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Original Article

MiR-146a rs2910164 polymorphism is associated with hepatocellular carcinoma: a meta-analysis

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Abstract: Results of published studies on the association between the miR-146a rs2910164 polymorphism and the risk of hepatocellular carcinoma (HCC) were inclusive. We performed a meta-analysis. A literature research was conducted using PubMed, Cochrane Library, Ovid, Embase, Wanfang and China National Knowledge Infrastructure (CNKI) databases, to identify studies. Statistical analyses were conducted in STATA version 11.0 (Stata Corporation, College station, TX, USA). A total of 12 publications were included in this meta-analysis. The results of this meta-analysis suggested that miR-146a rs2910164 was associated with an increased risk of HCC (OR = 1.09, 95% CI = 1.00-1.19). In sensitivity analysis, the result was still positive when excluding the studies without HWE (OR = 1.12, 95% CI = 1.01-1.23). In conclusion, this meta-analysis suggested a significant association between miR-146a rs2910164 polymorphism and HCC risk.

Keywords: Hepatocellular carcinoma, miR-146a, meta-analysis

Introduction

Hepatocellular carcinoma (HCC) accounts for 90% of cases of primary liver cancer and is the fifth most common cancer worldwide. It ranks third in mortality after gastric cancer and esophageal cancer, and half of the deaths from HCC occur in China [1]. Due to the high rate of recurrence or intrahepatic metastasis after curative resection, the overall prognosis of HCC patients remains poor despite obvious improvements in surgical techniques and perioperative management [2]. Accordingly, the development of effective therapeutic targets for HCC is urgently required.

MicroRNAs (miRNAs) are non-coding RNAs formed of 18-25 nucleotides that can cause the inhibition of gene expression at a post-transcriptional level by directly binding to the 3'-untranslational region (UTR) of mRNAs [3]. Deregulation of miRNAs, such as miR-204, miR-331, miR-125b, and miR-146a, has been demonstrated to play an important role in hepatocellular carcinoma [4, 5]. Huang et al. found that miR-146a plays a vital role in the cell growth and apoptosis of HCC cells and inducing miR-146a level might be a critical targeted molecular therapy strategy for HCC [6]. Rong et al. suggested that miR-146a expression in HCC tissues was lower compared with that in adjacent non-cancerous hepatic tissues. MiR-146a expression was also related to clinical TNM stage, metastasis, portal vein tumor embolus, and number of tumor nodes [7].

The location of rs2910164 is the stem region opposite to the mature miR-146a sequence, which results in a change from G:U pair to C:U mismatch in the stem structure of the miR-146a precursor. It has previously been shown that SNPs rs2910164 in miR-146a were associated with an increased susceptibility to HCC in an Asian population. However, the results were inconsistent [8-19]. Thus, we did a meta-analysis to assess the association between rs2910164 and the risk of HCC.

Methods

Publication search

A literature research was conducted using PubMed, Cochrane Library, Ovid, Embase, Wanfang and China National Knowledge

Table 1. Characteristics of included studies

Author	Year	Country	Ethnicity	Cases	Controls	HWE
Xu	2008	China	Asian	479	504	Yes
Akkiz	2011	Turkey	Caucasian	222	222	Yes
Zhang	2011	China	Asian	926	840	Yes
Zhou	2012	China	Asian	186	483	Yes
Xiang	2012	China	Asian	100	100	Yes
Kim	2012	Korea	Asian	159	201	Yes
Zhang	2013	China	Asian	997	998	Yes
Shan	2013	China	Asian	172	185	No
Kou	2014	China	Asian	271	532	No
Chu	2014	China	Asian	188	337	Yes
Cong	2014	China	Asian	206	218	Yes
Zhou	2014	China	Asian	266	281	No

HWE, Hardy-Weinberg equilibrium.

Infrastructure (CNKI) databases, to identify studies published prior to Jan 2015. Relevant studies were identified using the terms: "miR-146a or MicroRNA-146a" and "polymorphisms or variant" and "hepatocellular carcinoma or HCC". The search was confined to humans. A manual search of references of the original articles related with this topic was used to identify additional studies. If the data or data subsets were published in more than one paper, only the paper with the largest sample size was enrolled.

Inclusion and exclusion criteria

Studies were selected for meta-analysis if they met the inclusion criteria as follows: (1) case-control study design; (2) studies that investigated the association between the miR-146a rs2910164 and the risk of HCC; (3) study subjects were HCC patients confirmed by histopathology in case group. The exclusion criteria were: (1) reviews and summaries; (2) repetitive publications; (3) no raw data of the miR-146a rs2910164 genotype.

Data extraction

Data from published studies were extracted by two authors. For each study, we collected the following information: first author, year of publication, country, ethnicity, numbers of cases and controls, and evidence of HWE.

Statistical analysis

The overall effect was measured by ORs with its 95% CI. The significance of the pooled ORs was determined by the Z test with a *P* value less than 0.05 considering statistically significant. The dominant model was examined to assess this association. Between-studies heterogeneity was assessed by the I^2 test and the Q-statistic test. A random effects model was applied if there was heterogeneity ($P < 0.05$ or $I^2 > 50\%$), otherwise, a fixed effects model was employed. The publication bias was estimated by visual funnel plot inspection. To assess whether our results were substantially influenced by the presence of any individual study, we proceed a sensitivity analysis by removing the studies without HWE. Statistical analyses were conducted in STATA version 11.0 (Stata Corporation, College station, TX, USA). All the tests were two-sided.

Results

Study characteristics

According to the inclusion and exclusion criteria, a total of 12 publications were included in this meta-analysis. The 12 selected studies contained a total of 4172 HCC patients and 4901 healthy controls. Of the 12 studies, 11 studies were performed in Asians; only 1 study was performed in Caucasians. The sample sizes of the studies varied between 200-1995. Characteristics in this meta-analysis are summarized in **Table 1**.

Results of meta-analysis

Heterogeneity test revealed that no heterogeneity existed under allele and dominant models, and thus a fixed-effect model was used (P = 0.29). The results of this meta-analysis suggested that miR-146a rs2910164 was associated with an increased risk of HCC (OR = 1.09, 95% CI = 1.00-1.19; **Figure 1**). Subgroup analysis based on ethnicity indicated that the miR-146a rs2910164 increased the risk of HCC in Asian population (OR = 1.09, 95% CI = 1.00-1.19). In sensitivity analysis, the result was still positive when excluding the studies without HWE (OR = 1.12, 95% CI = 1.01-1.23; **Figure 2**). The funnel plot is symmetrical, suggesting no publication bias (**Figure 3**). Egger test further verified that no publication bias existed (P = 0.56).

Discussion

In the present study, we found that miR-146a rs2910164 was associated with an increased

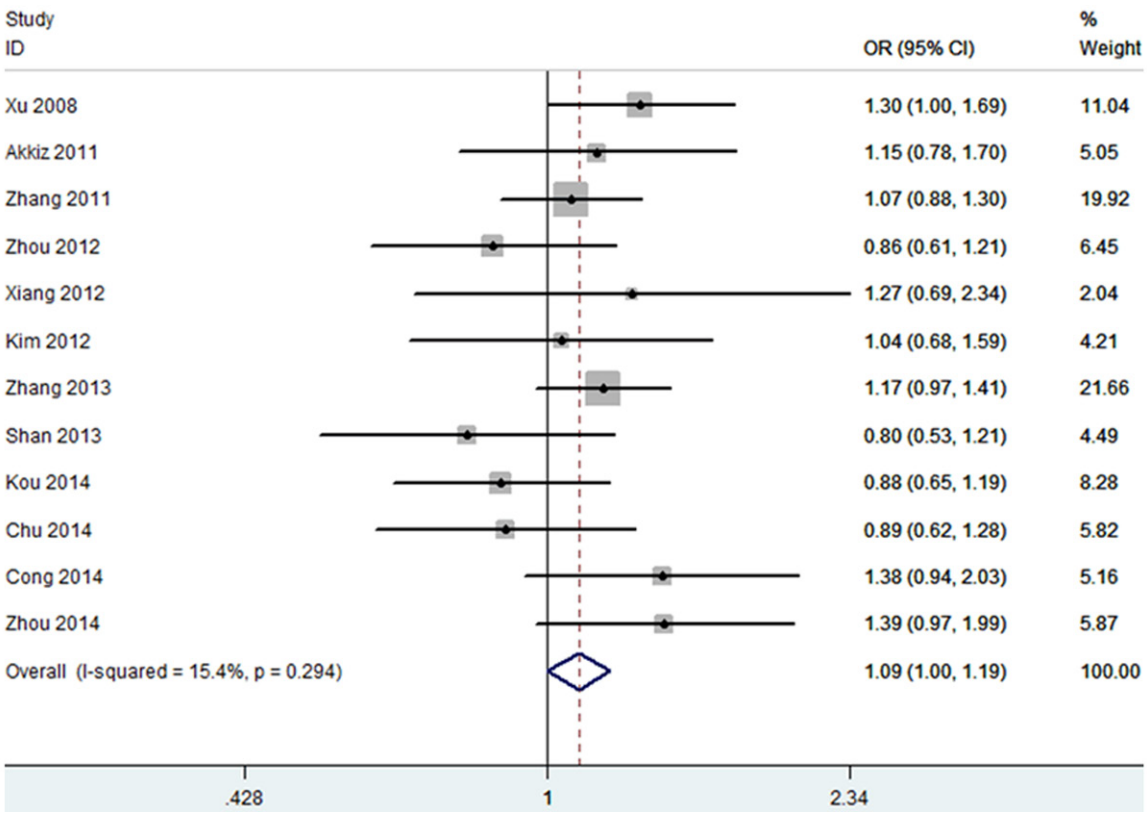

Figure 1. Meta-analysis for the association between miR-146a rs2910164 and HCC risk.

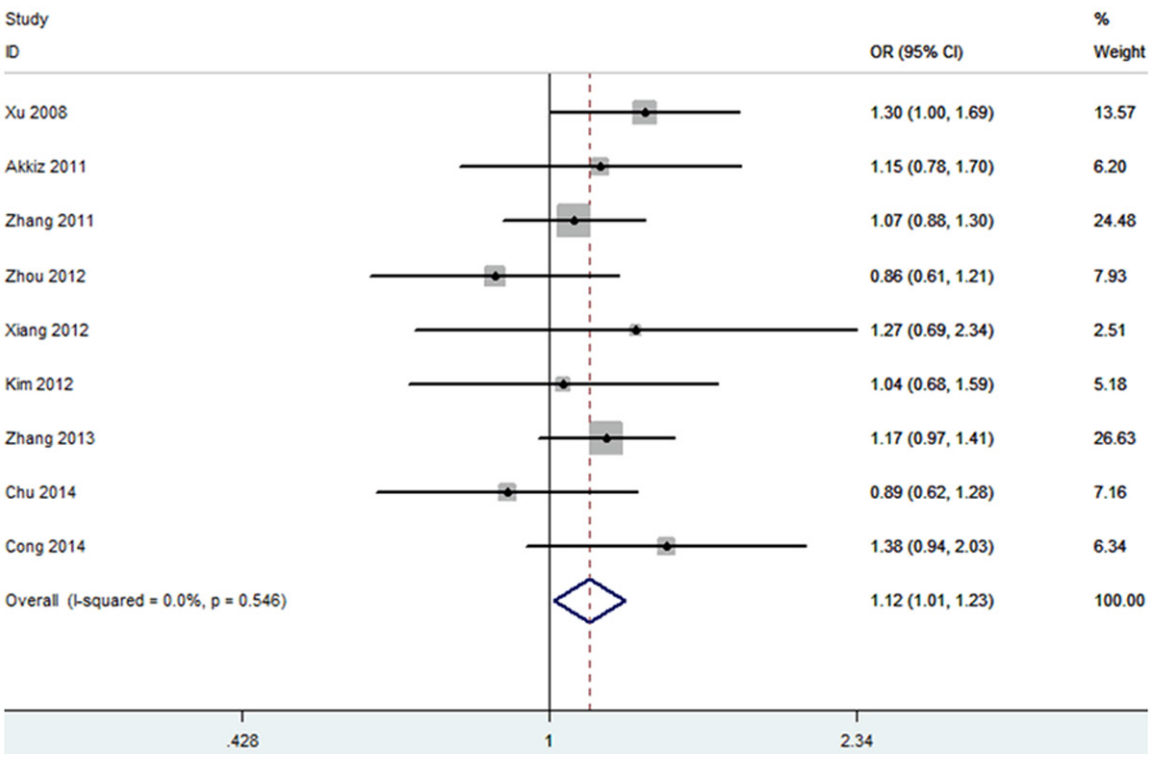

Figure 2. Sensitive analysis for the association between miR-146a rs2910164 and HCC risk.

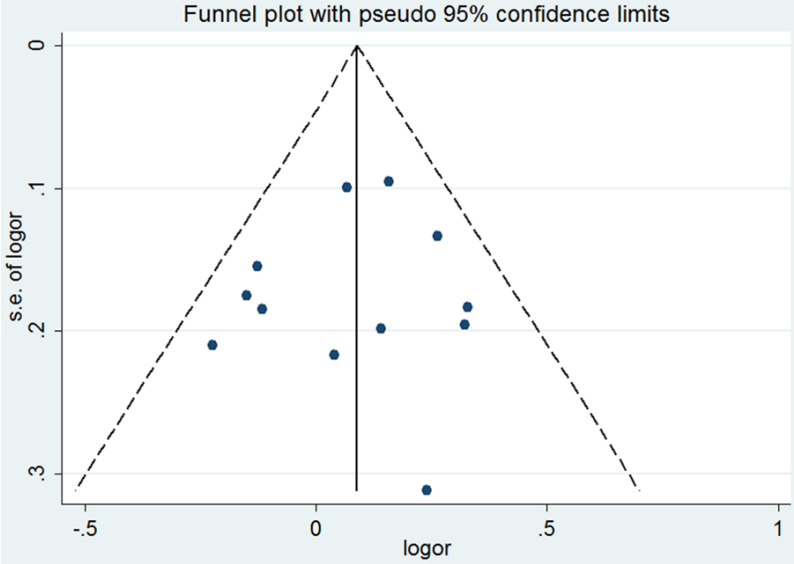

Figure 3. Funnel plot for the association between miR-146a rs2910164 and HCC risk.

risk of HCC. In addition, we also noticed that miR-146a rs2910164 increased the risk of HCC in Asian population. However, only one study used Caucasians. Thus, more studies are needed to confirm the result of this meta-analysis.

HCC represents a major form of primary liver malignancy in adults worldwide. The tumorigenesis and development of HCC is typical of a multistage process. Major risk factors for HCC include infection with HBV or HCV, alcoholic liver disease, and most probably nonalcoholic fatty liver disease [20]. The progression is considered to deregulate genes that are critical to biological cellular procedures such as cell cycle control, apoptosis, cell migration, and metastasis [21]. However, the sensitivity and specificity of these markers remain imperfect [22]. Therefore, new biomarkers are needed to help to understand the causes of hepatocarcinogenesis and to predict response possibilities towards different therapeutic methods.

MiR-146a rs2910164 polymorphism which locates in the passenger strand of miR-146a, can disturb the secondary structure and maturation of miR-146a [8]. Xie et al. suggested that digestive tract neoplasms might associate with miR-146a variant [23]. Sun and coworkers indicated that up-regulation of miR-146a expression in tissues was related to carcinogenesis and deterioration of papillary thyroid carcinoma [24].

In conclusion, this meta-analysis suggested a significant association between miR-146a rs2910164 polymorphism and HCC risk.

Disclosure of conflict of interest

None.

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