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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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META-ANALYSIS

Rs3746444 T>C locus in miR-499 increases the susceptibility to hepatocellular carcinoma: A meta-analysis 14812 subjects

Jia-Kai Jiang, Han-Shen Chen, Wei-Feng Tang, Yu Chen, Jing Lin

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Abstract

BACKGROUND

Recently, many investigations have suggested that the rs3746444 T>C locus in the microRNA (miR)-499 gene may contribute to the occurrence of cancer. However, reports on the association between rs3746444 and hepatocellular carcinoma (HCC) are conflicting.

AIM

To further understand and explore the potential correlation between the single-nucleotide polymorphism of rs3746444 and the incidence of HCC.

METHODS

In this meta-analysis, we obtained electronic literature by searching the PubMed, Embase and Chinese BioMedical Disc databases (through May 20, 2022). All eligible case-control, prospective cohort or nested case-control studies with sufficient data for calculating the odds ratios with their 95% confidence intervals were included.

RESULTS
Ultimately, a total of 17 independent studies were included. We identified that rs3746444 was associated with the development of HCC (C *vs* T: $P = 0.019$ and CC/CT *vs* TT: $P = 0.016$). In Asian individuals, rs3746444 was associated with susceptibility to HCC (C *vs* T: $P = 0.013$ and CC/CT *vs* TT: $P = 0.016$). In addition, this study identified that the miR-499 rs3746444 locus was associated with susceptibility to HCC in the normal/healthy control subgroup (C *vs* T: $P = 0.034$ and CC/CT *vs* TT: $P = 0.024$).

CONCLUSION
In summary, this meta-analysis highlights that rs3746444 in the miR-499 gene is involved in the occurrence of HCC, especially in Asian individuals.

Key Words: Polymorphism; MicroRNA-499; Hepatocellular carcinoma; Meta-analysis; Susceptibility

Core Tip: Many investigations have suggested that the rs3746444 T>C locus in the microRNA (miR)-499 gene may contribute to the occurrence of cancer. However, reports on the association between rs3746444 and hepatocellular carcinoma (HCC) are conflicting. This meta-analysis highlights that rs3746444 in the miR-499 gene is involved in the occurrence of HCC, especially in Asian individuals.

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INTRODUCTION

In 2020, liver cancer (LC) was the seventh most frequent malignancy, with 905677 new cases worldwide [1]. Accordingly, LC is ranked as the second leading cause of malignancy-related deaths, as it has resulted in death for 830180 individuals[1]. The incidence rates of LC and LC-related deaths remain higher in China than other parts of the world[2]. Hepatocellular carcinoma (HCC) is the predominant subtype of LC, accounting for approximately 75%-85% of primary LC cases[3]. Overall, the survival rate of HCC remains poor. To date, the etiology of HCC is not well established. Although it has been reported that chronic virus infection[4], type 2 diabetes[5,6], obesity[7,8], smoking[9,10], heavy alcohol intake[11-13] and aflatoxin-contaminated food stuffs[14] may contribute to the occurrence of HCC, other risk factors may also lead to the development of HCC, such as hereditary factors[15-18].

MicroRNAs (miRs) are noncoding RNAs of approximately 22 nucleotides in size. They may be implicated in the regulation of target genes and are involved in a number of cellular processes (*e.g.*, growth, proliferation, differentiation, apoptosis, migration and invasion)[19-24]. Recently, several investigations have reported that the expression profiling of serum miRs could be used as a marker for hepatitis C virus-related cases of HCC[25]. Variants within miRs may alter target recognition, transcription, or posttranscriptional processing and then lead to malignant diseases[26]. Additionally, most of the established miRs may influence many target genes; single-nucleotide polymorphisms (SNPs) in miRs could affect the level of multifarious proteins. MiR-499 is located within chromosome 20q. MiR-499 is involved in infection and inflammatory diseases[27]. Rs3746444 T>C in miR-499 was identified to be correlated with the development of ankylosing spondylitis[28], arthritis susceptibility [29], and bronchial asthma[27].

Additionally, a number of investigations have suggested that the rs3746444 SNP in miR-499 may contribute to the occurrence of cancer. Liu *et al*[30] reported that miR-499-5p could promote the metastasis of colorectal cancer and might be used as a vital target for colorectal cancer therapy. Additionally, a previous study identified that in HepG2 cells, miR-499 could inhibit the level of the E26 transformation specific sequence 1, which is an important proto-oncogene in the development of HCC [31]. The miR-499 variant rs3746444 has been suggested to play an important role in the occurrence of various malignancies, such as adenocarcinoma of the esophagogastric junction[32], prostate cancer[33], cervical squamous cell carcinoma[34], oral squamous cell cancer[35], and lung cancer[36]. Recently, a number of studies have focused on the relationship between rs3746444 in miR-499 and HCC[36-40]; however, the obtained findings are conflicting. Several meta-analyses also reported controversial results. Some pooled analyses have suggested that the rs3746444 C allele could not confer a risk to HCC

[41-44]. However, other publications have reported that the rs3746444 C allele may contribute to the occurrence of HCC[40,45-47]. These controversial findings may be due to the limited sample sizes included in these analyses. Recently, some case-control studies have been conducted to further explore this potential association[48-50]. An updated meta-analysis is needed to shed new light on the relationship between rs3746444 in miR-499 and HCC regarding all available publications. Therefore, this meta-analysis involved a large sample size to verify whether the miR-499 rs3746444 SNP could influence the occurrence of HCC. And these possible relationships might be beneficial to the prevention of liver carcinogenesis.

MATERIALS AND METHODS

Study research

In this meta-analysis, we obtained electronic literature by searching the PubMed, Embase and Chinese BioMedical Disc (CBM) databases (through May 20, 2022). We used the following keywords: (SNP OR variant OR polymorphism) AND (neoplasm OR carcinoma OR tumor OR cancer) AND (hepatocellular OR liver) AND (microRNA499 OR miR499 OR microRNA-499 OR miR-499 OR rs3746444). The references included in the retrieved publications and relevant reviews, as well as published meta-analyses, were hand-searched to obtain more related data. Due to no restriction on language, a large amount of data was collected. We also cited high-quality articles in *Reference Citation Analysis* (https://www.referencecitationanalysis.com).

Inclusion and exclusion criteria

The inclusion criteria for the eligible literature were as follows: (1) Assessing the relationship of rs3746444 in miR-499 with HCC susceptibility; (2) Full-text study; (3) Designed as a case-control study, a prospective cohort or a nested case-control study; and (4) Sufficient data could be used to calculate the odds ratios (Ors) with their 95% confidence intervals (CIs). When a publication contained more than one investigation, it was treated as an independent case-control study. Accordingly, letters, reviews, comments, non-case-control studies, studies that violated Hardy-Weinberg equilibrium (HWE), literature without sufficient data and duplicated data were excluded.

Data extraction

Two authors (Jiang JK and Lin J) reviewed the eligible literature and extracted the data independently. The following information was collected: The first author, year of publication, mean age (years), sex (male, %), drinking status (%), smoking status (%), country/ethnicity, hepatitis B surface antigen (HBsAg) (positive, %), number of subjects, HWE, genotyping method and genotype data. In a case of a conflicting assessment, another author (Tang WF) took part in a discussion until a consensus opinion was obtained.

Statistical methods

The results of this meta-analysis were assessed in four genetic models: A dominant model (CC/TC *vs* TT), recessive model (CC *vs* TT/TC), homozygote comparison (CC *vs* TT) and allelic model (C *vs* T). The correlation between rs3746444 in miR-499 and HCC susceptibility was determined by using Ors and the corresponding 95%CIs. The heterogeneity among the eligible studies was assessed by using the I^2 test and Q test. For heterogeneity, the level of significance was $P < 0.1$ and/or $I^2 \geq 50\%$. When it was significant, we used a random-effects model (DerSimonian and Laird) to assess the association between rs3746444 in miR-499 and HCC susceptibility[51,52]. Otherwise, we used a fixed-effects model (Mantel-Haenszel) to determine the potential association[53]. In this study, a Galbraith radial plot was used to confirm the source of the heterogeneity. Sensitivity analysis was performed to explore whether an individual investigation might significantly influence the assessment. We used Egger's test and Begg's funnel plots to measure the possible bias among the publications. For publication bias, the level of significance was $P < 0.1$. STATA 12.0 software (Stata Corp., College Station, Texas) was used to conduct statistical analysis. All P-values were measured with two-sided tests. By using Power-SampleSize software, the power value ($\alpha = 0.05$) was also used to assess the stability of our study[54]. We used the Newcastle-Ottawa Quality Assessment Scale to assess the quality of eligible studies and defined scores ≥ 7 stars as high-quality studies[55].

RESULTS

Study characteristics

An electronic search of the CBM, PubMed and Embase databases obtained 117 publications. After the titles or abstracts were reviewed by two authors (Jiang JK and Lin J), 47 duplicates were removed. Fifty articles were excluded based on the inclusion criteria (Figure 1). Thus, 20 articles were reviewed in full

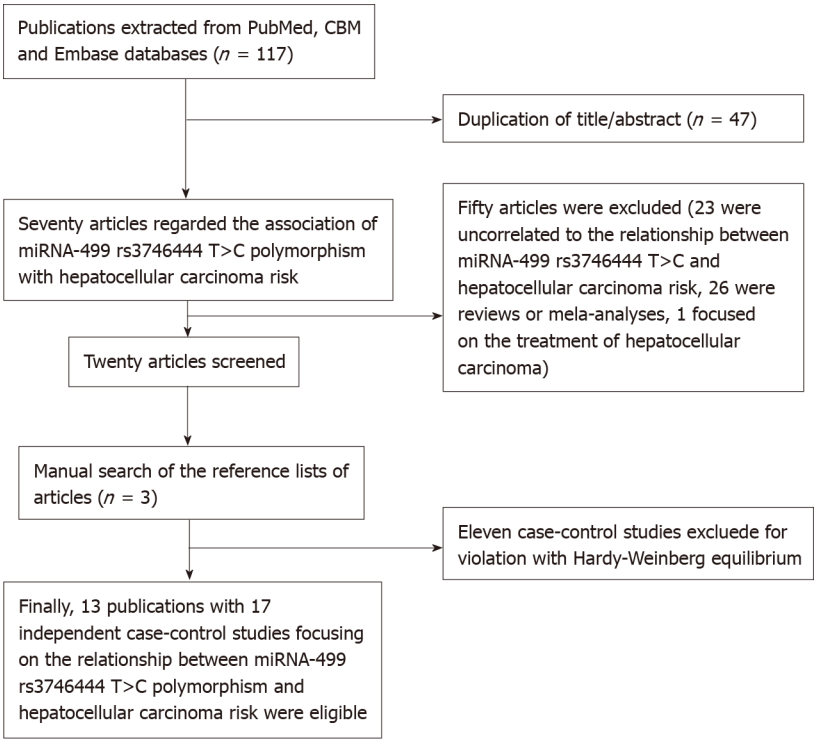

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Figure 1 Flow diagram of the meta-analysis. CBM: Chinese BioMedical Disc; miRNA: MicroRNA.

text. Three publications were included after reading the references of eligible articles. However, 11 case-control studies were excluded for violating HWE. Finally, 13 publications with 17 independent case-control studies focusing on the relationship between the rs3746444 polymorphism and HCC risk were included[40,48,50,56-65].

These included studies were published between 2012 and 2020, and in the eligible case-control studies, the participant number ranged from 100 to 1507. Table 1 shows the included terms in the eligible studies. In summary, 7 case-control studies involving Caucasian individuals were found[50,56-58], and the others focused on Asian individuals[40,48,59-65]. The distributions of the rs3746444 genotypes and alleles in the miR-499 SNP and the results of the quality assessment are summarized in Tables 1 and 2.

Main findings

The main results are summarized in Table 3. When we combined the included case-control studies, we identified that rs3746444 in miR-499 was associated with the development of HCC (C *vs* T: $P = 0.019$ and CC/CT *vs* TT: $P = 0.016$, Figure 2). In a subgroup analysis by different races, rs3746444 in miR-499 was found to be associated with susceptibility to HCC in the Asian population (C *vs* T: $P = 0.013$ and CC/CT *vs* TT: $P = 0.016$). When we considered the source of disease, the miR-499 rs3746444 locus was identified to be associated with susceptibility to HCC in normal/healthy control individuals (C *vs* T: $P = 0.034$ and CC/CT *vs* TT: $P = 0.024$) and hepatitis/virus-related control individuals (C *vs* T: $P = 0.007$, CC *vs* TT: $P = 0.014$ and CC/CT *vs* TT: $P = 0.018$).

Sensitivity analysis

To confirm the stability of our findings, we conducted a sensitivity analysis in this meta-analysis. We deleted an individual study in turn and calculated the Ors and CIs of the remaining studies to determine the influence of each datum. The findings suggested that these evaluations could not be altered by any eligible study (Figure 3).

Publication bias

By using Begg's and Egger's tests, publication bias among the eligible studies was determined. There was no significant bias among the eligible studies (Figure 4A, $P > 0.1$, data not shown).

Heterogeneity

In this meta-analysis, significant heterogeneity was identified. We conducted stratified analyses to explore the source of heterogeneity. Newcastle-Ottawa Scale (Nos) was used to evaluate the literature quality. We found an association between hospital-based (HB) studies, high-quality studies (Nos ≥ 7.0),

Table 1 Characteristics of the studies in meta-analysis

Ref.	Country	Ethnicity	Study design	Sex, male (%); case/control	Mean age (yr); case/control	Smoking (%); case/control	Drinking (%); case/control	HBsAg, positivee (%); case/control	Number cases/controls	Type of control	Case			Control			HWE
											TT	TC	CC	TT	TC	CC	
Zhang *et al*[59], 2016	China	Asian	HB	70.29/56.29	56.13/54.96	34.29/30.79	50.29/36.09	NA	175/302	Normal or healthy control	115	49	11	197	87	18	0.052
Li *et al*[60], 2015	China	Asian	PB	75.56/75.56	≥ 55 yr, 55.26/≥55 yr, 53.38	36.47/31.58	47.37/36.47	41.35/12.03	266/250	Normal or healthy control	150	92	24	166	83	17	0.140
Yan *et al*[61], 2015	China	Asian	PB	77.74/63.41	≥ 55 yr, 55.84/≥ 55 yr, 45.43	47.81/42.68	58.76/40.55	61.31/10.37	274/328	Normal or healthy control	147	98	29	188	112	28	0.060
Qi *et al*[62], 2014	China	Asian	PB	83.8/83.8	50.7/49.6	38.9/NA	27.4/NA	83.2/0.0	314/406	Normal or healthy control	195	117	2	301	101	4	0.157
Chu *et al*[63], 2014	China	Asian	HB	72.34/74.78	< 45 yr, 5.05, 45-59 yr, 30.85, ≥ 60 yr, 63.83/< 45 yr, 7.12, 45-59 yr, 40.06, ≥ 60 yr, 52.82	42.55/33.23	36.17/40.36	42.55/13.23	188/337	Normal or healthy control	119	60	9	281	55	1	0.321
Zhou *et al*[64], 2012	China	Asian	PB	82.8/NA	52.1/NA	NA/NA	NA/NA	NA/NA	186/483	Normal or healthy control	141	41	4	371	100	12	0.100
Xiang *et al*[65], 2012	China	Asian	HB	82/39	48.55/47.02	NA/NA	NA/NA	NA/NA	100/100	Hepatitis or virus related control	36	40	24	52	35	13	0.081
Xiang *et al*[65], 2012	China	Asian	HB	82/50	48.55/45.12	NA/NA	NA/NA	NA/NA	100/100	Normal or healthy control	36	40	24	54	36	10	0.284
Kim *et al*[40], 2012	Korea	Asian	PB	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	159/201	NA/NA	109	47	3	120	74	7	0.278
Zhang *et al*[48], 2020	China	Asian	HB	89.90/90.47	53.17/53.72	35.96/35.43	29.11/16.03	70.55/9.21	584/923	Normal or healthy control	409	154	12	669	230	22	0.673
Toraih *et al* [50], 2016	Egypt	Caucasian	HB	NA/NA	NA/NA	NA/NA	NA/NA	NA/NA	60/150	Normal or healthy control	28	23	9	57	66	27	0.307
Fteah *et al*[56], 2019, Abdel-Hamid *et al*	Egypt	Caucasian	HB	80.00/81.33	50.12/50.11	54.7/0.0	NA/NA	NA/NA	75/75	Normal or healthy control	41	32	2	31	30	14	0.175

[57], 2018	Egypt	Caucasian	HB	78.0/70.0	55.8/54.4	34.0/34.0	NA/NA	6.0/0.0	50/50	Normal or healthy control	3	32	15	16	23	11	0.617
Al-Qahtani *et al* [58], 2017	Saudi Arabia	Caucasian	HB	NA/68.4	NA/40.29	NA/NA	NA/NA	NA/100.00	145/585	Hepatitis or virus related control	48	70	27	219	273	93	0.607
Al-Qahtani *et al* [58], 2017	Saudi Arabia	Caucasian	HB	NA/79.7	NA/36.33	NA/NA	NA/NA	NA/100.00	145/222	Hepatitis or virus related control	48	70	27	87	100	35	0.486
Al-Qahtani *et al* [58], 2017	Saudi Arabia	Caucasian	HB	NA/94.25	NA/37.49	NA/NA	NA/NA	NA/0.0	145/400	Normal or healthy control	48	70	27	148	187	65	0.647
Al-Qahtani *et al* [58], 2017	Saudi Arabia	Caucasian	HB	NA/96.30	NA/30.80	NA/NA	NA/NA	NA/0.0	145/600	Normal or healthy control	48	70	27	216	291	93	0.758

PB: Population-based; HB: Hospital-based; NA: Not available; HBsAg: Hepatitis B surface antigen; HWE: Hardy-Weinberg equilibrium.

Asian individuals, and normal/healthy control subgroups and significant heterogeneity. The Galbraith radial plot test suggested that 4 outliers[40,56,63,65] might contribute to the significant heterogeneity (Figure 4B).

The power of the present study (α = 0.05)

By using Power-Sample Size software, the power value (α = 0.05) was also used to assess the stability of our study. As summarized in Table 3, in the overall comparison, the power value was more than 0.8 in the allele and dominant genetic models. In the subgroup analyses, the power value was more than 0.8 in Asian individuals and the normal/healthy control subgroups in the allele genetic model and in Asian individuals and the normal/healthy control subgroups in the dominant genetic model.

DISCUSSION

Recently, rs3746444 in miR-499 and its importance to the occurrence of HCC have been extensively investigated. However, several meta-analyses reported controversial results, which might be due to the limited sample sizes included in these analyses. Recently, some case-control studies have been conducted to further explore this potential association in different populations. Thus, an updated meta-analysis should be conducted to shed new light on the relationship between rs3746444 in miR-499 and HCC. As summarized in Table 3, we identified that rs3746444 in miR-499 was associated with the development of HCC in the allele and the dominant genetic models (the value of power ≥ 0.8).

The merit of this updated meta-analysis was that the present pooled analysis included a larger sample size to verify whether the miR-499 rs3746444 SNP could influence the occurrence of HCC. In this

Table 2 Quality assessment of the meta-analysis

Ref.	Selection				Comparability of the cases and controls	Exposure			Total stars
	Adequate case definition	Representativeness of the cases	Selection of the controls	Definition of Controls		Ascertainment of exposure	Same ascertainment method for cases and controls	Non-response rate	
Zhang *et al*[59], 2016	★	★	-	★	★★	★	★	-	7
Li *et al* [60], 2015	★	★	★	★	★★	★	★	-	8
Yan *et al* [61], 2015	★	★	★	★	★	★	★	-	7
Qi *et al* [62], 2014	★	★	★	★	★	★	★	-	7
Chu *et al* [63], 2014	★	★	-	★	★★	★	★	-	7
Zhou *et al*[64], 2012	★	★	★	★	★★	★	★	-	8
Xiang *et al*[65], 2012	★	★	-	★	★	★	★	-	6
Xiang *et al*[65], 2012	★	★	-	★	★	★	★	-	6
Kim *et al* [40], 2012	★	★	★	★	-	★	★	-	6
Zhang *et al*[48], 2020	★	★	-	★	★★	★	★	-	7
Toraih *et al*[50], 2016	★	★	-	★	-	★	★	-	5
Fteah *et al*[56], 2019	★	★	-	★	★★	★	★	-	7
Abdel-Hamid *et al*[57], 2018	★	★	-	★	★★	★	★	-	7
Al-Qahtani *et al*[58], 2017	★	★	-	★	-	★	★	-	5
Al-Qahtani *et al*[58], 2017	★	★	-	★	-	★	★	-	5
Al-Qahtani *et al*[58], 2017	★	★	-	★	-	★	★	-	5
Al-Qahtani *et al*[58],	★	★	-	★	-	★	★	-	5

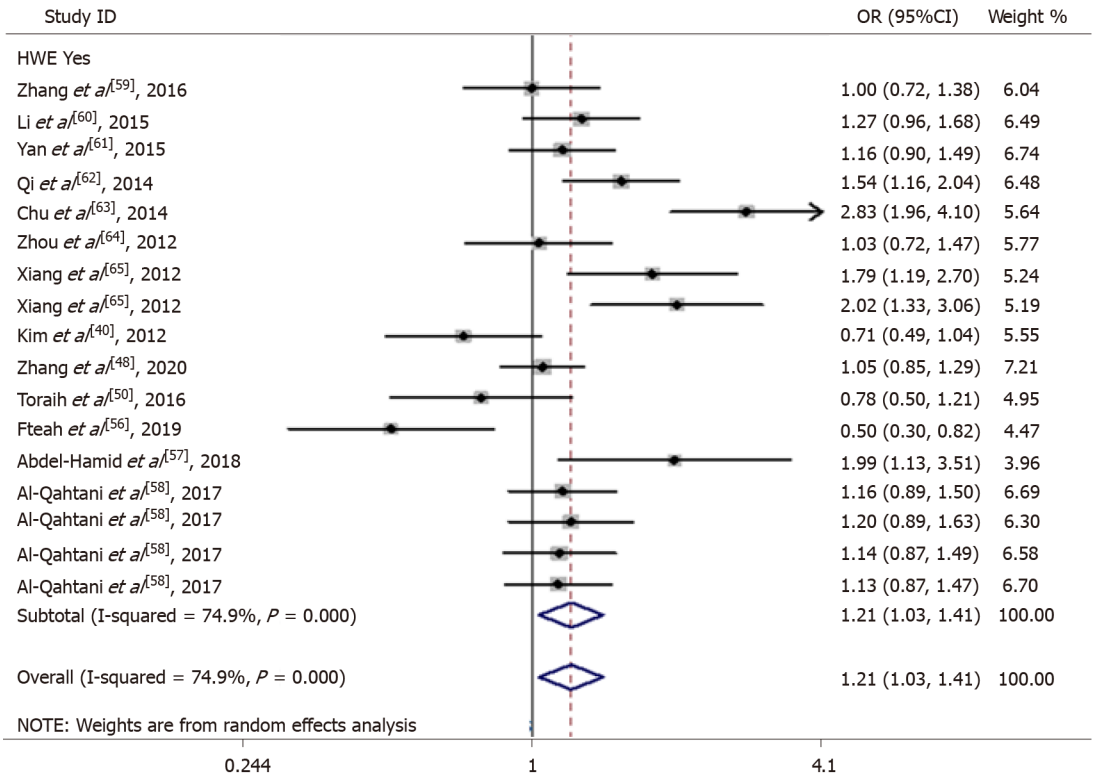

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Figure 2 Meta-analysis of the relationship between rs3746444 in microRNA-499 single-nucleotide polymorphism with the risk of hepatocellular carcinoma (C *vs* T, random-effects model). OR: Odds ratio; CI: Confidence interval.

study, we identified that the miR-499 rs3746444 SNP could confer a risk to HCC. Some meta-analyses have focused on the potential correlation between rs3746444 in miR-499 and the risk of HCC. A previous pooled analysis suggested that the rs3746444T allele in the miR-499 gene could not play a vital role in the tumorigenesis of HCC[42]. However, other meta-analyses reported that rs3746444 in miR-499 might confer susceptibility to HCC[40,45-47]. Additionally, some more recent case-control studies have been conducted to explore the potential association between rs3746444 in the miR-499 SNP and the risk of HCC[48-50]. The potential association was more controversial. Thus, we included 28 independent case-control studies with 5948 cases and 8864 controls and conducted an updated meta-analysis to focus on the relationship between rs3746444 in the miR-499 SNP and the risk of HCC. In this study, we identified that the miR-499 rs3746444 SNP could confer a risk to HCC.

Toraih *et al*[26] reported that in silico data analysis, the T to C substitution in the miR-499 rs3746444 SNP did not prominently affect the structure of the hairpin loop. Functional prediction revealed that different miR-499 rs3746444 alleles have different targets. The miR-499 rs3746444*C allele only has 58.2% of the gene targets of the rs3746444*T variant and generates 763 new gene targets. The miR-499 gene can target both alcohol dehydrogenase 1 beta polypeptide (ADH1B) and aldehyde dehydrogenase 1 family member A3 (ALDH1A3) genes. Pettinelli *et al*[66] suggested that hepatic ALDH1A3 was expressed at lower levels and was inversely correlated with the level of plasma retinol in nonalcoholic steatohepatitis cases, which may alter the risk for HCC. Recently, some studies have identified that the ADH1B gene may be involved in the development of HCC[67-69]. A previous study indicated that rs3746444 in miR-499 was correlated with susceptibility to ulcerative colitis and that the expression of miR-499 was decreased (5-fold) in ulcerative colitis cases with the rs3746444 TC genotype compared with those with the rs3746444 TT variant[70]. Taken together, these results indicate that the rs3746444 C allele in the miR-499 gene could decrease the expression of the miR-499 gene and alter the levels of the ADH1B and ALDH1A3 genes. Finally, this SNP could be implicated in the occurrence of HCC. However, the relationship between rs3746444 in miR-499 and HCC in different subgroups could not be well explained. In the future, more attention should be given to the potential mechanism by which hepatitis B virus infection acts in different ethnicities or statuses.

Since significant heterogeneity was found in this meta-analysis, subgroup analysis was performed to observe the major source of heterogeneity. The findings of the subgroup analysis indicated that the

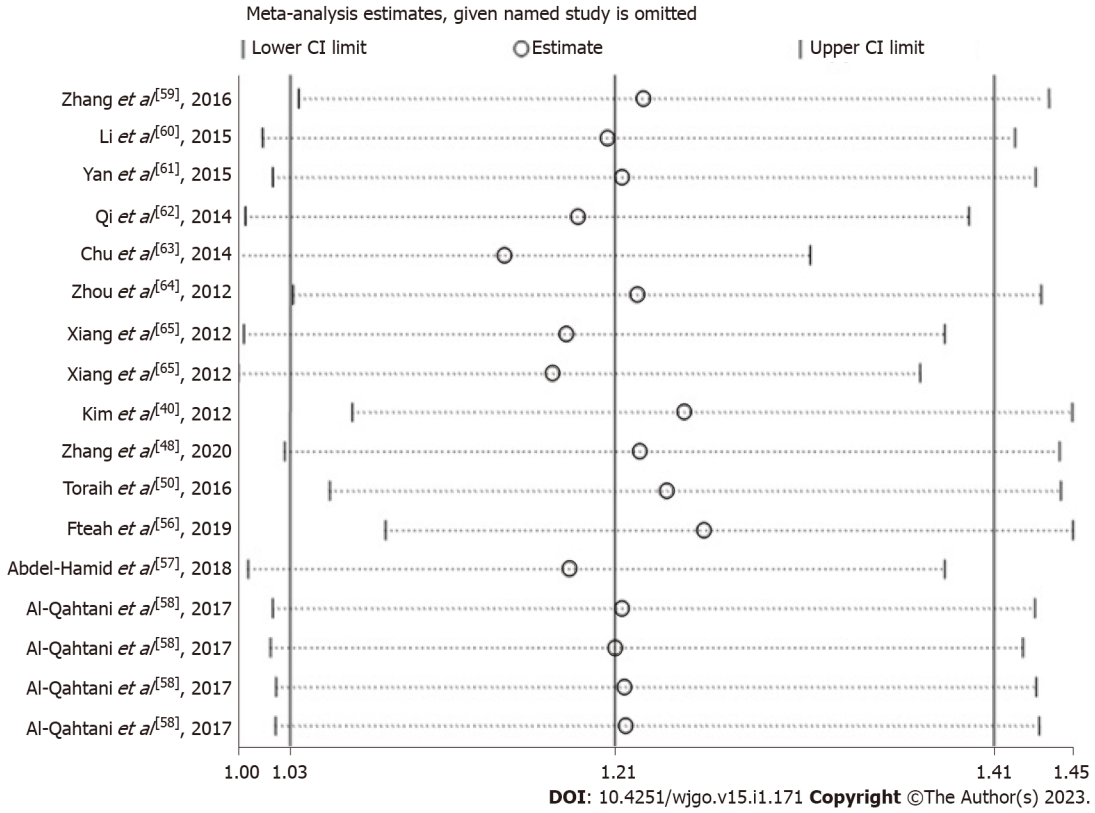

Figure 3 Sensitivity analysis of the influence of C *vs* T genetic model (random-effects model). CI: Confidence interval.

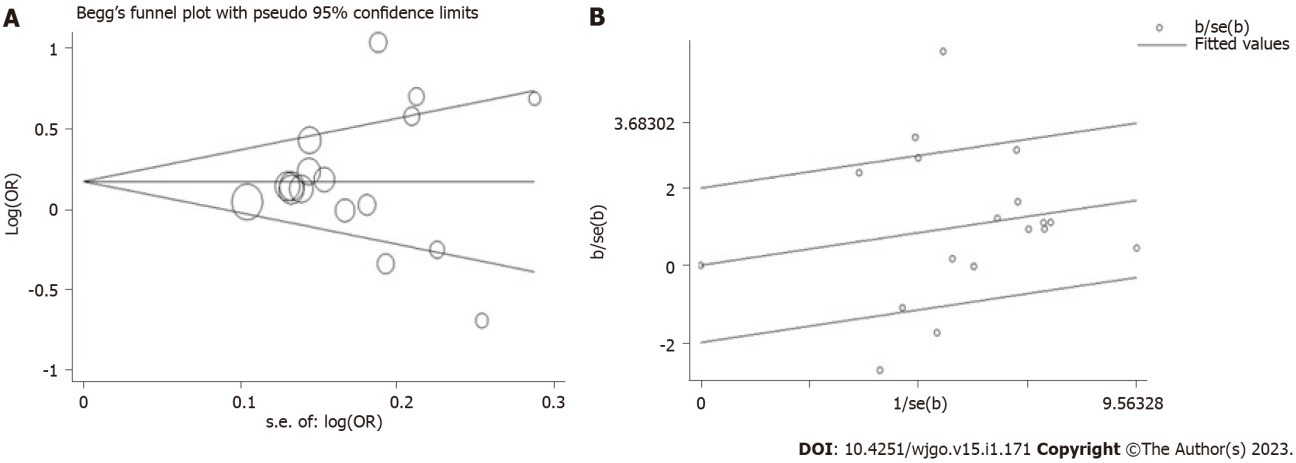

Figure 4 Plot of meta-analysis (C *vs* T, random-effects model). A: Begg's funnel; B: Galbraith radial. OR: Odds ratio.

normal/healthy control, Asian and HB subgroups could greatly increase the heterogeneity. Additionally, the Galbraith radial plot identified 4 outliers[40,56,63,65], which could contribute to the major source of heterogeneity.

There are some limitations in this meta-analysis. First, the electronic literature was only searched in the PubMed, Embase and CBM databases, and bias might have occurred. Second, all investigations have been conducted in Caucasian and Asian populations; thus, our findings were only appropriate for these populations. Third, due to insufficient data (*e.g.*, HBsAg, drinking, smoking, sex, age, body mass index and lifestyle) in this study, we did not consider these factors in the subgroup analysis. Fourth, due to the lack of environmental factors, we also did not take into account gene-environment interactions. Fifth, in this meta-analysis, significant heterogeneity was identified. Sixth, we did not pay close attention to the expression level of target genes, which could be controlled by rs3746444 T>C locus. Finally, in this study, we only included the relationship between rs3746444 in miR-499 and HCC risk. The potential role of other vital miR loci can't be ignored.

Table 3 Summary of results of the meta-analysis from different comparative genetic model

Genetic comparison	Population	OR (95%CI)	*P* value	Test of heterogeneity		Model	Power value
				P value	I^2		
C *vs* T	All	1.21 (1.03-1.41)	**0.019**	< 0.001	74.9%	R	1.000
	Ethnicity						
	Asians	1.32 (1.06-1.64)	**0.013**	< 0.001	79.4%	R	1.000
	Caucasians	1.06 (0.86-1.32)	0.586	0.010	64.2%	R	-
	Study design						
	HB	1.25 (1.01-1.54)	**0.039**	< 0.001	79.0%	R	0.999
	PB	1.13 (0.90-1.42)	0.285	0.027	63.6%	R	-
	Controls						
	Normal or healthy control	1.22 (1.02-1.48)	**0.034**	< 0.001	77.2%	R	0.998
	Hepatitis or virus related control	1.27 (1.07-1.52)	**0.007**	0.192	39.4%	F	0.785
	NA	0.71 (0.49-1.04)	0.080	-	-	-	-
	Nos quality assessment						
	≥ 7.0	1.24 (0.97-1.58)	0.088	< 0.001	81.2%	R	
	< 7.0	1.17 (0.96-1.43)	0.216	0.004	66.2%	R	
CC *vs* TT	All	1.33 (0.98-1.80)	0.071	0.002	57.3%	R	-
	Ethnicity						
	Asians	1.48 (0.97-2.26)	0.073	0.021	54.0%	R	-
	Caucasians	1.16 (0.72-1.87)	0.534	0.008	65.3%	R	-
	Study design						
	HB	1.44 (0.97-2.16)	0.074	< 0.001	67.7%	R	-
	PB	1.20 (0.83-1.73)	0.344	0.551	0.0%	F	-
	Controls						
	Normal or healthy control	1.31 (0.88-1.93)	0.183	0.001	62.8%	R	-
	Hepatitis or virus related control	1.56 (1.10-2.23)	**0.014**	0.329	10.1%	F	0.725
	NA	0.47 (0.12-1.87)	0.285	-	-	-	-
	Nos quality assessment						
	≥ 7.0	1.26 (0.71-2.25)	0.436	0.02	67.3%	R	
	< 7.0	1.41 (1.01-1.96)	**0.014**	0.086	43.8%	R	0.881
CC/CT *vs* TT	All	1.26 (1.04-1.51)	**0.016**	< 0.001	70.0%	R	0.999
	Ethnicity						
	Asians	1.34 (1.06-1.71)	**0.016**	< 0.001	75.7%	R	0.999
	Caucasians	1.12 (0.83-1.51)	0.468	0.021	59.7%	R	-
	Study design						
	HB	1.32 (1.03-1.70)	**0.031**	< 0.001	73.1%	R	0.999
	PB	1.16 (0.87-1.54)	0.309	0.014	67.9%	R	-
	Controls						
	Normal or healthy control	1.29 (1.03-1.60)	**0.024**	< 0.001	72.5%	R	0.999
	Hepatitis or virus related control	1.37 (1.06-1.77)	**0.018**	0.397	0.0%	F	0.697

	NA	0.68 (0.44-1.05)	0.084	-	-	-	-
	Nos quality assessment						
	≥ 7.0	1.33 (1.01-1.76)	**0.044**	< 0.001	78.2%	R	0.997
	< 7.0	1.18 (0.92-1.51)	0.191	0.026	56.1%	R	
CC *vs* TT/CT	All	1.21 (0.96-1.53)	0.109	0.049	39.4%	R	-
	Ethnicity						
	Asians	1.37 (0.95-1.97)	0.095	0.077	42.1%	R	-
	Caucasians	1.09 (0.87-1.37)	0.448	0.127	39.6%	F	-
	Study design						
	HB	1.25 (0.93-1.70)	0.145	0.014	53.7%	R	-
	PB	1.15 (0.80-1.65)	0.449	0.640	0.0%	F	-
	Controls						
	Normal or healthy control	1.18 (0.87-1.60)	0.284	0.029	47.5%	R	-
	Hepatitis or virus related control	1.36 (0.99-1.87)	0.061	0.421	0.0%	F	-
	NA	0.53 (0.14-2.10)	0.368	-	-	-	-
	Nos quality assessment						
	≥ 7.0	1.08 (0.68-1.71)	0.744	0.027	53.7%	R	
	< 7.0	1.30 (1.05-1.60)	**0.017**	0.284	18.5%	F	0.734

Bold values are statistically significant ($P < 0.05$). F: Indicates fixed model; R: Indicates random model; PB: Population-based; HB: Hospital-based; NA: Not available; OR: Odds ratio; CI: Confidence interval; NOS: Newcastle-Ottawa Scale.

CONCLUSION

In summary, this meta-analysis highlights that rs3746444 in miR-499 is involved in the occurrence of HCC, especially in Asian individuals. In the future, more investigations are needed to confirm our results.

ARTICLE HIGHLIGHTS

Research background

This meta-analysis highlights that rs3746444 in microRNA (miR)-499 is involved in the occurrence of hepatocellular carcinoma (HCC), especially in Asian individuals. These possible relationships might be beneficial to the prevention of liver carcinogenesis. In the future, more investigations are needed to confirm.

Research motivation

Recently, a number of studies have focused on the relationship between rs3746444 in miR-499 and HCC. However, the obtained findings are conflicting.

Research objectives

In summary, this meta-analysis highlights that rs3746444 in miR-499 is involved in the occurrence of HCC, especially in Asian individuals. In the future, more investigations are needed to confirm our results.

Research methods

This meta-analysis involved a large sample size to verify whether the miR-499 rs3746444 single-nucleotide polymorphism could influence the occurrence of HCC. These possible relationships might be beneficial to the prevention of liver carcinogenesis.

Research results

Reports on the association between rs3746444 and HCC are conflicting.

Research conclusions

The results of this meta-analysis were assessed in four genetic models: A dominant model (CC/TC *vs* TT), recessive model (CC *vs* TT/TC), homozygote comparison (CC *vs* TT) and allelic model (C *vs* T). The correlation between rs3746444 in miR-499 and HCC susceptibility was determined by using odd ratios and the corresponding 95% confidence intervals. We used a random-effects model (DerSimonian and Laird) to assess the association between rs3746444 in miR-499 and HCC susceptibility. Otherwise, we used a fixed-effects model (Mantel-Haenszel) to determine the potential association. We used the Newcastle-Ottawa Quality Assessment Scale to assess the quality of eligible studies and defined scores ≥ 7 stars as high-quality studies.

Research perspectives

Reports on the association between rs3746444 and HCC are conflicting. This meta-analysis highlights that rs3746444 in miR-499 is involved in the occurrence of HCC, especially in Asian individuals. These possible relationships might be beneficial to the prevention of liver carcinogenesis.

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FOOTNOTES

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