Relationship between vascular endothelial growth factor -2578C > a gene polymorphism and lung cancer risk: a meta-analysis

Hui-liu Zhao†, Jia-hua Yu†, Ling-sha Huang†, Pei-zhang Li, Ming Lao, Bo Zhu* and Chao Ou*

Abstract

Background: Several reports were published on the relationship between the vascular endothelial growth factor (VEGF) -2578C > A gene polymorphism and lung cancer risk; however, the results are debatable. This meta-analysis was conducted to assess the relationship between VEGF -2578C > A gene polymorphism and lung cancer risk.

Methods: The associated literatures were identified on the 1st of September 2018 from CBM-disc (China Biological Medicine Database) and PubMed.

Result: A total of 14 reports were recruited into our meta-analysis to assess the association between VEGF -2578C > A allele / CC genotype and lung cancer susceptibility. There was a marked association between VEGF -2578C > A A allele / CC genotype and lung cancer risk in overall and Asian populations (overall populations: A allele: OR = 1.26, 95% CI: 1.08–1.46, P = 0.003; CC genotype: OR = 0.72, 95% CI: 0.54–0.95, P = 0.02; Asians: A allele: OR = 1.33, 95% CI: 1.15–1.55, P = 0.0002; CC genotype: OR = 0.68, 95% CI: 0.50–0.93, P = 0.01). However, VEGF -2578C > A gene polymorphism was not associated with the risk of lung cancer in Caucasians.

Conclusion: VEGF -2578C > A A allele / CC genotype is associated with the lung cancer susceptibility in Asians and in overall populations.

Keywords: Lung cancer, Vascular endothelial growth factor (VEGF), -2578C > A, Gene polymorphism, Meta-analysis

Background

Lung cancer is a cancer with less than 15% survival rate and is a leading cause of patients’ death worldwide [1–4]. It is a complex process requiring the acquisition of genetic mutations which confer the malignant phenotype as well as epigenetic alteration s[5]. Unfortunately, the number of lung cancer related deaths is rapidly increasing each year, and the early diagnosis is crucial to increase the curability chance of patients.

Some genes were found to be associated with the risk of lung cancer [6–8]. The vascular endothelial growth factor (VEGF), is one of the key growth factors, that regulates vascular development and angiogenesis and plays an important role in the growth and progression of human cancers, including lung carcinoma [9, 10]. The current evidence indicated that VEGF gene polymorphism is associated with the susceptibility of some cancers [11]. There is lack of good diagnostic methods that predict the risk of lung cancer, and which etiology is complicated and not clear.

Several reports were published on the relationship between VEGF -2578C > A gene polymorphism and lung cancer susceptibility. We conducted this meta-analysis to evaluate the association between VEGF -2578C > A gene polymorphism and the risk of lung cancer.

Methods

Search strategy

The relevant literature was searched and included using the electronic databases of CBM-disc (China Biological
In this meta-analysis, VEGF -2578C > A A allele, and CC genotype were associated with lung cancer risk; however, the AA genotype was not found in overall populations (A allele: OR = 1.26, 95% CI: 1.08–1.46, P = 0.003, Fig. 2; AA genotype: OR = 1.29, 95% CI: 0.89–1.89, P = 0.18, Fig. 3; CC genotype: OR = 0.72, 95% CI: 0.54–0.95, P = 0.02, Fig. 4; Table 2).

Relationship between VEGF -2578C > a gene polymorphism and lung cancer susceptibility in Asians
In this meta-analysis, VEGF -2578C > A A allele, and CC genotype were associated with the risk of lung cancer in Asians; however, the AA genotype was not (A allele: OR = 1.33, 95% CI: 1.15–1.55, P = 0.0002; AA genotype: OR = 1.45, 95% CI: 0.92–2.28, P = 0.11; CC genotype: OR = 0.68, 95% CI: 0.50–0.93, P = 0.01; Table 2).

Relationship between VEGF -2578C > a gene polymorphism and lung cancer susceptibility in Caucasians
In this meta-analysis, VEGF -2578C > A gene polymorphism was not associated with the susceptibility of lung cancer in Caucasians (A allele: OR = 0.90, 95% CI: 0.74–1.11, P = 0.33; AA genotype: OR = 0.78, 95% CI: 0.55–1.12, P = 0.18; CC genotype: OR = 1.06, 95% CI: 0.76–1.47, P = 0.74; Table 2).

Sensitivity analysis
The sensitivity analysis for the association between VEGF -2578C > A gene polymorphism and lung cancer susceptibility was also performed by the source of the controls (population-based vs hospital-based). In the sensitivity analysis using population-based, the VEGF -2578C > A A allele and CC genotype were associated with lung cancer risk; however, the AA genotype was not (Table 2). In the sensitivity analysis using the hospital-based control, VEGF -2578C > A gene polymorphism was not associated with lung cancer susceptibility (Table 2).

Evaluation of publication bias
No publication bias was found for the overall populations (Begg P = 0.807, funnel plot was presented in Fig. 5;
Table 1  General characteristics of the included studies in this meta-analysis for VEGF -2578C > A gene polymorphism with lung cancer risk

| First author, year /District | Country | Ethnicity | Control source | Detecting methods | Case AA | CA | CC | Total | Control AA | CA | CC | Total |
|-----------------------------|---------|-----------|----------------|------------------|--------|----|----|-------|----------|----|----|-------|
| Wang 2008                   | China   | Asian     | Population-base | RFLP-PCR         | 23     | 127| 227| 377   | 22       | 107| 4   | 116   |
| Wang 2009                   | China   | Asian     | Population-base | RFLP-PCR         | 14     | 28 | 129| 171   | 4        | 56 | 1    | 117   |
| Liu 2010                    | China   | Asian     | Population-base | RFLP-PCR         | 13     | 74 | 85 | 172   | 7        | 65 | 4   | 171   |
| Liu 2010                    | China   | Asian     | Population-base | RFLP-PCR         | 12     | 25 | 113| 150   | 3        | 49 | 1   | 153   |
| Yuan 2011                   | China   | Asian     | Population-base | RFLP-PCR         | 18     | 108| 125| 251   | 8        | 93 | 4   | 154   |
| Li 2010                     | China   | Asian     | Population-base | RFLP-PCR         | 12     | 35 | 108| 155   | 3        | 33 | 3   | 115   |
| de Mello 2013               | Portugal | Caucasian | Population-base | RFLP-PCR         | 26     | 75 | 43 | 144   | 74       | 73 | 4   | 144   |
| Geng 2013                   | China   | Asian     | Population-base | RFLP-PCR         | 16     | 118| 126| 260   | 9        | 89 | 4   | 162   |
| Wang 2014                   | China   | Asian     | Population-base | RFLP-PCR         | 21     | 104| 175| 300   | 16       | 75 | 6   | 203   |
| Deng 2014                   | China   | Asian     | Population-base | RFLP-PCR         | 6      | 33 | 26 | 65    | 7        | 41 | 1   | 64    |
| Liu 2015                    | China   | Asian     | Population-base | RFLP-PCR         | 20     | 164| 230| 414   | 23       | 138| 17 | 354   |
| Krupnova 2015               | Belarus | Caucasian | Hospital-based  | RFLP-PCR         | 31     | 90 | 41 | 162   | 91       | 186| 9   | 360   |
| Naykoo 2017                 | India   | Asian     | Population-base | RFLP-PCR         | 5      | 170| 24 | 199   | 55       | 145| 20 | 401   |

RFLP-PCR  Restriction fragment length polymorphism polymerase chain reaction, VEGF Vascular endothelial growth factor

Fig. 1  Flow chart of the study search and selection
Egger \( P = 0.505 \), and Asians (Begg \( P = 0.938 \), Egger \( P = 0.827 \)).

**Discussion**

VEGF is regarded as an important factor taking part in the inactivation of pro-carcinogens, which contribute to cancer. In this study, we included 14 studies into our meta-analysis. We investigated whether the VEGF -2578C > A gene polymorphism is a valuable indicator for lung cancer susceptibility, and attempted to draw robust results. In our meta-analysis, we found that there was a marked association between VEGF -2578C > A A allele / CC genotype and lung cancer risk in overall and Asian populations. However, VEGF -2578C > A gene polymorphism was not associated with the risk of lung cancer in Caucasians. The sample size of the included studies was larger than that of other meta-analyses, and the results on the association between VEGF -2578C > A gene polymorphism and lung cancer risk might be more robust. The
pooled OR for A allele was 1.26 for overall populations and 1.33 for Asians; while, for the CC genotype the odds ratio was less than 1. It indicated that high CC genotype was a protective genotype (good genotype); however, A allele was a negative gene allele. The AA genotype was not associated with lung cancer risk, which might due to the small sample size of included studies, and therefore, more studies should be conducted to confirm this result. Nevertheless, the results for the Caucasian population were less robust, also due to the small number of included studies. Additional studies should be performed to confirm this result.

In the sensitivity analysis by the controls source, we found that, in the sensitivity analysis using the population-based control, the VEGF -2578C > A A
allele / CC genotype was associated with lung cancer susceptibility. However, in the sensitivity analysis using the hospital-based control, VEGF -2578C > A gene polymorphism was not associated with lung cancer susceptibility.

Publication bias was also analyzed, and we found that there was no publication bias for overall and Asians populations. This suggests that the conclusion from our meta-analysis was robust. However, additional well-designed studies should be performed to confirm this result in the future.

In a previous study, Deng et al.[15] recruited four reports into their study using a meta-analysis method, and showed that the CC genotype was associated with lung cancer; however, A allele and AA genotype were not. Chen et al.[28] also included four studies into their meta-analysis, and obtained a similar result. Lin et al.[29] included seven studies into their meta-analysis, and reported that the A allele was associated with lung cancer, but the AA and CC genotypes were not. Our meta-analysis indicated that there was an association between A allele, CC genotype and lung cancer risk in overall and Asian populations. The sample size in our meta-analysis was larger than the previous meta-analyses, and the outcome in our meta-analysis might be more robust.

In this study, we found that the CC genotype is the dominant genotype associated with lung cancer risk. We speculated that the CC genotype might be associated with high levels of VEGF, and that the increased VEGF was associated with lung cancer risk.

In the test of publication bias, two points were located on or out of scope, indicating publication bias. We deleted the two studies and conducted a further meta-analysis, and found the results were similar.

Conclusions

The results in our study support that VEGF -2578C > A allele / CC genotype was associated with lung cancer susceptibility in overall and Asian populations. However, additional well-designed investigations of this association are required to confirm these results.

Abbreviations

VEGF: Vascular endothelial growth factor

Acknowledgements

Not applicable.

Authors’ contributions

BZ and CO was in charge of conceived and designed the study. HLZ, JHY and LSH were responsible for collection of data and performing the statistical analysis and manuscript preparation. PZL and ML were responsible for checking the data. All authors were responsible for drafting the manuscript, read and approved the final version.

Funding

This work was supported by grant from Natural Science Foundation of Guangxi Province (2017GXNSFAA198015) or Medical Health Technology Development and Application Foundation of Guangxi Province (S2017104). The funding bodies played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
References

1. Yang J, Fang Z, Wu J, Yin X, Fang Y, Zhao F, Zhu S, Li Y. Construction and application of a lung cancer stem cell model: antitumor drug screening and molecular mechanism of the inhibitory effects of sanguinarine. Tumour Biol. 2016.

2. Gao H, Niu Z, Zhang W, Wu H, Xie Y, Yang Z, Li A, Jia Z, Zhang X. TNFSF15 promoter polymorphisms increase the susceptibility to small cell lung cancer: a case-control study. BMC Med Genet. 2019;20(1):129.

3. Li L, Guo G, Zhang H, Zhou B, Bai L, Chen H, Zhao Y, Yan Y. Association between H19 SNP rs2177272 and lung cancer risk in a Chinese population: a case control study. BMC Med Genet. 2018;19(1):136.

4. Regzedmaa O, Zhang H, Liu H, Chen J. Immune checkpoint inhibitors for small cell lung cancer: opportunities and challenges. OncoTargets Ther. 2019;12:4605–20.

5. Bhat IA, Pandith AA, Bhat BA, Naykoo NA, Qasim I, Rasool R, Aziz SA, Shah SA. Lack of association of a common polymorphism in the 3′-UTR of interleukin 8 with non small cell lung cancer in Kashmir. Asian Pac J Cancer Prev : APJCP. 2013;14(7):4403–4.

6. Liu M, Zhang H, Li Y, Wang R, Li Y, Zhang H, Ren D, Liu H, Kang C, Chen J. HOTAIR, a long noncoding RNA, is a marker of abnormal cell cycle regulation in lung cancer. Cancer Sci. 2018;109(9):2717–33.

7. Li Y, Zhang H, Gong H, Yuan Y, Li Y, Wang C, Li W, Zhang Z, Liu M. Liu H et al: miR-182 suppresses invadopodia formation and metastasis in non-small cell lung cancer by targeting cortactin gene. J Exp Clin Cancer Res : CR. 2018;37(1):141.

8. Yin Z, Cui Z, Li H, Li J, Zhou B. Polymorphisms in the H19 gene and the risk of lung cancer among female never smokers in Shenyang, China. BMC Cancer. 2018;18(1):893.

9. Holzer TR, Fulford AD, Reising LO, Nedderman DM, Zhang X, Benjamin LE, Schade AE, Nasir A. Profiling of vascular endothelial growth factor receptor heterogeneity identifies protein expression-defined subclasses of human non-small cell lung carcinoma. Anticancer Res. 2016;36(7):3277–88.

10. Hu K, Olsen BR. The roles of vascular endothelial growth factor in bone repair and regeneration. Bone. 2016;91:30–8.

11. Qasim I, Bhat IA, Masoodi KZ, Shah ZA. Role of +405G>C and +936C>T polymorphisms of the vascular endothelial growth factor gene and risk of esophageal cancer in the Kashmiri population. Asian Pac J Cancer Prev : APJCP. 2015;16(1):97–101.

12. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994;50(4):1088–101.

13. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical method. BMJ. 1997;315(7109):629–34.

14. de Mello RA, Ferreira M, Soares-Pires F, Costa S, Cunha J, Oliveira P, Hespanhol V, Reis RM. The impact of polymorphic variations in the 5p15, 6p12, 6p21 and 15q25 loci on the risk and prognosis of portuguese patients with non-small cell lung cancer. PLoS One. 2013;8(9):e72373.

15. Deng ZC, Cao C, Yu YM, Ma HY, Ye M. Vascular endothelial growth factor -634G/C and vascular endothelial growth factor -2578C/A polymorphisms and lung cancer risk: a case-control study and meta-analysis. Tumour Biol. 2014;35(3):1805–11.

16. Geng H. Study on the association of VEGF genetic polymorphisms with primary lung Cancer. Hebei Medical University. 2013.

17. Kroupnova EV, Shapetska MN, Mikhalenko EP, Chebotaryova NV, Shchayuk AN, Pisarchik SN, Prokhorov AV. Role of vascular endothelial growth factor in nonsmall cell lung cancer pathogenesis. Exp Oncol. 2015;37(3):213–7.

18. Li Y. Relationship between genetic polymorphism of VEGF, TGF-a gene and susceptibility to lung cancer in an ethnic Han group of North China. Exp Ther Med. 2012;3(4):563–6.

19. Liang J, Yu X, Liu X, Sun D, Liu H, Hu W, Qu A, Li Y. Vascular endothelial growth factor polymorphisms and risk of lung cancer. Chin-Ger J Clin Oncol. 2009;8(5):269–72.

20. Liu C, Zhou X, Gao F, Qi Z, Zhang Z, Guo Y. Correlation of genetic polymorphism of vascular endothelial growth factor gene with susceptibility to lung cancer. Cancer Gene Ther. 2015;22(6):312–6.

21. Liu D. Study of the association of VEGF genetic polymorphism with the risk of primary lung Cancer. Hebei Med Univ. 2010.

22. Wang T, Wang R, Zeng H. Vascular endothelial growth factor gene polymorphisms and risk of lung cancer. Acad Conf. 2008.

23. Wang T, Wang W, Duan Y, Li Y, Zeng H, Gao F, Yao J, Qi Z, Wang R. Correlation study on VEGF -2578C > a gene polymorphism with lung cancer susceptibility. Acad Conf. 2009.

24. Wang T, Wang W, Zeng H, Gao F, Zhang Z, Yao J, Guo Y, Qi Z, Wang R. Polymorphisms of VEGF gene and risk of lung cancer. Chin J Mod Med. 2014;24(7):11–4.

25. Yuan J. Study on the association of VEGF genetic polymorphisms with primary Lung Cancer. Hebei Medical University. 2011.

26. Naykoo N, Dil-Afroz, Rasool R, Shah S, Kharangar a, Bhat I, Siddiqi M, Shah Z. Single nucleotide polymorphisms, haplotype association and tumour expression of the vascular endothelial growth factor (VEGF) gene with lung carcinoma. Gene. 2017;608:95–102.

27. Chen Q, Zhou Z, Shan L, Hua Y, Zeng H, Liu P, Cai Z. Association of the vascular endothelial growth factor -2578C/A polymorphism with cancer risk: a meta-analysis update. Biomed Rep. 2014;6(1):23–30.

28. Lin L, Cao K, Chen W, Pan X, Zhao H. Four common vascular endothelial growth factor polymorphisms (−2578C>A, −460C>T, +936C>T, and +405G>C) in susceptibility to lung cancer: a meta-analysis. PLoS One. 2013;8(10):e75123.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.