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Original Article

Identification of an SCLC susceptibility rs7963551 genetic polymorphism in a previously GWAS-identified 12p13.33 *RAD52* lung cancer risk locus in the Chinese population

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Abstract: As a well-known DNA repair gene, RAD52 plays an essential role in homologous recombination repair of double strand break, maintenance of genomic stability and prevention of cell malignant transformation. Previous genome-wide association studies (GWASs) have identified common genetic variants at 12p13.33 *RAD52* locus associated with lung cancer risk in Caucasians. However, little or nothing has been known about the *RAD52* single nucleotide polymorphisms (SNPs) in small cell lung cancer (SCLC) in the Chinese population. As a result, we examined the association between six *RAD52* SNPs (rs10849605, rs1051669, rs10774474, rs11571378, rs7963551 and rs6489769) and SCLC susceptibility in Chinese. After 520 SCLC cases and 1040 controls in two independent case-control sets were genotyped, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by logistic regression. We found that only the *RAD52* rs7963551 SNP was significantly associated with SCLC risk among six *RAD52* SNPs genotyped. The odds of having the rs7963551 CA genotype in SCLC patients was 0.38 (95% CI = 0.24-0.62, P = 1.1×10^{-4}) compared with the CC genotype. Stratified analyses of association between rs7963551 SNP and SCLC risk indicated that the functional polymorphism was only significantly associated with decreased risk among smokers but not nonsmokers. Our results demonstrated that the functional *RAD52* rs7963551 SNP contributes to susceptibility to developing SCLC in the Chinese population.

Keywords: GWAS, RAD52, single nucleotide polymorphism, small cell lung cancer, susceptibility

Introduction

Lung cancer currently ranks as the foremost cause of cancer deaths among men and women in the world. Lung cancer includes two common histological subtypes: non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). Although only about 20% lung cancer patients suffered from SCLC, the disease shows much more aggressive phenotype compared to NSCLC [1-3]. SCLC shows rapid doubling time, high growth fraction and early development of widespread metastases, which might be major causes of its poor prognosis [2, 3]. Although the etiology of SCLC is not completely clear, tobacco smoking has been found as one of major risk factors [2, 3]. Recent genome-wide association studies (GWAS) have identified multiple novel genetic polymorphisms associated with risk of lung cancer among different ethnic populations [4-12], which indicate that susceptibility may play a part in the pathogenesis of SCLC. However, most identified risk loci do not impact lung cancer susceptibly differentially by histology, suggesting that different genetic components may contribute to SCLC risk [4-12].

Table 1. Distribution of selected characteristics among SCLC cases and controls

Variable	Huaian set			Jinan set		
	Cases	Controls	P^a	Cases	Controls	P^a
	n (%)	*n* (%)		*n* (%)	*n* (%)	
	200	400		320	640	
Age (year)[b]			1.000			0.615
≤ 57	99 (49.5)	198 (49.5)		156 (48.9)	301 (47.0)	
> 57	101 (50.5)	202 (50.5)		164 (51.2)	339 (53.0)	
Sex			0.479			0.480
Male	148 (74.0)	285 (71.3)		251 (78.4)	489 (76.4)	
Female	52 (26.0)	115 (28.7)		69 (21.6)	151 (23.6)	
Smoking status			< 0.001			< 0.001
Yes	157 (78.5)	113 (28.3)		249 (77.8)	219 (34.2)	
No	43 (21.5)	287 (71.8)		71 (22.2)	421 (65.8)	
Clinical stage[c]						
Limited	113 (56.5)			182 (56.9)		
Extensive	87 (43.5)			138 (43.1)		

Note: SCLC, small cell lung cancer. [a]Two-side χ^2 test. [b]Median ages of patients for Shandong set and Jiangsu set are 57 years. [c]Classified according to the Veterans' Administration Lung Study Group.

Previous genome-wide association studies (GWASs) have identified common genetic variants at the 12p13.33 RAD52 locus associated with lung cancer risk in Caucasians. Shi et al. reported that the 12p13.33 locus (RAD52, rs6489769) is a susceptibility locus for squamous cell lung carcinoma in a GWAS of 5,355 European smoking lung cancer cases and 4,344 smoking controls [13]. The association was successfully replicated in three independent European samples totaling 3,359 cases and 9,100 controls (Odds Ratio [OR] = 1.20, $P_{combined} = 2.3\times10^{-8}$) [13]. In a meta-analysis of 16 GWASs (14,900 cases and 29,485 controls of European descent), Timofeeva et al found histology-specific effects for the 12p13.33 locus (*RAD52*, rs10849605) on squamous cell lung carcinoma (OR = 0.87, 95% confidence intervals [CIs] = 0.83-0.92, $P = 5.69\times10^{-8}$) as well as SCLC (OR = 0.85, 95% CIs = 0.79-0.91, $P = 2.00\times10^{-6}$) in Caucasians [14]. To explore how these genetic findings translate into non-European populations, they repeated the study in a Han Chinese study of 2,338 lung cancer cases and 3,077 controls, but found no associations in either squamous cell lung carcinoma (OR = 0.67, 95% CIs = 0.84-1.08, P = 0.45) or SCLC (OR = 0.97, 95% CIs = 0.77-1.23, P = 0.81) [14]. However, little or nothing has been reported the involvement of other RAD52 locus single nucleotide polymorphism (SNPs) in SCLC in the Chinese population, especially the regulatory rs7963551 A > C polymorphism in 3'-untranslated region (3'-UTR). Accumulated evidences demonstrated that the rs7963551 A-to-C change decreases the binding affinity of miRNA let-7 and, thus, elevated RAD52 transcription [15]. Considering the importance of the 12p13.33 RAD52 locus in lung cancer, we investigated the association between RAD52 genetic polymorphisms and SCLC risk using two large independent case-control studies.

Materials and methods

Study subjects

Two case-control sets (Jinan case-control set and Huaian case-control set) were included in the current study (**Table 1**). Jinan set: there were a total of 320 SCLC cases from Shandong Cancer Hospital, Shandong Academy of Medical Sciences (Jinan, Shandong Province, China) and sex- and age-matched 640 healthy controls. Patients were recruited between June 2009 and November 2014 at Shandong Cancer Hospital. Control subjects were randomly selected from a pool of 4500 individuals from a community cancer-screening program for early detection of cancer conducted in Jinan city as described in detail previously [16-18]. Huaian set: there were 200 SCLC cases from Huaian No. 2 Hospital (Huaian, Jiangsu Province, China) and sex- and age-matched (±5 years) 400 controls. Patients were consecutively recruited between January 2009 and January 2015 at Huaian No. 2 Hospital. Controls were cancer-free individuals selected from a community cancer-screening program (3600 individuals) for early detection of cancer conducted in

Table 2. Associations between candidate RAD52 genetic variants and SCLC risk in Huaian case-control set (Training set)

No.	rs ID	Base change	MAF[1]	Genotypes (200 SCLC cases and 400 healthy controls)				
				Common[2]	Heterozygous[2]	Rare[2]	OR (95% CI)[3]	*P*[3]
1	rs10849605	C > T	0.665	25/50	82/168	93/182	0.98 (0.75-1.27)	0.862
2	rs1051669	G > A	0.190	134/271	55/106	11/23	0.98 (0.72-1.35)	0.917
3	rs10774474	A > T	0.307	94/188	90/178	15/34	0.12 (0.78-1.34)	0.859
4	rs11571378	T > A	0.225	121/236	70/147	8/16	1.04 (0.77-1.41)	0.768
5	rs7963551	C > A	0.206	161/258	34/119	5/23	0.48 (0.33-0.69)	3.4×10^{-5}
6	rs6489769	T > C	0.500	51/100	99/200	50/100	1.02 (0.80-1.31)	0.870

Abbreviations: SCLC, small cell lung cancer; OR, odds ratio; CI, confidence interval. [1]MAF in healthy controls. [2]Number of SCLC case/number of control. [3]Allelic OR calculated by logistic regression.

Huaian city as described in detail previously [16-18]. Individuals who smoked one cigarette per day for over 1 year were considered as smokers. All subjects were unrelated ethnic Han Chinese. This study was approved by the Institutional Review Boards of Huaian No. 2 Hospital and Shandong Cancer Hospital, Shandong Academy of Medical Sciences. At recruitment, the written informed consent was obtained from each subject.

SNP selection and genotyping

Six RAD52 SNPs (rs10849605, rs1051669, rs10774474, rs11571378, rs7963551 and rs6489769) were included in this study. The selection criteria have been reported previously [19, 20]. All RAD52 SNPs were analyzed by the Mass Array system (Sequenom Inc., San Diego, California, USA) as described previously [19, 20]. A 5% blind, random sample of study subjects was genotyped in duplicates and the reproducibility was 100%.

Statistics

Pearson's X^2 test was used to calculate the differences in demographic variables and genotype distributions of RAD52 SNPs between SCLC cases and controls. Associations between RAD52 genotypes and SCLC risk by OR and their 95% CIs were examined utilizing unconditional logistic regression model. During calculating associations between functional candidate SNPs in RAD52 and SCLC risk in Huaian case-control set, we used the common genotypes of rs10849605 CC, rs1051669 GG, rs10774474 AA, rs11571378 TT, rs7963551 AA and rs6489769 TT as the reference genotypes. All ORs were adjusted for age, sex and smoking status, where it was appropriate. A *P* value of less than 0.05 was considered statistical significance, and all statistical tests were two-sided. All analyses were performed with SPSS software package (Version 16.0, SPSS Inc., Chicago, IL).

Results

Subject characteristics

We conducted a two-stage case-control study with a total of 520 SCLC cases and 1040 healthy controls. Parts of the two independent case-control sets have been described previously [16-18]. In brief, there were 200 primary SCLC patients in the discovery set recruited between January 2009 and January 2015 at Huaian No. 2 Hospital. In addition, we randomly selected 400 age (±5 years) and sex frequency-matched control subjects from a subject pool of 3600 individuals selected from a community cancer-screening program for early detection of cancer conducted in Huaian city as described in detail previously [16-18]. A total of 320 SCLC cases were enrolled in the validation set from Shandong Cancer Hospital, Shandong Academy of Medical Sciences (Jinan, Shandong Province, China) between June 2009 and November 2014. Also, we selected 640 controls who were frequency matched to the cases by sex and age (±5 years) from a pool of 4500 individuals from a community cancer-screening program for early detection of cancer conducted in Jinan city as described in detail previously [16-18]. Individuals who smoked one cigarette per day for over 1 year were considered as smokers. All subjects were unrelated ethnic Han Chinese. This study was approved by the Institutional Review Boards of Huaian No. 2 Hospital and Shandong Cancer Hospital, Shandong Academy of Medical Sciences. At recruitment, the written informed consent was obtained from each subject.

Table 3. Genotype frequencies of RAD52 rs7963551 C > A genetic variant among patients and controls and their association with SCLC risk

Genotypes		*RAD52* rs7963551 C > A			
		Patients No. (%)	Controls No. (%)	OR (95% CI)[a]	*P*-value
Huaian set		*n* = 200	*n* = 400		
	CC	161 (80.5)	258 (64.5)	Reference	
	CA	34 (17.0)	119 (29.8)	0.38 (0.24-0.62)	1.1×10^{-4}
	AA	5 (2.5)	23 (5.7)	0.64 (0.36-1.11)	0.113
Jinan set		*n* = 320	*n* = 640		
	CC	234 (73.1)	415 (64.8)	Reference	
	CA	78 (24.4)	199 (31.1)	0.69 (0.49-0.97)	0.032
	AA	8 (2.5)	26 (4.1)	0.74 (0.48-1.13)	0.162
Total		*n* = 520	*n* = 1040		
	CC	395 (76.0)	673 (64.7)	Reference	
	CA	112 (21.5)	318 (30.6)	0.53 (0.43-0.74)	4.7×10^{-5}
	AA	13 (2.5)	49 (4.7)	0.69 (0.49-0.97)	0.032

Abbreviations: SCLC, small cell lung cancer; OR, odds ratio; CI, confidence interval. [a]Data were calculated by logistic regression with adjustment for age, sex and smoking status.

Table 4. Risk of SCLC associated with *RAD52* rs7963551 A > C genotypes by age, sex and smoking status

Variable	*RAD52* rs7963551 A > C			
	CC[1]	CA+AA[1]	OR (95% CI)[2]	P
Age (year)				
≤ 57	190/328	65/171	0.63 (0.43-0.91)	0.015
> 57	205/345	60/196	0.48 (0.33-0.70)	1.4×10^{-4}
Sex				
Male	295/494	104/280	0.59 (0.44-0.79)	3.8×10^{-4}
Female	100/179	21/87	0.43 (0.23-0.79)	0.007
Smoking status				
No	84/472	30/236	0.73 (0.47-1.14)	0.161
Yes	311/201	95/131	0.49 (0.35-0.67)	1.0×10^{-5}
Clinical stage				
Limited	226/673	69/367	0.53 (0.38-0.73)	1.0×10^{-4}
Extensive	169/673	56/367	0.55 (0.39-0.78)	0.001

Abbreviations: SCLC, small cell lung cancer; OR, odds ratio; CI, confidence interval. [1]Number of case patients with genotype/number of control subjects with genotype. [2]Data were calculated by logistic regression, adjusted for sex, age, and smoking status, where it was appropriate.

Allelic frequencies and genotype distributions of functional RAD52 SNPs

The genotype frequencies of RAD52 candidate SNPs (rs10849605 C > T, rs1051669 G > A, rs10774474 A > T, rs11571378T > A, rs7963551 C > A and rs6489769 T > C) are shown in **Table 2**. The minor allele frequencies (MAFs) for rs10849605 T, rs1051669A, rs10774474T, rs11571378A, rs7963551A and rs6489769C were 0.665, 0.190, 0.307, 0.225, 0.206 and 0.500 in healthy control subjects in Huaian training case-control set. In SCLC cases, the MAFs for rs10849605 T, rs1051669A, rs10774474T, rs11571378A, rs7963551A and rs6489769C were 0.670, 0.193, 0.302, 0.216, 0.110 and 0.498 in the same case-control set. All observed genotype frequencies in either controls or cases conform to Hardy-Weinberg equilibrium. Distributions of the rs10849605, rs1051669, rs10774474, rs11571378, rs7963551 and rs6489769 genotypes were then compared among cases and controls. Frequencies of rs7963551 CC, CA, and AA genotypes among SCLC cases differed significantly from those among controls (X^2 = 16.41, $P = 2.7\times10^{-4}$, df = 2), with the frequency of AA homozygote being significantly lower among patients than among controls (11.0% vs. 20.6%). However, no statistically significant differences of rs10849605, rs1051669, rs10774474, rs11571378 and rs6489769 genotypes were observed between cases and control subjects (all P > 0.05) (**Table 2**). Therefore, we did no other analyses of these five SNPs in the next studies.

Association between RAD52 rs7963551 SNP and SCLC risk

Unconditional logistic regression analyses were utilized to calculate associations between genotypes of *RAD52* rs7963551 C > A polymorphism and SCLC risk (**Table 3**). The *RAD52* rs7963551A allele was shown to be a protective allele. Individuals with the rs7963551 CA genotype had an OR of 0.38 (95% CI =

0.24-0.62, $P = 1.1\times10^{-4}$) for developing SCLC in Huaian Set, compared with individual having the rs7963551 CC genotype. However, the rs7963551 AA genotype was not associated with decreased SCLC risk compared with the CC genotype (OR = 0.64, 95% CI = 0.36-1.11, $P = 0.113$). In Jinan set, we observed that individuals with the rs7963551 CA genotype had a 0.69-fold decreased risk to develop SCLC compared to the CC genotype carriers (95% CI = 0.49-0.97, $P = 0.032$) (**Table 3**). However, there was no statistically significant association between the rs7963551 AA genotype and SCLC risk (OR = 0.74, 95% CI = 0.48-1.13, $P = 0.162$). In the combined analyses, we found that both rs7963551 CA and AA genotypes contributed to significantly decreased SCLC risk (OR = 0.53, 95% CI = 0.43-0.74, $P = 4.7\times10^{-5}$, or OR = 0.69, 95% CI = 0.49-0.97, $P = 0.032$) (**Table 3**). All ORs were calculated with adjustments of sex, age, and smoking status.

Stratified analyses of association between RAD52 rs7963551 SNP and SCLC risk

Associations between *RAD52* rs7963551 genotypes and SCLC risk by stratifying for age, sex, and smoking status were furtherer examined using the combined data of two case-control sets (**Table 4**). Significant associations were observed in most strata except for the subgroups of smoking status. In detail, nonsmokers carrying rs7963551 CA or AA genotype showed no significantly decreased risk to develop SCLC compared with CC carriers (OR = 0.73, 95% CI = 0.47-1.14, $P = 0.161$). Among smokers, there were significant associations between rs7963551 CA and AA genotypes and SCLC risk (OR = 0.49, 95% CI = 0.35-0.67, $P = 1.0\times10^{-5}$) (**Table 4**).

Discussion

In the current study, we examined the association between the 12p13.33 RAD52 locus genetic variants and SCLC susceptibility in a two-stage case-control design. Interestingly, we only identified RAD52 3'-UTR rs7963551 polymorphism was significantly associated with decreased SCLC risk in the Chinese population. Stratified analyses of association between the RAD52 rs7963551 polymorphism and SCLC risk indicated that the functional genetic variant was only significantly associated with SCLC susceptibility among smokers but not nonsmokers.

In yeast, RAD52 was originally identified as a key member in recombination repair. Through involving in strand exchange and annealing of strands during homologous recombination (HR), RAD52 is predominantly recruited for DNA repair during S phase of the cell cycle [13, 14]. In humans, RAD52, as a key member involved in the HR pathway, plays a crucial role in the regulation of HR-related genomic instability [21, 22]. RAD52 depletion in human cells with the deficient RAD52, PALB2 or BRCA2 gene, is synthetically lethal via decreasing cell survival by reducing rates of homologous recombination and by increasing damage-induced chromosomal abnormalities [23-25]. However, the role of RAD52 in SCLC remains elusive. Recent GWASs indentified the 12p13.33 RAD52 locus as a lung cancer susceptibility locus in Caucasians, especially in squamous cell lung carcinoma and SCLC. However, it is still unclear whether the 12p13.33 RAD52 locus polymorphisms contribute to SCLC risk in the Chinese population. We found that the rs7963551 polymorphism locating in the let-7 target sequence of the RAD52 3'-UTR is associated with SCLC risk, perhaps through impacting RAD52 expression.

Several limitations may exist in this study. First, there might be bias of inherent selection since all cases were from the hospital in this hospital-based study. As a result, validation of our findings in a population-based prospective study is important. Second, the relative small sample size may limit the statistical power of this study.

In summary, our study elucidated that functional RAD52 rs7963551 polymorphism was associated with SCLC risk in Chinese populations, especially in smokers. Given this fact, further efforts are warranted to explore whether RAD52 rs7963551 genetic variant could be potentially useful for diagnosis of SCLC.

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Disclosure of conflict of interest

None.

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