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Original Article

Vascular endothelial growth factor polymorphisms and lung cancer risk

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Abstract: The VEGF polymorphisms has been implicated in the susceptibility to lung cancer, but the results are not conclusive. The aim of this study is to investigate the association between the VEGF polymorphisms and the risk of lung cancer by meta-analysis. We searched PubMed, Embase, CNKI and Wanfang databases. A total of 7 case-control studies were included in this meta-analysis. We found that VEGF rs833061 polymorphism showed no significant association with lung cancer risk. Subgroup analysis on race suggested that CC genotype was significantly associated with lung cancer risk in Asian population. We found that VEGF rs699947 polymorphism showed significant association with lung cancer risk. Subgroup analysis on race showed that VEGF rs699947 polymorphism increased lung cancer risk in Asians. In conclusion, this meta-analysis suggested that the VEGF rs699947 is associated with increased risk of lung cancer.

Keywords: Lung cancer, VEGF, meta-analysis

Introduction

Lung cancer is a major public health problem all over the world. In 2014, there were an estimated 224,210 new cases with lung and bronchus cancer in the United States, in addition, the estimated deaths from lung cancer were 159,260 [1]. On top of that, more than 80% of lung cancer cases are of non-small cell lung cancer (NSCLC) [2] and it was estimated 51% of patients present with advanced disease at the time of diagnosis [3]. Although much progress had been made in optimizing the treatment of NSCLC (including multidisciplinary therapy, targeted therapy and etc), the 5-year overall survival rate remained about 15% of all stages [1]. Therefore it is important to search for new therapies that will improve the current overall treatment in battling against NSCLC.

Vascular endothelial growth factor (VEGF) is a key regulatory factor in angiogenesis and vascular permeability in both physiological and pathological states [4]. Along with fibroblast growth factors, transforming growth factors, tumor necrosis factor, interleukin-8, and various angiopoietins, VEGFs are potent inducers of the angiogenic switch. This switch is characterized by a sequence of steps beginning with vessel dilation and the detachment of pericytes from preexisting vessels followed by angiogenic sprouting and the proliferation of endothelial cells, new vessel formation, and recruitment of perivascular cells [5].

Several studies have reported the association between the VEGF polymorphisms with lung cancer risk [6-12], but the results were inconclusive. Some studies reported that the polymorphisms were associated with increased risk of lung cancer, while the others reported different results. Meta-analysis is a useful method for investigating the risk factors of genetic diseases, because it uses a quantitative approach to combine the results from different studies with the same topic, and can provide more reliable conclusions. Thus, we performed this meta-analysis.

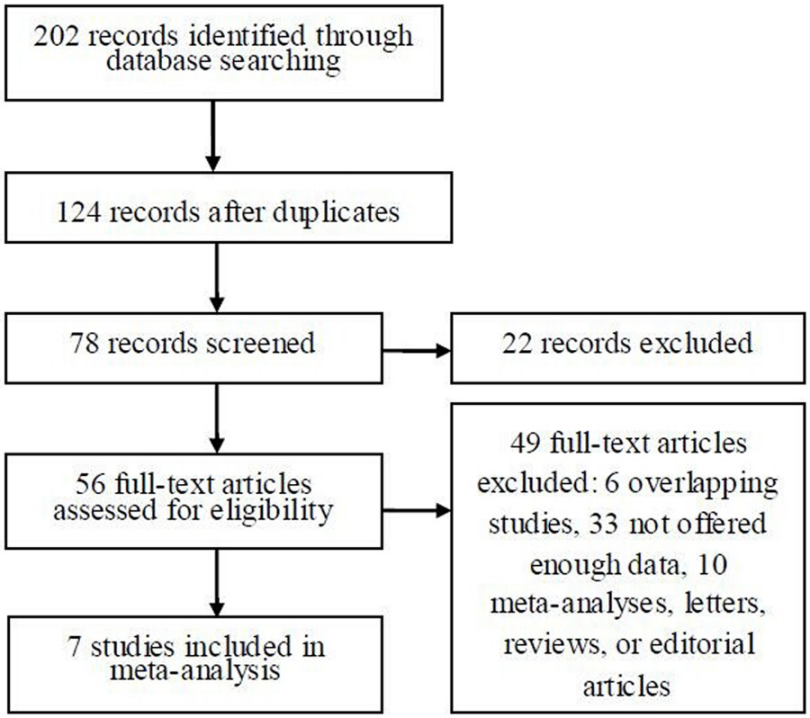

Figure 1. Flow of study identification, inclusion, and exclusion.

Methods

Publication search and inclusion

A systematic literature search in Pubmed database, Embase database, Wanfang database and CNKI database were carried out to identify studies involving the association between lung cancer risk and VEGF polymorphisms on Oct 9th, 2014. The search terms were as follows: "lung cancer" or "lung neoplasms" or "lung tumor" in combination with 'polymorphism or variant or mutation' and in combination with 'VEGF' or vascular endothelial growth factor. Inclusion criteria were defined as follows: (a) studies evaluated the association between VEGF and lung cancer risk; (b) the design had to be a case-control study based on unrelated individuals; (c) sufficient data (genotype distributions for cases and controls) was available to estimate an odds ratio (OR) with its 95% CI; (d) genotype distributions in control group should be consistent with HWE. Exclusion criteria were defined as follows: (a) duplicate of previous publication; (b) based on incomplete data; (c) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Two reviewers collected the data and reached a consensus on all items. The following items were extracted from each study if available: first author, year of publication, country of origin, ethnicity, sample size, and genotype number in cases and controls.

Statistical analysis

The strength of the association between the VEGF polymorphisms and the risk of lung cancer was measured by OR and 95% CI. OR was analyzed by fixed-effects model or random-effects model according to the results of heterogeneity. Heterogeneity was evaluated by an X^2 based Q statistic and was considered statistically significant when $P<0.10$. When the *P* value was >0.10, the pooled OR was calculated by the fixed effects model, otherwise, the random-effects model was used. The significance of the pooled OR was determined by the Z-test and was considered statistically when the *P* value was less than 0.05. To evaluate the ethnicity-specific effects, subgroup analyses by ethnic groups were performed. Publication bias was analyzed by Begg's funnel plots and Egger's test. Sensitivity analysis was performed by sequentially excluding individual study to assess the stability of the results. All statistical tests were performed using the Revman 4.2 and STATA 10.0 software.

Results

Studies characteristics

The flow chart in **Figure 1** summarizes this literature review process. A total of 7 case-control studies were included in this meta-analysis [6-12]. One study reported two polymorphisms. There were 5 studies of Asian population and 2 studies of Caucasian population. Four studies

Table 1. Characteristics of included studies

Study	Country	Race	Polymorphism	Case	Control
de Mello 2013 [6]	Portugal	Caucasian	rs833061, rs699947	144	144
Lee 2005 [7]	Korea	Asian	rs833061	432	432
Sun 2013 [8]	China	Asian	rs833061	126	160
Zhai 2008 [9]	USA	Caucasian	rs833061	1900	1458
Deng 2014 [10]	China	Asian	rs699947	65	110
Li 2012 [11]	China	Asian	rs699947	150	150
Liang 2009 [12]	China	Asian	rs699947	171	172

Table 2. Genotype distribution of cases and controls

	Case			Control		
	CC	CT	TT	CC	CT	TT
rs833061						
de Mello 2013	28	79	37	31	72	41
Lee 2005	18	184	228	27	168	237
Sun 2013	22	43	61	38	69	53
Zhai 2008	439	922	539	342	694	422
	CC	CA	AA	CC	CA	AA
rs699947						
de Mello 2013	43	75	26	44	73	27
Deng 2014	26	33	6	62	41	7
Li 2012	93	45	12	98	49	3
Liang 2009	129	28	14	112	56	4

assessed the association between *VEGF*, rs699947 polymorphism and lung cancer risk, respectively. The characteristics of each case-control study are listed in **Table 1**. The genotype numbers were showed in **Table 2**.

Results of meta-analysis

We found that VEGF rs833061 polymorphism showed no significant association with lung cancer risk (T vs. C: OR=1.07, 95% CI 0.91-1.26, P<0.41; TT vs. CC: OR=1.08, 95% CI 0.91-1.27, P=0.40; TT vs. TC: OR=1.01, 95% CI 0.79-1.29, P=0.95; (TT+TC) vs. CC: OR=1.08, 95% CI 0.93-1.24, P=0.99; TT vs. (TC+CC): OR=1.05, 95% CI 0.82-1.35, P=0.67). Subgroup analysis on race suggested that CC genotype was significantly associated with lung cancer risk in Asian population (TT vs. CC: OR=1.69, 95% CI 1.08-2.63, P=0.02). We found that VEGF rs699947 polymorphism showed significant association with lung cancer risk (A vs. C: OR=1.11, 95% CI 0.92-1.35, P=0.27; AA vs. CC: OR=1.76, 95% CI 1.10-2.81, P=0.02; AA vs. AC: OR=2.17, 95% CI 0.78-6.01, P=0.14; (AA+AC) vs. CC: OR=1.06, 95% CI 0.68-1.65, P=0.80; AA vs. (AC+CC): OR=1.94, 95% CI 0.89-4.25, P=0.10). Subgroup analysis on race showed that VEGF rs699947 polymorphism increased lung cancer risk in Asians (A vs. C: OR=1.20, 95% CI 0.84-1.72, P=0.32; AA vs. CC: OR=3.00, 95% CI 1.51-5.95, P=0.002; AA vs. AC: OR=3.15, 95% CI 1.00-9.91, P=0.05; AA vs. (AC+CC): OR=2.92, 95% CI 1.51-5.65, P=0.001). The results were listed in the **Table 3**.

After sequentially excluding each case-control study, statistically similar results were obtained, suggesting the stability of this meta-analysis (data not shown). The Egger's test was performed to provide statistical evidence of publication bias. The results indicated a lack of publication bias (P=0.56 and P=0.12).

Discussion

In this meta-analysis study, we analyzed *VEGF* polymorphisms for lung cancer susceptibility. Our results suggested that VEGF rs699947 polymorphism was significantly associated with the risk of lung cancer, suggesting that VEGF rs699947 polymorphism might be involved in pathogenesis of lung cancer. We demonstrated that VEGF rs833061 polymorphism was associated with an increased risk of lung cancer in Asians. Patients carrying those genotypes had a higher risk for lung cancer than those carrying the other genotypes. However, further studies are warranted to elucidate how these genotypes contribute to lung cancer.

A growing number of polymorphisms have been found to be associated with NSCLC susceptibility. For example, a meta-analysis of published studies suggested that the MPO polymorphisms may contribute to the susceptibility of lung cancer [13]. A case-control study has

Table 3. Results of this meta-analysis

	T vs. C			TT vs. CC			TT vs. TC			TT+TC vs. CC			TT vs. TC+CC		
	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
rs833061															
Overall	1.07 (0.91, 1.26)	0.41	54%	1.08 (0.91, 1.27)	0.40	41%	1.01 (0.79, 1.29)	0.95	54%	1.08 (0.93, 1.24)	0.99	0%	1.05 (0.82, 1.35)	0.67	60%
Asian	1.14 (0.95, 1.37)	0.15	79%	1.69 (1.08, 2.63)	0.02	0%	1.23 (0.60, 2.54)	0.58	83%	1.50 (0.98, 2.29)	0.06	0%	1.29 (0.64, 2.59)	0.48	85%
Caucasian	0.99 (0.91, 1.09)	0.91	0%	1.00 (0.83, 1.20)	0.96	0%	0.95 (0.81, 1.11)	0.51	0%	1.03 (0.88, 1.20)	0.73	0%	0.96 (0.83, 1.11)	0.62	0%
	A vs. C			AA vs. CC			AA vs. AC			(AA+AC) vs.CC			AA vs. (AC+CC)		
	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2	OR (95% CI)	P	I^2
rs699947															
Overall	1.11 (0.92, 1.35)	0.27	41%	1.76 (1.10, 2.81)	0.02	45%	2.17 (0.78, 6.01)	0.14	73%	1.06 (0.68, 1.65)	0.8	67%	1.94 (0.89, 4.25)	0.10	59%
Asian	1.20 (0.84, 1.72)	0.32	55%	3.00 (1.51, 5.95)	0.002	0%	3.15 (1.00, 9.91)	0.05	61%	1.08 (0.57, 2.04)	0.81	78%	2.92 (1.51, 5.65)	0.001	0%

shown that c.1471G>A genetic polymorphism in XRCC1 gene were associated with a risk of lung cancer [14]. A meta-analysis which included 14494 subjects with suggested that EPHX1 A139G polymorphism was associated with lung cancer risk [15].

Ma et al. constructed a plasmid encoding VEGF shRNA to knock down VEGF both in vitro and in vivo [16]. They demonstrated synergistic antitumor activity of combined VEGF shRNA expressing plasmids and low-dose DDP with no overt toxicity, suggesting potential applications of the combined approach in the treatment of lung cancer.

Some limitations should be acknowledged when explaining the results. Firstly, only published data which were included by the selected databases were included; it is possible that some relevant published studies or unpublished studies which had null results were missed, which might bias the results, while our statistical tests may not have totally shown it. Secondly, all case-control studies were from Asians and Caucasians; thus, the results may be applicable to these ethnic populations only. Thirdly, data were not stratified by other factors such as gender status, because sufficient information could not be extracted from the original studies.

In conclusion, this meta-analysis suggested that the VEGF rs699947 is associated with increased risk of lung cancer. More studies with a larger group of populations should be performed to analyze these associations.

Disclosure of conflict of interest

None.

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