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Original Article

Effects of FUS2 polymorphism on non-small cell lung cancer susceptibility and clinicopathological features

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Abstract: The FUS2 gene, residing in tumor suppressor gene region of human chromosome 3p21.3, has been considered as a promising tumor suppressor which may play critical roles in development of cancers. The present study was conducted to determine the effects of the FUS2 767A/T polymorphism on susceptibility and progression of NSCLC susceptibility in a Chinese population. The FUS2 767A/T polymorphism was genotyped in 252 NSCLC cases and 260 healthy controls using TaqMan method and DNA sequencing. Logistic regression was used to assess the genetic association between FUS2 767A/T polymorphism and occurrence and progression of NSCLC. The results revealed that subjects carrying T allele of the FUS2 767A/T polymorphism were at increased NSCLC risk as compared with the A allele carriers (T vs. A: adjusted OR=1.31, 95% CI=1.02-1.69, P=0.028). In addition, individuals carrying the AT genotype and at least 1 copy of T allele (dominant model) of the FUS2 767A/T polymorphism were confronted with increased NSCLC risk as compared with the wild-type AA genotype (AT vs. AA: adjusted OR=1.64, 95% CI=1.11-2.42, P=0.013; AT+TT vs. AA: adjusted OR=1.62, 95% CI=1.13-2.36, P=0.009). In subgroup analysis by smoking status, statistical significant increased NSCLC risk was observed among smokers. In association analysis between the FUS2 767A/T polymorphism and clinicopathological features of NSCLC, we found that patients carrying variant genotypes (AT+TT) had a significantly higher prevalence of advanced TNM stage, large tumor size, and positive lymph node metastasis. The results suggested that the functional FUS2 767A/T polymorphism may influence the susceptibility and progression of NSCLC in the Chinese population.

Keywords: Non-small cell lung cancer, FUS2, polymorphism, susceptibility, progression

Introduction

Lung cancer is the most commonly diagnosed cancer and is a leading cause of cancer-related deaths worldwide [1]. The majority of lung cancer cases are non-small cell lung cancer (NSCLC), which accounts for more than 80% of all lung cancer cases [2]. Patients with NSCLC have a poor prognosis, with a 5-year survival rate of about 15% because of limited efficacy of the treatment in most patients 3. Etiologically, carcinogenesis of NSCLC is a complex, multistep and multifactorial process, in which many factors are implicated [4]. It has been well established that cigarette smoking, air pollution, and asbestos exposure are most common risk factors for NSCLC [5, 6]. However, most people exposed to these risk factors never develop NSCLC and many NSCLC patients develop among individuals without exposure to the above risk factors, indicating that other factors such as genetic factors also play important roles in the development of NSCLC.

The FUS2 gene, which encodes a novel cytoplasmic acetyltransferase, resides in the tumor suppressor gene region on human chromosome 3p21.3 and has been considered a promising candidate tumor suppressor gene [7]. The FUS2 gene contains several important domains including the catalytic N-acetyltransferase (NAT) domain [8]. NATs are essential enzymes involved in many important cellular processes including proliferation, differentiation, and apoptosis. Two highly similar human genes for NAT, named NAT1 and NAT2, encode genetically invariant and variant NAT proteins, respectively [9]. It was reported that the both enzymes are capable of N-acetylation, O-acetylation, and N, O-acetylation and are implemented in the acti-

vation and detoxification of carcinogens [9]. Therefore, the NAT enzymes and the genes encoding them may be involved in susceptibility to cancers including NSCLC.

FUS2 767A/T polymorphism is one of the most common SNPs located in the coding region of the FUS2 gene. It was reported that the FUS2 767A/T polymorphism lead to a non-conservative amino acid change (R222W) located between the acetyltransferase and the proline-rich domains of the protein. Therefore, it is biological reasonable to hypothesize a potential relationship between the FUS2 767A/T polymorphism and cancer risk. Recently, the relationship between the FUS2 767A/T polymorphism and risk for nasopharyngeal carcinoma (NPC) has been evaluated 10. However, no studies, to date, have been conducted to investigate the role of the FUS2 767A/T polymorphism in NSCLC susceptibility and progression. In the present study, we investigate the association between the FUS2 767A/T polymorphism and NSCLC risk based on a case-control study in a Chinese population.

Materials and methods

Ethics statement

The study was approved by the ethics committee of the First People's Hospital Of Nanning and the First Affiliated Hospital of Guangxi Medical University. All of the participants provided written informed consent to be included in the study concerning the use of their blood samples for research.

Study population

The study is a hospital-based case-control study comprised a total of 512 subjects including 252 NSCLC cases and 260 healthy controls. All of the included patients and healthy controls were genetically unrelated Chinese from the surrounding areas of Nanning, Guangxi and were consecutively recruited from patients who were evaluated and treated at First People's Hospital Of Nanning and First Affiliated Hospital of Guangxi Medical University from January 2010 to October 2014.

The healthy controls were frequently matched to NSCLC cases based on age, sex, dinking, and smoking and were recruited from volunteers who came to the two hospitals for their routine checkups. Selection criteria for healthy controls included no evidence of any personal history of lung cancer or other malignant diseases. The NSCLC cases were newly diagnosed and pathologically confirmed with primary NSCLC and were gathered from the Department of Medical Oncology of the two hospitals. Tumor types and stages of NSCLC were classified according to the seventh edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system [11]. Clinical and pathological characteristics of NSCLC cases including age, sex, drinking, smoking, pathological type of cancer, TNM stage, tumor size, lymph node status, distant metastasis, and histological grade were collected from the patients' medical records with the help of the oncologist.

Sample collection and DNA extraction

Blood samples (4 ml) were collected from all of the participants in ethylenediaminetetraacetic acid (EDTA)-containing tubes and stored at -80°C until DNA extraction. Genomic DNA was isolated and purified from peripheral blood leucocytes using QIA-amp DNA Blood Mini Kit (Baosheng, Dalian, China) according to the manufacturer's instructions. The concentration of extracted DNA was determined spectrophotometrically.

Genotyping

FUS2 767A/T polymorphism was genotyped using TaqMan Assay (Applied Biosystems, Foster City, CA, USA) according to the protocols described by the manufacturers. The PCR primers used for FUS2 767A/T polymorphism were 5'-TGACCAGGTGCACTTCCATAC-3' (forward); and 5'-TGAGATGGTCAGGCACTCAG-3' (forward), respectively. PCR reactions were performed in a 10 μL reaction mixture containing 20 ng of genomic DNA, 3.5 μL of 2×TaqMan Genotyping Master Mix, 0.25 μL of the primer and probe mix, and 6.25 μL of double-distilled water. PCR cycle conditions consisted of an initial denaturation step at 94°C for 4 min, followed by 35 cycles of 20 sec at 94°C, 30 sec at 60°C, 30 sec at 72°C, and a final elongation at 72°C for 10 min. To validate the results from real-time PCR, around 10% of assays were repeated and 10% of the PCR-amplified DNA samples were randomly selected and geno-

Table 1. Distributions of selected variables in NSCLC patients and healthy controls

Groups	NSCLC patients (n=252)	Healthy controls (n=260)	P
Age (years) (mean ± SD)	51.79±11.67	52.87±12.27	0.308
Sex, n (%)			
Male	148 (58.7)	163 (62.7)	0.359
Female	104 (41.3)	97 (37.3)	
Drinking, n (%)			
Yes	153 (60.7)	171 (65.8)	0.236
No	99 (39.3)	89 (34.2)	
Smoking, n (%)			
Yes	144 (57.1)	129 (49.6)	0.088
No	108 (42.9)	131 (50.4)	
Histology, n (%)			
Squamous cell carcinoma	164 (65.1)		
Adenocarcinoma	88 (34.9)		
TNM stage, n (%)			
I+II	74 (29.4)		
III+IV	178 (70.6)		
Tumor size, n (%)			
T1+T2	92 (36.5)		
T3+T4	160 (63.5)		
Lymph node metastasis, n (%)			
Negative	103 (40.9)		
Positive	149 (59.1)		

NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis.

typed by DNA sequencing. The results were 100% concordant.

Statistical analyses

The genotype frequencies of the FUS2 767A/T polymorphism in healthy controls were tested against departure from Hardy-Weinberg equilibrium (HWE) using a goodness-of-fit χ^2 test. Differences in distributions of demographic parameters, selected variables, and genotypes and alleles between NSCLC cases and healthy controls were assessed using Student's t-test for continuous variables, and χ^2 test for categorical variables, respectively. The associations between the genotypes and alleles of the FUS2 767A/T polymorphism and NSCLC susceptibility and clinicopathological parameters were estimated by computing odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analyses adjusting for age, sex, drinking, and smoking. All tests were two-sided and a $P<0.05$ was considered statistical significant. All statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the study population

The demographic characteristics in NSCLC cases and healthy controls enrolled in this study are presented in **Table 1**. The NSCLC cases and healthy controls were well-matched for age (P= 0.308), sex (P=0.359), smoking (P=0.088), and drinking (P=0.236). Among the NSCLC patients, 65.1% were squamous cell carcinoma, and 34.9% were adenocarcinoma, respectively. The percentage of NSCLC patients with TNM stage I+II, and III+IV were 29.4%, and 70.6%, respectively. The NSCLC patients with tumor size T1+T2, and T3+T4 accounted for 36.5%, and 63.5%, respectively. There were 59.1% of NSCLC patients positive for lymph node metastasis.

Association of the FUS2 767A/T polymorphism with NSCLC risk

The genotype and allele distributions of the FUS2 767A/T polymorphism between NSCLC patients and healthy controls are presented in **Table 2**. The genotype frequencies of AA, AT, and TT for FUS2 767A/T polymorphism were 28.2%, 52.8%, and 19.0% in NSCLC patients, and were 38.8%, 44.6%, and 16.6% in healthy controls, respectively. The results suggested that the genotype distributions of the FUS2 767A/T polymorphism were consistent with HWE both in NSCLC patients (P=0.306) and healthy controls (P=0.326). Logistic regression analysis adjusted for age, sex, smoking, and drinking status revealed that subjects carrying the T allele of the FUS2 767A/T polymorphism were at increased

Table 2. Genotype and allele frequencies of FUS2 767A/T polymorphism between NSCLC patients and healthy controls

Polymorphisms	NSCLC patients n=252 (%)	Healthy controls n=260 (%)	OR (95% CI)[a]	P[a]
FUS2 767A/T				
Genotypes				
AA	71 (28.2)	101 (38.8)	1.00 (Ref)	
AT	133 (52.8)	116 (44.6)	1.64 (1.11-2.42)	0.013
TT	48 (19.0)	43 (16.6)	1.58 (0.95-2.65)	0.075
Allele				
A	275 (54.6)	318 (61.2)	1.00 (Ref)	
T	229 (45.4)	202 (38.8)	1.31 (1.02-1.69)	0.028
Dominant model				
AA	71 (28.2)	101 (38.8)	1.00 (Ref)	
AT+TT	181 (71.8)	159 (61.2)	1.62 (1.13-2.36)	0.009
Recessive model				
AA+AT	204 (81.0)	217 (83.4)	1.00 (Ref)	
TT	48 (19.0)	43 (16.6)	1.19 (0.75-1.87)	0.458

NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval. [a]Adjusted for age, sex, smoking and drinking status by logistic regression model.

NSCLC risk when compared with the A allele carriers (T vs. A: adjusted OR=1.31, 95% CI=1.02-1.69, P=0.028). Similarly, individuals carrying the AT genotype of the FUS2 767A/T polymorphism were at increased NSCLC risk when compared with the AA genotype (AT vs. AA: adjusted OR=1.64, 95% CI=1.11-2.42, P=0.013). In addition, we also found that subjects carrying at least 1 copy of T allele (dominant model) were 1.62 times more likely to develop NSCLC as compared with the A allele homozygote (AT+TT vs. AA: adjusted OR=1.62, 95% CI=1.13-2.36, P=0.009).

Stratification analysis of the FUS2 767A/T polymorphism and NSCLC risk

We further investigated the effect of the FUS2 767A/T polymorphism on NSCLC risk stratified by age, sex, smoking, and drinking status. As presented in **Table 3**, the results showed that the NSCLC risk was more pronounced among smokers (AT+TT vs. AA: adjusted OR=1.77, 95% CI=1.08-2.94, P=0.024).

Association of the FUS2 767A/T polymorphism with clinicopathological parameters of NSCLC

To determine the effects of the FUS2 767A/T polymorphism on clinicopathological parameters of NSCLC, we analyzed the association between the FUS2 767A/T polymorphism and a series of clinicopathological parameters, including histology, TNM stage, tumor size, and lymph node metastasis. As shown in **Table 4**, the distribution of the variant genotypes (AT+TT) of the FUS2 767A/T polymorphism was significantly higher in patients with advanced TNM stage (AT+TT vs. AA: adjusted OR=2.08, 95% CI=1.17-3.67, P=0.012), larger tumors (AT+TT vs. AA: adjusted OR=1.92, 95% CI=1.11-3.31, P=0.017), and positive lymph node metastasis (AT+TT vs. AA: adjusted OR=1.87, 95% CI=1.07-3.10, P=0.021), but not in patients with different histological types of NSCLC as compared with the wild AA genotype.

Discussion

The current study was performed to assess the effects of the FUS2 767A/T polymorphism on NSCLC susceptibility and clinicopathologic characteristics in 512 Chinese subjects. We found that the T allele of the FUS2 767A/T polymorphism was significantly associated with increased NSCLC susceptibility as compared with the A allele (T vs. A: adjusted OR=1.31, 95% CI=1.02-1.69, P=0.028). The heterozygous AT genotype and the combined AT and TT genotypes (dominant model) of the FUS2 767A/T polymorphism were correlated with a significant increased NSCLC risk when compared with the AA homozygote (AT vs. AA: adjusted OR=1.64, 95% CI=1.11-2.42, P=0.013; AT+TT vs. AA: adjusted OR=1.62, 95% CI=1.13-2.36, P=0.009). In subgroup analysis by different potential confounding factors, we found that the FUS2 767A/T polymorphism enhances the NSCLC susceptibility among smokers (AT+TT vs. AA: adjusted OR=1.77, 95% CI=1.08-2.94, P=0.024). In addition, in association analysis between the FUS2 767A/T polymorphism and clinicopathological characteristics, the results revealed that combined AT and

Table 3. Stratification analyses between the FUS2 767A/T polymorphism and NSCLC risk

Variables	Cases/ Controls	Genotypes (cases/controls)				OR (95% CI)[a]	P[a]
		AT+TT		AA			
		n	%	n	%		
Age, y							
<60	103/106	73/62	70.9/58.5	30/44	29.1/41.5	1.70 (0.95-2.98)	0.087
≥60	149/154	108/97	72.5/63.0	41/57	27.5/37.0	1.52 (0.93-2.22)	0.112
Sex							
Males	148/163	99/94	66.9/57.7	49/69	33.1/42.3	1.46 (0.91-2.32)	0.093
Females	104/97	82/65	78.8/67.0	22/32	21.2/33.0	1.81 (0.95-3.41)	0.074
Smoking status							
Smoker	144/129	105/78	72.9/60.5	39/51	27.1/39.5	1.77 (1.08-2.94)	0.024
Non-smoker	108/131	76/81	70.4/61.8	32/50	29.6/38.2	1.46 (0.84-2.50)	0.171
Drinking status							
Drinker	153/171	114/111	74.5/64.9	39/60	25.5/35.1	1.54 (0.93-2.16)	0.097
Non-drinker	99/89	67/48	67.7/53.9	32/41	32.3/46.1	1.73 (0.94-2.83)	0.089

NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval. [a]Adjusted for age, sex, smoking and drinking status by logistic regression model.

Table 4. Association between the FUS2 767A/T polymorphism and clinicopathological features of NSCLC

Variables	Genotypes		OR (95% CI)[a]	P[a]
	AT+TT	AA		
Histology, n (%)				
Adenocarcinoma	67 (76.1)	21 (23.9)	1.00 (Ref)	
Squamous cell carcinoma	114 (69.5)	50 (30.5)	0.73 (0.41-1.32)	0.265
TNM stage, n (%)				
I+II	45 (60.8)	29 (39.2)	1.00 (Ref)	
III+IV	136 (76.4)	42 (25.6)	2.08 (1.17-3.67)	0.012
Tumor size, n (%)				
T1+T2	58 (63.0)	34 (37.0)	1.00 (Ref)	
T3+T4	123 (76.9)	37 (23.1)	1.92 (1.11-3.31)	0.017
Lymph node metastasis, n (%)				
Negative	66 (64.1)	37 (35.9)	1.00 (Ref)	
Positive	115 (77.2)	34 (22.8)	1.87 (1.07-3.10)	0.021

NSCLC, non-small cell lung cancer; OR, odds ratio; CI, confidence interval. [a]Adjusted for histology, TNM stage, tumor size, and lymph node metastasis.

TT genotypes (dominant model) of the FUS2 767A/T polymorphism were significantly associated with TNM stage, tumor size, and lymph node metastasis of NSCLC.

The FUS2 gene, encoding a novel cytoplasmic acetyltransferase, resides in tumor suppressor gene region of lung, breast, and head and neck cancer on human chromosome 3p21.3 [7, 12]. FUS2 is a single copy gene which express a 1.9 kb mRNA in many normal human tissues including lung and breast [7]. Bioinformatics analysis revealed that the FUS2 protein was a soluble nuclear protein with several important domains and motifs including an acetyltransferase domain and a proline-rich domain, which overlaps with the Wilms' tumor protein signature [10]. The presence of these important domains suggests the probability that the FUS2 gene may be directly involved in critical cellular process including apoptosis, cell cycle regulation, proliferation, and differentiation and play critical roles in tumor development. Indeed, increased expression of FUS2 transgenes in lung and NPC cells have demonstrated suppression of tumor formation and growth in animal models [13].

FUS2 767A/T polymorphism is a common SNP with non-conservative amino acid change (R222W) located between the acetyltransferase and the proline-rich domains of the protein [10]. It is quite possible that the FUS2 767A/T

polymorphism may impair either the protein function or RNA splicing and affect the tumor suppressor function of FUS2, which may result in altered susceptibility to cancers. Moreover, the FUS2 767A/T polymorphism has been demonstrated to associate with altered susceptibility to nasopharyngeal cancer (NPC) [10]. In the present study, we investigated the association between the FUS2 767A/T polymorphism and NSCLC risk in a Chinese population, the results suggested that the FUS2 767A/T polymorphism was correlated with increased NSCLC susceptibility, which was consistent with the above hypothesis and the results from previous studies.

Smoking is a predominant risk factor for lung cancer and the magnitude of the effect of smoking on lung cancer was far outweighed all other factors [14, 15]. Many studies have demonstrated that the strong association of smoking with lung cancer risk [16, 17]. In the present study, we further analyzed the role of the FUS2 767A/T polymorphism in the development of NSCLC stratified by smoking status. The results revealed that the AT+TT genotype of the FUS2 767A/T polymorphism was significantly associated with increased NSCLC risk among smokers (AT+TT vs. AA: adjusted OR= 1.77, 95% CI=1.08-2.94, P=0.024). The exact mechanism of how FUS2 767A/T polymorphism affects NSCLC risk remains unknown. The possible explanation may be that the non-conservative amino acid change of the FUS2 767A/T polymorphism may impair the tumor suppressor function of FUS2 and thus enhance the NSCLC risk posted by tobacco smoking.

Clinicopathological characteristics have been well established as the most critical prognostic factors for cancers [18, 19]. In the present study, the distribution of clinicopathological characteristics and genotypes of the FUS2 767A/T polymorphism in NSCLC patients were estimated to investigate the association of the FUS2 767A/T polymorphism with clinicopathological parameters of NSCLC. The Clinicopathological parameters assessed included histology, TNM stage, tumor size, and lymph node metastasis. The results demonstrated that the AT+TT genotype of the FUS2 767A/T polymorphism was significantly associated with various clinicopathological parameters involved in NSCLC progression including advanced TNM stage (III+IV), large tumor size (T3+T4), and lymph node metastasis (Positive). The results suggested that the NSCLC patients with the AT+TT genotype of the FUS2 767A/T polymorphism were more likely to have a poor prognosis.

Some potential limitations in this study should be acknowledged. First, the study subjects in our study were from hospitals and may not be representative of the of the entire target population. Second, the study population was limited to the Guangxi population; therefore, the findings may not be generalized to other populations. Third, the number of study population was relatively small, especially for stratification analyses and association analyses of the FUS2 767A/T polymorphism with clinicopathological parameters of NSCLC. Therefore, the results of this research should be interpreted with caution considering these limitations.

In conclusion, our study suggests that the FUS2 767A/T polymorphism affects the susceptibility and progression of NSCLC in a Chinese population.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.
[2] Binder D, Hegenbarth K. Emerging options for the management of non-small cell lung cancer. Clin Med Insights Oncol 2013; 7: 221-34.
[3] Pastorino U. Lung cancer screening. Br J Cancer 2010; 102: 1681-6.

[4] Kang S, Ma Y, Liu C, Cao C, Hanbateer, Qi J, Li J, Wu X. Assoication of XRCC1 gene polymorphisms with risk of non-small cell lung cancer. Int J Clin Exp Pathol 2015; 8: 4171-6.
[5] Hecht SS. Lung carcinogenesis by tobacco smoke. Int J Cancer 2012; 131: 2724-32.
[6] Dresler C. The changing epidemic of lung cancer and occupational and environmental risk factors. Thorac Surg Clin 2013; 23: 113-22.
[7] Lerman MI, Minna JD. The 630-kb lung cancer homozygous deletion region on human chromosome 3p21.3: identification and evaluation of the resident candidate tumor suppressor genes. The International Lung Cancer Chromosome 3p21.3 Tumor Suppressor Gene Consortium. Cancer Res 2000; 60: 6116-33.
[8] Gatphayak K, Knorr C, Chen K, Brenig B. Structural and expression analysis of the porcine FUS2 gene. Gene 2004; 337: 105-11.
[9] Hickman D, Risch A, Buckle V, Spurr NK, Jeremiah SJ, McCarthy A, Sim E. Chromosomal localization of human genes for arylamine N-acetyltransferase. Biochem J 1994; 297: 441-5.
[10] Duh FM, Fivash M, Moody M, Li Lung M, Guo X, Stanbridge E, Dean M, Voevoda M, Hu LF, Kashuba V, Zabarovsky ER, Qian CN, Godbole S, Tean Teh B, Lerman MI. Characterization of a new SNP c767A/T (Arg222Trp) in the candidate TSG FUS2 on human chromosome 3p21.3: prevalence in Asian populations and analysis of association with nasopharyngeal cancer. Mol Cell Probes 2004; 18: 39-44.
[11] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010; 17: 1471-4.
[12] Zegerman P, Bannister AJ, Kouzarides T. The putative tumour suppressor Fus-2 is an N-acetyltransferase. Oncogene 2000; 19: 161-3.
[13] Fang Y, Guan X, Guo Y, Sham J, Deng M, Liang Q, Li H, Zhang H, Zhou H, Trent J. Analysis of genetic alterations in primary nasopharyngeal carcinoma by comparative genomic hybridization. Genes Chromosomes Cancer 2001; 30: 254-60.
[14] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Personal habits and indoor combustions. Volume 100 E. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Hum 2012; 100: 1-538.
[15] de Groot P, Munden RF. Lung cancer epidemiology, risk factors, and prevention. Radiol Clin North Am 2012; 50: 863-76.
[16] Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. Transl Lung Cancer Res 2015; 4: 327-38.
[17] Margaritopoulos GA, Vasarmidi E, Jacob J, Wells AU, Antoniou KM. Smoking and interstitial lung diseases. Eur Respir Rev 2015; 24: 428-35.
[18] Lin J, Qiu M, Xu R, Dobs AS. Comparison of survival and clinicopathologic features in colorectal cancer among African American, Caucasian, and Chinese patients treated in the United States: Results from the surveillance epidemiology and end results (SEER) database. Oncotarget 2015; 6: 33935-43.
[19] Yan Y, Liu L, Zhou J, Li L, Li Y, Chen M, Wang L, He W, Guan X, Zu X, Qi L. Clinicopathologic characteristics and prognostic factors of sarcomatoid renal cell carcinoma. J Cancer Res Clin Oncol 2015; 141: 345-52.