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CC genotype in hsa-mir-608 gene polymorphism is associated with a decreased risk of specific types of cancer in Asian populations

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Abstract: Several studies have been conducted to examine the association between miR-608 (rs4919510) gene polymorphism and cancer risk, but the conclusions remain controversial. The aim of our study was to investigate whether miR-608 rs4919510 polymorphism is associated with the risk of cancer. We conducted a search of PUBMED, EMBASE and the Cochrane Library up to April 2015. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined as measures of the strength of association between miR-608 rs4919510 polymorphism and cancer risk. The combined results based on all studies showed that miR-608 (rs4919510) gene polymorphism had a statistically significant decreased risk of cancer development under four comparison models (C versus G: $p < 0.001$; CC versus GG: $p < 0.001$; CC+GC versus GG: $p = 0.034$; CC versus GC+GG: $p < 0.001$). Among Asian subgroups, the combined results showed that a statistically significant decreased risk of cancer development was observed under three comparison models (C versus G: p = 0.026; CC versus GG: p = 0.018; CC versus GC+GG: $p < 0.001$). The pooled results of this meta-analysis suggested that the CC genotype of the rs4919510 polymorphism within hsa-mir-608 was significantly associated with a decreased risk of cancer among Asians.

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1. Introduction

MicroRNAs (miRNAs) are short non-coding endogenous RNA molecules, 20–25 nucleotides in length, that negatively regulate multiple genes in biological pathways [1] at the posttranscriptional level by sequence-specific translational repression and/or degradation of target messenger RNA [2]. Approximately one third of human genes have been reported to be conserved miRNA targets, indicating that miRNAs are involved in a multitude of biological pathways [3]. The interest in miRNAs has grown up with the discovery of their implications as key regulators in many diseases including cancer [4]. Single nucleotide polymorphisms (SNPs) have been identified within miRNAs. However, the presence of SNPs directly in miRNAs genes may have an even higher impact on cancer. SNPs in miRNA genes are thought to affect function through the transcription of the primary transcript, pri-miRNA and pre-miRNA processing, or effects on miRNA–mRNA interactions [5]. Several SNPs in miRNA-related genes have been previously associated with the risk of cancer.

Recently, a study conducted by Zhang et al [6] finds that miR-608 regulate chordoma malignancy by regulating EGFR, MET and Bcl-xL. Several studies have also investigated the association between miR-608 (rs4919510) gene polymorphism and the risk of cancer. However, the results of the relevant studies have generally been inconsistent, in part because of the differences from the sample sizes, the types of cancer, and the ethnicity of the patients. No study has yet investigated the association of miR-608 rs4919510 polymorphism with cancer risk based on an analysis of a large number of samples. Therefore, we performed a meta-analysis to derive a more powerful estimation of the association between miR-608 rs4919510 polymorphism and the risk of cancer.

2. Materials and Methods

2.1. Publication search

The meta-analysis was conducted according to PRISMA statement [7] and Cochrane Collaboration guidelines (http://handbook.cochrane.org/). The major electronic databases (PUBMED, EMBASE and the Cochrane Library, up to May 2015) were searched to identify case-control studies that investigated the association between miR-608 rs4919510 polymorphism and cancer risk. The search strategies were based on combinations of the following terms: "miR-608 or mir-608 or microRNA-608 or rs4919510" AND "polymorphism or polymorphisms or variation or mutation" AND "cancer or tumor or carcinoma or neoplasm". We did not restrict our search to specific publication dates. In addition, reference lists of all identified articles were manually screened and reviewed for relevant studies.

2.2. Eligibility criteria

Studies were included in the meta-analysis if they satisfied the following criteria: (1) They were case-control studies in human beings; (2) The study assessed the association between miR-608 rs4919510 polymorphism and the risk of cancer; (3) The study provided complete genotypes distribution data; (4) The study fulfilled Hardy—Weinberg equilibrium (HWE) in the control group; (5) Genotyping method in each study was universally acknowledged; (6) The article was written in English. If it was written in any other language, the article was excluded. If more than one study were published using the same case series, we included the study with the most cases or the most recent analysis. Two reviewers (Guoming Su and June Wang) independently identified eligible studies according to the selection criteria. Any disagreement between reviewers was solved by discussion.

2.3. Data extraction and quality assessment

Data were extracted by two reviewers (Guoming Su and Li Zhou) independently from eligible studies. Then another reviewer (June Wang) verified them and any discrepancies were resolved by consensus. The following data were extracted from each study: name of first author, year of publication, country of origin, ethnicity, genotyping method, types of cancer, source of controls, numbers of cases and controls, genotype frequency in cases and controls, Hardy-Weinberg equilibrium in control groups, respectively.

We assessed the quality of the studies using a set of predetermined criteria that was extracted and modified from previous studies [8, 9]. This scale for quality assessment was presented in the Table 1. The scores ranged from the lowest zero to the highest 18. Those studies with scores $\geqslant$ 12 were classified as "high quality"; otherwise, the studies were classified as "low quality".

Table 1. Scale for Quality Assessment.

Criterion	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathology archives, but without description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (caner-free patients)	1
Not described	0
Case-control match	
Matched by age and gender	3
Not matched by age and gender	0
Specimens used for determining genotypes	
White blood cells or normal tissues	3
Tumor tissue or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
>1000	3
>500 and <1000	2
>200 and <500	1
<200	0

2.4. Statistical analysis

HWE was evaluated by Pearson's goodness-of-fit $\chi 2$ test for each study in the controls, and a p value of less than 0.05 was considered as deviation from HWE [10]. The strength of the association between the miR-608 rs4919510 polymorphism and cancer risk was assessed by calculating crude odds ratios (ORs) along with their 95 % confidence intervals (CIs) under the following gene comparisons: C versus G, GC versus GG, CC versus GG, CC + GC versus GG, and CC versus GC + GG, respectively. Heterogeneity was determined using

the Cochrane's Q test and I2 statistics [11]. When the Q-test showed a $p < 0.05$ or I2 test exhibited > 50%, the random-effect model was used for the meta-analysis [12]; otherwise, the fixed-effect model was chosen [13]. We performed stratified analyses based on ethnicity and cancer types. Sensitivity analyses were also carried out by sequential omission of each study one at a time to ensure the stability of our results. Publication bias of the selected articles was assessed using Begg's funnel plot [14] and Egger's linear regression method [15]. All statistical analyses were performed by using STATA version 12 (Stata Corpotion, College Station, Texas).

3. Results

3.1. Study characteristics

A total of 44 records were initially identified from PUBMED and EMBASE. But no record was identified from the Cochrane Library. We give the detailed search strategies and results in Table 2. The flow diagram summarizing the literature review process and final participation is shown in Fig. 1. The study of Qiu et al [16] presented separate OR by different source of samples (southern Chinese and eastern Chinese). Thus, each of them was considered separately in this meta-analysis. Finally, a total of 8 studies including 5,319 cases and 6,628 controls were used in the meta-analysis [16-22]. The publication year of included articles ranged from 2012 to 2015. Each study investigated a single type of cancer, except for one study [17] which investigated both 828 patients with papillary thyroid cancer (PTC) and 488 patients with benign thyroid tumor (BN). But we excluded BN section. The distribution of genotypes in the controls of all studies was in agreement with HWE ($p \geqslant 0.05$). The quality scores of all studies ranged from 11 to 18, with 75% (6/8) of the selected studies classified as high quality ($\geqslant 12$). The main characteristics of the selected studies are presented in Table 3.

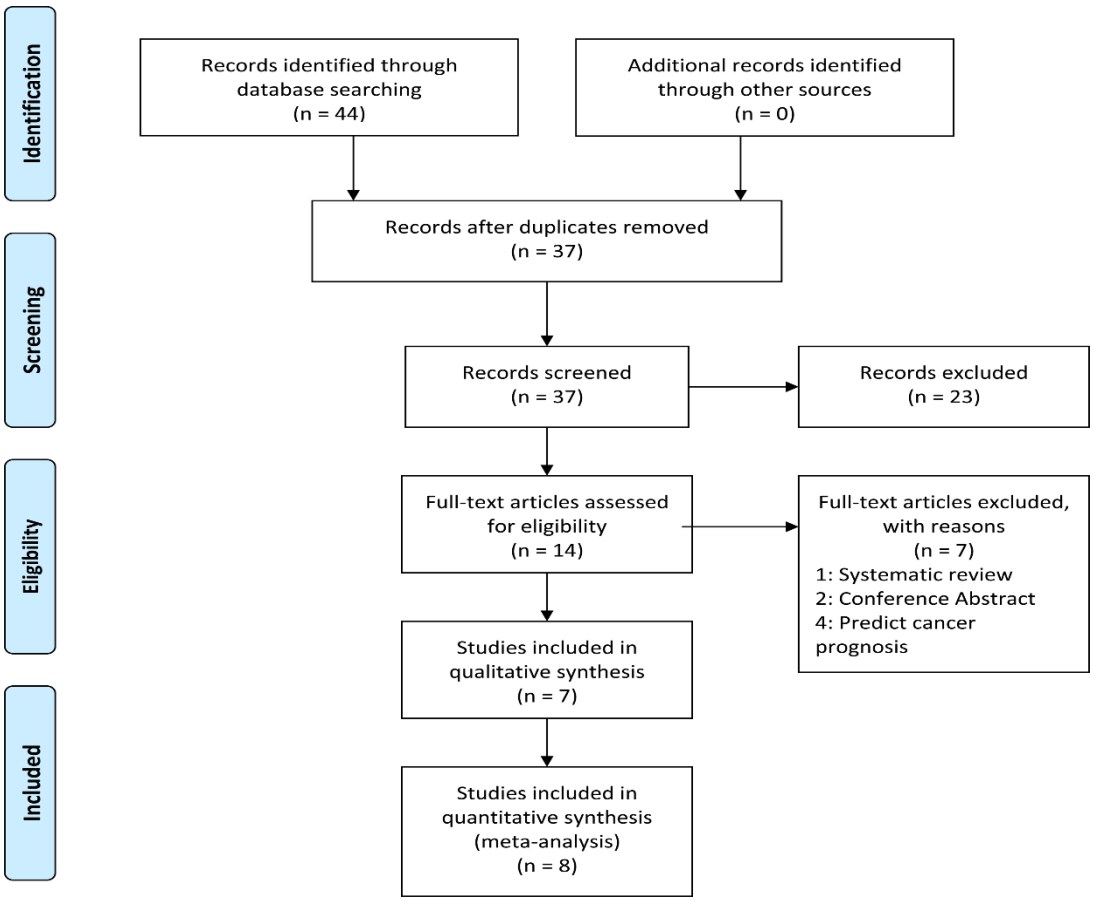

Fig. 1. Articles identified with criteria for inclusion and exclusion.

Table 2. The detailed search strategies and results.

Database	Last Update	Search Strategy	Results
PubMed	April 29, 2015	((((miR-608[All Fields] OR mir-608[All Fields]) OR microRNA-608[All Fields]) OR rs4919510[All Fields]) AND ((((("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) OR ("polymorphism, genetic"[MeSH Terms] OR ("polymorphism"[All Fields] AND "genetic"[All Fields]) OR "genetic polymorphism"[All Fields] OR "polymorphisms"[All Fields])) OR variation[All Fields]) OR ("mutation"[MeSH Terms] OR "mutation"[All Fields]))) AND ((((("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) OR ("tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields])) OR ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields])) OR ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]))	19
Embase	April 29, 2015	#1 'mir 608' OR 'microrna 608' OR rs4919510 #2 polymorphism OR polymorphisms OR variation OR mutation #3 cancer OR tumor OR carcinoma OR neoplasm #4 #1 AND #2 AND #3	25
Cochrane	Issue 4 of 12, April 2015	#1 microRNA-608 in Title, Abstract, Keywords or mir-608 or miR-608 or rs4919510 #2 polymorphism in Title, Abstract, Keywords or polymorphisms or variation or mutation #3 cancer in Title, Abstract, Keywords or tumor or carcinoma or neoplasm #4 #1 AND #2 AND #3	0

Table 3. Characteristics of the selected studies in the present meta-analysis.

First author	Year	Country	Ethnicity	Genotyping method	Tumor type	Source of controls	Cases			Controls			HWE (*p*)	Quality score
							GG	GC	CC	GG	GC	CC		
Wei WJ [16]	2014	China	Asian	MassARRAY	PTC	PB	266	428	130	326	503	202	0.750	17
Wang R [17]	2014	China	Asian	MassARRAY	HCC	PB	304	500	189	318	497	177	0.475	14
Kupcinskas J [18]	2014	Multicenter	Caucasian	TaqMan	GC	HB	25	88	250	13	86	251	0.108	11
Qiu F [15]	2015	China(southern)	Asian	TaqMan	NPC	PB	255	460	191	254	532	286	0.829	18
Qiu F [15]	2015	China(eastern)	Asian	TaqMan	NPC	PB	191	343	150	222	437	248	0.284	18
Kupcinskas J [19]	2014	Multicenter	Caucasian	TaqMan	CRC	HB	7	47	138	12	96	318	0.155	11
Ryan BM [20]	2012	America	Mix	TaqMan	CRC	Mix	19	96	124	36	166	231	0.427	12
Huang AJ [21]	2012	China	Asian	SNPlex	BC	PB	381	545	192	456	684	277	0.476	14

PTC, papillary thyroid cancer; HCC, hepatocellular carcinoma; GC, gastric cancer; NPC, nasopharyngeal carcinoma; CRC, colorectal cancer; BC, breast cancer; HB, hospital-based; PB, population-based; HWE, Hardy-Weinberg equilibrium in the control groups.

3.2. Main results of meta-analysis

The results of the meta-analysis are presented in detail in Table 4. In the overall analysis, no significant heterogeneity ($I^2 < 50\%$ and $p > 0.05$) was identified in all comparison models. Therefore, fixed effects model was used to pool the results. The combined results based on all studies showed that miR-608 (rs4919510) gene polymorphism had a significantly decreased risk of cancer development under four comparison models (C versus G: OR = 0.905, 95% CI = 0.859-0.955, $p < 0.001$; CC versus GG: OR = 0.806, 95% CI = 0.722-0.900, $p < 0.001$; CC+GC versus GG: OR = 0.913, 95% CI = 0.839-0.993, p = 0.034; CC versus GC+GG: OR = 0.841, 95% CI = 0.770-0.919, $p < 0.001$). Forest plot of cancer risk associated with the miR-608 rs4919510 polymorphism (CC versus GG) is shown in Fig. 2.

Table 4. Summary of pooled ORs in the meta-analysis.

Comparisons	Number of genotypes		Test of association			Test of heterogeneity	
	Cases	Controls	OR	95 % CI	*p* value	I^2 (%)	*p* value
Total studies (n = 8)							
C versus G	5235/5403	6981/6275	0.905	0.859-0.955	**< 0.001**	33.2	0.163
GC versus GG	2507/1448	3001/1637	0.959	0.877-1.048	0.354	0	0.62
CC versus GG	1364/1448	1990/1637	0.806	0.722-0.900	**< 0.001**	39.3	0.117
CC+GC versus GG	3871/1448	4991/1637	0.913	0.839-0.993	**0.034**	16.7	0.299
CC versus GC+GG	1364/3955	1990/4638	0.841	0.770-0.919	**< 0.001**	17.7	0.29
Asians (n = 5)							
C versus G	3980/5070	5033/5805	0.906	0.830-0.988	**0.026**	57.8	0.05
GC versus GG	2276/1397	2653/1576	0.966	0.882-1.059	0.459	0	0.632
CC versus GG	852/1397	1190/1576	0.808	0.678-0.964	**0.018**	57.2	0.053
CC+GC versus GG	3128/1397	3843/1576	0.92	0.844-1.003	0.058	26.8	0.243
CC versus GC+GG	852/3673	1190/4229	0.828	0.750-0.914	**< 0.001**	48.9	0.098
Caucasians (n = 2)							
C versus G	911/ 199	1320/ 232	0.834	0.674-1.030	0.092	0	0.761
GC versus GG	135/32	182/25	0.621	0.347-1.114	0.11	0	0.47
CC versus GG	388/32	569/25	0.583	0.335-1.015	0.057	0	0.547
CC+GC versus GG	523/32	751/25	0.591	0.341-1.025	0.061	0	0.52
CC versus GC+GG	388/167	569/207	0.871	0.681-1.114	0.271	0	0.983
CRC (n = 2)							
C versus G	667/ 195	1360/ 358	0.935	0.765-1.141	0.507	0	0.592
GC versus GG	143/26	262/48	1.02	0.607-1.716	0.94	0	0.654
CC versus GG	262/26	549/48	0.934	0.563-1.549	0.791	0	0.586
CC+GC versus GG	405/26	811/48	0.966	0.589-1.584	0.892	0	0.578
CC versus GC+GG	262/169	549/310	0.912	0.714-1.164	0.459	0	0.744
NPC (n = 2)							
C versus G	1485/1695	2037/1921	0.826	0.753-0.907	**< 0.001**	0	0.804
GC versus GG	803/446	969/476	0.884	0.753-1.036	0.128	0	0.725
CC versus GG	341/446	534/476	0.682	0.565-0.823	**< 0.001**	0	0.774
CC+GC versus GG	1144/446	1503/476	0.812	0.699-0.944	**0.007**	0	0.728
CC versus GC+GG	341/1249	534/1445	0.74	0.633-0.864	**< 0.001**	0	0.917

OR, odds ratio; 95 % CI, 95 % confidence interval; n, number of included studies; CRC, Colorectal cancer; NPC, Nasopharyngeal carcinoma.

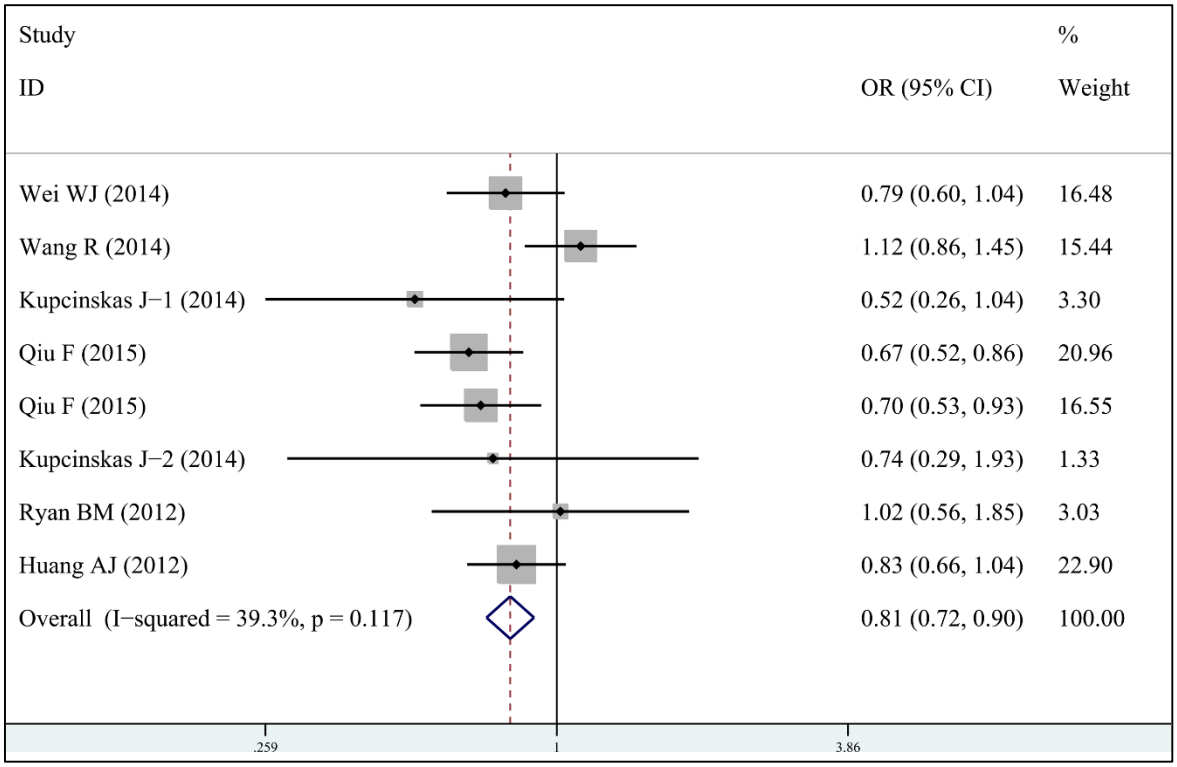

Fig. 2. Forest plots of odds ratios for the association of the miR-608 rs4919510 polymorphism (CC versus GG) with cancer risk in overall analyses. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

One stratified analysis was conducted according to ethnicity (Asians and Caucasians). In Asians, significant statistical heterogeneity was identified in the two comparison models (C versus G and CC versus GG) so that random-effects model was used. Fixed-effects model was used in other three comparison models. The combined results showed that a significantly decreased risk of cancer development was observed under three comparison models (C versus G: OR = 0.906, 95% CI = 0.830-0.988, p = 0.026; CC versus GG: OR = 0.808, 95% CI = 0.678-0.964, p = 0.018; CC versus GC+GG: OR = 0.828, 95% CI = 0.750-0.914, $p < 0.001$) among Asians. In Caucasians, there was no significant association between miR-608 rs4919510 polymorphism and cancer risk in all comparison models, however, a trend of reduced risk could be seen (see Table 4).

Another stratified analysis was also performed according to cancer types (CRC and NPC). No significant heterogeneity ($I^2 < 50\%$ and $p > 0.05$) was identified in all comparison models. As for NPC, a significantly decreased risk of cancer development was observed under four comparison models (C versus G: OR = 0.826, 95% CI = 0.753-0.907, $p < 0.001$; CC versus GG: OR = 0.682, 95% CI = 0.565-0.823, $p < 0.001$; CC+GC versus GG: OR = 0.812, 95% CI = 0.699-0.944, $p = 0.007$; CC versus GC+GG: OR = 0.740, 95% CI = 0.633-0.864, $p < 0.001$). However, as for CRC, no significant association was observed in all comparison models.

3.3. Sensitivity analysis

Sensitivity analysis showed that the study conducted by Wang et al [18] was the main origin of heterogeneity as shown in Fig. 3. When we removed this study, the heterogeneity was effectively decreased (CC versus GG: $I^2 = 0.0\%$, $p_{\text{heterogeneity}} = 0.670$). In addition, no other single study influenced the pooled OR for miR-608 rs4919510 polymorphism by sensitivity analysis (data not shown), indicating that the results of this meta-analysis were statistically reliable.

3.4. Publication bias

The results of Egger's test and Egger's test did not provide statistical evidence of publication bias (C *vs* G: $p = 0.902$ for Begg's test and $p = 0.734$ for Egger's test; GC vs GG: $p = 0.266$ for Begg's test and $p = 0.326$ for

Egger's test; CC vs GG: p = 0.902 for Begg's test and p = 0.725 for Egger's test; CC+GC vs GG: p = 0.266 for Begg's test and p = 0.378 for Egger's test; CC vs GC+GG: p = 0.536 for Begg's test and p = 0.614 for Egger's test). As shown in Fig. 4, the shape of the funnel plot did also not reveal any evidence of obvious asymmetry in the all comparison models.

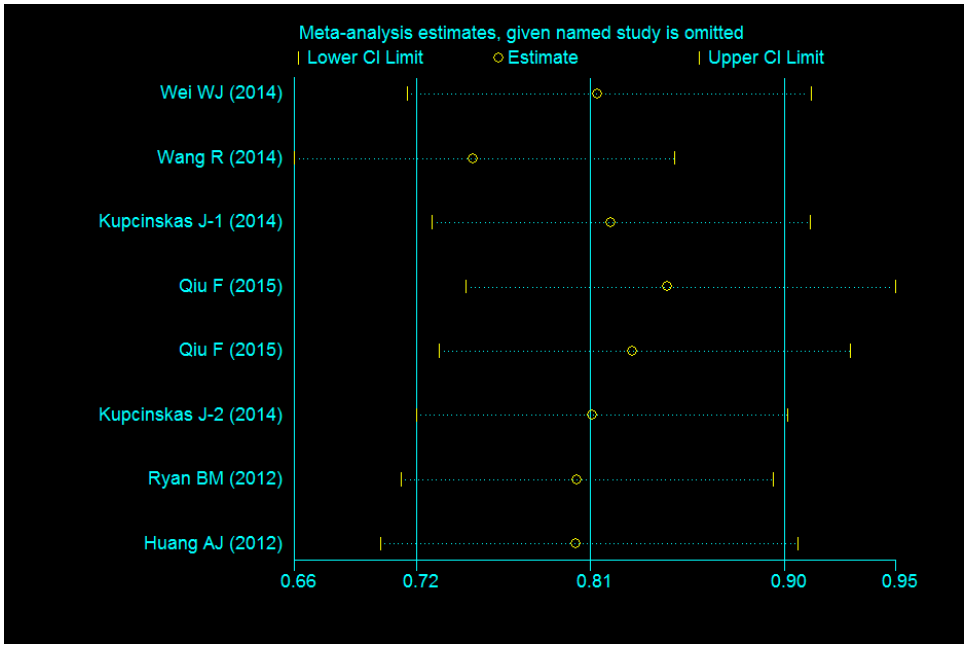

Fig. 3. Influence analysis of the summary odds ratio coefficients on the association for CC versus GG with risk of cancer.

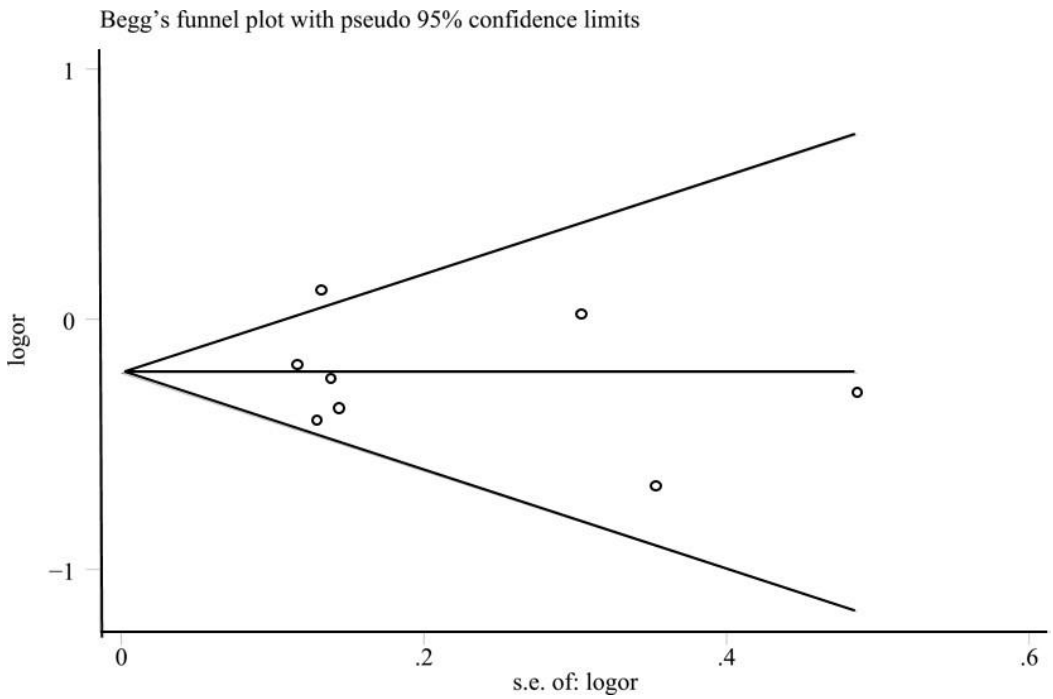

Fig. 4. Begg's funnel plot for publication bias test (CC versus GG). Log OR is plotted versus standard error of Log OR for each included study. Horizontal line means effect size. Every circle dot represents a separate study for the indicated association.

4. Discussion

As it is well known, miRNAs play an important role in a wide variety of physiological and pathological processes [23-25]. In recent years, some researchers have examined the association of miR-608 (rs4919510) gene polymorphism and the risk of various cancers, such as nasopharyngeal carcinoma [16], papillary thyroid cancer [17], hepatocellular carcinoma [18], gastric cancer [19], colorectal cancer [20, 21], and breast cancer [22]. But the results were not conclusive and consistent. As for the inconsistent results from individual studies for all types of cancer, this meta-analysis based on 5,319 cases and 6,628 controls in total was built to assess the association between the miR-608 rs4919510 polymorphism and cancer risk.

In present meta-analysis, we found statistically significant relationship between the miR-608 rs4919510 polymorphism and the overall risk of developing cancer using Mantel-Haenszel fixed effects model. For the rs4919510 polymorphism, we compared subjects carrying the GG genotype with those carrying either the CC genotype or the GC genotype. The pooled results suggested that the CC genotype of miR-608 (rs4919510) gene polymorphism was significantly associated with a decreased risk of cancer among Asians. Although no significant association was observed in Caucasians, a trend of reduced risk could be seen. Significant association between miR-608 rs4919510 polymorphism and cancer risk might be detected if we have more records included. Besides, the ethnic background might be another important factor affecting the results in a population-based genetic susceptibility study.

Similarly, stratified analysis conducted according to cancer types shown that the CC genotype of miR-608 (rs4919510) gene polymorphism was associated with a significantly decreased risk of nasopharyngeal carcinoma. But this result should be considered with caution due to data from the same study. However, there was no significant association between the miR-608 rs4919510 polymorphism and the risk of colorectal cancer. We thus thought that G-C variant in hsa-mir-608 gene was associated with a decreased likelihood of several, but not all, cancer types. Other than the above, we did perform stratified analysis based on other cancer.

A previous cross phenotype meta-analysis (CPMA) conducted by Hu et al [26] suggested that no significant association was observed for the rs4919510 polymorphism in terms of the overall risk of cancer or the risk of specific types of cancer. Their study with small sample size has insufficient statistical power to detect a small effect, while our meta-analysis included eight eligible case-control studies with 5,319 cases and 6,628 controls. So the reasons for inconsistent results might be that larger sample sizes may lead to the identification of statistically significant correlation.

Several limitations of this meta-analysis should be summarized and addressed. Firstly, the sample size was still relatively small for some stratified analyses and lack of adequate data prevented us from performing additional stratified analyses by papillary thyroid cancer, gastric cancer, breast cancer, etc. Secondly, although we retrieved studies published in any language by a comprehensive search, language bias should not be completely avoided because of all included studies written in English. Thirdly, although we did not detect a publication bias using Begg's funnel plot and Egger's test, unpublished data and ongoing studies were not included in our meta-analysis, which may still have somehow biased our results. Finally, our results were based on unadjusted estimates. However, a more precise analysis should be conducted if there were more detailed individual data, such as age, gender, family history and other risk factors.

In conclusion, the pooled results of this meta-analysis suggested that the CC genotype of miR-608 (rs4919510) gene polymorphism was significantly associated with a decreased risk of cancer, especially among Asian populations. However, further well-designed studies with large sample sizes are warranted to confirm our findings in other ethnic populations.

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