

## ORIGINAL RESEARCH ARTICLE

# Association of *POLR2E* rs3787016 polymorphism with lung cancer risk and efficacy of platinum-based chemotherapy: A case–control study

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## Abstract

**Introduction:** Lung cancer is one of the most prevalent cancers, with high mortality rate. Chemotherapy is a fundamental component of the treatment. However, the response varies among individuals.

**Objective:** This study investigated the association of the *POLR2E* rs3787016 polymorphism with lung cancer susceptibility and platinum-based chemotherapy response.

**Methods:** The study included 498 pulmonary carcinoma patients and 213 healthy individuals. Of these, 467 cases received at least two cycles of platinum-based chemotherapy. The *POLR2E* rs3787016 genotyping was performed using time-of-flight mass spectrometry. Unconditional logistic regression analyses were used to evaluate the association of the genotype with pulmonary carcinoma susceptibility, as well as platinum-based chemotherapy response.

**Results:** The study found no statistically significant association between *POLR2E* rs3787016 and susceptibility to pulmonary carcinoma (additive model: adjusted OR [aOR] = 1.012, 95% confidence interval [CI] = 0.781–1.310,  $p=0.930$ ; dominant model: aOR = 0.794, 95% CI = 0.518–1.217,  $p=0.289$ ; recessive model: aOR = 1.303, 95% CI = 0.847–2.003,  $p=0.228$ ). Logistic regression analysis demonstrated no meaningful association between *POLR2E* rs3787016 and the efficacy of platinum-based chemotherapy (additive model: aOR = 0.901, 95% CI = 0.688–1.181,  $p=0.450$ ; dominant model: aOR = 0.900, 95% CI = 0.578–1.401,  $p=0.642$ ; recessive model: aOR = 0.840, 95% CI = 0.541–1.306,  $p=0.439$ ). Besides, no substantial association was found between *POLR2E* rs3787016 polymorphism and the 5-year overall survival.

**Conclusion:** Current evidence does not support *POLR2E* rs3787016 as a potential biomarker for predicting susceptibility to pulmonary carcinoma and the therapeutic efficacy of platinum-based chemotherapy in Chinese patients.

**Keywords:** *POLR2E* rs3787016; Pulmonary carcinoma; Platinum-based chemotherapy; Cancer risk

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## 1. Introduction

Lung cancer ranks as the second most prevalent malignancy across the globe, and it remains a primary contributor to tumor-related mortality.<sup>1–5</sup> Current epidemiological data indicate that the annual incidence of this disease exceeds 2.2 million new cases.

Alongside this, there are 1.79 million deaths resulting from lung cancer each year—a figure that accounts for over 20% of the global cancer mortality burden. This number even surpasses the combined fatality rates of prostate, mammary, and colorectal neoplasms.<sup>1,6–8</sup> Despite the fact that modern therapeutic advancements have been made, encompassing surgery, radiotherapy, chemotherapy, molecular targeted therapy, and immunotherapy, the average 5-year survival rate for lung cancer remains only 19%.<sup>9–13</sup> Chemotherapy, to this day, remains a cornerstone of treatment; however, two key issues limit its efficacy. One is the rapid development of drug resistance, and the other is the interindividual variability in treatment response. Moreover, due to the individual differences in sensitivity that exist among patients, only a small proportion of them actually benefit from chemotherapy. At the same time, these patients are facing the risk of serious toxic reactions. Hence, there is a pressing and urgent need to discover possible predictive biomarkers. These biomarkers should be able to anticipate the prognosis of lung cancer patients as well as their treatment response. This endeavor is paramount for advancing personalized medicine, optimizing treatment efficacy, and improving patient outcomes.<sup>5,14,15</sup>

Emerging research highlights the critical roles of long non-coding RNAs (lncRNAs), which are defined by their length exceeding 200 nucleotides, in modulating drug responses and toxicity. These lncRNAs have emerged as potential diagnostic and prognostic indicators for various malignancies. In addition, single-nucleotide polymorphisms (SNPs) are key genetic factors influencing gene expression and function, and implicated in influencing the predisposition to a wide array of complex human illnesses, cancer being one of them. RNA polymerase II (Pol II)—a critical enzyme for transcribing protein-coding genes—requires its subunit POLR2E for functional integrity. The SNP rs3787016 is situated within the fourth intron of the *POLR2E* gene. Previous studies have explored the potential associations between *POLR2E* rs3787016 polymorphism and cancer risk in gastric, prostate, breast, cervical, thyroid cancer, as well as squamous cell carcinoma. However, conflicting results exist due to small sample sizes and differences in the racial backgrounds of study populations. In addition, its role in lung cancer susceptibility and platinum chemotherapy response remains unexplored despite biological plausibility. This gap is clinically urgent given the high variability in platinum efficacy and the lack of reliable SNP biomarkers to guide lung cancer treatment.

Our study aims to address a dual unmet need by conducting the first comprehensive analysis of rs3787016 in both lung cancer risk and platinum-based chemotherapy

outcomes, aiming to resolve conflicting evidence from prior cross-cancer studies while advancing precision oncology through biomarker validation or exclusion. Based on the aforementioned background, we conducted the first comprehensive study evaluating *POLR2E* rs3787016 for both lung cancer risk and platinum-based chemotherapy outcomes in a Chinese cohort. Our work aims to resolve inconsistencies from prior cross-cancer studies and advance precision oncology by validating or excluding this SNP as a candidate biomarker.

## **2. Materials and methods**

### **2.1. Participants**

This research included lung cancer patients who were admitted to Xiangya Hospital and the Affiliated Cancer Hospital of Central South University. These patients were admitted during the period between November 2011 and February 2013. The inclusion criteria for these patients are as follows: (i) They must have had a cytologically or histologically confirmed primary lung cancer diagnosis; (ii) They must have received at least two cycles of platinum-based combination chemotherapy; (iii) They must not have undergone prior radiotherapy or biological therapy before or during chemotherapy, and they must be eligible for follow-up assessments. Individuals who had acute infections or other malignant tumors were excluded from the study. The platinum-based chemotherapy regimens that were used in the study encompassed various combinations. These combinations included platinum combined with etoposide (which is referred to as EP), gemcitabine (referred to as GP), paclitaxel (referred to as TP), docetaxel (referred to as DP), pemetrexed (referred to as PP), and other combinations (such as those combined with irinotecan or lobaplatin). The healthy controls for this study were selected from individuals who were undergoing routine physical examinations at the Xiangya Hospital Health Examination Center during the corresponding timeframe. The study protocol was approved by the Ethics Committee of Xiangya Hospital, Central South University (Approval No.: CTXY-110008-2).

### **2.2. Data collection and toxicity assessment**

Clinical information, including age, gender, smoking history, histopathological characteristics of the tumor, and performance status score, was collected from the hospital's electronic information system. After the patients had completed two cycles of chemotherapy, their therapeutic outcomes were evaluated using the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines.<sup>12</sup> Based on these guidelines, the therapeutic outcomes were categorized into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Among

these categories, CR and PR were grouped together as responders, while SD and PD were grouped together as non-responders.

### 2.3. DNA isolation and genotyping

Genomic DNA was isolated from venous blood samples, and these samples were collected before chemotherapy. After collection, the venous blood samples were kept in blood tubes containing ethylenediaminetetraacetic acid for preservation. Isolation of genomic DNA from the preserved venous blood sample was conducted using a whole-genome DNA extraction kit (Promega, USA). Once the genomic DNA was isolated, it was preserved at a temperature of  $-20^{\circ}\text{C}$  before any further analysis of the DNA. The genotyping of the *POLR2E* rs3787016 polymorphism was performed by means of time-of-flight mass spectrometry. DNA integrity was verified through 1.5% agarose gel electrophoresis, with all samples exhibiting sharp, high-molecular-weight bands without degradation (smearing) or contamination (extraneous bands). Purity and concentration were assessed spectrophotometrically (NanoDrop™ 2000), with  $\text{OD}_{260}/\text{OD}_{280}$  ratios maintained at 1.7–2.0 and working concentrations adjusted to 10–30 ng/ $\mu\text{L}$ . The *POLR2E* rs3787016 (C>T) variant was genotyped using the Sequenom MassARRAY® iPLEX™ Gold platform (USA). Locus-specific polymerase chain reaction (PCR) and extension primers were designed using the Assay Design 3.1 software (Sequenom). The extension primers, after synthesis, underwent stringent pre-optimization validation via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. All extension primers demonstrated single-peak spectra matching theoretical molecular masses within  $\pm 0.1\%$  tolerance and >95% purity, confirming the absence of truncated sequences or impurities. During genotyping, each 96-well plate included eight no-template controls (NTCs) to monitor contamination and 10% random sample duplicates to assess reproducibility. Samples with undetermined genotypes following triplicate PCR amplification were excluded, resulting in a final genotyping success rate of 98.2%. Post-genotyping quality assessment confirmed 100% concordance in duplicate samples and zero amplification in NTCs across all plates. Genotype cluster separation was visually verified using the MassARRAY™ Typer 4.0 software, demonstrating unambiguous allele discrimination.

### 2.4. Statistical analysis

Analyses were comprehensively conducted utilizing PASW Statistics v18.0, PLINK 1.9, and R (v4.4.3) software. Descriptive statistics, including counts and proportions, were applied to categorical dataset. Chi-square tests were assessed differences in gender and age between cases and

controls. Hardy–Weinberg equilibrium in controls was tested by goodness-of-fit chi-square analysis. Unconditional logistic regression, adjusted for age and gender, evaluated associations with lung cancer risk and calculated adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Associations with chemotherapy response were similarly analyzed after adjustment for age, gender, smoking history, disease stage, histology, and chemotherapy regimen. To account for multiple comparisons arising from testing associations under three genetic models (additive, dominant, recessive) for each clinical outcome, we applied false discovery rate (FDR) correction using the Benjamini-Hochberg procedure.<sup>16</sup> Survival curves were generated using the Kaplan-Meier method. Cox proportional hazards regression assessed survival differences. *Post hoc* power analyses were performed to determine the probability of detecting clinically relevant effects given our sample size. Threshold effect sizes were defined *a priori* as odds ratio (OR)  $\geq 1.5$  for lung cancer susceptibility (based on IARC guidelines for genetic associations) and OR  $\geq 1.8$  for therapeutic response (consistent with RECIST criteria for non-small cell lung cancer [NSCLC] chemotherapy efficacy).<sup>17</sup> Calculations utilized the pwr package (v1.3-0) with empirically derived control event rates: 77.5% risk allele carriage in controls (165/213) for cancer risk, and 35.9% response rate in non-risk genotypes (66/184) for treatment efficacy.<sup>18</sup> All tests were two-tailed, with a statistical significance threshold set at  $p < 0.05$ .

## 3. Results

### 3.1. Participants and descriptive data

This study included 498 patients (predominantly male, 79.1%, and younger, 48.6% <57 years) with 213 controls (predominantly female, 62.4%, and older, 65.3%  $\geq 57$  years), showing highly significant differences in sex and age distribution ( $p = 0.000$  for both). Therefore, age and gender were adjusted for lung cancer risk association analysis. Among patients, the vast majority (86.1%) had NSCLC, primarily adenocarcinoma (43.6%) or squamous cell carcinoma (37.9%), while 13.9% had small cell lung cancer (SCLC). Nearly all NSCLC patients (97.0%) presented with advanced stage (III/IV) disease, and SCLC patients were nearly evenly distributed between limited (52.2%) and extensive (47.8%) stages. The most common first-line platinum-based chemotherapy regimens were platinum plus gemcitabine (41.4%) or pemetrexed (29.3%), with platinum plus etoposide (14.6%) also frequently used.

Detailed information of clinical characteristics is shown in Table 1. A total of 467 patients with sufficient clinical data were included in the therapeutic response analysis. There were 283 non-responders and 184 responders. Responders

had a higher proportion of males (84.8% vs. 76.0%) and were more likely to have SCLC (22.8% vs. 9.2%), while non-responders had a higher prevalence of NSCLC (85.2% vs. 70.7%). Among NSCLC patients, a higher percentage of the responders had SCC (41.3% vs. 32.2%), whereas a much higher percentage of the non-responders had adenocarcinoma (ADC) (53.0% vs. 29.3%). Advanced disease (stage III/IV) was common in both groups for NSCLC and SCLC. Regimen analysis revealed responders received platinum plus etoposide more frequently (23.4% vs. 8.8%), a regimen often used for SCLC, while non-responders more commonly received platinum plus pemetrexed (36.0% vs. 19.0%), which was typically used

for non-squamous NSCLC. Their characteristics are summarized in Table 2.

### 3.2. The association between *POLR2E* rs3787016 with the risk of lung cancer

The genotyping success rate of *POLR2E* rs3787016 in the study population is 98.2%, which indicates a high quality of genotyping data. In healthy controls, the SNP genotypes were found to be in Hardy-Weinberg equilibrium, with a *p*-value of 0.596, suggesting that the control group is representative of the general population. We then set out to evaluate the relationship between *POLR2E* rs3787016 and tumor susceptibility. After adjusting for potential

**Table 1. Demographics of lung cancer patients and healthy controls**

Characteristics	Patients (n=498)	Controls (n=213)	<i>p</i>
Sex			
Male	394 (79.1)	80 (37.6)	0.000*
Female	104 (20.9)	133 (62.4)	
Age (years)			
<57	242 (48.6)	74 (34.7)	0.000*
≥57	256 (51.4)	139 (65.3)	
Histology			
NSCLC	429 (86.1)		
SCLC	69 (13.9)		
Others	23 (4.6)		
NSCLC			
SCC	189 (37.9)		
ADC	217 (43.6)		
Stage (NSCLC)			
I, II	13 (3.0)		
III, IV	416 (97.0)		
Stage (SCLC)			
Limited	36 (52.2)		
Extensive	33 (47.8)		
Regimen			
Platinum+Gemcitabine	192 (41.4)		
Platinum+Etoposide	68 (14.6)		
Platinum+Pemetrexed	137 (29.3)		
Platinum+Paclitaxel	27 (5.8)		
Platinum+Docetaxel	29 (6.2)		
Platinum+Irinotecan or platinum+Navelbine	14 (3.0)		

Notes: Data are expressed as *n* (%). \**p*<0.05. "Others" histology refers to mixed-cell or undifferentiated carcinoma.  
Abbreviations: ADC: Adenocarcinoma; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer.

**Table 2. Demographics of lung cancer patients who received platinum-based chemotherapy**

Characteristics	Non-responders (n=283)	Responders (n=184)	<i>p</i>
Sex			
Male	215 (75.97)	156 (84.78)	0.021*
Female	68 (24.03)	28 (15.22)	
Age (years)			
<57	145 (51.24)	89 (48.37)	0.545
≥57	138 (48.76)	95 (51.63)	
Histology			
NSCLC	241 (85.16)	130 (70.65)	0.045*
SCLC	26 (9.19)	42 (22.83)	
Others	16 (5.65)	12 (6.52)	
NSCLC			
SCC	91 (32.2)	76 (41.3)	0.000*
ADC	150 (53.0)	54 (29.3)	
Stage (NSCLC)			
I, II	8 (2.8)	4 (2.2)	0.868
III, IV	249 (88.0)	138 (75.0)	
Stage (SCLC)			
Limited	11 (3.9)	24 (13.0)	0.234
Extensive	15 (5.3)	18 (9.8)	
Regimen			
Platinum+Gemcitabine	110 (38.87)	82 (44.57)	0.000*
Platinum+Etoposide	25 (8.83)	43 (23.37)	
Platinum+Pemetrexed	102 (36.04)	35 (19.02)	
Platinum+Paclitaxel	18 (6.36)	9 (4.89)	
Platinum+Docetaxel	20 (7.07)	9 (4.89)	
Platinum+Irinotecan or platinum+Navelbine	8 (2.83)	6 (3.26)	

Notes: Data are expressed as *n* (%). \**p*<0.05. "Others" histology refers to mixed-cell or undifferentiated carcinoma.  
Abbreviations: ADC: Adenocarcinoma; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer.



confounding variables such as age and gender, which could influence the results, we analyzed the data and found no evidence of a statistically significant correlation between *POLR2E* rs3787016 and tumor susceptibility. This lack of significance was consistent across different genetic models: in the additive model, the aOR was 1.012, with a 95% CI of 0.781–1.310 ( $p=0.930$ ,  $p_{FDR}=0.930$ ); in the dominant model, the aOR was 0.794, with a 95% CI of 0.518–1.217 ( $p=0.289$ ,  $p_{FDR}=0.434$ ); in the recessive model, the aOR was 1.303, with a 95% CI of 0.847–2.003 ( $p=0.228$ ,  $p_{FDR}=0.434$ ) (Table 3). *Post hoc* power analysis confirmed that effects with OR  $\geq 1.5$  in all genetic models can be detected with a power of  $>99.99\%$ , indicating that the study had sufficient statistical power to identify such associations if they existed. The 95% CIs for both the additive and dominant models excluded the clinical threshold, as their upper bounds were  $\leq 1.310$ , while the point estimate of the recessive model was close to the null value. To gain a deeper understanding of potential correlations, we performed a stratified examination to investigate the possible link between *POLR2E* rs3787016 and tumor risk. As shown in Figure 1, even after stratifying the subjects by gender, age, and histological type, no significant correlation was observed.

### 3.3. The correlation between *POLR2E* rs3787016 and platinum-based chemotherapy response

Among the 467 patients who had undergone at least two cycles of platinum-based chemotherapy, their therapeutic efficacy was evaluated using the RECIST criteria. Of these patients, 184 achieved a CR or PR and were classified as responders, while 283 had SD or PD and were classified as non-responders. After adjusting for a range of variables including age, gender, smoking status, disease stage, tumor

histology, and chemotherapy regimen, we conducted a logistic regression analysis. The results showed that in the additive model (aOR = 0.901, 95% CI = 0.688–1.181,  $p=0.450$ ,  $p_{FDR}=0.642$ ), dominant model (aOR = 0.900, 95% CI = 0.578–1.401,  $p=0.642$ ,  $p_{FDR}=0.642$ ), and recessive model (aOR = 0.840, 95% CI = 0.541–1.306,  $p=0.439$ ,  $p_{FDR}=0.642$ ), there was no significant correlation identified between *POLR2E* rs3787016 and therapeutic efficacy (Table 3). For the treatment response analysis, the power to detect OR  $\geq 1.8$  effects was 86.2% across all models, indicating adequate power for detecting such effects. In addition, all 95% CIs had upper bounds of  $\leq 1.401$ , which fall below the clinical threshold. To further explore potential relationships, we performed a further stratified analysis, but as shown in Figure 2, no correlation was revealed in this analysis either.

### 3.4. The association of *POLR2E* rs3787016 with lung cancer prognosis

Ultimately, the correlation of *POLR2E* rs3787016 and 5-year overall survival was evaluated. Three separate genetic models were employed to conduct the Kaplan-Meier survival analysis. In the additive model, no statistical difference was found among patients with different genotypes (AA, GA, and GG) ( $p=0.974$ ) (Figure 3A). Dominant (hazard ratio [HR] = 0.891, 95% CI = 0.6543–1.213,  $p=0.296$ ) and recessive models (HR = 1.191, 95% CI = 0.8853–1.603,  $p=0.448$ ) similarly showed no significant differences either (Figure 3B and C).

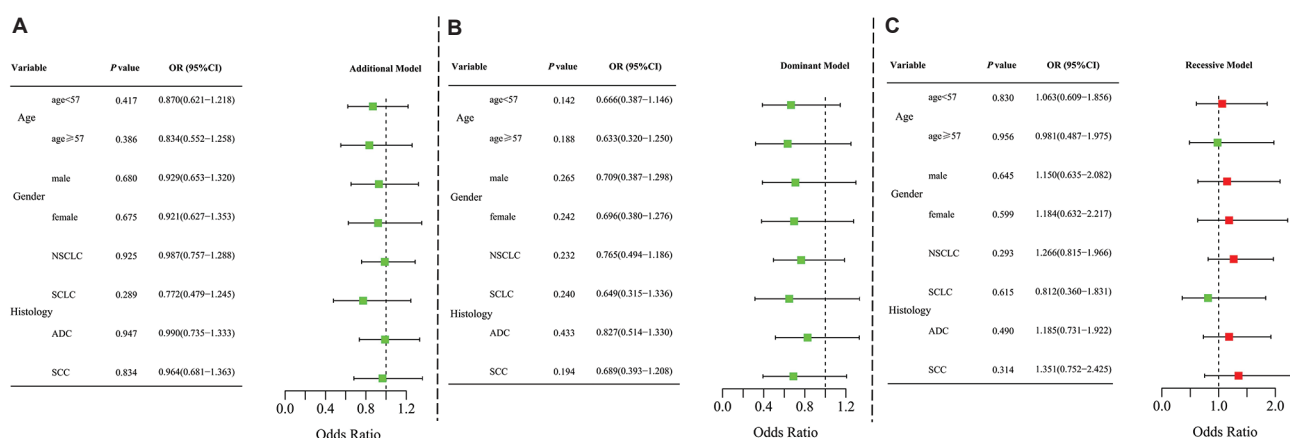
## 4. Discussion

This research systematically examined and explored the association between *POLR2E* rs3787016 and lung

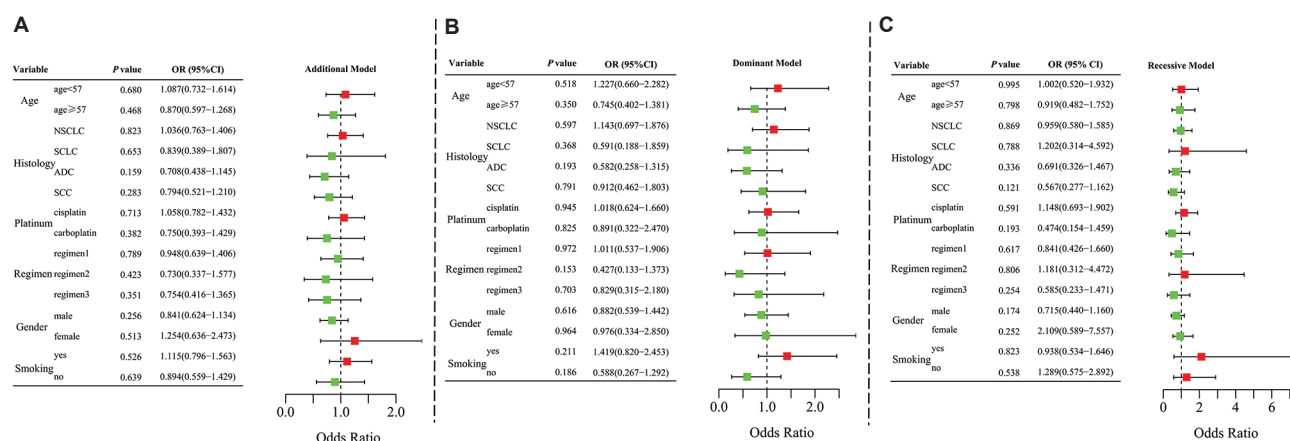
**Table 3. Association of *POLR2E* rs3787016 with cancer susceptibility and clinical outcomes in patients who received platinum-based chemotherapy**

Type	Genotype	<i>n</i> (%)	<i>n</i> (%)	Additive model			Dominant model			Recessive model		
				OR (95% CI)	<i>p</i>	<i>p</i> <sub>FDR</sub>	OR (95% CI)	<i>p</i>	<i>p</i> <sub>FDR</sub>	OR (95% CI)	<i>p</i>	<i>p</i> <sub>FDR</sub>
Susceptibility		Case	Control	1.012 (0.781–1.310)	0.930	0.930	0.794 (0.518–1.217)	0.289	0.434	1.303 (0.847–2.003)	0.228	0.434
	AA	164 (32.9)	43 (20.2)									
	GA	231 (46.4)	120 (56.3)									
	GG	99 (19.9)	45 (21.1)									
Chemotherapy response		Responder	Non- responder	0.901 (0.688–1.181)	0.450	0.642	0.900 (0.578–1.401)	0.642	0.642	0.840 (0.541–1.306)	0.439	0.642
	AA	49 (26.6)	66 (23.3)									
	GA	87 (47.3)	139 (49.1)									
	GG	46 (25.0)	74 (26.1)									

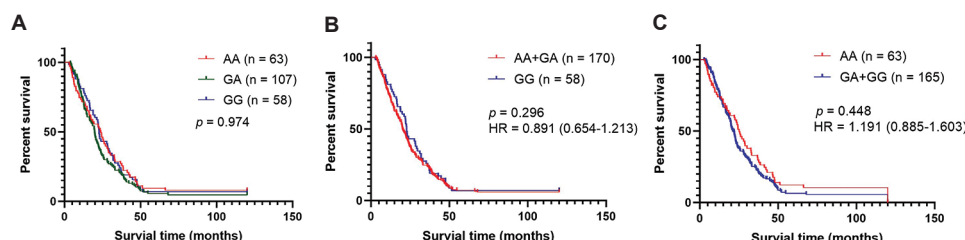
Abbreviations: CI: Confidence interval; OR: Odds ratio;  $p_{FDR}$ : *p*-value adjusted for false discovery rate (FDR).



**Figure 1.** Stratification analyses of the association of *POLR2E* rs3787016 with lung cancer risk. (A-C) Additive (A), dominant (B), and recessive models (C) with adjustments for age and sex. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). Abbreviations: ADC: Adenocarcinoma; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer



**Figure 2.** Stratification analyses of the association of *POLR2E* rs3787016 with platinum-based chemotherapy response. (A-C) Additive (A), dominant (B), and recessive models (C) with adjustments for age, sex, stage, histological type, smoking status, and chemotherapy regimens. Each box and horizontal line represent the odds ratio (OR) and 95% confidence interval (CI). Statistical significance is set at  $p < 0.05$ . “regimen 1” refers to Platinum + gemcitabine; “regimen 2” refers to platinum + etoposide; “regimen 3” refers to platinum + pemetrexed. Abbreviations: ADC: Adenocarcinoma; NSCLC: Non-small cell lung cancer; SCC: Squamous cell carcinoma; SCLC: Small cell lung cancer



**Figure 3.** Genotype of *POLR2E* rs3787016 and its association with 5-year overall survival. (A) AA versus GA versus GG; (B) AA+GA versus GG; (C) AA versus GA+GG

cancer risk, as well as the response to platinum-based chemotherapy. Initially, it analyzed the correlation between *POLR2E* rs3787016 and tumor susceptibility in a group consisting of 498 cases and 213 controls. The results obtained indicated that there is no significant association between *POLR2E* rs3787016 and lung cancer risk or

chemotherapy efficacy, and this conclusion holds true both in the overall analysis and the stratified analyses.

Platinum-based chemotherapy is pivotal in lung cancer therapy, but its efficacy varies significantly among different individuals. Therefore, identifying biomarkers that can predict susceptibility to lung cancer and chemotherapy

response is essential for improving treatment outcomes. In recent years, with the continuous development of personalized medicine, growing evidence has emerged to link genetic polymorphisms to lung cancer risk and chemotherapy efficacy. POLR2E is one of the subunits of RNA polymerase II, and it plays a vital role in mRNA synthesis. As predicted by the SNP nexus database, rs3787016 may modulate the splice processes of the *POLR2E* gene.<sup>19</sup> Furthermore, structural predictions suggest that this SNP could alter the centroid secondary structure and minimum free energy of *POLR2E*, which has the potential to impact its function.<sup>20</sup> The splicing alterations or structural changes induced by rs3787016 might lead to dysfunctional POLR2E. This dysfunction might then impair Pol II activity, consequently affecting the transcription of critical downstream targets, including lncRNAs. Previous studies have reported its association with susceptibility to various cancers, including gastric cancer,<sup>21</sup> prostate cancer,<sup>22,23</sup> breast cancer, cervical cancer,<sup>19</sup> as well as thyroid micropapillary carcinoma,<sup>24</sup> esophageal squamous carcinoma,<sup>25</sup> and endometrial carcinoma.<sup>26</sup> Although there are contradictory conclusions in these studies, most studies generally indicate that *POLR2E* rs3787016 may be a genetic locus that affects cancer susceptibility. Chen *et al.*<sup>23</sup> investigated the predictive value of *POLR2E* rs3787016 in susceptibility to lung cancer and found no significant association, consistent with our findings. The discrepancies in the study results on the relationship of *POLR2E* rs3787016 with varying levels of tumor risks may be attributed to differences in the genetic backgrounds of the study populations, sample sizes, and types of diseases. While previous studies predominantly focused on *POLR2E* rs3787016 as a susceptibility biomarker for solid tumors, its role in predicting chemotherapy response remains unexplored. Yu *et al.* identified POLR2E as one of 24 DNA-directed RNA polymerase-associated lncRNAs that form an independent prognostic model for lung adenocarcinoma. This model correlated with significant changes in immunological markers and, crucially, showed that the high-risk subgroup was more sensitive to certain chemotherapy drugs.<sup>27</sup> By incorporating *POLR2E* in a novel seven-gene prognostic signature for SCLC, Liu *et al.*<sup>28</sup> found that this model effectively predicted overall survival and immune function status, with the low-risk group enriched for immune-related functions.

The current study is the first to systematically evaluate the association of *POLR2E* rs3787016 polymorphism with platinum-based chemotherapy efficacy in lung cancer, addressing a critical gap given platinum's pivotal role in first-line treatment. In addition, this study delves into the association between the *POLR2E* rs3787016 and the lung cancer risk, contributing to a deeper insight into the

function of genetic factors in lung cancer development. While our rigorous analysis revealed no significant associations with lung cancer susceptibility or therapeutic efficacy ( $p > 0.05$  across all stratified subgroups), these definitive negative outcomes hold substantial scientific significance: they decisively exclude rs3787016 as a clinically viable biomarker in Chinese populations, thereby obviating the need for fundamental genetic testing and instead highlighting the importance of exploring polygenic or epigenetic markers. *Post hoc* power analysis confirmed a >99.99% power to detect OR  $\geq 1.5$  for cancer risk across all genetic models. The 95% CIs for additive and dominant models excluded the clinical threshold (upper bounds  $\leq 1.31$ ). For treatment response, power to detect OR  $\geq 1.8$  was 86.2%, with all 95% CIs excluding this threshold (upper bounds  $\leq 1.40$ ). While smaller effects cannot be ruled out, our findings robustly exclude clinically relevant associations at predefined thresholds. Crucially, this underscores the necessity for future multi-ethnic validation to advance precision oncology by eliminating dead ends and prioritizing biologically grounded research avenues. In addition, based on our research results, susceptibility to cancer and sensitivity to chemotherapy may be affected by several genetic and environmental factors. This emphasizes the necessity of future research to consider the combined effects of various genetic and environmental factors, rather than focusing solely on a single factor when exploring susceptibility to cancer and treatment response. Therefore, we should further integrate clinical research, basic experiments, and bioinformatics analysis to further reveal the molecular mechanisms of *POLR2E* rs3787016 in the occurrence, development, as well as chemotherapy efficacy in future studies.

Several limitations of this study should be highlighted. Firstly, the exclusive focus on Chinese participants inherently limits the generalizability of findings to other ethnic groups. This is particularly true for those with distinct genetic backgrounds, such as European or African populations. This necessitates larger studies on global populations to achieve the desired power thresholds. Second, due to the lack of smoking status data in healthy controls, we did not adjust for this factor in the analysis of lung cancer risk. Third, the recruitment of both case and control participants occurred during the period of 2011–2013. As treatment paradigms and diagnostic/therapeutic standards have evolved considerably in recent years, findings based on data from this specific timeframe may have limited relevance to current clinical practice. This could potentially affect the clinical translatability of the results. Fourthly, our study employed a case-control design where the healthy control group differed significantly from the patient group in terms of age and gender distribution. While age and sex were statistically

adjusted for in all association analyses using logistic regression models, we acknowledge that such adjustments may not fully account for all potential confounding effects arising from these demographic imbalances. Age and sex are well-established factors that influence both cancer risk and population genetic architecture. Consequently, the possibility of residual confounding cannot be entirely ruled out, and this should be considered when interpreting the associations reported herein. Future studies utilizing prospectively matched cohorts or employing techniques like propensity score matching would be valuable. Such investigations would help validate these findings further while minimizing the impact of demographic confounding. Finally, susceptibility to cancer and sensitivity to chemotherapy may be influenced by the combined effects of multiple genetic factors. Thus, future research needs to comprehensively consider the interaction of more relevant genetic loci and environmental factors.

## 5. Conclusion

Based on the current research results obtained through systematic analysis, *POLR2E* rs3787016 polymorphism is not a promising predictor of lung cancer risk and platinum-based chemotherapy efficacy in the Chinese population examined in this study. Future research should comprehensively consider the combined effects of multiple factors such as genetic loci, environmental influences, and clinical characteristics. Moreover, such research should be conducted in large cohorts to ensure adequate statistical power. This would facilitate further validation and generate novel insights and methodologies, which could inform the development of individualized chemotherapy regimens and contribute to more effective, targeted treatment strategies for lung cancer patients.

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## Conflict of interest

All authors declare that they have no financial or competing interests.

## Author contributions

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## Ethics approval and consent to participate

The ethical conduct of this research was approved by the Ethics Committee of Xiangya Hospital, Central South University (Approval No.: CTXY-110008-2).

## Consent for publication

Not applicable.

## Availability of data

The data sets in this study may be made available on reasonable request to the corresponding author.

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