RESEARCH ARTICLE

Association of the miRNA146a rs2910164 C>G Polymorphism with Head and Neck Cancer Risk: A Meta-analysis

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Abstract

Objective: To investigate any association of the miRNA146a rs2910164 C>G polymorphism with head and neck cancer risk. Materials and Methods: The Medline, PubMed, PUBMED, EMBASE, Web of Science, WanFang and CNKI databases were searched and a meta-analysis was conducted using RevMan 5.2 software. Results: After searching and evaluating the literature, a total seven papers involving 2,766 patients with head and neck cancer and 6,603 healthy controls were included into this meta analysis. The results showed that there were no significant differences between patients and healthy controls overall for the miRNA rs2910164 C>G gene polymorphism (dominant model:OR=0.78, 95%CI:0.58-1.04, P=0.09; recessive model:OR=0.86, 95%CI:0.67-1.12, P=0.27;GG:CC:OR=0.75, 95%CI:0.52-1.08, P=0.12;GC:CC:OR=0.79, 95%CI:0.60-1.04, P=0.10). However, a significant association of miRNA rs2910164 C>G gene polymorphism with Chinese head and neck cancer risk was noted, limited to the dominant model (OR=0.68, 95%CI:0.50-0.95, P=0.02;GG:CC:OR=0.62, 95%CI:0.42-0.92, P=0.02;GC:CC:OR=0.72, 95%CI:0.520.99, P=0.04). Conclusions: miRNA146a rs2910164 C>G polymorphism is not associated with head and neck cancer risk in general, but tehre may be link in Chinese.

Keywords: Head and neck cancer - miRNA146a rs2910164 C>G - polymorphism - meta analysis - Chinese

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Introduction

MircoRNAs (miRNAs) are small fragment RNAs containing approximately 20-22 nucleotides, which can target specific mRNAs and negatively regulate their translational efficiency and stability. (Bartel 2004) Previous studies revealed that one miRNA could influence expression of several target genes. According to regulating different target RNAs, miRNAs can participate in cellular processes including proliferation, differentiation, and survival (Ambros, 2004).

It has been shown that aberrant expression of miRNAs was related to the etiology, diagnosis and prognosis of many tumors, including head and neck cancer. (Liu et al., 2010; Lung et al., 2013) Single nucleotide polymorphism (SNP) is a variation of DNA sequence that occurs when nucleotides (included A, T, C or G) change in at least 1% of a certain population. The epidemiologic evidence shows that miRNA genetic variations are associated with progression to head and neck cancer. (Orsós et al., 2013)miR-146a function as a tumor suppressor in most cases. (Lu et al., 2005). The miR-146 family consists of two miRNAs, miR-146a and miR-146b. (Labbaye et al., 2012) To obtain adequate power for evaluating the potential association, increased documents investigated the association of miRNA rs2910164 C>G polymorphism with cancer risk. (Wang et al., 2012; Xu et al., 2013; Li et al., 2014) Although lots of published studies shown the relation between miRNA rs2910164 C>G polymorphism with cancer risk, a less knowledge about the head and neck cancer risk is marked.

In here, we investigate the association of miRNA rs2910164 C>G polymorphism with cancer risk by a meta analysis.

Materials and Methods

Study selection

A Medline, PubMed, PUBMED, EMBASE, Web of Science, WanFang, CNKI databases search was performed on all studies between January 2000 and September 2014. The following English keywords were used: "miRNA", "miRNA146a", "neoplasms" or "carcinoma" or "tumor" and "polymorphism". Only studies on human and in English were considered for inclusion. This search was supplemented by manual research and a review of reference lists. We were not blind to author, institutions, journals while we selected trials or extracted the data .

Data extraction and quality assessment

Data were extracted by two independent reviewers using standard forms. The recorded data included first author, year of publication, country or district, tumor type, gene type. All relevant text, tables and figures were

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reviewed for data extraction. Discrepancies between the two reviews were resolved by discussion and consensus. The quality of all selected studies was ranked in accordance with the score of the non-randomized controlled clinical trial quality evaluation standard.

Statistical methods

Related-data from the comparative groups was compared using X^2 test for categorical data, a significant difference was considered when *P* was less than 0.05; the meta-analysis was performed using the Review Manager (RevMan) software, version 5.2.We analyzed dichotomous variables using estimation of odds ratios (OR) with a 95% confidence interval (95%CI). Heterogeneity was evaluated byX^2 and I^2. We considered heterogeneity to be present if the I^2 statistic was >50%, *P*<0.05 was considered significant.

Results

In here, total seven papers involved 2766 patients with head and neck cancer and 6603 healthy control were included into this meta analysis. (Liu et al., 2010; Chu et al., 2012; Hung et al., 2012; Lung et al., 2013; Orsós et al., 2013; Huang et al., 2014; Lin et al., 2014) Among five papers involving Chinese, one was involving American and Hungarians, respectively. Two papers involving oral cancer and nasopharyngeal carcinoma and squamous cell carcinoma, respectively, one involving laryngeal cancer. More detail could be found in Table 1.

No association between miRNA rs2910164 C>G gene polymorphism and tumors

In here, there were 7 documents shown that miRNA rs2910164 C>G gene polymorphism involved in the

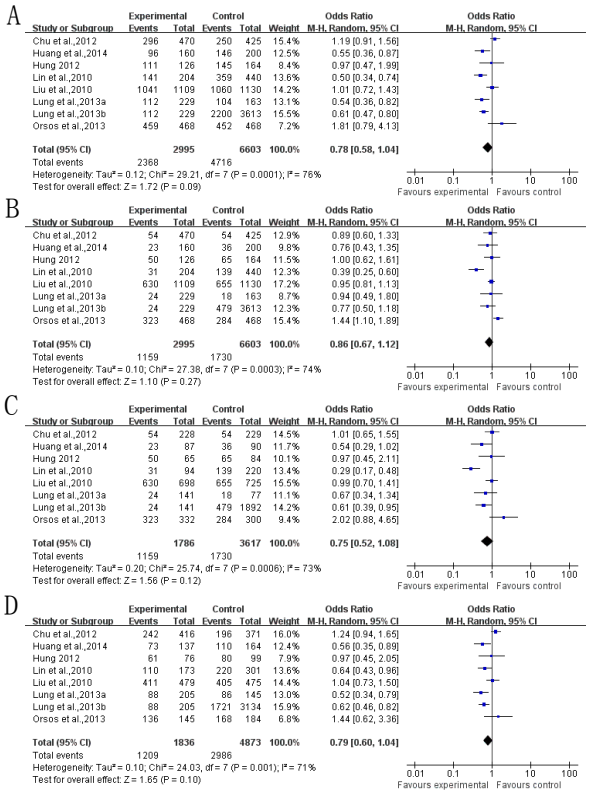

Figure 1. Meta-analysis of the Association between miRNA146a rs2910164 Polymorphism and Susceptibility to Cancer Risk. A) Dominant model. B) Recessive model.C) GG vs CC. D) GC *vs* CC

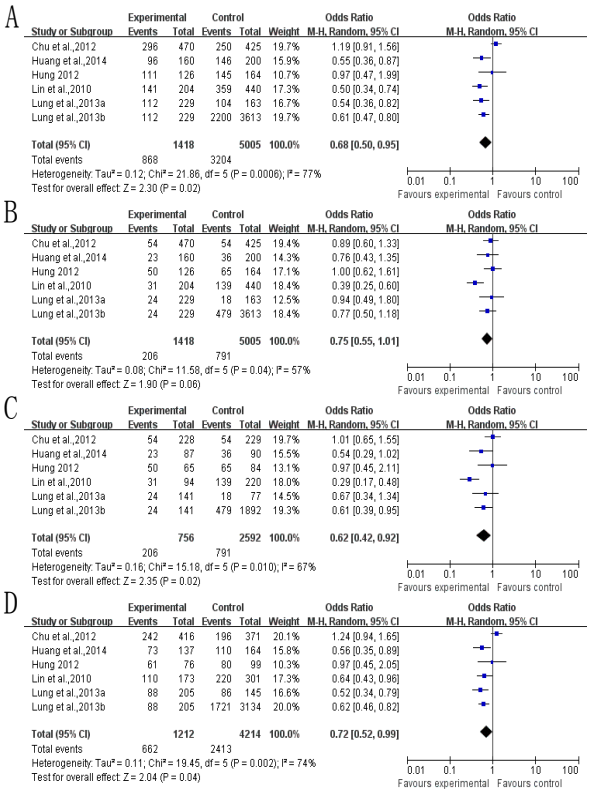

Figure 2. Meta-analysis of the Association between miRNA146a rs2910164 Polymorphism and Susceptibility to Cancer Risk in Chinese. A) Dominant model. B) Recessive model.C) GG *vs* CC. D) GC vs CC

Table 1. Charateristics of Studies Included in the Meta-analysis

Study	Year	Ethnicity	tumor type	Case				Control			
				CC	CG	GG	N	CC	CG	GG	N
Chu	2012	chinese	Oral Cancer	174	242	54	470	175	196	54	425
Huang	2014	chinese	nasopharyngeal carcinoma	64	73	23	160	54	110	36	200
Hung	2012	chinese	oral carcinoma	15	61	50	126	19	80	65	164
lin	2014	chinese	laryngeal cancer	63	110	31	204	81	220	139	440
Liu	2010	American	squamous cell carcinoma	68	411	630	1109	70	405	655	1130
Lung	2013a*	chinese	Nasopharyngeal Carcinoma	117	88	24	229	59	86	18	163
	2013b*			117	88	24	229	1413	1721	479	3613
orsos	2013	Hungarians	squamous cell carcinoma	9	136	323	468	16	168	284	468

* from the same study

risk of cancer in all ethnicity. The meta analysis results shown that there were no significant differences between patients and healthy control on association of miRNA rs2910164 C>G gene polymorphism involved in the risk of cancer. (Dominant model:OR=0.78, 95%CI:0.58-1.04, *P*=0.09; Recessive model:OR=0.86, 95%CI:0.67-1.12, *P*=0.27; GG:CC:OR=0.75, 95%CI:0.52-1.08, *P*=0.12; GC:CC:OR=0.79, 95%CI:0.60-1.04, *P*=0.10)(Figure 1).

Part association between miRNA rs2910164 C>G gene polymorphism and tumors in Chinese

As shown in Figure 2A, C and D, the meta analysis results in the subgroup analysis by ethnicity revealed that there were a significant differences on association of miRNA rs2910164 C>G gene polymorphism with Chinese head and neck cancer risk between case and healthy control. (Dominant model:OR=0.68, 95%CI:0.50-0.95, *P*=0.02; GG:CC:OR=0.62, 95%CI:0.42-0.92, *P*=0.02; GC:CC:OR=0.72, 95%CI:0.520.99, *P*=0.04) However, no differences were found in Recessive model.(OR=0.75, 95%CI:0.55-1.01, *P*=0.06) (Figure 2B)

Discussion

In here, we investigated the association of miRNA rs2910164 C>G gene polymorphism and cancer risk. The meta analysis results shown that there were no significant differences between patients and healthy control on association of miRNA rs2910164 C>G gene polymorphism involved in the cancer risk. However, there was a part association of miRNA rs2910164 C>G gene polymorphism with cancer risk in Chinese.

It is well known that individual susceptibility plays an important role in the development of most cancers. Genes polymorphisms involved in oncogenesis may have accounted for the susceptibility. Therefore, genetic susceptibility, especially single nucleotide polymorphism (SNP), to cancer has been a research focus in scientific community. Many studies have been done for figuring out the role of SNPs present in precursor and mature miRNA and their influences on susceptibility and progression of various cancers. Recent studies have identified that miRNA196 may interact with several transcription factors and involve in cancer development and progression (Li et al., 2010; Chen et al., 2011). Some findings suggest that overexpression of miRNA196 leads to more favorable prognosis and survival in leukemia (Popovic et al., 2009). In addition, miRNA196 is associated with inflammation in specific cancers (Schetter et al., 2009). Furthermore, Christensen et al., reports a polymorphism in the mature sequence of miRNA196a2 in a case-control study (n = 1, 039) of head and neck squamous cell carcinoma (HNSCC) (Christensen et al., 2010). When the authors stratified on tumor site they did not observe a significant association between oral cancer and miRNA196a2, though the effect estimate was protective, similar to the results presented in this study. Although the reason for those discrepancies is not well-known, the different results from the report and the present study may relate to the racial/ethnic difference. In our meta analysis, there was no significant differences on the association of miRNA rs2910164 C>G gene polymorphism with cancer risk, however, no difference between Chinese patients and healthy control on the relation between miRNA rs2910164 C>G gene polymorphism and cancer risk.

The meta analysis shown a significant association between miR-146a(rs2910164) with hepatocellular carcinoma, cervical squamous cell carcinoma and prostate cancer, (Yin et al., 2013) but not with head and neck cancer risk in our result, indicating that miRNA146a rs2910164 polymorphism may play different roles in various human malignancies.

In conclusion, our meta analysis results show that miRNA 146a rs2910164 gene polymorphism more likely contribute to be associated with cancer risk in Chinese. Future well-designed and larger population studies are of great value to confirm these findings.

References

Ambros V (2004). The functions of animal microRNAs. *Nature*, **431**, 350-5

Bartel DP (2004). MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*, **116**, 281-97.

Chen C, Zhang Y, Zhang L, et al (2011). MicroRNA-196:critical roles and clinical applications in development and cancer. *J Cell Mol Med*, **15**, 14-23.

Christensen BC, Avissar-Whiting M, Ouellet LG, et al (2010). Mature microRNA sequence polymorphism in MIR196A2 is associated with risk and prognosis of head and neck cancer. *Clin Cancer Res*, **16**, 3713-20.

Chu YH, Tzeng SL, Lin CW, et al (2012). Impacts of microRNA gene polymorphisms on the susceptibility of environmental factors leading to carcinogenesis in oral cancer. *PLoS One*, **7**, 39777.

Huang GL, Chen ML, Li YZ, et al (2014). ssociation of miR-146a gene polymorphism with risk of nasopharyngeal carcinoma in the central-southern Chinese population. *J Hum Genet*, **59**, 141-4.

Hung PS, Chang KW, Kao SY, et al (2012). Association between the rs2910164 polymorphism in pre-mir-146a and oral carcinoma progression. *Oral Oncol*, **48**, 404-8.

Labbaye C and Testa U(2012) The emerging role of MIR-146A in the control of hematopoiesis, immune function and cancer. *J Hematol Oncol*, **27**, 13.

Lin D, Dong WD, Lu MP, et al (2014). The association between rs2910164 C>G polymorphism in pre-microRNA-146a and laryngeal cancer in Jiangsu Han population. *J Otolaryngol Ophthal Shandong Univ*, **28**, 46-50.

Liu Z, Li G, Wei S, et al (2010). Genetic variants in selected pre-microRNA genes and the risk of squamous cell carcinoma of the head and neck. *Cancer*, **116**, 4753-60.

Li YJ, Zhang ZY, Mao YY, et al (2014). A genetic variant in miR-146a modifies digestive system cancer risk: a meta-analysis. *Asian Pac J Cancer Prev*, **15**, 145-50.

Li Y, Zhang M, Chen H, et al (2010). Ratio of miR-196s to HOXC8 messenger RNA correlates with breast cancer cell migration and metastasis. *Cancer Res*, **70**, 7894-904.

Lu J, Getz G, Miska EA, et al (2005). MicroRNA expression profiles classify human cancers. *Nature*, **435**, 834-8

Lung RW, Wang X, Tong JH, et al (2013). A single nucleotide polymorphism in microRNA-146a is associated with the risk for nasopharyngeal carcinoma. *Mol Carcinog*, **52**, 28-38.

Orsós Z, Szanyi I, Csejtei A, et al (2013). Association of pre-miR-146a rs2910164 polymorphism with the risk of head and neck cancer. *Anticancer Res*, **33**, 341-6.

Popovic R, Riesbeck LE, Velu CS, et al (2009). Regulation of mir-196b by MLL and its overexpression by MLL fusions contributes to immortalization. *Blood*, **113**, 3314-22.

Schetter AJ, Nguyen GH, Bowman ED, et al (2009). Association of inflammation-related and microRNA gene expression with cancer-specific mortality of colon adenocarcinoma. *Clin Cancer Res*, **15**, 5878-87.

Wang J, Bi J, Liu X, et al (2012). Has-miR-146a polymorphism (rs2910164) and cancer risk: a meta-analysis of 19 case-control studies. *Mol Biol Rep*, **39**, 4571-9.

Xu Y, Li L, Xiang X, et al (2013). Three common functional polymorphisms in microRNA encoding genes in the susceptibility to hepatocellular carcinoma: a systematic review and meta-analysis. *Gene*, **527**, 584-93.

Yin ZH, Yan L, Cui Z, et al (2013). Effects of common polymorphisms rs2910164 in miR-146a and rs3746444 in miR-499 on cancer susceptibility: a meta-analysis. *Mol Biol Rep*, **40**, 3003-13.