Contribution of Genotype of DNA Double-strand Break Repair Gene *XRCC3*, Gender, and Smoking Behavior to Lung Cancer Risk in Taiwan

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Abstract. *Aim: The present study evaluated the contribution of genotype of X-ray repair cross-complementing group 3 (XRCC3), age, gender, and smoking to lung cancer risk in Taiwan. Materials and Methods: A total of 358 patients with lung cancer and 716 controls were investigated for their XRCC3 rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539, rs28903081 genotype, epidemiological and clinical data for association and gene-Iifestyle interactions. Results: The results showed that CT and TT genotypes of XRCC3 rs861539 were associated with increased lung cancer risk (odds ratio=1.81, 95% confidence interval=1.18-2.78; odds ratio=3.43, 95% confidence interval=1.12-10.60, respectively). This polymorphism also influenced lung cancer susceptibility in males and smokers (p=0.0017 and 0.0045, respectively). Conclusion: The T allele of XRCC3 rs861539 contributes to increased risk of lung cancer in Taiwanese, particularly those who are male and smokers.*

Worldwide, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths worldwide, accounting for 13% (1.6 million) of total cancer cases and 18% (1.4 million) of cancer-related deaths (1). In China, a yearly 1.63% increase in lung cancer incidence from 1988 to 2005 has been reported, and the mortality rate of lung cancer has increased by more than 4-fold during the past 30 years (2). Previous studies have revealed several risk factors for lung cancer, including smoking tobacco and inhaling second-hand smoke; environmental exposure to radon gas, asbestos or radiation; and family history. In addition, mounting evidence has shown that individual differences in susceptibility may be inherited in genes encoding DNA repair proteins, which may be closely associated to personal cancer risk (3-9).

The X-ray repair cross-complementing group 3 (*XRCC3*) gene, located on human chromosome 14q32.3, encodes for the DNA repair protein XRCC3. XRCC3 is a member of RAD51 recombinase-related protein family that plays a role in homologous recombination to repair DNA double-strand breaks (DSBs) and maintains the overall integrity of the human genome (10). In recent years, several studies were performed to evaluate the relationship between the rs861539 C/T polymorphism (also named Thr241Met, T241M, C18067T and C722T) of the *XRCC3* gene and lung cancer risk, making it the most commonly studied polymorphism of *XRCC3* (11-14). In addition, following the central dogma of molecular biology, variants of this polymorphism may affect the function of the encoded protein, altering DNA repair capacity and the level of bulky DNA adducts in leukocytes of healthy individuals (11). Thus, the rs861539 C/T polymorphism and other polymorphic sites may play a role in the pathogenesis and development of lung cancer.

To our knowledge, the genotypes of *XRCC3* among Taiwanese have never been examined and neither has its association with lung cancer been investigated. To examine the contribution of *XRCC3* genotype to lung cancer risk in

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Key Words: Gender, genotype, lung cancer, polymorphism, smoking, Taiwan, *XRCC3*.

Table I. *Distribution of selected demographic data of the 358 patients with lung cancer and the 716 matched controls.*

Characteristic	Controls (n=716)			Patients (n=358)			*p*-Value[a]
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)			64.8 (6.8)		64.0 (6.9)	0.5871	
Gender						0.3642	
Male	488	68.1%		254	70.9%		
Female	228	31.9%		104	29.1%		0.3642
Smoking status							
Ever smokers	563	78.6%		293	81.8%		
Non-smokers	153	21.4%		65	18.2%		0.2282
Histology							
Adenocarcinoma				218	60.9%		
SCC				106	29.6%		
Other				34	9.5%		

[a]Based on Chi-square test; SCC: squamous cell carcinoma.

Table II. *Summary of the rs numbers, primers, amplicon length before and after enzyme digestion, restriction enzymes for all the X-ray repair cross-complementing group 3 single nucleotide polymorphisms investigated in this study.*

rs Number	Primer sequence	Restriction enzyme	Amplicon length (bp)	Genotypes and enzymatic fragment sizes (bp)
rs1799794	F: 5'-CACACTGCGGTCTTGCAGTG-3' R: 5'-CAGGCTGGGTCTGGATACAA-3'	*Bts*CI	505	G: 505 A: 289+216
rs45603942	F: 5'-GGGATGCAGGTTCAACTGAC-3' R: 5'-AACTTGGACTGTGTCAAGCA-3'	*Alu*I	352	C: 352 T: 187+165
rs861530	F: 5'-CCGAGGAACGTGCTGAACTT-3' R: 5'-CTCCCTAACAGCCTCCATGT-3'	*Fat*I	497	G: 497 A: 293+204
rs3212057	F: 5'-CCATGACCGCAGGCACTTGT-3' R: 5'-AGAACGCGACAAGGATGGTA-3'	*HpyCH4*III	455	G: 455 A: 235+220
rs1799796	F: 5'-GG AACCAGTTGT GTGAGCCT-3' R: 5'-CCTGGTTGATGCACAGCACA-3'	*Alu*I	430	G: 430 A: 226+204
rs861539	F: 5'-GACACCTTGT TGGAGTGTGT-3' R: 5'-GTCTTCTCGATGGTTAGGCA-3'	*Fat*I	358	C: 358 T: 200+158
rs28903081	F: 5'-CTGCTTCCTGTTTCTCAGGT-3' R: 5'-GCACTGATCGTGTAGGAACA-3'	*BstU*I	198	A: 198 G: 102+96

Taiwan, we determined the genotypic frequencies of seven polymorphisms of the *XRCC3* gene at promoter A-315G (rs1799794), promoter C-280T (rs45603942), intron 5 (rs861530), exon 6 (rs3212057), intron 7 (rs1799796), exon 8 (rs861539) and exon 10 (rs28903081), and evaluate the possible influence of gene-lifestyle interaction.

Materials and Methods

Sample collection. Three hundred and fifty-eight patients diagnosed with lung cancer were recruited at the Outpatient Clinics of General Surgery at the China Medical University Hospital, Taichung, Taiwan. The clinical characteristics of patients, including histological details,

Table III. *Distribution of X-ray repair cross-complementing group 3 genotypes among patients with lung cancer and controls.*

Genotype	Controls (n=716)		Patients (n=358)		*p*-Value[a]	Odds ratio (95% CI)[b]
	n	%	n	%		
rs1799794					0.8686	
GG	177	24.7%	86	24.0%		1.00 (Reference)
AG	392	54.8%	202	56.4%		1.06 (0.78-1.44)
AA	147	20.5%	70	19.6%		0.98 (0.67-1.44)
rs45603942					0.8782	
CC	661	92.3%	333	93.0%		1.00 (Reference)
CT	47	6.6%	22	6.2%		0.93 (0.55-1.57)
TT	8	1.1%	3	0.8%		0.74 (0.20-2.82)
rs861530					0.8359	
AA	212	29.6%	112	31.3%		1.00 (Reference)
AG	388	54.2%	191	53.3%		0.93 (0.70-1.24)
GG	116	16.2%	55	15.4%		0.90 (0.61-1.33)
rs3212057					1.0000	
GG	716	100.0%	358	100.0%		1.00 (Reference)
AG	0	0.0%	0	0.0%		1.00
AA	0	0.0%	0	0.0%		1.00
rs1799796					0.7611	
AA	325	45.4%	170	47.5%		1.00 (Reference)
AG	352	49.2%	171	47.8%		0.93 (0.72-1.20)
GG	39	5.4%	17	4.7%		0.83 (0.46-1.52)
rs861539					0.0022*	
CC	660	92.2%	307	85.8%		1.00 (Reference)
CT	51	7.1%	43	12.0%		1.81 (1.18-2.78)*
TT	5	0.7%	8	2.2%		3.43 (1.12-10.60)*
rs28903081					1.0000	
GG	716	100.0%	358	100.0%		1.00 (Reference)
AG	0	0.0%	0	0.0%		1.00
AA	0	0.0%	0	0.0%		1.00

[a]Based on Chi-square test. [b]CI: confidence interval. *Statistically significant.

were all graded and defined by expert surgeons of Dr. Hsia's team. All participants voluntarily completed a self-administered questionnaire and provided their peripheral blood samples. In the case-control study design, twice as many non-lung cancer healthy volunteers as controls were selected by matching for age, gender and personal habits after initial random sampling from the Health Examination Cohort of our hospital. The exclusion criteria of the controls included previous malignancy, metastasized cancer from other or unknown origin, and any genetic or familial diseases. All the demographic information of the cases and controls are listed in Table I. Our study was approved by the Institutional Review Board of the China Medical University Hospital (DMR100-IRB-284) and written-informed consent was obtained from all participants.

Genotyping conditions. Genomic DNA was extracted from peripheral blood leucocytes using the QIAamp Blood Mini Kit (Blossom, Taipei, Taiwan). In this study, a total of seven polymorphic sites were analyzed in all the participants of both the control and case groups. Briefly, all of the seven polymorphic sites were genotyped by means of a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). PCR was performed on a BioRad Mycycler (BioRad, Hercules, CA, USA) following the normal manufacturer's instructions. Each PCR reaction consisted of 5 min initial cycle at 94˚C for 5 min; 40 cycles of 94˚C for 30 s, 55˚C for 30 s, and 72˚C for 30 s; and a final extension at 72˚C for 10 min. Then the single nucleotide polymorphism (SNP)-containing DNA amplicons were subjected to individual overnight digestion by restriction endonucleases following the manufacturer's instructions. Following digestion, each sample was immediately analyzed by 3% agarose gel electrophoresis. Details such as the primer sequences, and enzymatic digestion conditions for each SNP analyzed in this study are summarized in Table II.

Statistical analyses. To ensure that the controls used were representative of the general population and to exclude the possibility of genotyping error, the deviation of the genotype frequencies of *XRCC3* SNPs in the controls from those expected under the Hardy–Weinberg equilibrium was assessed using the goodness-of-fit test. Pearson's Chi-square test was used to compare the distribution of the *XRCC3* genotypes between cases and controls. Cancer risk associated with the genotypes was estimated and evaluated as odds ratio (OR) and 95% confidence intervals (CIs)

Table IV. *Distribution of X-ray repair cross-complementing group 3 alleles among patients with lung cancer and controls.*

Allele	Controls		Patients		p-Value[a]
	n	%	n	%	
rs1799794					
Allele G	746	52.1%	374	52.2%	0.9635
Allele A	686	47.9%	342	47.8%	
rs45603942					
Allele C	1369	95.6%	688	96.1%	0.6504
Allele T	63	4.4%	28	3.9%	
rs861530					
Allele A	812	56.7%	415	58.0%	0.6110
Allele G	620	43.3%	301	42.0%	
rs1799796					
Allele A	1002	70.0%	511	71.4%	0.5148
Allele G	430	30.0%	205	28.6%	
rs861539					
Allele C	1371	95.7%	657	91.8%	0.0003*
Allele T	61	4.3%	59	8.2%	

[a]Based on Chi-square test. *Statistically significant.

using unconditional logistic regression. Data were recognized as significant when the statistical *p*-value outcome was less than 0.05.

Results

The frequency distributions of demographic characteristics for the 358 patients with lung cancer and 716 non-cancer controls are summarized in Table I. Since we applied frequency matching to select the non-cancer healthy controls, the distribution of age and gender were comparable among the cases and the controls (Table I). The cases had a slightly higher percentage of smokers (81.8%) than the controls (78.6%) ($p>0.05$) (Table I).

The distributions of the *XRCC3* genotypic frequencies of rs1799794, rs45603942, rs861530, rs3212057, rs1799796, rs861539 and rs28903081 among the controls and the patients with lung cancer are analyzed and shown in Table III. The data showed that the genotypes of *XRCC3* rs861539 were differently distributed between lung cancer and healthy control groups ($p=0.0022$) (Table III). Statistically speaking, the *XRCC3* rs861539 heterozygous CT and homozygous TT genotypes were more significantly associated with higher lung cancer risk (OR=1.81, 95% CI=1.18-2.78; OR=3.43, 95% CI=1.12-10.60, respectively) compared to the wild-type CC genotype (Table III). The distributions of the *XRCC3* genotypes of rs1799794, rs45603942, rs861530 and rs1799796 were not different between the controls and the patients (Table III). Differently from Caucasian populations, Taiwanese had only one genotype at *XRCC3* rs3212057 (GG) and rs28903081 (GG) (Table III).

Table V. *Distribution of X-ray repair cross-complementing group 3 rs861539 genotype among patients with lung cancer after stratification by gender.*

Variable	rs861539 Genotype			p-Value[a]
	CC, n (%)	CT, n (%)	TT, n (%)	
Males				
Controls	451 (92.4%)	34 (7.0%)	3 (0.6%)	0.0017*
Cases	215 (84.6%)	32 (12.6%)	7 (2.8%)	
Females				
Controls	209 (91.7%)	17 (7.5%)	2 (0.9%)	0.6340
Cases	92 (88.5%)	11 (10.6%)	1 (1.0%)	

[a]Based on Chi-square test. *Statistically significant.

Subsequently, the distributions of the *XRCC3* allelic frequencies of rs1799794, rs45603942, rs861530, rs1799796 and rs861539 among the controls and the patients are analyzed and shown in Table IV. Supporting the finding that the CT and TT genotypes of *XRCC3* rs861539 were associated with an increased lung cancer risk, the T allele was found at a higher percentage (8.2%) among the patients with lung cancer than the controls (4.3%) and with statistical significance ($p=0.0003$) (Table IV). The distributions of the *XRCC3* allelic frequencies for other polymorphic sites were not different between controls and patients with lung cancer (Table IV).

Among the patients, 70.9% were male and only 29.1% were female (Table I). We were interested in the genotypic contribution of *XRCC3* rs861539 to difference of lung cancer risk by gender in Taiwan. After stratification by gender, it was found that the genotypes of *XRCC3* rs861539 were differently distributed among the males ($p=0.0017$) but not among the females ($p=0.6340$) (Table V), with T allele carriers being more frequent.

Since lung cancer is a smoking-related cancer, we were also interested in the interaction of the genotype of *XRCC3* rs861539 and the smoking status of the participants. The results showed that the genotypic distributions of the variant genotypes of *XRCC3* rs861539 were significantly different between the lung cancer and the control groups who were ever smokers ($p=0.0045$), again due to the T allele but not different among the non-smokers ($p=0.4706$) (Table VI).

Discussion

Loss of maintenance of genome integrity is closely associated with carcinogenesis, and cancer may occur more frequently among those who carry inherited defects in their DNA repair genes such as *XRCC3*. *XRCC3*, playing a role in homologous

Table VI. *Distribution of X-ray repair cross-complementing group 3 rs861539 genotype among patients with lung cancer after stratification by personal smoking habit.*

Variable	rs861539 Genotype			*p*-Value[a]
	CC, n (%)	CT, n (%)	TT, n (%)	
Smokers				
Controls	520 (92.4%)	39 (6.9%)	4 (0.7%)	0.0045*
Cases	251 (85.7%)	35 (11.9%)	7 (2.4%)	
Non-smokers				
Controls	140 (91.5%)	12 (7.8%)	1 (0.7%)	0.4706
Cases	56 (86.2%)	8 (12.3%)	1 (1.5%)	

[a]Based on Chi-square test. *Statistically identified as significant.

recombination and removal of DNA DSBs, helps maintain the stability of the human genome (10). In this case-control study of lung cancer in Taiwan, we examined seven polymorphic genotypes of *XRCC3*, and their contribution to determining individual susceptibility to lung cancer. We found that *XRCC3* rs861539 CT and TT genotypes were not only associated with an increased lung cancer risk (Tables III and IV), but also may closely interact with gender (Table V) and personal smoking (Table VI) status.

Previous studies have reported that individuals carrying the T allele at *XRCC3* rs861539 have a significantly higher level of bulky DNA adducts in their lymphocyte DNA than those carrying the C allele (11, 15). Thus, it supports our findings that people with *XRCC3* rs861539 CT and TT genotypes were at higher risk for lung cancer than those with wild-type CC genotype. On the contrary, it was reported that among patients with non-small cell lung cancer who were treated with cisplatin-based chemotherapy, those with lower DNA repair capacity had a longer survival time (16). The explanation for this may be that XRCC3 protein may play a minor role in the excision repair system involved in the removal of cisplatin-induced DNA damage, and other DNA repair proteins and their functions should be better predictors for this prognosis outcome. This may also provide an explanation that although there have been a few studies investigating the correlation between the *XRCC3* rs861539 genotype and responses to cisplatin-based chemotherapy, no significant association has been proposed (13, 17). In 2012, Chen and colleagues found that among the patients with non-small cell lung cancer treated with cisplatin but non-gemcitabine treatment, the average survival time for those with *XRCC3* rs861539 TT genotype was longer than those with CC or CT (18). The results indicate that *XRCC3* rs861539 genotype may play a role in the pharmacogenomics of cisplatin treatment. From the radiological viewpoint, the genotype of rs861539 was associated with G2 chromosomal radiosensitivity in addition to lung cancer susceptibility in 2007 (19). However, four years later, the same group failed to repeat their previous data findings for the association between rs861539 and cancer risk or G2 chromosomal radiosensitivity (20). All the above results indicate that association studies, especially those regarding chemo- or radiosensitivity should be confirmed in repeated and representative populations with adequate sample size. In 2010 and 2013, two meta-analyses found that *XRCC3* rs861539 might not be associated with lung cancer risk (21, 22). In the current study in Taiwan, the results demonstrated that *XRCC3* rs861539 was associated with an increased risk of lung cancer. We agree with the concept that we should pay attention to the differences among various ethinicities with different genetic background and environmental exposure (23).

Regarding *XRCC3* rs1799794, a recent study found that the minor allele G carriers of *XRCC3* rs1799794 had lower non-small cell lung cancer risk (24). In the same study, the authors did not find any association of *XRCC3* rs1799796 with non-small cell lung cancer risk (24). In our study, no association was found for *XRCC3* rs1799794 nor *XRCC3* rs1799796 polymorphic sites (Tables III and IV). Another study also suggested that there were no associations between *XRCC3* rs1799796 genotype and the susceptibility of urothelial bladder cancer (25). However, *XRCC3* rs1799796 genotype has been associated with breast cancer risk (26). From the viewpoint of haplotype, Jacobsen and colleagues found that rs1799796 in combination with another two polymorphisms, rs1799794 and rs861539, as a haplotype AAC was associated with relatively high risk of lung cancer (27). In addition to SNP-SNP interaction in *XRCC3* itself, the function of *XRCC3* rs861539 may be affected *via* gene-gene and gene-environment/lifestyle interactions. In 2013, Guo andcolleagues demonstrated that *XRCC3* rs861539 had a synergistic effect with XRCC1 Arg399Gln on determining lung cancer risk (14).

There is a gender difference regarding lung cancer, with twice as many males as females suffering from lung cancer in Taiwan. Smoking is a risk factor for lung cancer all over the world. Therefore, the present study also aimed to investigate the interactions of *XRCC3* genotypes together with gender and smoking lifestyle to reveal a more realistic etiology for lung cancer in Taiwan. We found that the association between *XRCC3* rs861539 genotypes with lung cancer risk was obvious among males (p=0.0017) but not females (p=0.6340) (Table V). As for smoking lifestyle, it was found that the association between *XRCC3* rs861539 genotypes and lung cancer risk was obvious among ever smokers (p=0.0045) (Table VI); however, there was no such differential genotypic distribution among the non-smokers (p=0.4706) (Table VI). Tobacco smoke contains pro-

carcinogenic compounds that are metabolized into reactive intermediates and cause DNA damage, which may interact with *XRCC3* rs861539 TT genotype leading to higher risk of lung cancer (28). In the current study, we found that males and smokers carrying the *XRCC3* rs861539 variant genotype (CT and TT) indeed had higher risk of lung cancer. However, since there were only eight and five people of the TT genotype at *XRCC3* rs861539, further stratified analysis according to gender and smoking status at the same time needs to be performed in a larger sample to confirm whether male smokers are at even higher risk than male non-smokers. This means that male gender and smoking status may have synergistic effects on lung cancer susceptibility for those carrying variant genotypes.

In conclusion, our findings suggested that the T allele of *XRCC3* rs861539 is associated with increased lung cancer risk, especially in males and smokers.

Acknowledgements

The Authors appreciate Lin-Lin Hou, Tzu-Chia Wang, Yun-Ru Syu and Tissue-bank of China Medical University Hospital for their excellent technical assistance. This study was supported by research grants from Terry Fox Cancer Research Foundation and Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002). The Authors declare no conflict of interest.

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Received April 17, 2015
Revised May 15, 2015
Accepted May 18, 2015