Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.1.29

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (1): 245–256

REVIEW PAPER

The X-ray repair cross-completing gene 1 (XRCC1) polymorphisms and lung cancer incidence – a confirmatory umbrella review of observational evidence

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ABSTRACT

Introduction and aim. Lung cancer (LC) is a leading cause of cancer-related deaths worldwide, with X-ray repair cross-complementing gene 1 (XRCC1) playing a crucial role in DNA repair and influencing LC risk through genetic mutations. Despite numerous meta-analyses, results have been inconsistent. This study systematically evaluated existing meta-analyses to clarify the association between XRCC1 gene variations and LC.

Material and methods. A comprehensive literature search was conducted using Scopus, Web of Science, Embase, and Cochrane databases. The present Umbrella review followed PRISMA and MOOSE guidelines. The AMSTAR tool assessed the methodological quality of the included studies.

Analysis of the literature. A total of 28 data sets were analyzed: 9 for the rs25487 (codon 399), 11 for the rs1799782 (codon 194), and 8 for the rs25489 (codon 280) polymorphisms. Significant associations were found with odds ratios ranging from 0.93 to 1.92 ($p<0.05$) in 16 data sets. XRCC1 rs25487/codon 399 and rs1799782/codon 194 were strongly linked to LC risk, while rs25489 (codon 280) was not. Twelve datasets showed significant heterogeneity, and publication bias was not detected in 24 datasets. Most meta-analyses demonstrated high methodological quality.

Conclusion. These findings suggest that XRCC1 (rs25487/codon 399 and rs1799782/codon 194) gene polymorphisms have the potential to serve as biomarkers for the early identification and management of LC risk.

Keywords. case-control, DNA repair, genetic susceptibility, lung cancer, meta-analysis, XRCC1 gene

Introduction

Lung cancer (LC) is the most prevalent form of cancer and the leading cause of cancer-related deaths around the world. In 2020, it was responsible for more than 1.7 million fatalities and 2.2 million new cases.[1] LC primarily manifests in two types: non-small cell LC (NSCLC) and small cell LC (SCLC). NSCLC is the most common type, comprising approximately 80-85% of cases including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma.[2,3] SCLC represents 10-15% of LC and typically exhibits faster growth and spread compared to NSCLC.[4] The fatality rate for LC is remarkably high, with

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Received: 28.08.2024 / Revised: 5.11.2024 / Accepted: 24.11.2024 / Published: 30.03.2025

Velmurugan S, Ganesan K, Rajendran R, Subbaraj GK. The X-ray repair cross-completing gene 1 (XRCC1) polymorphisms and lung cancer incidence – a confirmatory umbrella review of observational evidence. *Eur J Clin Exp Med.* 2025;23(1):245–256. doi: 10.15584/ejcem.2025.1.29.

more than 80% of individuals dying of the illness. The main factors contributing to this high fatality rate are delayed detection and cancer's high degree of malignancy.[5] The prevalence of active smoking or past smoking among patients on the day of diagnosis varies from 60% to 90% across different global regions. Extensive epidemiological evidence has conclusively identified tobacco smoking and second-hand smoke exposure as predominant risk factors for the development of LC.[6] Among patients who have never smoked tobacco, it is identified that 19% of female LC cases are observed, in contrast to 9% in male LC cases.[7] Other factors associated with a higher risk of developing LC include exposure to environmental air pollutants like ozone, particular matter (PM) nitrogen oxides, dietary habits and supplements, alcohol consumption, low physical activity, air pollution, workplace exposure, and sulfur dioxide.[7,8] One possible rationale is that prolonged exposure to air pollution could raise the risk of LC by causing oxidative damage, which occurs as a result of inflammatory injury and the generation of reactive oxygen species (ROS), although the findings from population studies continue to be debated due to variations in study designs and participant numbers.[9] However, certain studies have shown that the development of LC is influenced by the interplay of an individual's genetic predisposition and environmental risk factors. In addition, scientific evidence suggests a strong connection between genetic makeup and the onset of LC.[10] Lack of early diagnosis often leads to fatalities from LC, as the disease is frequently identified only in advanced stages. Effective treatment of LC requires a comprehensive knowledge of the disease's underlying causes, reliable early diagnostic techniques, and the appropriate use of medications.[11] Thus, early detection of LC is vital, particularly for high-risk groups such as smokers and individuals employed in oil fields or other industries with toxic exposures. There is an urgent necessity to uncover new biomarkers for this purpose.[12] Precise diagnosis is crucial for tailored LC treatments. Therefore, identifying sensitive biomarkers for early detection is essential.

Recent research has focused on genetic markers to anticipate cancer onset. Single nucleotide polymorphisms (SNPs) are emerging as potential indicators of cancer risk. Previous studies have associated variations in DNA repair genes with increased LC susceptibility.[13,14] The human genome is protected by the DNA repair mechanism against ongoing harm caused by oxidizing and alkylating chemicals, ionizing radiation, nicotine and cigarette smoke, environmental exposures, and occupational hazards.[15] The complex DNA repair machinery in the human body includes several intricate systems, with base excision repair (BER) playing a vital role. BER is tasked with repairing minor DNA lesions, such as those caused by ionizing radiation, potent alkylating agents, and cellular metabolic byproducts like ROS that can harm DNA bases.[16] DNA glycosylases are a group of enzymes that remove the damaged base from the DNA. Subsequently, AP endonucleases, including APE1 enzymes, are tasked with breaking the phosphodiester link at the site of damage. This cleavage produces a 5'dRP and 3'OH, which are used for DNA repair and joining. The base excision repair (BER) process has long and short repair paths. X-ray repair cross-completing gene 1 (XRCC1) is crucial for BER, binding to DNA ligase III and polβ. It also helps detect DNA breaks with PARP.[16,17]

XRCC1 is situated on the human chromosome 19q13.2-13.3 and contains three fairly common polymorphic codons at positions 399(Arg/Glu), 194(Arg/Trp), 280(Arg/His), which have the potential to impact the amino acid sequence.[18] Cells deficient in the XRCC1 gene may exhibit increased sensitivity to ultraviolet light, mitomycin, ionizing radiation, and hydrogen peroxide. Nonetheless, XRCC1 plays a crucial role in the BER system. Consequently, it is plausible to suggest that gene expression could influence cancer development.[19] The relationship between specific gene polymorphisms XRCC1 (rs25487/codon 399, rs1799782/codon 194, and rs25489/codon 280) and the development of LC remains unclear. Extensive research, including meta-analyses and case-control studies, has been undertaken to explore this connection. Research findings on the link between these genetic variations and LC risk are inconsistent. Some studies have found no connection, while others have identified a significantly elevated risk. Given the complexities and inconsistencies in the existing literature regarding the association between XRCC1 polymorphisms and LC risk, an umbrella review is proposed.

Aim

This review aims to systematically collate and assess the findings from multiple meta-analyses, providing a holistic understanding of the genetic factors involved in LC susceptibility. These studies are synthesized to clarify the conflicting evidence surrounding XRCC1 (rs25487/codon 399, rs1799782/codon 194, and rs25489/codon 280) polymorphisms and their implications for LC risk. This comprehensive approach not only addresses existing inconsistencies but also provides insights that could inform clinical practice regarding genetic screening and risk stratification in LC patients. The study findings may contribute as a biomarker to identifying high-risk populations and improving early detection strategies, which are crucial for enhancing patient outcomes.

Material and methods

An umbrella review was performed, by systematically gathering and assessing systematic reviews and meta-analyses focused on a particular research topic. The umbrella review followed PRISMA (Preferred Reporting Item for Systemic Review and Meta-Analysis)

and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines. Before its initiation, the review protocol was registered in PROSPERO (ID: CRD42024571433).

Literature search

A comprehensive search of the literature was performed across a various online databases, including Scopus, Web of Sciences, Embase, and Cochrane databases of systemic review. The focus was on meta-analyses of case-control studies investigating LC and the XRCC1 gene, without any time limitations. The literature search was independently conducted by two authors, Velmurugan and Subbaraj using the MeSH terms and keywords "Lung Cancer," "XRCC1," "gene polymorphisms," "Meta-Analysis," "adenocarcinoma," "non-small cell LC," "neoplasm," and "case-control. Duplicate data were removed before the screening phase. Each retrieved article reviewed at the title, abstract, and full-text level to assess eligibility, and any discrepancies between the authors were resolved through discussion to reach a consensus.

Inclusion and exclusion criteria

Meta-analyses were selected based on the following inclusion criteria: (i) The study included only meta-analyses using case-control studies (ii) The study explored the link between XRCC1 polymorphisms and LC risk. (iii) The scope of this study was limited to the English language (iv) The studies reported pooled odds ratios (ORs) with 95% confidence intervals (CIs) to quantify the strength of the relationship. The exclusion criteria comprised protocols, reviews, editorials, conference proceedings, and abstracts as these sources do not provide the primary data or quantitative outcomes. In the cases of multiple meta-analyses reported similar findings, the analysis with the highest number of included studies was prioritized. However, no studies were excluded based on this criterion, as all relevant analyses contributed valuable insights to our review.

Data extraction

The data from the selected papers was independently collected by two authors, Velmurugan and Subbaraj who used standardized form to collect details on primary author, publication year, number of studies, study design, total cases and controls, participant ethnicity, and genotyping methods. Furthermore, ORs and their CIs for each qualifying meta-analysis were obtained from all available genetic models. Furthermore, the extracted outcomes encompassed p-values for the overall pooled effect, Egger's test for publication bias, and the I^2 statistic for heterogeneity. Additionally, we documented the quality assessment criteria used in the selected meta-analyses. Data were organized and managed using Microsoft Excel.

Assessment of methodological quality

The methodological quality of the included meta-analyses of case-control studies was assessed using the "A MeaSurement to Assess Systemic Reviews (AMSTAR) tool". The AMSTAR tool comprises 16 items, each question can be answered with 'Yes", "No" and "Partially yes". A score of 1 for a positive response and 0 points for other responses. The total score is the accumulation of these 16 items. A score of ≥8 is deemed as high quality, 4-7 points indicate moderate quality, and a score of ≤3 or lower reflects low quality.[20] Disagreements regarding AMSTAR ratings were addressed through discussion.

Data analysis

The outcome data, ORs, and their corresponding 95% CI from each of the published studies were extracted for conducting available meta-analyses. A p-value<0.05 indicated statistically significant findings in the pooled meta-analysis. Heterogeneity was assessed using the I^2 and Q statistics at a significance level of p<0.1. The potential publication bias was also examined using Egger's test, also at a significance level of p<0.1. Instead of recalculating summary estimates with 95% confidence intervals, the existing effect sizes and 95% CI for each variable were directly extracted.

Analysis of the literature

Search results

The flow diagram in Figure 1 illustrates the process of selecting articles, starting with the identification of 250 articles and the removal of duplicates.

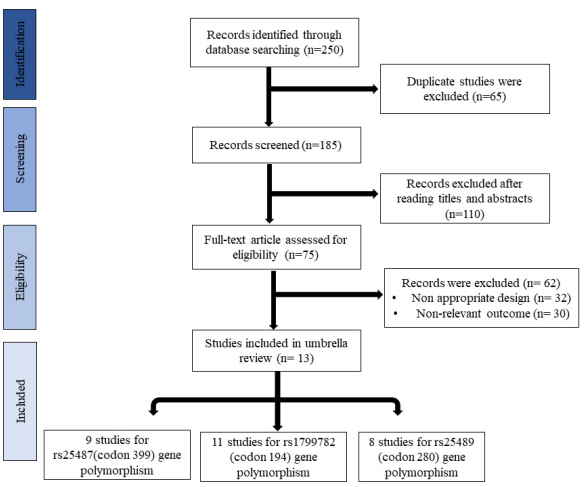

Fig. 1. Flowchart of literature screening for X-ray repair cross-completing gene 1 gene polymorphisms and lung cancer risk

Following a comprehensive assessment, 13 primary meta-analyses were discovered.[21-33] These analyses delved into the connections between XRCC1 rs25487/codon399, rs1799782/codon 194, and rs25489/codon

Table 1. Summary of Odds Ratios (OR) with 95% Confidence Intervals (95% CI) for each meta-analysis on lung cancer risk associated with XRCCI rs25487 (codon 399) polymorphism across various genetic models

SNPs	*Study*	*Ethnicity*	*Genotyping method*	*No. of studies included in the meta-analysis*	*Case/Control*	*Contrast*	*OR (95% CI)*	*Heterogeneity (p-value)*	*Publication bias (Egger's P)*	*Quality assessment scale and outcome*
rs25487 (codon 399)	Chen et al.,2015	Caucasian	PCR-RFLP	10	2187/3453	Arg/Gln + Gln/Gln	0.93 (0.82-1.04)	0.7	Absence of publication bias	NO
	Li et al., 2014	Asian, Caucasian	PCR-RFLP	31	5701/6924	Arg/Gln + Gln/Gln	0.974 (0.905- 1.049)	0.022	0.217	NO
	Wang et al., 2014	Asian, Caucasian, African, Mixed	PCR-RFLP	46	23,033/26,225	M vs. C	1.06 (1.01-1.12)	<0.001	Absence of publication bias	NO
						MM vs. CC	1.19 (1.05-1.34)	<0.001	Absence of publication bias	
						MM vs. CM+CC	1.19 (1.06-1.33)	<0.001	Absence of publication bias	
						MM+CM vs. CC	1.04 (0.98-1.10)	<0.001	Absence of publication bias	
	Huang et al., 2013	African, Asian, Caucasian	PCR-RFLP, TaqMan	41	14,156/16,667	Recessive	1.57 (1.02-2.42)	0.026	0.767	NO
						Dominant	1.00 (0.94-1.07)	0.009	0.546	
						Additive model	1.05 (0.93-1.19)	0.003	0.984	
	Dai et al., 2012	Asian, Caucasian	PCR-RFLP	39	12,303/14,965	Arg/Gln	0.98 (0.92-1.06)	0.03	0.76	NO
						Gln/Gln	1.05 (0.91-1.21)	0.0005	0.49	
						Arg/Gln + Gln/Gln	1.00 (0.93-1.07)	0.009	0.78	
	Kiyohara et al., 2010	African, Asian, Caucasian, Mixed	Sequencing, Replication	24	8,684/10,913	Arg/Gln	0.97 (0.89-1.05)	0.153	Absence of publication bias	NO
						Gln/Gln	1.00 (0.86-1.17)	0.004	Absence of publication bias	
	Zheng et al., 2009	Asian	PCR-RFLP	8	1242/1343	Arg/Gln + Gln/Gln vs. Arg/Arg	1.16 (1.00-1.36)	0.07	0.148	NO
	Wang et al., 2009	Asian, Caucasian	PCR-RFLP	30	10214/12599	Arg/Gln	1.00 (0.95-1.06)	0.05	0.407	NO
						Gln/Gln	1.06 (0.89-1.25)	<0.0001	0.992	
						Arg/Gln + Gln/Gln	1.00 (0.92-1.09)	0.005	0.343	
	Kiyohara et al., 2006	Asian, Caucasian	PCR-RFLP	18	7385/9380	Arg/Gln	0.99 (0.93-1.06)	0.026	0.052	Assessed homogeneity of the study population
						Gln/Gln	0.94 (0.80-1.11)	0.179	Absence of publication bias	

Table 2. Summary of Odds Ratios (OR) with 95% Confidence Intervals (95% CI) for each meta-analysis on lung cancer risk associated with XRCCI rs1799782 (codon 194) polymorphism across various genetic models

SNPs	*Study*	*Ethnicity*	*genotyping method*	*No. of studies included in the meta-analysis*	*Case/Control*	*Contrast*	*OR (95% CI)*	*Heterogeneity (P-value)*	*Publication Bias (Egger's P)*	*Quality assessment scale and outcome*
rs1799782 (codon 194)	Chen et al., 2015	Caucasian	PCR-RFLP	6	857/2108	Arg/Trp + Trp/Trp	0.94 (0.73-1.21)	0.44	Absence of publication bias	NO
	Zhang et al., 2014	Asian, Caucasian	Illumina, PCR-RFLP, TaqMan	25	8,876/11,210	Trp vs. Arg	0.97 (0.92-1.03)	0.3	0.33	NO
						ArgTrp vs. ArgArg	0.92 (0.85-0.98)	0.017	0.12	
						TrpTrp vs. ArgArg	1.07 (0.92-1.23)	0.38	0.65	
						(TrpTrp + ArgTrp) vs. ArgArg	0.93 (0.87-1.00)	0.047	0.25	
						TrpTrp vs. (ArgTrp + ArgArg)	1.08 (0.94-1.25)	0.255	0.5	
	Li et al., 2014	Asian, Caucasian	PCR-RFLP	16	1793/2190	Arg/Trp + Trp/Trp	0.948 (0.872- 1.030)	0.118	0.336	NO
	Huang et al., 2013	African, Asian, Caucasian	PCR-RFLP, TaqMan	23	7,426/9,603	Recessive	1.23 (1.05-1.44)	0.216	0.416	NO
						Dominant	0.96 (0.86-1.07)	0.042	0.588	
						Additive model	1.22 (1.04-1.44)	0.107	0.555	
	Dai et al., 2012	Asian, Caucasian	PCR-RFLP	22	7,534/9,753	Arg/Trp	0.93 (0.86-1.00)	0.46	0.093	NO
						Trp/Trp	1.19 (1.01-1.39)	0.23	0.83	
						Arg/Trp + Trp/Trp	0.96 (0.89-1.03)	0.24	0.22	
	Huang et al., 2011	Chinese	Taqman, PCR-RFLP	10	3303/3594	Trp/Trp Vs. Arg/ Trp + Arg/Arg	1.31 (1.13-1.53)	0.007	0.869	NO
	Kiyohara et al., 2010	African, Asian, Caucasian, Mixed	Sequencing, Replication	13	4,431/6,320	Arg/Trp	0.89 (0.79-1.00)	0.467	Absence of publication bias	Assessed homogeneity of the study population
						Trp/Trp	1.15 (0.80-1.67)	0.51	Absence of publication bias	Assessed homogeneity of the study population
	Jiang et al., 2010	Chinese, Italian, European	PCR-RFLP	22	7515/9560	Arg/Trp VS Arg/Arg	0.91 (0.85- 0.99)	0.49	0.56	NO
						Trp/Trp VS Arg/Arg	1.22 (1.04-1.44)	0.11	0.07	
						Trp/Trp + Arg/Trp VS Arg/Arg	0.95 (0.88-1.02)	0.12	0.26	
	Wang et al., 2009	Asian, Caucasian	PCR-RFLP	16	4848/6592	Arg/Trp	0.88 (0.79-0.97)	0.37	0.183	NO
						Trp/Trp	1.07 (0.85-1.33)	0.21	0.21	
						Arg/Trp + Trp/Trp	0.91 (0.83-1.00)	0.21	0.34	
	Zheng et al., 2009	Asian	PCR-RFLP	6	1020/1038	Arg/Trp + Trp/Trp vs. Arg/Arg	1.06 (0.89-1.27)	0.74	0.794	NO
	Kiyohara et al., 2006	Asian, Caucasian	PCR-RFLP	9	3714/5385	Arg/Trp	0.89 (0.78-1.03)	0.392	Absence of publication bias	Assessed homogeneity of the study population
						Trp/Trp	1.19 (0.76-1.86)	0.407	Absence of publication bias	NO

Table 3. Summary of Odds Ratios (OR) with 95% Confidence Intervals (95% CI) for each meta-analysis on lung cancer risk associated with XRCCI rs25489 (codon 280) polymorphism across various genetic models

SNPs	*Study*	*Ethnicity*	*genotyping method*	*No. of studies included in meta-analysis*	*Case/Control*	*Contrast*	*OR (95% CI)*	*Heterogeneity (P-value)*	*Publication Bias (Egger's P)*	*Quality assessment scale and outcome*
rs25489 (codon 280)	Chen et al., 2015	Caucasian	PCR-RFLP	5	894/1133	Arg/His + His/His	1.13 (0.73-1.76)	0.06	Absence of publication bias	NO
	Li et al., 2014	Asian, Caucasian	PCR-RFLP	10	611/708	Arg/His + His/His	1.03 (0.85- 1.25)	0.036	0.569	NO
	Guo et al., 2013	Asian, European	PCR-RFLP	16	8,736/9,924	His vs. Arg	1.00 (0.84-1.20)	0.967	0.05	NO
						HisHis vs. ArgArg	1.53 (1.08-2.16)	0.016	0.06	
						HisHis vs. ArgArg/ArgHis	1.55 (1.10-2.19)	0.012	0.07	
						HisHis/ArgHis vs. ArgArg	0.96 (0.79-1.17)	0.702	0.08	
	Huang et al., 2013	African, Asian, Caucasian	PCR-RFLP, TaqMan	16	6,211/6,763	Dominant	1.04 (0.83-1.29)	0.001	0.292	NO
						Recessive	1.30 (0.71-2.37)	0.065	0.52	
						Additive model	1.46 (0.99-2.15)	0.146	0.292	
	Dai et al., 2012	Asian, Caucasian	PCR-RFLP	12	5,292/5,934	Arg/His	0.98 (0.88-1.10)	0.17	0.69	NO
						His/His	1.42 (0.89-2.26)	0.33	0.26	
						Arg/His + His/His	0.99 (0.89-1.11)	0.08	0.53	
	Kiyohara et al., 2010	African, Asian, Caucasian, Mixed	Sequencing, Replication	13	4,431/6,320	Arg/Trp	0.89 (0.79-1.00)	0.467	Absence of publication bias	Assessed homogeneity of the study population
						Trp/Trp	1.15 (0.80-1.67)	0.51	Absence of publication bias	
	Zheng et al., 2009	Asian	PCR-RFLP	3	599/402	Arg/His + His/His vs Arg/Arg	0.63 (0.28-1.41)	0.0002	0.08	NO
	Kiyohara et al., 2006	Asian, Caucasian	PCR-RFLP	7	3640/3981	Arg/His	1.03 (0.88-1.20)	0.741	Absence of publication bias	Assessed homogeneity of the study population
						Arg/His or His/His	1.06 (0.91-1.23)	0.564	Absence of publication bias	

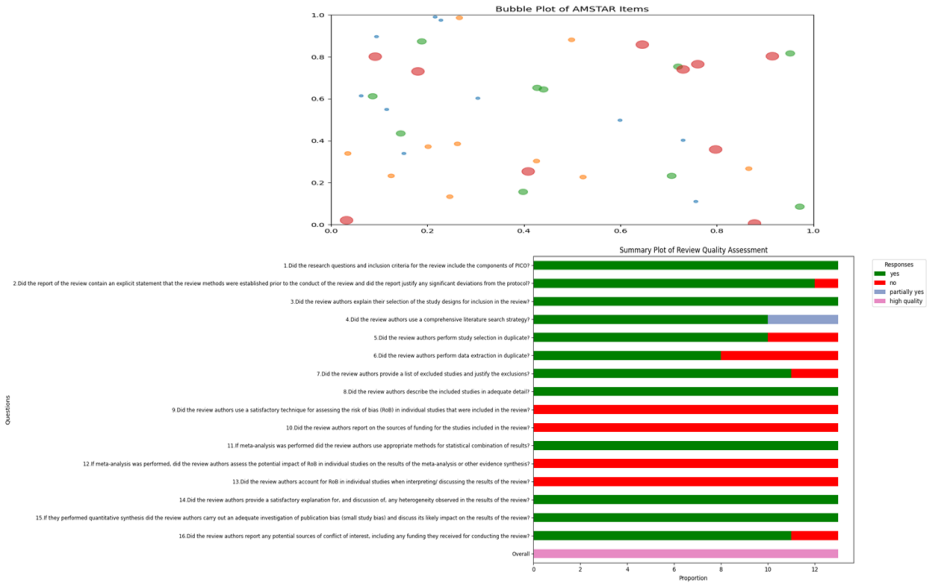

Fig. 2. Quality assessment of the included studies using the AMSTAR tool. The bubble plot illustrates associations with color-coding based on their classification output, with bubble size indicating the annual number of citations received by the study. Additionally, the bar plot summarizes the assessment

280 polymorphisms and the risk of LC. The study design included only case-control studies in all meta-analyses, a total of 504 case-control studies. These 13 qualified papers covered 28 meta-analyses across three main areas: XRCC1 rs25487/codon399 polymorphism (n=9), XRCC1 rs1799782/codon 194 polymorphism (n=11), and XRCC1 rs25489/codon 280 polymorphism (n=8). The eligible articles were published between 2006 and 2015. There was a median of 6,798 case subjects and a larger median of 8,072 control subjects per meta-analysis. Ten studies contained data from the Asian population, while data from 9 studies were included for Caucasians. Additionally, 3 studies included data from the African population, 2 from mixed populations, 2 from the European population, 2 from the Chinese population, and 1 from the Italian population. The majority of the meta-analyses did not conduct methodological quality assessments, although some studies assessed the homogeneity of the study population. The included primary studies were predominantly high-quality trials and their control groups generally adhered to Hardy-Weinberg equilibrium (HWE). Detailed characteristics of the eligible studies are provided in Tables 1, 2, and 3.

Heterogeneity and publication bias

Out of the 28 meta-analyses conducted, the Q test revealed that 16 datasets exhibited no significant heterogeneity among the studies ($p \geq 0.1$), while 12 displayed substantial heterogeneity ($p < 0.1$). In terms of publication bias, 24 outcomes did not demonstrate statistical evidence of it ($p \geq 0.1$), whereas 4 outcomes indicated the presence of publication bias ($p < 0.1$) based on Egger's test.

Quality assessment of included meta-analyses

A methodological quality assessment of the 13 included articles was conducted using the AMSTAR criteria. The review achieved a total score of 8-12 out of 16, corresponding to a percentage score of 75%, classifying it as high quality. This indicates that the review was conducted with a strong methodological approach, reflecting robustness in its design and execution (Fig. 2).

The review's strengths included the prior registration of a protocol, which ensured transparency and minimize bias, and a comprehensive literature search that effectively captured a wide range of relevant studies. Additionally, the review rigorously assessed the risk of bias in the included studies and provided clear disclosure of any potential conflicts of interest, enhancing the credibility of its findings. Despite these strengths, the review had a few minor limitations. It did not perform a sensitivity analysis, which could have explored the robustness of the results under different assumptions. Additionally, the review provided incomplete information on the sources of funding for the included studies, which could affect the interpretation of potential biases. Overall, however, the high AMSTAR score confirms that this review is of high quality (Table 4). These minor limitations do not significantly detract from its reliability, making it a valuable and credible source of evidence in its field.

Summary and description of association for XRCC1

The study evaluated the relationships between the XRCC1 rs25487/codon399, rs1799782/codon 194, and rs25489/codon 280 polymorphisms and the onset of LC by analyzing various genetic models including dominant, recessive, and codominant models, as well as specific allelic forms (homozygote and heterozygote). In

Table 4. Quality assessment of systematic reviews and meta-analyses: Response to AMSTAR checklist questions and overall quality rating*

Study	*Q1*	*Q2*	*Q3*	*Q4*	*Q5*	*Q6*	*Q7*	*Q8*	*Q9*	*Q10*	*Q11*	*Q12*	*Q13*	*Q14*	*Q15*	*Q16*	*AMSTAR Score (%)*	*Over all*
Chen et al., 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	75	High quality
Zhang et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	75	High quality
Li et al., 2014	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	68.75	High quality
Wang et al., 2014	Yes	Yes	Yes	Partially yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	68.75	High quality
Huang et al., 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	75	High quality
Guo et al., 2013	Yes	Yes	Yes	Yes	Yes	NO	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	68.75	High quality
Dai et al., 2012	Yes	Yes	Yes	Yes	NO	NO	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	62.5	High quality
Huang et al., 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	75	High quality
Kiyohara et al., 2010	Yes	Yes	Yes	Partially Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	68.75	High quality
Jiang et al., 2010	Yes	Yes	Yes	Partially Yes	NO	NO	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	NO	50	High quality
Zheng et al., 2009	Yes	Yes	Yes	Yes	NO	NO	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	62.5	High quality
Wang et al., 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	Yes	Yes	75	High quality
Kiyohara et al., 2006	Yes	NO	Yes	Yes	Yes	NO	NO	Yes	NO	NO	Yes	NO	NO	Yes	Yes	NO	50	High quality

* AMSTAR – assessment of Methodological Quality of Systematic Reviews, Q – question

this study, all meta-analyses calculated ORs with 95% CIs for all meta-analyses to determine the connection between variations in the XRCC1 gene and the risk of LC. Among the 28 data sets examined, 16 (57.14%) revealed statistically significant summary findings, with ORs between 0.93 to 1.92 ($p<0.05$). These strong correlations were observed across different genetic models, covering 3 comparisons: 5 (31.25%) for the XRCC1 rs25487/codon399 polymorphism, 8 (50%) for the XRCC1 rs1799782/codon 194 polymorphism, and 3 (18.75%) for the XRCC1 rs25489/codon 280 polymorphisms. Additionally, 12 (42.86%) of the datasets examined produced statistically non-significant summary results, with odds ratios ranging from 0.93 to 1.92 ($p > 0.05$). Noteworthy associations were identified across different genetic models, involving 3 comparisons: 4 (33.33%) for the XRCC1 rs25487/codon399 polymorphism, 3 (25%) for the XRCC1 rs1799782/codon 194 polymorphisms, and 5 (41.67%) for the XRCC1 rs25489/codon 280 polymorphisms. A summary of the findings is depicted in Fig. 3. The findings indicate that XRCC1 rs1799782/codon 194 gene polymorphisms demonstrate a strong association with LC risk. Additionally, a more significant association was discovered between XRCC1 rs25487/codon399 polymorphisms and LC risk. However, the current study suggests that XRCC1 rs25489/codon 280 polymorphisms may not be strongly linked to susceptibility to LC risk.

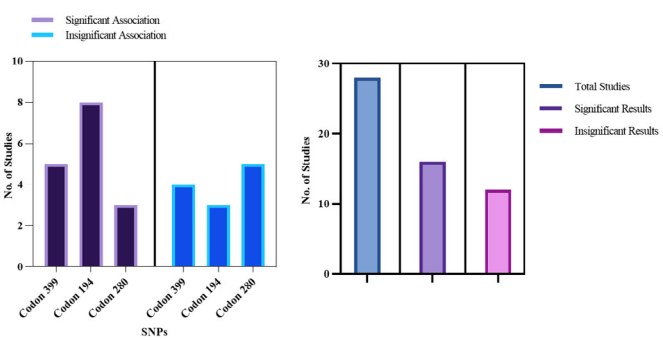

Fig. 3. A summary of the results from the current study investigating the relationship between X-ray repair cross-complementing gene 1 (XRCC1) gene polymorphisms and the risk of lung cancer

Discussion

LC develops through complex pathways, encompassing multiple stages and a multifaceted process. The precise cause of LC remains incompletely comprehended.[34] Various genes are linked to the onset of LC. Furthermore, the levels of gene expression related to DNA damage repair significantly influence the likelihood of developing malignant tumor.[35] The XRCC1 gene is one of about 20 genes involved in fixing DNA damage caused by radiation or certain chemicals. It helps repair bro-

ken DNA strands and damaged DNA bases.[36] XRCC1 is crucial for repairing broken DNA. It facilitates the rejoining of DNA strands by interacting with polynucleotide kinase (PNK) and coordinating the repair process. Hence, this gene is regarded as a pivotal candidate gene that influences susceptibility to LC.[37] Although many comprehensive population studies have explored the correlation between XRCC1 gene variants and the likelihood of developing LC, the results have been inconsistent and conflicting. Karaagac et al. identified XRCC1 gene polymorphisms as prognostic markers for survival and recommended considering them as predictive markers for guiding treatment decisions in patients with NSCLC.[38] Likewise, Minina et al. found a higher LC risk in a coal-mining population associated with the XRCC1 rs25487/codon399 genetic variant.[39] According to Yang et al., specific variants of the XRCC1 gene (rs25487/codon399) are associated with varying responses to radiotherapy and its side effects in NSCLC patients. These findings highlight the potential of DNA repair genes as predictors of treatment effectiveness.[40] Al-Rawi et al. also indicated that the XRCC1 rs1799782/codon 194 may be associated with LC within this specific population group.[41] The study revealed that naphthalene and phenanthrene exposure were positively associated with LC risk and that the XRCC1 rs25487 (codon 399) polymorphism modified this risk through PAH-gene interaction analysis.[42] Similarly, Ezzeldin et al. reported that gene-gene and gene-environment interactions involving the XRCC1 gene polymorphism indicated an elevated LC risk. However, no association was found between XRCC1 rs25487 and LC in combination with ERCC1 or CHRNA3 variants, and the association varied across different ethnic groups. Further studies are needed to clarify these findings.[43] The findings by Karaagac et al. suggested NSCLC patients with certain SNPs exhibit a higher stage and more advanced disease at initial diagnosis, with XRCC1 and TP53 gene polymorphisms predicting metastasis risk, supporting their use in biomarker assessment.[44] The current study's findings are in line with these previous discoveries.

This study involved a systematic identification and analysis of 13 meta-analyses of observational studies to evaluate the relationship between XRCC1 polymorphisms and LC development. The findings reveal a consistent and strong relationship between the XRCC1 rs1799782/codon 194 gene polymorphisms and an increased susceptibility to LC. Moreover, a clear association was identified between the XRCC1 rs25487/codon399 polymorphisms and LC risk in the majority of the studies analyzed.[21,22,24-33] In contrast, the majority of studies did not find a significant association between XRCC1 rs25489/codon 280 polymorphisms and LC susceptibility.[23,30] Additionally, several factors could have influenced the results, such as the limited number of studies, small sample sizes, absence of study quality assessment, and HWE deviations. The considerable heterogeneity found across the original studies is a primary contributor to these discrepancies. Among the 28 datasets analyzed, 12 exhibited notable heterogeneity, while 16 demonstrated a lack of heterogeneity. The diverse range of adjusted factors such as age, gender, environmental exposure, alcohol consumption, family history, treatment usage, race, and smoking habits across studies might introduce bias and heterogeneity, affecting the reliability of our analysis. Additionally, of the 28 datasets analyzed, 24 showed no evidence of publication bias, while four indicated potential publication bias, suggesting that some negative study results might be published. Selection bias may influence the findings, when the researchers give priority to publishing positive results, resulting in an overabundance of such outcomes in academic literature. This bias can distort the overall understanding of the relationship between XRCC1 polymorphisms and lung cancer risk. Information bias is another concern, as inconsistencies in how genetic variants and lung cancer outcomes were measured across studies could introduce inaccuracies. For example, differences in the definitions of lung cancer stages or diagnostic criteria may lead to varying conclusions regarding the role of XRCC1 polymorphisms. Additionally, the studies included in our review were rated as high quality according to AMSTAR criteria. They demonstrated strong adherence to methodological standards, including rigorous protocol registration, comprehensive literature searches, and thorough risk of bias assessments. These factors contribute to the reliability and robustness of this current findings, enhancing the overall validity of the meta-analysis results.

Unlike traditional systematic reviews or meta-analyses, umbrella reviews offer a broader perspective by summarizing the findings of multiple studies on a particular phenomenon or research question.[45] The present study is the first to apply this strategy for a comprehensive critical evaluation of the published associations between XRCC1 rs25487/codon399, rs1799782/codon 194, and rs25489/codon 280 gene polymorphisms and LC incidence. Additionally, the present study included primary studies with notably large sample sizes, which minimized the potential for bias compared to smaller studies. Moreover, the genotype distributions for the majority of control SNPs aligned with HWE, thereby strengthening the robustness of our findings.

In advanced NSCLC, patients are often treated with platinum-based chemotherapy, which induces DNA damage. The XRCC1 gene polymorphism is also a predictor of clinical outcomes in NSCLC patients receiving platinum-based chemotherapy.[46] The study reported by Bushra et al. identified the XRCC1 G>A (rs25487) polymorphism as a predictive biomarker in advanced NSCLC

treated with platinum-based chemotherapy. This variant is significantly associated with severe toxicities and therapeutic responses.[47] The results suggest that the XRCC1 rs25487-GG genotype is associated with better overall response rates (ORR) in NSCLC patients undergoing platinum-based chemotherapy. However, no association was found between XRCC1 rs1799782 and the clinical outcomes of platinum-based chemotherapy.[48] This study elucidates the role of XRCC1 gene polymorphisms in the development of LC, potentially enhancing our understanding of genetic susceptibility to this disease. By identifying specific genetic markers, this research could improve risk assessment, facilitate early detection, and inform personalized treatment strategies for individuals at higher risk. The findings underscore the importance of conducting studies across diverse populations to capture variability in XRCC1 polymorphisms and their interactions with environmental factors in LC etiology.

The umbrella review has limitations including the exclusion of relevant data published in other languages due to analysis being restricted to meta-analyses published in English. Presence of heterogeneity in the meta-analyses, possibly due to selection bias and other factors. Discrepancies in participant demographics and controlled variables across studies contribute to heterogeneity. Furthermore, the individual XRCC1 SNPs were focused, omitting haplotype analyses due to a lack of available data. Future research should explore XRCC1 haplotypes to provide a more comprehensive understanding of their association with lung cancer risk. Most studies included in the review were conducted in Asian and Caucasian populations. Due to insufficient studies across diverse groups, we did not perform a subgroup analysis by ethnicity. Future research should focus on larger, multi-ethnic samples to improve generalizability.

Conclusion

This umbrella review seeks to comprehensively examine the collective evidence from multiple systematic reviews and meta-analyses on the association between XRCC1 gene variations and the development of LC. This comprehensive approach aimed to provide a consolidated analysis of the available literature to better understand the relationship between XRCC1 gene variations and LC susceptibility. The present review shows that there is a substantial link between XRCC1 (rs25487/codon399 and rs1799782/codon194) gene polymorphisms and the risk of LC. However, there is no noticeable link between the XRCC1 rs25489/codon gene polymorphisms and the onset of LC. Furthermore, the observed associations may vary across different demographic factors, such as ethnicity, age, gender, and tobacco habits. For instance, certain populations may exhibit an increased susceptibility to the effects of these polymorphisms due to environmental interactions and lifestyle factors, including smoking, which is a well-established risk factor for LC. Gender-specific responses to these genetic variations could also influence risk, with emerging evidence suggesting differential susceptibility between males and females.

Therefore, further investigation is necessary to clarify and authenticate these results. A thorough investigation of the potential connection between genetic and environmental factors requires methods such as longitudinal cohort studies to track changes over time, genome-wide association studies to identify specific genetic variants, environmental exposure assessments using geographic information systems, and multidisciplinary collaboration among researchers in genetics, epidemiology, and environmental science. Discovering genetic markers has the potential to aid in risk assessment, early detection, and personalized treatment strategies. Therefore, these findings emphasize the importance of conducting comprehensive research across varied populations.

Acknowledgement

The authors would like to thank the management of Chettinad Academy of Research and Education (Deemed to be University) for providing facilities to perform this study.

Declarations

Funding

This study did not receive external funding.

Author contributions

Conceptualization, G.K. and K.G.; Methodology, S.V.; Software, S.V.; Validation, G.K., K.G. and R.R.; Formal Analysis, R.R.; Investigation, S.V.; Resources, K.G.; Data Curation, K.G.; Writing – Original Draft Preparation, S.V.; Writing – Review & Editing, G.K.; Visualization, G.K.; Supervision, G.K.; Project Administration, G.K.; Funding Acquisition, G.K.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Data availability

Data and materials used/analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval

This study does not involve experiments with animals or human subjects.

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