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Original Article

Lysyl oxidase single-nucleotide polymorphism (SNP) (G473A) is negatively associated with ovarian cancer prognosis

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Abstract: Ovarian cancer is the deadliest of all gynecologic cancers. Lysyl oxidase (LOX) is an extracellular matrix enzyme that catalyzes the cross-linking of collagens or elastin in the extracellular compartment. A novel single-nucleotide polymorphism (SNP) in the LOX gene, G473A (rs1800449), has been reported as being a risk factor for different diseases. To evaluate the association of single-nucleotide polymorphism (SNP) in Lysyl oxidase (LOX) (G473A) with the increased ovarian cancer (OA) risk and the reduced survival of OA patients, TaqMan SNP genotype analysis was performed in 178 OA cases and 121 age-matched controls. Chi-square test and multivariate analysis were used to assess the association of SNP or genotype with clinicopathological characteristics. The survival analysis (overall survival (OS) and recurrence-free survival (RFS)) was performed with the Kaplan-Meier method. Results demonstrated that LOX (G473A) was significantly associated with OA risk (AA vs. GG vs. GA, P = 0.0062). And we observed a greater prevalence of "A" allele (P = 0.0025) in OA patients. It was significantly associated with the tumor differentiation degree (P = 0.0035) or with lymph node metastasis (P = 0.0187). The OS or RFS was significantly different between the two groups (P = 0.0281 for OS, P = 0.0392 for RFS). And the multivariate Cox proportional hazards analysis indicated LOX (AA) genotype was an independent factor for the prognosis of ovarian cancer (P = 0.0452, 1.671 (1.232-5.853)). This study indicates that the LOX variant 473 A>G is correlated with an increase in OA risk. AA genotype had a worse prognosis than GG and GA genotypes. LOXSNP (G473A) may serve as a prognosticator.

Keywords: Ovarian cancer, lysyl oxidase polymorphism (G473A), prognosis

Introduction

Ovarian cancer is one of the most common types of [1] and the most lethal type [2] of gynecological neoplasms. Epidemiological surveys have indicated that the etiologic factors for ovarian cancer include but not limit to genetic factors and environmental factors, such as inherited susceptibility, too early menarche, too late menopause, estrogen/hormone-replacement therapy and obesity [3, 4]. In addition, the standard therapy results in various outcomes, posing a therapeutic challenge for ovarian cancers [5]. The clinical outcomes of radical operation and adjuvant platinum-based chemotherapy for ovarian cancer patients were significantly associated with the genetic polymorphisms [6, 7]. Therefore, the genetic susceptibility plays an important role in the developing risk and the prognosis of ovarian cancers.

The ovarian cancer-associated genetic variants have been found in recent years. It has been demonstrates that such genetic variants may be involved in the process of ovarian carcinogenesis [8], as *RAD51C* [9, 10], *CASP8* [11], *LIN28B* [12], *ERCC4 (FANCQ)* [13], *PROGINS* [14]. Particularly, the genome-wide association studies (GWAS) have more efficiently found several common susceptibility alleles for ovarian cancers [15]. However, the identification of ovarian cancer-associated genes requires fur-

Table 1. Clinicopathological characteristics of ovarian cancer or control subjects

Characteristics	Ovarian cancer (N = 178) (%)	Control subjects (N = 121) (%)	*P* value
Age (years)			0.1270
≤50	58 (32.58)	46 (41.44)	
>50	120 (67.42)	65 (58.56)	
Tumor size (cm)			
<10	98 (55.06)		
≥10	80 (44.94)		
Tumor histology			
Serous	131 (73.60)		
Others	47 (26.40)		
Degree of Differentiation			
Low	125 (70.22)		
Middle and high	53 (29.78)		
FIGO stage			
I&II	59 (33.15)		
II&IV	119 (66.85)		
Lymph node metastasis			
Negative	117 (65.73)		
Positive	61 (34.27)		
Ca125 (U/ml)			
>65	128 (71.91)		
≤65	50 (28.09)		
LOX (rs1800449) (observed vs. expected)			
P value	0.256	0.682	

FIGO, International Federation of Gynecology and Obstetrics; Ca125, Cancer antigen 125.

ther investigation, because only a few genetic variants exhibited strong evidence of an association with ovarian cancer from the reported approximately 1100 genetic variants in more than 200 candidate genes and 20 intergenic regions [16].

Lysyl oxidase (LOX) is a family of extracellular copper-dependent enzymes that catalyzes formation of aldehydes from lysine residues in collagen and elastin precursors [17], including LOX and four LOX-like proteins (LOXL1-4) [18]. LOX is cleaved extracellularly by bone morphogenetic protein-1 (BMP-1) into the mature LOX protein and an 18-kDa propeptide (LOX-PP) [19], which promotes metastasis of the existing tumor, causing it to become malignant and cancerous [20, 21]. Moreover, the LOX SNP (G473A) polymorphism has recently reported to be closely associated with susceptibility to coronary artery diseases [22], to oral submucous fibrosis [23], and even to cancers, such as gastric cancer [24], to non-small cell lung cancer [25]. However, it is not yet known about the prognostic role of LOX SNP (G473A) for ovarian cancers.

In the present study, we investigated the polymorphisms in the promoter region of LOX gene and tested the LOX SNP (G473A), and associated the LOX SNP (G473A) polymorphism with the prognosis of ovarian cancers. Our results suggest that LOX (G473A) might play a significant role in human EOC development and progression.

Materials and methods

Patients and samples

This study included 178 patients with epithelial ovarian cancer (mean age of 54.6 ± 10.4 years, 28-69 Years old) in Department of Obstetrics and Gynecology, the Affiliated Yantai Yuhuangding Hospital of Medical College, Qingdao University (Shandong, China), who were registered between April 2009 and October 2011. Clinicopathological characteristics, including age at diagnosis, tumor size, tumor histology, differentiation degree, FIGO stage, lymph node metastasis or Ca125 level were presented in **Table 1**. In addition, 121 matched healthy women (mean age of 56.3 ± 11.7 years, 29-71 Years old) were recruited as control subjects, who are undergoing physical examination in our hospital. Consent written form was obtained from each participant in the present study. And the present study was permitted by the Ethical Committee of the Affiliated Yantai Yuhuangding Hospital of Medical College, Qingdao University (Shandong, China). Peripheral blood samples (Non-anticoagulant, 2 ml) were obtained from all participants and were stored

Table 2. The LOX (G473A) genotype and allele distribution in ovarian cancer or control subjects

Groups	Ovarian cancer (N = 178) (%)	Control subjects (N = 121) (%)	*P* value	OR 95% CI
Genotype 1				
GG	112 (63.00)	88 (73.00)		Ref. 1.000
GA	43 (24.00)	30 (24.50)	0.6487	0.694 (0.296-2.513)
AA	23 (13.00)	3 (2.50)	0.0062	2.636 (1.243-4.531)
Genotype 2				
GG + GA	155 (87.00)	118 (97.50)		Ref. 1.000
AA	23 (13.00)	3 (2.50)	0.0016	3.241 (1.527-6.476)
Genotype 3				
GG	112 (63.00)	88 (73.00)		Ref. 1.000
GA + AA	66 (37.00)	33 (27.00)	0.0710	0.874 (0.562-2.860)
Allele distribution				
G	267 (75.00)	206 (85.25)		Ref. 1.000
A	89 (25.00)	36 (14.75)	0.0025	1.894 (1.413-4.832)

Table 3. Association of LOX (G473A) with the clinicopathological characteristics

Characteristics	GG + GA (%)	AA (%)	*P* value	OR 95% CI
Age (years)			0.5662	
≤50	50 (31.85)	8 (38.10)		Ref. 1.000
>50	107 (68.15)	13 (61.90)		0.795 (0.343-2.473)
Tumor size (cm)			0.4657	
<10	88 (56.05)	10 (47.62)		Ref. 1.000
≥10	69 (43.95)	11 (52.38)		0.488 (0.138-1.834)
Tumor histology			0.1957	
Serous	118 (75.16)	13 (61.90)		Ref. 1.000
Others	39 (24.84)	8 (38.10)		0.411 (0.163-1.730)
Degree of Differentiation			0.0035	
Low	116 (73.89)	9 (42.86)		Ref. 1.000
Middle and high	41 (26.11)	12 (57.14)		3.728 (1.422-8.605)
FIGO stage			0.6080	
I&II	51 (32.48)	8 (38.10)		Ref. 1.000
II&IV	106 (67.52)	13 (61.90)		0.597 (0.132-2.643)
Lymph node metastasis			0.0187	
Negative	108 (68.79)	9 (42.86)		Ref. 1.000
Positive	49 (31.21)	12 (57.14)		2.654 (1.257-7.786)
Ca125 (U/ml)			0.5692	
>65	114 (72.61)	14 (66.67)		Ref. 1.000
≤65	43 (27.39)	7 (33.33)		0.569 (0.115-2.487)

FIGO, International Federation of Gynecology and Obstetrics.

at -80°C before use. DNA samples were extracted with PureLink® Genomic DNA (Thermo Fisher Scientific, Waltham, MA, USA) under the guidance of the kit's protocol and were stored at -80°C before use. The DNA concentration and purity were determined using a Nanodrop ND-2000 spectrophotometer (NanoDrop Technologies, Rockland, DE, USA).

Genotyping analysis of LOX SNP (G473A)

Genotyping of the LOX SNP (G473A) was performed using PCR and sequencing. The primers were designed according to the reference SNP number rs1800449 and the NM_002317.6 sequence with Primer Premier 5.0 software (PREMIER Biosoft International, Palo Alto, California, USA). The primer sequences were as following: Forward primer 5'-GGCGCCGCCGTCCCTGGTG-3' and Reverse primer 5'-CGTATCCGGGCCGGTACCTGC-3'. The PCR product size was 394 bp. PCR amplification was performed in a final volume of 50 μL, containing 2 μL of genomic DNA (50 ng/μl), 6 μL of 2.5 mM dNTPs mix, 5 μL of PFU buffer, 2 μL of each primer and 1 μL of high fidelity PFU Polymerase (Promega, Madison, WI, USA). The PCR amplification was performed under the conditions: 94°C for 5 min, followed by 39 cycles of 94°C for 30 sec, 61°C for 30 sec, and 72°C for 40 sec, and a final extension step of 72°C for 10 min. All sequencing was performed by Sangon Biotech Co., Ltd. (Shanghai, China) and was analyzed using Chromas 2.4.1 (Technelysium Pty,

Table 4. Multivariate Cox proportional hazards analysis of predicting factors for ovarian cancer patients

Characteristics	Hazard ratio	95% CI	*P* value
Degree of Differentiation			0.0018
Low vs. Middle and high	2.836	1.386-6.526	
Lymph node metastasis			0.0247
Negative vs. Positive	2.371	1.225-6.468	
Genotype			0.0452
GG + GA (%) vs. AA (%)	1.671	1.232-5.853	

Tewantin, Queensland, Australia) and Lasergene 7.1 (MegAlign) software (GATC Biotech, Konstanz, Germany).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.0 software (GraphPad Software, La Jolla, CA, USA). Chi-square test was used to assess the association between LOX SNP (G473A) and the clinicopathological characteristics of epithelial ovarian cancers. Hardy-Weinberg equilibrium (HWE) test was performed by comparing observed and expected genotype frequencies using Chi-square test. And the Chi-square test was also utilized to analyze the frequencies of the genotypes and alleles of LOX SNP (G473A) between two groups. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression. The survival analysis (overall survival and recurrence-free survival) was performed with the Kaplan-Meier method for each of the different genotypes. And the multivariate Cox proportional hazards analysis was performed to evaluate whether the LOX (AA) was an independent hazard factor. P<0.05 was considered as statistically significant.

Results

Clinical and pathological characteristics of the study subjects

A total of 178 epithelial ovarian cancer patients and 121 normal subjects were recruited for the present study. Clinical and pathological characteristics of these subjects were presented in **Table 1**. Cases and controls did not reveal any statistical significance with regard to age (P = 0.1270). The mean age was 54.6 (median 54.6, SD 10.4; range 28-69) years for epithelial ovarian cancer patients and was 56.3 (median 56.3, SD 11.7; range 29-71) years for control subjects. For most epithelial ovarian cancer patients, the tumor was diagnosed in FIGO stage III-IV (n = 119, 66.85%). And 125 cases (70.22%) poorly differentiated, whereas the other 53 cases (29.78%) were differentiated to a middle or high degree.

Increased LOX variant 473 (A>G) in ovarian cancer patients

The genotype and allele frequencies of the LOX (G473A) SNP were analyzed for all 178 epithelial ovarian cancer patients and 121 control subjects. Cases were distributed according to the Hardy-Weinberg equilibrium (HWE>0.05, P = 0.256 for Ovarian cancer group, P = 0.682 for Control group, **Table 1**). As summarized in **Table 2**, the genotype distributions of LOX SNP (G473A) was statistically different between the two groups. The 473 AA genotype posed a significantly increased frequency in ovarian cancer patients than in controls (AA vs. GG vs. GA, P = 0.0062, OR = 2.636, 95% CI [1.243-4.531]) in the log-additive genetic model. And the recessive genetic model also indicated a significant difference between the two groups (AA vs. GG + GA, P = 0.0016, OR = 3.241, 95% CI [1.527-6.476]; GG vs. GA + AA, P = 0.0710, OR = 0.874, 95% CI [0.562-2.860]). And we observed a greater prevalence of "A" allele (P = 0.0025, OR = 1.894, 95% CI [1.413-4.832]) in ovarian cancer patients compared to the controls. Thus, the present study indicates that the LOX variant 473 A>G is correlated with an increase in ovarian cancer risk.

Positive association of the LOX (AA) genotype with the cancer differentiation and lymph node metastasis of ovarian cancer patients

To assess the promotion of the LOX SNP (G473A) to the ovarian cancer progression, we analyzed the association of LOX SNP (G473A) with the clinicopathological variables of ovarian cancer patients, such as age at diagnosis, tumor size, tumor histology, differentiation degree, FIGO stage, lymph node metastasis or Ca125 level. As was summarized in **Table 3**, there was no significant association between the LOX SNP (G473A) (GG + GA vs. AA) and age (P = 0.5662), tumor size (P = 0.4657), tumor histology (P = 0.1957), FIGO stage (P = 0.6080), or Ca125 level (P = 0.5692). However, it was

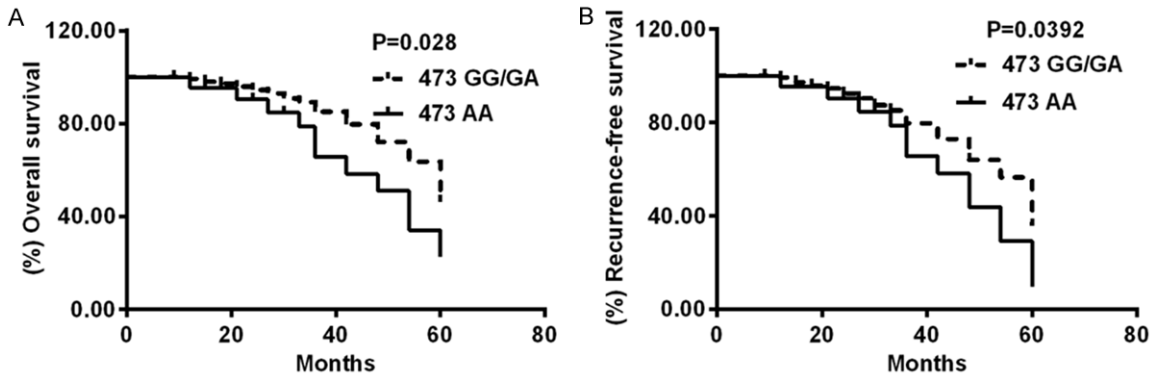

Figure 1. Kaplan-Meier analysis using log rank test regarding LOX (G473A) for the overall survival and recurrence-free survival of patients with ovarian cancer.

significantly associated with the tumor differentiation degree (P = 0.0035, or 0.0057, adjusted by multivariate analysis) or with lymph node metastasis (P = 0.0187, or 0.0233, adjusted by multivariate analysis).

Negative association of LOX SNP (G473A) with the survival of ovarian cancer patients

We analyzed the overall survival and recurrence-free survival of epithelial ovarian cancer patients using Kaplan-Meier method (**Figure 1**). The follow-up investigation was performed for at last 60 months for all 187 patients, in which, 171 cases were included and the other 16 cases were lost to follow-up. Results demonstrated that the mean survival time was 54 months for the patients with AA genotype, whereas was 60 months for the patients with LOX GG or GA genotype. And the overall survival rate was 46.32% for the GG/GA patients, whereas was 22.68% for the LOX AA patients within the 60 months' follow-up period. The overall survival was significantly different between the two groups (P = 0.0281, HR = 2.810, 95% CI 1.159-6.814). And the recurrence-free survival was markedly lower for the LOX AA patients (P = 0.0392, HR = 2.420, 95% CI 1.193-5.357). Thus, epithelial ovarian cancer patients with AA genotype had a worse prognosis compared to those cases with GG and GA genotypes.

Discussion

LOX protein is known to regulate collagen degradation during the ovulatory process; deregulated LOX has been observed in the ovaries of rats with polycystic ovary syndrome [26]. LOX plays a crucial role in follicular development [27]. The LOX signaling has also been reported to promote the ovarian cancer progression. HIF-1α/LOX/E-cadherin pathway was indicated to mediate the reactive oxygen species-promoted ovarian cancer progression [28]. LOX SNP (G473A) has been recognized to associate with various types of tumors [20, 21, 24, 25]. Recently, we found that the LOX SNP (G473A) was also associated with an upregulated risk of ovarian cancers [29, 30]. However, it is not yet known about the association of the LOX SNP (G473A) with the progression of ovarian cancers and about the prognostic role of LOX SNP (G473A) for ovarian cancers.

In the current study, we tested the LOX (G473A) SNP in the promoter region of LOX in epithelial ovarian cancer patients. And our results revealed that the LOX SNP (G473A) was associated with increased risk of epithelial ovarian cancer and promoted the ovarian cancer progression, in an association with a lower tumor differentiation degree and with the lymph node metastasis. The tumor differentiation was one of key determinants for the tumor prognosis. Multiple differentiation-associated factors are prognostic to ovarian cancers. The overexpression of cyclooxygenase (COX)-2 [31] or tumor necrosis factor receptor-associated protein 1 (TRAP1) [32] was related to the differentiation and poor prognosis of ovarian cancers [31]. And some SNPs, such as p73 rs6695978 G>A [33], A61G polymorphism in the EGF gene [34] were also significantly associated with the differentiation and prognosis of ovarian cancers. Our results demonstrated that the LOX SNP

(G473A) correlated with the low tumor differentiation of ovarian cancers.

The metastasis is one of key risk factors for poor prognosis of ovarian cancers. The overexpression of ubiquitin-specific protease 7 correlates with lymph node metastasis and is a prognostic factor in epithelial ovarian cancer [35]. The proteases cathepsin D and cathepsin L are potential regulators to the metastasis of epithelial ovarian cancer. Particularly, the lymph node metastasis, which were promoted by the elevated MAC30 expression [36], by ubiquitin-specific protease 7 overexpression [35] predict and unfavorable prognosis in patients with epithelial ovarian cancer. The present study showed that LOX SNP (G473A) was significantly associated with lymph node metastasis. We speculated that the association of LOX SNP (G473A) with the tumor differentiation and lymph node metastasis might contribute the prognostic role of it in epithelial ovarian cancer.

Conclusion

In summary, this case-control study provided evidence that LOX SNP (G473A) was associated with increased susceptibility to epithelial ovarian cancer and predicts poor prognosis of this disease. Therefore, the LOX SNP (G473A) may be considered as an key biomarker for the cancer. It implies that LOX inhibitors might have potential as an adjunct to lung cancer therapy.

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Informed consent was obtained from all individual participants included in the study.

Disclosure of conflict of interest

None.

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