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Original Article

Relationship between *ADH2* Arg47His variation and hepatocellular carcinoma susceptibility: a meta analysis

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Abstract: Background: To further investigate the relationship between *ADH2* Arg47His variation and hepatocellular carcinoma (HCC) susceptibility through a meta-analysis. Methods: The related articles were searched in PubMed, Embase and CNKI databases. And finally 518 cases and 607 controls were included in our meta-analysis Odds ratios (ORs) with 95% confidence intervals (95% CIs) were used to assess the relationship between *ADH2* Arg47His variation and HCC risk. A fixed-effect model or a random-effect model was applied according to the between-study heterogeneity. Results: Quantitative synthesis demonstrated that no significant association was found between *ADH2* Arg47His variation and HCC susceptibility (His/His vs. Arg/Arg: OR=0.99, 95% CI=0.79-1.25; His/His + Arg/His vs. Arg/Arg: OR=1.01, 95% CI=0.86-1.20; His/His vs. Arg/Arg + Arg/His: OR=0.90, 95% CI=0.74-1.11; His vs. Arg: OR=0.98, 95% CI=0.86-1.11; Arg/His vs. Arg/Arg: OR=1.05, 95% CI=0.82-1.34). Conclusion: Our analysis showed that *ADH2* Arg47His vvariation may not be associated with HCC susceptibility.

Keywords: *ADH2*, variation, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC), a main form of liver cancer, is the third leading cause of cancer death in the world. The incidence of HCC is increased rapidly and it has been considered as the major health problem in the worldwide [1-3]. Alcohol drinking, smoking and chronic viral infections including hepatitis B virus and hepatitis C virus may contribute to increase HCC risk [4-9]. Additionally, genetic factors are considered to be associated with the risk for HCC [10, 11].

Alcohol dehydrogenase (ADH) isoenzyme is a metabolic barrier against self-administer ethanol produced in carbohydrates through the fermentation of bacteria [12, 13]. *ADH2*, a well known member of ADH family, locates on chromosome 4q22-23, and includes three alleles, namely *ADH2* 1, ADH2* 2* and *ADH2* 3*. *ADH2* gene is mainly responsible for the conversion of ethanol to carcinogenic metabolite during the elimination phage [14-16]. Additionally, *ADH2* expression could result in high blood acetaldehyde levels, which can easily lead to DNA damage, and finally cause the occurrence of cancer [17-19]. Previous studies have found that *ADH2* gene was associated with some cancers, such as colorectal cancer and esophageal cancer [20, 21].

ADH2 has numerous polymorphic sites, and one of the most studied functional polymorphisms in *ADH2* gene is Arg47His with an acid substitution of arginine (Arg) to histidine (His) at codon 47. In addition, Arg47His shows great impact on enzyme activities, and ultimately causes the occurrence of diseases. Several studies have investigated the association of *ADH2* Arg47His polymorphism with HCC risk [22-24]. Based on the published studies, our meta-analysis was aimed to make clear the relationship between *ADH2* Arg47His polymorphism and HCC risk.

Methods

Search strategy

The related articles were searched in PubMed, Embase and CNKI databases with the terms of

Table 1. Principle characteristics of the studies included in the meta-analysis

First author	Year	Country	Ethnicity	Control source	Genotyping method	Case	Control	HWE
Takeshita_Male	2000	Japan	Asian	Hospital based	RFLP	85	101	0.158
Takeshita_Female	2000	Japan	Asian	Hospital based	RFLP	17	24	0.102
Sakamoto T	2006	Japan	Asian	Hospital based	PCR-CTPP	209	275	0.475
Ding J	2008	China	Asian	Population based	PCR-RFLP	207	207	0.806

RFLP: restriction fragment length polymorphism; PCR-CTPP: PCR-confronting two-pair primers; PCR-RFLP: PCR-restriction fragment length polymorphism; *1*1, *1*2 and *2*2 represent non-risk homozygous genotype, heterozygous genotype, and risk homozygous genotype, respectively; HWE: Hardy-Weinberg equilibrium.

"*ADH2*" or "alcohol dehydrogenase 2", "polymorphism" or "variant", "hepatocellular carcinoma", "HCC" or "liver". Studies were included according to the following inclusion criteria: (1) evaluating the association between *ADH2* Arg47His and HCC; (2) case-control study; (3) with sufficient data for evaluating odds ratios (ORs) with 95% confidence intervals (95% CIs). When numerous articles were published with overlapping data, only the largest or most recent studies were included. The literature search was updated on December 17, 2014.

Data extraction

All the following data were extracted by two independent investigators: name of first author, publication date, ethnicity, country of origin, number of cases and controls, genotyping methods, genotype frequencies, and Hardy-Weinberg equilibrium (HWE), as displayed in **Table 1**.

Statistical analysis

Crude ORs with 95% confidence intervals (95% CIs) were used to evaluate the correlation between *ADH2* Arg47His polymorphism and HCC risk. The pooled ORs were analyzed under the following 5 genetic models: His/His vs. Arg/Arg, His/His + Arg/His vs. Arg/Arg, His/His vs. Arg/Arg + Arg/His, His vs. Arg, and Arg/His vs. Arg/Arg. Z test was used to estimate whether the pooled ORs were significant, and $P < 0.05$ was considered to be statistically significant. Q test was used to testify between-study heterogeneity. The pooled ORs were calculated by the fixed-effects model or random-effects model in the presence ($P \leq 0.10$) or absence ($P > 0.10$) of heterogeneity. Sensitivity analysis was performed to estimate the stability of the results. Begg's funnel plots and Egger's test were used to testify publication bias. HWE was checked by χ^2 test. Statistical analysis was conducted using STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

A total of 150 studies were identified through databases in which 65 studies were precluded for unrelated titles and abstracts, 56 studies were excluded for duplicate publications, and 25 studies were precluded for no case-control studies. And finally 518 cases and 607 controls were included in our study.

Quantitative synthesis

As displayed in **Table 2** and **Figure 1**, there was no significant association between *ADH2* Arg47His polymorphism and HCC risk (His/His vs. Arg/Arg: OR=0.99, 95% CI=0.79-1.25; His/His + Arg/His vs. Arg/Arg: OR=1.01, 95% CI=0.86-1.20; His/His vs. Arg/Arg + Arg/His: OR=0.90, 95% CI=0.74-1.11; His vs. Arg: OR=0.98, 95% CI=0.86-1.11; Arg/His vs. Arg/Arg: OR=1.05, 95% CI=0.82-1.34).

Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of each individual study on the pooled ORs. The overall results were not altered when any individual study was excluded, suggesting our results were statistically steady.

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias. The shape of the funnel plot seemed symmetrical. Additionally, no significant publication bias was detected by Egger's test in the meta-analysis ($P = 0.64$). Therefore, there existed no apparent publication bias and the results were statistically credible (**Figure 2**).

Table 2. Association of *ADH2* Arg47His polymorphism and HCC risk

	His/His vs. Arg/Arg		His/His+Arg/His vs. Arg/Arg		His/His vs. Arg/Arg		His vs. Arg		Arg/His vs. Arg/Arg	
	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*
Fixed-effects model										
Total	0.99 (0.79, 1.25)	0.989	1.01 (0.86, 1.20)	0.995	0.90 (0.74, 1.11)	0.193	0.98 (0.86, 1.11)	0.830	1.05 (0.82, 1.34)	0.964

Ph: *P*-value of heterogeneity test; *1*1, *1*2 and *2*2 represent non-risk homozygous genotype, heterozygous genotype, and risk homozygous genotype, respectively.

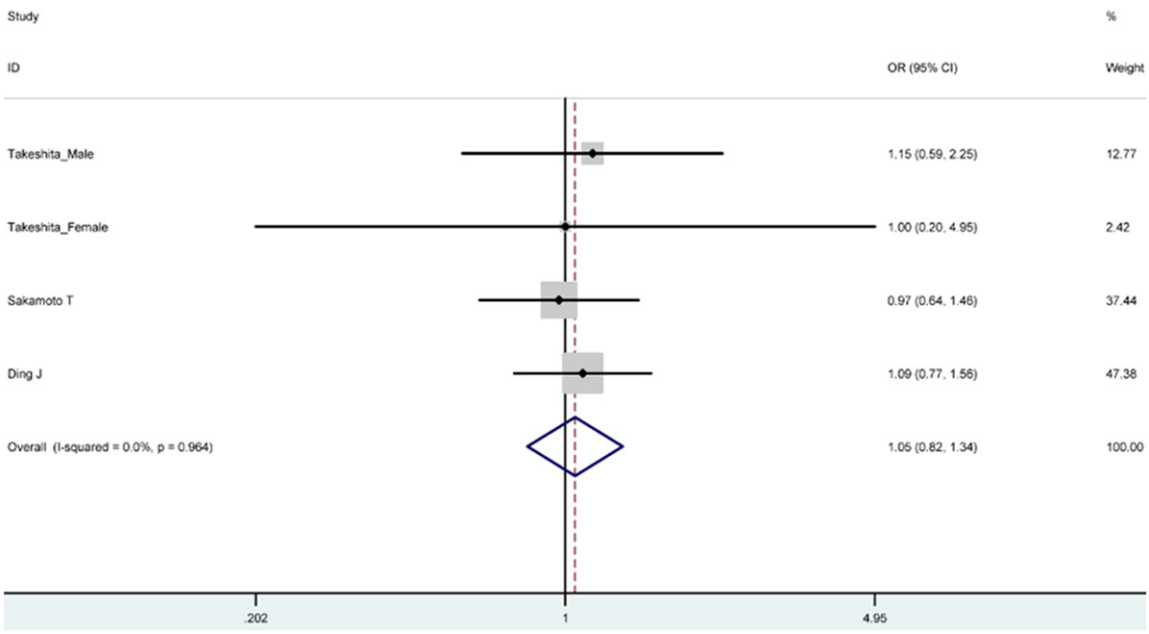

Figure 1. Forest plot analysis of association of *ADH2 Arg47His* polymorphism and HCC risk under Arg/His vs. Arg/Arg genetic model.

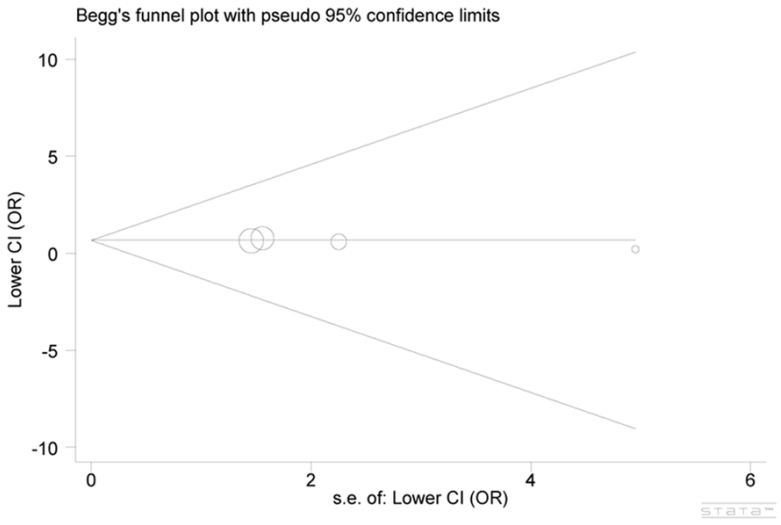

Figure 2. Publication bias test.

Discussion

HCC is one of the most common cancers in Asian populations [25]. Although some measures have been taken to improve the diagnosis of HCC, the results are still unsatisfactory due to the unclear etiology [26-29]. It has been demonstrated that both environmental and genetic factors may play significant roles in the etiology of HCC [4, 11]. The risk of HCC associated with exposure to exogenous xenobiotics or endogenous substances may be modified by genetic variations in metabolic detoxification activities. Therefore, the effects of genetic polymorphisms on HCC risk cannot be ignored.

Some epidemiological studies have investigated the relationship between *ADH2* Arg47His polymorphism and HCC susceptibility. In a large-scale study conducted by Ding et al., HCC patients were divided into drinkers and non-drinkers. Compared to the non-drinkers with active *ADH2* genotypes, the drinkers with inactive *ADH2* genotypes showed no high risk for HCC, thus the results revealed that *ADH2* Arg47His polymorphism was not related with increased risk of HCC [23]. Similar to the above study, Sakamoto T et al. divided HCC patients into non-drinkers, light, moderate, and heavy drinkers and they drew a same conclusion on the relationship of *ADH2* Arg47His and HCC [25].

Our meta-analysis, including 518 cases and 607 controls, was conducted to obtain a more precise assessment on the relationship between *ADH2* Arg47His polymorphism and HCC risk. And the results demonstrated that *ADH2* Arg47His polymorphism was not associated with HCC risk.

Some limitations in our study should be addressed. Firstly, our analysis was performed based on Asians, without considering other ethnic groups. Secondly, our study ignored the effects of gender on HCC risk. Thirdly, the sample size was relatively small. Finally, the results were summarized with unadjusted estimates, which might affect the validity of results. Therefore, further well-designed investigations performed in a larger scale are needed to clarify this point of view.

Disclosure of conflict of interest

None.

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