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Association of interleukin-23 receptor gene polymorphisms with risk of ovarian cancer

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Abstract Among gynecological malignancies, ovarian cancer is the leading cause of death. The overall 5-year survival rate remains poor, and the pathogenesis is unknown. The interleukin-23 receptor (IL23R) is known to be critically involved in the carcinogenesis of different malignant tumors. To assess the role of *IL23R* in ovarian cancer, we conducted a study to investigate the polymorphisms of the *IL23R* gene in 96 Han Chinese women with histologically proven ovarian cancer. Polymerase chain reaction–restriction fragment length polymorphism was used for genotyping. In all three single nucleotide polymorphisms of *IL23R* studied, the distribution of genotype and allele frequencies of rs10889677 differed significantly between patients and controls. The frequency of allele C of rs10889677 was significantly increased in cases compared with controls (0.281 vs. 0.183, odds ratio OR = 1.752, 95% confidence interval CI = 1.107–2.772). Furthermore, when stratified by tumor stage, we found that the allele frequencies of rs11465817 differed significantly between FIGO stage I + II and III + IV. The higher frequency of allele A was significantly associated with advanced ovarian cancer ($P = 0.027$, OR = 2.087, 95% CI = 1.083–4.023). These findings indicate that *IL23R* polymorphisms may play an important role in the susceptibility and prognosis of ovarian cancer in the Chinese population.

1. Introduction

Ovarian cancer continues to be the leading cause of death among gynecological tumors despite improvements in surgery and chemotherapy. The 5-year survival rate remains ~30% for advanced-stage disease. Nearly 70% of the ovarian cancer patients present with advanced stages at the time of diagnosis [1].

Early detection requires a reliable screening test, one that is easy to perform and that has high sensitivity, high specificity, and patient acceptance. The three screening techniques currently available at this time do not actually diagnose ovarian cancer but only suggest its presence; these include pelvic examination, cancer antigen 125 (CA-125) level, and transvaginal ultrasound [2]. Thus, new predictive and prognostic factors for ovarian cancer are needed to improve clinical management.

Ovarian cancer is a polygenic disease, and genetic factors must play an important role in the induction of this malignancy. Germline mutations in two important genes, *BRCA1* and *BRCA2*, are associated with an increased risk for breast cancer and ovarian cancer [3,4]. The tumor protein p53 gene (*TP53*) and DNA mismatch repair genes have also been reported to play an important role in the development of human ovarian cancer [5–7].

Interleukin-23 (IL23), one of several newly reported cytokines, comprises the interleukin-12 (IL12) p40 subunit and a novel p19 subunit [8]. IL23R is a novel receptor subunit binding to IL23 along with interleukin-12 receptor β1 (IL12Rβ1) [9]. A member of the erythropoietin receptor superfamily, IL23R is encoded by the *IL23R* gene, which maps within 151 kb of the *IL12RB2* gene on chromosome 1 (1p31.2~32.1), of which the extracellular domain

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contains a signal sequence, an N-terminal immunoglobulin-like (Ig-like) domain, and two cytokine receptor domains.

Polymorphisms of the *IL23R* gene have been reported to be associated with susceptibility to inflammatory diseases and autoimmune diseases, such as psoriasis [10], inflammatory bowel disease [11], Graves ophthalmopathy [12], osteonecrosis of femoral head [13] and multiple sclerosis [14]. Though to date there has been little information about the association between *IL23* or *IL23R* polymorphism and malignancies, the role of IL23 in tumor-promoting inflammation has been demonstrated in mice lacking IL23 p19 [15].

Based on these data, we analyzed the influence of *IL23R* polymorphisms on the prevalence of ovarian cancer in a Han Chinese population and its correlation with established clinical prognostic factors.

2. Materials and Methods

2.1. Patient and control populations

A total of 110 patients with histologically confirmed ovarian cancer were allocated to this trial. They were treated between 2004 and 2008 in the West China Second University Hospital, Sichuan University. Excluded were 10 patients with borderline ovarian tumors, based on their different tumor entities [16]; also excluded were patients with two or more different malignancies, because of possible cross influence. The control subjects were healthy women visiting the medical examination center for regular gynecological examination. The samples were collected consecutively between 2004 and 2008. Overall, 96 women with ovarian cancer and 115 women with no history of cancer were analyzed (Table 1). All the subjects gave written or oral informed consent.

Table 1
Descriptive characteristics of ovarian cancer cases

Variable	Value
Sample size	$n = 96$
Mean age, yr, ±SD (range)	52.5 ± 11.1 (13–71)
Tumor status, no. (%)	
Primary	89 (92.7)
Recurrent	7 (7.3)
Histology, no. (%)	
Serous–papillary	51 (53.1)
Endometrioid	10 (10.4)
Mucinous	3 (3.1)
Clear cell	8 (8.3)
Mixed and other	24 (25)
FIGO stage, no. (%)	
I–II	25 (26)
III–IV	71 (74)
Tumor grade, no. (%)	
G1	2 (2.5)
G2	11 (13.9)
G3	66 (83.6)

For the age-matched control group ($n = 115$), mean age ± SD = 50.2 ± 9.8 years (range, 22–65 years).

2.2. Genetic Studies

One milliliter of blood was drawn from a peripheral vein, and DNA was extracted using a whole-blood DNA isolation kit (Bioteke, Beijing, China). DNA was stored at −20°C until analyzed. A total of three polymorphic sites regarding IL23R were selected in terms of their location, allele frequencies and relevance to diseases, based on public databases (dbSNP; http://www.ncbi.nlm.nih.gov/SNP/and http://www.hapmap.org/). All three SNPs are tag SNPs that represent the common allelic variation. Significant association has been reported with other diseases, including inflammatory bowel disease [11], Graves ophthalmopathy [12], and dilated cardiomyopathy [17]. A genomic DNA fragment was amplified by polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) methods to determine *IL23R* genotypes.

The 25-μL PCR reaction system contained 75 mmol/L Tris HCl (pH 9), 1.5 mmol/L $MgCl_2$, 150 mmol/L KCl, 2 mmol/L $(NH_4)SO_4$, 200 pmol dNTP, 10 pmol of each primer, and 1.5 U of *Taq* DNA polymerase and 50 ng DNA samples. The genome was amplified using a Mastercycler gradient thermocycler (Eppendorf, Hamburg, Germany). The PCR products (rs7517847 133 bp, rs11465817 132 bp, and rs10889677 152 bp) were visualized in a 6% polyacrylamide gel electrophoresis stained by the rapid silver staining method to detect the quality and the quantity of the amplified products. The PCR products were digested with corresponding endonucleases overnight and were analyzed in 6% polyacrylamide gels with silver staining. Primer sequences and reaction conditions are given in Table 2.

2.3. Statistical analysis

Hardy–Weinberg equilibrium was tested among cases and controls for each sequence variant using Pearson's chi-square test. Age between cases and controls was compared with Student's *t*-test. Genotype and allele frequency differences between cases and controls were evaluated using chi-square analysis, with odds ratios (OR) and 95% confidence intervals (95% CI). $P < 0.05$ was considered statistically significant. The SPSS for Windows version 11.0 software package (SPSS, Chicago, IL) was used for statistical analyses.

3. Results

The characteristics of the women with ovarian cancer are summarized in Table 1. There was no significant difference in age between cases and controls ($P = 0.08$).

Genotyping data were in Hardy–Weinberg equilibrium for the three SNP sites tested in this Han Chinese population. Comparing genotype and allele frequencies between cases and controls (Table 3), there was a significant

Table 2
Primer sequences and reaction conditions for genotyping three SNPs of the interleukin-23 receptor gene (*IL23R*)

db SNP ID[a]	Position	Primer sequence	T_a, °C	Endonuclease	Product size, bp
rs7517847	intron 6	5′-CCTTTCACCTATTCCCAAGGCC-3′	66.6	*Stu*I	G: 133
		5′-TTATGGGCTGTCTCCTAGGCCC-3′			T: 113 + 20
rs11465817	intron 9	5′-CATTAAGTAAGAGATGAAAACTTTGG-3′	56	*Hae*III	A: 132
		5′-CTGTAGTGAGCTGTGACCATG-3′			C: 106 + 26
rs10889677	3′UTR	5′-CTGTGCTCCTACCATCACCA-3′	62.6	*Mnl*I	A: 152
		5′-TGCTGTTTTTGTGCCTGTATG-3′			C: 82 + 70

Abbreviations: SNP, single-nucleotide polymorphism; T_a, annealing temperature.
[a] http://www.ncbi.nlm.nih.gov/SNP/.

difference for the genotype frequencies of rs10889677 between patients and controls, and the allele C gene frequency of rs10889677 was significantly increased in cases, compared with controls (0.281 vs. 0.183, OR = 1.752, 95% CI = 1.107−2.772).

In refinement of the statistical analysis, the following subgroups were summarized: FIGO stages I + II and stages III + IV (International Federation of Gynecology and Obstetrics); histological grade G1 + G2 and grade G3; histological type, serous and others; tumor status, recurrent and primary; age, <50 and ⩾50 years old. The allele frequencies of rs11465817 for stages I + II versus III + IV were significantly different ($P = 0.027$, OR = 2.087, 95% CI = 1.083−4.023). No statistically significant differences were observed in the other subgroups for any of the three SNPs (Tables 4−6).

4. Discussion

Recent findings in the field of tumor immunology have extended understanding of immune system−tumor cell interactions. The cancer immunoediting hypothesis not only depicts a role for the immune system to eliminate immunogenic tumor cells actively, but also emphasizes the importance of immunity in promoting the outgrowth of less immunogenic tumor cell variants. A handful of articles have reviewed the three phases of cancer immunoediting: elimination, equilibrium, and escape [18−20]. Interactions between the immune system and tumor cells could lead to a variety of outcomes. The cancer immunoediting hypothesis means that, although one outcome is complete elimination of a developing tumor, another is the generation of a group of tumor cells that display either reduced immunogenicity [21] or an increased capacity to inhibit protective antitumor immune responses [22].

Interleukin-23, which is secreted predominantly by activated dendritic cells and phagocytic cells [23], is a factor in all three stages of immunoediting hypothesis. First, the dominance of IL23-mediated pathways in the early chemical carcinogenesis suggests a role in evading detection or elimination of $CD8^+$ T cells. Second, IL23 promotes the tissue restructuring and neoangiogenesis required by growing malignancies. Finally, the significant expression of IL23 during progression of carcinomas through clinical

Table 3
Association analysis of *IL23R* gene polymorphisms with risk of ovarian cancer

SNP[a] genotype or allele	Cases, no. (%)	Controls, no. (%)	χ^2	*P*-value	OR (95% CI)
rs7517847					
GG	17 (17.7)	18 (15.7)	0.160	0.923	
GT	52 (54.2)	64 (55.7)			
TT	27 (28.1)	33 (28.7)			
G	86 (44.8)	100 (43.5)	0.073	0.787	1.055 (0.717−1.551)
T	106 (55.2)	130 (56.5)			
rs11465817					
AA	40 (41.7)	55 (47.8)	1.554	0.460	
AC	41 (42.7)	48 (41.7)			
CC	15 (15.7)	12 (10.4)			
A	121 (63.0)	158 (68.7)	1.504	0.220	0.777 (0.518−1.164)
C	71 (37.0)	72 (31.3)			
rs10889677					
AA	48 (50.0)	79 (68.7)	7.920	0.019*	
AC	42 (43.8)	30 (26.1)			
CC	6 (6.3)	6 (5.2)			
A	138 (71.9)	188 (81.7)	5.794	0.016*	1.752 (1.107−2.772)
C	54 (28.1)	42 (18.3)			

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.
[a] http://www.ncbi.nlm.nih.gov/SNP/.
* $P < 0.05$.

Table 4
Genotypes of patients with ovarian cancer, by clinicopathological parameters, for the rs7517847 single-nucleotide polymorphism

	Genotype				Allele			
Characteristic	GG	GT	TT	*P*-value[a]	G	T	*P*-value[a]	OR (95% CI)
FIGO stage								
I–II	6	15	4	0.225	27	23	0.128	1.651 (0.863–3.159)
III–IV	11	37	23		59	83		
Tumor grade								
G1–G2	2	7	4	0.999	11	15	0.991	OR = 0.995 (0.425–2.331)
G3	10	36	20		56	76		
Histological type								
Serous	9	25	17	0.453	43	59	0.434	OR = 0.797 (0.450–1.479)
Other	8	27	10		43	47		
Tumor status								
Recurrent	0	3	4	0.151	3	11	0.068	OR = 0.312 (0.084–1.157)
Primary	17	49	23		83	95		
Age, yr								
< 50	7	28	8	0.115	42	44	0.310	OR = 1.345 (0.759–2.385)
⩾ 50	10	24	19		44	62		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Chi-square test.

severity suggests a role for IL23 in the final escape from equilibrium [24]. The IL23 receptor is expressed on the surface of T cells, natural killer cells, and natural killer T cells, with lower levels of IL23 receptor complexes also found on monocyte, macrophage, and dendritic cell populations [9]. The biological effect of IL23 can be traced only in terms of the two subunits of IL23 binding to the two subunits of IL23 receptor complex.

Nair et al. [25] reported that three SNPs that map near *IL12B* p40, *IL23A* p19, and *IL23R* are significantly associated with psoriasis. Dysregulated IL23 signaling could predispose certain individuals to inappropriate chronic immune responses that target epithelial cells and ultimately result in psoriasis. Although *IL12B* p40 and *IL23* p19 form a heterodimer that binds to *IL23R*, no significant evidence for epistasis of the three SNPs was detected.

The role of IL23 in tumorigenesis is clearly demonstrated by mice lacking IL23 p19. These mice are almost completely resistant to endogenous tumor formation when challenged in a chemical carcinogenesis protocol [15]. These authors also observed that expression of IL23 was significantly elevated in the vast majority of human carcinoma samples from various organ types which include ovary. Interleukin-17 (IL17) overexpression was concomitant with IL23 expression within the tumor tissue. IL17 is an important cytokine in tumorigenesis because it can promote angiogenesis in a variety of models and induces matrix metalloproteinases, two events that potentiate tumor

Table 5
Genotypes of patients with ovarian cancer, by clinicopathological parameters, for the rs11465817 single-nucleotide polymorphism

	Genotype				Allele			
rs11465817	AA	AC	CC	*P*-value[a]	A	C	*P*-value[a]	OR (95% CI)
FIGO stage								
I–II	6	13	6	0.094	25	25	0.027*	2.087 (1.083–4.023)
III–IV	34	28	9		96	46		
Tumor grade								
G1–G2	9	2	2	0.091	20	6	0.169	1.968 (0.740–5.234)
G3	26	31	9		83	49		
Histological type								
Serous	23	19	9	0.509	65	37	0.830	1.067 (0.593–1.918)
Other	17	22	6		56	34		
Tumor status								
Recurrent	4	3	0	0.446	11	3	0.211	2.267 (0.610–8.417)
Primary	36	38	15		110	68		
Age, yr								
< 50	20	17	6	0.683	57	29	0.400	1.290 (0.713–2.333)
⩾ 50	20	24	9		64	42		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Chi-square test.
* $P < 0.05$.

Table 6
Genotypes of patients with ovarian cancer, by clinicopathological parameters, for the rs10889677 single-nucleotide polymorphism

	Genotype				Allele			
rs10889677	AA	AC	CC	*P*-value[a]	A	C	*P*-value[a]	OR (95% CI)
FIGO stage								
I–II	12	10	3	0.382	34	16	0.479	0.776 (0.385–1.565)
III–IV	36	32	3		104	38		
Tumor grade								
G1–G2	5	6	2	0.146	16	10	0.134	0.512 (0.211–1.240)
G3	36	28	2		100	32		
Histological type								
Serous	25	24	2	0.539	74	28	0.825	1.074 (0.572–2.016)
Other	23	18	4		64	26		
Tumor status								
Recurrent	4	3	0	0.759	11	3	0.787	1.472 (0.394–5.497)
Primary	44	39	6		127	51		
Age, yr								
< 50	19	20	4	0.402	58	28	0.218	0.673 (0.358–1.266)
$\geqslant 50$	29	22	2		80	26		

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Chi-square test.

growth [26–28]. Cells with cytotoxic potential (including $CD8^+$ T cells, γδ T cells, and natural killer T cells) produce IL17 instead of interferon γ in response to IL23 [29–31]. An earlier study [32] found that endogenous IFNγ has a rate-limiting role in tumor immune surveillance.

The IL23–IL17 immune pathway has more and more been shown to have an important role in the pathogenesis of autoimmune disease and inflammatory disease [33]. This immunologic pathway also has a role in tumorigenesis [24]. Kato et al. [34] found that IL17 was expressed in ovarian cancer in 11 of the 17 patients tested, but was not expressed in normal ovary. The number of vascular endothelial cells per tumor was significantly higher in IL17-positive tumors ($173.4 \pm 55.1/mm^2$) than in IL17-negative tumors ($107.7 \pm 57.8/mm^2$) ($P = 0.0002$). This outcome suggests the participation of IL17, and perhaps also IL23, in ovarian carcinogenesis. Nonetheless, the association between the expression of IL17 in ovarian cancer with the *IL23R* gene polymorphism still needs further investigation.

Ovarian cancer is an immune-associated malignancy. With regard to other cytokines, Sehouli et al. [35] reported that patients who were heterozygous at allele 2 for IL1 receptor antagonist (IL-RA 1/2) had a significantly higher risk for ovarian cancer, with a calculated odds ratio of 2.7 (95% CI = 1.5–4.9), but no difference was found in the correlation between IL1 RA 1/2 polymorphism and the clinical parameters. Hefler et al. [36] found that the mutant −174C allele of IL6 influenced the biological phenotype of ovarian cancer, being associated with early stage and improved disease-free survival and overall survival. The −174C IL6 polymorphism was considered to be the best predictor of disease-free survival in the model. Another report on IL6 [37] also indicated that the −174 GG genotype has a strong, independent, and favorable impact on survival for women with ovarian and peritoneal carcinoma (longer overall survival, $P = 0.0007$). Furthermore, median serum levels of IL6, IL7, IL8, IL10, and monocyte chemotactic protein 1 were higher in ovarian cancer patients than in healthy control subjects ($P < 0.001$ to $P < 0.03$). Higher levels of these cytokines were associated with a shorter progression-free and overall survival in the univariate analysis [38].

In the present study, we observed that rs10889677 A/C polymorphism of the *IL23R* gene might be significantly associated with ovarian cancer. The cases with a higher frequency of allele C seem to be more subject to ovarian cancer. A genome-wide study found that several SNPs in *IL23R* gene, including rs10889677 and rs7517847, were associated with inflammatory bowel disease [11], and rs10889677 was also significantly associated with Graves ophthalmopathy [12] and with dilated cardiomyopathy [17]. All these findings suggest that SNP rs10889677 may contribute to the regulation of IL23 signaling pathway and thus eventually to the susceptibility to certain diseases. Furthermore, patients with a higher frequency of allele A of rs11465817 were significantly associated with advanced ovarian cancer. Nonetheless, the association between SNP at these three sites and the transcription and expression of *IL23R* needs to be investigated further.

To our knowledge, the present findings are novel in demonstrating an association between *IL23R* gene polymorphisms and ovarian cancer. Nevertheless, when interpreting the results of this study, we should keep in mind the possible limitations in statistical validity of studies with small sample size. Furthermore, we have not addressed the association between *IL23R* polymorphisms and 5-year survival rate, which is an important consideration in malignant tumor. Moreover, other variants that were not tested in this study may also be associated with ovarian cancer, so studies of other *IL23R* variants and their roles in determining the risk of ovarian cancer are warranted. Finally, because polymorphisms often vary between ethnic groups,

more studies are needed to clarify the association of *IL23R* polymorphisms with ovarian cancer in diverse ethnic populations.

Ovarian cancer is known to be a polygenic disease, and genetic factors must play an important role in the induction of this malignancy, whereas only some of the genes were identified in ovarian cancer patients. Therefore, the interactions among the present data of polymorphic genes that are associated with ovarian cancer, such as the progesterone receptor gene (*PGR*) [39] and the matrix metalloproteinase-1 gene (*MMP1*) promoter [40], should be studied further to understand ovarian cancer more clearly.

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