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Effect of *IL2RA* and *IL2RB* gene polymorphisms on lung cancer risk

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ABSTRACT

Background: Inflammation is crucial for lung cancer development. Variants of multiple genes in inflammation pathways may lead to susceptibility to lung cancer. In the present study, we aimed to assess the influence of polymorphisms in inflammation-related genes (*IL2RA* and *IL2RB*) on lung cancer risk.

Methods: A total of 507 patients with lung cancer and 503 healthy controls were genotyped for seven polymorphisms of *IL2RA* and *IL2RB* using the Agena MassARRAY platform. We evaluated the relationship of the genotypes with lung cancer susceptibility using odds ratio (OR), 95% confidence interval (95% CI) and chi square test.

Results: We found that *IL2RA* rs12722498 was significantly associated with a decreased risk of lung cancer in dominant ($p = 0.040$, OR = 0.71, 95% CI = 0.51–0.98), additive ($p = 0.016$, OR = 0.68, 95% CI = 0.50–0.93) and allele ($p = 0.019$, OR = 0.69, 95% CI = 0.51–0.94) models. After stratification analysis, the results showed that *IL2RA* rs12569923 (non-smokers), *IL2RA* rs791588 (≤60 years old, non-drinkers, BMI < 24 kg/m^2), *IL2RA* rs12722498 (≤60 years old, non-drinkers, BMI < 24 kg/m^2, female) and *IL2RB* rs2281089 (female, stage) significantly decreased the risk of lung cancer. Additionally, the haplotypes of rs12569923 and rs791588 in *IL2RA* had strong relationships with lung cancer in the subgroups of BMI < 24 kg/m^2, age ≤ 60 years old, non-smokers and non-drinkers.

Conclusion: Our results showed that the *IL2RA* and *IL2RB* polymorphisms were associated with lung cancer risk in the Chinese Han population, which suggests roles for *IL2RA* and *IL2RB* polymorphisms in lung cancer.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with approximately 1.59 million deaths occurring annually [1,2]. Environmental factors greatly affect the development of lung cancer, including smoking status and alcohol consumption. However, an increasing number of studies have shown that single nucleotide polymorphisms (SNPs) are related to lung cancer susceptibility, suggesting an important role for genetic factors in the development of lung cancer [3,4].

Inflammation is a physiologic response to cellular and tissue damage. It is now evident that inflammation alters the bronchial epithelium and the lung microenvironment, inducing pulmonary carcinogenesis [5]. Genetic variants of inflammation-related genes could regulate gene function and cause imbalances, influencing the inflammatory response and the susceptibility to disease [6,7]. Epidemiologic evidence also supports the function of inflammation in lung carcinogenesis [8]. Additionally, interleukin (IL), an inflammatory cytokine, plays a vital role in inflammatory responses by activating and regulating immune cells.

Interleukin 2 (IL-2) and the IL-2 receptor (IL-2R) play critical roles in controlling both immune system homeostasis and tolerance. IL-2 is a T cell growth factor, promoting proliferation and differentiation of activated T cells [9]. The IL-2R is composed of three subunits: IL-2Rα (CD25, encoded by *IL2RA*), IL-2Rβ (CD122, encoded by *IL2RB*) and γ_c (CD132, encoded by *IL2RG*) [10,11]. The human *IL2RA* is located on the short arm of chromosome 10 (10p15-p14). *IL2RA* is expressed constitutively on regulatory T cells, which have an important influence on lymphocyte development and the modulation of T cell effector function [12,13]. The high level of expression of *IL2RA* in activated circulating immune cells and Tregs has been exploited by IL-2 immunotherapies for tumors and autoimmune disease treatments. Moreover, the SNPs of *IL2RA* are associated with breast cancer and ovarian cancer [13,14], but their association with lung cancer is still unknown.

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The interleukin-2 receptor subunit beta (*IL2RB*) gene, a cytokine signaling gene, is involved in T cell-mediated immune responses. This protein is primarily expressed in the hematopoietic system. Genetic associations between different polymorphisms located within the *IL2RB* loci and several diseases, including lung cancer, have been reported, but there are no data on the relationship between *IL2RB* polymorphisms (rs2281089, rs3218264, rs9607418, and rs1573673) and lung cancer risk [7]. Therefore, we hypothesized that polymorphisms in inflammation-related genes (*IL2RA* and *IL2RB*) may be associated with lung cancer risk.

The aim of this study was to explore whether genetic variations of *IL2RA* and *IL2RB* influence the susceptibility to lung cancer development. We conducted this case-controlled study and focused on seven polymorphisms (rs12569923, rs791588, and rs12722498 of *IL2RA* and rs2281089, rs3218264, rs9607418, and rs1573673 of *IL2RB*) to assess the associations of genotypes with lung cancer risk.

2. Materials and methods

2.1. Study population

For this study, 507 lung cancer patients (352 males, 155 females) and 503 heathy controls (354 males, 149 females) were enrolled from Shaanxi Provincial Cancer Hospital. All cases were newly diagnosed and previously untreated primary lung cancer, as judged by clinical examinations. The exclusion criteria included people who suffered from previous malignancies, inflammation or other autoimmune diseases. The healthy controls were randomly recruited from cancer-free individuals living in the same region during the same time as the lung cancer patients. Prior to initiating this study, we collected written informed consents from all individuals in compliance with the World Medical Association ethics regulations. The study protocol was approved by the Ethics Committee of Shaanxi Provincial Cancer Hospital.

2.2. SNPs selection and genotyping

According to the data of the Han Chinese population in Beijing (CHB) from the 1000 Genomes Project and previously published studies, we selected three SNPs (rs12569923, rs791588, and rs12722498) of the *IL2RA* gene and four SNPs (rs2281089, rs3218264, rs9607418, and rs15673673) of the *IL2RB* gene, with minor allele frequency (MAF) > 5%. Genomic DNA from all participants was isolated from peripheral blood via a blood DNA kit (GoldMag Co. Ltd., Xi'an, China) and stored at −80 °C until use. The genotyping of *IL2RA* and *IL2RB* was conducted with an Agena MassARRAY system (Agena, San Diego, CA, USA). We used the Agena MassARRAY Assay Design 3.0 Software (San Diego, CA USA) to design PCR and extension primers for each SNP (Supplemental Table 1). In addition, we used the Agena Typer 4.0 Software (San Diego, CA, USA) for data management and analysis [15,16]. We used HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) to predict the potential functions of the candidate polymorphisms.

2.3. Statistical analysis

All statistical analyses were conducted with SPSS version 21.0 software (SPSS, Chicago, IL, USA). We used the chi square test and Student's *t*-test to determine the differences in demographic variables and distributions of genotype in the lung cancer patients and the healthy controls. The Hardy-Weinberg equilibrium (HWE) for each SNP in the control group was analyzed using Fisher's exact test. The associations of all SNPs with lung cancer risk were estimated by odds ratios (ORs) and 95% confidential intervals (95% CI) using logistic regression adjusted for sex and age. Subsequently, an allelic model and genetic models (codominant, dominant, recessive, and additive) were evaluated by the chi square test and PLINK software. We then used the Haploview software (version 4.2) and the PLINK software for linkage disequilibrium (LD) and haplotype analysis. All of the tests in our study were two-sided, and a $p < 0.05$ was regarded as statistical significance [16].

Table 1
Demographic and clinical characteristics of participants.

Variables	Cases	Controls	*p* value
Number	507	503	
Age (mean ± SD), years	60.79 ± 9.96	59.94 ± 9.58	0.164
> 60	272 (53.6%)	274 (54.5%)	
≤60	235 (46.4%)	229 (45.5%)	
Sex			0.784
Male	352(69.4%)	354 (70.4%)	
Female	155 (30.6%)	149 (29.6%)	
BMI (mean ± SD), kg/m^2	22.79 ± 3.47	24.43 ± 4.16	< 0.001
< 24	316 (62.3%)	138 (27.4%)	
≥24	177 (34.9%)	151 (30.0%)	
Absence	14 (2.8%)	214 (42.54%)	
Smoking status			0.182
Yes	250 (49.3%)	158 (31.4%)	
No	251 (49.5%)	129 (25.6%)	
Absence	6 (1.2%)	216 (42.9%)	
Drinking status			< 0.001
Yes	114 (22.5%)	110 (21.9%)	
No	356 (70.2%)	120 (23.9%)	
Absence	37 (7.3%)	273 (54.2%)	
Histology			
Adenocarcinoma	119 (23.5%)		
Squamous	188 (37.1%)		
Absence	200 (39.4%)		
LN metastasis			
Yes	213 (42.0%)		
No	83 (16.4%)		
Absence	211 (41.6%)		
Stage			
I, II	84 (16.6.3%)		
III, IV	260 (51.3%)		
Absence	163 (32.1%)		

BMI: body mass index, LN: lymph node.
$p < 0.05$ indicates statistical significance.

3. Results

3.1. Subject characteristics

A total of 507 patients with lung cancer and 503 healthy controls were recruited in our study. The demographic and clinical characteristics of all individuals are presented in Table 1. There were no significant differences in the distribution of age, sex, and smoking status between the lung cancer cases and the healthy controls ($p > 0.05$). However, body mass index (BMI) and drinking status were significantly different between the two groups ($p < 0.001$). Additionally, we collected the clinical characteristics of the patients, including histology, lymph node metastasis and stage of lung cancer.

3.2. Association of IL2RA and IL2RB polymorphisms with lung cancer susceptibility

The basic information and potential function predicted by the HaploReg database of the selected SNPs are listed in Table 2. Genotype frequency distributions in the controls of all selected SNPs were in HWE ($p > 0.05$). The allele and genotype distributions of *IL2RA* and *IL2RB* in lung cancer patients and healthy controls are presented in Table 3 and Supplemental Table 2. The polymorphism of *IL2RA* rs12722498 showed a significant association with lung cancer in dominant ($p = 0.040$, OR = 0.71, 95% CI = 0.51–0.98) and additive ($p = 0.016$, OR = 0.68, 95% CI = 0.50–0.93) models. Moreover, individuals carrying the G allele of rs12722498 had a lower risk of developing lung

Table 2
Primary information of *IL2RA* and *IL2RB* polymorphisms.

Gene	Polymorphism	Location: Position	Alleles	MAF-case	MAF-control	HWE *p*	HaploReg
IL2RA	rs12569923	Chr10: 6042690	C/G	0.188	0.194	0.568	Enhancer histone marks, motifs changed
IL2RA	rs791588	Chr10: 6047379	G/T	0.368	0.392	0.709	Enhancer histone marks, motifs changed
IL2RA	rs12722498	Chr10: 6053873	C/T	0.077	0.108	0.817	Promoter and enhancer histone marks, motifs changed, DNAse, proteins bound
IL2RB	rs2281089	Chr22: 37136132	A/G	0.23	0.243	0.904	Enhancer histone marks
IL2RB	rs3218264	Chr22: 37145958	C/T	0.472	0.484	0.372	Promoter and enhancer histone marks, motifs changed, DNAse, proteins bound, selected eQTL hits
IL2RB	rs9607418	Chr22: 37156854	A/C	0.111	0.105	0.636	Enhancer histone marks, motifs changed
IL2RB	rs1573673	Chr22: 37172630	C/T	0.343	0.358	0.439	Enhancer histone marks, motifs changed, GRASP QTL hits

SNP: single nucleotide polymorphism, MAF: minor allele frequency, HWE: Hardy—Weinberg equilibrium.

cancer ($p = 0.019$, OR = 0.69, 95% CI = 0.51–0.94).

3.3. Stratification analysis

To further investigate the relationships of the seven SNPs with lung cancer, we conducted a subgroup analysis stratified by age, sex, BMI, smoking and drinking statuses (Table 4). For participants ≤60 years old, rs791588 and rs12722498 of *IL2RA* significantly decreased the susceptibility to lung cancer in multiple models (rs791588: homozygote, $p = 0.033$, OR = 0.54; dominant, $p = 0.037$, OR = 0.67; additive, $p = 0.021$, OR = 0.73; allele, $p = 0.019$, OR = 0.73; rs12722498: heterozygote, $p = 0.028$, OR = 0.55; dominant, $p = 0.010$, OR = 0.50; additive, $p = 0.005$, OR = 0.49; allele, $p = 0.003$, OR = 0.48). When stratified by sex, we found that rs12722498 of *IL2RA* and rs2281089 of *IL2RB* had positively significant associations with a decreased lung cancer risk in females. For *IL2RA* rs12722498, the individuals with the G allele had a lower risk of lung cancer ($p = 0.007$, OR = 0.50, 95% CI = 0.30–0.93), but it had an association with susceptibility to lung cancer in heterozygote ($p = 0.026$, OR = 0.53, 95% CI = 0.30–0.93), dominant ($p = 0.012$, OR = 0.49, 95% CI = 0.28–0.86), and additive ($p = 0.007$, OR = 0.48, 95% CI = 0.28–0.82) models among females. In addition, the heterozygote rs22810898 variant (AG) was associated with a significantly increased risk of lung cancer ($p = 0.038$, OR = 0.60, 95% CI = 0.37–0.97) compared to subjects with homozygous wild-type genotype (AA) after adjusting for risk factors in the female subgroup. In the individuals who had a BMI < 24 kg/m^2 and were non-drinkers, the rs791588 and rs12722498 of *IL2RA* was also associated with a decreased risk of lung cancer in allelic and genomic models ($p < 0.05$). The *IL2RA* rs12569923 polymorphism was related to lung cancer in non-smoking patients in homozygote ($p = 0.021$, OR = 0.32, 95% CI = 0.12–0.84), recessive ($p = 0.025$, OR = 0.34, 95% CI = 0.13–0.87) and allele ($p = 0.048$, OR = 0.69, 95% CI = 0.48–1.00) models.

Moreover, we conducted stratification analysis by clinical parameters, including histology (adenocarcinoma and squamous), LN metastasis and stage of lung cancer. As shown in Table 5, we observed that *IL2RB* rs2281089 was significantly associated with lung cancer risk in the stage subgroup (heterozygote, $p = 0.011$, OR = 0.29, 95% CI = 0.11–0.75; recessive: $p = 0.008$, OR = 0.29, 95% CI = 0.11–0.72). Nevertheless, we did not find that the *IL2RA* and *IL2RB* polymorphisms had a strong relationship with lung cancer risk stratified by histology and LN metastasis.

3.4. Haplotype analysis

We further performed the LD and haplotype analyses on the polymorphisms of *IL2RA* and *IL2RB*. These analyses revealed one block in *IL2RA*, including rs12569923 and rs791588 (Fig. 1). The frequency distribution of haplotype in the two groups is presented in Supplemental Table 3. Then, we analyzed the associations between gene haplotypes and lung cancer risk in the subgroups. As shown in Table 6, haplotypes “CC” and “CT” increased lung cancer risk (respectively: $p = 0.014$, OR = 1.45, 95% CI = 1.08–1.96; $p = 0.014$, OR = 1.46, 95% CI = 1.08–1.97) in the BMI < 24 kg/m^2 subgroup. For the individuals 60 years of age or younger, the *IL2RA* haplotype was protective against lung cancer ($p = 0.021$, OR = 0.73, 95% CI = 0.56–0.95). In contrast, the haplotype “CT” in this block was associated with an increased susceptibility to lung cancer ($p = 0.003$, OR = 1.65, 95% CI = 1.18–2.29) in non-smokers. Additionally, in the non-drinker subgroup, the *IL2RA* haplotypes also showed a relationship with lung cancer risk (CC: $p = 0.038$, OR = 0.73, 95% CI = 0.55–0.98; CT: $p = 0.006$, OR = 1.55, 95% CI = 1.14–2.12).

4. Discussion

In this study, we examined the influence of seven SNPs in two inflammation-related genes on the susceptibility to lung cancer, including three in *IL2RA* (rs12569923, rs791588 and rs12722498) and four in

Table 3
Frequencies of gene alleles and genotypes of lung cancer patients and controls.

Gene	Polymorphism	Genotype	Control (503)	Case (507)	OR (95% CI)	*p*
IL2RA	rs12722498					
	Codominant	GG	6	0	-	-
		GA	95	77	0.75 (0.54–1.05)	0.094
		AA	396	422	1.00	
	Dominant	GG-GA	422	77	0.71 (0.51–0.98)	**0.040**
		AA	396	422	1.00	
	Recessive	GG	6	0	-	-
		GA-AA	491	499	1	
	Additive				0.68 (0.50–0.93)	**0.016**
	Allele	G	107	77	0.69 (0.51–0.94)	**0.019**
		A	887	921	1.00	

OR: odds ratio, CI: confidence interval.
$p < 0.05$ indicates statistical significance.
“-” indicates no data.
Significant values are marked in bold.

Table 4
Stratification analyses of the association of *IL2RA* and *IL2RB* polymorphisms with susceptibility to lung cancer.

Polymorphisms	Subgroups	Homozygote		Heterozygote		Dominant		Recessive		Additive		Allele	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
IL2RA													
rs12569923	Non-smoker	0.32 (0.12–0.84)	**0.021**	0.86 (0.53–1.38)	0.524	0.74 (0.48–1.16)	0.187	0.34 (0.13–0.87)	**0.025**	0.7 (0.49–1.00)	0.053	0.69 (0.48–1.00)	**0.048**
rs791588	Age (≤60)	0.54 (0.31–0.95)	**0.033**	0.72 (0.48–1.07)	0.103	0.67 (0.46–0.98)	**0.037**	0.65 (0.39–1.09)	0.102	0.73 (0.56–0.95)	**0.021**	0.73 (0.56–0.95)	**0.019**
	BMI (< 24)	0.48 (0.26–0.88)	**0.018**	0.69 (0.43–1.11)	0.125	0.63 (0.40–0.98)	**0.040**	0.59 (0.35–1.02)	0.057	0.69 (0.51–0.93)	**0.015**	0.70 (0.53–0.94)	**0.016**
	Non-drinker	0.51 (0.28–0.90)	**0.022**	0.93 (0.58–1.5)	0.777	0.78 (0.51–1.21)	0.270	0.52 (0.31–0.88)	**0.015**	0.74 (0.55–0.99)	**0.041**	0.74 (0.55–1.00)	**0.047**
rs12722498	Age (≤60)	-	-	0.55 (0.32–0.94)	**0.028**	0.50 (0.30–0.85)	**0.010**	-	-	0.49 (0.30–0.80)	**0.005**	0.48 (0.30–0.79)	**0.003**
	Females	-	-	0.53 (0.30–0.93)	**0.026**	0.49 (0.28–0.86)	**0.012**	-	-	0.48 (0.28–0.82)	**0.007**	0.50 (0.30–0.83)	**0.007**
	BMI (< 24)	-	-	0.63 (0.37–1.10)	0.105	0.57 (0.34–0.98)	**0.044**	-	-	0.54 (0.33–0.90)	**0.018**	0.51 (0.31–0.81)	**0.004**
	Non-drinker	-	-	0.65 (0.39–1.09)	0.101	0.60 (0.36–1.00)	0.051	-	-	0.57 (0.35–0.93)	**0.024**	0.58 (0.36–0.92)	**0.021**
IL2RB													
rs2281089	Females	1.02 (0.38–2.71)	0.970	0.60 (0.37–0.97)	**0.038**	0.65 (0.41–1.02)	0.063	1.24 (0.48–3.25)	0.656	0.77 (0.53–1.13)	0.180	0.77 (0.53–1.12)	0.172

OR: odds ratio, CI: confidence interval.
$p < 0.05$ indicates statistical significance.
"-" indicates no data.
Significant values are marked in bold.

Table 5
The association of the *IL2RB* polymorphism with susceptibility to lung cancer stratified by stage.

Polymorphism	Genotype	Control	Case	OR (95% CI)	*p*
rs2281089					
Homozygote	GG	10	10	0.29 (0.11–0.75)	**0.011**
Heterozygote	GA	28	97	1.07 (0.62–1.83)	0.811
	AA	46	152	1.00	
Dominant	GG-GA	38	107	0.86 (0.52–1.41)	0.551
	AA	46	152	1.00	
Recessive	GG	10	10	0.29 (0.11–0.72)	**0.008**
	GA-AA	249	74	1	
Additive				0.73 (0.49–1.08)	0.118
Allele	G	48	117	0.73 (0.49–1.08)	0.115
	A	120	401	1.00	

$p < 0.05$ indicates statistical significance.
Significant values are marked in bold.

Fig. 1. Haplotype block map for the SNPs of *IL2RA*.
Block includes rs12569923 and rs791588. The LD between two SNPs is standardized by D′.

IL2RB (rs2281089, rs3218264, rs9607418 and rs1573673). Our results showed that rs12722498 of *IL2RA* was significantly associated with a decreased lung cancer risk.

Inflammation is involved in all stages of tumorigenesis, from tumor initiation to the establishment of tumor metastases. The inflammation-associated mechanisms that promote lung cancer are through two main pathways: one pathway is due to genetic alterations that lead to neoplasia and inflammation, while the other pathway is the result of inflammatory conditions that increase the risk of lung cancer [17]. IL-2/IL-2R signaling promotes T and B cell growth and survival, which are involved in primary and memory immune responses in vivo [18,19]. IL-2 binds to the heterodimeric IL-2Rβγ receptor, resulting in the desired expansion of tumor-killing $CD8^+$ memory effector T (CD8 T) cells at high doses. IL-2 also binds to its heterotrimeric receptor IL-2Rαβγ with a greater affinity, which expands Tregs expressing high constitutive levels of IL-2Rα and, hence, represents an undesirable effect of IL-2 for

Table 6
IL2RA haplotype frequencies and the association with the risk of lung cancer in subgroups.

Subgroup	SNP	Haplotype	Frequency		OR (95% CI)	*p*
			Cases	Controls		
Age (≤60), years	rs12569923|rs791588	CC	0.340	0.415	0.73 (0.56–0.95)	**0.021**
		GT	0.789	0.823	0.79 (0.57–1.12)	0.187
		CT	0.551	0.592	0.84 (0.64–1.10)	0.197
BMI (< 24), kg/m^2	rs12569923|rs791588	CC	0.630	0.544	1.45 (1.08–1.96)	**0.014**
		GT	0.823	0.836	1.02 (0.69–1.49)	0.937
		CT	0.451	0.370	1.46 (1.08–1.97)	**0.014**
Non-smoker	rs12569923|rs791588	CC	0.819	0.760	0.83 (0.61–1.12)	0.226
		GT	0.446	0.337	1.42 (0.99–2.04)	0.057
		CT	0.371	0.419	1.65 (1.18–2.29)	**0.003**
Non-drinker	rs12569923|rs791588	CC	0.372	0.446	0.73 (0.55–0.98)	**0.038**
		GT	0.816	0.788	1.18 (0.82–1.69)	0.370
		CT	0.442	0.342	1.55 (1.14–2.12)	**0.006**

SNP: single nucleotide polymorphism, OR: odds ratio, CI: confidence interval, BMI: body mass index.
$p < 0.05$ indicates statistical significance.
Significant values are marked in bold.

lung cancer immunotherapy [20]. Moreover, mice deficient in either IL-2 or the α- or β-chain of the IL-2R develop a hyper-proliferative disorder [21,22]. These results suggest that *IL-2* is involved in lung cancer development. In addition, there are a few published studies on the polymorphisms of inflammation-related genes that have shown linkages with lung cancer risk [23,24]. Hence, *IL-2* polymorphisms may affect inflammation and, subsequently, influence lung cancer development.

Many reports have emphasized that some polymorphisms of *IL2RA* are linked to a risk of cancer, such as rectal cancer and renal cell carcinoma [25,26]. The dysregulation of *IL2RA* has been observed in many pulmonary diseases and has also been verified as an increased risk factor for lung cancer in patients who had lung infections and in immunosuppressed individuals [27], suggesting that *IL2RA* affects the development of lung cancer. In this study, we are the first to reveal the association between *IL2RA* polymorphisms and the risk of lung cancer. Additionally, in vivo, IL-2RB signaling controls immunosuppressive $CD4^+$ T cells in the draining lymph nodes and the lungs during allergic airway inflammation [28]. Specially, *IL2RB* SNPs could be used for risk prediction for lung cancer in smokers [7]. However, we did not observe strong associations between the four SNPs in *IL2RB* and lung cancer risk. Hence, further studies are needed to verify this conclusion in a larger and well-designed study.

Since many studies have demonstrated the contribution of age and sex in the development of cancer, we further stratified our results by age and sex, and our study showed that rs791588 and rs12722498 of *IL2RA* had strong protective effects against lung cancer among the individuals aged 60 years or younger. Furthermore, Gauderman et al. demonstrated an age-specific genetic incidence rate for lung cancer [29]. All of them have revealed that lung cancer is an age-dependent disease. Additionally, for females, *IL2RA* rs12722498 and *IL2RB* rs2281089 significantly decreased the risk for lung cancer, suggesting a sex-dependent effect of *IL2RA* and *IL2RB* on lung cancer. In addition, an elevated BMI has been explored as a risk factor for lung cancer in the world [27]. Inflammation or oxidative stress induced by high BMI may explain this effect. We also studied the relationship between the polymorphisms in these inflammation-related genes and lung cancer risk in the BMI subgroup. The results showed that rs791588 and rs12722498 of *IL2RA* had notable associations with a decreased risk of lung cancer.

Smoking is a major environmental risk factor, which has been demonstrated to have a significant association with lung cancer risk [30–32]. Therefore, we estimated the relationship of *IL2RA* and *IL2RB* polymorphisms with susceptibility to lung cancer stratified by smoking status. We found that a protective effect of *IL2RA* rs12569923 on the risk of lung cancer among non-smokers. It is possible that the protective effect of the *IL2RA* variant allele will be evident in non-smokers due to the lower levels of inflammation from the lack of cigarette smoking.

In addition, it has been shown that alcohol consumption plays a role in lung carcinogenesis [33]. In our study, rs791588 and rs12722498 of *IL2RA* did significantly decrease the lung cancer risk for non-drinkers.

Furthermore, the clinical characteristics of the patients showed a strong relationship between gene polymorphisms and lung cancer risk. In our study, *IL2RB* rs2281089 was associated with the decreased susceptibility to lung cancer for patients in stage III/IV, which suggests that the *IL2RB* polymorphism is involved in the progression of lung cancer. However, the exact mechanism of the genetic polymorphisms in lung cancer development needs to be studied further.

5. Conclusion

In summary, this present study provides evidence that polymorphisms of *IL2RA* and *IL2RB* may be associated with lung cancer susceptibility, implying a vital role for *IL2RA* and *IL2RB* in the development of lung cancer.

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Declaration of Competing Interest

We confirm that there are no conflicts of interest in this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.105716.

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