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Association of miR-4293 rs12220909 polymorphism with cancer risk

A meta-analysis of 8394 subjects

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Abstract

Background: Several studies have investigated miR-4293 rs12220909 polymorphisms and cancer susceptibility and yielded different results. Because of this controversy, we designed a meta-analysis to assess comprehensively the association of the rs12220909 polymorphism with cancer risk.

Methods: Relevant articles were collected by searching the databases of PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and WanFang. Data on rs12220909 in cancer patients and controls were extracted. Sensitivity analyses and publication bias assessments were performed.

Results: Five studies with 3820 cases and 4574 controls were included in our meta-analysis. Pooled analyses showed that the rs12220909 polymorphism was not associated with cancer risk in any genetic model. (C vs G: odds ratio [OR] = 0.89, 95% confidence interval [CI] = 0.74–1.07; GC vs GG: OR = 0.83, 95% CI = 0.67–1.03; CC vs GG: OR = 1.06, 95% CI = 0.82–1.36; CC+GC vs GG: OR = 0.84, 95% CI = 0.69–1.03; CC vs GC+GG: OR = 1.10, 95% CI = 0.85–1.40).

Conclusions: Our results indicate that rs12220909 is not associated with cancer risk. Larger, well-designed multicenter studies are needed to further explore the association of miR-4293 rs12220909 polymorphism with cancer risk.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, OR = odds ratio.

Keywords: cancer, meta-analysis, polymorphism, rs12220909

1. Introduction

There were ~18.1 million new cancer cases and 9.6 million cancer deaths in 2018.[1] Cancer is a major cause of death and places a heavy burden on the global medical systems. The etiology of cancer is closely related to heredity, diet, lifestyle, and environmental factors. Among them, genetic factors may play a key role in cancer progression.

miRNAs are a class of small non-coding single-stranded RNAs (20–24 nucleotides) with the function of regulating gene expression by binding to the 3′-untranslated region of the target mRNA.[2] miRNAs play an indispensable role in controlling

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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various processes, including differentiation, proliferation, metabolism, hemostasis, apoptosis, and inflammation.[3–9] Previous studies have shown that many miRNAs are associated with tumor progression and can be used for clinical purposes such as diagnosis and prognostication.[10,11] Single nucleotide polymorphisms (SNPs) are the most common form of genetic variation in the human genome. SNPs in miRNA-coding genes can alter normal miRNA regulatory pathways, leading to cancer susceptibility.[12] Many miRNA SNPs have been closely related to cancer risk.[13–16]

miR-4293 is a new miRNA located on chromosome 10. One study reported that the rs12220909G>C genetic polymorphism located in the seed region of miR-4293 alters its function, expression, and binding activities.[17] Several recent studies have described an association of the miR-4293 rs12220909 polymorphism with cancer risk.[18–22] Qiu et al[19] and Danesh et al[21] found no association of miR-4293 rs12220909 polymorphism with the risk of breast cancer or nasopharyngeal carcinoma. However, Cai et al[22] concluded that the polymorphism was clearly associated with an increased risk in homozygous models of hepatocellular carcinoma in Chinese women. In addition, Fan et al[18] found that the rs12220909 polymorphism was significantly associated with a reduced risk of non-small cell lung cancer in heterozygous and dominant models. Zhang et al[20] reported a reduced risk of esophageal squamous cell carcinoma for the heterozygous and dominant models. Because of these discrepant findings, the exact relationship between miR-4293 rs12220909 polymorphism and cancer risk is still unclear. Therefore, we summarized the existing evidence and performed a meta-analysis to comprehensively evaluate the association between miR-4293 rs12220909 polymorphism and cancer risk.

2. Methods

2.1. Search strategy

Two independent researchers searched articles in the PubMed, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), and WanFang databases. The keywords were: (miR-4293 or rs12220909) and (tumor or cancer or carcinoma) and (polymorphism or SNP or allele or variation). Articles published from January 2015 to October 2019 were searched. We screened the titles, abstracts, full text, and reference lists to identify studies for possible inclusion. This study does not require the approval of the ethics committee.

2.2. Study selection

The articles were considered eligible if they met the following criteria: investigated the association of miR-4293 rs12220909 polymorphism and cancer risk in human beings, had a case-control study design, and included detailed genotype data for estimating odds ratios (ORs) with 95% confidence intervals (CIs). Studies were excluded if insufficient data were provided or they were case reports, animal studies, or reviews.

2.3. Data extraction

The relevant information included the first author's surname, publication year, country, subject ethnicity, tumor type, number of genotyped cases and controls, and genotyping methods. Two of the authors extracted the data independently. Disagreement was resolved through discussion.

2.4. Statistical analysis

We used ORs and the corresponding 95% CIs to calculate the pooled data. Five genetic models (allele contrasts [G vs C], and homozygous [GG vs CC], heterozygous [CG vs CC], dominant [GG/CG vs CC], and recessive models [GG vs CG/CC]) were analyzed. Heterogeneity was assessed with the I^2 statistic. A random-effects model was used if I^2 exceeded 50%. Otherwise, the fixed-effects model was used. Sensitivity analysis was implemented to verify the reliability of the combined results. Publication bias was detected using funnel plot. All analyses were performed using STATA version 12.0 software (Stata Corporation, College Station, TX). $P<.05$ was considered statistically significant.

3. Results

3.1. Study characteristics

Searches of the specified databases yielded 35 articles. After screening the titles and abstracts, we identified 5 studies that evaluated the association of the miR-4293 rs12220909 polymorphism with cancer risk. A flow diagram of the study selection process is shown in Fig. 1. A total of 8394 subjects were involved, including 3820 cases and 4574 healthy controls. Four studies were conducted in China, and 1 was performed in Iran. Breast cancer, hepatocellular carcinoma, non-small cell lung cancer, nasopharyngeal carcinoma, and esophageal squamous cell carcinoma were analyzed in the studies. Mass ARRAY was used in 2 of the studies, and 3 adopted other methods. The genotype distributions of the controls were in agreement with Hardy-Weinberg equilibrium. Basic information on all the studies is listed in Table 1.

3.2. Meta-analysis findings

The association of miR-4293 rs12220909 polymorphism with cancer risk was analyzed in 5 case-control studies. The results revealed no significant association between miR-4293 rs12220909 polymorphism and cancer risk in any of the genetic models (C vs G: OR=0.89, 95% CI=0.74–1.07; GC vs GG: OR=0.83, 95% CI=0.67–1,03; CC vs GG: OR=1.06, 95% CI=0.82–1.36; CC+GC vs GG: OR=0.84, 95% CI=0.69–1.03; CC vs GC+GG: OR=1.10, 95% CI=0.85–1.40). Forest plots are shown in Figs. 2–6. Significant heterogeneity was observed among the studies in C versus G, CC+GC versus GG, and GC versus GG models. Random-effects models were used in the 3 genetic models. Subgroup analysis based on the country (China or Iran), genotyping (Mass ARRAY or other), sample size (>1800 or <1800) were conducted. However, each subgroup remained significant heterogeneity (Table 2).

3.3. Sensitivity analysis

Sensitivity analysis was performed in C versus G, CC+GC versus GG, and GC versus GG models by removing 1 study at a time. With the deletion of Qiu et al[19] in GC versus GG model, I^2 decreased from 72.4% to 48.7%. The results were not different from the complete analysis, indicating that the outcome was stable (Fig. 7).

3.4. Publication bias

Funnel plots were generated to evaluate the publication bias. Begger and Egger tests were performed to provide statistical evidence for funnel plot symmetry. The funnel plots were almost symmetric in all genetic models (Fig. 8). Egger test results did not show evidence of publication bias.

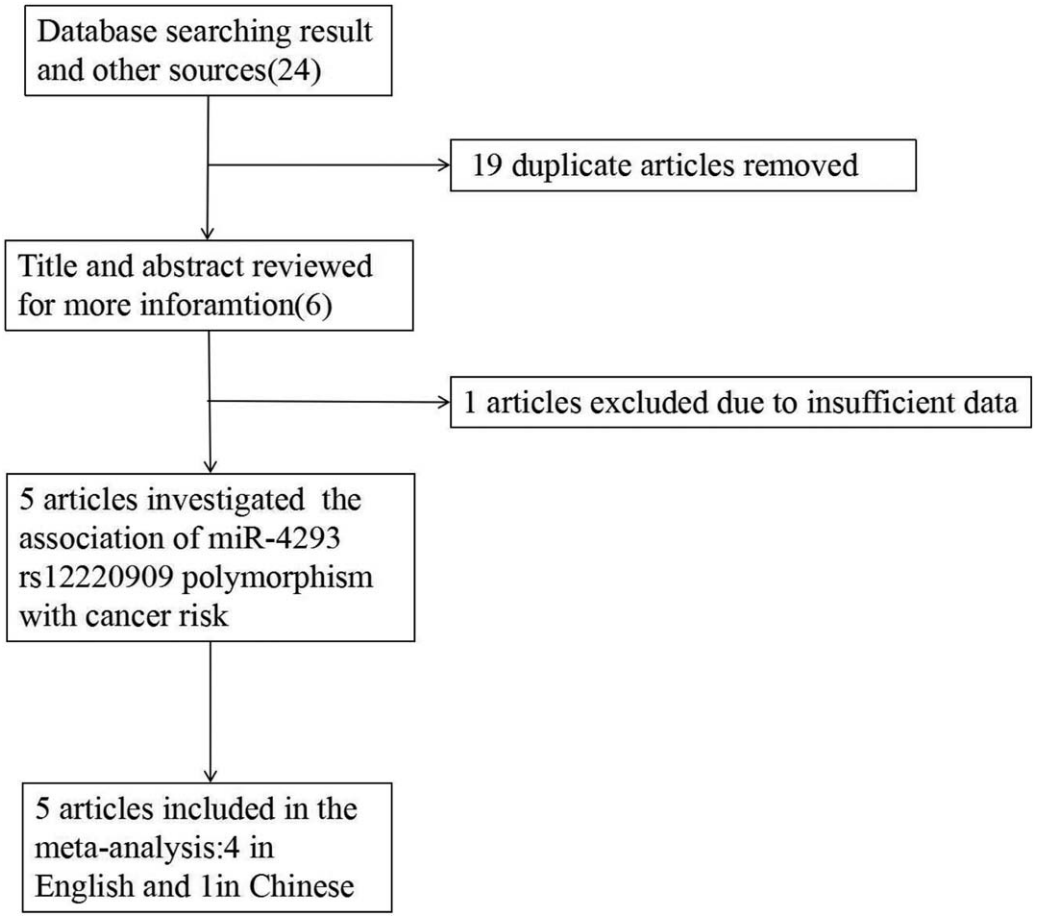

Figure 1. Flow diagram of the study selection process.

Table 1

Characteristics of all included studies.

Study	Year	Country	Cancer-type	Genotyping methods	Case/control	Genotypes case GG/GC/CC	Genotypes control GG/GC/CC	Ethnicity
Fan	2017	China	NSCLC	Mass ARRAY	995/1454	753/220/22	999/419/36	Asian
Zhang	2015	China	ESCC	SNaPshot	751/882	562/172/17	602/257/23	Asian
Qiu	2015	China	NPC	TaqMan	906/1072	543/308/55	658/353/61	Asian
Cai	2016	China	HCC	Mass ARRAY	904/884	642/231/31	611/256/17	Asian
Danesh	2018	Iran	BC	PCR-RFLP	264/282	259/5/0	282/0/0	Asian

BC = breast cancer, ESCC = esophageal squamous cell carcinoma, HCC = hepatocellular carcinoma, NPC = nasopharyngeal carcinoma, NSCLC = non-small cell lung cancer.

Table 2

Subgroup analysis based on gene models with significant heterogeneity.

Variables	N	C versus G OR (95%CI)	*P*	GC versus GG OR (95%CI)	*P*	CC+GC versus GG OR (95%CI)	*P*
Country							
China	4	0.88 (0.74–1.05)	.159	0.82 (0.68–1.00)	.051	0.84 (0.69–1.03)	.87
Iran	1						
Genotyping							
Mass ARRAY	2	0.86 (0.66–1.12	.26	0.77 (0.63–0.94)	.021	0.8 (0.62–1.03)	.083
Other	3	0.94 (0.66–1.33)	.716	0.92 (0.60–1.42)	.72	0.88 (0.60–1.28)	.509
Sample size							
>1800	2	0.89 (0.64–1.24)	.496	0.86 (0.57–1.29)	.46	0.87 (0.58–1.29)	.48
<1800	3	0.90 (0.66–1.22)	.487	0.81 (0.60–1.08)	.154	0.82 (0.65–1.03)	.081

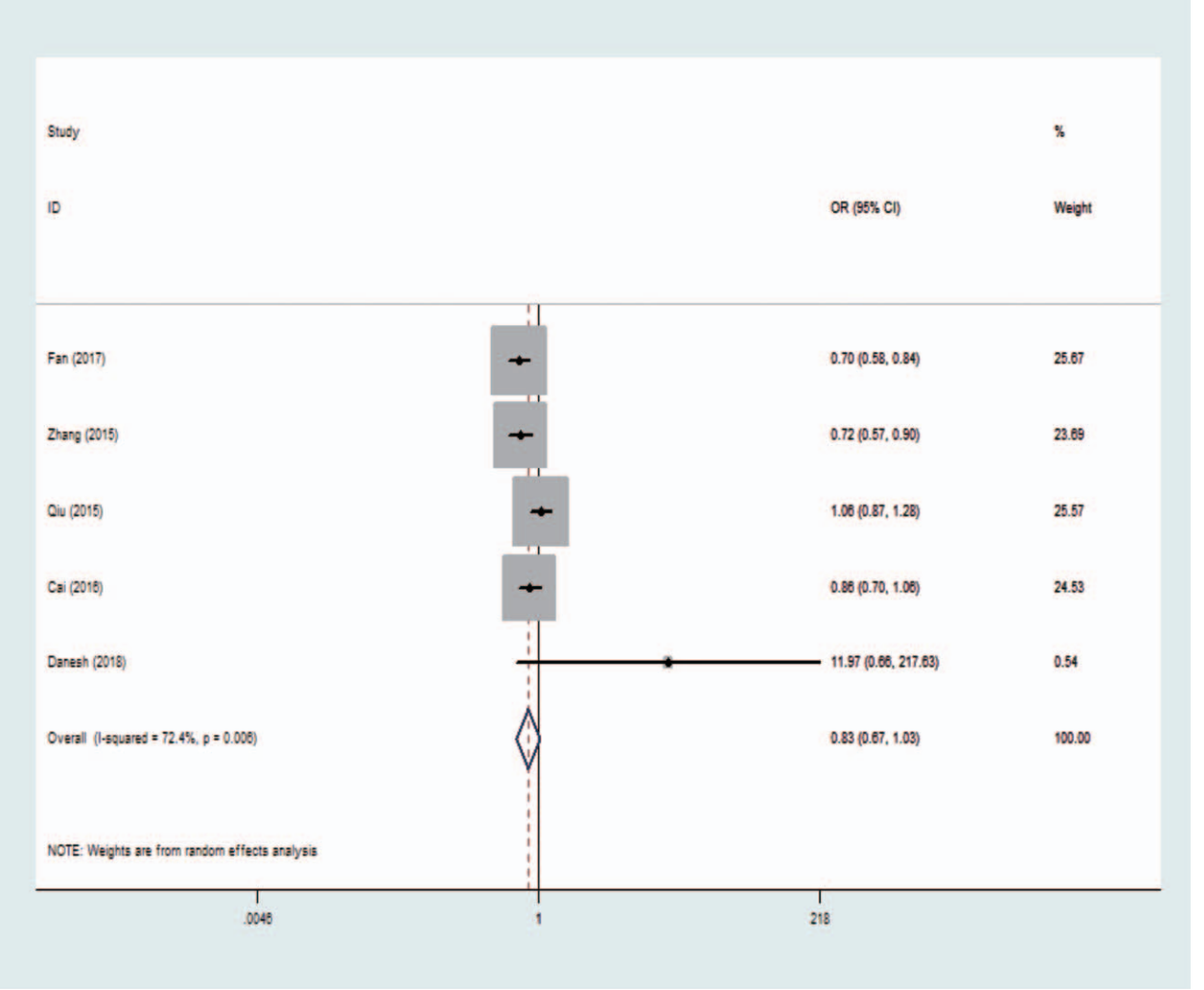

Figure 2. Forest plot of cancer risk associated with rs12220909 (allele: C vs G).

4. Discussion

Some findings showed that there was no association between miR-4293 rs12220909 polymorphism and breast cancer, nasopharyngeal carcinoma, and hepatocellular carcinoma.[19,21,22] A study revealed that CC genotype of miR-4293 polymorphism was related to an increased risk of hepatocellular carcinoma for woman.[22] Moreover, other studies suggested rs12220909 polymorphism referred to the decreased risk of non-small cell lung cancer and esophageal squamous cell carcinoma.[18,20] These results indicate that miR-4293 rs12220909 polymorphism has different effect in different tumors, which reflects the complexity of tumorigenesis. In addition, population differences such as living habits, environment, genetic characteristics, and sex could also cause miR-4293 rs12220909 polymorphism to have different effects.

Gong et al[17] found that the energy change was −0.5 kcal/mol for G to C, suggesting that the C allele is more stable. Furthermore, the target gene was largely lost after the mutation. Zhang et al[20] found that rs4938723 was obviously associated with a reduced risk of esophageal squamous cell carcinoma, possibly by regulating the PTCH1 gene. Fan et al[18] reported that rs12220909 was also significantly associated with decreased susceptibility to non-small cell lung cancer. They proposed that rs4938723 could regulate some genes and affect the expression of downstream proteins, such as SLC43A2 and SLC7A5, ultimately decreasing non-small cell lung cancer susceptibility. At present, the exact mechanisms remain unknown and warrant further investigation.

To our knowledge, this is the first meta-analysis to investigate the relationship between rs12220909 polymorphism and cancer risk. A total of 5 case-control studies that used blood samples for genotype detection were included. Three studies reported a significant relationship between the miR-4293 rs12220909 polymorphism and cancer risk. The other 2 found no association. Collectively, our results indicated that there was no significant association between miR-4293 rs12220909 polymorphism and cancer risk in any of the genetic models.

There were certain limitations in our meta-analysis. First, the genotyping methods varied among studies. Second, there was heterogeneity in some of the genetic models, which limits the strength of our conclusions. Third, some clinical factors such as age, sex, living environment, and biochemical features were not analyzed due to the lack of data. Last but not least, all studies in the meta-analysis were conducted in Asia. This may affect the generalizability of the results. Future investigations involving patients of different races and countries are therefore warranted.

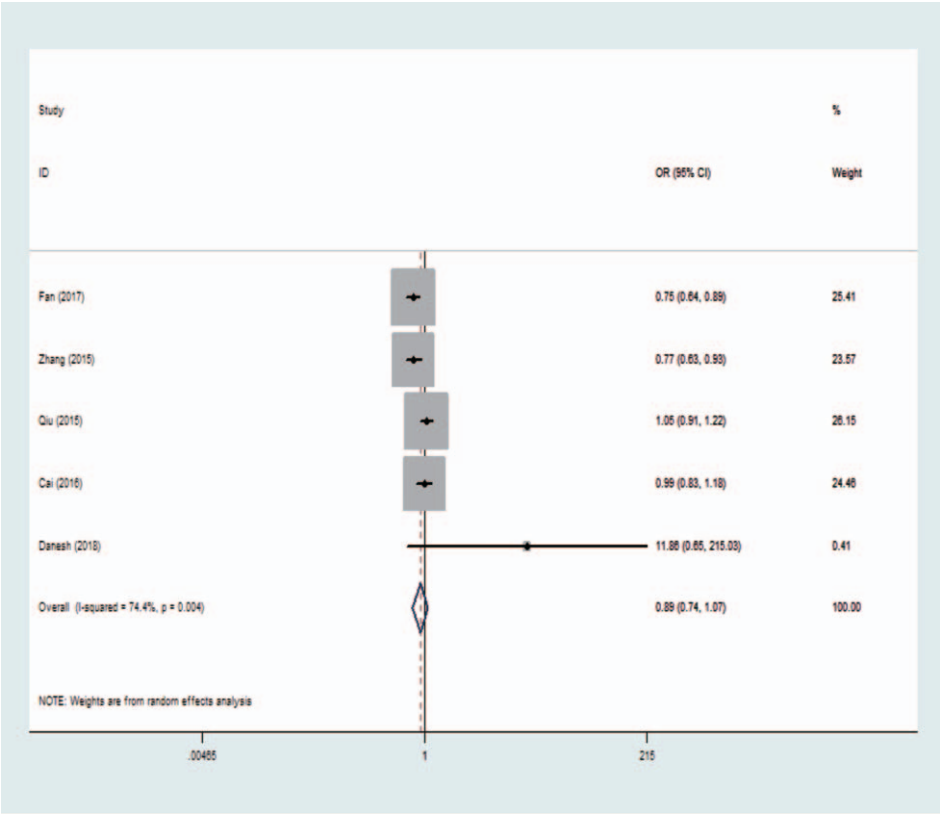

Figure 3. Forest plot of cancer risk associated with rs12220909 (heterozygote model: GC vs GG).

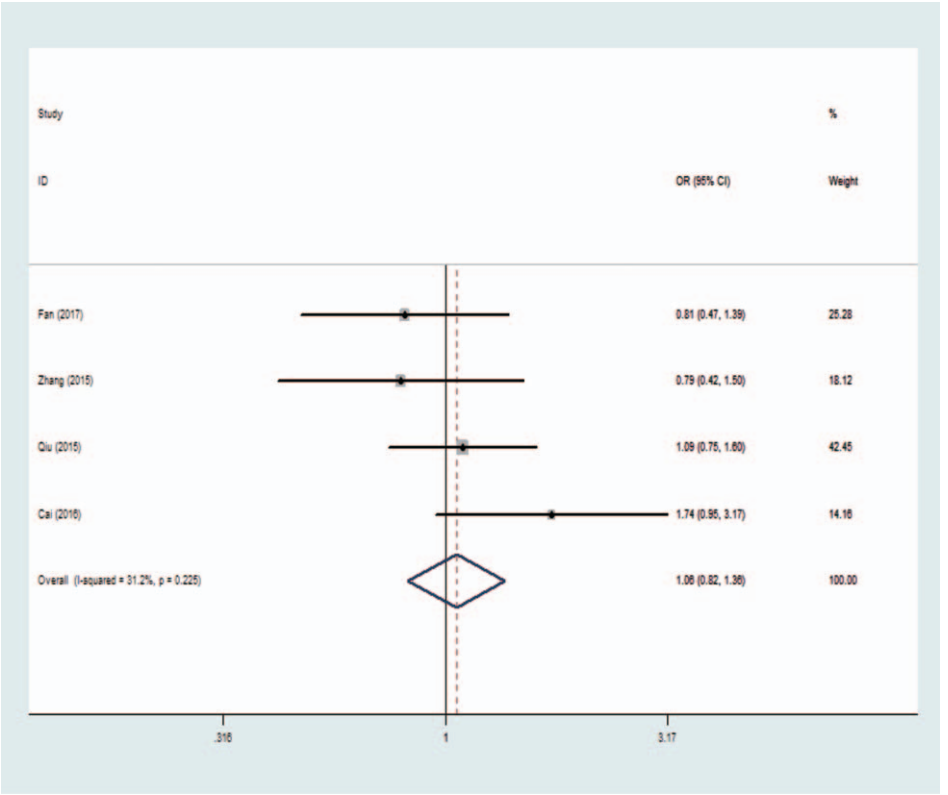

Figure 4. Forest plot of cancer risk associated with rs12220909 (homozygote model: CC vs GG).

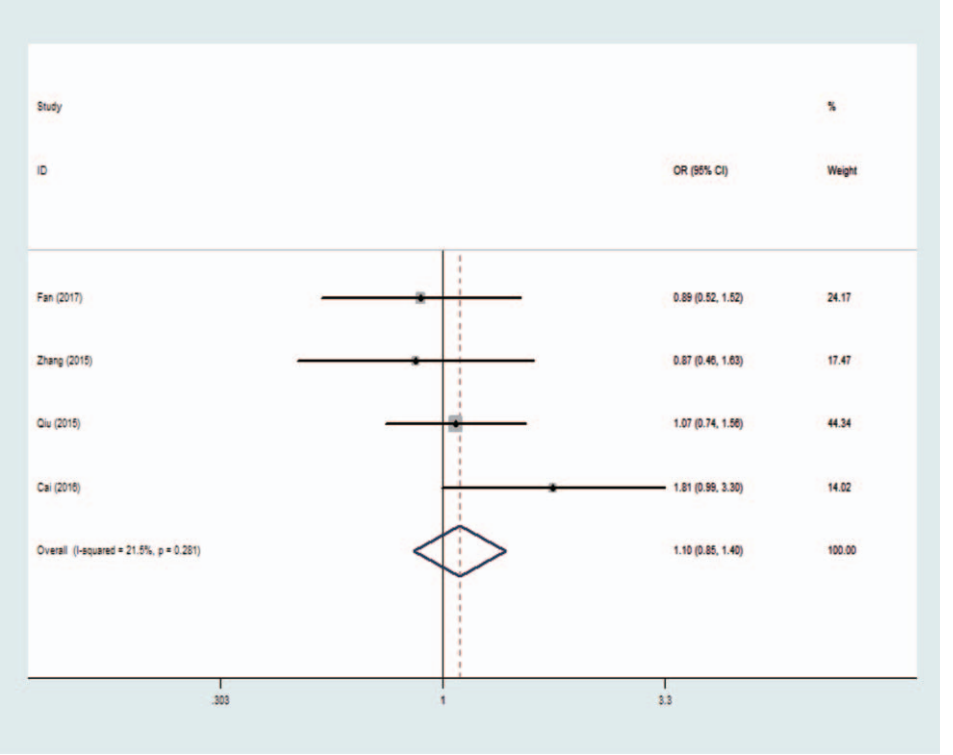

Figure 5. Forest plot of cancer risk associated with rs12220909 (dominant model: CC+GC vs GG).

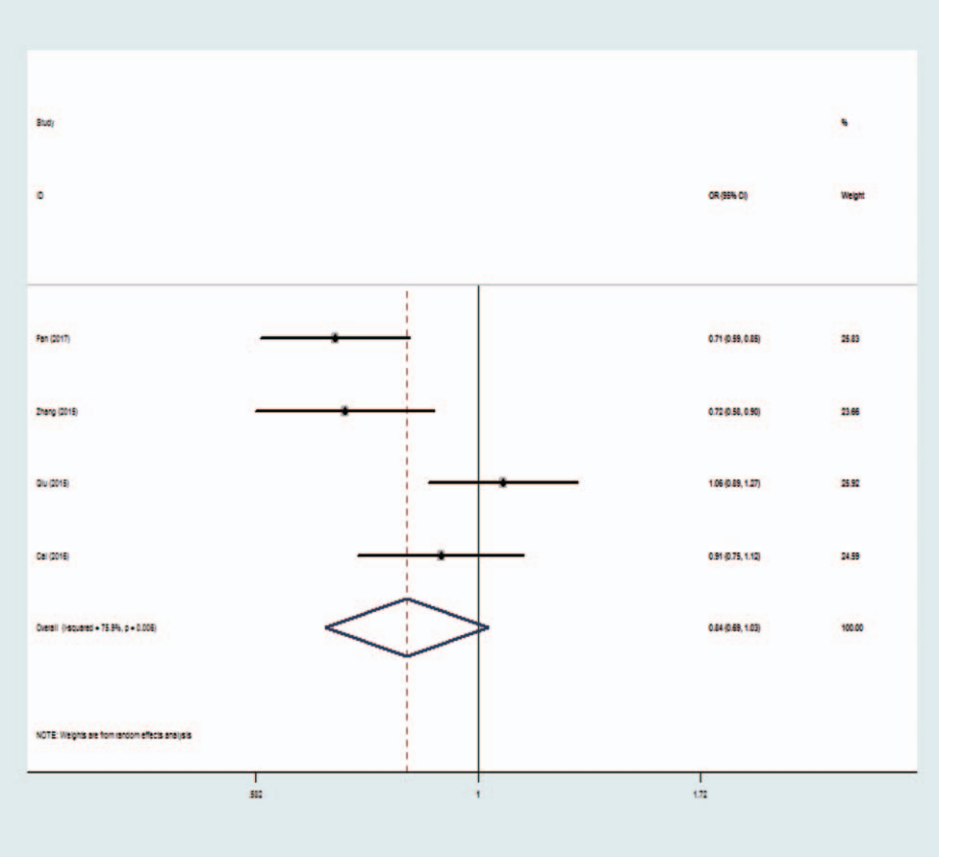

Figure 6. Forest plot of cancer risk associated with rs12220909 (recessive model: CC vs GC+GG).

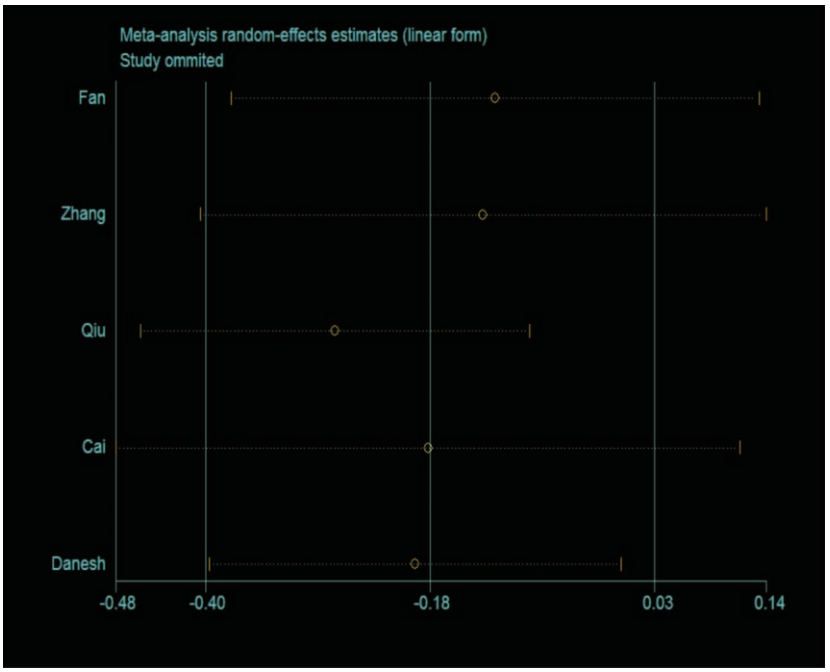

Figure 7. Sensitivity analysis of the heterozygote model.

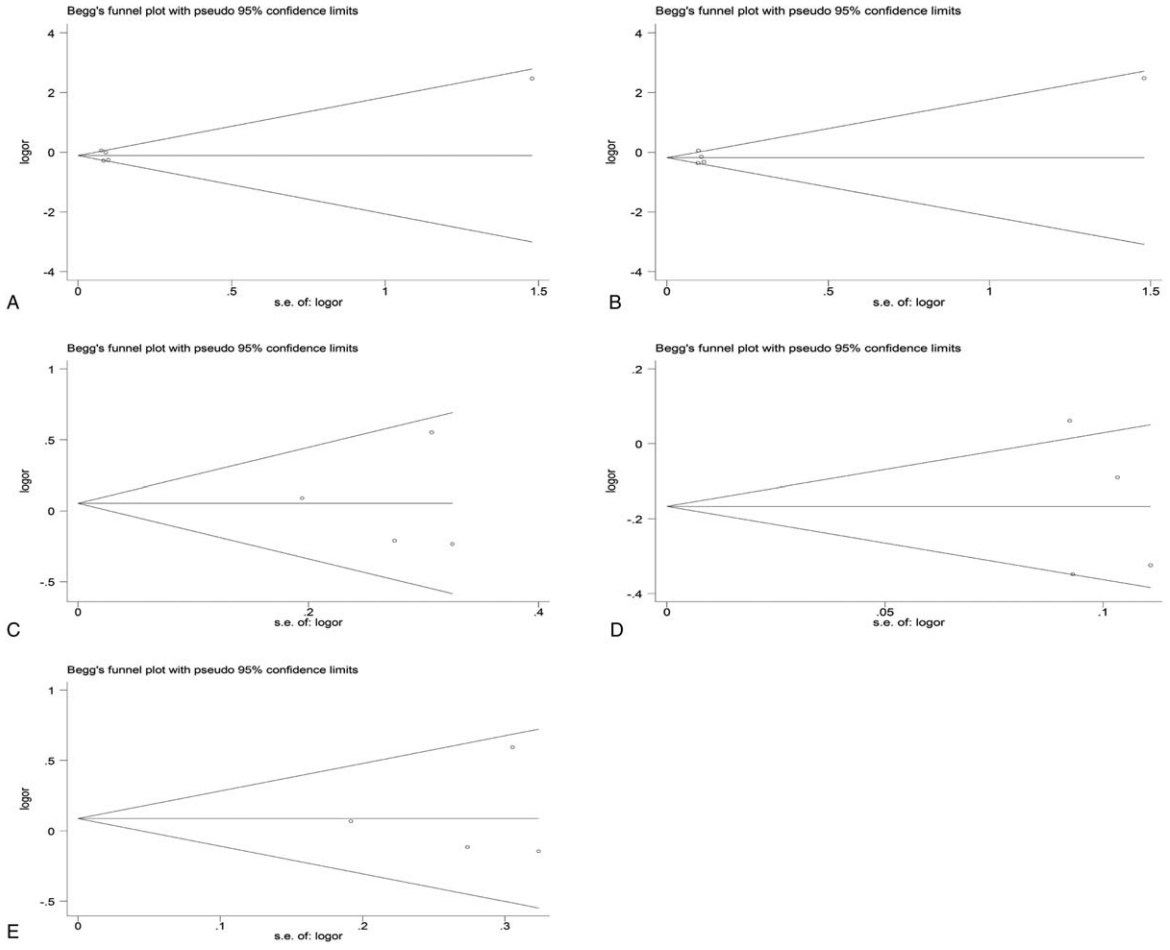

Figure 8. Funnel plots for publication bias. A: allele; B: heterozygote model; C: homozygote model; D: dominant model; E: recessive model.

In summary, our meta-analysis showed that rs12220909 is not associated with cancer risk. However, all 5 studies assessed limited numbers of patients. Larger, well-designed, multicenter studies are needed to further explore the association of miR-4293 rs12220909 polymorphism with cancer risk.

Author contributions

Guarantor of the article: Shao Yi. Shao Yi contributed study inception and design, literature search, analysis. Rongqiang Liu, Hongyuan Fu and Yajie Yu contributed to the literature search, analysis and writing of the manuscript. Other authors contributed to the study design and study supervision. All authors approved the final version of the manuscript.

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