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ORIGINAL RESEARCH

The association between miR-499 polymorphism and cancer susceptibility: a meta-analysis

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Zhongfei Xu
Enjiao Zhang
Weiyi Duan
Changfu Sun
Shuang Bai
Xuexin Tan

Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, Shenyang, People's Republic of China

Background: MicroRNAs are a class of new noncoding RNA that play important roles in the pathogenesis of tumor. Rs3746444 in miR-499 is suggested to be associated with cancer susceptibility. In the present study, we assess the association between miR-499 rs3746444 polymorphism and cancer susceptibility through a meta-analysis.

Methods: We searched relevant articles from the PubMed and Embase databases. We screened all the resulting articles for adherence to the inclusion and exclusion criteria. The associations between miR-499 polymorphism and cancer susceptibility were estimated by computing the odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using Stata software.

Results: There are 18 datasets included in the analysis. Statistically significant associations were found between the miR-499 rs3746444 polymorphism and susceptibility to cancer (GG versus AA: OR =1.24, 95% CI: 1.01–1.52; G versus A: OR =1.11, 95% CI: 1.01–1.23). A subsequent analysis, on the basis of ethnicity for the population characteristic, showed that Asians had increased susceptibility to cancer (GG versus AA: OR =1.32, 95% CI: 1.09–1.59; GG + AG versus AA: OR = 1.17, 95% CI: 1.01–1.37). In the subgroup analysis of tumor type, none of the genetic models had statistically significant results. The meta-regression suggested that race and cancer types are not the source of heterogeneity in the present meta-analysis. No publication bias was detected by either the inverted funnel plot or Egger's test.

Conclusion: Rs3746444 in miR-499 might be related to susceptibility to cancer.

Keywords: microRNA, single-nucleotide polymorphism, tumor, risk factor

Background

MicroRNAs (miRNAs) are a class of single-stranded noncoding RNAs typically composed of about 17–25 nucleotides that widely exist in human cells and play an important regulating role in many cellular processes, including proliferation, differentiation, and apoptosis, and also function as tumor suppressors and oncogenes.[1,2] By specifically binding to the 3′-untranslated region of the target messenger (m)RNA, which leads to the degradation of the target mRNA or suppression of protein synthesis, miRNAs can regulate gene expression at the posttranscriptional level.[3] It was also found by several previous studies that many miRNAs are abnormally expressed in different kinds of cancer,[3–4] and one study found that more than 50% of miRNA genes are located in cancer-related genomic regions or in fragile sites,[5] so miRNAs potentially exert significant effects on the development of human malignant tumors.

Single-nucleotide polymorphisms (SNPs), the most common type of mutations in the human genome, have become a focus in cancer research. One study has reported that miRNA regulates more than 30% of human genes;[6] even small changes in miRNA expression or function may have an enormous effect on the pathogenesis of numerous diseases. So SNPs in miRNA sequence may affect the

Correspondence: Zhongfei Xu
Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University, No 117, Nanjing North Street, Heping District, Shenyang 110002, People's Republic of China
Tel +86 24 2289 1026
Fax +86 24 8660 2310
Email xzf7090@outlook.com

miRNA biosynthesis and expression of coding genes and have an association with cancer susceptibility. There are some well-known SNPs in miRNA that affect the pathogenesis of human cancers, and the most widely studied have been miR-146a and miR-196a2 polymorphisms, including in primary research studies and meta-analyses.[7–15] A study by Zhou et al found that rs3746444 A/G polymorphism in miRNA-499 increases the risk of cervical squamous cell carcinoma.[3] Tian et al reported that rs3746444 A/G polymorphism was not associated with lung cancer risk.[11] In a population-based case-control study by Srivastava et al which tried to elucidate the association between rs3746444 polymorphism and gallbladder cancer susceptibility, the researchers failed to find any significant results.[16] Although the miRNA-499 gene polymorphism and cancer relationship has been studied by many researchers, many conclusions drawn from the different studies on the same topic are inconsistent and have not reached consensus. This may be due to the restrictions of sample size and heterogeneity in cancer type and ethnicities.

Meta-analysis is a statistical technique for amalgamating, summarizing, and reviewing previous quantitative research. By using meta-analysis, a wide variety of questions can be investigated, as long as a reasonable body of primary research studies exists. In statistics, meta-analysis comprises statistical methods for contrasting and combining results from different studies in the hope of identifying patterns among study results, sources of disagreement among those results, or other interesting relationships that may come to light in the context of multiple studies.[17] Meta-analysis has been used to give helpful insight into the overall effectiveness of interventions, the relative impact of independent variables, and the strength of relationships between variables. The inconsistent published results of the association between miR-499 polymorphisms and cancer susceptibility may be attributed to the size of the samples, the ethnicity of the sample population, etc. In order to contribute to a better understanding of the role of this gene in the occurrence of cancer, we performed an updated meta-analysis on all available case-control studies, combining data together to reach a larger sample size, to get more statistical power to evaluate the relationship between miRNA-499 and cancer risk.

Materials and methods

Data sources

We retrieved articles from PubMed using the following terms: "miRNA or miR-499" and "cancer" and "polymorphism". We evaluated potentially relevant publications by examining their titles and abstracts, and all studies matching the eligibility criteria were retrieved.

Study selection and data extraction

Qualifying studies were selected according to the following explicit inclusion requirements: 1) evaluation of the miR-499 rs3746444 polymorphism and cancer risks; 2) using the methodology of a case-control study or cohort study; and 3) sufficient published data for the computation of odds ratios (ORs) with 95% confidence intervals (CIs).

Duplicate and obviously unrelated articles were eliminated by a single reviewer (ZX). Abstracts of the remaining articles were examined independently by two reviewers (ZX and EZ) to determine whether the full-text article should be obtained. The following data were extracted from each included article: first author's name, publication date, country of origin, ethnicity, cancer type, control characteristics, total number of cases and controls, and numbers of cases and controls with miR-499 rs3746444 genotypes.

Statistical methods

Hardy–Weinberg equilibrium (HWE) was firstly assessed for each included study among control groups using the chi-square test. We investigated the between-study heterogeneity by the Cochran's Q test and quantified by I^2 (a significance level of $P<0.05$ and/or $I^2 \geq 50\%$). To obtain summary associations between miRNA polymorphism and cancer risk, we performed initial analyses with a fixed-effects model and then with a random-effects model if there was significant heterogeneity. The summary associations between miR-499 rs3746444 polymorphism and cancer risk were assessed by pooled ORs corresponding to 95% CIs. Pooled ORs were obtained by five genetic comparison models: heterozygote comparison (AG versus AA for rs3746444); homozygote comparison (GG versus AA for rs3746444); dominant model (GG + AG versus AA for rs3746444); recessive model (GG versus AG + AA for rs3746444); and allelic model (G versus A for rs3746444). The subgroup analysis according to ethnicity was investigated to estimate ethnic-specific ORs for Asians and Caucasians with five genetic comparison models. Meanwhile, stratified analyses by tumor type were also applied for each genetic comparison model.

The effect of publication bias was examined by inverted funnel plots and the Egger's test. The significance of the intercept was determined by the Egger's *t*-test as suggested by the Egger's test. All *P*-values were two-sided, and all analyses were performed using Stata software version 11.0 (StataCorp LP, College Station, TX, USA).

Results

According to the inclusion and exclusion criteria, a total of 39 articles were eligible. Nine of them were meta-analyses and two were comments. Ten studies were excluded because of no cancer risk and missing data. Finally, 18 articles were included and used in quantitative synthesis for systematic review. There were 7,906 cases and 9,392 controls in the 18 datasets for miR-499 (rs3746444) SNP. A flowchart of the study selection process is shown in Figure 1. The characteristics of the selected studies are summarized in Table 1. In the 18 studies, sample sizes ranged from 190 to 3,746. There were seven studies of Europeans and eleven studies of Asians. Almost all of the cases were histologically confirmed. Controls were mainly frequency matched by sex and age. The distribution of genotypes in the controls was mostly in HWE, except for four datasets of rs3746444. Studies with the controls not in HWE were subjected to a sensitivity analysis.

In the control group, the G allele of miR-499 polymorphism across different ethnicities ranged from 0.21 to 0.58. The average G allele frequencies among Asians and Caucasians were 17.8% and 24.5%, respectively.

Data in Table 2 show that miR-499 rs3746444 polymorphism might be associated with cancer susceptibility in two genetic models. Compared with individuals carrying the AA genotype, individuals with the GG genotype were more likely to develop cancer, and significant results were also seen in the additive model (GG versus AA: OR =1.24, 95% CI: 1.01–1.52, P=0.014 for heterogeneity, I^2=47.1%; G versus A: OR =1.11, 95% CI: 1.01–1.23, P=0.000 for heterogeneity, I^2=65.6%) (Figures 2 and 3). Other genotypes had no statistically significant results (AG versus AA: OR =1.06, 95% CI: 0.94–1.21, P=0.000 for heterogeneity, I^2=62.7%; GG + AG versus AA: OR =1.11, 95% CI: 0.99–1.24, P=0.000 for heterogeneity, I^2=61.1%; GG versus AG + AA: OR =1.19, 95% CI: 0.97–1.48, P=0.002 for heterogeneity, I^2=55.5%) (Table 2).

Due to the heterogeneity in analysis, we characterized by ethnicity and cancer type for the stratified analysis (Table 3).

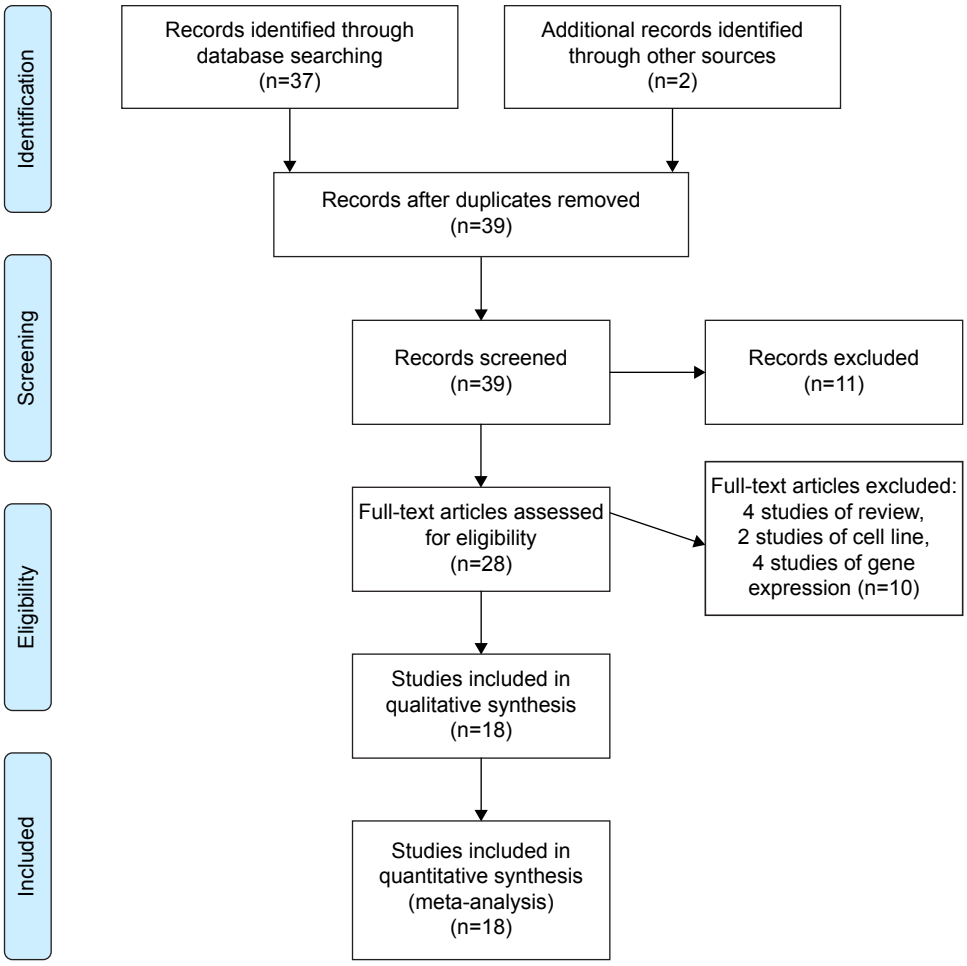

Figure 1 Flowchart of the study selection process.

Table 1 Characteristics of all the studies in the meta-analysis

Authors, year	Country	Ethnicity	Cancer type	Genotyping method	Study design	Number (cases/controls)	Cases				Controls				HWE (*P*)
							AA	AG	GG	Frequency of G allele	AA	AG	GG	Frequency of G allele	
Hu et al[4] 2009	People's Republic of China	Asian	BC	PCR-RFLP	PB	1,009/1,093	707	258	44	0.171	816	248	29	0.140	0.06
Tian et al[11] 2009	People's Republic of China	Asian	LC	PCR-RFLP	PB	1,058/1,035	781	253	24	0.142	755	254	26	0.148	0.40
Srivastava et al[16] 2010	India	Caucasian	GBC	PCR-RFLP	PB	230/230	112	97	21	0.302	121	94	15	0.270	0.57
Liu et al[19] 2010	USA	Caucasian	SCCHN	PCR-RFLP	HB	1,109/1,130	745	309	55	0.189	710	366	54	0.210	0.44
Okubo et al[20] 2010	Japan	Asian	GC	PCR-RFLP	HB	552/697	364	151	37	0.204	466	198	33	0.189	0.05
Catucci et al[21] 2010	Italy, Germany	Caucasian	BC	TaqMan PCR	PB	1,579/2,167	950	545	84	0.226	1,305	742	120	0.227	0.28
Zhou et al[3] 2011	People's Republic of China	Asian	CSCC	PCR-RFLP	PB	226/309	134	84	8	0.221	223	71	15	0.163	0.005[a]
George et al[22] 2011	India	Caucasian	PC	PCR-RFLP	PB	159/230	48	98	13	0.390	104	92	34	0.348	0.07
Mittal et al[23] 2011	India	Caucasian	BC	PCR-RFLP	PB	212/250	95	92	25	0.335	121	94	35	0.328	0.02[a]
Akkiz et al[24] 2011	Turkey	Caucasian	HCC	PCR-RFLP	PB	222/222	45	87	90	0.601	47	93	82	0.579	0.04[a]
Zhou et al[25] 2012	People's Republic of China	Asian	HCC	PCR-RFLP	PB	186/483	141	41	4	0.132	371	100	12	0.128	0.1
Xiang et al[26] 2012	People's Republic of China	Asian	HCC	PCR-RFLP	HB	100/100	36	40	24	0.440	54	36	10	0.280	0.28
Kim et al[27] 2012	Korea	Asian	HCC	PCR-RFLP	PB	159/201	109	47	3	0.167	120	74	7	0.219	0.28
Wei et al[28] 2013	People's Republic of China	Asian	ESCC	PCR	HB	358/376	291	60	7	0.103	289	76	11	0.130	0.110
Vinci et al[29] 2013	Italy	Caucasian	CRC	TaqMan PCR	HB	160/178	93	32	35	0.319	105	56	17	0.253	0.083
Hu et al[30] 2014	People's Republic of China	Asian	CRC	PCR-RFLP	HB	276/373	157	49	5	0.140	282	81	10	0.135	0.376
Hasani et al[31] 2014	Iran	Asian	ALL	TARMS-PCR	HB	75/115	35	28	12	0.347	61	42	12	0.287	0.514
Omrani et al[32] 2014	Iran	Asian	BC	PCR	HB	236/203	131	44	61	0.352	130	48	25	0.241	0.000[a]

Note: [a]The distribution of genotypes in the controls was not in HWE when its *P*-value was <0.05.

Abbreviations: ALL, acute lymphocytic leukemia; BC, breast cancer; CRC, colorectal cancer; CSCC, cervical squamous cell carcinoma; ESCC, esophageal squamous cell carcinoma; GBC, gallbladder cancer; GC, gastric cancer; HB, hospital-based; HCC, hepatocellular carcinoma; HWE, Hardy–Weinberg equilibrium; LC, lung cancer; PB, population-based; PC, prostate cancer; PCR, polymerase chain reaction; PCR-RFLP, PCR–restriction fragment length polymorphism; SCCHN, squamous cell carcinoma of head and neck; TARMS-PCR, tetra-primer amplification refractory mutation system polymerase chain reaction.

Table 2 Association between miR-499 (rs3746444) and cancer risk

	Number of datasets	Fixed-effects, OR (95% CI)	Random-effects, OR (95% CI)	*P*-value of heterogeneity	I^2 (%)
AG versus AA	18	1.03 (0.96–1.10)	1.06 (0.94–1.21)	0.000	62.7
GG versus AA	18	1.21 (1.06–1.39)	1.24 (1.01–1.52)	0.014	47.1
GG + AG versus AA	18	1.05 (0.99–1.12)	1.11 (0.99–1.24)	0.000	61.1
GG versus AG + AA	18	1.18 (1.04–1.35)	1.19 (0.97–1.48)	0.002	55.5
G versus A	18	1.07 (1.01–1.13)	1.11 (1.01–1.23)	0.000	65.6

Notes: The between-study heterogeneity was assessed by *P*-values of the Cochran's Q test (Phet) and I^2 (a significance level of $P<0.05$ or $I^2 \geq 50\%$). The significance of association was evaluated by odds ratios (ORs) and their 95% confidence intervals (CIs) in a fixed-effects or random-effects model.

In Asians, comparing with wild genotype (AA), homozygote genotype significantly increased the susceptibility to cancer (GG versus AA: OR =1.32, 95% CI: 1.09–1.59), and a significant result also could be found among those with the dominant model (GG + AG versus AA: OR =1.17; 95% CI: 1.01–1.37). For the Caucasians, there were not significant results for any model. In the stratified analysis by tumor type, the relationship between rs3746444 polymorphism and cancer susceptibility did not have statistical significance.

When discussing source of heterogeneity, meta-regression demonstrated no statistical significance for race and cancer type ($P>0.05$). Therefore, these two factors were not the source of heterogeneity in the present meta-analysis.

Sensitivity analyses suggested that the present results were stable. Every single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the pooled ORs. This procedure did not change the pooled ORs, supporting the robustness of our findings.

No publication bias was detected by either the inverted funnel plot or Egger's test. The shapes of the funnel plot for the comparison of G-allelic and A-allelic rs3746444 SNP seemed approximately symmetrical. *P*-values of the Egger's

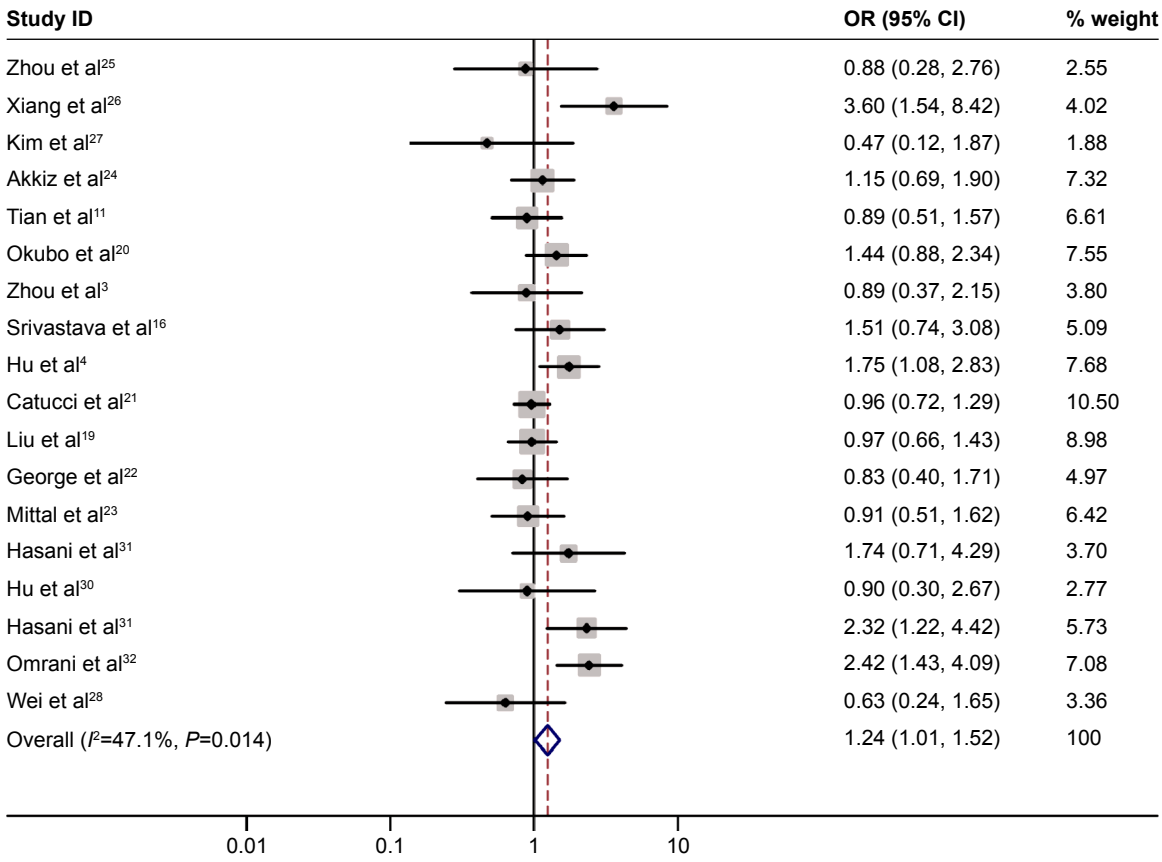

Figure 2 Meta-analysis of the association between miR-499 polymorphism and cancer risk under the homogeneity model (GG versus AA).
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

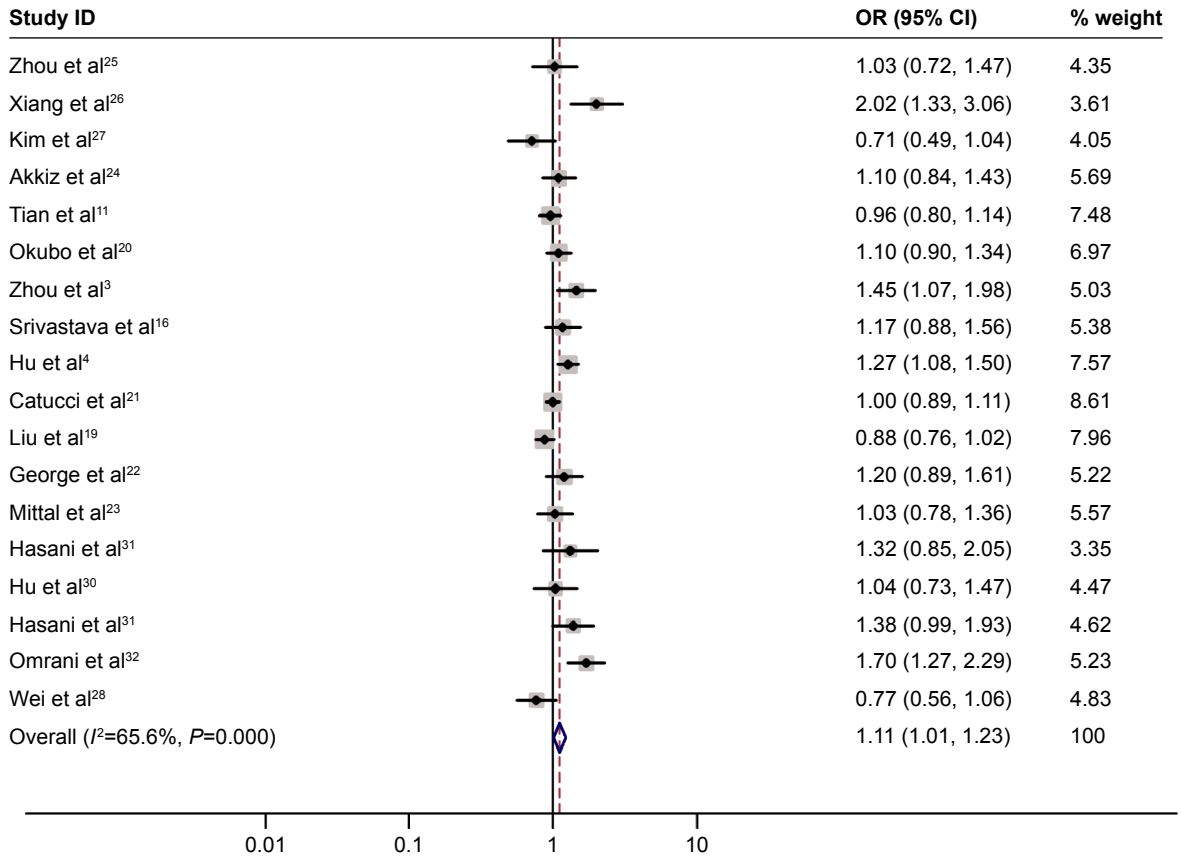

Figure 3 Meta-analysis of the association between miR-499 polymorphism and cancer risk under the allelic model (G versus A).
Note: Weights are from random-effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

tests were not statistically significant (AG versus AA: t=0.76, P=0.456; GG versus AA: t=0.27, P=0.789; GG + AG versus AA: t=1.30, P=0.212: GG versus AG + AA: t=0.17, P=0.867; G versus A: t=1.43, P=0.169).

Discussion

SNP is the most common type of human genetic variation associated with cancer susceptibility and one of the important causes of population diversity. Much research effort has been directed toward understanding the role of SNPs located in precursor and mature miRNA and their influences on susceptibility to and progression of various diseases. Studies have pointed out that the SNP in miRNA precursor and mature miRNA may affect the process of gene coding and splicing of the miRNA sequence, thus affecting varieties of cancer susceptibility. These variations also make a contribution to cancer susceptibility through modulating the transcription of the primary transcript of miRNA processing and maturation and miRNA–miRNA interaction, so playing an important role in the carcinogenesis of various cancers.[4,16,18] Clarifying the association between miRNA SNP and cancer risk will help to further elucidate the mechanism underlying the carcinogenesis, in turn providing a new biomarker for screening high-risk populations for cancer and promoting the development of molecular-targeted therapy. Although there are many studies on the association between miR-499 polymorphism and cancer susceptibility, researchers cannot reach a definitive conclusion, possibly due to small sample size and differences in cancer type and ethnicity. So, in order to derive a more precise assessment of the relationship, we performed this meta-analysis.

It is known that incidence of gene polymorphism varies in different ethnicities. In our meta-analysis of association between miR-499 rs3746444 and cancer risk, we found that carriers of GG genotype have an increased risk for cancer compared with carriers of AA genotype in an Asian population, but not in a Caucasian population.

In the subgroup analysis of cancer type, we failed to find any statistically significant associations between rs3746444 and risk of several specific kinds of cancer, such

Table 3 Pooled ORs and 95% CIs for miR-499 polymorphism from stratified meta-analysis

Subgroup	Genotype	Number of studies	Test of association		Test of heterogeneity		
			OR (95% CI)	*P*-value	Model	Phet	I^2 (%)
Asian	AG versus AA	13	1.14 (0.97–1.35)	0.113	R	0.001	63.3
	GG versus AA	13	1.32 (1.09–1.59)	0.004	F	0.024	48.8
	GG + AG versus AA	13	1.17 (1.01–1.37)	0.044	R	0.001	62.9
	GG versus AG + AA	13	1.14 (0.84–1.54)	0.418	R	0.004	58.4
	G versus A	13	1.14 (1.00–1.31)	0.050	R	0.000	66.5
Caucasian	AG versus AA	5	0.93 (0.84–1.03)	0.159	F	0.161	39.0
	GG versus AA	5	1.11 (0.92–1.35)	0.277	F	0.125	44.5
	GG + AG versus AA	5	0.96 (0.87–1.06)	0.388	F	0.321	14.6
	GG versus AG + AA	5	1.24 (0.92–1.66)	0.156	R	0.059	56.0
	G versus A	5	1.04 (0.91–1.18)	0.599	R	0.081	51.8
HCC	AG versus AA	4	0.99 (0.78–1.26)	0.963	F	0.156	42.5
	GG versus AA	4	1.27 (0.60–2.69)	0.540	R	0.040	63.8
	GG + AG versus AA	4	1.09 (0.73–1.64)	0.674	R	0.024	68.2
	GG versus AG + AA	4	1.26 (0.70–2.27)	0.447	R	0.107	50.8
	G versus A	4	1.12 (0.78–1.62)	0.547	R	0.004	77.5
BC	AG versus AA	4	1.07 (0.96–1.19)	0.210	F	0.395	0.0
	GG versus AA	4	1.37 (0.86–2.17)	0.181	R	0.070	75.6
	GG + AG versus AA	4	1.11 (1.00–1.22)	0.051	F	0.133	46.4
	GG versus AG + AA	4	1.33 (0.83–2.14)	0.242	R	0.003	78.3
	G versus A	4	1.20 (0.97–1.49)	0.100	R	0.002	79.6
CC	AG versus AA	2	0.86 (0.52–1.43)	0.558	R	0.119	58.8
	GG versus AA	2	1.61 (0.65–3.99)	0.306	R	0.141	53.8
	GG + AG versus AA	2	1.05 (0.78–1.41)	0.729	F	0.924	0.0
	GG versus AG + AA	2	1.68 (0.58–4.86)	0.340	R	0.085	66.3
	G versus A	2	1.20 (0.95–1.53)	0.129	F	0.243	26.6

Notes: The significance of association was evaluated by ORs and their 95% CIs. The between-study heterogeneity was assessed by *P*-values of the Cochran's Q test (Phet) and I^2 (a significance level of $P<0.05$ or $I^2 \geq 50\%$).

Abbreviations: BC, breast cancer; CC, colorectal cancer; CI, confidence interval; F, fixed-effects model; HCC, hepatocellular carcinoma; OR, odds ratio; R, random-effects model.

as hepatocellular carcinoma, lung cancer, breast cancer, and gallbladder cancer. This may be due to the small sample size and limited number of studies on the types of cancer involved in our study, which could not provide a sufficient statistical power for detecting the associations. More studies on special kinds of malignant tumors should be considered to verify the relationship in the future.

There are several limitations existing in this study that should be considered. First, although the funnel plots and Egger's tests did not show statistical significance, we only used English-language articles in the meta-analysis, so certain publication bias will exist. Second, the lack of original data in some valuable research restricted us to continue studying only some potential interactions, such as age, sex, family history, environmental exposure factors, and lifestyle. Third, this study lacks data from an African population.

Conclusion

We found that miR-499 rs3746444 GG genotype can increase the risk for cancer in an Asian population. However, the conclusion that rs3746444 in miR-499 is associated with cancer risk needs more study to be confirmed, and further consideration should be given to the influence of interactions between genes and exposure factors on cancer.

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Disclosure

The authors report no conflicts of interest in this work.

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