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Review Article

Association between hsa-mir-149C>T (rs2292832) and susceptibility to hepatocellular carcinoma: a meta-analysis

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Abstract: miRNAs are a family of small non-coding RNAs that participate in diverse biological processes and play an important role in tumor progression. Single nucleotide polymorphisms miRNA genes may influence the expression and biological function of some miRNAs. In this meta-analysis, we calculated the odds ratio (OR) and 95% confidence interval (CI) for rs2292832 and its correlation with the risk of hepatocellular carcinoma (HCC) based on 1700 cases and 2044 controls. Our results suggest that rs2292832is associated with the risk of HCC, TT/CT may play a conservative role in disease progression (T vs. C: OR=0.91, 95% CI=0.74-1.13, P=0.400, p_h=0.008; TT/CT vs. CC: OR=0.80, 95% CI=0.67-0.95, P=0.013, p_h=0.286; TT vs. CT/CC: OR=0.94, 95% CI=0.70-1.26, P=0.672, p_h=0.018; TT vs. CC: OR=0.77, 95% CI=0.62-0.95, P=0.014, p_h=0.068; CT vs. CC: OR=0.82, 95% CI=0.68-0.99, P=0.035, p_h=0.799; CT vs. CC/TT: OR=0.94, 95% CI=0.82-1.07, P=0.330, p_h=0.533).

Keywords: Hepatocellular carcinoma, hsa-mir-149C>T, rs2292832, miRNA polymorphism, meta-analysis

Introduction

Liver cancer is the fifth most frequent type of cancer, and accounts for almost 2.5% of deaths worldwide, together with other end-stage liver disease [1, 2]. Liver cancer can be divided into the following types [2, 3]: hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), combined or mixed HCC/CCA, hepatoblastoma, and others. HCC comprises most cases (70-85%) of liver cancer [1, 3]. With its rising incidence in many countries and a strong tendency towards hemorrhage, degeneration and necrosis [4], HCC mortality remains obstinately high. Early diagnosis can improve prognosis, so a proper process of surveillance with the aim of enhancing survival is actively being pursued. Currently, α-fetoprotein (AFP) serology, radiology and biopsy are the main diagnostic tests for HCC. AFP and ultrasound (US) surveillance shows a survival benefit over non-surveillance control, although for effective surveillance, AFP serology lacks adequate sensitivity and specificity [4, 5]. Radiology can help to assess the size, number, location and pathological changes in the nidus of tumors, however, contrast-enhanced US may confuse HCC and CCA [4], and contrast agents may have limitations in patients with renal insufficiency. Biopsy is considered a gold standard for diagnosis; it has some advantages in the diagnosis of small liver cancer, although it also has the risk of needle track seeding. Therefore, to screen for HCC as early as possible, optimized surveillance indicators are needed.

Genetic diagnosis has potential for screening the HCC-susceptible population, and may pro-

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 (cancer-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 genotype	
White blood cells or normal tissues	3
Tumor tissues 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

vide a new dimension for its clinical treatment. To date, we have seen major advances in diagnostic biomarkers [6-9] and drug therapy [10-15] for HCC, as well in other end-stage liver disease [16-18]. And genetic mutation may have great influence on the progress of HCC via different signalling pathway.

miRNAs are a family of endogenous non-coding RNAs of 19-25 bases. They participate in the translation and expression of hundreds of genes by combining specific mRNA sequences [19-21], thus having a close correlation with tumor occurrence, progression and prognosis. miRNAs participate in the regulation of many oncogenes and anti-oncogenes, and have a significant influence on a variety of tumors including HCC [14, 19, 20]. After intranuclear transcription, primary miRNAs (pri-miRNAs) are sheared into hairpin ring, structured precursor miRNAs (pre-miRNAs) by Drosha and transported to the cytoplasm by exportin-5/RanGTP. pre-miRNAs are matured by Dicer and combine with functional proteins to form RNA-induced silencing complexes, which regulate the translation and degradation of target mRNAs [21]. Single nucleotide polymorphisms (SNPs) in miRNA genes can contribute to dysfunction of miRNA processing or target binding by interfering pri-miRNAs, pre-miRNAs and mature miRNAs, which may influence tumorigenesis. Therefore, miR-SNPs have attracted our interest. rs2292832 is an SNP located on chromosome 2: 240456086, which is on the coding gene of hsa-mir-149 (chr2: 240456001-240456089 [+], miRBase), and the latter is modified into mature sequence hsa-miR-149-5p (hsa-miR-149) or hsa-miR-149-3p (hsa-miR-149*) to execute its specific biological function. There have been several case-control studies of hsa-mir-149C>T (rs2292832) and its association with HCC, although they have reported divergent opinions on whether it has an influence on the risk of HCC [22-26]. Here, we carried out a systematic analysis of this question.

Materials and methods

Search strategy

We searched Pubmed, EBSCO, Embase, Cochrane Library, Web of Science, Science Direct, Ovid, and Wiley Online Library, using the terms "(rs2292832 or miRNA-149 or microRNA 149) and (cancer or tumor or carcinoma)". The latest data were from May 2015.

Inclusion and exclusion criteria

Duplicate studies were preliminarily excluded. Then, we ruled out studies that were: not about HCC or rs2292832 polymorphism; not in humans; not case-control original studies; or lacking detailed genotype and SNP phenotype data. Quality assessment was performed under a set of predetermined criteria [27, 28] (**Table 1**), articles were considered as "high quality" when scoring ≥ 12, and all the internalized studies in our meta-analysis were under the Hardy-Weinberg equilibrium expectation in control.

Data extraction

Data were collected by two independent investigators using the standard criteria in **Table 1**,

Table 2. Characteristics of case-control study

Author	Year	Country	Ethnicity	HWE of control	Genotyping methods	Case/Control	Quality score	Reference
Kim	2012	Korean	Asian	0.345	PCR-RFLP	159/201	12	[23]
Kou	2014	Chinese	Asian	0.877	PCR-RFLP	270/532	12	[24]
Liu	2014	Chinese	Asian	0.054	PCR	327/327	15	[25]
Wang	2014	Chinese	Asian	0.863	Sequenom MassARRAY	944/984	16	[26]

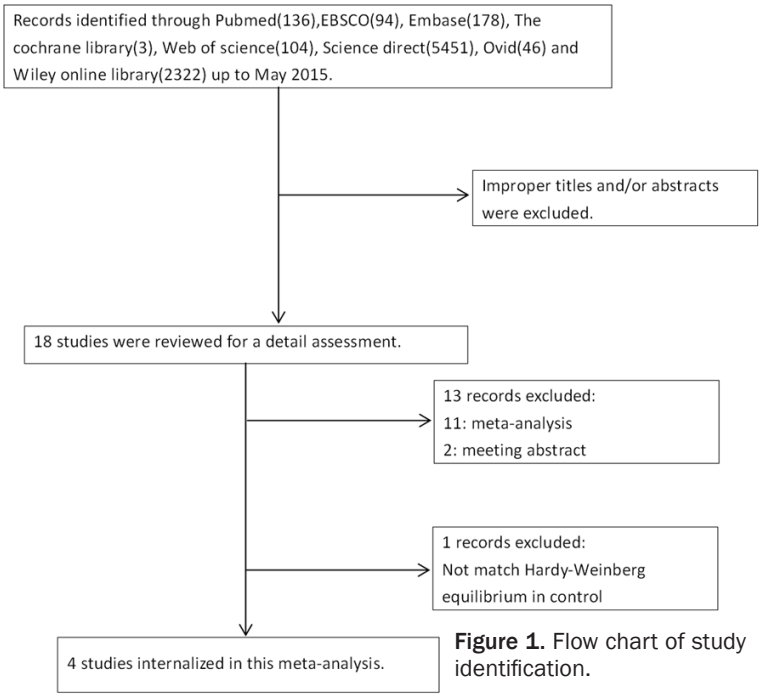

Figure 1. Flow chart of study identification.

and they reached agreement on all items. A third reviewer participated in the discussion to resolve any problems when discrepancies occurred. The following data were obtained from the eligible studies (**Table 2**): authors' surname; publication year; country and ethnicity of the study population; sources of case-control; specimens and genotyping methods used for each study; total number and genotype distribution of study population; *p* value for the control of Hardy-Weinberg equilibrium (HWE).

Statistical analysis

STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used for data analysis, and helped us understand the association between rs2292832 polymorphism and the risk of HCC. We calculated the odds ratio (OR) and 95% confidence interval (CI) for different types of genetic model, as described previously [29, 30]: allele model (T vs. C); dominant model (TT/CT vs. CC); recessive model (TT vs. CT/CC); homozygous model (TT vs. CC); heterozygous model (CT vs. CC); and complete over-dominant model (CT vs. CC/TT). Subgroup analysis was performed for different countries.

Stata commands "metan" and "metagen" were used to calculate the pooled OR (P<0.05 was considered of statistical significance) and decipher the most plausible genetic model [29]. We used the χ^2 test to calculate the *p* value of HWE in each control group of included studies, and P<0.05 was considered to show deviation from HWE. We use the χ^2-based Q test to check the heterogeneity among eligible studies, and heterogeneity was considered present at P<0.05. Then, we used the random-effects model (Der Simonian-Laird method), or else we used the fixed-effects model (Mantel-Haenszel method) to calculate combined OR [31, 32]. A sensitivity analysis was carried out to establish the contribution of each study to the overall heterogeneity when it occurred (Stata command: meta inf). To determine whether there was a publication bias, we used Egger's test and Begg's funnel plot for consultation [33], and P<0.05 for Egger's test was considered to show significant publication bias.

Results

Study characteristics

We searched Pubmed, EBSCO, Embase, Cochrane Library, Web of Science, Science Direct,

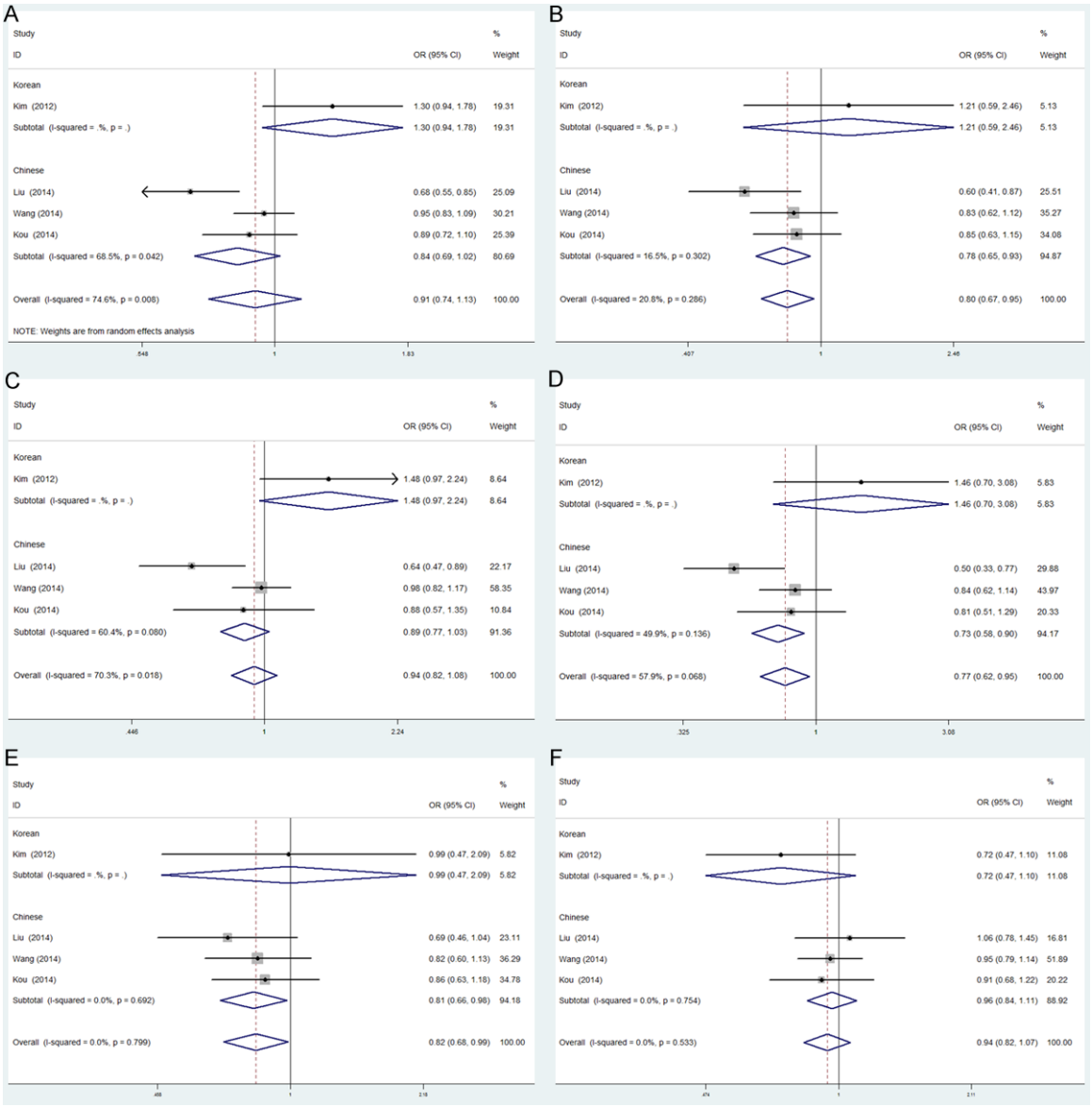

Figure 2. Forest plot of hepatocellular carcinoma susceptibility associated with miR149 rs2292832 polymorphism in different genetic models. A. Allele model: T versus C; B. Dominant model: TT/CT versus CC; C. Recessive model: TT versus CT/CC; D. Homozygous model: TT versus CC; E. Heterozygous model: CT vs. CC; F. Complete overdominant model: CT vs. CC/TT.

Ovid, and Wiley Online Library, and retrieved 136, 94, 178, 3, 104, 5451, 46, and 2322 records, respectively (**Figure 1**). We excluded articles that had unrelated titles and/or abstracts. Next, meta-analyses and meeting abstracts were removed. Four studies including 1700 cases and 2044 controls were used in our systematic analysis [23-26]. As shown in **Table 1**, all the included studies were of high quality and the frequency departures of the control in these studies are under the expectation of HWE. One of these four studies [23] was from Korea, while the other three [24-26] were from China, and we carried out a subgroup analysis by country to determine population-based heterogeneity.

Meta-analysis

There were 1700 cases and 2044 controls in our systematic analysis. The random-effects model were used for the allele model (p_h=0.008) and recessive model (p_h=0.018), as they both had an overall *P* value for heterogeneity of <

0.05, whereas the fixed-effects model was used for the dominant model (p_h=0.286), homozygous model (p_h=0.068), heterozygous model (p_h=0.799) and complete over-dominant model (p_h=0.533) (**Figure 2**). There was a significant decrease in the risk of HCC for mutant genes versus wild-type among TT/CT versus CC (OR=0.80, 95% CI=0.67-0.95, P=0.013), TT versus CC (OR=0.77, 95% CI=0.62-0.95, P=0.014), and CT versus CC (OR=0.82, 95% CI=0.68-0.99, P=0.035). There was no significant decrease in overall OR for T versus C (OR=0.91, 95% CI=0.74-1.13, P=0.400), TT versus CT/CC (OR=0.94, 95% CI=0.70-1.26, P=0.672), and CT versus CC/TT (OR=0.94, 95% CI=0.82-1.07, P=0.330) (**Figure 2**).

In subgroup analysis based on countries, there was a strong association between rs2292832 polymorphism and HCC susceptibility in Chinese people (**Figure 2**): TT/CT versus CC (OR=0.78, 95% CI=0.65-0.93, P=0.007, p_h=0.302), TT versus CC (OR=0.73, 95% CI=0.58-0.90, P=0.004, p_h=0.136), and CT versus CC (OR=0.81, 95% CI=0.66-0.98, P=0.030, p_h=0.692). There was no association between polymorphism and HCC risk in the genetic models of T versus C (OR=0.84, 95% CI=0.69-1.02, P=0.086, p_h=0.042), TT versus CT/CC (OR=0.89, 95% CI=0.77-1.03, P=0.108, p_h=0.080), and CT versus CC/TT (OR=0.96, 95% CI=0.84-1.11, P=0.600, p_h=0.754). There was only one study on Korean people, therefore, we did not perform a similar analysis on this population.

Genetic model optimization

The Stata command metagen, which is based on logistic regression, was used to screen the optimized genetic model. We set "$OR_{(CT\ vs.\ CC)}=OR_{(TT\ vs.\ CC)}$" as the null hypothesis and achieved a supportable result for the hypothesis: $OR_{(CT\ vs.\ CC)}$=0.801, 95% CI=0.665-0.966, P=0.020; $OR_{(TT\ vs.\ CC)}$=0.794, 95% CI=0.652-0.967, P=0.022; p_h=0.118; $p_{genetic\ model}$= 0.095>0.05. As the null hypothesis was established and both of the ORs≠1, we selected the dominant model as the most optimized for rs2292832 polymorphism in HCC [29].

Publication bias

Egger's test and Begg's funnel plot were used to appraise the publication bias of the meta-data. As shown in **Figure 3**, there was no significant asymmetry under all genetic models using Begg's funnel plot. Similarly, Egger's test also did not find obvious bias among all the genetic models: T versus C (t=0.18, P=0.872), TT/CT versus CC (t=0.46, P=0.693), TT versus CT/CC (t=0.01, P=0.991), TT versus CC (t=0.53, P=0.652), CT versus CC (t=1.00, P=0.423), and CT versus CC/TT (t=-0.78, P=0.517).

Sensitivity analysis

Using the Stata command metainf, we assessed the statistical robustness by deleting one study at a time to calculate the OR, and compared it with the original pooled OR. The results show that no individual studies significantly influenced overall OR (**Figure 4**).

Discussion

Modulation of miRNAs may have a critical influence on the progression of HCC, by regulating cellular differentiation, proliferation, apoptosis, invasion and metastasis; thus, some of them should be considered as oncogenes or tumor suppressor genes, which may be potential targets for diagnosis and therapy [14, 34]. hsa-mir-149 acts as an oncogene or tumor suppressor gene in different types of carcinoma. *Ke et al.* [35] found that miR-149 acted as a tumor suppressor by inhibiting expression of forkhead box M1 in non-small-cell lung cancer. Wang [36] also found that miR-149 inhibited proliferation and cell cycle progression in human gastric cancer by partially targeting the zinc finger and BTB domain holding 2 oncogenes (ZBTB2). Others showed that miR-149 suppressed apoptosis by directly regulating PUMA expression or through adjusting the mitochondrial network, and may act as an oncogene [37]. There are also inconsistent results on the function of miR-149* in different carcinomas. It may induce apoptosis of HeLa cells and the Be2C neuroblastoma cell line by inhibiting Akt1 and E2F1 [38]. In contrast, miR-149* increases the expression of Mcl-1 by targeting glycogen synthase kinase-3α and resistance to apoptosis in melanoma cells, thus, it functions as an oncogene and p53-responsive miRNA [39]. There are still gaps in our knowledge of how miR-149 and miR-149* work in HCC. One study found that miR-149 inhibited the proliferation and tumorigenicity of HCC by targeting the AKT/mTOR pathway [40]. This reminds us that SNPs

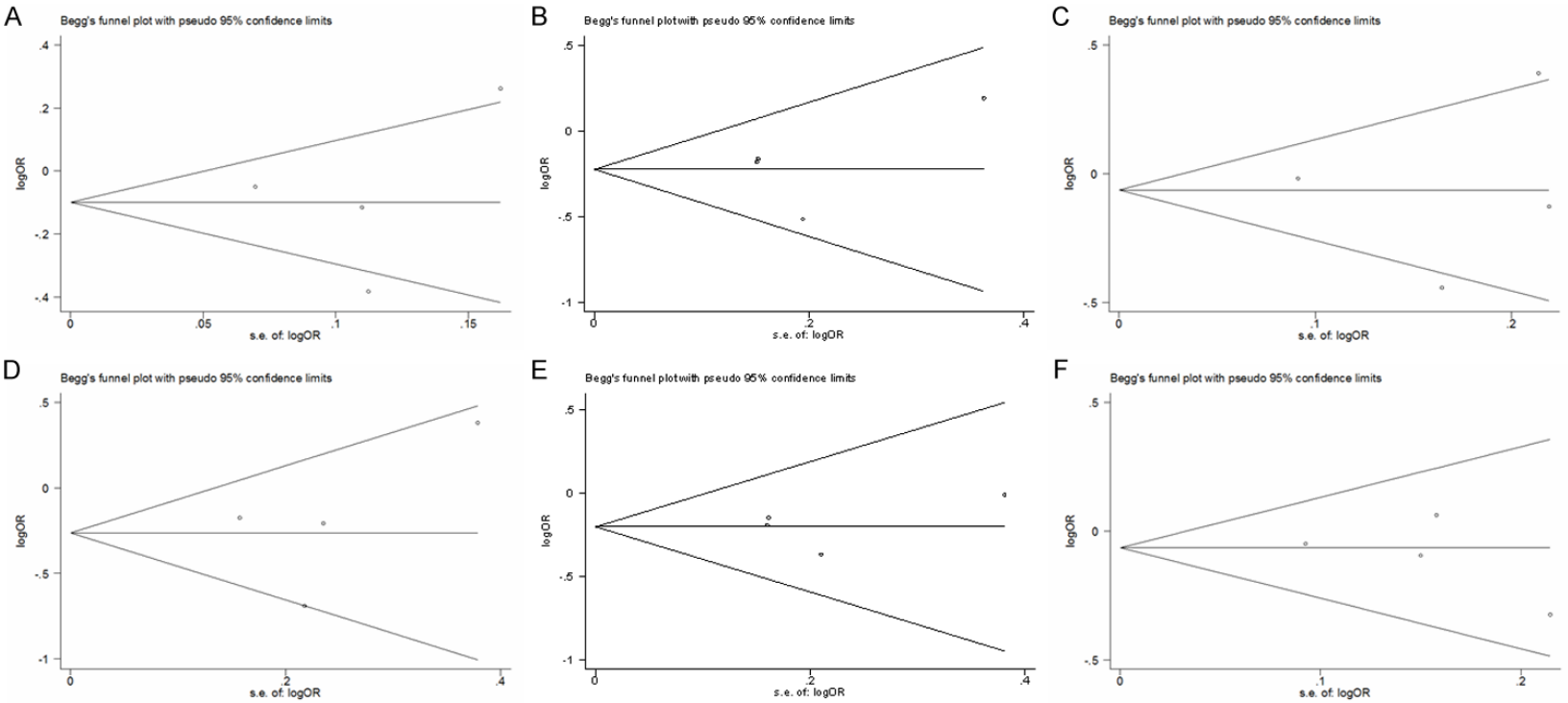

Figure 3. Begg's funnel plot for publication bias test. A. Allele model: T versus C; B. Dominant model: TT/CT versus CC; C. Recessive model: TT versus CT/CC; D. Homozygous model: TT versus CC; E. Heterozygous model: CT vs. CC; F. Complete overdominant model: CT vs. CC/TT. Each point represent a separate study for the indicated study. OR means odds ratio, Log OR is the nature logarithm of OR, and the horizontal line represent size of effect.

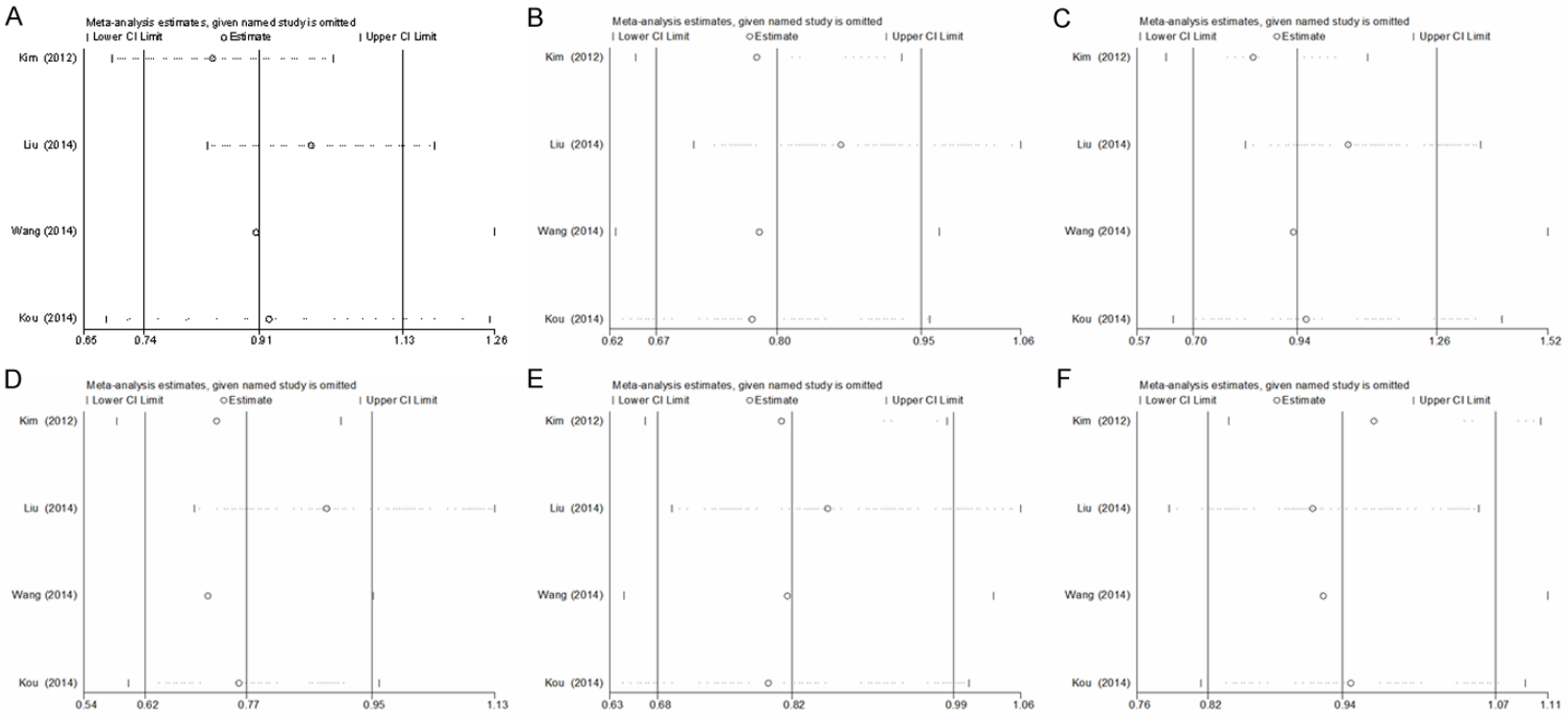

Figure 4. Sensitivity analysis for the influence on pooled OR by each study. A. Allele model: T versus C; B. Dominant model: TT/CT versus CC; C. Recessive model: TT versus CT/CC; D. Homozygous model: TT versus CC; E. Heterozygous model: CT vs. CC; F. Complete overdominant model: CT vs. CC/TT. Each study was omitted to caculate the specific OR, which presented by circles above. Dashed lines were used to represent each 95% CI correspondingly.

on miR-149 gene may lead to changes in its regulation pathway in HCC, either by affecting expression of miR-149/miR-149* or some other unknown pathways. In the present study, we found that rs2292832 polymorphism may have a significant influence on the risk of HCC, especially in the Chinese population. Compared to people with wild-type CC, those with TT/CT genotype had a lower risk of HCC in the dominant model, which may be the optimized model selected by logistic regression. In the homozygous and heterozygous models, our results also suggest that wild-type CC may have an association with higher susceptibility to HCC compared to TT and CT genotypes. In contrast, there was no significant difference in the allele, recessive and complete over-dominant models. The random-effects model was used to calculate the OR in the allele model for its p_h=0.008, and we could not reduce the heterogeneity to a acceptable range, even through subgroup analysis, so we can not overlook the associated error. Therefore, a large case-control study and further investigation of the pathway for how rs2292832 mutation influences HCC progression are still required.

Our meta-analysis had some limitations. First, although 1700 cases and 2044 controls were included, the sample size was still too small because we only had four studies in the meta-analysis. Second, although we did not find a single study that had a significant influence on the overall OR based on sensitivity analysis, heterogeneity remains in our genetic models. Third, there exist the bais that brought by language and grey literatures we couldn't avoid. Fourth, we did not take into account the environmental influence on individual gene expression because of a lack of relevant data. Lastly, we did not draw any reliable conclusion on whether different genotyping methods would have influenced the test results.

In conclusion, hsa-mir-149C>T (rs2292832) may have a significant influence on the risk of HCC, and TT/CT may play a conservative role in disease progression. This may help us find an earlier screening method for HCC, which can improve prognosis. Further studies on the rs2292832 polymorphism and its relationship with HCC are still required.

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Disclosure of conflict of interest

None.

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References

[1] Bosch FX, Ribes J, Borràs J. Epidemiology of primary liver cancer. Semin Liver Dis 1999; 19: 271-85.

[2] Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006; 45: 529-38.

[3] The general rules for the clinical and pathological study of primary liver cancer. Liver Cancer Study Group of Japan. Jpn J Surg 1989; 19: 98-129.

[4] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-2.

[5] Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004; 130: 417-22.

[6] Zhu R, Yang J, Xu L, Dai W, Wang F, Shen M, Zhang Y, Zhang H, Chen K, Cheng P, Wang C, Zheng Y, Li J, Lu J, Zhou Y, Wu D, Guo C. Diagnostic Performance of Des-gamma-carboxy Prothrombin for Hepatocellular Carcinoma: A Meta-Analysis. Gastroenterol Res Pract 2014; 2014: 529314.

[7] Yang J, Li J, Dai W, Wang F, Shen M, Chen K, Chen K, Cheng P, Zhang Y, Wang C, Zhu R, Zhang H, Zheng Y, Wang J, Xia Y, Lu J, Zhou Y, Guo C. Golgi protein 73 as a biomarker for hepatocellular carcinoma: A diagnostic meta-analysis. Exp Ther Med 2015; 9: 1413-20.

[8] Llovet JM, Fuster J, Bruix J; Barcelona-Clínic Liver Cancer Group. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004; 10: S115-20.

[9] El-Serag HB, Marrero JA, Rudolph L, Reddy KR. Diagnosis and treatment of hepatocellular carcinoma. Gastroenterology 2008; 134: 1752-63.
[10] Cheng P, Dai W, Wang F, Lu J, Shen M, Chen K, Li J, Zhang Y, Wang C, Yang J, Zhu R, Zhang H, Zheng Y, Guo CY, Xu L. Ethyl pyruvate inhibits proliferation and induces apoptosis of hepatocellular carcinoma via regulation of the HMGB1-RAGE and AKT pathways. Biochem Biophys Res Commun 2014; 443: 1162-8.
[11] Jie L, Fan W, Weiqi D, Yingqun Z, Ling X, Miao S, Ping C, Chuanyong G. The hippo-yes association protein pathway in liver cancer. Gastroenterol Res Pract 2013; 2013: 187070.
[12] Wang F, Dai W, Wang Y, Shen M, Chen K, Cheng P, Zhang Y, Wang C, Li J, Zheng Y, Lu J, Yang J, Zhu R, Zhang H, Zhou Y, Xu L, Guo C. The synergistic in vitro and in vivo antitumor effect of combination therapy with salinomycin and 5-fluorouracil against hepatocellular carcinoma. PLoS One 2014; 9: e97414.
[13] Dai W, Wang F, Lu J, Xia Y, He L, Chen K, Li J, Li S, Liu T, Zheng Y, Wang J, Lu W, Zhou Y, Yin Q, Abudumijiti H, Chen R, Zhang R, Zhou L, Zhou Z, Zhu R, Yang J, Wang C, Zhang H, Zhou Y, Xu L, Guo C. By reducing hexokinase 2, resveratrol induces apoptosis in HCC cells addicted to aerobic glycolysis and inhibits tumor growth in mice. Oncotarget 2015; 6: 13703-17.
[14] Morishita A, Masaki T. miRNA in hepatocellular carcinoma. Hepatol Res 2015; 45: 128-41.
[15] Dai W, Wang F, He L, Lin C, Wu S, Chen P, Zhang Y, Shen M, Wu D, Wang C, Lu J, Zhou Y, Xu X, Xu L, Guo C. Genistein inhibits hepatocellular carcinoma cell migration by reversing the epithelial-mesenchymal transition: partial mediation by the transcription factor NFAT1. Mol Carcinog 2015; 54: 301-11.
[16] Cheng P, Chen K, Xia Y, Dai W, Wang F, Shen M, Wang C, Yang J, Zhu R, Zhang H, Li J, Zheng Y, Wang J, Zhang Y, Lu J, Zhou Y, Guo C. Hydrogen sulfide, a potential novel drug, attenuates concanavalin A-induced hepatitis. Drug Des Devel Ther 2014; 8: 1277-86.
[17] Zhang H, Yang J, Zhu R, Zheng Y, Zhou Y, Dai W, Wang F, Chen K, Li J, Wang C, Li S, Liu T, Abudumijiti H, Zhou Z, Wang J, Lu W, Wang J, Xia Y, Zhou Y, Lu J, Guo C. Combination therapy of ursodeoxycholic acid and budesonide for PBC-AIH overlap syndrome: a meta-analysis. Drug Des Devel Ther 2015; 9: 567-74.
[18] Zhang Y, Li S, He L, Wang F, Chen K, Li J, Liu T, Zheng Y, Wang J, Lu W, Zhou Y, Yin Q, Xia Y, Zhou Y, Lu J, Guo C. Combination therapy of fenofibrate and ursodeoxycholic acid in patients with primary biliary cirrhosis who respond incompletely to UDCA monotherapy: a meta-analysis. Drug Des Devel Ther 2015; 9: 2757-66.
[19] Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer 2006; 6: 857-66.
[20] Cheng G. Circulating miRNAs: Roles in cancer diagnosis, prognosis and therapy. Adv Drug Deliv Rev 2015; 81: 75-93. 21.
[21] Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. Nat Rev Cancer 2010; 10: 389-402.
[22] Chu YH, Hsieh MJ, Chiou HL, Liou YS, Yang CC, Yang SF, Kuo WH. MicroRNA gene polymorphisms and environmental factors increase patient susceptibility to hepatocellular carcinoma. PLoS One 2014; 9: e89930.
[23] Kim WH, Min KT, Jeon YJ, Kwon CI, Ko KH, Park PW, Hong SP, Rim KS, Kwon SW, Hwang SG, Kim NK. Association study of microRNA polymorphisms with hepatocellular carcinoma in Korean population. Gene 2012; 504: 92-7.
[24] Kou JT, Fan H, Han D, Li L, Li P, Zhu J, Ma J, Zhang ZH, He Q. Association between four common microRNA polymorphisms and the risk of hepatocellular carcinoma and HBV infection. Oncol Lett 2014; 8: 1255-1260.
[25] Liu MF, Chen WQ, He YZ, Gu YL. Role of miR-149C>T polymorphisms on the risk of hepatocellular carcinoma in a Chinese population. Genet Mol Res 2014; 13: 7184-9.
[26] Wang R, Zhang J, Ma Y, Chen L, Guo S, Zhang X, Ma Y, Wu L, Pei X, Liu S, Wang J, Hu H, Liu J. Association study of miR149 rs2292832 and miR608 rs4919510 and the risk of hepatocellular carcinoma in a largescale population. Mol Med Rep 2014; 10: 2736-44.
[27] Jiang DK, Wang WZ, Ren WH, Yao L, Peng B, Yu L. TP53 Arg72Pro polymorphism and skin cancer risk: a meta-analysis. J Invest Dermatol 2011; 131: 220-8.
[28] Zou YF, Wang F, Feng XL. TP53 Arg72Pro polymorphism may have little involvement in the pathogenesis of skin cancer in Caucasians. J Investi Dermatol 2011; 131: 781-2.
[29] Bagos PG, Nikolopoulos GK. A method for meta-analysis of case-control genetic association studies using logistic regression. Stat Appl Genet Mol Biol 2007; 6: Article 17.
[30] Lewis CM, Knight J. Introduction to genetic association studies. Cold Spring Harb Protoc 2012; 2012: 297-306.
[31] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177-88.
[32] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies. J Natl Cancer Inst 1959; 22: 719-48.

[33] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-34.
[34] Dai W, Wang C, Wang F, Wang Y, Shen M, Chen K, Cheng P, Zhang Y, Yang J, Zhu R, Zhang H, Li J, Zheng Y, Lu J, Zhou Y, Xu L, Guo C. Anti-miR-197 inhibits migration in HCC cells by targeting KAI 1/CD82. Biochem Biophys Res Commun 2014; 446: 541-8.
[35] Ke Y, Zhao W, Xiong J, Cao R. miR-149 Inhibits Non-Small-Cell Lung Cancer Cells EMT by Targeting FOXM1. Biochem Res Int 2013; 2013: 506731.
[36] Wang Y, Zheng X, Zhang Z, Zhou J, Zhao G, Yang J, Xia L, Wang R, Cai X, Hu H, Zhu C, Nie Y, Wu K, Zhang D, Fan D. MicroRNA-149 inhibits proliferation and cell cycle progression through the targeting of ZBTB2 in human gastric cancer. PLoS One 2012; 7: e41693.
[37] Ding SL, Wang JX, Jiao JQ, Tu X, Wang Q, Liu F, Li Q, Gao J, Zhou QY, Gu DF, Li PF. A pre-microRNA-149 (miR-149) genetic variation affects miR-149 maturation and its ability to regulate the Puma protein in apoptosis. J Biol Chem 2013; 288: 26865-77.
[38] Lin RJ, Lin YC, Yu AL. miR-149* induces apoptosis by inhibiting Akt1 and E2F1 in human cancer cells. Mol Carcinog 2010; 49: 719-27.
[39] Jin L, Hu WL, Jiang CC, Wang JX, Han CC, Chu P, Zhang LJ, Thorne RF, Wilmott J, Scolyer RA, Hersey P, Zhang XD, Wu M. MicroRNA-149*, a p53-responsive microRNA, functions as an oncogenic regulator in human melanoma. Proc Natl Acad Sci U S A 2011; 108: 15840-5.
[40] Zhang Y, Guo X, Xiong L, Yu L, Li Z, Guo Q, Li Z, Li B, Lin N. Comprehensive analysis of microRNA-regulated protein interaction network reveals the tumor suppressive role of microRNA-149 in human hepatocellular carcinoma via targeting AKT-mTOR pathway. Mol Cancer 2014; 13: 253.