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RAD52 variants influence NSCLC risk in the Chinese population in a high altitude area

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Abstract

Background: Non-small cell lung cancer (NSCLC) accounts for approximately 80% of diagnosed lung cancer patients. *RAD52* has been reported to be associated with the development of squamous cell lung carcinoma. In this study, we assessed the relationships of *RAD52* genetic polymorphisms and NSCLC risk among the Chinese population at high altitude.

Methods: Eight single nucleotide polymorphisms (SNPs) of *RAD52* were genotyped in the Agena MassARRAY platform among 506 NSCLC patients and 510 healthy controls. We examined the association of *RAD52* polymorphisms with NSCLC risk using odds ratios (ORs) and 95% confidence intervals (CIs) *via* multiple genetic models.

Results: The rs10774474 A allele was related to a decreased risk of NSCLC in a high altitude population of China (OR = 0.82, 95% CI = 0.69–0.98, $p = 0.032$), whereas mutant alleles of rs1051672, rs7310449, rs1051669, rs6413436, rs4766377 and rs10849605 significantly increased NSCLC risk. Haplotype analysis showed that four haplotypes of *RAD52* polymorphisms conferred an enhanced susceptibility to NSCLC ($A_{rs1051672}G_{rs7310449}T_{rs1051669}A_{rs6413436}$: OR = 1.29, $p = 0.021$; $G_{rs1051672}A_{rs7310449}C_{rs1051669}G_{rs6413436}$: OR = 1.21, $p = 0.027$; $G_{rs4766377}C_{rs12822733}T_{rs10774474}C_{rs10849605}$: OR = 1.26, $p = 0.032$; $A_{rs4766377}C_{rs12822733}A_{rs10774474}T_{rs10849605}$: OR = 1.21, $p = 0.032$).

Conclusions: Our findings suggested the remarkable association of *RAD52* polymorphisms with NSCLC risk among the Chinese population in a high altitude area.

The reviews of this paper are available via the supplemental material section.

Keywords: chemotherapy, clinical index, high altitude, non-small cell lung cancer, *RAD52*

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Introduction

Lung cancer has a high incidence and mortality in the global population, with 2.1 million new cases and 1.8 million deaths in 2018.[1] In China, the incidence and mortality of lung cancer was increasing in the past decades, which imposes a great burden on individuals and society.[2] Histological classification distinguishes non-small cell lung cancer (NSCLC) from small cell lung cancer (SCLC), and NSCLC is mainly composed of adenocarcinoma and squamous cell cancer.[3] It has been reported that NSCLC accounts for approximately 80% of cases of lung cancer with a low 5-year survival rate.[4] The pathogenesis of NSCLC has not been fully elucidated. Although tobacco smoke exposure is a crucial etiological factor for lung cancer,[5] increasing numbers of studies have emphasized the important role of inherited genetics factors in tumor etiology.[6–8] Genome-wide association studies (GWASs) in Europeans have provided three polymorphic variations at 5p15.33, 6p21.33 and 15q25.1 that could influence the susceptibility to lung cancer.[9–13] In addition, three susceptibility regions at 3q28, 13q12.12 and 22q12.2 have been identified to be correlated to lung cancer based on GWAS research in Asian populations.[14,15] Two rare variants on chromosome 13q (*BRCA2*) and 22q (*CHEK2*) have been found to be associated with squamous lung cancer as well.[16]

As a well-known DNA repair gene, *RAD52* (*RAD52* homolog, DNA repair protein) is responsible for DNA double-strand break repair and homologous recombination.[17] Shi *et al.* detected a

susceptible marker at 12p13.33 (*RAD52*, rs6489769) affecting the risk of squamous cell lung carcinoma in European smokers.[3] Timofeeva *et al.* found histology-specific effects of 12p13.33 locus (*RAD52*, rs10849605) on squamous cell lung carcinoma and SCLC in Caucasians.[18] However, a study focused on a Han Chinese population did not observe any significant correlations of rs10849605 with squamous cell lung cancer or SCLC.[18] In addition, Song *et al.* examined the association of *RAD52* polymorphisms and SCLC susceptibility in a Chinese group, and they found that rs7963551 was significantly associated with SCLC risk.[17]

Although *RAD52* gene variants were linked to lung cancer susceptibility, most studies were conducted in European populations. And the involvement of *RAD52* single nucleotide polymorphisms (SNPs) in the development of NSCLC among the Chinese plateau population is rarely reported. An area with elevations over 1500 meters is considered as high altitude. Exposing to high altitude and hypoxia conditions, some genetic variations were assumed to be associated with NSCLC. Considering the importance of 12p13.33 *RAD52* locus in lung cancer, we investigated the correlations between *RAD52* genetic polymorphisms and NSCLC risk in a Chinese population from a high altitude area. Cisplatin-based doublet chemotherapy is the feasible therapy for lung cancer, we also evaluated the effect of *RAD52* polymorphisms on patients' response to cisplatin combination chemotherapy.

Materials and methods

Study participants

A total of 506 NSCLC patients (mean age: 59.80 ± 9.08 years) and 510 healthy controls (mean age: 59.80 ± 10.63 years) were recruited in our study. All patients came from the Qinghai Province Cancer Hospital and were pathologically diagnosed with NSCLC. The controls were enrolled from the physical examination center of the Qinghai Province Cancer Hospital. All of the participants were confirmed to live in the high altitude area of China. We collected the information on cases and controls, such as carcinoembryonic antigen (CEA), alpha fetoprotein (AFP) and carbohydrate antigen 50 (CA50). Tumor location, histology subtypes and lymph node metastasis status, treatment and adverse effects of cases were also recorded. Nausea and vomiting were obvious adverse responses to the therapy. Individuals without these responses were classified in the unresponsive group. Informed consents were collected from all participants before this study. Our study was approved by the Ethical Committee of the Qinghai Province Cancer Hospital and conformed to the Declaration of Helsinki.

SNP genotyping

Eight SNPs (rs1051672, rs7310449, rs1051669, rs6413436, rs4766377, rs12822733, rs10774474 and rs10849605) of the *RAD52* gene were selected for genotyping. The genomics DNA was extracted from whole blood with the GoldMag-Mini Whole Blood Genomic DNA Purification Kit (GoldMag Co. Ltd., Xi'an City, China). Concentration of the purified DNA was detected by Nanodrop 2000 (Thermo Fisher Scientific, USA). The on-line software (https://agenacx.com/online-tools/) was used to design genotyping primers (Supplementary Table 1). The Agena MassARRAY platform (Agena Bioscience, SanDiego, CA, USA) and Agena Bioscience Typer 4.0 were applied for SNP genotyping and data analysis, respectively.

Statistical analysis

And exact test was carried out to confirm the compliance of SNP allele frequency with Hardy–Weinberg equilibrium (HWE).[19] The genotype and allele distributions were compared between the case and control groups by chi-square test. Associations of variations with individual NSCLC susceptibility, clinical characteristics and cisplatin combination chemotherapy response were examined using a logistic regression model. PLINK 1.07 software was used to calculate odds ratios (ORs) with 95% confidence intervals (95% CIs) by logistic regression analysis. Haploview v.4.2 was used for linkage disequilibrium analysis and haplotype construction.[20,21]

Results

We present the characteristics of 506 patients with NSCLC and 510 controls from a Chinese high altitude area in Table 1. There was no significant difference in the distributions of age and gender between cases and controls ($p > 0.05$). The total number of individuals of stages I–II and stages III–IV groups were 93 and 286, respectively. We

Table 1. The basic information on cases and controls.

Variables	Cases	Controls	*p* value
Age (years)			0.992
⩽59	235	235	
>59	271	275	
n (mean ± SD)	506 (59.80 ± 9.08)	510 (59.80 ± 10.63)	
Gender			0.987
Male	350	353	
Female	156	157	
BMI			
⩽24	133	138	0.564
>24	81	181	0.347
Information loss	292	191	
Smoking status			
Yes	242	108	0.887
No	161	180	0.700
Information loss	103	222	
Drinking status			
Yes	109	103	0.829
No	267	156	0.087
Information loss	130	251	
Tumor location			
Left	218	510	0.977
Right	264	510	0.549
Information loss	24	0	
Histology subtypes			
Squamous carcinoma	174	510	0.059
Adenocarcinoma	212	510	0.441
Information loss	37	0	
Lymph node metastasis			0.355
(+)	269		
(–)	103		

(Continued)

Table 1. (Continued)

Variables	Cases	Controls	*p* value
Information loss	50		
Tumor stage			0.869
(III–IV)	286		
(I–II)	93		
Information loss	78		
Clinical index			
CEA	275	206	
Quantity in serum (ng/ml)	20.90 ± 23.95	2.15 ± 1.15	<0.001*
AFP	288	205	
Quantity in serum (ng/ml)	6.96 ± 4.21	3.24 ± 1.66	<0.001*
CA50	161	158	
Quantity in serum (U/ml)	9.84 ± 18.66	7.40 ± 5.39	0.113
Chemotherapy effect			
Response			0.723
Yes	42 (57.90 ± 11.22)		
No	100 (57.25 ± 9.52)		
Toxic and side effects			0.061
Yes	37 (59.78 ± 9.27)		
No	152 (56.53 ± 9.45)		

AFP, alpha fetoprotein; BMI, body mass index; CA50, carbohydrate antigen 50; CEA, carcinoembryonic antigen.
*$p < 0.05$ indicates statistical significance.

found significant differences in the quantity of crucial clinical markers (CEA, AFP, CA50) between cases and controls ($p < 0.001$). Some patients were treated by chemotherapy based on cisplatin, and we detected their responses to the treatment and toxic side effects. Among them, 42 NSCLC patients showed an obvious positive response, whereas 100 NSCLC patients did not. In terms of toxic side effects, there were 37 cases with severe effects and 152 patients with no effect.

Basic information and allele frequencies of SNPs in *RAD52* between NSCLC cases and controls are shown in Table 2. HWE p values were greater than 0.05 for all of the variants, which means that they were all in accordance with HWE and the study population is in genetic equilibrium. Except rs12822733, the other seven SNPs had significant differences in allele frequency between cases and controls. Compared with rs10774474 T allele carriers, individuals carrying the A allele had a lower risk of NSCLC (OR = 0.82, 95% CI = 0.69–0.98, $p = 0.032$), while the mutant allele of other SNPs (rs1051672, rs7310449, rs1051669, rs6413436, rs4766377 and rs10849605) increased NSCLC risk. The rs1051672 A allele was significantly associated with an increased risk of NSCLC (OR = 1.29, 95% CI = 1.04–1.60, $p = 0.021$). The rs7310449 G allele carriers had a 1.23-fold elevated risk of developing NSCLC (OR = 1.23,

Table 2. Basic information on candidate SNPs in this study.

SNP	Gene	Chromosome	Position	Alleles A/B	MAF		HWE *p* value	OR (95% CI)	*p* value
					Case	Control			
rs1051672	*RAD52*	12	912391	A/G	0.227	0.185	0.107	1.29 (1.04–1.60)	0.021*
rs7310449	*RAD52*	12	912949	G/A	0.497	0.446	0.655	1.23 (1.03–1.46)	0.021*
rs1051669	*RAD52*	12	913286	T/C	0.225	0.182	0.373	1.30 (1.05–1.62)	0.016*
rs6413436	*RAD52*	12	913513	A/G	0.491	0.446	0.788	1.20 (1.01–1.43)	0.042*
rs4766377	*RAD52*	12	929576	G/A	0.227	0.184	0.184	1.30 (1.05–1.62)	0.017*
rs12822733	*RAD52*	12	946864	G/C	0.097	0.094	0.295	1.03 (0.77–1.39)	0.848
rs10774474	*RAD52*	12	951120	A/T	0.383	0.429	0.857	0.82 (0.69–0.98)	0.032*
rs10849605	*RAD52*	12	955272	C/T	0.326	0.283	0.663	1.23 (1.01–1.48)	0.035*

95% CI, 95% confidential interval; A/B, minor/major alleles on the control sample frequencies; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium; OR, odds ratio; SNP, single nucleotide polymorphism.
HWE-*p* was used to assess whether the study population is in genetic equilibrium, *p* value was to show the allele difference between cases and controls.
*$p < 0.05$ indicates statistical significance.

95% CI = 1.03–1.46, $p = 0.021$). The rs1051669 T allele (OR = 1.30, 95% CI = 1.05–1.62, $p = 0.016$), the rs6413436 A allele (OR = 1.20, 95% CI = 1.01–1.43, $p = 0.042$), the rs4766377 G allele (OR = 1.30, 95% CI = 1.05–1.62, $p = 0.017$), and the rs10849605 C allele (OR = 1.23, 95% CI = 1.01–1.48, $p = 0.035$) showed remarkable correlations of NSCLC susceptibility in a Chinese population from a high altitude area.

The genotype distribution of cases and controls with the NSCLC risk were compared under different models (Table 3). The frequencies of variant genotypes AT and AA were significantly higher compared with the rs10774474 TT genotype, and the TT genotype was related to a decreased risk of NSCLC under the co-dominant model (OR = 0.72, 95% CI = 0.55–0.95, $p = 0.021$), dominant model (OR = 0.73, 95% CI = 0.56–0.94, $p = 0.014$) and log-additive model (OR = 0.83, 95% CI = 0.70–0.99, $p = 0.036$). The variable genotypes of rs1051672, rs7310449, rs1051669, rs6413436, rs4766377 and rs10849605 all increased NSCLC risk under different genetic models. The rs1051672 AG genotype carriers had a 1.41-fold elevated risk of developing NSCLC when compared with GG genotype carriers under the co-dominant model (OR = 1.41, 95% CI = 1.07–1.84, $p = 0.013$). Rs1051672 was also associated with an increased NSCLC risk under dominant and log-additive models. Rs7310449 was associated with an increased risk of NSCLC under the co-dominant (OR = 1.50, 95% CI = 1.06–2.11, $p = 0.022$), recessive (OR = 1.39, 95% CI = 1.04–1.87, $p = 0.027$) and log-additive (OR = 1.22, 95% CI = 1.03–1.45, $p = 0.024$) models. Compared with rs1051669 CC genotype carriers, the TC genotype carriers had a 1.39-fold elevated risk of developing NSCLC under the co-dominant model (OR = 1.39, 95% CI = 1.06–1.81, $p = 0.017$), and rs1051669 was associated with an increased NSCLC risk under dominant and log-additive models. Rs6413436 was associated with an increased risk of NSCLC under multiple models (co-dominant: OR = 1.44, 95% CI = 1.02–2.03, $p = 0.040$; recessive: OR = 1.38, 95% CI = 1.03–1.86, $p = 0.030$; log-additive: OR = 1.19, 95% CI = 1.00–1.41, $p = 0.047$). Compared with rs4766377 AA genotype carriers, the carriers with the GA genotype had a 1.41-fold elevated NSCLC risk under the co-dominant model (OR = 1.41, 95% CI = 1.07–1.84, $p = 0.013$). Rs4766377 was associated with an increased NSCLC risk under dominant and log-additive models as well. Under the co-dominant model, the CC genotype of rs10849605 was associated with an increased risk of NSCLC (OR = 1.57, 95% CI = 1.02–2.41, $p = 0.040$), and rs10849605

Table 3. Genotype frequencies of *RAD52* SNPs and their associations with NSCLC risk.

SNP	Model	Genotype	Case	Control	With adjustment	
					OR (95% CI)	*p* value
rs1051672	Co-dominant	GG	301	344	1	
		AG	176	143	1.41 (1.07–1.84)	0.013*
		AA	26	23	1.29 (0.72–2.31)	0.389
	Dominant	GG	301	344	1	
		AG+AA	202	166	1.39 (1.08–1.80)	0.012*
	Recessive	GG+AG	477	487	1	
		AA	26	23	1.16 (0.65–2.05)	0.624
	Log-additive	–	–	–	1.28 (1.03–1.58)	0.024*
rs7310449	Co-dominant	AA	136	159	1	
		GA	237	247	1.12 (0.84–1.50)	0.436
		GG	133	104	1.50 (1.06–2.11)	0.022*
	Dominant	AA	136	159	1	
		GA+GG	370	351	1.23 (0.94–1.62)	0.131
	Recessive	AA+GA	373	406	1	
		GG	133	104	1.39 (1.04–1.87)	0.027*
	Log-additive	–	–	–	1.22 (1.03–1.45)	0.024*
rs1051669	Co-dominant	CC	303	344	1	
		TC	178	146	1.39 (1.06–1.81)	0.017*
		TT	25	20	1.42 (0.77–2.61)	0.260
	Dominant	CC	303	344	1	
		TC+TT	203	166	1.39 (1.07–1.80)	0.012*
	Recessive	CC+TC	481	490	1	
		TT	25	20	1.27 (0.70–2.32)	0.431
	Log-additive	–	–	–	1.30 (1.05–1.61)	0.017*
rs6413436	Co-dominant	GG	140	158	1	
		AG	234	249	1.06 (0.79–1.42)	0.691
		AA	131	103	1.44 (1.02–2.03)	0.040*
	Dominant	GG	140	158	1	

(Continued)

Table 3. (Continued)

SNP	Model	Genotype	Case	Control	With adjustment	
					OR (95% CI)	*p* value
		AG+AA	365	352	1.17 (0.89–1.54)	0.255
	Recessive	GG+AG	374	407	1	
		AA	131	103	1.38 (1.03–1.86)	0.030*
	Log-additive	–	–	–	1.19 (1.00–1.41)	0.047*
rs4766377	Co-dominant	AA	301	344	1	
		GA	177	144	1.41 (1.07–1.84)	0.013*
		GG	26	22	1.35 (0.75–2.43)	0.318
	Dominant	AA	301	344	1	
		GA+GG	203	166	1.40 (1.08–1.81)	0.011*
	Recessive	AA+GA	478	488	1	
		GG	26	22	1.21 (0.67–2.16)	0.527
	Log-additive	–	–	–	1.29 (1.04–1.60)	0.019*
rs10774474	Co-dominant	TT	202	167	1	
		AT	217	248	0.72 (0.55–0.95)	0.021*
		AA	84	95	0.73 (0.51–1.05)	0.085
	Dominant	TT	202	167	1	
		AT+AA	301	343	0.73 (0.56–0.94)	0.014*
	Recessive	TT+AT	419	415	1	
		AA	84	95	0.87 (0.63–1.21)	0.418
	Log-additive	–	–	–	0.83 (0.70–0.99)	0.036*
rs10849605	Co-dominant	TT	235	264	1	
		CT	209	203	1.16 (0.89–1.50)	0.277
		CC	60	43	1.57 (1.02–2.41)	0.040*
	Dominant	TT	235	264	1	
		CT+CC	269	246	1.23 (0.96–1.57)	0.102
	Recessive	TT+CT	444	467	1	
		CC	60	43	1.47 (0.97–2.22)	0.068
	Log-additive	–	–	–	1.22 (1.01–1.47)	0.039*

95% CI, 95% confidential interval; NSCLC, non-small cell lung cancer; OR, odds ratio.
*$p < 0.05$ indicates statistical significance.

Table 4. The association between SNPs of *RAD52* and demographic and clinical features of NSCLC.

SNP	Variables		OR (95% CI)					
			Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
rs1051672	Age	⩽59	1.29 (0.95–1.76)	1.11 (0.49–2.54)	**1.55 (1.04–2.29)**	**1.48 (1.02–2.15)**	0.96 (0.42–2.15)	1.29 (0.95–1.76)
		>59	1.29 (0.95–1.74)	1.45 (0.62–3.37)	1.29 (0.89–1.87)	1.31 (0.91–1.87)	1.34 (0.58–3.09)	1.25 (0.93–1.69)
	Gender	Male	**1.34 (1.03–1.74)**	1.05 (0.52–2.11)	**1.63 (1.18–2.27)**	1.54 (1.12–2.10)	0.90 (0.45–1.79)	**1.32 (1.02–1.71)**
		Female	1.19 (0.82–1.74)	2.11 (0.69–6.41)	1.03 (0.64–1.66)	1.13 (0.71–1.77)	2.08 (0.69–6.26)	1.19 (0.82–1.75)
	BMI	⩽24	1.18 (0.77–1.79)	1.49 (0.49–4.53)	1.21 (0.70–2.07)	1.25 (0.75–2.07)	1.41 (0.47–4.22)	1.21 (0.80–1.84)
		>24	**1.73 (1.10–2.74)**	1.31 (0.37–4.64)	**2.09 (1.16–3.76)**	**1.95 (1.11–3.43)**	1.03 (0.30–3.60)	1.56 (0.99–2.46)
	Drinking status	Yes	1.28 (0.80–2.06)	0.62 (0.17–2.23)	**1.98 (1.07–3.65)**	1.66 (0.94–2.94)	0.50 (0.14–1.78)	1.27 (0.80–2.02)
		No	1.26 (0.90–1.77)	1.29 (0.57–2.90)	1.39 (0.90–2.17)	1.38 (0.91–2.08)	1.16 (0.52–2.57)	1.25 (0.90–1.73)
	Tumor type	Squamous carcinoma	**1.35 (1.01–1.82)**	1.68 (0.80–3.53)	1.38 (0.94–2.03)	1.42 (0.99–2.05)	1.51 (0.73–3.14)	1.34 (1.00–1.78)
		Adenocarcinoma	1.19 (0.90–1.58)	0.90 (0.39–2.07)	1.33 (0.93–1.88)	1.27 (0.90–1.77)	0.82 (0.36–1.87)	1.15 (0.87–1.52)
	LN metastasis	(–)	1					
		(+)	0.78 (0.54–1.13)	0.67 (0.26–1.74)	0.74 (0.46–1.21)	0.73 (0.46–1.16)	0.75 (0.29–1.91)	0.78 (0.54–1.13)
rs7310449	Age	⩽59	1.25 (0.97–1.61)	1.59 (0.96–2.65)	1.22 (0.79–1.90)	1.34 (0.88–2.03)	1.40 (0.92–2.13)	1.26 (0.98–1.63)
		>59	1.21 (0.95–1.53)	1.38 (0.86–2.23)	1.05 (0.71–1.55)	1.14 (0.79–1.65)	1.34 (0.89–2.03)	1.17 (0.92–1.48)
	Gender	Male	1.16 (0.94–1.43)	1.33 (0.88–2.00)	1.11 (0.79–1.57)	1.18 (0.85–1.62)	1.25 (0.88–1.78)	1.15 (0.94–1.41)
		Female	**1.40 (1.02–1.91)**	**1.97 (1.04–3.74)**	1.18 (0.68–2.02)	1.39 (0.83–2.32)	**1.77 (1.05–3.00)**	**1.40 (1.02–1.93)**
	BMI	⩽24	1.19 (0.85–1.67)	1.51 (0.78–2.94)	0.92 (0.52–1.61)	1.09 (0.65–1.83)	1.59 (0.89–2.84)	1.20 (0.87–1.67)
		>24	1.19 (0.82–1.72)	1.30 (0.63–2.70)	0.97 (0.52–1.80)	1.07 (0.60–1.90)	1.33 (0.71–2.48)	1.13 (0.78–1.63)
	Drinking status	Yes	1.19 (0.81–1.75)	1.24 (0.58–2.67)	1.46 (0.79–2.70)	1.39 (0.79–2.46)	1.01 (0.51–1.99)	1.16 (0.79–1.68)
		No	1.30 (0.99–1.73)	1.66 (0.96–2.87)	1.04 (0.65–1.66)	1.23 (0.80–1.90)	1.63 (1.02–2.59)	1.28 (0.98–1.67)
	Tumor type	Squamous carcinoma	1.19 (0.93–1.51)	1.38 (0.86–2.21)	0.94 (0.62–1.42)	1.08 (0.73–1.57)	1.43 (0.96–2.14)	1.16 (0.92–1.48)
		Adenocarcinoma	1.24 (0.99–1.56)	1.49 (0.94–2.5)	1.25 (0.85–1.85)	1.32 (0.92–1.90)	1.29 (0.88–1.89)	1.22 (0.97–1.53)
	LN metastasis	(–)	1					
		(+)	0.90 (0.65–1.25)	0.80 (0.43–1.49)	0.91 (0.53–1.57)	0.87 (0.52–1.44)	0.85 (0.50–1.43)	0.89 (0.66–1.22)
rs1051669	Age	⩽59	1.30 (0.95–1.78)	1.19 (0.50–2.83)	**1.51 (1.02–2.23)**	**1.46 (1.01–2.13)**	1.02 (0.43–2.42)	1.31 (0.96–1.80)
		>59	1.31 (0.97–1.77)	1.59 (0.67–3.81)	1.27 (0.88–1.85)	1.31 (0.91–1.87)	1.47 (0.62–3.50)	1.27 (0.94–1.72)

(Continued)

Table 4. (Continued)

SNP	Variables		OR (95% CI)					
			Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
	Gender	Male	**1.36 (1.05–1.77)**	1.17 (0.56–2.45)	**1.59 (1.15–2.21)**	**1.53 (1.12–2.09)**	1.01 (0.49–2.10)	**1.35 (1.04–1.76)**
		Female	1.19 (0.82–1.74)	2.11 (0.69–6.41)	1.03 (0.64–1.66)	1.13 (0.71–1.77)	2.08 (0.69–6.26)	1.19 (0.82–1.75)
	BMI	⩽24	1.18 (0.77–1.80)	1.57 (0.47–5.20)	1.20 (0.70–2.05)	1.25 (0.75–2.07)	1.48 (0.45–4.86)	1.22 (0.80–1.87)
		>24	**1.68 (1.06–2.66)**	1.28 (0.36–4.53)	**1.96 (1.08–3.54)**	**1.84 (1.05–3.24)**	1.03 (0.30–3.60)	1.50 (0.95–2.73)
	Drinking status	Yes	1.29 (0.80–2.08)	0.72 (0.19–2.67)	1.82 (0.99–3.34)	1.60 (0.90–2.84)	0.60 (0.16–2.19)	1.29 (0.80–2.06)
		No	1.25 (0.89–1.75)	1.23 (0.55–2.79)	1.41 (0.91–2.19)	1.38 (0.91–2.08)	1.10 (0.49–2.46)	1.24 (0.89–1.73)
	Tumor type	Squamous carcinoma	**1.38 (1.03–1.86)**	1.95 (0.91–4.18)	1.36 (0.93–1.99)	1.43 (1.00–2.06)	1.77 (0.83–3.75)	**1.38 (1.03–1.85)**
		Adenocarcinoma	1.17 (0.88–1.56)	0.87 (0.35–2.11)	1.28 (0.90–1.81)	1.23 (0.88–1.72)	0.80 (0.33–1.93)	1.13 (0.85–1.51)
	LN metastasis	(–)	1					
		(+)	0.73 (0.50–1.06)	0.59 (0.23–1.57)	0.69 (0.43–1.12)	0.68 (0.43–1.08)	0.68 (0.26–1.77)	0.73 (0.50–1.06)
rs6413436	Age	⩽59	1.17 (0.90–1.51)	1.39 (0.84–2.30)	1.17 (0.75–1.82)	1.24 (0.82–1.88)	1.25 (0.82–1.91)	1.18 (0.91–1.52)
		>59	1.23 (0.97–1.56)	1.46 (0.90–2.37)	0.98 (0.67–1.45)	1.11 (0.77–1.59)	1.48 (0.97–2.25)	1.18 (0.93–1.50)
	Gender	Male	1.13 (0.92–1.40)	1.27 (0.85–1.92)	1.06 (0.75–1.49)	1.12 (0.82–1.55)	1.23 (0.87–1.76)	1.12 (0.92–1.38)
		Female	1.36 (0.99–1.86)	1.90 (1.00–3.62)	1.09 (0.64–1.88)	1.30 (0.78–2.17)	**1.79 (1.05–3.05)**	1.37 (1.00–1.89)
	BMI	⩽24	1.19 (0.85–1.67)	1.57 (0.80–3.07)	0.81 (0.47–1.42)	1.01 (0.60–1.70)	1.77 (0.98–3.19)	1.21 (0.87–1.68)
		>24	1.16 (0.80–1.68)	1.22 (0.58–2.54)	0.96 (0.51–1.79)	1.04 (0.58–1.85)	1.25 (0.66–2.35)	1.09 (0.75–1.58)
	Drinking status	Yes	1.21 (0.82–1.78)	1.31 (0.61–2.83)	1.43 (0.78–2.63)	1.39 (0.79–2.46)	1.07 (0.54–2.14)	1.18 (0.81–1.73)
		No	1.25 (0.94–1.65)	1.53 (0.89–2.63)	1.02 (0.64–1.62)	1.18 (0.77–1.82)	1.52 (0.95–2.41)	1.23 (0.94–1.60)
	Tumor type	Squamous carcinoma	1.16 (0.91–1.48)	1.34 (0.84–2.14)	0.87 (0.58–1.31)	1.01 (0.69–1.47)	1.45 (0.97–2.18)	1.14 (0.90–1.45)
		Adenocarcinoma	1.21 (0.96–1.52)	1.41 (0.89–2.22)	1.17 (0.79–1.72)	1.24 (0.86–1.78)	1.28 (0.87–1.87)	1.19 (0.94–1.49)
	LN metastasis	(–)	1					
		(+)	0.89 (0.64–1.23)	0.77 (0.41–1.44)	0.89 (0.52–1.53)	0.85 (0.51–1.40)	0.83 (0.49–1.41)	0.88 (0.64–1.20)
rs4766377	Age	⩽59	1.31 (0.96–1.78)	1.20 (0.52–2.77)	**1.52 (1.03–2.26)**	**1.48 (1.02–2.15)**	1.03 (0.45–2.35)	1.31 (0.96–1.79)
		>59	1.30 (0.96–1.75)	1.44 (0.62–3.36)	1.30 (0.89–1.89)	1.32 (0.92–1.88)	1.33 (0.57–3.07)	1.26 (0.93–1.70)

(Continued)

Table 4. (Continued)

SNP	Variables		OR (95% CI)					
			Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
	Gender	Male	**1.36 (1.04–1.76)**	1.11 (0.55–2.26)	1.63 (1.17–2.26)	**1.55 (1.13–2.11)**	0.95 (0.47–1.92)	**1.34 (1.03–1.74)**
		Female	1.19 (0.82–1.74)	2.11 (0.69–6.41)	1.03 (0.64–1.66)	1.13 (0.71–1.77)	2.08 (0.69–6.26)	1.19 (0.82–1.75)
	BMI	⩽24	1.19 (0.78–1.81)	1.51 (0.50–4.59)	1.22 (0.71–2.10)	1.26 (0.76–2.10)	1.42 (0.47–4.25)	1.23 (0.81–1.86)
		>24	**1.70 (1.07–2.70)**	1.31 (0.37–4.62)	**2.00 (1.10–3.62)**	**1.88 (1.07–3.31)**	1.04 (0.30–3.64)	1.52 (0.96–2.41)
	Drinking status	Yes	1.25 (0.78–2.01)	0.61 (0.17–2.20)	**1.90 (1.03–3.51)**	1.60 (0.90–2.84)	0.50 (0.14–1.78)	1.24 (0.78–1.97)
		No	1.27 (0.90–1.79)	1.31 (0.58–2.93)	1.41 (0.91–2.20)	1.39 (0.92–2.11)	1.16 (0.53–2.58)	1.26 (0.91–1.75)
	Tumor type	Squamous carcinoma	**1.38 (1.02–1.84)**	1.76 (0.83–3.73)	1.39 (0.95–2.05)	**1.45 (1.01–2.08)**	1.58 (0.76–3.31)	**1.36 (1.02–1.82)**
		Adenocarcinoma	1.18 (0.89–1.57)	0.93 (0.40–2.14)	1.29 (0.91–1.83)	1.24 (0.88–1.74)	0.85 (0.37–1.96)	1.14 (0.86–1.51)
	LN metastasis	(–)	1					
		(+)	0.75 (0.51–1.09)	0.65 (0.25–1.70)	0.69 (0.43–1.12)	0.69 (0.43–1.09)	0.75 (0.29–1.92)	0.75 (0.52–1.08)
rs12822733	Age	⩽59	1.14 (0.73–1.78)	2.38 (0.21–26.54)	1.11 (0.69–1.81)	1.15 (0.71–1.85)	2.33 (0.21–26.00)	1.17 (0.74–1.84)
		>59	0.95 (0.64–1.42)	1.78 (0.16–20.01)	0.90 (0.59–1.40)	0.92 (0.60–1.42)	**1.81 (0.16–20.37)**	0.95 (0.63–1.42)
	Gender	Male	0.83 (0.58–1.19)	0.98 (0.14–7.01)	0.80 (0.54–1.19)	0.81 (0.55–1.19)	1.02 (0.14–7.28)	0.83 (0.57–1.19)
		Female	1.62 (0.95–2.75)	N/A	1.51 (0.85–2.68)	1.60 (0.91–2.82)	N/A	1.65 (0.96–2.85)
	BMI	⩽24	1.58 (0.87–2.87)	N/A	1.52 (0.80–2.87)	1.57 (0.83–2.97)	N/A	1.61 (0.86–2.99)
		>24	0.70 (0.37–1.35)	N/A	0.72 (0.36–1.46)	0.71 (0.35–1.42)	N/A	0.70 (0.35–1.39)
	Drinking status	Yes	0.97 (0.43–2.21)	N/A	N/A	0.95 (0.41–2.24)	N/A	0.95 (0.41–2.24)
		No	1.05 (0.65–1.71)	N/A	0.97 (0.58–1.64)	1.02 (0.61–1.71)	N/A	1.07 (0.65–1.76)
	Tumor type	Squamous carcinoma	**0.56 (0.34–0.94)**	0.95 (0.08–10.74)	**0.48 (0.28–0.84)**	**0.49 (0.29–0.85)**	1.06 (0.09–11.93)	**0.53 (0.31–0.89)**
		Adenocarcinoma	**1.60 (1.14–2.27)**	4.07 (0.66–24.94)	**1.62 (1.10–2.39)**	**1.68 (1.15–2.45)**	3.66 (0.60–22.36)	1.68 (1.17–2.40)
	LN metastasis	(–)	1					
		(+)	1.17 (0.66–2.07)	N/A	1.05 (0.57–1.94)	1.09 (0.59–2.01)	N/A	1.13 (0.63–2.04)
rs10774474	Age	⩽59	0.78 (0.60–1.01)	0.65 (0.38–1.13)	**0.67 (0.45–1.00)**	**0.66 (0.46–0.97)**	0.81 (0.49–1.34)	0.78 (0.60–1.01)
		>59	0.87 (0.68–1.10)	0.84 (0.52–1.36)	0.79 (0.54–1.16)	0.80 (0.56–1.15)	0.96 (0.62–1.47)	0.90 (0.71–1.14)
	Gender	Male	0.88 (0.71–1.08)	0.82 (0.54–1.25)	0.76 (0.54–1.06)	0.77 (0.57–1.06)	0.96 (0.66–1.40)	0.88 (0.72–1.08)
		Female	**0.71 (0.51–0.99)**	0.53 (0.26–1.07)	0.66 (0.40–1.07)	**0.63 (0.39–0.99)**	0.67 (0.35–1.27)	**0.71 (0.51–0.99)**

(Continued)

Table 4. (Continued)

SNP	Variables		OR (95% CI)					
			Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
	BMI	⩽24	0.86 (0.61–1.21)	0.78 (0.39–1.55)	**0.54 (0.31–0.94)**	0.60 (0.36–1.01)	1.12 (0.62–2.05)	0.83 (0.60–1.17)
		>24	0.74 (0.50–1.08)	0.45 (0.19–1.11)	1.11 (0.62–1.99)	0.90 (0.52–1.58)	**0.43 (0.19–0.97)**	0.76 (0.52–1.13)
	Drinking status	Yes	0.87 (0.59–1.27)	0.77 (0.37–1.63)	1.02 (0.54–1.92)	0.93 (0.52–1.68)	0.77 (0.40–1.45)	0.89 (0.61–1.29)
		No	0.78 (0.59–1.04)	0.67 (0.38–1.19)	0.69 (0.44–1.08)	0.68 (0.45–1.04)	0.82 (0.49–1.37)	0.80 (0.61–1.05)
	Tumor type	Squamous carcinoma	0.87 (0.68–1.12)	0.84 (0.52–1.38)	**0.67 (0.45–0.99)**	0.72 (0.50–1.03)	1.05 (0.67–1.64)	0.87 (0.68–1.12)
		Adenocarcinoma	**0.77 (0.61–0.98)**	0.64 (0.39–1.05)	0.76 (0.53–1.08)	0.73 (0.52–1.02)	0.75 (0.48–1.18)	0.79 (0.63–1.00)
	LN metastasis	(–)	1					
		(+)	1.31 (0.94–1.83)	**2.11 (1.02–4.37)**	0.91 (0.55–1.50)	1.13 (0.71–1.81)	**2.23 (1.14–4.36)**	1.31 (0.95–1.80)
rs10849605	Age	⩽59	1.29 (0.98–1.69)	1.68 (0.89–3.17)	1.26 (0.86–1.86)	1.33 (0.92–1.92)	1.50 (0.81–2.75)	1.28 (0.97–1.69)
		>59	1.17 (0.90–1.52)	1.46 (0.81–2.63)	1.06 (0.74–1.52)	1.13 (0.81–1.58)	1.42 (0.81–2.51)	1.15 (0.89–1.48)
	Gender	Male	**1.26 (1.00–1.59)**	1.47 (0.88–2.44)	1.31 (0.95–1.79)	1.34 (0.99–1.80)	1.30 (0.80–2.13)	1.24 (1.00–1.56)
		Female	1.15 (0.82–1.61)	1.85 (0.83–4.15)	0.89 (0.55–1.42)	1.02 (0.65–1.58)	1.96 (0.90–4.26)	1.15 (0.82–1.62)
	BMI	⩽24	1.10 (0.76–1.60)	2.05 (0.86–4.91)	0.75 (0.44–1.26)	0.92 (0.57–1.50)	2.32 (0.99–5.40)	1.13 (0.79–1.63)
		>24	**2.02 (1.36–3.01)**	2.48 (0.99–6.21)	**2.89 (1.61–5.19)**	**2.80 (1.60–4.90)**	1.48 (0.62–3.51)	**1.91 (1.27–2.86)**
	Drinking status	Yes	1.18 (0.78–1.79)	1.25 (0.51–3.05)	1.26 (0.71–2.26)	1.26 (0.73–2.17)	1.14 (0.48–2.68)	1.16 (0.78–1.73)
		No	1.26 (0.93–1.71)	1.54 (0.80–2.97)	1.23 (0.81–1.89)	1.30 (0.87–1.93)	1.41 (0.75–2.63)	1.24 (0.92–1.66)
	Tumor type	Squamous carcinoma	1.29 (1.00–1.68)	1.75 (0.98–3.11)	1.24 (0.85–1.80)	1.33 (0.94–1.90)	1.59 (0.92–2.75)	1.30 (1.00–1.68)
		Adenocarcinoma	1.14 (0.89–1.46)	1.29 (0.73–2.27)	1.05 (0.75–1.49)	1.10 (0.79–1.52)	1.26 (0.73–2.17)	1.10 (0.86–1.41)
	LN metastasis	(–)	1					
		(+)	0.75 (0.53–1.05)	0.67 (0.33–1.38)	0.63 (0.38–1.04)	0.64 (0.40–1.02)	0.84 (0.43–1.65)	0.77 (0.55–1.06)

OR and 95% CI of significant association is presented in bold.
95% CI, 95% confidential interval; BMI, body mass index; LN, lymph node; NSCLC, non-small cell lung cancer; OR, odds ratio.

was linked to an increased NSCLC risk under the log-additive model.

We performed stratification analysis to explore the relationships between *RAD52* SNPs and NSCLC risk in the subgroup of age, gender, body mass index (BMI), drinking status, tumor type and lymph node metastasis (Table 4). Stratification analysis of age showed that rs1051672, rs1051669 and rs4766377 significantly increased NSCLC risk in individuals equal to or younger than 59 years whereas rs10774474 significantly decreased NSCLC risk. In addition, rs12822733 significantly increased NSCLC risk among individuals older than 59 years. Rs1051672, rs1051669, rs4766377 and rs10849605 were associated with an increased NSCLC risk among men. In women, rs7310449 and rs64131436 were associated with an increased NSCLC risk, and rs10774474 was associated with a decreased risk of NSCLC. Rs10774474 was correlated to a decreased NSCLC risk in the subgroup of BMI $\leqslant 24$. Rs1051672, rs1051669, rs4766377 and rs10849605 significantly increased NSCLC risk, while rs10774474 significantly decreased the NSCLC susceptibility in individuals with BMI >24. In drinking status stratification analysis, rs1051672 and rs4766377 were associated with increased NSCLC risk in drinkers. When stratified by tumor histology type, rs1051672, rs1051669 and rs4766377 were associated with an increased squamous carcinoma risk, whereas rs12822733 and rs10774474 presented the associations with a decreased squamous carcinoma risk. Rs12822733 was related to an increased risk of adenocarcinoma, rs10774474 was associated with a decreased adenocarcinoma risk. In the lymph node metastasis stratification analysis, rs10774474 was associated with metastasis status.

In Table 5, we present the relationship between NSCLC clinical markers and *RAD52* SNPs. We observed significant differences among rs12822733 genotypes in serum ferritin (SF; $p=0.020$). The individuals carrying the rs12822733 GG genotype had the highest SF level, followed by GC genotype carriers, and CC genotype carriers had lowest expression. For tumor necrosis factor (TNF) expression analysis, the variations of rs1051672, rs1051669 and rs4766377 could significantly influence TNF expression, with the lowest expression quantity of the AA genotype, TT genotype and GG genotype, respectively. We also analyzed the association between the other six tumor associated markers with *RAD52* SNPs, which included CEA, CA50, AFP, neuron-specific enolase (NSE), cytokeratin-19-fragment (CF211) and pro-gastrin-releasing peptide (ProGRP), there was no association between these indicators and *RAD52* SNPs (Supplementary Table 2).

Some patients were treated by chemotherapy based on cisplatin; we detected the association of *RAD52* gene polymorphisms with chemotherapy effects and toxin side effects. There was no association between the eight SNPs and chemotherapy based on cisplatin; the results are shown in Supplementary Table 3.

The association between *RAD52* haplotypes and NSCLC risk were analyzed. Figure 1 showed two linkage disequilibrium (LD) blocks in *RAD52*. Table 6 showed the association between different haplotypes and NSCLC risk. The haplotypes AGTA and GACG conducted by rs1051672, rs7310449, rs1051669 and rs6413436 significantly increased the NSCLC risk (OR = 1.29, 95% CI = 1.04–1.60, $p=0.021$; OR = 1.21, 95% CI = 1.02–1.44, $p=0.027$). The haplotypes GCTC and ACAT conducted by rs4766377, rs12822733, rs10774474 and rs10849605 were also associated with an increased risk of NSCLC (OR = 1.26, 95% CI = 1.02–1.57, $p=0.032$; OR = 1.21, 95% CI = 1.02–1.44, $p=0.032$).

Discussion

We conducted an association study in the *RAD52* gene and NSCLC risk among the Chinese population living at a high altitude; rs10774474 was significantly associated with a decreased NSCLC risk, rs1051672, rs7310449, rs1051669, rs6413436, rs4766377 and rs10849605 significantly increased NSCLC risk. Four haplotype blocks were associated with an increased risk of NSCLC ($A_{rs1051672}G_{rs7310449}T_{rs1051669}A_{rs6413436}$, $G_{rs1051672}A_{rs7310449}C_{rs1051669}G_{rs6413436}$, $G_{rs4766377}C_{rs12822733}T_{rs10774474}C_{rs10849605}$, $A_{rs4766377}C_{rs12822733}A_{rs10774474}T_{rs10849605}$). The expression quantity of tumor-associated markers (SF and TNF) were significantly different in cases and controls. Our results suggest that *RAD52* genetic polymorphisms might influence the NSCLC risk in a high altitude area of China.

The *RAD52* gene plays a role in DNA strand exchange.[22] Previous studies reported that *RAD52* variants were associated with a risk of glioma,[23]

Table 5. The association between SNPs of *RAD52* and clinical index of NSCLC.

Clinical index	SNP	Genotype	Number	Quantity in serum (mean ± SD)	95% CI	*p* value
SF (ng/ml)	rs1051672	AA	13	123.18 ± 89.00	69.40–176.97	0.428
		AG	95	246.72 ± 304.62	184.66–308.77	
		GG	175	235.88 ± 339.25	185.26–286.49	
	rs1051669	TT	12	126.24 ± 92.24	67.63–184.85	0.471
		TC	97	245.60 ± 298.25	185.49–305.71	
		CC	177	239.80 ± 341.94	189.08–290.53	
	rs4766377	AA	175	241.51 ± 343.52	190.26–292.76	0.417
		GA	96	247.26 ± 299.37	186.60–307.91	
		GG	13	123.18 ± 89.00	69.40–176.97	
	rs12822733	CC	222	226.70 ± 300.14	187.00–266.39	0.020*
		GC	58	257.77 ± 366.13	161.50–354.04	
		GG	3	740.20 ± 689.02	–971.42–2451.82	
TNF (mol/ml)	rs1051672	AA	11	0.79 ± 0.24	0.63–0.95	0.002*
		AG	66	0.88 ± 0.06	0.87–0.89	
		GG	124	0.88 ± 0.07	0.87–0.89	
	rs1051669	TT	10	0.77 ± 0.24	0.60–0.95	<0.001*
		TC	66	0.88 ± 0.06	0.87–0.89	
		CC	125	0.88 ± 0.07	0.87–0.89	
	rs4766377	AA	123	0.88 ± 0.07	0.87–0.89	0.002*
		GA	65	0.88 ± 0.06	0.87–0.89	
		GG	11	0.79 ± 0.24	0.63–0.95	
	rs12822733	CC	160	0.88 ± 0.06	0.87–0.89	0.316
		GC	37	0.87 ± 0.05	0.85–0.88	
		GG	1	–	–	

95% CI, 95% confidential interval; NSCLC, non-small cell lung cancer; SF, serum ferritin; TNF, tumor necrosis factor.
*$p < 0.05$ indicates statistical significance.

breast cancer[24] and colorectal cancer[25] in the Chinese Han population. They suggested that the effects of the *RAD52* gene on multiple diseases may be related to DNA strand exchange. Song *et al.* found that *RAD52* rs7963551 contributes to susceptibility to SCLC in the Chinese population.[17] In this study, we evaluated the association between eight SNPs and NSCLC susceptibility in

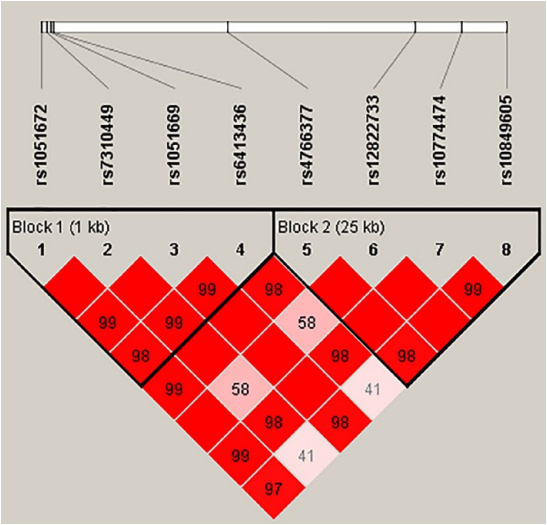

Figure 1. D′ linkage map for the eight SNPs in *RAD52*. SNP, single nucleotide polymorphism.

Chinese from a high altitude area, and we found seven *RAD52* polymorphisms had a significant association with NSCLC risk. Our finding enriched the association study between *RAD52* and lung cancer.

In humans, *RAD52* was involved in the HR pathway and plays a key role in regulating HR-related genomic instability.[26] NSCLC is particularly associated with smoking; the variation in *RAD52* may potentially decrease the ability to repair carcinogen-induced damage and influences the risk of lung cancer. In addition, the depletion of *RAD52* changed the cell cycle distribution by decreasing G0/G1 and increasing G2/M, the SNPs in *RAD52* may influence *RAD52* and then influence tumor cells division. It revealed the molecular mechanism of *RAD52*, which may be involved in NSCLC.

In the stratification analysis of tumor histology subtype, we found that rs12822733 had an association with decreased squamous carcinoma risk and increased adenocarcinoma risk, but not with NSCLC, so we speculate that it may be that tumor heterogeneity hampered the detection of the association signal when all lung cancers were analyzed.

A previous study found that *RAD52* variants could predict platinum resistance and the prognosis of cervical cancer.[27] In this study, there was no significant association between the SNPs and chemotherapy based on cisplatin; it may be attributed to the different role of *RAD52* variants to platinum resistance in different cancers.

Table 6. *RAD52* haplotype frequencies and the association with NSCLC risk.

Haplotype	Frequency		OR (95% CI)	*p* value
	Case	Control		
rs1051672|rs7310449|rs1051669|rs6413436				
AGTA	0.222	0.181	1.29 (1.04–1.60)	0.021*
GGCA	0.264	0.259	1.02 (0.84–1.25)	0.823
GACG	0.497	0.447	1.21 (1.02–1.44)	0.027*
rs4766377|rs12822733|rs10774474|rs10849605				
GCTC	0.222	0.182	1.26 (1.02–1.57)	0.032*
ACTC	0.898	0.899	0.99 (0.75–1.32)	0.954
ACAT	0.619	0.571	1.21 (1.02–1.44)	0.032*
AGTT	0.095	0.094	1.01 (0.74–1.37)	0.955
ACTT	0.805	0.809	0.98 (0.78–1.22)	0.845

95% CI, 95% confidential interval; NSCLC, non-small cell lung cancer; OR, odds ratio.
*$p < 0.05$ indicates statistical significance.

Several limitations may exist in this study. First, selection bias is inevitable, because all individuals were recruited from the hospital, validation of our findings in a population-based prospective study is important. Second, the analysis of the *BRCA2* status of these patients was limited. Finally, the relationships of *RAD52* haplotypes with NSCLC risk in a Chinese high altitude area is still not enough to explain the molecular mechanism of *RAD52* with the onset and development of NSCLC, further studies are needed to validate and expand our results.

Conclusion

In conclusion, we found that *RAD52* polymorphisms were associated with the risk of NSCLC in the Chinese high altitude population. Future studies are mainly focused on these directions, one is to demonstrate the association between *RAD52* and NSCLC risk in larger sample sizes and different populations, the other is to investigate the exact mechanisms of *RAD52* influence on NSCLC risk.

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Author contribution(s)

Miao Li: Investigation; Supervision; Writing-original draft.

Rong Chen: Formal analysis; Investigation; Methodology; Writing-review & editing.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics approval and consent to participate

The informed consents were collected from all participants before this study. Our study was approved by the Ethical Committee of the Qinghai Province Cancer Hospital and conformed to the Declaration of Helsinki.

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Supplementary material

The reviews of this paper are available via the supplemental material section.

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