

Associations between *FAS* rs2234767 and *FASL* rs763110 polymorphisms and the risk of lung cancer: a meta-analysis of 39,736 subjects

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Background: Previous studies have investigated the associations between the common polymorphisms in *FAS*/*FASL* genes and lung cancer risk; however, the results remain inconsistent and inconclusive. Hence, we performed a meta-analysis to reassess the relationships between *FAS* rs2234767 and *FASL* rs763110 polymorphisms and the risk of lung cancer.

Methods: Eligible studies retrieved by an electronic search were pooled to calculate the strength of the associations using the odds ratio (OR) and 95% confidence interval (95% CI).

Results: A total of 13 case-control studies involving 39,736 subjects (9,237 cases and 10,838 controls on *FAS* rs2234767 and 8,957 cases and 10,704 controls on *FASL* rs763110) were included in the meta-analysis. The results showed a significant association between *FAS* rs2234767 polymorphism and increased risk of lung cancer (A vs G: OR = 1.07, 95% CI = 1.01–1.13; AA vs GG: OR = 1.23, 95% CI = 1.06–1.43; AA vs GA + GG: OR = 1.24, 95% CI = 1.08–1.43). Similar association was also observed in Asian population (AA vs GA + GG: OR = 1.30, 95% CI = 1.01–1.67) and in the studies with large sample size (A vs G: OR = 1.07, 95% CI = 1.00–1.14; AA vs GG: OR = 1.30, 95% CI = 1.07–1.58). However, no significant association between *FASL* rs763110 polymorphism and lung cancer risk was found other than in the Asian population (CC vs TC + TT: OR = 1.35, 95% CI = 1.01–1.80).

Conclusion: The meta-analysis indicated that *FAS* rs2234767 polymorphism was significantly associated with an increased risk of lung cancer and *FASL* rs763110 polymorphism may not contribute to susceptibility to lung cancer other than in Asian population.

Keywords: *FAS*, *FAS* ligand, polymorphism, lung cancer, meta-analysis, risk, apoptosis

Introduction

Apoptosis is a genetically mediated physiological mechanism of programmed cell death, playing a vital role in the regulation of cell growth, homeostasis, and development of adult multicellular organisms, and elimination of unwanted or potentially dangerous cells.^{1,2} However, defects in the regulation of apoptosis result in unchecked cell growth and proliferation, causally contributing to tumorigenesis.³ Acquired ability to resist apoptosis is one of the hallmarks of malignancies including lung cancer, which usually arises from the genetic alterations of apoptotic genes such as *FAS*, *FASL*, *TNF*, *TP53*, *Bcl-2*, and so on.^{4–6}

Acting as an important member of the tumor necrosis factor superfamily, *FAS* (also known as *TNFSF6*, *CD95*, or *APO-1*, located on chromosome 10q24.1), a cell surface receptor, has been delineated as a primary contributor to programmed cell death by the interaction with its natural ligand *FASL* (also *CD95L*, located on chromosome 1q23) to initiate the extrinsic pathway of apoptosis.^{7,8} In the *FAS*/*FASL* signaling

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system, FAS receptor is found to be extensively expressed in diverse tissues, while expression of FASL is restricted on the cells within the immune system, such as activated T-cells and natural killer cells.⁹ Decreased expression of FAS and/or elevated expression of FASL are frequently observed in a variety of cancers including lung cancer in numerous studies, suggesting the potential importance of FAS/FASL signaling system in the formation of malignancy.^{10–12} As was strongly evidenced, decreased expression of FAS may protect tumor cells from apoptosis induced by antitumor immune responses, but increased expression of FASL may facilitate the ability of tumor cells to counterattack the immune system by damaging the FAS-sensitive lymphocytes and escape immunologic surveillance, thereby contributing to the development of cancer.^{13–16}

Recently, two common polymorphisms (a G to A transition at position –1,377 in *FAS* gene, rs2234767 and a T to C transition at position –844 in *FASL* gene, rs763110) in the promoter regions of FAS and FASL have been found to be linked to the changeable expressions of the two genes and often associated with the altered risk of lung cancer.^{9,17} However, the results reported in previous studies regarding associations between the two common polymorphisms and the risk of lung cancer remain inconsistent and inconclusive, which may be partially attributed to the limited sample size of some published studies and variation in ethnicities. Accordingly, to derive a more precise estimation, we performed a meta-analysis with all available studies to comprehensively reevaluate the concerned associations.

Materials and methods

Literature search

A comprehensive electronic search in an attempt to retrieve relevant studies regarding the associations of *FAS* rs2234767 and *FASL* rs763110 polymorphisms with the risk of lung cancer was carried out in PubMed, Embase, Web of Science, Google Scholar, Cochrane Library, China National Knowledge Infrastructure, and Chinese Biomedicine Database (up to December 2015). We developed the search strategy using the following keywords (“FAS/CD95/TNFSF6/APO-1”, “FASL/CD95L”, “polymorphism/polymorphisms/variant/genotype”, and “lung cancer/lung carcinoma”) in various combinations with the limits humans and articles in English or Chinese. Reference lists of the identified articles were also further checked for additional potentially eligible studies. In case of duplication, only the study with the largest sample size was selected. For the studies conducted in different ethnicities, each study should be treated independently.

Inclusion criteria and data extraction

The eligible studies for inclusion must satisfy the following criteria: 1) case–control studies; 2) studies evaluating the associations of *FAS* rs2234767 and *FASL* rs763110 polymorphisms with the risk of lung cancer; 3) diagnoses of all cases pathologically confirmed in the studies; 4) studies presenting sufficient information to calculate the odds ratios (ORs) with their 95% confidence intervals (CIs); and 5) studies with available extracted frequencies in case and control. Studies without control or with incomplete data, family-based studies, or case reports, editorials, review articles, and meta-analysis were excluded. Data were independently extracted by two investigators using a standardized form. Any discrepancy between the two investigators was settled by discussion and consultation with a third investigator until a consensus was reached. The following information was extracted from each study: first author, year of publication, country, ethnicity, sample size, source of control, genotype method, allele or genotype frequencies in cases and controls, and evidence of Hardy–Weinberg equilibrium.

Statistical analysis

Individual ORs with 95% CIs were utilized to evaluate the strength of associations between *FAS* rs2234767 and *FASL* rs763110 polymorphisms and lung cancer risk using Review Manager version 5.2 software (Cochrane Collaboration, Oxford, UK; <http://www.cochrane.org/software/revman.htm>) in five genetic models (allele model, homozygote model, heterozygote model, dominant model, and recessive model). The significance of pooled OR was determined by Cochrane *Z* test ($P < 0.05$ was considered significant) using a fixed-effect model or random-effect model according to the heterogeneity across studies.¹⁸ The heterogeneity between studies was measured by the *Q*-test and *I*² statistics, and the random-effect model was applied if the heterogeneity was significant ($P_h < 0.1$); otherwise, the fixed-effect model was used.^{19–21} In addition, the subgroup analysis was performed based on the ethnicity and sample size. The study with more than 2,000 subjects enrolled was regarded as having a large sample size; if not, it was defined as having small sample size. Moreover, sensitivity analysis by sequential omission of each individual study was performed to assess the stability of results. Potential publication bias was evaluated graphically by Begg’s funnel plots, which was further assessed by Egger’s linear regression test using Stata 12.0 software (StataCorp LP, College Station, TX, USA) and $P < 0.05$ was considered statistically significant.^{22,23}

Results

Characteristics of included studies

Based on the search strategy, 39 potentially relevant articles were retrieved by the initial research. However, 13 individual studies from six publications with a total of 39,736 subjects were finally enrolled in the meta-analysis, according to the selection criteria.^{1,3,6,9,24,25} The flow chart of study selection is shown in Figure 1. The study by Truong et al.²⁵ investigated the associations of *FAS* rs2234767 and *FASL* rs763110 polymorphisms with the risk of lung cancer in Asian and Caucasian populations, respectively, which were treated independently. Therefore, there were seven case-control studies involving 9,237 cases and 10,838 controls focusing on the association between *FAS* rs2234767 polymorphism and susceptibility to lung cancer, among which four and three studies were conducted in Asian and Caucasian populations, respectively. Also, six case-control studies involving 8,957 cases and 10,704 controls were included to reevaluate the association between *FASL* rs763110 polymorphism and the risk of lung cancer, of which there were four and two studies for Asian and Caucasian populations, respectively. No significant deviation from Hardy-Weinberg equilibrium was reported in the controls of all studies, except for the studies by Gormus et al.,²⁴ Zhang et al.,⁹ and

Truong et al.²⁵ The main characteristics of the included studies are listed in Table 1.

Meta-analysis results

The main results of the meta-analysis are shown in Table 2 and Figure 2. Overall, a significant association between *FAS* rs2234767 polymorphism and increased risk of lung cancer was observed in allele model (A vs G: OR=1.07, 95% CI=1.01–1.13), homozygote model (AA vs GG: OR=1.23, 95% CI=1.06–1.43), and recessive model (AA vs GA + GG: OR=1.24, 95% CI=1.08–1.43). In the subgroup analysis based on ethnicity, the *FAS* rs2234767 polymorphism was associated with an increased risk of lung cancer (AA vs GA + GG: OR=1.30, 95% CI=1.01–1.67) in Asian population, but not in Caucasian population. In addition, the subgroup analysis by sample size represented an increased lung cancer risk associated with *FAS* rs2234767 polymorphism (A vs G: OR=1.07, 95% CI=1.00–1.14; AA vs GG: OR=1.30, 95% CI=1.07–1.58) in large sample size rather than small sample size.

For *FASL* rs763110 polymorphism, no significant overall risk of lung cancer was revealed in any genetic model. However, an increased risk of lung cancer associated with this variant was detected in Asian population in recessive

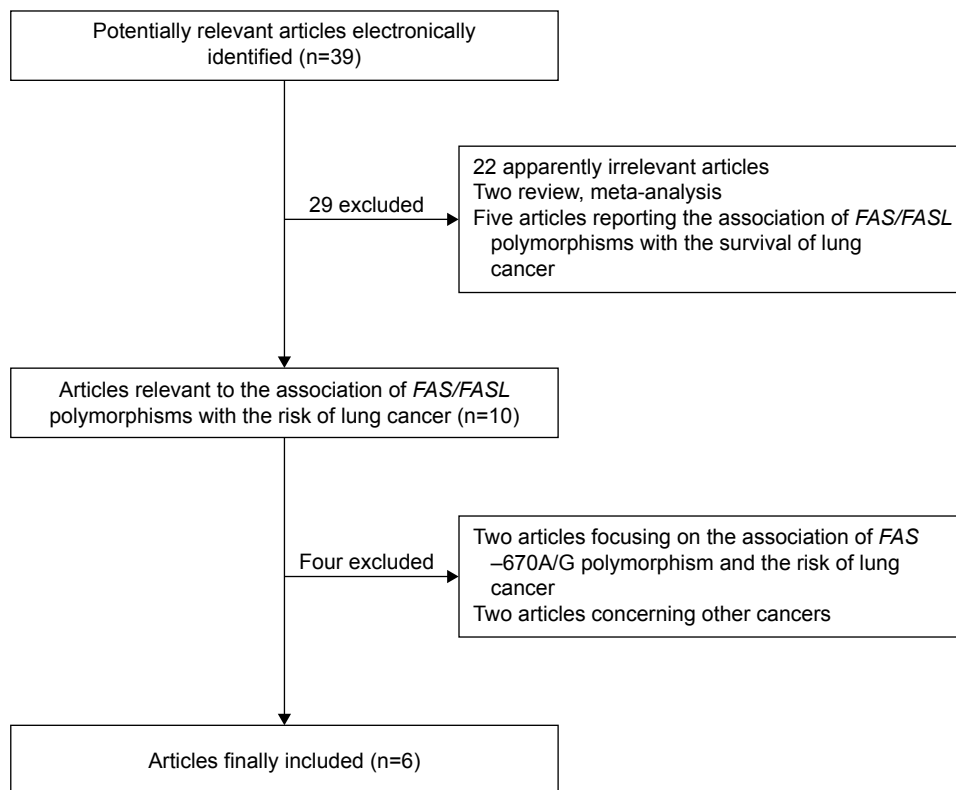


Figure 1 Flowchart of the selection procedure.

Table 1 Characteristics of studies included in the meta-analysis

First author	Year	Country	Ethnicity	Genotype – case		Genotype – control		Source of control	Genotype method	Polymorphisms	HWE test
				VR Ho/Ht/WT Ho	VR Ho/Ht/WT Ho	VR Ho/Ht/WT Ho	VR Ho/Ht/WT Ho				
Gormus et al ²⁴	2007	Turkey	Caucasian	0/73/21	0/37/13	Population	PCR-RFLP	FAS rs2234767	N		
Ter-Minassian et al ³	2008	USA	Caucasian	37/492/1,645	23/336/1,138	Population	TaqMan	FAS rs2234767	Y		
Zhang et al ⁹	2008	USA	Caucasian	789/1,036/322	576/684/230	Population	TaqMan	FASL rs763110	Y		
Truong et al ²⁵	2005	People's Republic of China	Asian	154/433/413	130/601/539	Population	PCR-RFLP	FAS rs2234767	N		
	2005	People's Republic of China	Asian	612/324/64	601/560/109	Population	PCR-RFLP	FASL rs763110	Y		
	2010	Multiple	Caucasian	1,970/2,005/549	2,840/2,881/832	Population	TaqMan	FASL rs763110	N		
	2010	Multiple	Asian	228/160/41	251/221/40	Population	TaqMan	FASL rs763110	Y		
	2010	Multiple	Caucasian	55/931/3,613	77/1,274/5,218	Population	TaqMan	FAS rs2234767	Y		
	2010	Multiple	Asian	88/252/173	87/278/208	Population	TaqMan	FAS rs2234767	Y		
Zhao et al ⁶	2015	People's Republic of China	Asian	53/133/89	38/138/121	Hospital	PCR-RFLP	FAS rs2234767	Y		
	2015	People's Republic of China	Asian	140/103/32	117/128/52	Hospital	PCR-RFLP	FASL rs763110	Y		
Park et al ¹	2006	Korea	Asian	95/300/187	97/313/172	Population	PCR-RFLP	FAS rs2234767	Y		
	2006	Korea	Asian	307/228/47	308/227/47	Population	PCR-RFLP	FASL rs763110	Y		

Abbreviations: Ht, heterozygote; HWE, Hardy-Weinberg equilibrium; N, not in agreement with HWE; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; VR, variant; VR Ho, variant homozygote; WT, wild type; WT Ho, wild-type homozygote; Y, in agreement with HWE.

Table 2 Meta-analysis results of FAS/FASL polymorphisms and lung cancer risk

Polymorphisms	Study group	Sample size (N) (case/control)	Allele contrast		VR Ho vs WT Ho		Ht vs WT Ho		Dominant model		Recessive model	
			OR (95% CI)	P _h /I ² (%)	OR (95% CI)	P _h /I ² (%)	OR (95% CI)	P _h /I ² (%)	OR (95% CI)	P _h /I ² (%)		
FAS rs2234767	Overall	9,237/10,838	1.07 (1.01–1.13)	0.21/28	1.23 (1.06–1.43)	0.12/42	1.03 (0.96–1.10)	0.58/0	1.05 (0.99–1.12)	0.48/0	1.24 (1.08–1.43)	0.1/45
	Asian	2,370/2,722	1.11 (0.98–1.27)	0.07/57	1.29 (0.98–1.70)	0.07/58	0.99 (0.88–1.12)	0.27/23	1.06 (0.95–1.19)	0.16/43	1.30 (1.01–1.67)	0.06/59
	Caucasian	6,867/8,116	1.04 (0.97–1.12)	0.95/0	1.06 (0.79–1.41)	0.81/0	1.05 (0.96–1.13)	0.84/0	1.05 (0.97–1.13)	0.87/0	1.05 (0.78–1.40)	0.79/0
	Large sample	7,773/9,336	1.07 (1.00–1.14)	0.38/0	1.30 (1.07–1.58)	0.16/45	1.03 (0.95–1.10)	0.52/0	1.05 (0.97–1.12)	0.94/0	1.26 (0.92–1.73)	0.09/58
	Small sample	1,464/1,502	1.10 (0.93–1.30)	0.09/53	1.15 (0.92–1.44)	0.11/54	1.05 (0.89–1.23)	0.34/11	1.08 (0.93–1.26)	0.15/43	1.15 (0.94–1.41)	0.19/40
FASL rs763110	Overall	8,957/10,704	1.14 (0.98–1.31)	<0.00/187	1.17 (0.95–1.43)	0.01/67	1.04 (0.95–1.15)	0.61/0	1.07 (0.98–1.17)	0.22/29	1.19 (0.96–1.46)	<0.00/189
	Asian	2,286/2,661	1.24 (0.99–1.55)	<0.00/183	1.32 (0.91–1.92)	0.03/67	0.97 (0.79–1.21)	0.39/1	1.19 (0.97–1.45)	0.12/49	1.35 (1.01–1.80)	<0.00/183
	Caucasian	6,671/8,043	1.00 (0.96–1.05)	0.4/0	1.03 (0.93–1.14)	0.55/0	1.06 (0.96–1.18)	0.83/0	1.05 (0.95–1.16)	0.87/0	0.99 (0.92–1.06)	0.26/21
	Large sample	7,671/9,313	1.13 (0.92–1.40)	<0.00/194	1.16 (0.90–1.50)	0.01/78	1.06 (0.96–1.17)	0.9/0	1.07 (0.98–1.18)	0.28/21	1.17 (0.85–1.61)	<0.00/195
	Small sample	1,286/1,391	1.14 (0.92–1.42)	0.04/70	1.18 (0.75–1.87)	0.06/65	0.97 (0.74–1.27)	0.22/33	1.08 (0.83–1.39)	0.11/56	1.20 (0.93–1.55)	0.07/62

Notes: The results are given in bold if the 95% CI excluded 1 or P<0.05. P_h, P-value of Q-test for heterogeneity test, and random-effect model was used when P-value for heterogeneity test <0.1; otherwise, fixed-effect model was used in the analysis.

Abbreviations: CI, confidence interval; Ht, heterozygote; OR, odds ratio; VR, variant; VR Ho, variant homozygote; WT, wild type; WT Ho, wild-type homozygote.

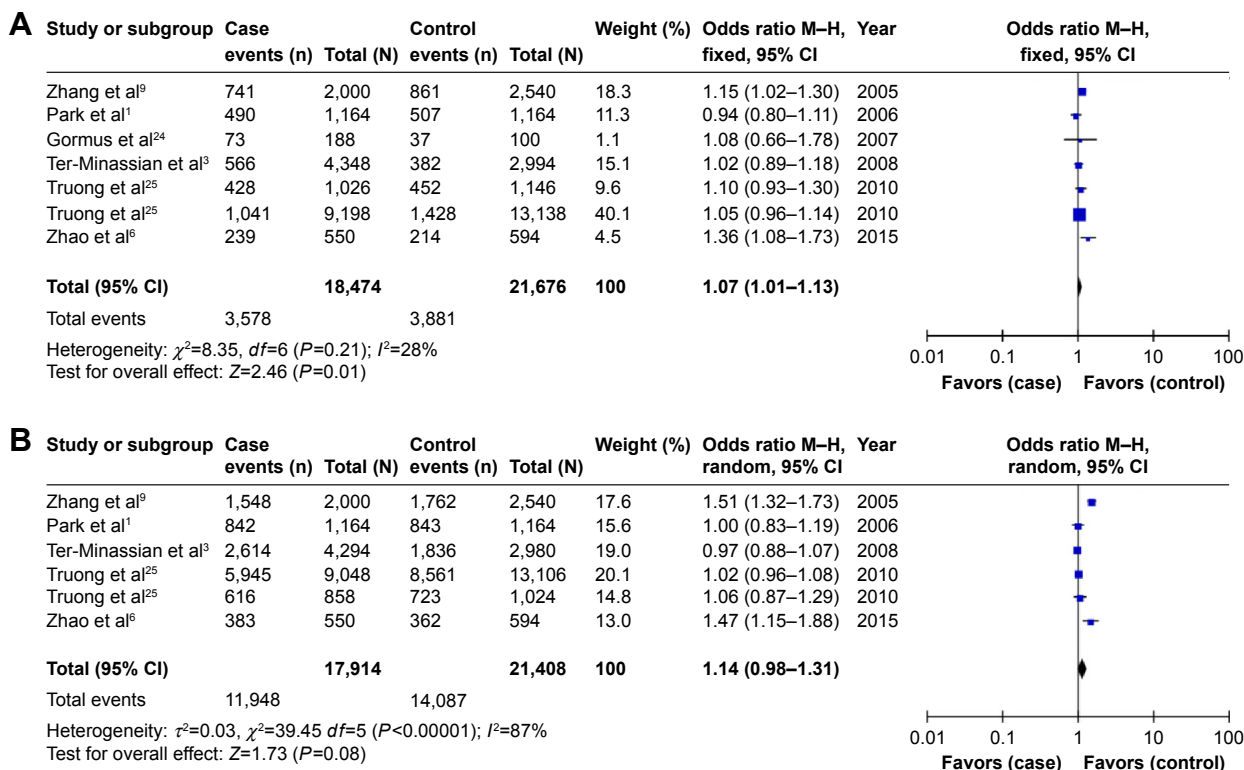


Figure 2 Forest plots of lung cancer risk associated with variants of *FAS/FASL* gene in the allele contrast.

Notes: (A) *FAS* -1377G/A, rs2234767; (B) *FASL* rs763110, rs763110.

Abbreviations: CI, confidence interval; df , degrees of freedom; M-H, Mantel-Haenszel.

model (CC vs TC + TT: OR = 1.35, 95% CI = 1.01–1.80) in the subgroup analysis based on ethnicity, while such an association was not found in Caucasian population. Similarly, no obvious association between *FASL* rs763110 polymorphism and susceptibility to lung cancer was indicated in the stratification analysis by sample size.

Sensitivity analysis and publication bias test

Sensitivity analysis by sequential omission of each individual study was performed to assess the stability of the results. In the present study, no quantitative alternation of overall ORs were observed under any genetic model in the sensitivity analysis for the association between *FAS* rs2234767 polymorphism and the risk of lung cancer, with the exception of the allele contrast model by excluding the study by Zhang et al⁹ (pooled OR = 1.05, 95% CI = 0.99–1.12, $P=0.1$), the homozygote by excluding the studies by Zhang et al⁹ (pooled OR = 1.12, 95% CI = 0.94–1.33, $P=0.22$), Ter-Minassian et al³ (pooled OR = 1.23, 95% CI = 0.98–1.55, $P=0.08$), and Truong et al²⁵ (pooled OR = 1.22, 95% CI = 0.95–1.56, $P=0.12$), as well as the recessive model (pooled OR = 1.12, 95% CI = 0.95–1.32, $P=0.19$ for Zhang et al,⁹ pooled OR = 1.24, 95% CI = 1.00–1.54, $P=0.06$ for Ter-Minassian et al,³ pooled OR = 1.24,

95% CI = 0.98–1.57, $P=0.08$ for Truong et al²⁵). Nevertheless, most results of the sensitivity analysis suggested at least a borderline significance of this association. For the *FASL* rs763110 polymorphism, the significance of the pooled OR was not affected excessively in any of the genetic models, indicating the robustness of the results. Furthermore, as shown in Figure 3, no obvious asymmetry was observed in Begg's funnel plots for the two studied polymorphisms and no supportive evidence was provided for potential publication bias by the Egger's test (dominant model: $P=0.513$ for *FAS* rs2234767 polymorphism and $P=0.592$ for *FASL* rs763110 polymorphism), further supporting the absence of evident publication bias.

Discussion

The present study involving 39,736 subjects was the first to comprehensively evaluate the associations between two common polymorphisms in *FAS/FASL* signal and susceptibility to lung cancer, demonstrating an increased risk of lung cancer associated with *FAS* rs2234767 polymorphism, whereas it suggested no significant association between *FASL* rs763110 polymorphism and lung cancer risk other than in an Asian population.

Over decades, accumulative evidence has shed light on the advances in basic lung cancer research that apoptosis and

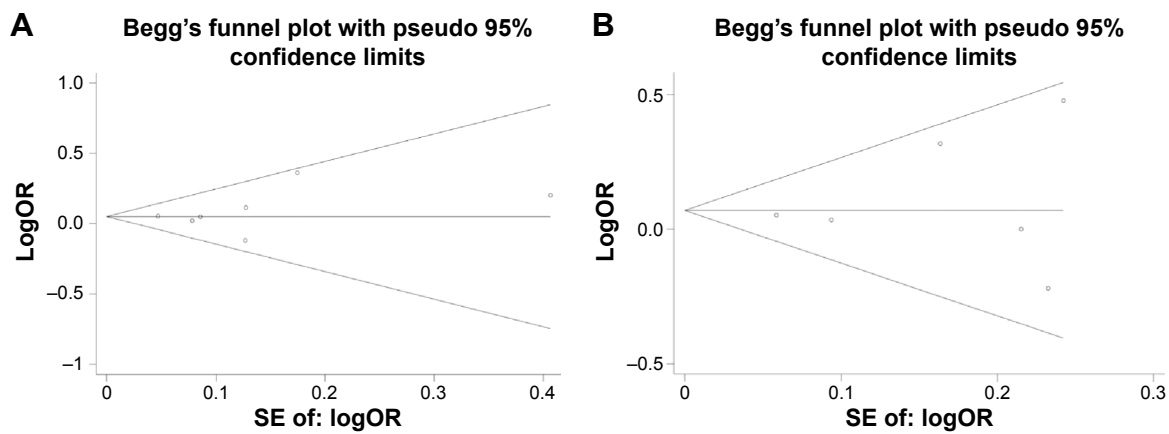


Figure 3 Begg's funnel plots for publication bias test on the associations of *FAS*/*FASL* gene polymorphisms with lung cancer risk in the dominant contrast.

Notes: (A) *FAS* -1377G/A, rs2234767; (B) *FASL* rs763110, rs763110.

Abbreviations: OR, odds ratio; SE, standard error.

apoptosis-related genes may contribute vastly to the development of the malignant phenotype by conferring enhanced ability to resist apoptotic stimuli to some tumor cells or by inducing apoptosis of tumor-specific lymphocytes.^{26,27} Remarkably, the discovery of *FAS*/*FASL* signaling system primarily involved in apoptosis has enabled us to recognize carcinogenesis of apoptosis-related genes, with aberrant expressions of *FAS* and *FASL* observed in lung cancer, which was supported by numerous lines of evidence.^{11,28} In this regard, the existence of two paths for the *FAS*/*FASL* system in lung cancer has been widely accepted: *FASL* on T-lymphocytes is able to promote apoptosis in *FAS*-expressing lung cancer cells through cell-mediated cytotoxic reactions against cancer; in contrast, lung cancer cells can escape from the immune system by downregulating *FAS* expression and/or inducing the apoptosis of lymphocytes by the expression of *FASL*.²⁹⁻³¹ Given the important role of *FAS*/*FASL* system in lung cancer, it is biologically plausible to propose that several polymorphisms in *FAS*/*FASL* genes may be significant in the genetic susceptibility to lung cancer on account of the fact that these polymorphisms possess the potential to alter the expression of *FAS* and/or *FASL*.⁶ For instance, the *FAS* rs2234767 polymorphism was found to be capable of disrupting Sp1 transcription factor binding sites, thus diminishing the promoter activity and decreasing the expression of *FAS* gene;³² the C allele of the *FASL*-844T>C polymorphism could create a binding site for a transcription factor, CAAT/enhancer-binding protein, and thus is significantly related to increased basal expression of *FASL*,³³ which are both able to result in altered risk of lung cancer via the aforementioned mechanism. Nevertheless, current studies investigating the relationships between *FAS* rs2234767 and *FASL* rs763110 polymorphisms and the risk

of lung cancer reported inconsistent results, which prompts us to perform a meta-analysis to reassess the associations with a powerful approach.

In this meta-analysis, 13 published studies with a total of 39,736 subjects were enrolled to determine the associations between the two potentially functional polymorphisms within *FAS* and *FASL* and the lung cancer risk. Overall, the study suggested a significant association between *FAS* rs2234767 polymorphism and increased risk of lung cancer, particularly evident in Asian population, which was in keeping with the findings by Xu et al.³⁴ They performed a meta-analysis to investigate the association of *FAS* rs2234767 polymorphism with overall cancer risk and reported that the polymorphism was associated with a higher cancer risk including lung cancer and the overall cancer risk associated with the polymorphism was particularly evident in Asian population, although a smaller sample size was included in their study compared to that in the current study. Overall, our study along with the previous study has further validated this association in a more confident manner. Also, the subgroup analysis based on sample size in the present study revealed that this association was particularly evident in a larger sample size, suggesting the importance of sample size in determining the concerned association. Furthermore, the association of *FASL* rs763110 polymorphisms with the risk of lung cancer was also assessed in the present study; however, we failed to show a significant association between this polymorphism and the overall risk of lung cancer. But an elevated lung cancer risk associated with *FASL* rs763110 variant was observed, although modest, in Asian population but not in Caucasian population, indicating the possible contribution of ethnicity variation to the association between *FASL* rs763110 polymorphisms with lung cancer risk. However, this association should be further

verified with high-quality and homogeneous studies in light of the obvious heterogeneity in several genetic models.

In spite of the powerful approach, several limitations of the study remain to be taken into consideration. First, the included studies were all reported in English and Chinese; some other studies in other languages satisfying the inclusion criteria would have been inevitably omitted. Second, our results are based on unadjusted estimates; some important compounding factors such as smoking, age, and occupation, which may significantly impact the risk of lung cancer, were not considered due to lack of original data. Third, the significance of the studied polymorphisms in different subtypes of lung cancer may be inconsistent; however, we are unable to perform subgroup analysis by subtype due to the limited information because the subtypes of lung cancer in most studies were not clearly clarified.

Conclusion

In summary, the meta-analysis further indicated that *FAS* rs2234767 polymorphism was significantly associated with an increased risk of lung cancer and *FASL* rs763110 polymorphism may not contribute to susceptibility to lung cancer other than in Asian population; however, it remains to be further verified considering the modesties of the association and the heterogeneity presented. A definite conclusion with more confidence should be drawn with more high-quality and -uniformity case-control studies in different ethnicities in the future. Nevertheless, these findings may raise the public awareness on the role of concerned polymorphisms in the development of lung cancer, the detection of which would certainly be one of the most promising strategies in preventing cancer by identifying the possible susceptible populations.

Disclosure

The authors report no conflicts of interest in this work.

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