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Association between CYP2A13 Polymorphisms and Lung Cancer Risk: A Systematic Review and Meta-Analysis of Case–Control Studies

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Abstract

Objectives Lung cancer remains a leading cause of cancer-related deaths worldwide, with cigarette smoking as a major risk factor. Genetic variations in the cytochrome P450 family, particularly CYP2A13 polymorphisms, have been suggested to influence lung cancer susceptibility. However, their role remains unclear, particularly in relation to smoking status and regional populations differences. This systematic review and meta-analysis aimed to evaluate the association between CYP2A13 combination and homozygous variants and lung cancer risk, stratified by smoking status and geographic region.

Materials and Methods A comprehensive search of electronic databases (PubMed, ScienceDirect, SCOPUS, and Google Scholar) was conducted up to November 11, 2024, to identify eligible case–control studies on CYP2A13 polymorphisms and lung cancer. Inclusion and exclusion criteria were based on exposure of interest, study design, language, type of publication, and reported outcome. Data from 10 studies (2,853 lung cancer cases and 3,651 controls) were pooled to calculate odds ratios (OR) with 95% confidence intervals (CIs), using a random-effects model. Subgroup analyses were performed by smoking status and geographic region. Publication bias was assessed using Egger's test and funnel plots.

Results A significant association was observed between CYP2A13 polymorphisms and lung cancer risk in specific populations. In East Asian populations, the homozygous variant was associated with an increased lung cancer risk (pooled OR: 1.37, 95% CI: 1.13–1.66). Among smokers in Europe, the combination variant showed a pooled OR of 1.64 (95% CI: 1.21–2.23). In East Asian smokers, the homozygous variant had a pooled OR of 1.52 (95% CI: 1.17–1.96). No significant publication bias was detected.

Conclusion This meta-analysis suggests that CYP2A13 polymorphisms may contribute to lung cancer susceptibility, with smoking serving as a key modifier. The findings are particularly relevant in East Asian and European populations, but given the heterogeneity between studies and limited sample sizes, further large-scale investigations are necessary. These insights provide a foundation for future research on CYP2A13 as a potential biomarker for lung cancer risk.

Keywords
- CYP2A13
- lung cancer
- genetic polymorphism
- smoking
- meta-analysis
- East Asian
- European

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Introduction

Lung cancer is one of the most common and deadly cancers worldwide, primarily caused by prolonged exposure to tobacco smoke, including both active smoking and secondhand inhalation.[1] While nicotine is the main ingredient that makes cigarettes addictive, about 80% of inhaled nicotine is eliminated by CYP2A6-mediated metabolism in the liver.[2] CYP2A6 belongs to the CYP2A gene cluster which shares 93.5% protein similarity with CYP2A13,[3] which is predominantly expressed in respiratory tissues.[4]

CYP2A13 plays a significant role in activating tobacco-specific carcinogens, particularly 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a potent lung carcinogen.[5,6] Compared to CYP2A6, CYP2A13 demonstrates higher catalytic activity in NNK metabolism,[7] suggesting its potential involvement in lung cancer development. Interestingly, CYP2A13 expression has been found to be downregulated in non-small cell lung carcinoma,[8,9] further indicating its role in lung cancer progression.

Several studies have investigated the association between CYP2A13 polymorphisms and lung cancer risk, with inconsistent findings across different populations and smoking statuses. Some studies suggest that CYP2A13 polymorphisms reduce lung cancer risk,[10] while others indicate an increased risk among smokers or specific genetic variants.[11–14] Additionally, research on CYP2A13 polymorphisms in other cancers, such as nasopharyngeal,[15,16] bladder,[17,18] and pancreatic cancer,[19] has also yielded mixed results. These discrepancies highlight the need for further investigation.

To address this gap, we conducted a meta-analysis to examine the association between CYP2A13 polymorphisms and lung cancer risk. We specifically focused on both heterozygous/homozygous variants and their associations in overall populations as well as among smokers. Understanding these associations could provide new insights into lung cancer etiology and contribute to future research on cancer prevention.

Materials and Methods

Literature Search Strategy

The present study applied the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (►**Supplementary Materials 1** and **2**, available in the online version).[20] Suitable peer-reviewed articles were systematically searched in four online databases: ScienceDirect, PubMed, Scopus, and Google Scholar. Relevant articles were searched from database from the point of commencement until November 11, 2024. The search for eligible studies in the databases involved using Medical Subject Headings (MeSH) terms and keywords in the titles and abstracts of articles. Boolean operators "AND" and "OR" were applied to combine keywords such as "cytochrome P450 2A13" or "CYP2A13" with terms including "lung cancer," "lung carcinoma," "non-small cell carcinoma," "lung adenocarcinoma," "non-small cell lung cancer," "NSCLC," "pulmonary carcinoma," "small cell lung carcinoma," and "lung squamous cell carcinoma."

The full texts of suitable studies were downloaded for further screening. Duplicate copies were removed, and eligible studies were examined based on the inclusion and exclusion criteria. In addition, backward citation tracking was conducted for the included studies to ensure that all qualified studies were counted in the article by Sim and Sim.[21] Two authors independently reviewed the full text of all citations ($N = 92$) that were identified as potentially relevant. The quality of each study's methodology was evaluated using the Newcastle–Ottawa Scale (NOS).[22] Any disagreements in the article screening process were resolved through consensus between both authors. After the selection process, both authors independently reviewed the included articles to extract and tabulate data in spreadsheets. Disagreements were resolved through consensus between both authors.

Study Selection

All articles obtained from literature search were examined thoroughly for their relevancy on the titles and abstracts based on the specific inclusion and exclusion criteria.

Inclusion Criteria

1. Observational studies containing lung cancer case population and control population.
2. Articles investigating the polymorphism of CYP2A13.
3. Articles written in English.

Exclusion Criteria

1. Review articles, meta-analysis, and letter to the editor.
2. Articles written in languages other than English.
3. Articles with replicated data.
4. Articles with inadequate data to do the statistical analysis.

Data Extraction

The data extracted from every selected study included the following: author, year and country of publication, ethnicity, histological type of lung cancer cases, source of control, matching criteria for case and control, sample size for case and control, and the genotypes of CYP2A13 polymorphism. Additionally, the information regarding smoking status were also abstracted from available studies for further analysis.

Statistical Analysis

The data collected in this meta-analysis were the total number of participants and the number of participants who were carrying the genotypes of interest in both case and control groups. The data were analyzed in five subgroups:

1. Overall CYP2A13 combination variants.
2. CYP2A13 combination variants in smokers only.
3. Overall CYP2A13 homozygous variants.
4. CYP2A13 homozygous variants in smokers only.
5. Regions in each of the above subgroups.

Dichotomous data were analyzed using the Mantel–Haenszel method and the inverse variance method, yielding odds ratio (OR) with the respective 95% CIs and weight for each estimate, and the results were presented in forest plots.

The pooled OR was symbolized by a solid diamond at the bottom of each forest plot. Statistical heterogeneity of the studies was assessed using the restricted maximum likelihood (REML) method and Q-profile method, and the result was expressed as τ^2 and I^2 with 95% CIs, as well as p-value. When $I^2 > 50\%$ or $p < 0.10$, heterogeneity was considered significant for pooled ORs. Egger's test was applied to assess publication bias via a funnel plot asymmetry.[23] The result of $p < 0.05$ was considered as an indicator for the potential presence of publication bias. All meta-analyses were performed using R version 4.3.1.[24] R statistics packages used for data analysis were "meta" version 6.5.0[25] and "metafor" version 4.4.0.[26]

Study Registration

This systematic review and meta-analysis have been registered with the Open Science Framework (OSF) to promote transparency and reproducibility in our research. The registration details, including the protocol and related materials, are accessible at https://doi.org/10.17605/OSF.IO/Y3KHQ.

Results

Characteristics of Included Studies

The study selection flowchart for this meta-analysis is presented in ►**Fig. 1**. There was a total of 92 studies retrieved from the literature search. Four duplicate studies were detected and eliminated before screening the articles. Subsequently, 28 articles were removed as they include book chapter, review articles, foreign language (Chinese), and mostly due to irrelevant content. Sixty full-text articles were screened for eligibility and 48 articles were excluded as they were not case–control or cohort studies. Two were removed due to incomplete data,[27,28] mainly because they were lacking control groups in their studies. After the selection process, there were a total of 10 articles included in the analysis, which consisted of 2,853 cases and 3,651 controls. The publication years for these 10 eligible studies[10–14,29–33] were between 2003 and 2022. Of all studies, two were conducted in Caucasians and eight in Asians. The main characteristics of the selected studies were presented in ►**Table 1**.

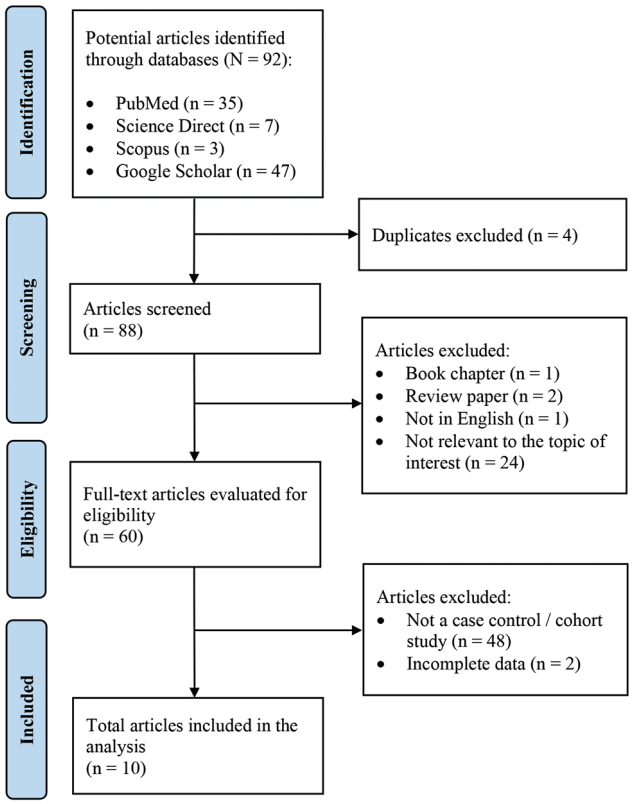

Fig. 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of included studies in the meta-analysis.

Meta-analysis

The pooled OR for overall CYP2A13 combination variants in the lung cancer case–control studies was 1.01 (95% CI: 0.81–1.26). This result indicated that there were statistically nonsignificant lower odds for CYP2A13 combination variants to be associated with the risk of lung cancer in the overall studies, which include smokers and nonsmokers. However, East Asia showed a significant decrease in OR at 0.78 (95% CI: 0.66–0.93), with heterogeneity variance estimated at $\tau^2 = 0.00$ (95% CI: 0.00–0.51), an I^2 value of 5.4% (95% CI: 0.0–85.5%), and $p = 0.37$ as portrayed in ►**Fig. 2A**.

For the subgroup analysis of smokers only, the pooled OR of the included data was 1.06 (95% CI: 0.78–1.46). This result indicated a higher probability of CYP2A13 combination variants to be associated with lung cancer among smokers. The result of East Asia showed a significant decreased OR at 0.77 (95% CI: 0.60–0.99) as indicated in ►**Fig. 2B**, whereas Europe showed a significant increased OR at 1.64 (95% CI: 1.21–2.23), with heterogeneity variance estimated at $\tau^2 = 0.00$, an I^2 value of 0.0%, and $p = 0.92$ as presented in ►**Fig. 2C**.

For the subgroup analysis of overall CYP2A13 homozygous variants in the lung cancer case–control studies, pooled OR of the included data was 0.98 (95% CI: 0.71–1.36). Similar to the result of CYP2A13 combination variants, this result showed statistically nonsignificant lower odds for CYP2A13 homozygous variants to be associated with the risk of lung cancer in the overall studies. Again, East Asia produced significant result in this subgroup with an increased OR at 1.37 (95% CI: 1.13–1.66), demonstrating that CYP2A13 homozygous variants might increase the lung cancer risk in the East Asian population. The heterogeneity variance of East Asia subgroup was estimated at $\tau^2 = 0.00$ (95% CI: 0.00–0.37), with an I^2 value of 0.0% (95% CI: 0.0–89.6%), and $p = 0.79$ as shown in ►**Fig. 2D**.

On further analysis on the subgroup of smokers only, the pooled OR of included studies was 1.07 (95% CI: 0.63–1.57), which indicated a higher chance of CYP2A13 homozygous variants to be associated with lung cancer among smokers. Significant increase in OR was found in East Asia subgroup at 1.52 (95% CI: 1.17–1.96), signifying the role of cigarette smoking in increasing the lung cancer risk among East Asians. The heterogeneity variance for East Asian smokers was estimated at $\tau^2 = 0.00$ (95% CI: 0.00–0.37), with an I^2 value of 0.0% (95% CI: 0.0–89.6%), and $p = 0.86$ as depicted in ►**Fig. 2E**. Summary of the above analyses is available in ►**Table 2**.

Table 1 Distribution of CYP2A13 genotype among cases of lung cancer and controls included in the meta-analysis

Author	Year	Country	Ethnicity	Histological type	Study type	Source of control	Case–control matching criteria	Total sample size (case/control)	Smoker sample size (case/control)	CYP2A13 combination variants	CYP2A13 homozygous variant	NOS score	Reference
Cauffiez et al.	2004	France	French Caucasian	Squamous cell carcinoma, small cell carcinoma, adenocarcinoma, others	Case–control	Volunteers without noncancerous lung diseases or any kind of cancer	Age, sex, hospital catchment area, and place of residence	204/201	204/201	C301T/WT	WT/WT	7	32
Hua et al.	2019	China	Han-Chinese	Squamous cell carcinoma, small cell carcinoma, adenocarcinoma, others	Case–control	Healthy volunteers	Date/time of recruitment	532/614	342/280	AG + GG	AA	6	13
Kiyohara et al.	2005	Japan	Japanese	Squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma	Case–control	Healthy participants	Sex (male)	179/183	N/A	CT + TT	N/A	8	12
Pathak et al.	2021	India	North Indian	Non-small cell lung cancer	Case–control	Healthy participants	Geographical area, gender, age, socioeconomic status, ethnicity	237/212	139/121	Heterozygous + mutant genotype (variants)	wt/wt	7	14
Ramadhani et al.	2022	Indonesia	Bataknese, Javanese, Malay, Chinese, Acehnese, Minang	Squamous cell carcinoma, adenocarcinoma	Case–control	Passive smokers without lung cancer	Sex (female), passive smokers >35 y of age with history of environmental tobacco smoke exposure for >10 y	52/52	N/A	CT + TT	CC	6	11
Soeroso et al.	2017	Indonesia	Bataknese sub-ethnic (Toba, Karo, Simalungun, Mandailing, Pakpak)	Squamous cell carcinoma, adenocarcinoma	Case–control	Healthy participants	Sex (male), history of cigarette smoking	70/70	70/70	CT + TT	CC	6	29
Soeroso et al.	2018	Indonesia	Bataknese, Javanese, Acehnese, Malay, Chinese	Squamous cell carcinoma, adenocarcinoma, large cell carcinoma	Case–control	Healthy participants	Sex (male), history of cigarette smoking	25/25	25/25	CT + TT	CC	6	31
Tamaki et al.	2011	Japan	Japanese	Squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell	Case–control	Cancer-free subjects	Age and sex	192/203	135/105	*1/*2, *1/*3, rare genotypes (*1/*4, *1/*5, *1/*7, *1/*10)	*1/*1	7	33

(*Continued*)

Table 1 (*Continued*) Distribution of CYP2A13 genotype among cases of lung cancer and controls included in the meta-analysis

Author	Year	Country	Ethnicity	Histological type	Study type	Source of control	Case–control matching criteria	Total sample size (case/control)	Smoker sample size (case/control)	CYP2A13 combination variants	CYP2A13 homozygous variant	NOS score	Reference
				carcinoma, adenosquamous cell carcinoma, unknown									
Timofeeva et al.	2009	Germany	Caucasian	Small cell lung cancer, non-small cell lung cancer	Case–control	Recruited participants	Age and sex	638/1,300	591/849	GA + AA, CT + TT, AG + GG	CC	6	30
Wang et al.	2003	China	Han-Chinese	Squamous cell carcinoma, small cell carcinoma, adenocarcinoma, undifferentiated cancer, bronchioalveolar carcinoma	Case-control	Cancer-free participants	Age and sex	724/791	421/334	CT + TT	CC	6	10

Abbreviations: CYP2A13, cytochrome P450 2A13; NOS, Newcastle-Ottawa Scale; N/A, not available.

Publication Bias

The publication bias of the 10 included studies was evaluated with Egger's test. The shape of the contour-enhanced funnel plot as depicted in ►**Fig. 3** did not show any obvious asymmetry in the overall meta-analysis. Moreover, there was no statistically significant publication bias found in any of the subgroup analyses: overall CYP2A13 combination variants ($p = 0.47$), CYP2A13 combination variants in smokers only ($p = 0.91$), overall CYP2A13 homozygous variants ($p = 0.13$), and CYP2A13 homozygous variants in smokers only ($p = 0.26$). Summary of publication bias is available in ►**Table 2**.

Discussion

The present meta-analysis examined the association between CYP2A13 polymorphism and lung cancer risk, with a focus on combination and homozygous variants. The findings indicate that while no significant association was observed in the overall population, subgroup analysis revealed a potential protective effect of CYP2A13 combination variants in East Asians. Conversely, among smokers, homozygous CYP2A13 variants were associated with an increased risk of lung cancer, particularly in the East Asian subgroup. These results highlight a potential ethnic and smoking-related influence in CYP2A13-associated lung cancer susceptibility.

Our findings are consistent with prior studies that identified ethnic differences in CYP2A13 polymorphism effects. For instance, Wang et al reported that CYP2A13 variant genotypes had a distinct influence on lung cancer risk, particularly adenocarcinoma, among nonsmokers in a Han-Chinese population.[10] Similarly, Kiyohara et al found that Japanese smokers with the CYP2A13 CC genotype had a significantly higher risk of developing lung cancer compared to nonsmokers with at least one copy of the T allele.[12] In contrast, Ramadhani et al reported that the CT genotype conferred a greater risk among Indonesian females,[11] suggesting potential gender-specific and ethnic variations. While our study did not analyze individual SNPs separately, the observed differences between ethnic groups may reflect variations in allele frequencies, gene–environment interactions, or differences in exposure to environmental carcinogens such as second-hand smoke.

It is important to clarify that this meta-analysis did not investigate specific single nucleotide polymorphisms (SNPs) in isolation. Instead, due to the limited number of available studies, CYP2A13 polymorphisms were categorized broadly into combination variants (heterozygous and mutant genotypes) and homozygous variants. This approach provided a more comprehensive overview of the potential association between CYP2A13 polymorphism and lung cancer risk while addressing challenges related to small sample sizes in individual studies. However, this pooling method may have masked variant-specific effects, which future research with larger datasets could explore in greater detail.

Another key consideration is the role of CYP2A13 in nicotine metabolism and lung carcinogenesis. Previous studies have demonstrated that CYP2A13 is more catalytically

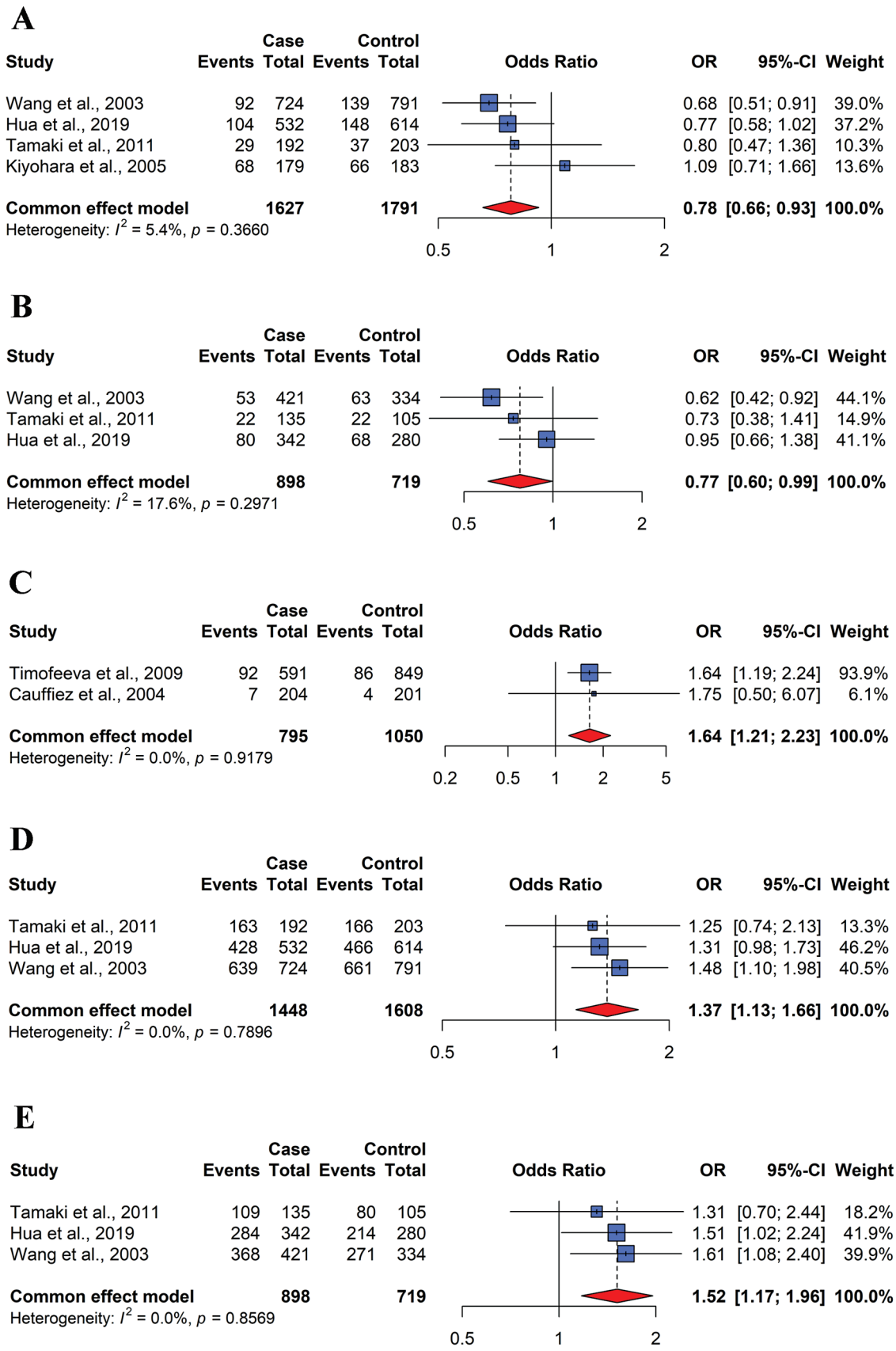

Fig. 2 (**A**) Forest plot showing the OR of CYP2A13 combination variants in the overall lung cancer case–control studies in the East Asia region. (**B**) Forest plot presenting the OR of CYP2A13 combination variants among smokers in East Asia region. (**C**) Forest plot depicting the OR of CYP2A13 combination variants among smokers in Europe region. (**D**) Forest plot illustrating the OR of CYP2A13 homozygous variants in East Asia region. (**E**) Forest plot displaying the OR of CYP2A13 homozygous variants among smokers in East Asia region. CI, confidence interval; OR, odds ratio.

Table 2 Pooled odds ratio for CYP2A13 genotype in meta-analyses

Population	Genotypes	Region	Number of studies	Statistical model	Pooled OR (95% CI)	*p*-Value[a]	*p*-Value[b] (publication bias)	*p*-Value[c] (heterogeneity)	I^2 (%)
All	Combination variants	Overall	10	Random effects model	1.011 (0.811–1.260)	0.925	0.359	0.014	56.6
		Asia	8	Random effects model	0.968 (0.748–1.254)	0.807	0.180	0.021	57.7
		East Asia	4	Fixed-effect model	**0.780 (0.657–0.926)**	**0.005**	0.388	0.366	5.4
		Europe	2	Fixed-effect model	1.177 (0.936–1.482)	0.164	N/A	0.524	0.0
		Southeast Asia	3	Fixed-effect model	1.263 (0.761–2.096)	0.367	0.629	0.223	33.4
Smokers only	Combination variants	Overall	8	Random effects model	1.063 (0.775–1.459)	0.704	0.886	0.007	64.3
		Asia	6	Random effects model	0.920 (0.667–1.269	0.612	0.653	0.091	47.3
		East Asia	3	Fixed-effect model	**0.773 (0.602–0.993)**	**0.044**	0.850	0.297	17.6
		Europe	2	Fixed-effect model	**1.643 (1.211–2.229)**	**0.001**	N/A	0.918	0.0
		Southeast Asia	2	Fixed-effect model	0.950 (0.508–1.777)	0.873	N/A	0.410	0.0
All	Homozygous variants	Overall	8	Random effects model	0.979 (0.706–1.358)	0.899	0.139	0.007	63.6
		Asia	7	Random effects model	1.009 (0.720–1.413	0.959	0.216	0.006	66.8
		East Asia	3	Fixed-effect model	**1.370 (1.132–1.656)**	**0.001**	0.701	0.790	0.0
		Southeast Asia	3	Fixed-effect model	0.792 (0.477–1.315)	0.367	0.629	0.223	33.4
Smokers only	Homozygous variants	Overall	7	Random effects model	1.069 (0.728–1.568)	0.734	0.240	0.016	61.8
		Asia	6	Random effects model	1.120 (0.752–1.667)	0.578	0.384	0.014	65.1
		East Asia	3	Fixed-effect model	**1.515 (1.174–1.956)**	**0.001**	0.285	0.857	0.0
		Southeast Asia	2	Fixed-effect model	1.052 (0.563–1.968)	0.873	N/A	0.410	0.0

Abbreviations: CI, confidence interval; CYP2A13, cytochrome P450 2A13; OR: odds ratio; N/A: not available.
[a]Random effects model was used when the *p*-value for heterogeneity test was <0.10 or $I^2 > 50\%$, otherwise the fixed-effect model was used.
[b]Egger's test to evaluate publication bias, *p*-value of <0.05 is considered statistically significant.
[c]*p*-value of <0.10 is considered statistically significant for Q statistics.

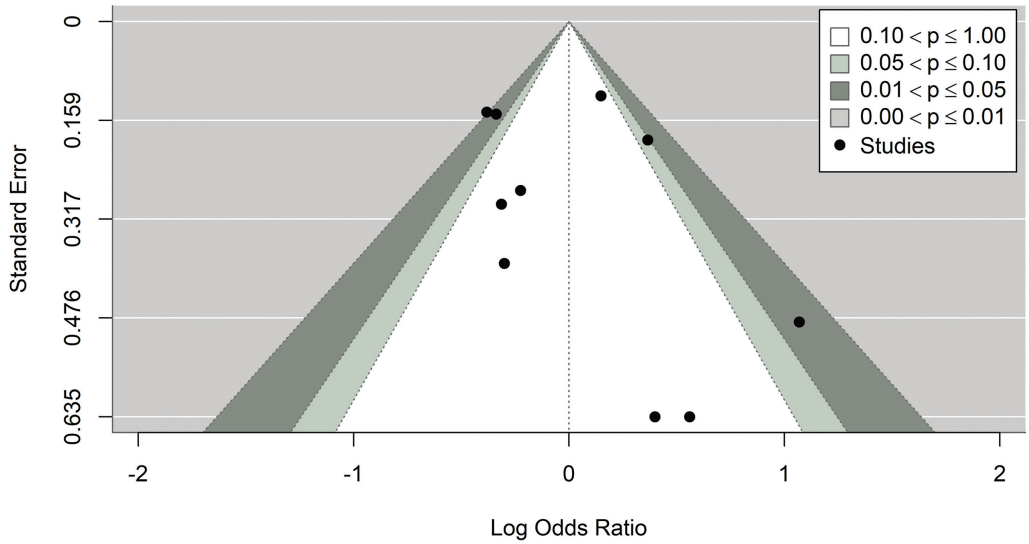

Fig. 3 Contour-enhanced funnel plot of included studies. Plot is centered on a log odds ratio of zero (null effect) and the dots plot the dispersion of effect sizes on the *x*-axis against the standard error on the *y*-axis. The shading indicates *p*-values. The dots in the unshaded (white) region correspond to *p*-values > 0.1; the light-grey shaded region indicates *p*-values between 0.1 and 0.05; and the dark grey region indicates *p*-values between 0.05 and 0.01. The region outside the funnel corresponds to *p*-values below 0.01.

active than CYP2A6 in activating the tobacco-specific nitrosamine NNK, a major lung carcinogen.[7] Our findings reinforce the hypothesis that genetic variation in CYP2A13 may influence lung cancer risk, particularly among smokers who have higher exposure to NNK. However, the exact mechanism by which different CYP2A13 variants modulate lung cancer susceptibility remains unclear, necessitating further functional studies.

There are several limitations to this meta-analysis. First, significant heterogeneity was observed in some subgroup analyses, which may have been influenced by differences in study design, ethnicity, and smoking status. Second, due to the relatively small number of eligible studies, particularly for populations other than Asians, the findings may not be generalizable across all ethnicities. Additionally, while our study examined overall CYP2A13 polymorphisms, data on gender-specific effects, cancer histological subtypes, and environmental exposures were limited, preventing a more detailed stratified analysis.

Despite these limitations, this study contributes valuable insights into the association between CYP2A13 polymorphism and lung cancer risk. By combining available data, our findings provide a foundation for future research exploring the functional impact of CYP2A13 variants, particularly in different ethnic groups and smoking populations. Further large-scale studies with more comprehensive genetic and environmental data are necessary to validate these findings and elucidate the underlying biological mechanisms.

Conclusion

The findings of this study demonstrated that the occurrence of CYP2A13 polymorphism is higher among active tobacco smokers, which was highly associated with lung cancer. This study also suggested that CYP2A13 homozygous variants had a higher association with lung cancer than CYP2A13 combination variants, with a prominent result among East Asians. These findings revealed a clinical significance that the presence of homozygous variants in CYP2A13 gene may increase the risk of developing lung cancer among tobacco smokers, which provided a direction for future studies in lung cancer on the gene variants of CYP2A13. Also, future research on the association of CYP2A13 polymorphism and lung cancer should take various factors into consideration such as ethnicities, genders, cancer histological types, genotype variants, and environmental tobacco smoke.

Data Availability Statement

The data used in this meta-analysis were obtained from publicly available case–control studies. All relevant data are cited within the manuscript, and the studies included in the analysis are referenced in the reference list. There are no additional datasets beyond those provided by the original studies.

Authors' Contributions

E.U-H.S. and F-L.V. conceptualized and designed the study. F-L.V. extracted the data and carried out the statistical analysis with support from E.U-H.S. Both authors have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. F-L.V. produced an initial draft of the manuscript and subsequent revisions to it. E.U-H.S. and F-L.V. critically revised the manuscript for important intellectual content. Both authors approved the final version.

Compliance with Ethical Principles

The authors confirm that this review has been prepared in accordance with COPE guidelines and regulations. Given the nature of this article, ethical approval is not required.

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Conflict of Interest
None declared.

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