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ORIGINAL ARTICLE

Mouse double minute-2 homolog (*MDM2*)-rs2279744 polymorphism associated with lung cancer risk in a Northeastern Chinese population

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Abstract

Background: Altered expression or function of mouse double minute-2 (*MDM2*) protein could contribute to lung carcinogenesis; thus, this study investigated *MDM2*-rs2279744 polymorphism together with other epidemiologic factors for their association with lung cancer risk.

Methods: A total of 500 lung cancer patients and 500 age and gender-matched healthy controls living in Northeastern China were recruited for genotyping of *MDM2*-rs2279744. Clinicopathological data was collected and subjected to univariate and multivariate analyses.

Results: In univariate analysis, the *MDM2*-rs2279744 G/G genotype versus T/T + T/G genotypes showed a tendency toward a higher incidence of lung cancer in the recessive model ($P = 0.043$). However, there were no significant differences when it was analyzed by the dominant, additive, or multiplicative models. A significantly increased lung cancer risk was observed associated with lower education level, lower body mass index, cancer family history, prior diagnosis of chronic obstructive pulmonary disease and pneumonia, exposure to pesticide or gasoline/diesel, tobacco smoking, and heavy cooking emissions when assessed by multivariate analyses. Moreover, *MDM2*-rs2279744 was still a significant risk factor even after incorporating environmental and lifestyle factors. However, there was no association between *MDM2*-rs2279744 and other factors.

Conclusions: The *MDM2*-rs2279744 G/G genotype was associated with a higher lung cancer risk, even after incorporating other epidemiologic factors.

Introduction

Lung cancer is one of the most commonly diagnosed malignancies in the world, accounting for 17.6% (1.18 million people) of worldwide cancer-related deaths annually.[1] In China, national death survey and cancer registration data shows that lung cancer is also the leading cause of cancer death in most Chinese cities.[2] Lung cancer is indeed a major global public health challenge. However, to date, the precise mechanisms of lung carcinogenesis are still not fully understood. A previous study showed that low-penetrance susceptibility genes in combination with environmental factors were of importance in lung cancer development and contributed to lung cancer risk.[3] Therefore, further studies in this field could lead to better understanding of lung cancer risk and susceptibility genes.

Toward this end, our research focuses on murine double minute-2 (*MDM2*), which is a negative regulator of p53 tumor suppressor. *MDM2* protein functions as an E3 ubiquitin ligase that recognizes the N-terminal transactivation domain of p53 protein, and inhibitor of p53 transcriptional activation. *MDM2* protein plays an important role in regulation of p53 pathway activity. A single nucleotide polymorphism (SNP) of *MDM2*-rs2279744 was identified as a functional SNP with a T-to-G transversion and has been proven to increase the affinity of the transcriptional activator Sp1 and lead to expression of higher *MDM2* messenger ribonucleic acid (mRNA) and protein levels, subsequently attenuating p53 pathway activity.[4] The elevated levels of *MDM2* protein in carriers of the G-allele will inhibit the p53-induced apoptotic responses to DNA-damage, thereby resulting in genetic instability (such as gene

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mutations in the cells) and eventually leading to tumorigenesis at a young age.[5]

However, the association between *MDM2*-rs2279744 SNP and lung cancer risk seems plausible; for example, Hu *et al.*[6] and Pine *et al.*[7] reported that there was no significant association between *MDM2* SNP309 variant genotypes and lung cancer risk, whereas studies conducted by Zhang *et al.*[8] and Lind *et al.*[9] showed that the G-allele in the *MDM2* promoter was associated with a higher lung cancer risk. Additionally, Chua *et al.* showed that the T-allele in the *MDM2* promoter increased lung cancer risk.[10] Other studies have demonstrated that *MDM2*-rs2279744 SNP is associated with lung cancer risk at an early age.[11,12] Thus, this case-control study investigated this functionally important *MDM2*-rs2279744 SNP in our hospital for association with lung cancer risk, together with other clinicopathological and epidemiologic data from lung cancer patients, as other factors, such as sociodemographic information, medical and family history, and lifestyle data, may also play a role in lung carcinogenesis.[13–19]

Patients and methods

Study population

The study was approved by the Ethics Committee of the First Hospital of Jilin Medical University, and conducted according to the Declaration of Helsinki Principles. All subjects signed a written informed consent form. This hospital-based case-control study recruited a total of 1000 subjects from Northeastern China between January 2010 and December 2012. Patients who met the following criteria were included in the study: (i) a minimum of 18 years of age; (ii) primary lung cancer confirmed by pathology; (iii) Han descent; (iv) reside in Northeastern China for at least 10 years; and (v) no radiotherapy or chemotherapy performed before blood withdrawal. Patients with any of the following conditions were excluded: (i) secondary (metastatic) lung cancer; (ii) double or multiple primary cancers; and (iii) relapse after operation. Healthy controls had no cancer history within five years of the interview date. These healthy controls were randomly selected individuals who received routine physical examinations in our hospital and were matched to cases by age, gender, and residential area.

Diagnostic criteria and data collection

Standardized interviews were conducted by well-trained interviewers at either the hospital or at the homes of the studied subjects. Sociodemographic information, medical and family history, lifestyle data, and cancer diagnosis were recorded (Table 1). Risk factors and peripheral blood lymphocytes were collected for the time prior and up to the index date (i.e. the time of diagnosis for cases and the interview date for controls). However, there were no data available on exposure to asbestos for analysis.

Genotyping and quality control

Genomic DNA was extracted from the peripheral blood lymphocytes of all subjects. MassArray (Sequenom, Inc., San Diego, CA, USA) was used for genotyping all markers by using allele specific matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Primers and multiplex reactions were designed using the RealSNP.com website. All lung cancer patients and healthy controls were genotyped for MDM2-rs2279744 polymorphisms. Concordance among the three genomic control DNA samples presented in duplicate was 100%. Of SNPs with genotyping data, the call rate was >95%.

Statistical analysis

The Hardy-Weinberg equilibrium was performed to analyze the balance of case and control using a goodness-of-fit chi-square (χ^2) test. The univariate χ^2 test was used to determine genotype frequencies with observed genotype frequencies in healthy controls versus lung cancer cases and association between *MDM2*-rs2279744 SNP and clinicopathological data from lung cancer patients. Multivariate logistic regression analysis was used to assess the association between risk factors (SNPs were included) and lung cancer risk. All categorical variables were set as dummy variables. The first category of each environmental variable was selected as the baseline, as well as the low-risk allele of each locus. All analysis was conducted using SPSS v19.0 software (SPSS, Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Univariate analysis of *MDM2*-rs2279744 polymorphism for association with lung cancer risk

A total of 1000 subjects (i.e. 500 incident lung cancer cases and 500 healthy controls) were recruited for genotyping of *MDM2*-rs2279744. Univariate analysis revealed that lung cancer occurred more frequently in individuals with a family history of cancer, history of chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, pneumonia, low body mass index (BMI), tobacco smoking, occupational exposure to pesticides, gasoline, or diesel, and exposure to cooking emissions, as well as a low education level (Table 1).

Furthermore, our data also showed that the genotype distribution of *MDM2*-rs2279744 polymorphism was followed by Hardy-Weinberg equilibrium ($P > 0.05$). *MDM2* G/G

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Table 1 Univariate analysis of the risk factors in cases and controls

Characteristic		Case (n = 500 [%])	Control (n = 500[%])	P-value
Gender	Male	305 (61.0)	302 (60.4)	0.846
	Female	195 (39.0)	198 (39.6)	
Age (years)	<30	2 (0.4)	5 (1.0)	0.421
	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)	0.000
	High school	97 (19.4)	144 (28.8)	
	Greater than high school	85 (17.0)	226 (45.2)	
Smoking (pack-years)		14.25 (0.0–36.0)	0.00 (0.0–6.9)	0.000
Occupational exposure	Absent	398 (79.6)	473 (94.6)	0.000
Pesticide	Present	102 (20.4)	27 (5.4)	
Exposure Gasoline /diesel	Absent	487 (97.4)	496 (99.2)	0.037
	Present	13 (2.6)	4 (0.8)	
Exposure to Ink	Absent	493 (98.6)	497 (99.4)	0.217
	Present	7 (1.4)	3 (0.6)	
Cooking emissions (total dish-years)	Absent	244 (48.8)	250 (50.0)	0.003
	≤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)	0.025
	Present	23 (4.6)	10 (2.0)	
COPD history	Absent	449 (89.8)	489 (97.8)	0.000
	Present	51 (10.2)	11 (2.2)	
Pulmonary tuberculosis history	Absent	470 (94.0)	486 (97.2)	0.016
	Present	30 (6.0)	14 (2.8)	
Bronchial asthma history	Absent	488 (97.6)	495 (99.0)	0.097
	Present	12 (2.4)	5 (1.0)	
Cancer family history	Absent	330 (66.0)	397 (79.4)	0.000
	Present	170 (34.0)	103 (20.6)	
BMI (kg/m^2)	<18.5	49 (9.8)	15 (3.0)	0.000
	18.5–24	302 (60.4)	230 (46.0)	
	≥24	149 (29.8)	255 (51.0)	

*Including large cell, mixed cell carcinoma, or undifferentiated carcinoma. BMI, body mass index; COPD, chronic obstructive pulmonary disease.

genotype occurred in 25.8%, G/T genotype in 48.8%, and T/T genotype in 25.4% of lung cancer cases, with a similar distribution in the healthy control ($P > 0.05$). Univariate analysis showed that when comparing G/G with T/T + T/G genotypes, the G/G had a tendency toward a higher incidence of lung cancer in the recessive model ($P = 0.043$; Table 2). However, there were no significant differences in the dominant, additive, or multiplicative models.

Table 2 Association of *MDM2*-rs2279744 polymorphism with lung cancer risk analyzed by univariate analysis

	Genotype	Exp (B)	95% CI	P-value
Additive model	T/T	1	Reference	—
	G/T	0.932	(0.691–1.258)	0.645
	G/G	1.295	(0.906–1.849)	0.156
Dominant model	T/T	1	Reference	—
	G/G + G/T	1.032	(0.777–1.370)	0.828
Recessive model	T/T + G/T	1	Reference	—
	G/G	1.357	(1.009–1.824)	0.043
Multiplicative model	G-allele	1.131	(0.947–1.351)	0.174

CI, confidence interval; *MDM2*, mouse double minute-2.

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Table 3 Multivariate risk model with adjusted odds ratios and 95% CI

Risk factors	Exp (B)	95% CI	*P*-value
Education level			0.000
Junior high school and lower	1.00	Reference	—
High school	0.307	0.211–0.446	0.000
Greater than high school	0.195	0.134–0.284	0.000
Smoking (pack-years)	1.032	1.023–1.041	0.000
Occupational exposure to pesticide			
Absent	1.00	Reference	—
Present	1.700	1.024–2.824	0.040
Exposure to gasoline /diesel			
Absent	1.00	Reference	—
Present	5.065	1.430–17.945	0.012
Cooking smoke (total dish-years)			0.004
≤50	1.00	Reference	—
51–100	1.417	0.998–2.011	0.869
101–150	0.962	0.610–1.519	0.006
>150	2.511	1.301–4.846	0.026
COPD history			
Absent	1.00	Reference	—
Present	4.162	1.950–8.883	0.000
Pneumonia history			
Present	1.00	Reference	—
Absent	0.369	0.151–0.902	0.029
Cancer family history			
Absent	1.00	Reference	—
Present	2.024	1.442–2.842	0.000
BMI (kg/m^2)			0.000
<18.5	1.00	Reference	
18.5–24	0.426	0.215–0.843	0.014
≥24	0.215	0.107–0.432	0.000
rs2279744			
T/T + G/T	1.00	Reference	—
G/G	1.475	1.153–1.887	0.002

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

Multivariate analysis of *MDM2*-rs2279744 polymorphism for association with lung cancer risk

Multivariate analysis showed a significantly increased lung cancer risk in individuals with a lower education level, lower BMI, cancer family history, prior diagnosis of COPD and pneumonia, exposure to pesticide or gasoline/diesel, tobaccco smoking, heavy cooking smoke, and *MDM2*-rs2279744 SNP. The latter was still a significant risk factor for lung cancer, even after incorporating environmental and lifestyle factors (Table 3).

Association of *MDM2*-rs2279744 SNP with clinicopathological patient data

We also evaluated *MDM2*-rs2279744 SNP for association with the clinicopathological data from lung cancer patients.

Table 4 Association of *MDM2*-rs2279744 SNP with the clinicopathological data from lung cancer patients

Characteristic		G/G (*n* = 231)	T/T + G/T (*n* = 769)	*P*-value
Gender	Male	141	466	0.965
	Female	90	303	
Age (years)	<30	3	4	0.530
	30–39	5	25	
	40–49	36	98	
	50–59	85	287	
	60–69	75	247	
	≥70	27	108	
BMI (kg/m^2)	<18.5	8	56	0.101
	18.5–24	130	402	
	≥24	93	311	
Histology types	Squamous cell	35	106	0.946
	Adenocarcinoma	48	128	
	Small cell	31	95	
	Other carcinomas*	15	42	

*Including large cell, mixed cell carcinoma, or undifferentiated carcinoma. BMI, Body mass index; *MDM2*, mouse double minute-2; SNP, single nucleotide polymorphism.

We did not find any statistically significant associations (Table 4).

Discussion

Several study models have been developed to predict the individual risk for lung cancer using patient characteristics, epidemiologic, social, and clinical risk factors.[13–19] Our current study genotyped *MDM2*-rs2279744 SNP in a Northeastern Chinese population to associate lung cancer risk, together with other clinicopathological and epidemiologic factors. We found that there were several factors associated with lung cancer risk, including family history of cancer, COPD, pneumonia, occupational exposure to pesticide or gasoline/diesel, duration of tobacco smoking, and heavy cooking smoke, as well as lower education level or BMI. Our current data are consistent with the findings of previous studies.[13–19] Furthermore, our current study also showed that the *MDM2*-rs2279744 G/G genotype was associated with lung cancer risk in recessive model analysis and was still associated with lung cancer risk after incorporating environmental and lifestyle factors. Thus, this study has demonstrated that the *MDM2*-rs2279744 G/G genotype is associated with lung cancer risk. Molecularly, *MDM2*-rs2279744 is a functional SNP and is able to regulate *MDM2* protein expression, that is, the *MDM2*-rs2279744 G-allele results in higher levels of *MDM2* mRNA and protein, which, in turn, attenuate the p53 stress response pathway through directly blocking p53 transcriptional activity and mediating p53 protein degradation.[4,20] The attenuation of p53 pathway activity will lead to lung carcinogenesis, which has been confirmed in an animal experiments,

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that is, suppression of the p53 pathway increased the lung tumor multiplicity in p53-mutated mice after they were exposed to tobacco smoke.[21,22] A predisposition to cancer has been presented in *MDM2* overexpressed mice.[23]

Furthermore, *MDM2*-rs2279744 SNP was not associated with any clinicopathological data from lung cancer patients. This was a surprising result, but mechanistically it may be rationalized that p53 expression is a result of p53 mutations in most lung cancers. In this case, the p53 gene pathway was already altered and the increased *MDM2* expression as a result of *MDM2*-rs2279744 G/G SNP did not contribute to tumor progression. Indeed, in previous studies, the p53 rs1042522 C-allele SNP was associated with reduced apoptotic potential in lung cancer patients compared to the p53 G-allele, and might modulate lung cancer risk, cancer progression, and/or response to treatment,[24–26] indicating that p53 plays an important role in the suppression of lung carcinogenesis.

There were a number of limitations in our study. Firstly, the *MDM2*-TP53 interaction played a pivotal role in regulation of the cell-cycle checkpoint, DNA repair, and apoptotic cell death. A common SNP at p53 rs1042522 has also been found to be of functional significance, with the C-allele having reduced the apoptotic potential compared to the G-allele, which may modulate the lung cancer risk, progression, and/or response to treatment.[24–26] Our current data would be much stronger in the prediction of lung cancer risk if we would combine this p53 SNP with *MDM2*-rs2279744 G/G SNP. Secondly, our current data may not be generalizable to other populations because this is a hospital-based case-control study, and, thus, needs external validation in other populations. Thirdly, our current analyses did not include all epidemiological factors, such as exposure to asbestos. Finally, this was a retrospectively designed study, and the sample size is relatively small; therefore, the results need to be validated by a large-scale and prospective design study.

Conclusion

In conclusion, *MDM2*-rs2279744 is associated with lung cancer risk in Northeastern Chinese population.

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Disclosure

No authors report any conflict of interest.

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