

Original Article

The miR-149 rs2292832 T/C polymorphism may decrease digestive cancer susceptibility: an updated meta-analysis

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Received June 18, 2015; Accepted September 7, 2015; Epub September 15, 2015; Published September 30, 2015

Abstract: MicroRNAs (miRNAs) are a class of short non-coding, single stranded RNAs, which perform post-transcriptional regulatory functions as tumor suppressors or oncogenes. Single nucleotide polymorphisms (SNPs) in miRs genes are currently being identified for contributing to cancer risk, prognosis and survival, however, an association between miR-149 rs2292832 T/C SNP and cancer risk is uncertain. Therefore, we performed an updated meta-analysis of all currently publications to clarify this relationship. From PubMed and Chinese language (WanFang) databases, we located articles published up to June 1, 2015, obtaining 21 case-control studies from 20 different articles containing 8913 cases and 9944 controls based on search criteria for cancer susceptibility related to the miR-149 rs2292832 T/C SNP. Odds ratios (OR) and 95% confidence intervals (CI) revealed association strengths. There had no association between this SNP and whole cancer risk. At the same time, in several subgroups, also no association was found in ethnicity, sex and smoking status. Nevertheless, poorly significant association was detected in cancer type (Digestive cancer: OR = 0.90, 95% CI = 0.81-1.00, Pheterogeneity = 0.142 for CT vs. TT) and source of control (population-based: OR = 1.15, 95% CI = 1.00-1.32, Pheterogeneity = 0.427 for CC vs. CT+TT) subgroups. The miR-149 rs2292832 T/C SNP may poorly decrease digestive cancer risk. Studies with larger samples and gene-environment interactions are warranted to understand the role of miR-149 polymorphisms, especially rs2292832 T/C SNP, in whole cancer risk.

Keywords: miR-149, sex, smoking, cancer, meta-analysis, polymorphism

Introduction

MicroRNAs are a family of short (approximately 22 nucleotides), non-coding, endogenous RNA molecules that regulate gene expression at the post-transcriptional level by suppressing translation of protein coding genes by destabilizing or cleaving target mRNAs [1]. Critical roles of miRNAs have been demonstrated in various key biological processes including growth of organism [2], hormone secretion [3], inflammatory reaction [4] and especially tumorigenesis [5, 6]. Many evidences indicate that miRNAs are involved in malignant transformation of human cells [7] and miRNA profiling is significantly altered in human cancer [8-10]. De-

regulation of miRNA expression seems to generate an important signaling cascade, since most of them have a large number of potential mRNA targets.

Sequence variants in miRNA genes are described as mechanisms that can contribute to their deregulation [11]. A mutation or a single nucleotide polymorphism (SNP) at a miRNA region might affect the transcription of miRNA primary transcripts, their processing to mature miRNA or miRNA target interactions [8, 12]. Although the role of miRNA genetic variants in cancer susceptibility is largely unknown, the importance of miRNA SNPs has been implicated in many cancers. It is well known that com-

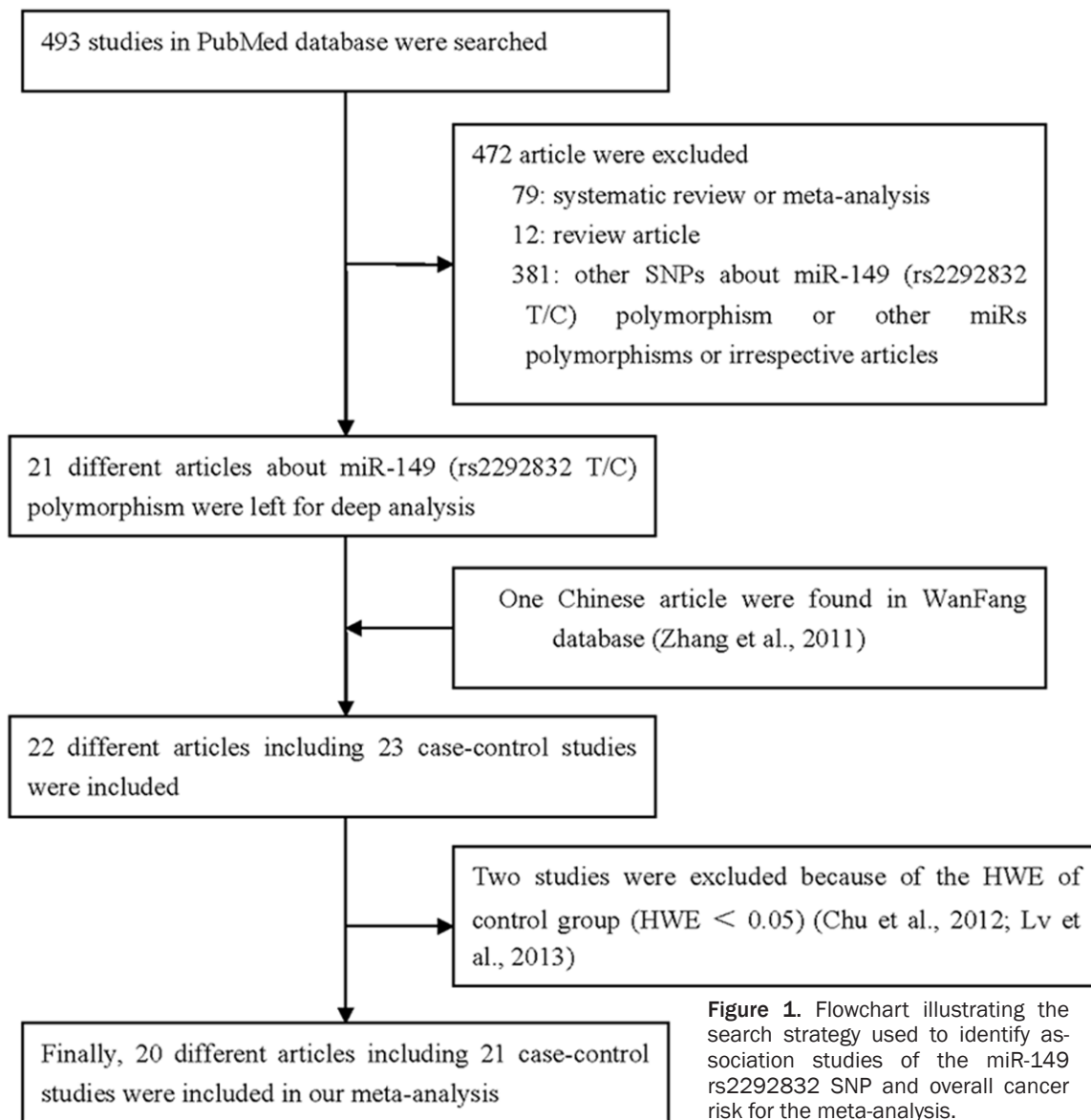


Figure 1. Flowchart illustrating the search strategy used to identify association studies of the miR-149 rs2292832 SNP and overall cancer risk for the meta-analysis.

mon SNPs in miRNAs and SNPs within their targets (miRNA-binding SNPs) may affect miRNA target expression and functions and thus may contribute to cancer risk [13].

So far, many studies have investigated the association between the miR-149 rs2292832 T/C SNP and cancer risk. But the results were not conclusive and consistent. Furthermore, several meta-analysis have reported that there was no significant association between this SNP and cancer susceptibility, after that, a number of larger studies have been published, and some novel findings may be found in our current study. So we performed this updated meta-analysis of 20 published studies [14-33] to derive a more powerful estimation of the

association between the miR-149 rs2292832 T/C SNP and cancer risk.

Materials and methods

Identification and eligibility of relevant studies

Searches were conducted in PubMed and in Chinese language (CNKI and WanFang) databases using key words 'mir', 'cancer' or 'tumor' or 'carcinoma', and 'polymorphism' or 'variant'. No restrictions were placed on language or publication year and the last search was updated on June 1, 2015. A total of 494 articles were retrieved using the abovementioned terms and 20 articles contained the inclusion criteria. References of the retrieved and review articles were also screened by hand.

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Table 1. Basic information for the included studies of the association between miR-149 rs2292832 T/C polymorphism and cancer risk

First author Year	Country Ethnicity	Source of Control	Cancer Type	Case/Control	Methods	HWE	Age in Cases/Controls (Mean ± SD)
Zhang (2012)	China/Asian	PB	BC	245/229	PCR-RFLP	0.213	54.66±11.18/54.51±11.41
Hu (2009)	China/Asian	PB	BC	1009/1093	PCR-RFLP	0.160	51.60±11.08/51.77±11.19
Min (2012)	South Korea/Asian	HB	CC	446/502	PCR-RFLP	0.948	61.89±12.35/61.74±12.11
Zhang (2012)	China/Asian	PB	CC	443/435	PCR-RFLP	0.431	62.39±10.81/62.24±10.62
Vinci (2013)	Italy/Caucasian	HB	CC	160/178	TaqMan	0.912	NA
Dikeakos (2014)	Greece/Caucasian	HB	GC	163/480	PCR-RFLP	0.450	60.58±9.67/61.15±13.12
Ahn (2012)	South Korea/Asian	HB	GC	461/447	PCR-RFLP	0.977	58.08±12.35/58.36±12.32
Zhang (2012)	China/Asian	PB	GC	274/269	PCR-RFLP	0.699	62.39± 10.81/62.24±10.62
Hu (2013)	China/Asian	HB	Glioma	680/690	SNaPshot	0.732	53.15±12.86/52.98±12.16
Liu (2010)	USA/Caucasian	HB	HNSCC	1109/1130	PCR-RFLP	0.271	NA
Tu (2012)	China-Taiwan/Asian	HB	HNSCC	273/122	PCR-RFLP	0.269	53.0±11.0/53.5±13.4
Wang (2014)	China/Asian	HB	HC	152/304	PCR-RFLP	0.623	53.5±9.4/53.0±11.5
Liu (2014)	China/Asian	HB	HC	327/327	Sequenom®	0.054	56.2±11.3/55.8±10.7
Kou (2014)	China/Asian	HB	HC	270/532	PCR-RFLP	0.877	55.8±10.6/52.6±11.2
Kim (2012)	South Korea/Asian	HB	HC	159/201	PCR-RFLP	0.345	56.06±11.02/53.58±11.17
Zhang (2011)	China/Asian	PB	LC	232/231	PCR-RFLP	0.123	64.4±10.0/63.9±9.9
Tian (2009)	China/Asian	PB	LC	1058/1035	PCR-RFLP	0.855	59.78±10.04/59.66±9.83
Vinci (2011)	Italy/Caucasian	HB	LC	101/129	HRMA	0.966	NA
Huang (2013)	China/Asian	HB	NC	158/242	PCR-RFLP	0.724	46.6±11.1/47.2±10.5
Wei (2014)	China/Asian	PB	PTC	838/1006	MALDI-TOF-MS	0.731	46.30±11.02/47.2±12.29
Du (2014)	China/Asian	HB	RCC	355/362	TaqMan	0.464	56.9±12.2/56.7±10.7

Annotation: BC, breast cancer; CC, colorectal cancer; GC, gastric cancer; HNSCC, head and neck squamous cell carcinoma; HC, hepatocellular carcinoma; LC, lung cancer; NC, nasopharyngeal carcinoma; PTC, papillary thyroid cancer; RCC, renal cell cancer; HB, hospital-based; PH, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MALDI-TOF-MS, matrix-assisted laser desorption/ionization time of flight mass spectrometry; HRMA, high-resolution melting analysis. ®: registered trademark.

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Table 2. Total and stratified subgroup analysis for miR-149 rs2292832 T/C polymorphism and cancer risk

Variables	N ^a	Cases/Controls	Heterozygote comparison		Dominant genetic model		Recessive genetic model	
			OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total	21	8913/9944	0.97 (0.92-1.04)	0.152	0.98 (0.90-1.07)	0.007	1.08 (0.95-1.24)	0.007
Ethnicity								
Asian	17	7380/8027	0.96 (0.90-1.03)	0.117	0.95 (0.87-1.05)	0.008	1.04 (0.90-1.20)	0.021
Caucasian	4	1533/1917	1.04 (0.90-1.20)	0.435	1.06 (0.92-1.22)	0.183	1.45 (0.90-2.34)	0.031
Chinese	14	6314/6877	0.99 (0.92-1.06)	0.141	0.98 (0.88-1.09)	0.009	1.04 (0.88-1.23)	0.007
None-Chinese	7	2599/3067	0.94 (0.84-1.06)	0.273	0.97 (0.87-1.08)	0.109	1.11 (0.93-1.33)	0.133
Cancer type								
BC	2	1254/1322	0.92 (0.78-1.08)	0.106	0.92 (0.79-1.07)	0.101	0.97 (0.75-1.26)	0.737
CC	3	1049/1115	0.85 (0.71-1.02)	0.992	0.89 (0.75-1.06)	0.937	1.14 (0.87-1.50)	0.570
GC	3	898/1196	0.93 (0.67-1.29)	0.064	1.00 (0.71-1.41)	0.030	1.28 (0.96-1.71)	0.223
OC	4	2031/2300	1.06 (0.93-1.20)	0.181	1.07 (0.87-1.32)	0.055	1.15 (0.85-1.56)	0.073
HNSCC	2	1382/1252	1.00 (0.85-1.18)	0.933	0.96 (0.82-1.12)	0.405	0.61 (0.27-1.42)	0.019
HC	4	908/1364	0.91 (0.68-1.23)	0.058	0.92 (0.63-1.33)	0.004	0.96 (0.59-1.54)	0.017
LC	3	1391/1395	1.05 (0.90-1.23)	0.928	1.08 (0.93-1.26)	0.755	1.19 (0.94-1.51)	0.304
Digestive cancer	10	2855/3675	0.90 (0.81-1.00)	0.142	0.94 (0.80-1.10)	0.013	1.14 (0.93-1.40)	0.083
None-digestive cancer	11	6058/6269	1.01 (0.94-1.09)	0.465	1.02 (0.95-1.10)	0.110	1.04 (0.86-1.26)	0.012
Source of control								
HB	14	4814/5646	0.98 (0.90-1.06)	0.156	0.99 (0.87-1.12)	0.008	1.04 (0.85-1.24)	0.003
PB	7	4099/4298	0.97 (0.89-1.07)	0.211	1.00 (0.92-1.09)	0.124	1.15 (1.00-1.32)	0.427
Sex								
Female	4	516/531	1.05 (0.80-1.37)	0.869	1.07 (0.84-1.36)	0.821	1.14 (0.74-1.77)	0.327
Male	4	894/857	0.84 (0.52-1.35)	0.012	0.91 (0.66-1.25)	0.037	0.99 (0.72-1.36)	0.570
Smoking status								
Smoker	4	487/468	1.01 (0.52-1.97)	0.015	1.07 (0.67-1.72)	0.019	0.87 (0.54-1.42)	0.182
Non-smoker	4	255/519	0.90 (0.61-1.33)	0.171	0.94 (0.69-1.28)	0.429	1.42 (0.83-2.42)	0.485

Annotation: a, Number of comparisons; b, P value of Q-test for heterogeneity test; BC, breast cancer; OC, other cancer; CC, colorectal cancer; GC, gastric cancer; HNSCC; head and neck squamous cell carcinoma; HC, hepatocellular carcinoma; LC, lung cancer; NC, nasopharyngeal carcinoma; PTC, papillary thyroid cancer; RCC, renal cell cancer HB, hospital-based; PH, population-based.

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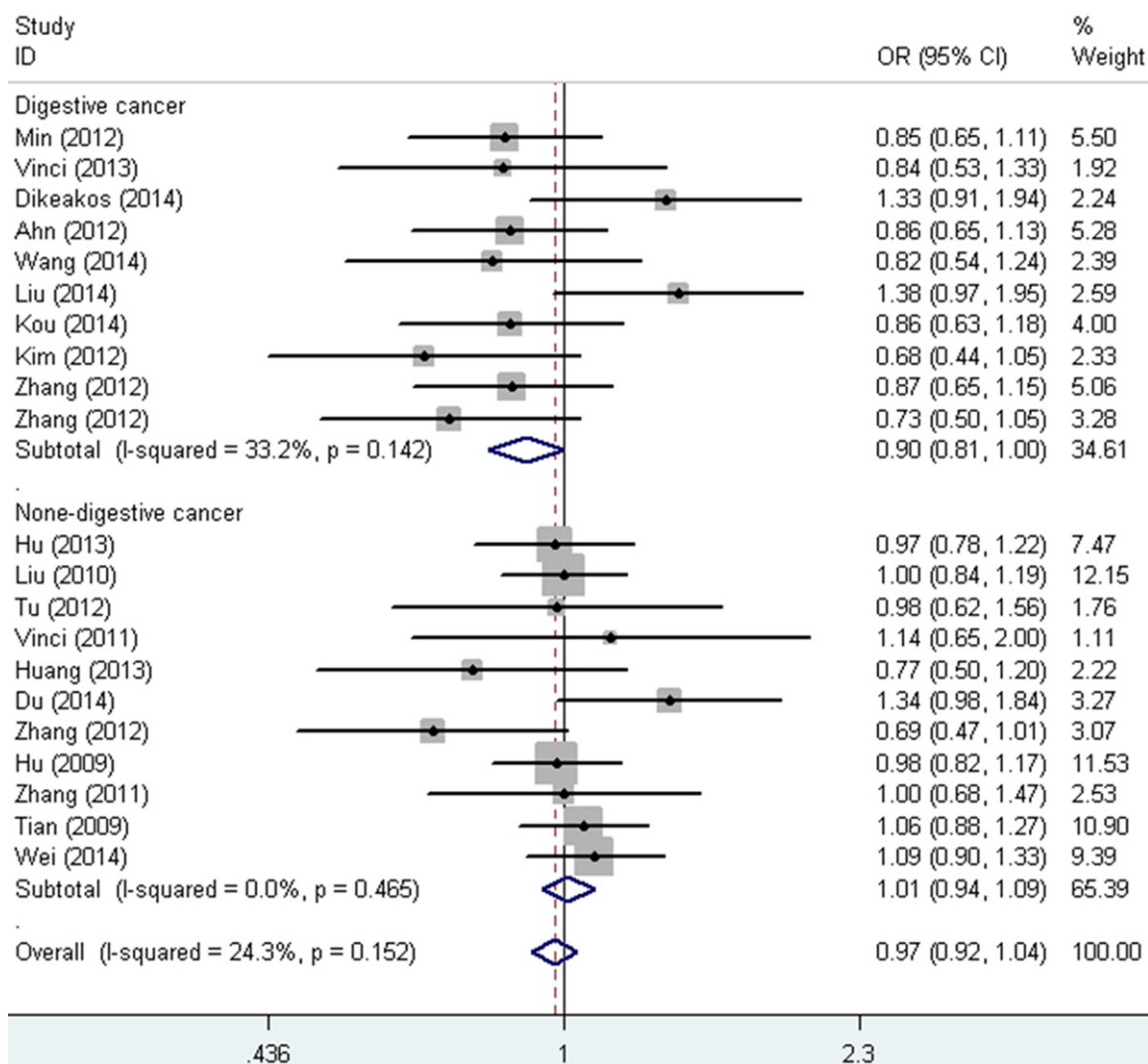


Figure 2. Forest plot of digestive risk associated with the miR-149 rs2292832 SNP (CT vs. TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Inclusion criteria and exclusion criteria

Studies that were included in our analysis had to meet all of the following criteria: (1) the correlation between cancer risk and the miR-149 rs2292832 T/C SNP; (2) case-control study and (3) sufficient genotype (TT, TC and CC) numbers for cases and controls. The following exclusion criteria were used: (1) lack of a control population; (2) lack of available genotype frequency data; and (3) duplicated study.

Data extraction

Two of the authors extracted all data independently according to the selection criteria. The following items were collected: last name of

first author, year of publication, country of origin, ethnicity, cancer type, the total and number of each genotype frequency in case/control groups, 'source of control', Hardy-Weinberg equilibrium (HWE) of controls, age range in case/control group, and genotyping method. Subgroup analysis, stratified by cancer type, was performed, especially including digestive cancer and none-digestive cancer. Ethnicity was categorized as Caucasian, Asian, Chinese and none Chinese. The 'source of control' subgroup analysis was performed on two groups and was classified as population-based (PB) or hospital-based (HB). Smoking (smoker or non-smoker) status and subject sex (male or female) were also included in our meta-analysis.

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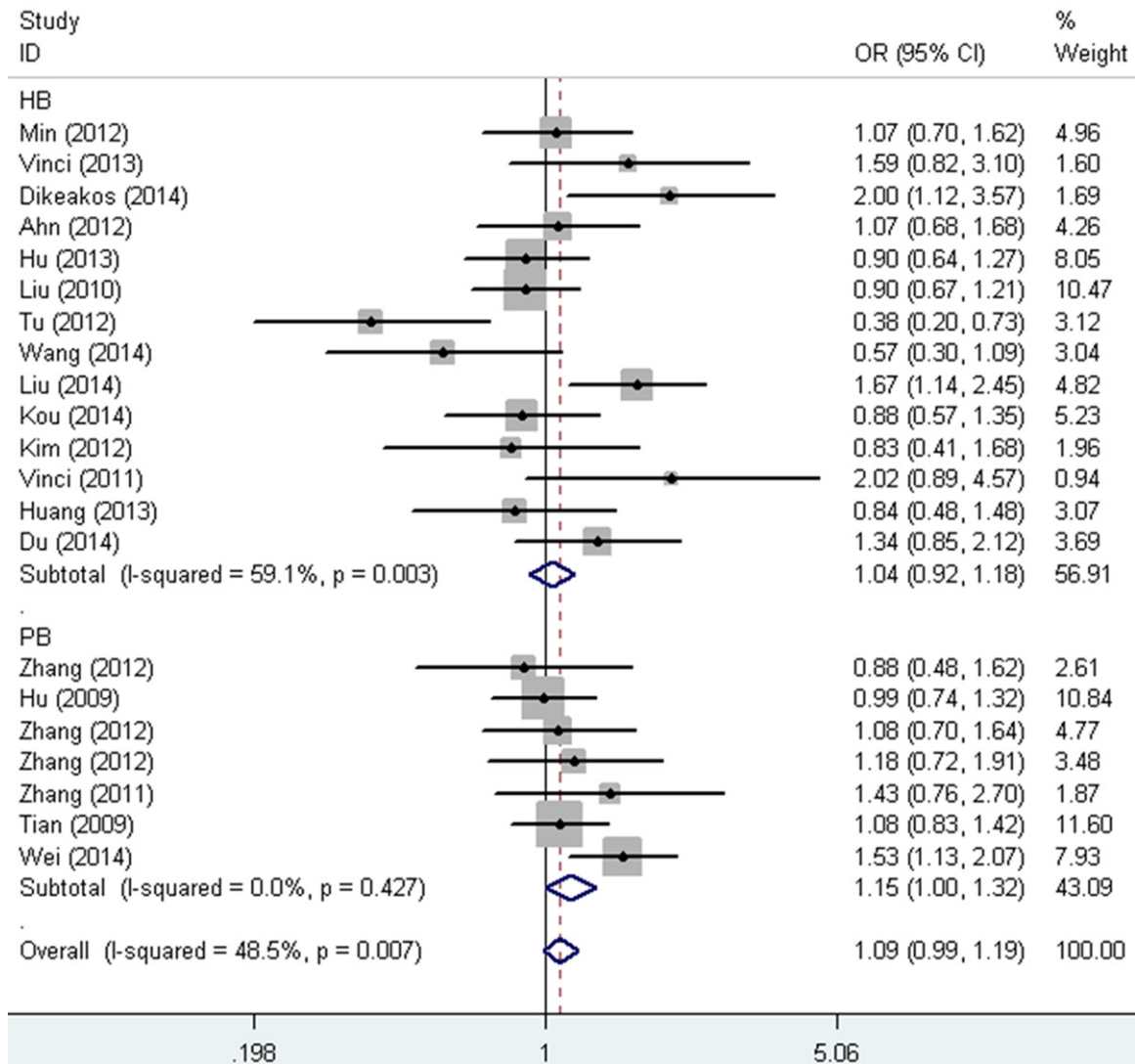


Figure 3. Forest plot of cancer risk associated with the miR-149 rs2292832 SNP (CC vs. CT+TT) by source of control. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Statistical analysis

Odds ratios (OR) with 95% confidence intervals (CI) were used to measure the strength of the association between the miR-149 rs2292832 T/C SNP. The statistical significance of the summary OR was determined with the Z-test. A heterogeneity assumption was evaluated among studies using a Chi-square-based Q-test. A P value of > 0.10 for the Q-test indicated a lack of heterogeneity among the studies. If significant heterogeneity was detected, the random-effects model (DerSimonian-Laird method) was used. Otherwise, the fixed-effects model (Mantel-Haenszel method) was chosen [34, 35].

We investigated the relationship between genetic variants of the miR-149 rs2292832 site and cancer risk by recessive genetic model (CC vs. CT+TT), comparison of heterozygotes (CT vs. TT) and the dominant genetic model (CC+CT vs. TT). A sensitivity analysis was performed by omitting studies, one after another, to assess the stability of results. The departure of the miR-149 rs2292832 SNP from expected frequencies under HWE was assessed in controls using the Pearson Chi-square test (P < 0.05 was considered significant). Publication bias was identified using Egger's linear regression method and a funnel plot. A P-value < 0.05 in Egger's linear regression indicated the pres-

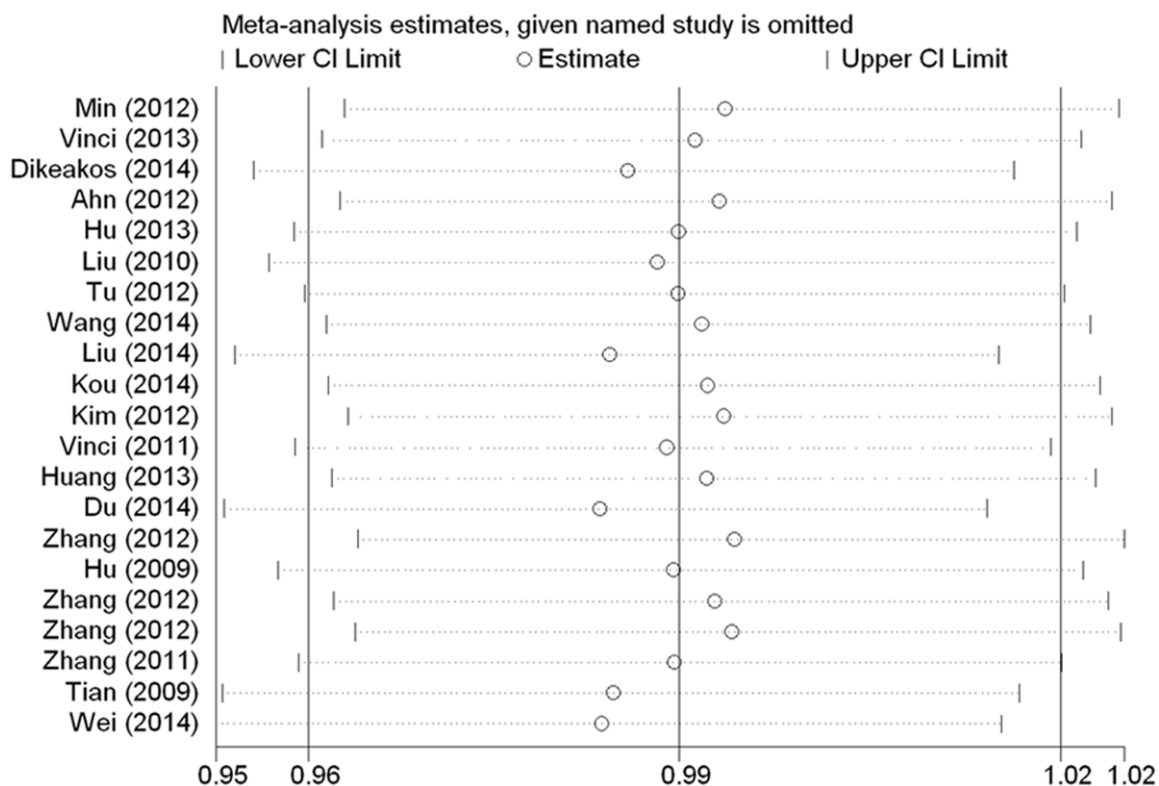


Figure 4. Sensitivity analysis between the miR-149 rs2292832 SNP polymorphism and whole cancer risk.

ence of potential publication bias [36]. All statistical tests for this meta-analysis were performed with Stata software (version 11.0; StataCorp LP, College Station, TX).

Genotyping methods

Methods for genotyping for the miR-149 rs2292832 SNP was conducted in the retrieved literature using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP); matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF-MS); high-resolution melting analysis (HRMA), TaqMan, SNaPshot and Sequenom®.

Results

Study characteristics

A total of 493 articles were collected from the PubMed database via a literature search using different combinations of key terms. As shown in Figure 1, 472 articles were excluded (79 were systematic review and meta-analysis, 12 were review, 381 were irrespective articles), furthermore, just only one article were found in

WanFang database. The distribution of genotypes among controls was not consistent with HWE in both Lv et al. [37] and Chu et al. [38], which were also excluded, finally, 20 different articles about 21 case-control studies were included in our meta-analysis. There were 8913 cases and 9944 controls, including several kinds of cancer types. Study characteristics from published studies on the relationship between the miR-149 rs2292832 SNP and cancer risk are summarized in Table 1. Four different articles included the genotype detail and smoking status, and also four articles included information regarding sex. The cancer type of included studies contains ten articles about digestive cancer. In most of the studies, cases were histologically diagnosed, and controls were cancer-free.

Quantitative synthesis

There were no association between miR-149 rs2292832 SNP and whole cancer susceptibility (Heterozygote comparison: OR = 0.97, 95% CI = 0.92-1.04, $P_{\text{heterogeneity}} = 0.152$, dominant model: OR = 0.98, 95% CI = 0.90-1.07, $P_{\text{heterogeneity}} = 0.007$ and recessive model: OR =

1.08, 95% CI = 0.95-1.24, $P_{\text{heterogeneity}} = 0.007$) (Table 2).

When studies were stratified according to ethnicity, no association was also found in Asian, Caucasian, Chinese or None-Chinese. In the subgroup for sex and smoking status, the same result was detected (Table 2). When studies were stratified by cancer type, a significant association was identified between miR-149 rs2292832 SNP and digestive cancer (Heterozygote comparison: OR = 0.90, 95% CI = 0.81-1.00, $P_{\text{heterogeneity}} = 0.142$, Figure 2), though no relationship was found for breast cancer, colorectal cancer, gastric cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma and lung cancer (Table 1). Interestingly, in the subgroup of source of control, increased association was found in PB (recessive model: OR = 1.15, 95% CI = 1.00-1.32, $P_{\text{heterogeneity}} = 0.427$, Figure 3), rather than HB (Table 2).

Sensitivity analysis and bias diagnosis

We used a sensitivity analysis to determine whether modifying the meta-analysis inclusion criteria affected the final results. No other single study influenced the summary OR qualitatively (Figure 4). Egger's test was performed to assess publication bias and to provide statistical evidence of funnel plot symmetry, and data did not reveal evidence of publication bias (date not shown).

Discussion

Recent studies have shown that miRNAs may play an important role in human carcinogenesis, and SNPs located either in the pre-miRNAs or within miRNA-binding sites are likely to affect the expression and function of the miRNA targets [39-41] and thus may contribute to the susceptibility to cancer.

Concerning miR-149, it is a pro-apoptotic miRNA that represses the expression of Akt1 and E2F1. Silencing of Akt1 and E2F1 induces apoptosis in human cancer cell lines [42, 43], moreover, miR-149 is known as a tumor suppressor with the function of inhibiting cell growth and invasion by binding to the target gene specificity protein 1 [44]. The miR-149 rs2292832 SNP may alter the expression of mature miRNAs or their binding activities to tar-

get mRNA, thereby influencing cancer risk through variable mechanisms.

To date, numerous genetic association studies have been conducted to examine the relationship between the miR-149 rs2292832 SNP and the risk of several cancers, including breast cancer, colorectal cancer, gastric cancer, head and neck squamous cell carcinoma, hepatocellular carcinoma and lung cancer. Conflicting results were obtained. Limited sample sizes may account for the inconclusive result. A meta-analysis provides a means for effectively increasing the size of the sample by pooling data from individual correlation studies, thus enhancing the statistical power of the analysis to estimate genetic effects [45]. So we applied this method to demonstrate statistically significant genetic associations.

We used the meta-analysis, containing 8913 cases and 9944 controls, to conclude a convincing association. In the present study, we found that individuals carried CT genotype may have a decreased association with digestive cancer than TT genotype. Recently, two meta-analysis, including Zhang et al. [46] and Xu et al., [47] did not find any association between the miR-149 rs2292832 SNP and cancer susceptibility. However, it is necessary to conduct large sample studies with homogeneous cancer patients and different ethnic backgrounds which may be a way to maximize study efficacy and overcome the limitations of individual studies.

Limitations in the present meta-analysis include the suboptimal number of published studies for a comprehensive analysis, especially in terms of linking smoking status, sex and other cancer types. Secondly, interactions between different polymorphic loci of the same miRNA may modulate cancer risk, which should be included in future research and analysis. In addition, our meta-analysis was based on unadjusted estimates. A more precise analysis should be conducted if individual data are available to adjust for other covariates including age, sex, family history, environmental factors, cancer stage, and lifestyle. Finally, controls may not have been truly healthy individuals.

In summary, in the present meta-analysis, a poorly decreased association was found between the miR-149 rs2292832 SNP and digestive cancer risk. To further confirm the results, larger scale case-control studies with

different ethnic groups and multiple cancer types are needed.

Acknowledgements

This work was supported by a grant from The National Natural Science Funds (No. 81101938). Shenyang Science and Technology Project (F14-231-1-56) and Liaoning Province Natural Science Funds (2015020516; 2015-020430).

Disclosure of conflict of interest

None.

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