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REPRODUCTIVE PHYSIOLOGY AND DISEASE

Correlation between SNPs of *PIK3CA*, *ERBB2* 3′UTR, and their interactions with environmental factors and the risk of epithelial ovarian cancer

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Abstract

Objective To study the correlation between SNPs at phosphatidylinositol-4, 5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) rs9838117 site, erb-b2 receptor tyrosine kinase 2 (*ERBB2*) rs1058808 site, and their interactions with environmental factors and the epithelial ovarian cancer (EOC) risk.

Methods Sanger sequencing was used to analyze the genotypes of *PIK3CA* rs9838117 and *ERBB2* rs1058808 site in 587 patients with epithelial ovarian cancer (EOC). Multi-factor dimensionality reduction (MDR) was applied to analyze the interaction between *PIK3CA* rs9838117 and *ERBB2* rs1058808 site and the clinical data.

Results The risk of EOC in T allele carriers at *PIK3CA* rs9838117 was 1.95 times (95%CI: 1.55–2.46, $P<0.01$) that of G allele carriers. The risk of EOC in G allele carriers at *ERBB2* rs1058808 was as 0.64 times (95%CI: 0.54–0.75, $P<0.01$) as the risk for C allele carriers. In the interaction model between clinical data, *PIK3CA* rs9838117 site and *ERBB2* rs1058808 SNP site, EOC risk in high-risk combination was 3.10 times (95%CI: 1.49–6.46, $P<0.01$) that of low-risk combination.

Conclusion The SNPs at *PIK3CA* rs9838117 and *ERBB2* rs1058808 loci were associated with the risk of EOC.

Keywords Epithelial ovarian cancer · PIK3CA · ERBB2 · Single nucleotide polymorphism · Susceptibility

Introduction

Ovarian cancer (OC) is the most lethal tumors of female reproductive system. Lacking of effective early screening methods, and the resistance to chemotherapy therapies lead to high mortality of patients with OC [1]. The occurrence of OC is caused by a variety of genes and environmental factors, thereby studying the combined effects of genes-genes and genes-environmental factors is critical for the prevention and treatment of OC [2–4].

The *PIK3CA* gene is located on human chromosome 3q26.32 and encodes the catalytic subunit of phosphatidylinositol 3-kinase α (PI3Kα). The mutation and aberrant activation of *PIK3CA* is one of the major genomic changes in ovarian cancer [5–7]. There are many single nucleotide polymorphisms (SNPs) sites on *PIK3CA* gene, of which the rs9838117 site is the single nucleotide variation (SNV) type of *PIK3CA* gene, and its position on the chromosome is 3:17895250. Previous study showed that SNP at rs9838117 locus is closely associated with the reduction in the incidence of radiation pneumonitis (RP) ≥ grade 3 [8]. Genome-wide copy number variation analysis showed that *PIK3CA* has a higher degree of copy number amplification in highly invasive/migrating ovarian cancer cell lines [9]. Correlation analysis indicated that SNPs at rs9838117 site on *PIK3CA* is associated with the occurrence of reflex pneumonia [8]. However, few researches have focused on the correlation between the rs9838117 SNPs of *PIK3CA* gene and the development of ovarian cancer.

ERBB2 gene, also named as *HER2*, is located on human chromosome 17q12. *ERBB2* is one of the proto-oncogenes with the high mutation rate. Activation of *ERBB2* contributes to the processes of cell mitosis, proliferation, survival, apoptosis and anti-apoptosis [10, 11]. There may be a correlation between the *Val* allele at Ile655Val locus of the *ERBB2* and

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the increased risk of OC and poor prognosis of patients with OC [12]. A number of studies suggest that the rs1058808 locus of *ERBB2* is closely associated with susceptibility to several types of solid tumors such as gastric cancer [13], cervical cancer [14] and osteosarcoma [15]. Analysis of functional polymorphism revealed that the G allele at rs1058808 site is related to the up-regulation of *HER2* expression [14]. But the correlation between SNPs of *ERBB2* rs1058808 site and the susceptibility to EOC remains unclear.

In the current study, with a case-control study, we analyzed the correlation between the SNPs of *PIK3CA* rs9838117 site and *ERBB2* rs1058808 site and the risk of EOC, as well as the correlation between the interaction between these SNPs sites and the subjects' clinical characteristics and the risk of EOC, providing reference for clinical prevention and treatment of EOC.

Materials and methods

Subjects

Subjects including 587 EOC patients were recruited from Longyan People Hospital and Weihai Central Hospital from January 2015 to October 2017. The age of enrolled OC patients was from 32 to 76 years old, with an average age of (58.97±8.71) years old. The 587 EOC patients were classified according to the American Joint Committee on Cancer (AJCC) [16] and the International Federation of Obstetricians and Gynecologists (FIGO) [17]. All the enrolled EOC patients were diagnosed by pathological diagnosis, and received surgical resection after routine pathological examination and immunohistochemistry. Patients with cancer history, patients with non-epithelial ovarian cancer and patients with immune system diseases were excluded from the present study. Another 650 women with no history of cancer were selected as the control group, aged from 34 to 85 years old, with an average age of (58.31±10.18) years old.

Genotyping analysis

Genomic DNA (gDNA) was prepared from peripheral blood using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA was quantified by NanoDrop 2000 ultraviolet spectrophotometer (Thermo Fisher Scientific, CA, USA) and stored at −80°C until use. DNA fragment containing *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 locus was amplified by PCR. The primers used for DNA amplification were shown as follows: *PIK3CA* rs9838117-F 5′-TGA TGG AGA AGG AAA AAG TGA TGG-3′, *PIK3CA* rs9838117-R 5′-TGT TGT GTC CAC ATT TCA AAA CAT-3′; *ERBB2* rs1058808-F 5′-TGA ACC AGC CAG ATG TTC GG-3, *ERBB2* rs1058808-R 5′-TCC CTG GGG AGA GAG TCT TG-3′. PCR was carried out in 50 μl reaction mixture containing 40 ng of gDNA, 4 μl of 2.5 mM dNTP, 10 μl polymerase buffer, 1 μl of 10 pM forward primer and reverse primer, and 0.5 U Prime STAR HS DNA polymerase (TaKaRa, Guangzhou, China). PCR amplification conditions were as follows: 94°C, 5 min; 98°C 20 s, 60°C 20 s, 72°C 2 min, 35 cycles; and 72°C 5 min. The genotype was determined according to the comparison with sequences in dbSNP (https://www.ncbi.nlm.nih.gov/snp/).

Statistical analysis

Continuous variables between groups were analyzed using *t* test and one-way analysis of variance. The χ^2 test was used for statistical analysis of categorical variables. The consistency between genotype frequencies of the SNPs at *PIK3CA* rs9838117 site and *ERBB2* gene rs1058808 site in the control group and Hardy-Weinberg equilibrium (HWE) was evaluated by χ^2 test. Logistic regression analysis of odds ratio (OR) and 95% confidence interval (CI) was used to analyze the genotypes and allele frequencies of SNPs at *PIK3CA* rs9838117 locus and *ERBB2* rs1058808, and to calculate the association between two genetic models (dominant model and sex model) and the risk of OC. They were also utilized to adjust for age, BMI, number live-born, smoking, drinking, ovarian cancer family history. The interaction between the *PIK3CA* rs9838117 locus and the *ERBB2* rs1058808 locus and the clinical characteristics of the subjects was analyzed using multi-factor dimensionality reduction (MDR). All the statistical analysis was performed using SPSS 22.0 (SPSS, IL, USA), and $P<0.05$ indicated statistically significant.

Results

Clinical characteristics of subjects

The general clinical characteristics of 587 EOC patients and 650 control individuals were summarized in Table 1. There was no statistically significant difference in age, body mass index (BMI), number live-born, smoking, drinking between EOC patients and control group ($P>0.05$). But the proportion of EOC family history in EOC patients was obviously higher than that in the control group ($P<0.05$). According to the classification standers of FIGO, among the 587 patients with EOC, 104 cases (17.72%) were stage I, 121 cases (20.61%) were stage II, 293 cases (49.91%) were stage III, and 69 cases were stage IV (11.75%). Among the recruited EOC patients, 59 cases (10.05%) were in tumor grade G1, 168 cases (28.62%) were in G2, and the left 360 patients (61.33%) were in G3. There were 364 cases (62.01%) of EOC patients with lymphatic metastasis, and 223 cases (37.99%) of OC patients without lymphatic metastasis.

Table 1 Comparison of clinical characteristics between OC patients and control group

Variables	EOC (*n*=587)	Control (*n*=650)	*P*
Age (years, mean ± SD)	58.97±8.71	58.31±10.18	0.22
<60	336 (51.69%)	384 (59.08%)	0.51
≥60	251 (38.62%)	266 (40.92%)	
BMI (kg/m^2, *n* (%))	25.44±2.15	25.39±2.13	0.68
<24	164 (27.94%)	197 (30.31%)	0.36
≥24	423 (72.06%)	453 (69.69%)	
Number live-born (*n* (%))			
0	47 (8.01%)	45 (6.92%)	0.31
1~2	364 (62.01%)	430 (66.15%)	
≥3	176 (29.98%)	175 (26.92%)	
Smoking (*n* (%))			
Yes	100 (17.04%)	114 (17.54%)	0.82
No	487 (82.96%)	536 (82.46%)	
Drinking (*n* (%))			
Yes	96 (16.35%)	98 (15.08%)	0.54
No	491 (83.65%)	552 (84.92%)	
OC family history (*n* (%))			
Yes	94 (16.01%)	22 (3.38%)	<0.01
No	493 (83.99%)	628 (96.62%)	
FIGO stage (*n* (%))			
I	104 (17.72%)		
II	121 (20.61%)		
III	293 (49.91%)		
IV	69 (11.75%)		
Tumor grade (*n* (%))			
G1	59 (10.05%)		
G2	168 (28.62%)		
G3	360 (61.33%)		
Lymphatic metastasis (*n* (%))			
Yes	364 (62.01%)		
No	223 (37.99%)		

BMI, body mass index; *FIGO*, International Federation of Gynecology and Obstetrics

Correlation between the polymorphism of *PIK3CA* and *ERBB2* and the risk of EOC

The correlation between different genotypes, genetic models and allele frequencies of *PIK3CA* rs9838117 site and *ERBB2* rs1058808 site and the risk of EOC were concluded in Table 2. The genotype frequencies of SNPs at *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 locus were in accordance with Hardy-Weinberg equilibrium (P>0.05). The TT genotype of *PIK3CA* rs9838117 locus, dominant model (GT+TT vs. GG), recessive model (TT vs. GG+GT) were associated with the increased risk of EOC (OR=6.54, 95%CI: 3.17–13.51, P<0.01; OR=1.68, 95%CI: 1.29–2.19, P<0.01; OR=6.20, 95%CI: 3.01–12.76, P<0.01). The risk of EOC in carriers of T allele at *PIK3CA* rs9838117 locus was 1.95 times that of carriers of G allele (95%CI: 1.55–2.46, P<0.01).

The GG genotype, dominant model (CG+GG vs. CC), recessive model (GG vs. CC+CG) at *ERBB2* rs1058808 locus were associated with the reduced risk of EOC (OR=0.22, 95%CI: 0.14–0.34, P<0.01; OR=0.73, 95%CI: 0.58–0.92, P<0.01; OR=0.23, 95%CI: 0.15–0.35, P<0.01). The risk of EOC in individuals with G allele at *ERBB2* rs1058808 locus was as 0.64 times as the risk for carriers of C allele (95%CI: 0.54–0.75, P<0.01)

Stratified analysis

To investigate the correlation between different genotypes of *PIK3CA* gene rs9838117 site and *ERBB2* gene rs1058808 site and the risk of ovarian cancer, enrolled subjects were classified based on age, BMI, number live-born, drinking history, smoking history and family history of ovarian cancer. As shown in Table 3, carriers of GT and TT genotypes of *PIK3CA* gene rs9838117 locus had higher risk of EOC than carriers of GG in people with the following features: less than 60 years old (OR=2.08, 95%CI: 1.48–2.95, P<0.01), BMI<24kg/m^2 (OR=2.51, 95%CI: 1.51–4.19, P<0.01), BMI ≥24kg/m^2 (OR=1.44, 95%CI: 1.06–1.97, P =0.03), number live-born 0–2 (OR=1.73, 95%CI: 1.26–2.36, P <0.01), smoking (OR=2.94, 95%CI: 1.52–5.69, P <0.01), no smoking history (OR=1.46, 95%CI: 1.09–1.95, P=0.01), drinking (OR=2.86, 95%CI: 1.47–5.57, P<0.01), no drinking history (OR=1.51, 95%CI: 1.13–2.02, P<0.01), no OC family history (OR=1.61, 95%CI: 1.22–2.13, P<0.01).

Individuals with CG and GG genotypes at *ERBB2* gene rs1058808 site had a lower risk of EOC than CC genotype carriers in people classified as follows: age <60 years (OR=0.69, 95%CI: 0.51–0.93, P =0.02), number live-born 0–2 (OR=0.72, 95%CI: 0.55–0.94, P=0.02), no smoking (OR=0.61, 95%CI: 0.48–0.79, P<0.01), no drinking (OR=0.73, 95%CI: 0.57–0.94, P=0.02), no ovarian cancer family history (OR=0.72, 95%CI: 0.57–0.92, P<0.01) (Table 4).

Multi-factor dimensionality reduction (MDR) analysis of the interaction between SNP sites of *PIK3CA* gene and *ERBB2* gene and clinical characteristic of subjects

The interaction between the *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 locus and the subject's age, BMI, number live-born, smoking, drinking, and OC family history was shown in Fig. 1. The *ERBB2* rs1058808 site had the strongest interaction with smoking, followed by *PIK3CA* gene rs9838117 site (Fig. 1). MDR analysis showed that the interaction model between age, BMI, number live-born, smoking,

Table 2 Correlation of genotype and allele frequency of *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 with the risk of EOC

	EOC (*n*=587)	Control (*n*=650)	HWE *P*	OR (95%CI) *	*P*
rs9838117					
GG	419 (71.38%)	525 (80.77%)	0.37	1.00 (reference)	
GT	121 (20.61%)	116 (17.85%)		1.31 (0.98–1.74)	0.08
TT	47 (8.01%)	9 (1.38%)		6.54 (3.17–13.51)	<0.01
GT+TT	168 (28.62%)	125 (19.23%)		1.68 (1.29–2.19)	<0.01
GG+GT	540 (91.99%)	641 (98.62%)		1.00 (reference)	
TT	47 (8.01%)	9 (1.38%)		6.20 (3.01–12.76)	<0.01
G	959 (81.69%)	1166 (89.69%)		1.00 (reference)	
T	215 (18.31%)	134 (10.31%)		1.95 (1.55–2.46)	<0.01
rs1058808					
CC	262 (44.63%)	241 (37.08%)	0.15	1.00 (reference)	
CG	298 (50.77%)	295 (45.38%)		0.93 (0.73–1.18)	0.59
GG	27 (4.60%)	114 (17.54%)		0.22 (0.14–0.34)	<0.01
CG+GG	325 (55.37%)	409 (62.92%)		0.73 (0.58–0.92)	<0.01
CC+CG	560 (95.40%)	536 (82.46%)		1.00 (reference)	
GG	27 (4.60%)	114 (17.54%)		0.23 (0.15–0.35)	<0.01
C	822 (70.02%)	777 (59.77%)		1.00 (reference)	
G	352 (29.98%)	523 (40.23%)		0.64 (0.54–0.75)	<0.01

HWE, Hardy-Weinberg equilibrium; *OR*, odds ratio; *CI*, confidence interval

*Adjust age, BMI, number live-born, smoking, drinking, ovarian cancer family history

drinking, OC family history, *PIK3CA* gene rs9838117 locus, and *ERBB2* gene rs1058808 locus was the best model for prediction of the risk of OC. The EOC risk of the "high-risk combination" was 3.10 times that of the "low-risk combination" (95%CI: 1.49–6.46, *P*<0.01). The training balanced accuracy was 0.7238, the testing balanced accuracy was 0.6377, and the cross-validation consistency was 10/10 (Table 5).

Correlation of SNPs at *PIK3CA* rs9838117 and *ERBB2* rs1058808 loci with the progression of EOC

The genotypes and allele frequency of rs9838117 locus of *PIK3CA* gene and rs1058808 locus of *ERBB2* gene were not associated with FIGO stage and lymphatic metastasis in patients with EOC (*P*>0.05, Supplementary Table 1 to Table 3).

Discussion

In the current study, we found SNPs at PIK3CA rs9838117 site and ERBB2 gene rs1058808 locus correlated with the risk of EOC. In addition, the interaction between SNP sites of *PIK3CA* rs9838117 and *ERBB2* rs1058808 loci and clinical data of subjects including age, BMI, number live-born, smoking, drinking, and OC family history was strongly associated with the risk of EOC.

EOC is a malignant tumor of the female reproductive system. Lacking of early diagnosis techniques and effective long-term treatment programs is the main reason for the high mortality rate of ovarian cancer [18, 19]. Therefore, there is an urgent need to find new tumor markers and therapeutic targets for clinical diagnosis and treatment of OC [20, 21]. In recent years, growing evidence supports that genetic polymorphisms are significantly associated with the occurrence and development of OC [3, 22, 23]. The influence of genetic polymorphisms of OC molecular markers on the occurrence and development of OC is also worthy of further researches.

PI3K/Akt signal pathway is the downstream transducing cascade of a variety of growth factors and cytokines. PI3K/Akt signal pathway closely correlates to the occurrence and development of tumors, and can promote cell proliferation, invasion, metastasis, and inhibits cell apoptosis [24–26]. The *PIK3CA* gene is the only gene with somatic mutations, and these mutations mostly appear in the regions coding the helical domain and kinase domain [27].

PIK3CA gene rs9838117 SNP site is located in the 3′ untranslated region (UTR). The present study showed that the T allele at *PIK3CA* rs9838117 site was associated with increased risk of OC. The possible reason is that the rs9838117 site may

Table 3 Stratified analysis of correlation between genotypes frequency at *PIK3CA* rs9838117 site and the risk of EOC

	EOC (*n*=587)	Control (*n*=650)	OR (95%CI) *	*P*
Age				
<60				
GG	228 (67.86%)	313 (81.51%)	1.00 (reference)	
GT+TT	108 (32.14%)	71 (18.49%)	2.08 (1.48–2.95)	<0.01
≥60				
GG	191 (76.10%)	212 (79.70%)	1.00 (reference)	
GT+TT	60 (23.90%)	54 (20.30%)	1.23 (0.81–1.87)	0.38
BMI (kg/m^2)				
<24				
GG	113 (68.90%)	167 (84.77%)	1.00 (reference)	
GT+TT	51 (31.10%)	30 (15.23%)	2.51 (1.51–4.19)	<0.01
≥24				
GG	306 (72.34%)	358 (79.03%)	1.00 (reference)	
GT+TT	117 (27.66%)	95 (20.97%)	1.44 (1.06–1.97)	0.03
Number live-born				
0–2				
GG	294 (71.53%)	386 (81.26%)	1.00 (reference)	
GT+TT	117 (28.47%)	89 (18.74%)	1.73 (1.26–2.36)	<0.01
≥3				
GG	125 (71.02%)	139 (79.43%)	1.00 (reference)	
GT+TT	51 (28.98%)	36 (20.57%)	1.58 (0.97–2.57)	0.09
Smoking				
Yes				
GG	66 (66.00%)	97 (85.09%)	1.00 (reference)	
GT+TT	34 (34.00%)	17 (14.91%)	2.94 (1.52–5.69)	<0.01
No				
GG	353 (73.08%)	428 (79.85%)	1.00 (reference)	
GT+TT	130 (26.92%)	108 (20.15%)	1.46 (1.09–1.95)	0.01
Drinking				
Yes				
GG	60 (62.50%)	81 (82.65%)	1.00 (reference)	
GT+TT	36 (37.50%)	17 (17.35%)	2.86 (1.47–5.57)	<0.01
No				
GG	359 (73.12%)	444 (80.43%)	1.00 (reference)	
GT+TT	132 (26.88%)	108 (19.57%)	1.51 (1.13–2.02)	<0.01
Ovarian cancer family history				
Yes				
GG	64 (68.09%)	19 (86.36%)	1.00 (reference)	
GT+TT	30 (31.91%)	3 (13.64%)	2.97 (0.82–10.81)	0.15
No				
GG	355 (72.01%)	506 (80.57%)	1.00 (reference)	
GT+TT	138 (27.99%)	122 (19.43%)	1.61 (1.22–2.13)	<0.01

BMI, body mass index; *OR*, odds ratio; *CI*, confidence interval

*Adjust age, BMI, number live-born, smoking, drinking, ovarian cancer family history

Table 4 Stratified analysis of correlation between genotypes frequency at *ERBB2* rs1058808 site and the risk of EOC

	EOC (*n*=587)	Control (*n*=650)	OR (95%CI) *	*P*
Age				
<60				
CC	156 (46.43%)	144 (37.50%)	1.00 (reference)	
CG+GG	180 (53.37%)	240 (62.50%)	0.69 (0.51–0.93)	0.02
≥60				
CC	106 (42.23%)	97 (36.47%)	1.00 (reference)	
CG+GG	145 (57.77%)	169 (63.53%)	0.79 (0.55–1.12)	0.21
BMI (kg/m^2)				
<24				
CC	77 (46.95%)	69 (35.03%)	1.00 (reference)	
CG+GG	87 (53.05%)	128 (64.97%)	0.61 (0.40–0.93)	0.03
≥24				
CC	185 (43.74%)	172 (37.97%)	1.00 (reference)	
CG+GG	238 (56.26%)	281 (62.03%)	0.79 (0.60–1.03)	0.10
Number live-born				
0–2				
CC	189 (45.99%)	180 (37.89%)	1.00 (reference)	
CG+GG	222 (54.01%)	295 (62.11%)	0.72 (0.55–0.94)	0.02
≥3				
CC	73 (41.48%)	61 (34.86%)	1.00 (reference)	
CG+GG	103 (58.52%)	114 (65.14%)	0.76 (0.49–1.16)	0.24
Smoking				
Yes				
CC	28 (28.00%)	47 (41.23%)	1.00 (reference)	
CG+GG	72 (72.00%)	67 (58.77%)	1.80 (1.02–3.20)	0.06
No				
CC	234 (48.05%)	194 (36.19%)	1.00 (reference)	
CG+GG	253 (51.95%)	342 (63.81%)	0.61 (0.48–0.79)	<0.01
Drinking				
Yes				
CC	44 (45.83%)	37 (37.76%)	1.00 (reference)	
CG+GG	52 (54.17%)	61 (62.24%)	0.72 (0.40–1.27)	0.32
No				
CC	218 (44.40%)	204 (36.96%)	1.00 (reference)	
CG+GG	273 (55.60%)	348 (63.04%)	0.73 (0.57–0.94)	0.02
Ovarian cancer family history				
Yes				
CC	41 (43.62%)	9 (40.91%)	1.00 (reference)	
CG+GG	53 (56.38%)	13 (59.09%)	0.90 (0.35–2.30)	0.82
No				
CC	221 (44.83%)	232 (36.94%)	1.00 (reference)	
CG+GG	272 (55.17%)	396 (63.06%)	0.72 (0.57–0.92)	<0.01

BMI, body mass index; *OR*, odds ratio; *CI*, confidence interval

*Adjust age, BMI, number live-born, smoking, drinking, ovarian cancer family history

Table 5 The best model prediction of the interaction between the *PIK3CA* gene rs9838117 and *ERBB2* gene rs1058808 sites and the clinical data of subjects

Model	Training balanced accuracy	Testing balanced accuracy	χ^2	OR (95%CI)	*P*	Cross-validation consistency
rs1058808	0.5666	0.5415	0.86	1.40 (0.69–2.87)	0.35	6/10
OC family history, rs9838117	0.5906	0.5500	1.53	1.64 (0.75–3.62)	0.21	8/10
Age, BMI, rs1058808	0.6092	0.5503	1.30	1.52 (0.74–3.14)	0.25	3/10
Age, BMI, rs9838117, rs1058808	0.6361	0.6233	7.55	2.77 (1.33–5.76)	<0.01	10/10
Age, BMI, OC family history, rs9838117, rs1058808	0.6538	0.6277	8.05	2.84 (1.37–5.90)	<0.01	10/10
Age, BMI, number live-born, drinking, rs9838117, rs1058808	0.6729	0.5913	4.12	2.09 (1.02–4.29)	0.04	4/10
Age, BMI, number live-born, smoking, drinking, rs9838117, rs1058808	0.6985	0.6124	6.23	2.50 (1.21–5.15)	0.01	6/10
Age, BMI, number live-born, smoking, drinking, ovarian cancer family history, rs9838117, rs1058808	0.7238	0.6377	9.36	3.10 (1.49–6.46)	<0.01	10/10

BMI, body mass index; *OR*, odds ratio; *CI*, confidence interval

be at the targeted binding region of microRNA targeting *PIK3CA*, and allelic variation may affect the regulatory effect of microRNA on the expression of their target gene *PIK3CA*, which needed to be verified by in vitro assays.

The *ERBB2* gene rs1058808 locus is also located in its 3′ UTR region. Individuals carrying G allele at *ERBB2* rs1058808 locus have a lower risk of EOC than carriers with C allele, suggesting that rs1058808 locus G allele may be a protective factor for EOC. Although there is no evidence that the SNPs at *ERBB2* gene rs1058808 locus is associated with the risk of OC, there has been research that SNPs at *ERBB2* rs1058808 locus is associated with the high risk of osteosarcoma [15]. But the study showed that G allele of *ERBB2* gene rs1058808 locus is one high risk factor for osteosarcoma,

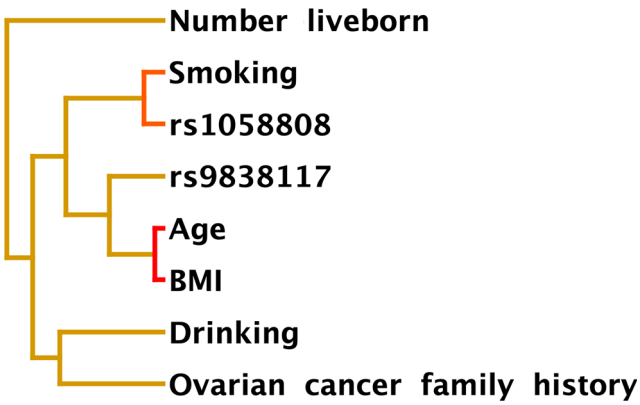

Fig. 1 MDR analysis for the interaction between SNP sites of *PIK3CA* gene and *ERBB2* gene and clinical data of subjects including age, BMI, number live-born, smoking, drinking, and OC family history. The distance was inversely proportional to the interaction

which is inconsistent with the results of the present study [15]. This may be due to the large differences in the genetic background of the individuals enrolled in this study. The frequency of the G allele of the *ERBB2* gene rs1058808 was 18% in the control group selected in the previous study, and was 40.23% in this proposed study. According to the data in the 1000 genome database, the frequency of the G allele at rs1058808 site in Han Chinese population in Beijing is 48.06%, which is close to the individuals selected in this study, indicating that the population selected herein is representative. In addition, the calculation of minimum sample size showed that the minimum sample size required for EOC patients and control groups in this study was 286 and 317, respectively, which were lower than the number of samples selected in the proposed study, which showed the objectivity of the obtained results.

Similarly, regarding the specific cause of the correlation between SNP at *ERBB2* rs1058808 and OC, we speculated that the rs1058808 site may be at the binding site of the microRNA targeting *ERBB2*, and allelic variation may change the interaction between *ERBB2* and microRNAs. At present, ERBB2 inhibitors have been used in clinical treatment, and they exert inhibitory effect on the proliferation and migration of ERBB2-positive OC cells. This finding implies that the association between genetic polymorphism and the risk of EOC may be reflected in the expressional level of ERBB2, which will be verified in in vitro cell model.

The occurrence of OC closely correlated with genes and environment, and the combined effects of genes and genes, genes and environment are related to the risk of ovarian cancer [28, 29]. The stratification of the clinical data of the subjects

significantly affected the correlation between the SNPs at *PIK3CA* gene rs9838117 and *ERBB2* rs1058808 loci and OC. Further MDR analysis displayed that the interaction model between age, BMI, number live-born, smoking, drinking, OC family history, *PIK3CA* rs9838117, and *ERBB2* rs1058808 locus is the best model for the risk of OC prediction. This analysis further proved that the interaction of *PIK3CA* rs9838117 and *ERBB2* rs1058808 sites with environmental factors has a significant correlation with the occurrence of EOC.

However, the present study still had the following deficiencies. In vitro analysis was required to further investigate the specific molecular mechanism of the correlation between the risk of OC and the SNPs at *PIK3CA* rs9838117 locus and the *ERBB2* rs1058808 locus. Additionally, the effect of SNPs at *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 locus on gene expression remained to be elucidated in future. Moreover, this study lacks the functional investigation of the SNPs at *PIK3CA* rs9838117 locus and *ERBB2* rs1058808 locus, which needs to be explored in future. Finally, in the present study, we did not include patient survival data, nor did we collect specific causes of death of EOC patients. In future studies, we need to supplement survival analysis data based on more detailed clinical characteristic.

Conclusion

In summary, SNPs of *PIK3CA* gene rs9838117 locus and *ERBB2* gene rs1058808 locus were strongly associated with the risk of EOC. The underlying mechanism was still needed to be further explored.

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Declarations

Ethics approval and consent to participate This study was approved by the ethics committee of Longyan People Hospital, and all the subjects signed an informed consent form.

Conflict of interest The authors declare no competing interests.

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