)	7 (35.00)	-	-
Unknown	38	19 (50.00)	19 (50.00)	-	-
CA125				43.897	0.001*
≤ 100	29	4 (13.79)	25 (86.21)	-	-
>100	101	81 (80.20)	20 (19.80)	-	-

Note: *P<0.05 indicates a significant association among the variables; Metastasis: pelvic lymph node metastases or nearby tissues and organs involved.
[a], others: clear cell carcinoma, 5 cases; mucinous carcinoma, 6 cases; transitional cell carcinoma, 3 cases; adeno-squamous carcinoma, 3 cases.

Table 2: Correlation of Gng13 expression with clinicopathological characteristics in ovarian cancer.

Characteristic	Gng13 expression (%)				
	n	Low or no 69)	High	Pearson χ^2	P-value
Age (years)				1.184	0.553
≤ 40	11	4 (36.36)	7 (63.64)	-	-
40-60	75	35 (46.67)	40 (53.33)	-	-
≥ 60	39	21 (53.85)	18 (46.15)	-	-
Tumor size (cm)				1.854	0.173
≤ 2 cm	60	25 (41.67)	35 (58.33)	-	-
>2 cm	65	35 (53.85)	30 (46.15)	-	-
Tumor grade				71.226	0.001*
I-II	55	3 (5.45)	52 (94.55)	-	-
III	70	57 (81.43)	13 (18.57)	-	-
ER				0.879	0.348
Negative	55	29 (52.73)	26 (47.27)	-	-
Positive	70	31 (44.29)	39 (55.71)	-	-
PR				0.006	0.939
Negative	85	41 (48.24)	44 (51.76)	-	-
Positive	40	19 (47.50)	21 (52.50)	-	-
HER-2 expression				0.045	0.832
Negative	99	48 (48.48)	51 (51.52)	-	-
Positive	26	12 (46.15)	14 (53.85)	-	-
Ki67				1.418	0.234
Low	59	25 (6.74)	34 (93.26)	-	-
High	66	35 (53.03)	31 (46.97)	-	-
Molecular classification				2.729	0.142
Luminal A	38	14 (36.84)	24 (63.16)	-	-
Luminal B	32	17 (53.13)	15 (46.88)	-	-
Her2-overexpression	23	12 (52.17)	11 (47.83)	-	-
TNBC	32	17 (53.13)	15 (46.88)	-	-
N stage				4.477	0.107
N0	86	30 (34.88)	56 (65.12)	-	-
N1+2+3	39	30 (76.92)	9 (23.08)	-	-
TNM stage				18.066	0.001*
Stage I-II	58	16 (27.59)	42 (72.41)	-	-
Stage III	67	44 (65.67)	23 (34.33)	-	-

Note: *P<0.05 indicates a significant association among the variables

Table 3: Correlation between the Gng13 expression and clinicopathological characteristics in breast cancer.

Association between GNG13 expression and OS and other clinical parameters

Univariate analysis showed OS was associated with GNG13 expression (P<0.001), tumor grade (P=0.031), CA125 expression (P<0.001), lymph node involvement (P=0.002), metastasis (P<0.001), subtype (P=0.029) and FIGO stage (P<0.001) among patients with EOC; and with GNG13 expression (P<0.001), histological grade (P<0.001) and TNM stage (P<0.001) among patients with BC (Table 4).

Variable	Univariate analysis			Multivariate analysis		
	HR	p value	95% CI	HR	p value	95% CI
Gng13 expression						
Low versus High	0.219	0.001*	0.123-0.391	0.259	0.003*	0.105-0.637
Age (years)						
≤ 60 versus >60	1.89	0.003*	1.236-2.890	1.815	0.013*	1.134-2.903
Grade						
Low	1.924	0.031*	1.062-	-	-	-

versus high			3.486			
Single or double						
None versus yes	1.46	0.09	0.942-2.262	-	-	-
CA125						
None versus yes	3.747	0.001*	1.711-8.205	-	-	-
Lymph nodes						
None versus yes	2.117	0.002*	1.314-3.411	-	-	-
Metastasis						
None versus yes	3.969	0.001*	2.515-6.263	-	-	-
Type						
Serous versus others	0.77	0.029*	0.609-0.974	-	-	-
Ascites cell						
None versus yes	1.608	0.153	0.839-3.082	-	-	-
FIGO						
Stage I versus stage II-IV	2.63	0.001*	1.788-3.867	1.853	0.038*	1.034-3.319

Note: Sc, serous carcinoma; Ec, endometrioid carcinoma; HR: Hazard ratio; CI: Confidence interval. *P<0.05.

Table 4: Univariate and multivariate Cox proportional hazard model analysis of prognostic markers for overall survival in ovarian cancer.

In multivariate analysis, OS was independently associated with GNG13 expression (hazard ratio [HR]: 0.259, P=0.003), FIGO stage (HR: 1.853, P=0.038) and age (HR: 1.815, P=0.013) among patients with EOC; and with GNG13 expression (HR 0.292, P=0.014) and TNM stage (HR, 2.664, P=0.003) among patients with BC (Table 5).

Variable	Univariate analysis			Multivariate analysis		
	HR	p value	95% CI	HR	p value	95% CI
Gng13 expression						
High versus low	0.161	0.001*	0.087-0.300	0.292	0.014*	0.110-0.777
Age (years)						
≤ 60 versus >60	1.121	0.602	0.730-1.721	-	-	-
ER expression						
Positive *vs.* negative	0.863	0.57	0.520-.1433	-	-	-
PR expression						
Positive *vs.* negative	0.583	0.857	0.493-1.488			
Her2 expression						
Positive *vs.* negative	0.974	0.935	0.517-1.834	-	-	-
Ki-67 expression						
Low *vs.* high	1.331	0.276	0.796-2.224	-	-	-
Molecular classification						
Luminal A *vs.* luminal B *vs.* Her-2 overexpression *vs.* triple negative	1.09	0.435	0.878-1.352	-	-	-
Histological grade						
I *vs.* II *vs.* III	4.391	0.001*	2.328-8.283	1.183	0.73	0.456-3.070
N stage						
N0 *vs.* N1+2+3	2.123	0.004	1.273-3.541	1.331	0.314	0.763-2.319
TNM stage						
Stage I-II *vs* Stage III	4.337	0.001*	2.338-8.046	2.664	0.004*	1.371-5.175

Note: [a]P<0.05. ER, estrogen receptor; PR, progesterone receptor; T, tumor stage: N, lymph node metastasis stage; TNM, tumor-node metastasis; HR, hazard ration; CI, confidence interval.

Table 5: Univariate and multivariate analysis of prognostic markers for overall survival in breast cancer.

Kaplan-Meier survival curves showed that both EOC patients and BC patients with low or no GNG13 expression had shorter OS than did their respective counterparts with high levels; and that patients with high FIGO-stage EOC and patients with TNM stage III BC (respectively) had shorter OS than patients with lower-stage disease (Figure 3).

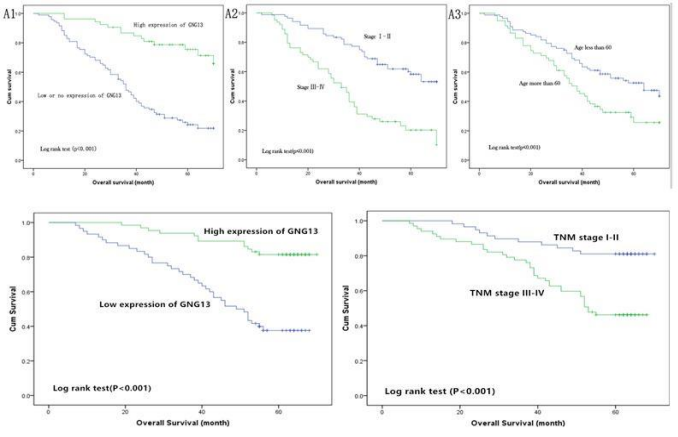

Figure 3: Survival curves by the Kaplan-Meier method and the log-rank test.

(A1) Overall survival curves of high Gng13 expression (blue line, 1) and low Gng13 expression (green line, 0); (A2) Overall survival curves by FIGO stage I-II (blue line, 1), FIGO stage III-IV (green line, 1); (A3) EOC patients diagnosed at older age (60) (green line, 1) had significantly

worse overall survival than patients diagnosed at younger age (<60)(blue line, 0). (B1) Overall survival rate in BC patients with low and no Eg5 expression (blue line) was statistically lower than that in BC patients with high cytoplasmic expression of Eg5 (green line). (B2) Overall survival rate in BC patients with advanced TNM stage III (green line) was statistically lower than that in BC patients with early TNM stage I-II (blue line).

Association between GNG13 expression and prognosis in Oncomine and Kaplan-Meier Plotter

To verify our finding of relationship between OS and GNG13 expression in EOC and BC, we used Oncomine to analyze our data. Consistent with our conclusions, GNG13 was lowly expressed in both cancers compared with normal tissues (Figure 4). The Kaplan-Meier Plotter found that high GNG13 expression is a prognostic factor for OS (HR: 0.84, 95% confidence interval: 0.75-0.94, P=0.0017; Figure 5).

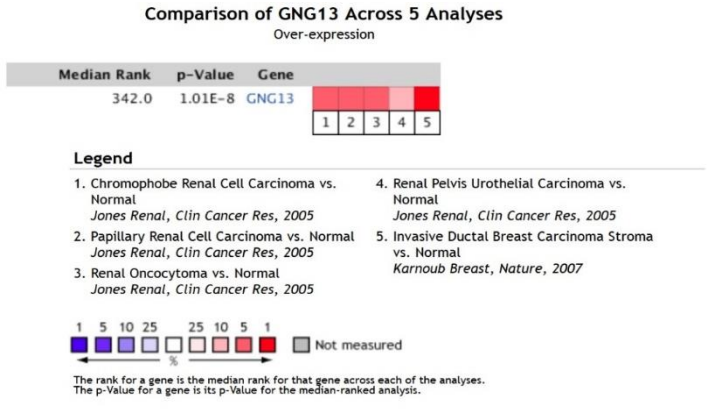

Figure 4: Two analyses were performed in comparing the RNA expression of Gng13 between gastric cancer and normal tissue.
The intensity of colour displayed the respective levels of Gng13.The red column revealed the Gng13 mRNA upregulation.

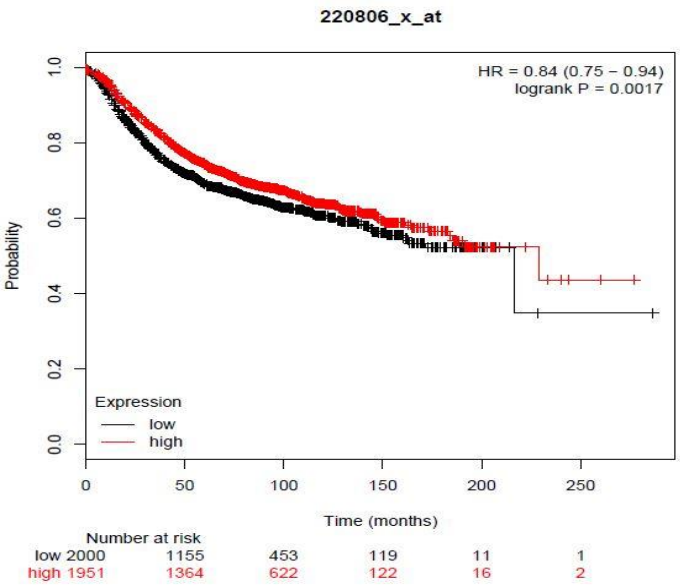

Figure 5: Prognostic value of Gng13 expression in Kaplan-Meier Plotter database. Gng13 probe number is 220806_x_at. 'Probability' on the y-axes represents the survival rates, the red line represents the patient with Gng13 expression above the median, the black line represents the patient with Gng13 expression below the median.

Discussion

To our knowledge, this is the first study to use TMA-IHC and bioinformatics analysis to investigate correlations between GNG13 protein levels and clinicopathological features of patients with EOC and BC.

Our results suggest that: (a) GNG13 protein expression in EOC and BC tissues is significantly lower than in non-cancerous tissues; (b) low GNG13 expression is significantly associated with FIGO stage, presence of metastasis and CA125 expression in EOC; and (c) low GNG13 expression is significantly associated with tumor grade and higher TNM stage in BC. To confirm our conclusions, the bioinformatic databases was used to identify relationships between GNG13 expression and prognosis, which were consistent with our analysis.

GNG13 encodes GNG13, which is part of a G-protein family that includes G α, G β and G γ subunits [14]. It couples metabolic receptors and downstream effectors. GNG13 is essential for photoreactions in all retinas in bipolar cells and is involved in ovarian development [15]. Ying Li found that abnormal expression of GNG13 may lead to functional constipation and proposed a new idea to understand emotional disorders [23].

These results indicate that GNG13 has a relationship with ovary development; the bioinformatic databases confirmed our prediction. However, the role of GNG13 in the development and/or progression of cancer has not been reported, as far as we know. As structures and sequence domains cannot predict function, and prior knowledge of GNG13 is limited, determining the mechanism of a metastasis-suppressing mechanism is challenging.

Knowledge of BRCA1 and BRCA2 has opened new therapeutic opportunities through wider understanding of breast and/or ovarian tumors [24]. Our results show that high GNG13 expression in BC and EOC specimens is significantly related to better survival. This biomarker could help predict prognosis and may be a metastasis suppressor in the two diseases. Therefore, our observations increase the understanding of the role of GNG13, especially in the development and progression of BC and EOC.

Our study has some limitations. First, it is retrospectively observational, and might not represent other BC and EOC populations. Second, more work should be done identify the function of GNG13; a genome-wide shRNA screen in *vivo* and *vitro* study might show whether GNG13 mediates metastasis. Further prospective study of this protein's mechanisms is needed to verify our findings.

Conclusion

The results of this study suggested that in breast cancer and ovarian cancer GNG13 expression significantly affects prognosis, As further study of GNG13 may illuminate new molecular pathways, it could present new therapeutic options for these two cancers.

Availability of Supporting Data

The data sets supporting the results of this article are included within the article.

Consent for Publication

Written informed consent for publication were obtained from all patients.

Availability of Data and Materials

Not Availability.

Conflicts of Interest

The authors declare no competing financial interests.

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Authors' Contributions

Xiaojing Zhang and Pei Chen performed the immunohistochemistry examination, Yuanlin Liu and Yunzhao Xu were major contributor in statistical analysis and writing the manuscript. Yue Qi and Mengjing Sun contributed to statistical analysis. All authors read and approved the final manuscript.

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