

## Original Article

# Association between survivin gene -31G/C and 9194A/G polymorphisms and lung cancer susceptibility: meta-analysis of six studies

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**Abstract:** Survivin expression may be associated with elevated cancer risk. Polymorphisms in survivin appear to be associated with lung cancer susceptibility, although the results remain inconclusive. Thus, a literature search was conducted using the PubMed, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases, and summary odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to clarify the relationship between survivin gene polymorphisms and lung cancer risk. A total of six eligible articles involving 1,221 lung cancer cases and 1,173 controls were included in this meta-analysis. The results revealed a significant association between the survivin gene -31G/C polymorphism and lung cancer risk (CC vs. CG: OR=1.52, 95% CI 1.24-1.86,  $P<0.0001$ ; recessive model: OR=1.53, 95% CI 1.11-2.11,  $P=0.009$ ) and between the survivin gene 9194A/G polymorphism and lung cancer risk (GG vs. AA: OR=1.79, 95% CI=1.15-2.79,  $P=0.009$ ; GG vs. GA: OR=1.79, 95% CI=1.13-2.82,  $P=0.01$ ; recessive model: OR=1.79, 95% CI=1.16-2.76,  $P=0.008$ ). No publication bias was observed in the present study. Our results suggest that survivin gene -31G/C and 9194A/G polymorphisms are associated with an increased risk of lung cancer. Nevertheless, caution should be taken when interpreting the results of our meta-analysis given the limited number of samples. Thus, further well-designed studies with larger sample sizes are needed to confirm the current findings.

**Keywords:** Lung cancer, survivin gene, genetic variant, meta-analysis

## Introduction

Lung cancer is the second most common cancer and poses a formidable threat to people's health in terms of morbidity and mortality [1]. Survivin, which is located on chromosome 17q25, is also called baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5). This inhibitor is 14.7 kb in length and contains 4 exons and 3 introns [2, 3]. The overexpression of survivin has been associated with disease development in various malignancies, including cancers [4-9]. Survivin can inhibit apoptosis and increase cell proliferation, thereby promoting tumor development and progression [10, 11].

A number of studies have been conducted to evaluate the association between survivin poly-

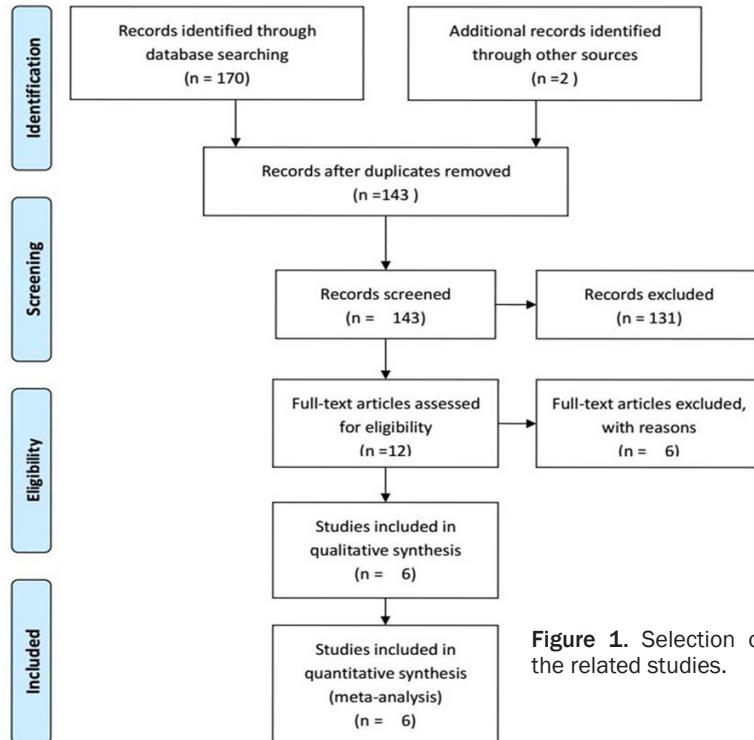
morphisms and lung cancer susceptibility in diverse populations. However, the observed associations in these studies are inconsistent [6, 12-16]. To date, no meta-analysis has been published to assess these associations. Therefore, we gathered all available publications to comprehensively meta-analyze the relationship between survivin and lung cancer risk.

## Methods

### Search strategy and selection

Relevant publications were identified through a literature search of the PubMed, Embase, Wanfang, and China National Knowledge Infrastructure (CNKI) databases using the following terms and keywords without language limitations: ("genetic polymorphism" OR "poly-

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**Figure 1.** Selection of the related studies.

morphism” OR “SNP” OR “single nucleotide polymorphism” OR “gene mutation” OR “genetic variant”) AND (“neoplasm” OR “cancer” OR “tumor” OR “carcinoma” OR “carcinogenesis”) AND “lung” AND (“survivin” OR “BIRC5”). The last search was updated on May 20, 2016. Reference lists were searched manually for other potential publications.

## *Inclusion and exclusion criteria*

Studies in our meta-analysis met the following criteria: (1) case-control studies comparing lung cancer cases with noncancerous controls; (2) studies investigating the association between polymorphisms in survivin and lung cancer susceptibility; and (3) availability of genotype or allele data for both the case and control groups. The major exclusion criteria were as follows: (1) studies with cases only; (2) meta-analysis, reviews, or abstracts; and (3) no available genotype or allele frequencies.

## *Data extraction*

Two reviewers (Hua Li and Baoxin Ma) strictly extracted relevant data from the retrieved articles according to the inclusion criteria. The following characteristics were extracted from the

included studies: first author, publication year, country of study subjects, ethnicity of patients, number of cases and controls, allele and genotype frequency, and evidence of Hardy-Weinberg equilibrium (HWE) in controls. In conflicting evaluations, a third investigator was consulted to discuss and make the final decision.

## *Statistical analysis*

The association between survivin gene polymorphisms and lung cancer was compared using the odds ratio (OR) corresponding 95% confidence interval (CI). The following models were used: allele model, co-dominant model, dominant model and recessive model. We tested whether the observed frequencies

of genotypes in controls departed from HWE using the  $\chi^2$  test. Between-study heterogeneities were estimated using  $I^2$  and  $P$  values.  $I^2$  values of 25%, 50%, and 75% were defined as no heterogeneity, moderate heterogeneity, and high heterogeneity, respectively. When no significant heterogeneity was noted ( $P > 0.10$ ), the fixed-effect model was utilized to calculate the pooled ORs. Otherwise, the random-effect model was used. Sensitivity analysis was performed by sequential omission of each study to assess the stability of the results. Begg's test was used to assess the potential publication bias ( $P < 0.05$  was considered statistically significant). Statistical analysis was performed with STATA version 11.0 software (Stata Corporation, College Station, TX, USA) and REVMAN5.3 software (Cochrane Collaboration). Two-tailed  $P < 0.05$  was considered statistically significant.

## **Results**

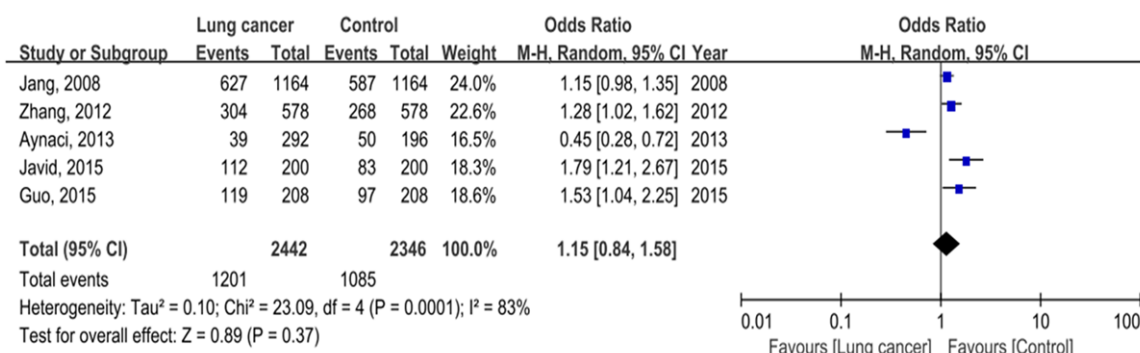
### *Identification of eligible studies*

The search initially yielded 143 relevant publications, 6 of which were considered potentially eligible. A total of 1,221 lung cancer cases and 1,173 genetically unrelated controls were

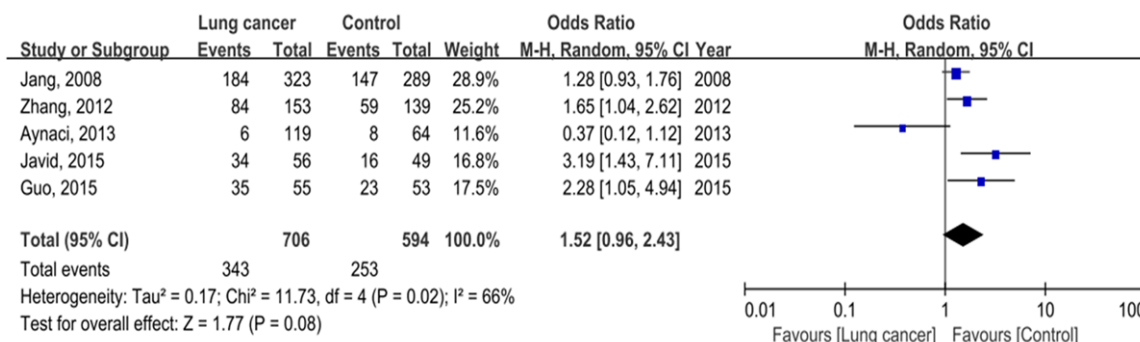
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**Table 1.** Characteristics of studies included in the meta-analysis

SNP	Study included	Year	Area	Ethnicity	Cases/controls	Genotypes of cases					Genotypes of controls					HWE test
						GG	CG	CC	C	G	GG	CG	CC	C	G	
-31G/C	Jang et al.	2008	Korea	Asian	582/582	139	259	184	627	537	142	293	147	587	577	0.87
	Zhang et al.	2012	China	Asian	289/289	69	136	84	304	274	80	150	59	268	310	0.46
	Aynaci et al.	2013	Turkey	European	146/98	113	27	6	39	253	56	34	8	50	146	0.39
	Guo et al.	2015	China	Asian	104/104	20	49	35	119	89	30	51	23	97	111	0.88
	Javid et al.	2015	India	Asian	100/100	22	44	34	112	88	33	51	16	83	117	0.61
-625G/C	Jang et al.	2008	Korea	Asian	582/582	314	215	53	321	843	300	231	51	333	831	0.49
	Aynaci et al.	2012	Turkey	European	146/98	72	57	17	91	201	56	32	10	52	144	0.88
	Guo et al.	2015	China	Asian	104/104	54	39	11	61	147	57	39	8	55	153	0.88



**Figure 2.** Meta-analysis of the -31G/C polymorphism and susceptibility to lung cancer (C vs. G).



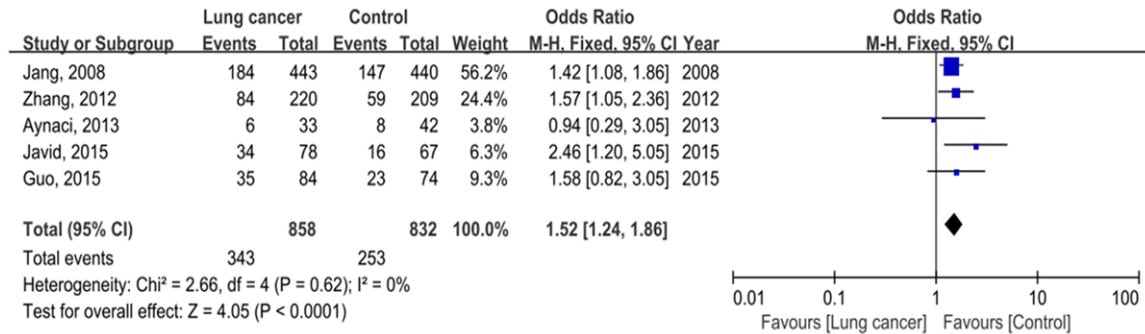
**Figure 3.** Meta-analysis of the -31G/C polymorphism and susceptibility to lung cancer (CC vs. GG).

enrolled in the six case-control articles published between 2008 and 2015 [6, 12-16]. The flow diagram of the study selection process is summarized in **Figure 1**. Five studies involved the -31G/C polymorphism [12-16]; three studies involved the -625G/C polymorphism [6, 13, 14], and two studies involved the 9194A/G and 9809T/C polymorphisms [13, 14]. All the patients were diagnosed with histopathologically confirmed lung cancers. All of the eligible studies were in HWE. The characteristics of the studies included in the meta-analysis are provided in **Table 1**.

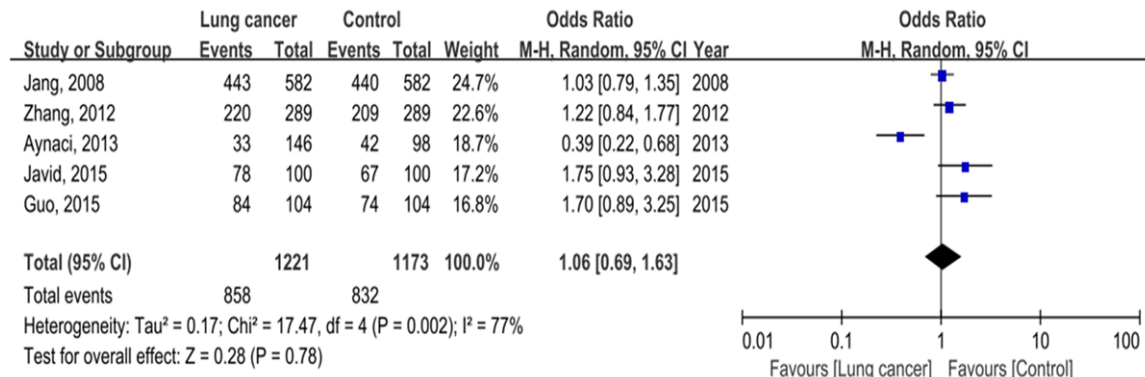
## Meta-analysis

**Association between survivin -31G/C polymorphism and lung cancer risk:** In the present study, five reports indicated that the survivin -31G/C gene polymorphism was involved in lung cancer risk [12-16]. As shown in **Figures 2-6** and **Table 2**, significant differences existed in the co-dominant and recessive genetic models (co-dominant model CC vs. CG: OR=1.52, 95% CI=1.24-1.86, P=0.000; recessive model: OR=1.53, 95% CI=1.11-2.11, P=0.009). Nevertheless, significant differences were not

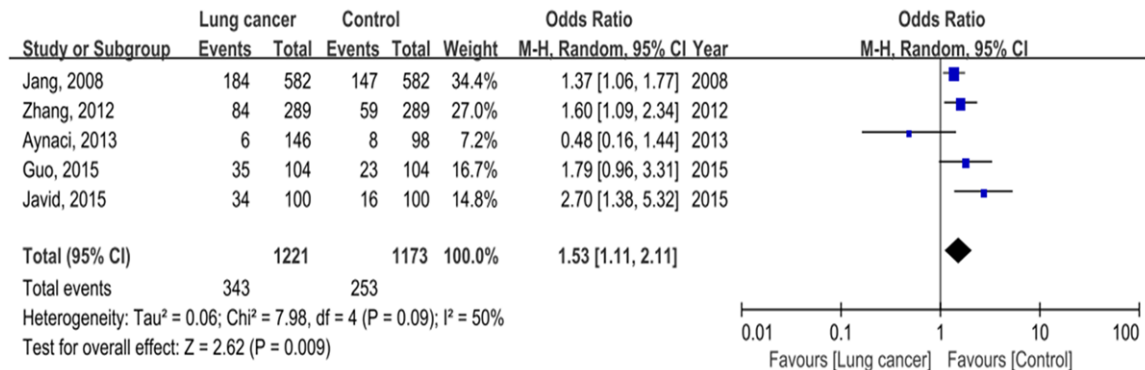
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**Figure 4.** Meta-analysis of the -31G/C polymorphism and susceptibility to lung cancer (CC vs. CG).



**Figure 5.** Meta-analysis of the -31G/C polymorphism and susceptibility to lung cancer (dominant model).



**Figure 6.** Meta-analysis of the -31G/C polymorphism and susceptibility to lung cancer (recessive model).

observed in other genetic models (allelic model: OR=1.15, 95% CI=0.84-1.58, P=0.37; co-dominant model CC vs. GG: OR=1.52, 95% CI=0.96-2.43, P=0.08; dominant model: OR=1.06, 95% CI=0.69-1.63, P=0.78).

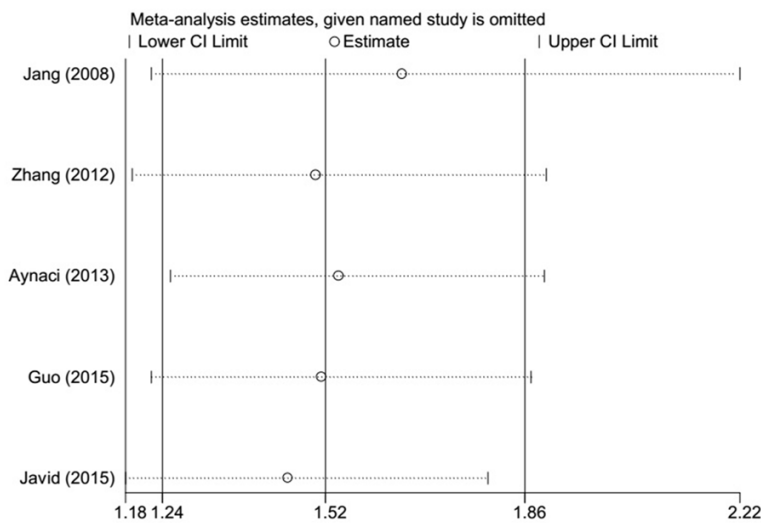
*Association between survivin 9194A/G polymorphism and lung cancer risk:* Two reports investigated the association between the

9194A/G polymorphism and lung cancer risk [13, 14]. As shown in **Table 2**, significant differences existed in the co-dominant and recessive genetic models (co-dominant model GG vs. AA: OR=1.79, 95% CI=1.15-2.79, P=0.009; co-dominant model GG vs. GA: OR=1.79, 95% CI=1.13-2.82, P=0.01; recessive model: OR=1.79, 95% CI=1.16-2.76, P=0.008). However, no significant differences existed in other

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**Table 2.** Main results of the meta-analysis of 4 polymorphisms and susceptibility to lung cancer

SNP	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association	
		Cases	Controls		I <sup>2</sup>	P-value	OR	95% CI
-31G/C	Allele model (C vs. G)	1221	1173	Random	83.00%	0.0001	1.15	0.84-1.58
	Co-dominant model (CC vs. GG)	1221	1173	Random	66.00%	0.02	1.52	0.96-2.43
	Co-dominant model (CC vs. CG)	1221	1173	Fixed	0.00%	0.62	1.52	1.24-1.86
	Dominant model (CC+CG vs. GG)	1221	1173	Random	77.00%	0.002	1.06	0.69-1.63
	Recessive model (CC vs. CG+GG)	1221	1173	Random	50.00%	0.09	1.53	1.11-2.11
-625G/C	Allele model (C vs. G)	832	784	Fixed	0.00%	0.38	1.02	0.87-1.18
	Co-dominant model (CC vs. GG)	832	784	Fixed	0.00%	0.70	1.09	0.77-1.55
	Co-dominant model (CC vs. CG)	832	784	Fixed	0.00%	0.87	1.12	0.78-1.60
	Dominant model (CC+CG vs. GG)	832	784	Fixed	12.00%	0.32	0.99	0.81-1.21
	Recessive model (CC vs. CG+GG)	832	784	Fixed	0.00%	0.84	1.10	0.79-1.55
9194A/G	Allele model (G vs. A)	686	686	Random	69.00%	0.07	1.27	0.85-1.89
	Co-dominant model (GG vs. AA)	686	686	Fixed	23.00%	0.25	1.79	1.15-2.79
	Co-dominant model (GG vs. GA)	686	686	Fixed	0.00%	0.66	1.79	1.13-2.82
	Dominant model (GG+GA vs. AA)	686	686	Fixed	58.00%	0.12	1.07	0.86-1.33
	Recessive model (GG vs. GA+AA)	686	686	Fixed	0.00%	0.38	1.79	1.16-2.76
9809T/C	Allele model (C vs. T)	686	686	Fixed	0.00%	0.72	0.99	0.85-1.15
	Co-dominant model (CC vs. TT)	686	686	Fixed	0.00%	0.62	1	0.73-1.36
	Co-dominant model (CC vs. CT)	686	686	Fixed	0.00%	0.76	1.1	0.83-1.46
	Dominant model (CC+CT vs. TT)	686	686	Fixed	0.00%	0.71	0.93	0.74-1.18
	Recessive model (CC vs. CT+TT)	686	686	Fixed	0.00%	0.71	1.06	0.81-1.38



**Figure 7.** Sensitivity analysis of each included study performed by omitting each data set from the meta-analysis (-31G/C co-dominant model CC vs. CG).

genetic models (allelic model: OR=1.27, 95% CI=0.85-1.89, P=0.25; dominant model: OR=1.07, 95% CI=0.86-1.33, P=0.55).

*Association between survivin -625G/C, 9809T/C polymorphism and lung cancer risk:* Only three reports explored the association of

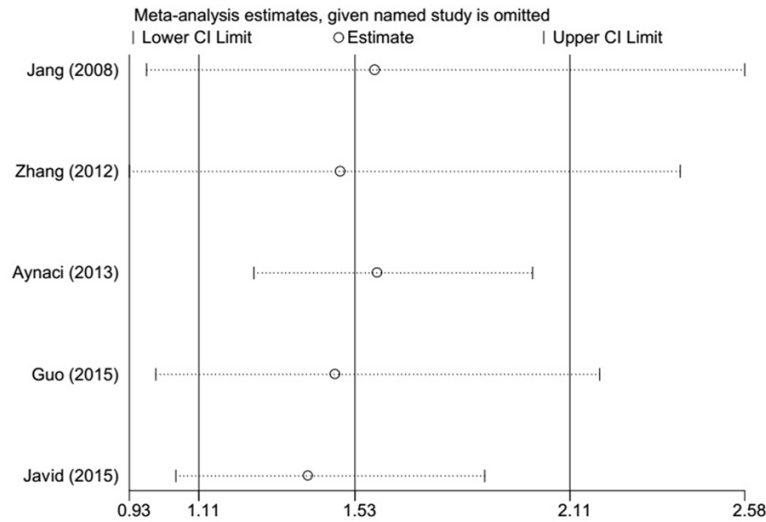
625G/C and 9809T/C polymorphisms and lung cancer risk [6, 13, 14]. As shown in **Table 2**, no significant differences were observed in any model.

### Sensitivity analysis and publication bias

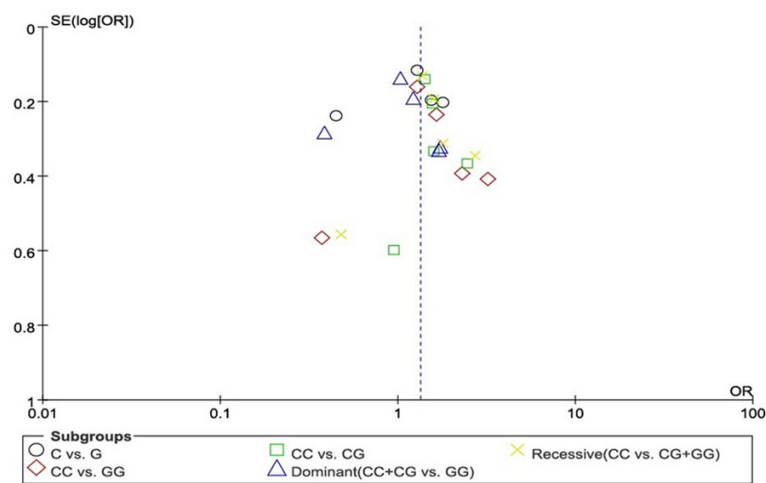
To investigate the stability of the pooled results, we further conducted sensitivity analysis by sequential omission of each study. The results showed that the pooled ORs were not significantly affected by any individual study (**Figures 7, 8**), thus indicating that our results were stable.

Begg's test was performed to assess the publication bias of the literature for the association between survivin -31G/C polymorphism and lung cancer risk. No obvious asymmetry was observed in the shape of the funnel plots (P=0.806 for C vs. G; P=0.806 for CC vs. GG; P=1.0 for CC vs. CG; P=0.462 for CC+CG vs.

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**Figure 8.** Sensitivity analysis of each included study performed by omitting each data set from the meta-analysis (-31G/C recessive model).



**Figure 9.** Funnel plot for publication bias (-31G/C).

GG;  $P=0.806$  for CC vs. CG+GG) (Figure 9). However, only two reports involved 9194A/G, and interpreting the result of publication bias was difficult.

### Discussion

To the best of our knowledge, this study is the first meta-analysis to comprehensively investigate the associations between polymorphisms in the survivin gene and lung cancer risk. We analyzed the correlation between four polymorphic loci (-31G/C, -625G/C, 9194A/G, and 9809T/C) of survivin and lung cancer risk. No significant associations were observed under

all genetic models for the association between survivin -625G/C and 9809T/C gene polymorphisms and lung cancer risk. However, significant differences existed between the survivin -31G/C gene polymorphism and lung cancer risk in two genetic models (CC vs. CG+GG, CC vs. CG models) and between the survivin 9194A/G gene polymorphism and lung cancer risk in three genetic models (GG vs. AA, GG vs. GA, and GG vs. GA+AA models). We conducted sensitivity analysis to assess the influence of each study on the combined estimates. Sensitivity analysis indicated that our results were stable, and the corresponding pooled ORs were not materially changed. Begg's test was performed to assess the publication bias of the included studies. No significant publication bias was observed in our meta-analysis, which indicated that our results were reliable.

Survivin is a novel member of the inhibitor of apoptosis protein (IAP) family that is involved in both cell division regulation and apoptosis inhibition [12, 17, 18]. The survivin -31G/C and -625G/C polymorphisms are both positioned in the survivin promoter [19]. The -31G/C polymorphism is located at the cell cycle-dependent elements and cell cycle homology regions repressor binding site. This mutation can derepress cell cycle-dependent transcription of the survivin gene and result in over-expression of survivin at both the mRNA and protein levels [19, 20]. However, the -625G/C polymorphism is not a cis-acting element or located in a putative transcription factor binding site. The survivin 9194A/G polymorphism leads to an amino acid change from Lys to Glu at codon 129 in exon 4, which is located at the C-terminal end of the protein (142 amino acids) [19]. The 9809C/T polymor-

phism is located in the 3'untranslated region of the survivin gene, and this polymorphism likely has no effect on the stability of survivin mRNA or its translational efficiency [21, 22]. Many studies have studied the polymorphisms of the survivin gene and suggested that they are associated with the risk of many cancers [23-25]. Yao et al. [26] and Zhou et al. [27] indicated that the survivin -31G/C polymorphism might be associated with colorectal cancer risk, and Qin et al. [28] revealed that the survivin -31G/C polymorphism was associated with elevated cancer risk, including colorectal, gastric and urothelial cancers. No association between 9809C/T in the survivin gene and the risk of hepatocellular carcinoma (HCC) was observed in the Chinese Han population, but 9809C/T was perhaps a protective haplotype for HCC [22].

In recent years, several studies have explored the correlation between survivin gene polymorphism and lung cancer risk, but the results of these studies are inconsistent. Moreover, the number of single studies is considerably low and might be insufficient to estimate the association of polymorphisms and lung cancer risk. Therefore, we conducted a meta-analysis to further elucidate this association. Our results suggest that survivin -31G/C and 9194A/G polymorphisms are associated with lung cancer risk.

Some limitations must be noted in the current meta-analysis. First, the lack of sufficient studies limited our analysis; only six case-control trials comprising 2,394 subjects were included in this study. Specifically, only two clinical trials were included in the analysis of survivin 9194A/G, -625G/C, and 9809T/C gene polymorphisms. The enrolled studies used a wide range of sample sizes from 200 to 1,164, which may have resulted in unreliable outcomes. Second, most of the data from the included papers were obtained from Asian populations, and only one study was conducted in a European population. Thus, we cannot derive precise conclusions for other population levels. Third, our result was based on unadjusted estimates that required further accuracy or correction. Numerous factors, including age, ethnicity, and other susceptible genes, are potentially associated with lung cancer risk. If individual data were available, a more precise analysis could be conducted.

In conclusion, the available data provide evidence that the survivin -31G/C and 9194A/G gene polymorphisms might be associated with lung cancer risk. Nevertheless, diversity was noted in relation to age, sample size, and region. Thus, further investigations using a much larger sample size are needed to confirm the findings of this meta-analysis.

### Disclosure of conflict of interest

None.

### Authors' contribution

HL participated in the design of the study, performed the statistical analysis, and drafted the manuscript. BXM conceived of the study and helped to draft the manuscript. SHY participated in the study design and coordination and helped to draft the manuscript. HL and BXM were responsible for document retrieval. DW and MLL participated in data extraction. DW helped with the statistical analysis. MLL performed the manuscript revision. All authors read and approved the final manuscript.

### Abbreviations

ORs, odds ratios; 95% CIs, 95% confidence intervals; HWE, Hardy-Weinberg equilibrium.

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