REVIEW ARTICLE

The association of family history with the risk of lung cancer: a pooled analysis of case-control studies

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ABSTRACT

The risk of lung carcinoma is influenced by genetic predisposition and other risk factors. This study aimed to explore the association between a family history of any type of cancer and the risk of lung carcinoma through a pooled analysis of case-control studies. A systematic literature search was performed across Google Scholar, PubMed, and Science Direct up to January 31, 2024. Eight observational case-control studies met the inclusion criteria, which required multivariate logistic regression analysis and a focus on familial cancer history. Using Review Manager software, pooled estimates and 95% confidence intervals were calculated. Out of 603 identified studies, eight were included. The meta-analysis found that individuals with a family history of cancer had a significantly higher risk of lung cancer (aOR = 1.64; 95% CI = 1.17–2.29; p = 0.004). These findings highlight the need for targeted screening and early detection strategies for high-risk individuals.

Keywords:
lung cancer, lung carcinoma, pulmonary cancer, family history, case-control study.

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INTRODUCTION

Lung carcinoma ranks as the second most prevalent carcinoma worldwide, following breast carcinoma, with 2,206,771 new cases recorded globally in 2020. Among males, it was the most common carcinoma, accounting for 1,435,943 instances, while in women, with approximately 770,828 cases. It was the third most frequent after breast and colon carcinomas[1]. According to estimates, lung carcinoma was the most common cause of death due to carcinoma for both men and women nationwide in 2020, resulting in 1,796,144 fatalities.[1]

Several common risk factors contribute to lung carcinoma development and can be categorized into non-modifiable and modifiable risks. Non-modifiable factors include age,[2] gender,[3–6] race or ethnicity[7], and family history.[8–16] These inherent factors may increase an individual's susceptibility to the disease. Modifiable risk factors, by contrast, involve behaviors or environmental exposures that can be altered.[17] Smoking is the primary modifiable risk factor, with tobacco smoke playing a major role in lung carcinoma development.[18–21] In addition, long-term exposure to air pollution is another modifiable factor that elevates lung carcinoma risk over time.[17]

Besides, genetic factors also play a crucial role, even though only a small number of particular genes and genetic variables have been identified.[22,23] Numerous studies have explored the link between family history and lung carcinoma risk.[24,12,11] Carcinoma risk is greatly influenced by genetic and familial variables, which frequently combine with environmental ones. Epidemiologists often rely on family history, especially among first-degree relatives, to estimate genetic risk because family history reflects genetic predispositions, shared environments, and behaviors.[25] Though the role of environmental exposures, such as tobacco smoke, air pollution, and occupational hazards, has been extensively studied, the contribution of genetic predisposition warrants a more nuanced exploration. Specific genetic mutations, such as those in the EGFR, KRAS, and TP53 genes, have been implicated in the development and progression of lung cancer, offering critical insights into its molecular underpinnings. For instance, EGFR mutations are frequently observed in non-small cell lung cancer (NSCLC) and are associated with responsiveness to targeted therapies, while TP53 mutations often correlate with poorer prognosis.[26,27]

Despite these advancements, the interaction between genetic susceptibility and environmental risk factors remains underexplored, particularly in the context of family history and its correlation with established risk factors, such as smoking and occupational exposures. This study seeks to address this research gap by investigating how familial genetic predisposition modulates the impact of environmental risk factors. By integrating genetic and environmental perspectives, this research aims to contribute to the development of personalized prevention and treatment strategies, ultimately improving patient outcomes.

In 2020, Ang et al. conducted a comprehensive review and meta-analysis on the relationship between the risk of lung carcinoma and a family history of the disease, categorizing data by geographic regions, research methods, gender, tobacco use, age, types of first-degree families, number of affected families, lung carcinoma histology, and whether the onset was early or late in affected relatives.[28] In contrast to earlier research that concentrated only on a family history of lung carcinoma, this meta-analysis broadens the scope of the study to include

all familial histories of carcinoma. This novel viewpoint seeks to provide a deeper understanding of the complex association between family carcinoma history and lung carcinoma risk by revealing more specific patterns.

MATERIAL AND METHOD

Source Records & Browse Strategy

This research adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to enhance transparency and reproducibility. A thorough literature search was conducted across Google Scholar, PubMed, and ScienceDirect until January 31, 2024. The search strategy incorporated Boolean operators and specific keywords such as "lung cancer," "lung carcinoma," or "pulmonary cancer," combined with "family history," "familial background," or "hereditary predisposition," along with "case-control study." These terms were employed to identify studies examining the relationship between familial cancer history and lung cancer risk within a case-control framework.

Beyond database searches, reference lists from pertinent systematic reviews and meta-analyses were reviewed to identify any additional relevant studies that may have been overlooked. This supplementary screening ensured a comprehensive and inclusive selection of literature, strengthening the study's validity by capturing all relevant research on the association between genetic background and lung cancer susceptibility.

Study Selection

The selection of studies was guided by specific inclusion criteria to ensure relevance and reliability. Only observational case-control studies that applied multivariate logistic regression analysis were considered. Additionally, eligible studies had to focus on patients diagnosed with lung cancer and examine the association between a family history of cancer and lung cancer risk. To maintain the integrity of the analysis, certain types of publications were excluded. Editorials, case series, and review articles were not considered, as they do not provide primary data suitable for statistical evaluation. This selection process ensured that the included studies offered robust and comparable findings for assessing familial cancer history as a risk factor for lung cancer.

Study Instruments

The papers were exported to Mendeley to remove duplicates and assessed using the Newcastle-Ottawa Quality Assessment Scale.[40] Studies were assigned a good, moderate, or low-quality rating using predetermined standards.

Statistical Analysis

All statistical analyses used review manager software to ensure accuracy and reliability. The study adopted a random-effects methodology to aggregate data, calculating 95% confidence intervals (CI) and adjusted odds ratios (aOR) for the included research. The random-effects model was chosen due to substantial heterogeneity among the included studies, as indicated by an I^2 value exceeding 50%. By applying a random-effects model, the analysis accounted for variations in effect sizes across studies rather than assuming a single fixed effect.

To assess the reliability of the synthesized results and identify potential biases, a funnel plot analysis was performed. This graphical tool evaluated the presence of publication bias by analyzing the distribution of study effect estimates in relation to the pooled effect size. A symmetrical funnel plot suggests minimal bias, whereas asymmetry may indicate selective reporting or heterogeneity among studies. Such discrepancies can arise from variations in study design, sample size, or

methodological differences, potentially influencing the overall findings.

Risk of Bias Assessment for Case-Control Studies

Bias was assessed using a standardized coding manual that evaluates three key domains: selection, comparability, and exposure. Each domain was assigned a rating based on established criteria to ensure a comprehensive evaluation of study quality. Comparability was evaluated by determining whether cases and controls were appropriately matched or if confounders were adjusted for in the analysis. Exposure assessment focused on the method of ascertainment (validated measurement, self-report, or no description) and the non-response rate, which could influence the reliability of study outcomes. Table 1 below explains the risk of bias assessment.

Ethical Clearance

This study was approved by Health Research Ethics Committee Ministry of Health, Semarang Health Polytechnic with the number of ethical clearance is No. 1136/EA/F.XXIII.38/2025. This declaration of ethics applies during the period September 9, 2025 until September 9, 2026.

Table 1. Risk of bias assessment

Study	Selection				Comparability	Assessment of Outcome	Non-response rate	Quality Score
	Adequacy of case definition	Representati-veness of cases	Selection of the control	Definition of controls				
Gao et al., (2009)	*	*	*	*	**	**	*	Good
Giacomazzi et al., (2023)	*	*	*	*	**	**	*	Good
Liang et al., (2019)	*	*	*	*	**	**	*	Good
Li et al., (2023)	*	*	*	*	**	**	*	Good
Lissowska et al., (2010)	*	*	*	*	**	**	*	Good
Ni et al., (2023)	*	*	*	*	**	**	*	Good
Xu et al., (2019)	*	*	*	*	**	**	*	Good
Zhao et al., (2017)	*	*	*	*	**	**	*	Good

Table 1 demonstrated that the scoring system assigned a maximum of four stars for bias, two stars for comparability, and three stars for exposure assessment, with an overall quality rating determined based on the total score. Studies scoring between seven and nine stars were classified as high quality, indicating a low risk of bias and greater reliability of findings. Those scoring between five and six stars were considered of moderate quality, while studies with four or fewer stars were categorized as having a high risk of bias. Studies with lower scores were interpreted with caution due to potential methodological limitations, which could impact the validity of the meta-analysis findings.

RESULTS

After conducting electronic searches, a total of 603 studies were found. Out of the 23 studies selected for further evaluation after screening titles and abstracts, eight were included in the analysis. These studies involved different geographic regions such as Europe, Brazil, and China, and involved a total of 37,064 respondents.

Research Characteristics

Table 2 outlines several key aspects of the selected studies. The included studies collectively involved 37,064 participants of various ages. Geographically, the studies spanned across regions. All the studies focused on participants from the general population who had been diagnosed with lung cancer.

Table 2. Articles Attributes and Results

No	Author (Year)	Location	Study Design	Sample (n)	Exposure	Outcome	Results
1.	Gao et al., (2009)	Italy	Case-control	1,946 cases and 2,116 controls	Cancer history from related	Lung cancer	aOR= 1.20 (1.03-1.40)
2.	Giacomazzi et al., (2023)	Brazil	Case-control	1,007 cases and 1,007 controls	Cancer history from related	Lung cancer	aOR= 30.2 (4.2-218.0)
3.	Liang et al., (2019)	China	Case-control	1,086 cases and 2,172 controls	Cancer history from related	Lung cancer	aOR= 1.92 (1.47-2.51)
4.	Li et al., (2023)	China	Case-control	7124 cases and 7480 controls	Cancer history from related	Lung cancer	aOR= 2.785 (2.462-3.150)
5.	Lissowska et al., (2010)	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, and United Kingdom	Case-control	2,861 cases and 3,118 controls	Cancer history from related	Lung cancer	aOR= 1.01 (0.88-1.15)
6.	Ni et al., (2023)	China	Case-control	320 cases and 640 controls	Cancer history from related	Lung cancer	aOR= 1.64 (1.26-2.08)

No	Author (Year)	Location	Study Design	Sample (n)	Exposure	Outcome	Results
7.	Xu et al., (2019)	China	Case-control	726 cases and 647 controls	Cancer history from related	Lung cancer	aOR= 1.70 (1.34-2.17)
8.	Zhao et al., (2017)	China	Case-control	2,871 cases and 8019 controls	Cancer history from related	Lung cancer	aOR= 1.09 (0.96-1.24)

Evaluation of Research Quality and Identification of Publishing Bias

Due to the limited number of included studies (fewer than 10), assessing publication bias was not possible. Nonetheless, all eight studies were deemed to be of high quality.

Review Results

Two studies did not establish a strong correlation, suggesting that a familial cancer history may not be a significant independent risk factor in certain populations or that other confounding variables could have influenced the findings.[31,32] These discrepancies could stem from differences in study design, sample size, geographic variations, or methodological limitations, such as inadequate adjustment for confounders like smoking history, environmental exposures, or genetic predisposition.

Meanwhile, the remaining six studies provided compelling evidence supporting a significant link between a familial history of cancer and increased lung cancer risk.[9,13,24,33,34,35] These findings reinforce the hypothesis that genetic susceptibility plays a crucial role in lung cancer development, possibly through inherited mutations, shared environmental exposures, or a combination of both. The consistency observed across these studies strengthens the argument for incorporating family history into lung cancer risk assessment models. However, the variation in findings across studies proves the need for further investigation to resolve inconsistencies and refine predictive models. Understanding these differences is essential for developing targeted prevention strategies, including enhanced screening programs and personalized interventions for high-risk individuals. Addressing these gaps can contribute to a comprehensive understanding of lung cancer etiology and improve public health outcomes for individuals with a familial predisposition to cancer.

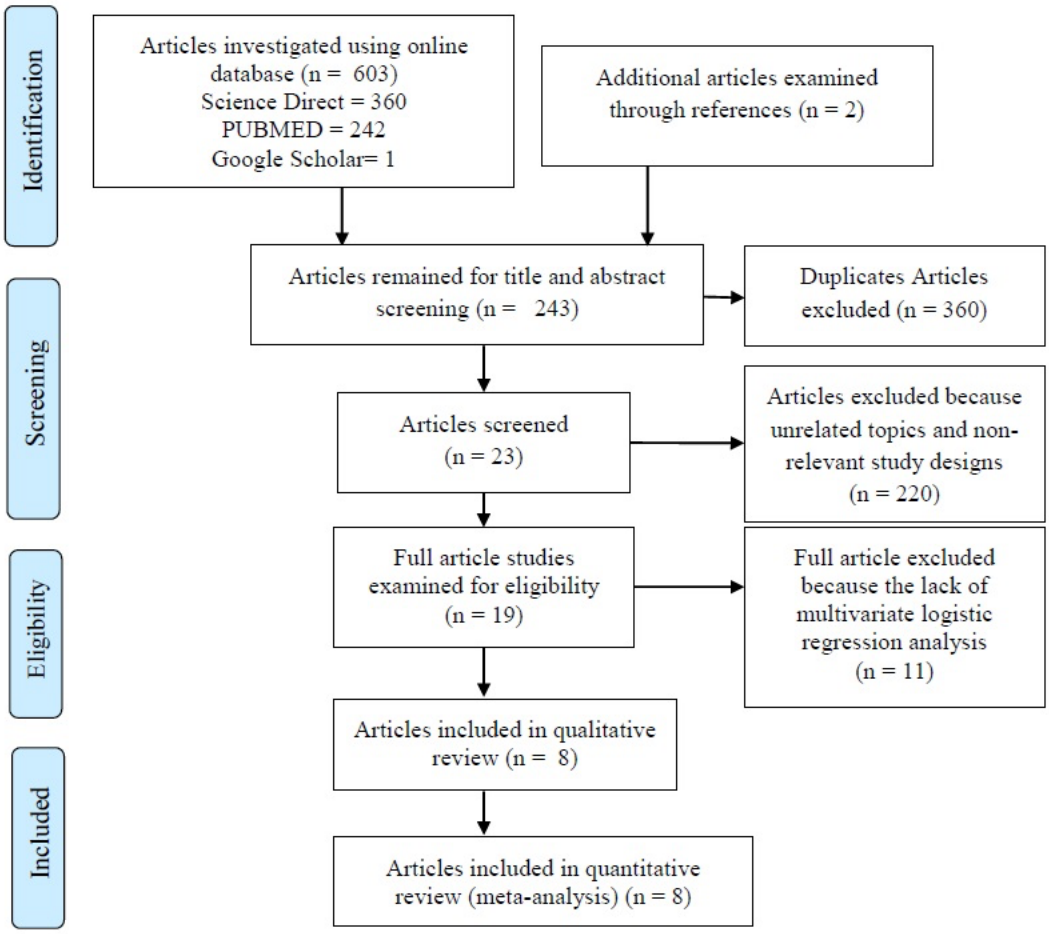

Figure1. PRISMA flow diagram

Results of the Meta-Analysis

The current meta-analysis was conducted using data from the eight primary studies. A random-effects model was utilized for the analysis due to the heterogeneity (I^2 = 96%) and its significance in statistical terms ($p < 0.05$). A hereditary factor of cancer has been reported with a risk estimate of 1.58, indicating a greater chance of developing lung cancer among individuals with hereditary factors of cancer compared to people without a family history (aOR = 1.64; 95% CI = 1.17 to 2.29; p = 0.004), following the forest plot as in Figure 2.

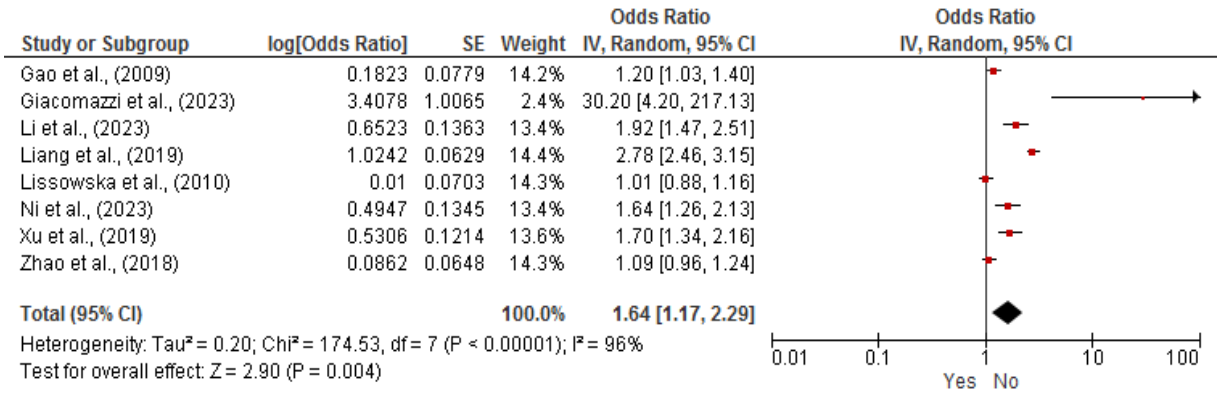

Figure 2. Forest Plot

The funnel plot (Figure 3) assessed potential publication bias. The plot displayed asymmetry, leaning towards the right, suggesting that selective reporting may have led to an overestimation of the results. Studies with non-significant outcomes may have been underreported, potentially inflating the effect size in the meta-analysis. This prejudice should be a concern when assessing the connection between lung cancer incidence and hereditary factors.

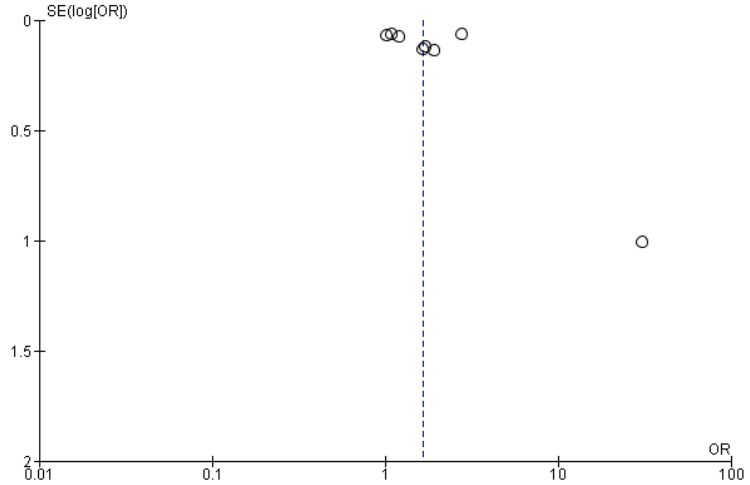

Figure 3. Funnel Plot

Conducting subgroup analyses may not be feasible due to data limitations in the primary studies included in this meta-analysis. First, the type of cancer in family history was generally specified in the studies, and the level of detail regarding specific cancer subtypes and age of onset in relatives was often insufficient or inconsistent across studies. Many studies did not differentiate between the types of cancers in the family (e.g., lung cancer vs. other types of carcinomas), limiting the ability to perform robust subgroup analyses. Second, the original data from the primary studies were already adjusted for probable confounders such as age, gender, and smoking status, which were common risk factors for lung cancer. Since these factors were controlled for in the initial analyses, the risk estimate (aOR = 1.64) reflected an adjusted odds ratio that accounted for these potential confounders.

Given that adjustments for key variables had already been made, further stratification by these factors in subgroup analyses may not have significantly altered the whole findings but could lead to small sample sizes in each subgroup, which could reduce statistical power.

While more detailed subgroup analyses would be ideal for providing deeper insights, the lack of consistency and granularity in reporting across studies, coupled with the fact that confounders have already been accounted for, makes it difficult to explore these subgroups comprehensively.

DISCUSSION

The findings of this meta-analysis indicate that individuals with a heredity of cancer have a significantly high risk of lung cancer. The aOR suggests that those with a familial cancer background tend to develop lung cancer by 1.64 times compared to those without such a history. The confidence interval (CI) of 1.17–2.29 indicates that this effect is statistically significant, as it does not include the null value (aOR = 1.0). Furthermore, the p-value of 0.004 reinforces the statistical robustness of this association, implying that the observed relationship is unlikely to be due to chance.

A meta-analysis by Ang et al. (2020) stated that they discovered a direct correlation between familial background of lung carcinoma and lung carcinoma occurrence, categorized by locations and sociodemographic determinants[30]. Furthermore, Gu et al. (2010) observed that the potential of lung carcinoma increased among first-degree families of affected individuals,[36] indicating a clear familial aggregation. Ni et al. (2023) suggested that the appearance of lung cancer in families may be influenced by genetic and environmental variables shared.[24]

Conversely, Braun et al. (1994) argued that inherited susceptibility plays a minor assignment in the growth of lung carcinoma. They concluded that genetic factors are unlikely to be significant factors of cancer in the lungs, particularly in male smokers over the age of 50, who make up the majority of cases.[23]

An added chance of acquiring a second carcinoma type, possibly unrelated to the first, has also been associated with a familial history of cancer. This second carcinoma could arise in the same tissues or organs as the first or in a completely different part of the body. Leukemia is one example, along with colorectal, pulmonary, kidney, intestine, and skin cancers, including melanoma and squamous cell carcinoma. Lung and colorectal carcinomas are two of the most prevalent secondary malignancies, and the risk is doubled in families with a history of these diseases.[38] Lichtenstein et al. (2000) found that in a study of twins, at least one type of cancer was found in 10,803 people.[9,512] Twins of those affected had a higher likelihood of developing stomach, colorectal, lung, breast, and prostate cancers.[22]

Cancer of the lung can be divided into two main types according to the type of cell that caused the disease: cancer of the lung, including small-cell and non-small-cell, each of which has further subtypes. As per the WHO classification in 2015, the most prevalent types of lung cancer comprise squamous cell cancer, adenocarcinoma of gland cells, and neuroendocrine tumors, which include carcinoid tumors, small cell neuroendocrine cancer, and large cell neuroendocrine cancer.[38]

Genetic alterations found in first-degree relatives with the same cancer type are referred to as familial cancer. External circumstances, variable gene expression, and genetic predisposition play a role in this illness. Since environmental predictors like pot or tobacco smoking, pollution of the air, and coal combustion frequently disguise the hereditary influence, the exact role those genetic determinants play in the

development of lung cancer is still unknown. However, research into hereditary lung cancer cases has shown evidence of genetic transmission across generations. Roughly 8% of lung cancers are hereditary or result from a genetic susceptibility.[37,16,15,40]

This study is grounded in the gene-environment interaction model, which posits that genetic susceptibility can modulate an individual's response to environmental exposures, thereby influencing disease risk. For instance, specific genetic mutations, such as those in the EGFR and TP53 genes, may not only drive oncogenic processes but also alter cellular responses to environmental carcinogens, such as tobacco smoke or asbestos.[26,27] In families with a history of lung cancer, inherited genetic variants may create a heightened vulnerability to environmental insults, potentially through mechanisms such as impaired DNA repair, altered metabolic pathways, or dysregulated immune responses. By examining these interactions, this study elucidates how familial genetic predisposition amplifies or modifies the effects of environmental risk factors. It provides a comprehensive theoretical framework for understanding lung cancer etiology.

A few limitations were found in the current study. Both geographic diversity and subgroup analysis were constrained by the few numbers of original research available, and the majority of analyses showed notable variation among studies. This study differs from the previous research in two significant ways. First, this study covers a wider range of cancer types across various relatives, which offers a holistic view of the association between these two factors. Second, it offers current insights into the association between family history of cancer and lung cancer risk in the general population. These developments result in a thorough and sophisticated understanding of the topic, with important ramifications for future studies and therapeutic procedures.

CONCLUSION AND RECOMMENDATION

This study concludes that the familial history of carcinoma is correlated with an elevated risk of lung cancer. A thorough review of the research's quality was ensured by the independent assessment of the study conducted by researchers adhering to predefined standards. Individuals with cancer heredity have a significantly increased risk of developing lung cancer. These findings emphasize the need for targeted and personalized health interventions. To mitigate this risk, targeted screening programs should be implemented for individuals with a first-degree relative diagnosed with lung cancer. These individuals may benefit from early and frequent screenings, such as low-dose CT scans or chest X-rays, to enhance early detection and improve prognosis. Additionally, tailored counseling services should be made available to individuals with a family history of specific cancers, which guides genetic predispositions and environmental risk factors. Counseling can also offer strategies to reduce risk, such as smoking cessation programs and lifestyle modifications.

Enhancing health literacy through public education campaigns is also crucial to ensure that individuals with a familial cancer background fully understand their risk. These campaigns should focus on the correlation between genetic and environmental factors in lung cancer development and provide accessible resources through community centers, healthcare clinics, and digital platforms. By

implementing these targeted strategies, the findings can be translated into effective health interventions, which ultimately improve lung cancer prevention and early detection efforts.

AUTHOR CONTRIBUTIONS

A. W. : conceptualization, methodology, and supervision. J.R.A.: validation, writing, review, and editing. R.B.A.: data curation and formal analysis. A.W.: investigation and resources. A.A.: visualization and writing the original draft. S.U.: project administration and funding acquisition. A.S.F.: software development and data curation. J.T.A.: methodology and validation process.

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CONFLICTS OF INTEREST

Addressing the study, text, and/or publication of the current article, the authors stated no possible conflicts of interest.

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