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Original Article

Study of the association between five polymorphisms and risk of hepatocellular carcinoma: A meta-analysis

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Abstract

Background: Recently, several studies have investigated the association between polymorphisms in miR-146a rs2910164, miR-196a2 rs11614913, miR-499 rs3746444, miR-149 rs229283, miR-34b/c rs4938723, and hepatocellular carcinoma (HCC), which showed inconclusive results.

Methods: A publication search was performed in PubMed, ExcerptaMedica Database, Chinese Biomedical Literature Database, and Chinese National Knowledge Infrastructure to collect relevant medical data published through February 2016. The aim of this study was to ascertain the association between HCC and micro-RNAs. A total of 21 studies were included in our study, which showed that miR-146a rs2910164 polymorphism has a significant association with HCC in the allele, recessive, and homozygous models overall [allele model: odds ratio (OR) = 0.927, 95% confidence interval (CI): 0.869−0.988, $p = 0.02$; recessive model: OR = 0.893, 95% CI: 0.814−0.981, $p = 0.018$; homozygous model: OR = 0.853, 95% CI: 0.744−0.978, $p = 0.023$] and in Asian populations (allele model: OR = 0.921, 95% CI: 0.863−0.983, $p = 0.014$; recessive model: OR = 0.893, 95% CI: 0.814−0.981, $p = 0.019$; homozygous model: OR = 0.851, 95% CI: 0.741−0.977, $p = 0.022$). For miR-196a2 rs11614913, significant statistical heterogeneity overall and in Asian populations was identified in the comparison of the allele, recessive, homozygous, and heterozygous models (overall: allele model: OR = 0.889, 95% CI: 0.842−0.94, $p < 0.001$; recessive model: OR = 0.837, 95% CI: 0.723−0.970, $p = 0.018$; homozygous model: OR = 0.722, 95%CI: 0.575−0.906, $p = 0.005$; heterozygous model: OR = 0.532, 95% CI: 0.37−0.765, $p = 0.001$), and also has a decreased risk of HCC in Caucasians in all genetic models except for the heterozygous model (allele model: OR = 0.658, 95% CI: 0.49−0.885, $p = 0.006$; dominant model: OR = 0.641, 95% CI: 0.418−0.981, $p = 0.041$; recessive model: OR = 0.489, 95% CI: 0.278−0.862, $p = 0.013$; homozygous model: OR = 0.414, 95% CI: 0.222−0.772, $p = 0.005$). Only the recessive models produced a significant association between miR-499 rs3746444 polymorphism and HCC risk (recessive model: OR = 1.283, 95% CI: 1.008−1.632, $p = 0.043$).

Results: The analysis for miR-146a rs2910164 polymorphisms by racial decent found the same association between miR-146a rs2910164 polymorphism and susceptibility to HCC in Asians, but no significance risk association was observed in Caucasians. The meta-analysis results showed that miR-196a2 rs11614913 was associated with a decreased risk of HCC in Caucasians in all genetic models except for the heterozygous model. In the Asian population, miR-499 rs3746444 polymorphism was associated with a decreased risk of HCC in recessive models. This meta-analysis showed that no significant statistical heterogeneity was identified in miR-149 rs2292832 and miR-34b/c rs4938723.

Conclusion: Our findings supported the proposition that the polymorphisms of miR-146a rs2910164, miR-196a2 rs11614913, and miR-196a2 rs11614913 may contribute to the susceptibility of HCC.

Keywords: hepatocellular carcinoma; meta-analysis; micro-RNA; polymorphisms

Conflicts of interest: The authors declare that they have conflicts of interest related to the subject matter or materials discussed in this article.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and is the second leading cause of cancer death worldwide.[1] In 2012, 782,500 new HCC cases and 745,500 deaths were caused by this persistent disease worldwide, with about 50% of the total number of cases and deaths occurring in China. Currently, HCC is a predominant histological subtype of human liver malignancy, which accounts for 70−85% of primary malignancies in the liver.[2] Hepatitis B virus, hepatitis C virus, obesity, and alcohol abuse lead to HCC, which has been recognized as an insidious malignancy with a very poor prognosis. Unfortunately, most HCC patients enter the late stage when diagnosed and have already missed the window of opportunity to have radical treatments. However, HCC is usually highly malignant and quick to metastasize. Therefore, it is of great importance and benefit for patients with HCC to develop early and noninvasive diagnostic biomarkers.

Micro-RNAs (miRNAs) are small, noncoding, single-stranded RNA molecules with a typical length of 22 nucleotides. They also play an important role in physiologic and pathologic processes including cell differentiation, proliferation, apoptosis, and carcinogenesis,[3] and have been implicated in the initiation and progression of various cancers.[4] A miRNA, which has even a slight variation in the function or expression, may affect a wide spectrum of mRNA targets, including many oncogenes and tumor suppressor genes.[5] Single-nucleotide polymorphisms (SNPs) can reportedly alter expressions or functions of miRNAs; related to cancer risk, they are the most common type of genetic variation, which are associated with population diversity, disease susceptibility, and individual response to medicine.[6] Research focusing on both SNPs in miRNAs and human cancer has provided another insight into the molecular mechanisms of cancer development. Recent studies have demonstrated that genetic factors could also contribute to the etiology of HCC.[7] In recent years, we have paid significant attention to genetic polymorphisms due to their etiological roles in defining the risk of HCC development. According to recent research, miR-34b/c, miR-218, miR-146a, miR-149, miR-196a-2, miR-499, and miR106b-25 are related to HCC.[8−22] A small sample size may not be adequate to detect the effects of SNPs on HCC, so we collected 21 studies for this meta-analysis and explored the associations between polymorphisms of miRNAs and HCC.

2. Methods

A publication search was performed in PubMed, ExcerptaMedica Database, Chinese Biomedical Literature Database, and Chinese National Knowledge Infrastructure, to collect relevant medical literature published up to February 2016, using the combined words “microRNA or mir or miRNA,” “gene or allele or polymorphism or variation,” or “HCC or liver cancer.” Publication language was not restricted in our search. Examining the reference lists manually to further identify potentially relevant studies, we also made use of e-mail addresses to contact the corresponding authors of conference abstracts that lacked sufficient data to get additional information.

2.1. Selection

The studies were incorporated into our meta-analysis only if they met the following criteria: (1) HCC and miRNA polymorphism data; (2) independent case−control studies for humans; (3) sources of cases and sufficient available data to estimate an odds ratio (OR) with 95% confidence interval (CI); (4) available genotype frequency; and (5) only full-text manuscripts. We included the latest study if serial studies of the same population were from the same group. The exclusion criteria were as follows: (1) non-HCC studies; (2) the paper being an abstract, comment, editorial, and review; or (3) insufficient data.

2.2. Data abstraction

The included studies were carefully extracted by two well-qualified investigators. The information derived from each study included author, publication date, country of origin, ethnicity, genotyping method, total number of cases and controls, and genotype frequencies of cases and controls. The two investigators reviewed the data extraction for the purpose of arriving at a consensus.

2.3. Quantitative data synthesis

Strength of the association between the SNPs and HCC, including five genetic models (the allele, dominant, recessive, homozygous, and heterozygous models), was measured by ORs with 95% CIs. The *Z*-test was used to determine the significance of the pooled ORs, and $p < 0.05$ was considered statistically significant. Publication bias of literature was assessed by the use of Begg's funnel plots and Egger's test. If a p value of Egger's test was <0.05, we regarded it as representative of statistically significant publication bias.[23] When we used Begg's funnel plot, the standard error of logarithm (Log) for OR was plotted against its OR, and Log OR was plotted versus standard error of Log OR for each enrolled study.[24] Heterogeneity of the studies was checked by the chi-square test-based Q-test,[25,26] and the random-effect model was chosen (DerSimonian and Laird method)[27] when the existence of heterogeneity was detected ($p < 0.10$ for the Q-test, $I^2 > 50\%$). If not, the fixed-effect model (the Mantel−Haenszel method)[28] was selected. The Hardy−Weinberg equilibrium was calculated using the goodness-of-fit chi-square test. A p value < 0.05 was considered significant disequilibrium. All statistical analyses were carried out using STATA 12.0 StataCorp LLC (4905 Lakeway Drive College Station, Texas 77845, USA) and all p values were two sided.

3. Results

3.1. Study characteristics

A total of 52 articles were retrieved after the first search in PubMed, ExcerptaMedica Database, Chinese Biomedical