

The rs28757157 and rs59429575 Polymorphisms in *CYP19A1* are Associated with Lung Cancer in Chinese Han Population

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Abstract

Background Lung cancer is the leading cause of cancer death globally. Recent studies have revealed that the *CYP19A1* gene played a crucial role in cancer initiation and development.

Objectives The aim of this study was to assess the association of *CYP19A1* genetic polymorphisms with the risk of lung cancer in Chinese Han population.

Method This study randomly recruited 507 lung cancer patients and 505 healthy controls. The genotypes of four SNPs of *CYP19A1* gene were identified by Agena MassARRAY technique. Genetic model analysis was used to assess the association between genetic variation and lung cancer risk. Odds ratio (OR) values and 95% confidence intervals (CIs) were provided for the evaluation of the lung cancer risk effect.

Results Rs28757157 and rs59429575 polymorphisms of *CYP19A1* were significantly correlated with the risk of lung cancer. In stratified analysis, rs28757157 was associated with increased cancer risk in males and smoker. Meanwhile, rs59429575 was identified as a risk biomarker in female and lung adenocarcinoma patients ($p < 0.05$). While rs28757157 exerted protective role among people with a BMI greater than 24 ($p = 0.033$).

Conclusions This study identified two new SNPs (rs28757157 and rs59429575) of *CYP19A1* associated with lung cancer in Chinese Han population. These findings provide data support for further functional studies of *CYP19A1* in lung cancer.

Introduction

Lung cancer is a kind of malignant tumor with high morbidity and mortality¹. In China, this malignant tumor has the highest mortality rate, accounting for about 25% of cancer-related deaths². At present, there are many risk factors were found to increase the risk of lung cancer. Among them, smoking seems to be most strongly associated with lung cancer risk³. However, new research shows that about 10–15% of people diagnosed with lung cancer are non-smokers, indicating the importance of other risk factors such as exogenous air pollution, environmental factors and genetic factors. According to the latest statistics, about 8% of lung cancer cases are estimated to be caused by genetics alone^{4,5}. The fact that the risk of lung cancer in the immediate family of a patient with lung cancer increased by 2.4 times further confirms the decisive role of genetic factors in disease risk⁶.

In addition, among non-smoking related lung cancer patients, women have a higher risk of lung cancer than men, especially adenocarcinoma. The incidence of lung cancer in non-smokers is 15% in women and only 10% in men. These findings have drawn attention to the effects of the estrogen on lung cancer risk⁷. It has been reported that both estrogen receptor and aromatase are present in human lung tumors^{8–10}. These results suggest that estrogen may play a role in the biological behavior of human lung cancer.

Cytochrome p450 (CYP450) enzymes are pivotal for biological homeostasis. CYP450 enzymes also play a key role in the metabolism of many endogenous substrates and exogenous carcinogens as well as aromatic and heterocyclic amines. They then covalently combine with DNA to form DNA adducts, which in turn cause cancer^{11,12}. The CYP450 family 19, subfamily A, polypeptide 1 (*CYP19A1*) gene encodes aromatase, which is a member of the CYP450 superfamily of enzymes and a key enzyme in oestradiol biosynthesis. Mutations in the *CYP19A1* gene can result in either increased or decreased aromatase activity, and aromatase plays an important role in lung cancer^{13,14}. This suggests that *CYP19A1* genetic variation may indirectly affect the progression of lung cancer, but the exact mechanism is unclear. At the same time, many literatures have reported the inseparable relationship between *CYP19A1* gene and lung-related diseases, including lung cancer^{15–17}.

Based on previous research, the present study explored the relationship between four single nucleotide polymorphisms (SNPs) of *CYP19A1* gene and lung cancer susceptibility through case-control study, with particular attention to sex and smoking status of the participants.

Materials And Methods

Participants

From May 2015 to February 2018, we recruited 507 pathologically confirmed lung cancer patients from the Shaanxi Provincial Cancer Hospital. The control group was composed of 505 healthy subjects who were volunteer blood donors from physical examination center at the same hospital as the cases. Eligible study participants were screened by completing a specialized questionnaire, including demographic characteristics, disease history, lung status, and family history of other types of tumors. All participants were Chinese Han ancestry from northwest China.

SNP selection

Based on 1000 genome database (<http://www.internationalgenome.org/>), the dbSNP database (<http://www.biointo.org.cn>) and the Han Chinese in Beijing (CHB) population data, we screened four SNPs (rs28757157, rs3751592, rs3751591, and rs59429575) in *CYP19A1* of which the minor allele frequencies more than 5% to ensure the valid statistical analysis.

SNP genotyping

Genomic DNA was extracted from collected peripheral blood samples using a DNA purification extraction kit (GoldMag Xi'an, China). The concentration and purity of DNA were determined quantitatively by ultraviolet spectrophotometer (Nanodrop 2000, Thermo, USA). Multiplexed SNP MassEXTEND assay was designed with the Agena Bioscience Assay Design Suite software, version 3.0 (Agena Bioscience, USA). SNP genotyping was conducted utilizing the MassARRAY platform (Agena Bioscience, USA). Data processing carried out with Agena Bioscience TYPER software, version 4.0 (Agena Bioscience, San Diego, CA, USA) ¹⁸.

Statistical analysis and Bioinformatics analysis

SPSS software (SPSS 22.0, USA) and Microsoft Excel were used for statistical analysis. The differences in sex and age distribution between the case group and the control group were determined by the χ^2 test and independent sample *t*-test, respectively. χ^2 test was used to determine whether individual polymorphisms were in Hardy-Weinberg equilibrium (HWE). In addition, χ^2 test was used to difference detection on allele and genotype frequencies between cases and controls. The PLINK software (<http://www.cog-genomics.org/plink2/>) was adopted to define the relationship between the polymorphisms and risk of lung cancer among Chinese Han nationality population in different genetic model analysis (genotype model, model of dominant and recessive models and additive model). Logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval (CIs) to evaluate the lung cancer risk effect ¹⁹⁻²¹. The $p < 0.05$ was considered statistically significant in all tests. The functionality of candidate SNPs were annotated using the HaploReg v4.1 database. (<https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php>).

Results

Study population

In this study, a random sample of 507 lung cancer patients (353 males and 154 females) was involved as well as 505 healthy control people (354 males and 151 females), with an average age of 60.75 ± 9.98 and 60.40 ± 7.39 (Table 1). There was no significant difference in sex and age distribution between the case group and the control group ($p > 0.05$). In addition, the characteristics of the study population were collected for subsequent studies, including body mass index (BMI), smoking and drinking history, pathological type, pathological stage, and lymph node metastasis (LNM).

Table 1
Characteristics of the study population

	Cases	Controls	<i>p</i>
Total	507	505	
Age			0.524 [†]
Mean ± SD	60.75 ± 9.98	60.40 ± 7.39	
≤ 60	236(47%)	235(47%)	
> 60	271(53%)	270(53%)	
Sex			0.891 [‡]
Male	353(70%)	354(70%)	
Female	154(30%)	151(30%)	
BMI			
≤ 24	316(62%)	146(29%)	
> 24	177(35%)	161(32%)	
Absence	74(3%)	198(39%)	
Smoking			
Yes	251(50%)	136(27%)	
No	250(49%)	140(28%)	
Absence	6(1%)	229(45%)	
Drinking			
Yes	114(22%)	109(22%)	
No	356(70%)	135(27%)	
Absence	37(8%)	261(51%)	
Pathological type			
Squamous cell carcinoma.	119(23%)		
Adenocarcinoma	187(37%)		
Absence	201(40%)		
Stage			
I-II	83(16%)		
III-IV	260(51%)		
Absence	146(33%)		
LNM			

SD: standard deviation; BMI: body mass index; LNM: lymph node metastasis.

[†]*p* values were calculated from independent sample *t*-test.

[‡]*p* values were calculated from two-sided χ^2 test.

	Cases	Controls	<i>p</i>
Negative	84(17%)		
Positive	214(42%)		
Absence	209(41%)		
SD: standard deviation; BMI: body mass index; LNM: lymph node metastasis.			
† <i>p</i> values were calculated from independent sample <i>t</i> -test.			
‡ <i>p</i> values were calculated from two-sided χ^2 test.			

Basic information of the selected SNPs

Four SNPs in *CYP19A1* were genotyped among the subjects. The basic information of all candidate SNPs is listed in Table 2. All SNPs are located on chromosome 15 and in the different position of *CYP19A1* gene. The deviation of Hardy-Weinberg equilibrium in the control group was evaluated, and the results showed that the candidate SNPs all met the expected *p* value ($p > 0.05$), and all SNPs satisfied further study. In addition, under the allele risk model, there was no significant difference in the distribution of alleles of each SNP between the lung cancer cases and the control group. ($p > 0.05$). Functional prediction of SNPs were conducted in HaploReg v4.1 database to explore their regulatory effect. The results showed that the four SNPs exhibited potential biological functions in gene regulation.

Table 2
Basic information of candidate SNPs in the study

SNP ID	Genes	Chr.	Position	Alleles A/B	MAF		<i>p</i> - HWE [†]	<i>p</i> [‡]	OR (95%CI)	HaploReg
					Case	Control				
rs28757157	CYP19A1	Chr15	51253204	A/G	0.225	0.208	0.501	0.359	1.11(0.11–0.89)	Enhancer histone marks, Motifs changed, Selected eQTL hits
rs3751592	CYP19A1	Chr15	51314381	A/G	0.135	0.126	1.000	0.532	1.09(0.13–0.84)	Promoter histone marks, Enhancer histone marks, DNase, Motifs changed, Selected eQTL hits
rs3751591	CYP19A1	Chr15	51314513	C/T	0.143	0.131	0.695	0.458	1.10(0.13–0.85)	Promoter histone marks, Enhancer histone marks, DNase, Motifs changed
rs59429575	CYP19A1	Chr15	51314880	C/T	0.172	0.161	0.869	0.511	1.08(0.12–0.86)	Promoter histone marks, Enhancer histone marks, DNase, Proteins bound, Motifs changed

SNP = single nucleotide polymorphism, MAF = minor allele frequency, OR = odds ratio, 95%CI = 95%confidence interval.

[†]HWE *p*-value were calculated from Fisher's exact test.

[‡]*p* values were calculated from two-sided χ^2 test.

*Bold values indicate statistical significance ($p < 0.05$).

Genetic model analyses of the selected SNPs

Four genetic models analysis for the relationship between rs28757157 and rs59429575 polymorphism and risk of lung cancer are listed in Table 3. Our results revealed an association between rs28757157 and increased risk of lung cancer in the genotype model (OR = 1.33, 95% CI: 1.03–1.73, $p = 0.032$). Rs59429575 was also associated with an increased risk of lung cancer in recessive model (OR = 2.03, 95% CI: 1.00-4.11, $p = 0.049$).

Table 3
Analysis of association between rs28757157 and rs59429575 polymorphism and risk of lung cancer

SNP ID	Model	Genotype	Case(N)	Control(N)	Crude		Adjusted [†]	
					OR(95%CI)	<i>p</i> [‡]	OR(95%CI)	<i>p</i> [‡]
rs28757157	Genotype	CC	276	313	1			
		CT	201	172	1.33(1.02–1.72)	0.034*	1.33(1.03–1.73)	0.032*
		TT	9	19	0.54(0.24–1.21)	0.132	0.53(0.24–1.20)	0.130
	Dominant	CC	276	313	1		1	
		CT-TT	210	191	1.25(0.97–1.61)	0.089	1.25(0.97–1.61)	0.085
	Recessive	CC-CT	477	485	1		1	
		TT	9	19	0.48(0.22–1.08)	0.075	0.48(0.21–1.07)	0.072
	Additive	–	–	–	1.12(0.89–1.40)	0.332	1.12(0.89–1.41)	0.324
	rs59429575	Genotype	CC	357	354	1		
CT			126	138	0.91(0.68–1.20)	0.491	0.91(0.68–1.20)	0.496
TT			24	12	1.98(0.98–4.03)	0.058	1.98(0.97–4.01)	0.060
Dominant		CC	357	354	1		1	
		CT-TT	150	150	0.99(0.76–1.3)	0.951	0.99(0.76–1.30)	0.955
Recessive		CC-CT	483	492	1		1	
		TT	24	12	2.04(1.01–4.12)	0.048*	2.03(1.00–4.11)	0.049*
Additive		–	–	–	1.08(0.86–1.35)	0.523	1.08(0.86–1.35)	0.523

[†]Adjusted for age and sex in a logistic regression model.

[‡]*p* values were calculated from wald-test.

*Bold values indicate statistical significance ($p < 0.05$).

In addition, we conducted a stratified analysis to explore the risk effects of these SNPs in specific groups of people. Stratified analysis of the clinical characteristics of rs28757157 polymorphism are showed in Table 4. The results indicated that rs28757157 heterozygote genotype (CT) was associated with increased susceptibility to lung cancer in people under 60 years of age (OR = 1.6, 95% CI: 1.09–2.35, $p = 0.016$). While the CC-CT genotype of rs28757157 exerted protective role in the development of lung cancer among people under 60 years and people with a BMI greater than 24.(age \leq 60: OR = 0.11, 95% CI: 0.01–0.87, $p = 0.036$; BMI > 24: OR = 0.19, 95% CI: 0.04–0.87, $p = 0.033$). In addition, rs28757157 was identified as a genetic risk factor for lung cancer susceptibility in the allele, dominant, and additive models in the smoking population (allele model: OR = 1.48, 95% CI: 1.00–2.18, $p = 0.048$; dominant model: OR = 1.58, 95% CI: 1.01–2.47, $p = 0.045$; additive model: OR = 1.57, 95% CI: 1.03–2.4, $p = 0.036$).

Table 4
Stratification analyses by clinical characteristics about the rs28757157 polymorphism

Variables		p^\dagger , OR (95% CI)					
		Allele	Homozygote	Heterozygote	Dominant	Recessive	Additive
Age	≤ 60	0.521, 1.11(0.81– 1.50)	0.059, 0.14(0.02– 1.08)	0.016, 1.60(1.09– 2.35)	0.051, 1.45(0.99– 2.12)	0.036, 0.11(0.01– 0.87)	0.283, 1.21(0.86– 1.70)
	> 60	0.542, 1.10(0.82– 1.49)	0.959, 0.97(0.36– 2.64)	0.367, 1.19(0.82– 1.72)	0.837, 1.17(0.81– 1.67)	0.863, 0.92(0.34– 2.46)	0.498, 1.12(0.81– 1.53)
BMI	≤ 24	0.221, 1.26(0.89– 1.80)	0.516, 1.70(0.34– 8.46)	0.215, 1.30(0.86– 1.98)	0.188, 1.32(0.87– 1.99)	0.596, 1.54(0.31– 7.60)	0.177, 1.30(0.89– 1.91)
	> 24	0.980, 1.01(0.70– 1.44)	0.052, 0.21(0.04– 1.02)	0.133, 1.42(0.90– 2.25)	0.351, 1.24(0.79– 1.93)	0.033, 0.19(0.04– 0.87)	0.973, 1.01(0.68– 1.48)
Smoking	Yes	0.048, 1.48(1.00– 2.18)	0.283, 3.27(0.38– 28.49)	0.062, 1.54(0.98– 2.41)	0.045, 1.58(1.01– 2.47)	0.348, 2.81(0.32– 24.30)	0.036, 1.57(1.03– 2.40)
	No	0.736, 0.39(1.17– 0.82)	0.677, 0.74(0.17– 3.11)	0.163, 1.37(0.88– 2.12)	0.204, 1.32(0.86– 2.04)	0.557, 0.65(0.16– 2.72)	0.315, 1.23(0.82– 1.82)
Drinking	Yes	0.293, 1.30(0.80– 2.11)	0.585, 0.51(0.04– 5.83)	0.142, 1.54(0.87– 2.73)	0.180, 1.47(0.84– 2.60)	0.504, 0.44(0.04– 4.98)	0.272, 1.35(0.79– 2.30)
	No	0.320, 1.19(0.84– 1.69)	0.863, 0.90(0.26– 3.08)	0.169, 1.34(0.88– 2.04)	0.201, 1.31(0.87– 1.97)	0.725, 0.80(0.24– 2.73)	0.292, 1.22(0.84– 1.77)
BMI: body mass index.							
Allele: C > T; Homozygote: TT; Heterozygote: CT; Dominant: CC vs CT-TT; Recessive: CC-CT vs TT.							
$^\dagger p$ values were calculated from wald test.							
Bold values indicate statistical significance ($p < 0.05$).							

Stratification analyses by clinical characteristics of the rs59429575 polymorphism are summarized in Table 5. Stratified analysis by sex demonstrated a remarkable relationship between enhanced lung cancer risk and the GG-GC genotype of rs59429575 (OR = 5.18, 95% CI: 1.12–24.05, $p = 0.036$). In addition, in the patients with lung adenocarcinoma, rs59429575 was identified as a risk factor for lung cancer development. (Homozygote: OR = 2.37, 95% CI: 1.01–5.56, $p = 0.047$; recessive model: OR = 2.55, 95% CI: 1.09–5.95, $p = 0.03$).

Table 5
Stratification analyses by clinical characteristics about the rs59429575 polymorphism

Variables		p^\dagger , OR (95% CI)					
		Allele	Homozygote	Heterozygote	Dominant	Recessive	Additive
Sex	Male	0.514, 1.10(0.83– 1.46)	0.417, 1.41(0.61– 3.24)	0.834, 1.04(0.74– 1.46)	0.663, 1.08(0.78– 1.49)	0.427, 1.40(0.61– 3.19)	0.523, 1.09(0.83– 1.44)
	Female	0.839, 1.04(0.69– 1.58)	0.051, 4.64(0.99– 21.68)	0.738, 0.68(0.41– 1.13)	0.464, 0.84(0.52– 1.35)	0.036, 5.18(1.12– 24.05)	0.843, 1.04(0.70– 1.56)
Tumor type	LUAD	0.729, 1.06(0.77– 1.46)	0.047, 2.37(1.01– 5.56)	0.160, 0.75(0.50– 1.12)	0.488, 0.88(0.6– 1.28)	0.030, 2.55(1.09– 5.95)	0.873, 1.03(0.75– 1.41)
	LUSC	0.367, 1.18(0.82– 1.71)	0.212, 1.96(0.68– 5.65)	0.701, 1.10(0.69– 1.75)	0.476, 1.18(0.75– 1.83)	0.226, 1.91(0.67– 5.47)	0.311, 1.21(0.83– 1.77)
LNM	(–)	1.00					
	(+)	0.256, 1.34(0.81– 2.22)	0.365, 2.04(0.44– 9.60)	0.621, 1.17(0.64– 2.13)	0.450, 1.25(0.70– 2.23)	0.389, 1.97(0.42– 9.18)	0.349, 1.26(0.78– 2.06)
Stage	I ~ II	1.00					
	III ~ IV	0.122, 1.48(0.90– 2.44)	0.077, 6.31(0.82– 48.41)	0.957, 1.02(0.57– 1.83)	0.410, 1.27(0.72– 2.23)	0.077, 6.28(0.82– 48.00)	0.153, 1.41(0.88– 2.24)
LUAD: Lung Adenocarcinoma; LUSC: Lung Squamous cell carcinoma; LNM: lymph node metastasis.							
Allele: G > C; Homozygote: CC; Heterozygote: GC; Dominant: GG vs GC-CC; Recessive: GG-GC vs CC.							
$^\dagger p$ values were calculated from wald test.							
Bold values indicate statistical significance ($p < 0.05$).							

Discussion

In this study, we examined four SNPs of *CYP19A1* gene in correlation to the susceptibility of lung cancer in a Chinese Han cohort. Statistical and bioinformatics results revealed the important roles of rs28757157 and rs59429575 in the outset of lung cancer in total or stratified population, which helped improve our understanding of *CYP19A1* in this disease.

CYP19A1 gene encoding an aromatase responsible for the final step in the biosynthesis of estrogens, estradiol (E2) and estrone (E1), have been intensively investigated^{22,23}. SNPs in the intron region of *CYP19A1* have been identified to play an important role in the transcriptional regulation and splicing of *CYP19A1*, producing some different enzymes with diverse enzyme activity compared with normal gene products. Variations in the allele frequency of several *CYP19A1* SNPs have been documented in different populations and ethnic groups around the world. SNPs in *CYP19A1* were found to be associated with cancer risk in European Americans, North Indians, and Chinese^{24,25}. In particular, *CYP19A1* SNPs have been shown to be significantly associated with lung-related diseases.

A previous study has shown that SNP rs3764221 is significantly correlated with *CYP19A1* expression in non-cancerous lung tissues, and affects the susceptibility of lung adenocarcinoma. The authors suggest that *CYP19A1* polymorphisms may lead to elevated levels of local estrogen in the surrounding lung, and that this local excess estrogen production may be one of the factors associated with the polycentric development of adenocarcinoma¹⁵. Recent result has suggested that *CYP19A1*

polymorphism is involved in lung bronchioloalveolar carcinoma and atypical adenomatous hyperplasia risk by causing differences in estrogen levels¹⁶. It is clear that *CYP19A1* polymorphism may cause changes in estrogen levels around the lungs, which in turn can affect the susceptibility of lung cancer.

Zhang et al. have shown that *CYP19A1*-rs727479 was significantly associated with the incidence of lung cancer. In particular, haplotype rs727479|rs730154|rs10046-ACA was only significantly associated with nonsmokers and female nonsmokers¹⁷. These results indicated that *CYP19A1* polymorphism is significantly associated with the susceptibility to lung cancer, and is gender-specific. Our research showed that *CYP19A1*-rs28757157 was associated with increased cancer risk in males and smoker, and *CYP19A1*-rs59429575 was identified as risk biomarker in female and lung adenocarcinoma patients. These two SNPs are located in the intron region of the *CYP19A1* gene. Combined with previous studies and database predictions, we speculated that *CYP19A1* intron single nucleotide polymorphisms may alter mRNA splicing, leading to changes in the activity of CYP19A1 and related estrogens, and may affect disease susceptibility. Since the statistical significance of the correlation between *CYP19A1* gene polymorphism and the risk of lung cancer is slightly weak, further experimental studies are needed to verify the results of this study.

Our study has several limitations. All subjects were enrolled from the same hospital and the limitations of sample selection may affect the accuracy of this experiment. Additional studies that encompass more geographical regions, additional ethnic groups, and larger sample size should be performed. In order to verify the results of this study, it is necessary to clarify the relationship between *CYP19A1* gene and lung cancer through subsequent functional studies.

In summary, our study defined two new SNPs of *CYP19A1* that were significantly associated with lung cancer susceptibility. These variants may be considered as markers in lung cancer risk assessment for Chinese Han population.

Declarations

Compliance with Ethical Standards

The authors declare no competing financial interests.

Our study was conducted with appropriate approval of ethnics committee from the Shaanxi Provincial Cancer Hospital. All procedures performed in this study were in accordance with the ethical standards of the ethics committee from the Shaanxi Provincial Cancer Hospital and with the 1964 Helsinki declaration and its later amendments.

Informed consent was obtained from each participant at recruitment after fully describing our research to them.

Consent for publication

Not applicable

Data availability

The datasets generated during the current study are available.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

Tonghua Yang designed the experiment, Chan Zhang and Yujing Cheng performed the experiment, Wanlu Chen and Qi Li processed the data, Chan Zhang Wrote the manuscript, Yajie Wang revised the manuscript.

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