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XRCC1 rs25487 polymorphism is associated with lung cancer risk in epidemiologically susceptible Chinese people

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ABSTRACT. Base excision repair (BER) plays an important role in maintaining genome integrity and anti-cancer drug resistance. Single nucleotide polymorphisms (SNPs) in BER genes were detected in 500 lung cancer patients and 500 cancer-free controls. A logistic regression model was applied to analyze the relationship between lung cancer susceptibility and BER SNPs coupled with a wide range of epidemiological factors in a Chinese population. SNPs including rs25487 in the X-ray repair cross-complementing group 1 gene, rs1052133 in the 8-oxoguanine DNA glycosylase gene, and rs1136410 in the poly (ADP-ribose) polymerase 1 gene were identified. Multivariate analysis showed that the rs25487-AG genotype was associated with a higher incidence of lung cancer compared with the GG genotype. The rs25487 SNP was associated with the pathological distribution of lung cancer. Moreover, rs1052133-GG was associated with early age of lung cancer onset compared with the CC genotype. Our data demonstrated that the SNPs rs25487 and rs1052133 are risk factors for lung cancer in epidemiologically susceptible Chinese people.

Key words: Base excision repair; Lung cancer; 8-Oxoguanine DNA glycosylase rs1052133; poly(ADP-ribose) polymerase 1 rs1136410; Single nucleotide polymorphisms; X-ray repair cross-complementing group 1 rs25487

INTRODUCTION

Over the past few decades, great advances have been made in the management of cancer patients because of a combination of earlier detection, better access to care, and improved treatment methods (Karim-Kos et al., 2008). However, cancer prevention remains challenging (Janssen-Heijnen and Coebergh, 2003; Lutz et al., 2003). Lung cancer is one of the most fatal forms of cancer, particularly in China (Parkin et al., 2005). Cigarette smoking is considered to be an important risk factor for lung cancer, but only approximately 10-15% of smokers develop this disease. This suggests that individual variation exists in the genetic susceptibility to lung cancer in the general population (Shields and Harris, 2000). Thus, reliable biomarkers for identifying high-risk populations for lung cancer are urgently required. Genetic susceptibility markers will guide not only individualized cancer therapy but also early preventive care.

Base excision repair (BER) is critical for the maintenance of genome integrity, and dysregulation of BER is related to cancer risk and premature aging (Maynard et al., 2009). Several single nucleotide polymorphisms (SNPs) in BER genes have been found to be associated with lung cancer. The rs25487 (Arg399Gln) in X-ray repair cross-complementing group 1 (*XRCC1*), rs1052133 (Ser326Cys) in 8-oxoguanine DNA glycosylase (*OGG1*), and rs1136410 (Val762Ala) in poly(ADP-ribose) polymerase 1 (*PARP1*) are all functional SNPs, but their roles in lung cancer susceptibility remain unclear. Moreover, conflicting results have been reported for the association of the *XRCC1* Arg399Gln polymorphism and lung cancer risk (Zhou et al., 2003; Popanda et al., 2004; Matullo et al., 2006; Ryk et al., 2006). Similarly, inconclusive results have been obtained for the *OGG1* Ser326Cys polymorphism regarding its association with cancer (Janssen et al., 2001; Vodicka, et al., 2007; Hatt et al., 2008; Obtulowicz et al., 2010; Jensen et al., 2012). In addition, little is known regarding the relationship between the *PARP1* rs1136410 (Val762Ala) polymorphism and lung cancer risk (Zhang et al., 2005). To determine the functional association of SNPs in BER genes and the risk of lung cancer in a Chinese population, we analyzed the relationship between lung cancer susceptibility and the polymorphisms rs25487 (Arg399Gln) in *XRCC1*, rs1052133 in *OGG1* (Ser326Cys), and rs1136410 (Val762Ala) in *PARP1*. In addition, we evaluated the roles of these SNPs in combination with a wide range of epidemiological factors, including education level, body mass index, family history of cancer, prior diagnosis of chronic obstructive pulmonary disease or pneumonia, duration of smoking, heavy cooking emissions, and occupational exposure to pesticides, gasoline, or diesel.

MATERIAL AND METHODS

Study population

This was a hospital-based case-control study involving a total of 1000 subjects from the northeastern region of China (Changchun city, Jilin Province). All subjects were local residents of the Han Province, including 500 clinically diagnosed lung cancer patients and 500 cancer-free controls. Eligible patients had histologically confirmed primary lung cancers with no previous cancer history and were not receiving radiotherapy or chemotherapy for other conditions. Control participants were randomly selected individuals receiving routine physical examinations in our hospital. They were demographically matched to the cases by age, gender, and residential area. The study was approved by the Ethics Committee of the First Hospital of Jilin Medical University, and conducted according to the Declaration of Helsinki. All subjects signed an informed consent form.

Diagnostic criteria and data collection

Standardized interviews were conducted by trained interviewers at the hospital or participant's home. Information recorded included sociodemographic details, medical history, family history, lifestyle history, and cancer diagnosis (Table 1). Risk factor information and peripheral blood lymphocytes were collected for the time prior and up to the diagnosis of patients, and the interview date for controls.

Genotyping and quality control

We examined 3 non-synonymous gene polymorphisms in the BER pathway, including rs25487 (Arg399Gln) in *XRCC1*, rs1052133 in *OGG1* (Ser326Cys), and rs1136410 (Val762Ala) in *PARP1*. Genomic DNA was isolated from peripheral blood lymphocytes of the study subjects. MassArray (Sequenom, San Diego, CA, USA) was used to genotype all markers using allele-specific matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry. Primers and multiplex reactions were designed using an online program (www.RealSNP.com). Concordance among the 3 genomic control DNA samples presented in duplicate was 100%. Of the SNPs with genotyping data, the call rate was greater than 95%.

Statistical analysis

Hardy-Weinberg equilibrium (HWE) was evaluated using a chi-square (χ^2) test to compare the expected genotype frequencies with observed genotype frequencies in cancer-free controls, as well as to determine whether there were differences in the distributions of genotypes and alleles between cases and controls. Clinico-pathological data from lung cancer patients were also examined. A logistic regression model was used to test the associations between risk factors including SNPs and lung cancer in the case-control study. All categorical variables were set as dummy variables. The first category of each environmental variable was selected as a baseline, and the low-risk allele of each locus was selected as the baseline. All analyses were conducted using the SPSS software version 19.0 (SPSS, Inc., Chicago, IL, USA). A P value of less than 0.05 was considered to be statistically significant.

RESULTS

Participant characteristics and genotypes

We recruited 500 cases of lung cancer and 500 cancer-free controls between 2010 and 2012. Most lung cancer cases in the study population presented with non-small cell lung cancer. The genotype distribution of the rs25487, rs1052133, and rs1136410 polymorphisms were in Hardy-Weinberg equilibrium in healthy participants ($P > 0.05$). Specifically, in lung cancer patients and healthy participants, 259 (51.8%) and 273 (54.6%) had the *XRCC1* rs25487-GG genotype, respectively, 24 (4.8%) and 43 (8.6%) had the *XRCC1* rs25487-AA genotype, 77 (15.4%) and 80 (16.0%) had the *OGG1* rs1052133-CC genotype, 182 (36.4%) and 165 (33.0%) had the *OGG1* rs1052133-GG genotype, 151 (30.2%) and 140 (28.0%) had the *PARP1* rs1136410-TT genotype, and 97 (19.4%) and 109 (21.8%) had the *PARP1* rs1136410-CC genotype. The distribution of *XRCC1* rs25487, *OGG1* rs1052133, and *PARP1* rs1136410 in lung cancer patients and healthy participants, as well

as the distribution of study-specific risk factors between cases and controls, are shown in Table 1.

Table 1. Demographics and genotypes of cases and control group.

Characteristics	Case group (N = 500)	Control group (N = 500)
rs25487		
GG	259 (51.8%)	273 (54.6%)
AA	24 (4.8%)	43 (8.6%)
AG	217 (43.4%)	184 (36.8%)
rs1052133		
GG	77 (15.4%)	80 (16.0%)
CC	182 (36.4%)	165 (33.0%)
GC	241 (48.2%)	255 (51.0%)
rs1136410		
TT	151 (30.2%)	140 (28.0%)
CC	97 (19.4%)	109 (21.8%)
TC	252 (50.4%)	251 (50.2%)
Gender		
male	305 (61%)	302 (60.4 %)
female	195 (39%)	198 (39.6%)
Age		
<30	2 (0.4%)	5 (1.0%)
30-39	14 (2.8%)	16 (3.2%)
40-49	64 (12.8%)	70 (14.0%)
50-59	176 (35.2%)	196 (39.2%)
60-69	174 (34.8%)	148 (19.7%)
≥70	70 (14.0%)	65 (13.0%)
Education		
Junior high school and lower	318 (63.6%)	130 (26.0%)
High school	97 (19.4%)	144 (28.8%)
Further education	85 (17.0%)	226 (45.2%)
Smoking		
(Pack/years)	14.25 (0-36.0)	0.0 (0.0-6.9)
Exposure to pesticide		
Absent	398 (79.6%)	473 (94.6%)
Present	102 (20.4%)	27 (5.4%)
Exposure to gasoline/diesel		
Absent	487 (97.4%)	496 (99.2%)
Present	13 (2.6%)	4 (0.8%)
Exposure to ink		
Absent	493 (98.6%)	497 (99.4%)
Present	7 (1.4%)	3 (0.6%)
Cooking emissions		
(Total dish/years)		
Absent	244 (48.8%)	250 (50.0%)
≤50	149 (29.8%)	152 (30.4%)
51-100	61 (12.2%)	80 (16.0%)
101-150	46 (9.2%)	18 (3.6%)
Pneumonia		
History Absent	477 (95.4%)	490 (98.0%)
History Present	23 (4.6%)	10 (2.0%)
COPD		
History Absent	449 (89.8%)	489 (97.8%)
History Present	51 (10.2%)	11 (2.2%)
Pulmonary tuberculosis		
History Absent	470 (94.0%)	486 (97.2%)
History Present	30 (6.0%)	14 (2.8%)
Bronchial asthm		
History Absent	488 (97.6%)	495 (99.0%)
History Present	12 (2.4%)	5 (1.0%)
Family history		
of cancer		
History Absent	330 (66.0%)	397 (79.4%)
History Present	170 (34.0%)	103 (20.6%)
BMI		
(kg/m^2)		
<18.5	49 (9.8%)	15 (3.0%)
18.5-24	302 (60.4%)	230 (46.0%)
≥24	149 (29.8%)	255 (51.0%)

Multivariate analysis of the association between *XRCC1* rs25487, *OGG1* rs1052133, and *PARP1* rs1136410 polymorphisms and lung cancer risk

Multivariate analysis demonstrated a significantly increased risk of lung cancer with lower education levels, decreased body mass index, family history of cancer, prior diagnosis of chronic obstructive pulmonary disease or pneumonia, occupational exposure to pesticide, occupational exposure to gasoline or diesel, heavy smoking, and heavy cooking emissions. Compared with the GG and AA genotypes, the *XRCC1* rs25487-AG genotype was generally associated with a higher incidence of lung cancer (P = 0.038) when environmental and life-style factors were incorporated into the model (Table 2).

Table 2. Multivariate risk model with adjusted odds ratios and 95% confidence intervals.

Risk factors	Exp (B)	95%CI	P value
Education	0.000		
Junior high school and lower	1.00	Reference	
High school	0.316	(0.217-0.459)	0.000
Further education	0.190	(0.131-0.276)	0.000
Smoking (Pack/years)	1.031	(1.023-1.040)	0.000
Occupational exposure to pesticide			
Absent	1.00	Reference	0.036
Present	1.723	(1.037-2.862)	
Exposure to gasoline/diesel			
Absent	1.00	Reference	
Present	4.907	(1.376-17.496)	0.014
Cooking emissions (Total dish/years)	0.004		
≤50	1.00	Reference	
51-100	1.420	(1.001-2.016)	0.049
101-150	0.946	(0.598-1.496)	0.812
>150	2.354	(1.219-4.544)	0.011
COPD			
History Absent	1.00	Reference	0.000
History Present	4.058	(1.893-8.700)	
Pneumonia			
History Present	1.00	Reference	0.023
History Absent	0.361	(0.150-0.869)	
Family history of cancer			
History Absent	1.00	Reference	0.000
History Present	2.106	(1.498-2.962)	
BMI (kg/m2)			
<18.5	1.00	Reference	0.000
18.5-24	0.436	(0.221-0.864)	0.017
≥24	0.227	(0.113-0.455)	0.000
XRCC1 rs25487			
GG	1	Reference	
AG	1.393	(1.018-1.907)	0.038
AA	0.722	(0.384-1.357)	0.311

Associations between *XRCC1* rs25487, *OGG1* rs1052133, and *PARP1* rs1136410 and clinicopathological characteristics of lung cancer

We next evaluated the associations between pathological type, age at onset, and gender of lung cancer patient and *XRCC1* rs25487, *OGG1* rs1052133, and *PARP1* rs1136410 in the case-only analysis with 500 patients. There was a statistically significant difference between pathological types of lung cancer and *XRCC1* rs25487 (P = 0.023). However, there was no significant difference between the *OGG1* rs1052133 or *PARP1* rs1136410 SNP in the

pathological type of lung cancer (Table 3). We further analyzed the age at onset of lung cancer. The mean ages of lung cancer onset for the CC, GG, and GC genotypes of *OGG1* rs1052133 were 59.65 ± 10.46, 56.56 ± 9.94, and 58.79 ± 9.45 years, respectively. *OGG1* rs1052133 GG was associated with early onset of lung cancer compared with CC (P = 0.022). There was no significant difference in age of onset of lung cancer with the *XRCC1* rs25487 as well as *PARP1* rs1136410 SNPs. Finally, we evaluated the gender at onset of lung cancer for these 3 SNPs, but found no statistically significant association (Table 3).

Table 3. Association of SNPs with clinico-pathological data from lung cancer patients.

Characteristics		Gender		P value	Age (yrs.)	P value	Histology types				P value
		M	F				SQ	AD	SC	OC	
rs25487	GG	155	104	0.190	58.81 ± 10.09	reference	72	84	73	30	0.023
	AA	11	13		57.50 ± 11.29	0.536	3	16	5	0	
	AG	139	78		58.83 ± 9.63	0.533	66	76	48	27	
rs1052133	GG	117	65	0.481	56.56 ± 9.94	reference	53	57	49	23	0.517
	CC	44	33		59.65 ± 10.46	0.022	17	35	17	8	
	GC	144	97		58.79 ± 9.451	0.086	71	84	60	26	
rs1136410	TT	94	57	0.487	59.37 ± 9.27	reference	48	50	35	18	0.757
	CC	54	43		57.80 ± 9.79	0.226	21	38	26	12	
	TC	157	95		58.76 ± 10.38	0.420	72	88	65	27	

M = male; F = female; SQ = squamous cell; AD = adenocarcinoma; SC = small cell; OC = other carcinomas.

DISCUSSION

In this study, we found that lower education, decreased body mass index, family history of cancer, prior diagnosis of chronic obstructive pulmonary disease or pneumonia, heavy smoking, exposure to heavy cooking emissions, and occupational exposure to pesticide, gasoline and/or diesel were significantly associated with the risk of lung cancer. Most importantly, we discovered that the *XRCC1* rs25487-AG genotype was a risk factor of lung cancer when environmental and lifestyle factors were taken into consideration. *OGG1* rs1052133-GG was associated with early age of lung cancer onset.

Reactive oxygen species generated during normal cellular metabolism and in response to exogenous genotoxins lead to DNA base damage (Feig et al., 1994; Bjelland and Seeberg, 2003; Toyokuni and Akatsuka, 2007). The predominant DNA repair pathway that removes oxidized and alkylated bases is the BER pathway. A series of enzymes are involved in BER, including OGG1, XRCC1, and PARP1, which harbor polymorphisms associated with the risk of malignancy. A functional SNP in *XRCC1* rs25487 with a G to A base change leads to an arginine to glutamine substitution (Kohno et al., 2006). Duell et al. (2002) reported that the minor allele (A) for rs25487, the 399Gln allele, was associated with a higher frequency of glycophorin mutation, elevated DNA adduct levels, higher baseline sister chromatid exchange frequency, and increased sensitivity to ionizing radiation, all of which may occur because of reduced BER function. Accumulating evidence has demonstrated that this SNP is associated with the risk of lung cancer (Ito et al., 2004; Shen et al., 2005; Zhang et al., 2005; Zienolddiny et al., 2006). In agreement with these findings, our results showed that the *XRCC1* rs25487-AG genotype was related to a higher incidence of lung cancer compared with GG genotypes in a Chinese population.

rs1052133 OGG1 is also a functional SNP. The change from C to G in rs1052133

OGG1 leads to a serine to cysteine (Ser326Cys) substitution. Though the epidemiological studies of the association between the *OGG1* Ser326Cys polymorphism and cancer have revealed a weak association (Le Marchand et al., 2002; Park et al., 2004; Hung et al., 2005a,b), homozygous carriers of the Ser326Cys genotype were shown to have a higher risk of lung cancer. However, several studies have reported that the *OGG1* Ser326Cys polymorphism does not contribute to lung cancer risk (Liang et al., 2005; Qian et al., 2011). In our study, no apparent relationship between the SNP of *OGG1* rs1052133 and lung cancer risk was observed. Interestingly, we found that *OGG1* rs1052133-GG was associated with early age of lung cancer onset. Some studies examining the relationship between the *OGG1* Ser326Cys genotype and BER repair activity or OGG1 expression have revealed that the *OGG1* Ser326Cys polymorphism is not associated with differences in repair capacity or OGG1 expression (Janssen et al., 2001, 2012), whereas other studies have reported that the Ser326Cys genotype causes substantially decreased repair activity or higher mRNA levels of *OGG1* (Vodicka et al., 2007; Hatt et al., 2008; Obtulowicz et al., 2010). Thus, based on the literature, we cannot draw conclusions regarding the association between the *OGG1* Ser326Cys polymorphism and the level of DNA damage and repair capacity of BER in the general population. Further studies involving transgenic mouse models are needed to determine the underlying mechanisms.

Human PARP1 plays a crucial role in the BER pathway (Dantzer et al., 1999; Wieler et al., 2003). PARP1 is constitutively expressed, and its catalytic activity is strongly stimulated in response to single- or double-stranded DNA breaks (Lindahl et al., 1995). An SNP in the *PARP1* gene at rs1136410 is located in the 6th helix of the catalytic domain, and a T-to-C transition at *PARP1* rs1136410 results in a valine to alanine substitution at codon 762 (Lockett et al., 2004). Although several studies have suggested that *PARP1* rs1136410 is associated with the risk of several cancers (Hao et al., 2004; Lockett et al., 2004; Figueroa et al., 2007; Roszak et al., 2013; Tang et al., 2013), little is known regarding the association between *PARP1* rs1136410 and lung cancer (Zhang et al., 2005). In this study, we did not observe a relationship between *PARP1* rs1136410 and lung cancer risk in our Chinese population. Additional epidemiological studies including different countries should be conducted.

This study is novel for a number of reasons. First, the SNPs examined are functional SNPs. Second, as environmental and lifestyle factors are very important in the development of cancer, the effects of an SNP may be weakened or dismissed when environmental and lifestyle factors are incorporated into the model. Thus, very few studies of lung cancer susceptibility and SNPs have examined a large number of environmental and lifestyle factors. When environmental and lifestyle factors were incorporated, the rs25487 *XRCC1* SNP was still significantly associated with lung cancer, indicating that this locus is strongly related to lung cancer development. In addition, the relationship between rs25487 *XRCC1* and lung cancer risk can be explained by the recently elucidated molecular functions of rs25487 *XRCC1* (Duell et al., 2002; Ito et al., 2004; Shen et al., 2005; Zhang et al., 2005; Kohno et al., 2006; Zienolddiny et al., 2006).

Because there are many SNPs in genes encoding other important components of the BER pathway, it is important to combine all BER genes with SNPs in order to improve the classification of lung cancer risk. Moreover, this was a retrospective study and the sample size was not large; therefore, the results must be validated by a large-scale prospective cohort study.

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Conflicts of interest

The authors declare no conflict of interest.

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