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Original Article

Impact of gene polymorphisms located near ADAM17 and additional SNP-SNP interaction on ovarian cancer risk in Chinese women

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Abstract: *Objectives*: The aim of this study was to investigate the impact of single nucleotide polymorphisms (SNPs) located near A disintegrin and metalloproteinase 17 (ADAM17) and additional SNP-SNP interaction on ovarian cancer (OC) risk. *Methods:* Four SNPs were detected by Taqman fluorescence probe, and ABI Prism 7000 software and allelic discrimination procedure was used for genotyping. Generalized multifactor dimensionality reduction (GMDR) model and logistic regression model was used to examine the SNP-SNP interaction on OC risk, odds ratio (OR) and 95% confident interval (95% CI) were calculated. *Results:* OC risk was higher in carriers of the rs11684747-G allele than those with AA genotype (AG + GG versus AA), adjusted OR (95% CI)=1.63 (1.29-2.19), and higher in carriers of the rs12692386-G allele than those with AA genotype (AG + GG versus AA), adjusted OR (95% CI)=1.72 (1.46 - 2.08). However, we did not find any significant association between rs1524668 and rs11689958 and OC risk before or after covariates adjustment. GMDR analysis indicated a significant two-locus model (p=0.0107) involving rs11684747 and rs12692386. Subjects with rs11684747-AG or GG and rs12692386-AG or GG genotype have the highest OC risk, compared to subjects with rs11684747-AA and rs12692386-AA genotype, OR (95% CI)=2.78 (1.79 - 3.98). *Conclusions:* rs11684747 and rs12692386 and additional combined effect of rs11684747-rs12692386 interaction were associated with increased OC risk.

Keywords: ADAM17, ovarian cancer, single nucleotide polymorphism, interaction

Introduction

Ovarian cancer (OC) is the third most common gynecological cancer but the most lethal gynecological malignancy worldwide [1, 2]. Generally, higher incidence was observed in developed counties such as Northern Europe (11.3/100,000) and Northern America (10.7/100,000), while China (3.2/100,000) has been found with the lower incidence [3]. But in recent years, the incidence of ovarian cancer in China showed an upward trend [4]. Previous epidemiologic studies have demonstrated several risk factors of EOC, such as nulliparity, obesity, early menarche and late menopause, as well as a strong familial aggregation [5, 6] with a wide inter-individual genetic variability in the susceptibility of OC. Previously published genome-wide association studies (GWASs) also reported several single nucleotide polymorphisms (SNPs) that confer low-penetrance susceptibility to EOC [7-9].

A disintegrin and metalloproteinase 17 (ADAM17) is a membrane-anchored metalloproteinase that controls the release of tumor necrosis factor α (TNF-α) and ligands of the epidermal growth factor receptor (EGFR) from cells [10]. ADAM17 is highly expressed in cancers of the breast, brain, lung, ovary, colon, and pancreas [11-14]. ADAMs family gene plays an important role in remodeling or processing of cell membrane proteins. Several of the substrates processed by ADAMs, especially ADAM17, have been implicated in the pathogenesis or progression of cancer [15, 16], however, no population based study focused on the association between genes located near ADAM17 polymorphism and OC was conducted previously, particularly in Chinese population. In

Table 1. Description and Probe sequence for 4 SNPs used for Taqman fluorescence probe analysis

SNP ID	Chromosome	Functional Consequence	Nucleotide substitution	Probe sequence
rs11684747	2:9557042	Upstream variant 2KB	A > G	5'-AACCGGACCTGGTCTGTACATCTGA [A/G] GTATAAAATATCTTTATTAAACATA-3'
rs11689958	2:9557277	Upstream variant 2KB	G > A	5'-TTGTAACTTTAGTAGATCGTAGATT [G/A] TATTATTTTGGTATCCCCAACAGCT-3'
rs1524668	2:9557243	Upstream variant 2KB	A > C	5'-CTTTTCTGAACATCCAGTCACCATA [A/C] TGTCCGGCTTGTAACTTTAGTAGAT-3'
rs12692386	2:9555777	Utr variant 5 prime	A > G	5'-TTCTACCGCCAGGCTCGACGCCCCC [A/G] GAAGTGCAGGTGGCGTTACCAAAGG-3'

addition, OC was determined by many types of genes and different SNPs, so it is necessary to investigate the impact of SNP-SNP interaction on OC risk. So the aim of current study was to investigate the impact of four SNPs of ADAM17 and additional SNP-SNP interaction on OC susceptibility in Chinese women.

Materials and methods

Subjects

Chinese OC patients were consecutively recruited from the No. 5 Affiliated Hospital of Southern Medical University between January 2008 and September 2014. All patients were diagnosed and graded according to the criteria of the International Federation of Gynaecology and Obstetrics (FIGO) [17]. The ovarian tissue samples (cancerous and non-cancerous) were fixed routinely in formaldehyde, embedded in paraffin, cut into thin slices and stained with hematoxyline/eosin for pathological examination. The normal controls were selected from community volunteers, with the selection criteria of no individual family history of cancer, as well as frequency-matched age (± 5 years) and residential areas to the EOC cases, in addition without any type of cancer, including OC. At last, a total of 822 females were included in this study, including 410 OC patients and 412 normal controls. The mean age of all subjects was 62.2 ± 14.5 years old. The selected subjects were similar to those who were not selected in terms of age, smoking status, alcohol consumption, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation. Data on general demographic information, lifestyle information and gynecological diseases for all participants were obtained using a questionnaire administered by trained staffs. Body weight, height and waist circumference (WC) was measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Cigarette smokers were those who self-reported smoking cigarettes at least once a day for 1 year or more. Alcohol consumption was expressed as the sum of milliliters of alcohol per week from wine, beer, and spirits. Blood samples were collected in the morning after at least 8 hours of fasting. Written informed consent was obtained from all participants. This study was supported by Science and technology project of Guangdong Provincial Administration of traditional Chinese Medicine (20131180).

Genomic DNA extraction and genotyping

We selected SNP located near ADAM17 gene according to the following standard, including: 1) more studied SNPs in previous studies, such as rs12692386 and rs1524668, which have been reported to be associated with others type of cancer [12-14]; and 2) the others SNP, which was not reported having associations with OA, but with others diseases, such as ischemic stroke [18], Alzheimer's disease [19] and sepsis [20], such as rs11684747 and rs11689958, in order to find new SNP associated with OC in Chinese population. At last, four SNPs were selected for genotyping in current case-control study: rs11684747, rs12692386, rs1524668 and rs11689958. Genomic DNA from participants was extracted from EDTA-treated whole blood, using the DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. A 25 μL reaction mixture including 1.25 μL SNP Genotyping Assays (20×), 12.5 μL Genotyping Master Mix (2×), 20 ng DNA, and the conditions

Table 2. General characteristics of study participants in case and control group

Variables	Cases group (n=410)	Control group (n=412)	*p*-values
Age (years)	61.7 ± 14.8	62.4 ± 14.2	0.489
Smoke N (%)	13 (3.2)	10 (2.4)	0.518
Alcohol consumption N (%)	11 (2.7)	10 (2.4)	0.816
WC (cm)	79.2 ± 14.5	81.8 ± 15.2	0.012
BMI (kg/m^2)	23.2 ± 6.8	24.4 ± 6.6	0.010
Tubal ligation	10 (2.44)	12 (2.91)	0.674
Excision of uterus	8 (1.95)	9 (2.18)	0.814
Use of hormone replacement therapy (HRT)	26 (6.3)	30 (7.3)	0.593
Number of pregnancies			0.299
1	16	20	
2-3	321	334	
More than 4	73	58	
Family history of OC	81 (19.8)	63 (15.3)	0.092

NOTE: Means ± standard deviation for age, WC, BMI. WC, waist circumference; BMI, body mass index.

were as follows: initial denaturation for 10 min at 95°C, denaturation for 15 s at 92°C, annealing and extension for 90 s at 60°C for 50 cycles. Four SNPs were detected by Taqman fluorescence probe, and Probe sequences of four SNPs were shown in **Table 1**. ABI Prism 7000 software and allelic discrimination procedure was used for genotyping of fore-mentioned four SNPs. Genotyping results were confirmed by randomly assaying 10% of the original specimens for replication to exclude genotyping errors. There were no discrepancies between genotypes determined in duplicate.

Statistical analysis

The mean and SD was calculated for normally distributed continuous variables, and *t* test was used for comparison between cases and normal controls. The percentage was calculated for categorical variable, X^2 test was used for comparison between cases and normal controls. Genotype and allele frequencies were obtained by direct count. Genotype distributions in OC patients and controls were evaluated by X^2 test using SPSS (version 19.0; SPSS Inc., Chicago, IL). Hardy-Weinberg equilibrium (HWE) was performed by using SNPStats (available online at http://bioinfo.iconcologia.net/SNPstats). Logistic regression model was used to examine the association between SNPs located near ADAM17 and OC risk, and the impact of SNP-SNP interaction on OC, odds ratio (OR) and 95% confident interval (95% CI) were calculated. Odds were adjusted for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation. To correct for multiple testing, we defined a Bonferroni threshold of $p=0.05/C_4^2=0.0083$.

Generalized multifactor dimensionality reduction (GMDR) [21] was used to analyze the gene-gene interaction, cross-validation consistency, the testing balanced accuracy, and the sign test, to assess each selected interaction were calculated. The cross-validation consistency score is a measure of the degree of consistency with which the selected interaction is identified as the best model among all possibilities considered. The testing balanced accuracy is a measure of the degree to which the interaction accurately predicts case-control status with scores between 0.50 (indicating that the model predicts no better than chance) and 1.00 (indicating perfect prediction). Finally, a sign test or a permutation test (providing empirical *p*-values) for prediction accuracy can be used to measure the significance of an identified model.

Results

A total of 822 participants were included in this study, including 410 OC patients and 412 normal controls. The mean age of all participants was 62.2 ± 14.5 years old. Characteristics for cases and controls were shown in **Table 2**. The distributions of smoking, alcohol consumption, and number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation and mean of age were not different between cases and controls. The mean of BMI and WC were lower in cases than that in controls.

All genotypes were distributed according to Hardy-Weinberg equilibrium (all *p* values were

Table 3. Association between four SNPs located near ADAM17 and OC risk

SNPs	Genotypes and Alleles	Frequencies N (%)		*OR (95% CI)*[a]	*P*-values[b]	*HWE test for controls*
		Case (n=410)	Control (n=412)			
rs11684747						
	Additive					
	AA	202 (49.3)	260 (63.1)	1.00	0.000096	0.127
	AG	161 (39.3)	128 (31.1)	1.52 (1.26-1.98)[c]		
	GG	47 (11.5)	24 (5.8)	2.01 (1.42-2.85)[c]		
	Dominant					
	AA	202 (49.3)	260 (63.1)	1.00		
	AG + GG	208 (50.7)	152 (36.9)	1.63 (1.29-2.19)[c]	0.000064	
	A	565 (68.9)	648 (78.6)		0.000007	
	G	255 (31.1)	176 (21.4)			
rs11689958						
	Additive					
	GG	216 (52.7)	236 (57.3)	1.00	0.269	0.190
	GA	154 (37.6)	145 (35.2)	1.18 (0.95-1.47)		
	AA	40 (9.7)	31 (7.5)	1.36 (0.91-1.72)		
	Dominant					
	GG	216 (52.7)	236(57.3)	1.00		
	GA + AA	194 (47.3)	176(42.7)	1.20 (0.94-1.49)	0.198	
	G	586 (71.5)	617 (74.9)		0.159	
	A	234 (28.5)	207 (25.1)			
rs12692386						
	Additive					
	AA	209 (51.0)	263 (63.8)	1.00	0.000448	0.420
	AG	164 (40.0)	129 (31.3)	1.42 (1.21-1.85)[c]		
	GG	37 (9.0)	20 (4.9)	2.27(1.63-3.14)[c]		
	Dominant					
	AA	209 (51.0)	263 (63.8)	1.00		
	AG + GG	201 (49.0)	149 (36.2)	1.72 (1.46-2.08)[c]	0.000193	
	A	582 (71.0)	655 (79.5)		0.000064	
	G	238 (29.0)	169 (20.5)			
rs1524668						
	Additive					
	AA	219 (53.4)	240 (58.2)	1.00	0.420	0.318
	AC	158 (38.5)	144 (35.0)	1.14 (0.93-1.47)		
	CC	33 (8.1)	28 (6.8)	1.26 (0.88-1.62)		
	Dominant					
	AA	219 (53.4)	240 (58.2)	1.00		
	AC + CC	191 (46.6)	172 (41.8)	1.18 (0.91-1.50)	0.287	
	A	596 (72.7)	624 (75.7)		0.183	
	C	224 (27.3)	200 (24.3)			

[a]Adjusted for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation; [b]the comparison of the genotype/allele between case and control group; *P*-values less than 0.05 were considered statistically significant; [c]p<0.0125 (Bonferroni correction threshold).

more than 0.05). There were significant differences in rs11684747 and rs12692386 alleles and genotypes distributions between cases and controls (**Table 3**). The frequency for the G

Table 4. Best combination on SNP-SNP interaction by using GMDR analysis

Locus no.	Best combination	Cross-validation consistency	Testing accuracy	*p-values*
SNP-SNP interaction[a]				
2	rs11684747 rs12692386	10/10	0.6217	0.0107
3	rs11684747 rs12692386 rs1524668	9/10	0.5590	0.0547
4	rs11684747 rs12692386 rs1524668 rs11689958	8/10	0.5577	0.1719
Gene-environment interaction[b]				
2	rs11684747 obesity	8/10	0.5399	0.1719
3	rs11684747 rs12692386 obesity	7/10	0.5590	0.0547
4	rs11684747 rs12692386 rs1524668 obesity	6/10	0.4958	0.3770
5	rs11684747 rs12692386 rs1524668 rs11689958 obesity	6/10	0.4958	0.4258

[a]Adjusted for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation. [b]Adjusted for age, smoke and alcohol consumption status, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation.

Table 5. Interaction analysis for rs11684747 and rs12692386 on OC risk by using logistic regression

rs11684747	rs12692386	OR (95% CI)[a]	*P*-values
AA	AA	1.00	-
AG or GG	AA	1.31 (1.12-1.67)[b]	0.001
AA	AG or GG	1.52 (1.23-1.92)[b]	0.00012
AG or GG	AG or GG	2.78 (1.79-3.98)[b]	0.00006

[a]Adjusted for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation; [b]p<0.0125 (Bonferroni correction threshold).

allele of rs11684747 was higher in cases (31.1% in OC patients and 21.4% in controls, *p*=0.000007). Logistic analysis showed that the OC risk was higher in carriers of the rs11684747-G allele than those with AA genotype (AG + GG versus AA), adjusted OR (95% CI)=1.63 (1.29 - 2.19). The frequency for the G allele of rs12692386 was higher in cases (29.0% in OC patients and 20.5% in controls, p=0.000064. Logistic analysis showed that the OC risk was higher in carriers of the rs12692386-G allele than those with AA genotype (AG + GG versus AA), adjusted OR (95% CI)=1.72 (1.46 - 2.08). However, we did not find any significant association between other two SNPs and OC risk before or after covariates adjustment for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation.

GMDR analysis was used to assess the impact of the ADAM17 SNP-SNP interaction on OC risk. **Table 4** summarizes the results obtained from GMDR analysis for two- to four-locus models. We found a significant two-locus model (p=0.0107) involving rs-11684747 and rs12692386. The cross-validation consistency of two-locus models is 10/10, and the testing accuracy is 62.17%. Because BMI was different between cases and controls, so we also included obesity (BMI more than 24 kg/m^2), but we did not find any significant gene-obesity combinations in the GMDR model. In the logistic regression analysis, we found that subjects with rs11684747-AG or GG and rs12692386-AG or GG genotype have the highest OC risk, compared to subjects with rs11684747-AA and rs12692386-AA genotype, OR (95% CI)=2.78 (1.79 - 3.98), after adjustment for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation (**Table 5**).

Discussion

The result of this study indicated that the OC risk was higher in carriers of the rs11684747-G allele than those with AA genotype (AG + GG versus AA). The OC risk was also higher in carriers of the rs12692386-G allele than those with AA genotype (AG + GG versus AA). However, we did not find any significant association between other two SNPs and OC risk before or after covariates adjustment for age, smoke and alcohol consumption status, WC, number of pregnancies, use of hormone replacement therapy, excision of uterus and tubal ligation.

The ADAMs was a family of multidomain proteins, which play important role in both proteolysis and cell adhesion [22, 23]. The best established role for ADAMs is the activation of the proforms of certain growth factors and cytokines as well as the shedding of the extracellular domains of growth factor receptors and adhesion proteins. Previously, several studies focused on the association between ADAM17 gene polymorphism and others diseases have been conducted previously [12-14]. However, till now, no study reported the association between ADAM17 polymorphism and OC, and to the best of our knowledge, this is the first study that has identified ADAM17 polymorphism to be associated with an increased OC risk. ADAM17 is up-regulated in tumor and could therefore conceivably contribute to tumorigenesis, particularly if aberrant activity amplifies shedding of EGFR ligands with known roles in cancer, such as TGF-α, HB-EGF, and amphiregulin [24]. An increased expression of individual ADAM family members in various types of cancer has been described even though in several cases the precise cellular expression pattern and the relevance for tumor progression is not clear. However, increased mRNA or protein expression of ADAM17 was shown in several different tumour tissues, including ovary [25]. Rosso et al. [26] conducted a study and indicated that the ADAM17/TACE molecule was expressed in EOC cell lines and ADAM17/TACE silencing by specific small interfering RNA-reduced ALCAM shedding, so ADAM17/TACE takes part in ALCAM-mediated adhesion, which may be relevant to EOC invasive potential and relevant step in EOC motility.

The pathogenesis of OC is diverse, and OC is associated with several genetic factors, and the synergistic effect among many related genetic factors, and was determined by many SNPs in ADAM17 gene, so it is necessary to investigate the impact of SNP-SNP interaction on OC risk. Current study investigates this interaction on OC susceptibility in Chinese women by using GMDR model. To our knowledge, this is the first study involved in SNP-SNP interaction in ADAM17 gene. We found a significant two-locus model (p=0.0107) involving rs11684747 and rs12692386, and subjects with rs11684747-AG or GG and rs12692386-AG or GG genotype have the highest OC risk, compared to subjects with rs11684747-AA and rs12692386-AA genotype. The underlying mechanism for impact of this SNP-SNP interaction on OC risk was not well known. Yamashita *et al*. [27] suggested that activation of TACE/ADAM17 via a PKC-induced c-Src-dependent manner mediates proteolytic activation of the EGF-like factors that are involved in the induction of granulosa cell differentiation, cumulus expansion, and meiotic maturation of porcine oocytes *in vitro*. ADAM17 (also known as TNF-α converting enzyme or TACE) is the major sheddase for TNF-α, amphiregulin, HB-EGF and epiregulin [28, 29]. Given the involvement of the EGFR in the development of tumors of epithelial origin and the importance of ADAM17 in its control, several studies have focused on this ADAM protein. For example, ADAM17 overexpression was found in many types cancer, including OC [20]. Overexpression of ADAM17 increases invasion and proliferation of MCF-7 (human breast adenocarcinoma cell line) cells, whereas down-regulation of ADAM17 expression decreases invasion and proliferation of MDA-MB-435 (a melanoma cell line) cells.

Several limitations of this study should be considered. Firstly, More SNPs located near ADAM17 should been included in the study, not only locate near in ADAM17, but also in other ADAM family, this association should be checked in different nationality, especially in ethnic minority of China, and gene-environment interaction should be conducted in the future studies. Secondly, although the number of study participants met the requirement for analysis, the present sample size was relatively small. Thirdly, we did not obtain the information on survival, so we could not analyze the influence of survival bias on the results in this study.

In conclusion, our results indicated that the OC risk was higher in carriers of the rs11684747-G allele than those with AA genotype (AG + GG versus AA), the OC risk was also higher in carriers of the rs12692386-G allele than those with AA genotype (AG + GG versus AA). We also found a significant two-locus model (p= 0.0107) involving rs11684747 and rs12692386, and subjects with rs11684747-AG or GG and rs12692386-AG or GG genotype have the highest OC risk, compared to subjects with

rs11684747-AA and rs12692386-AA genotype.

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Disclosure of conflict of interest

None.

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