

Original Article

Association between *ALDH2* 487G/A polymorphism and hepatocellular carcinoma

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Abstract: Background: Although many studies have investigated the association of *ALDH2* 487G/A polymorphism with the risk of hepatocellular carcinoma (HCC), their conclusions are controversial. So a meta-analysis was carried out to further determine the correlation between the two sides. Methods: The eligible studies were searched in PubMed, ELSEVIER, and Chinese National Knowledge Infrastructure (CNKI) databases. Finally, 10 studies including 1,495 cases and 2,048 controls were incorporated in this meta-analysis. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated by the random or fixed effects model to evaluate the association between *ALDH2* 487G/A polymorphism and risk of HCC. The heterogeneity among studies was analyzed by Q-test and the publication bias was checked with the Begg's funnel plot and Egger's linear regression analysis. Results: The overall result showed that no significant association between *ALDH2* 487G/A polymorphism and risk of HCC was found under five genetic models including *2*2 vs. *1*1 (OR=1.06, 95% CI=0.80-1.40), *2*2 + *1*2 vs. *1*1 (OR=0.92, 95% CI=0.69-1.23), *2*2 vs. *1*2 + *1*1 (OR=1.22, 95% CI=0.83-1.79), *2 vs. *1 (OR=0.93, 95% CI=0.73-1.19) and *1*2 vs. *1*1 (OR=0.95, 95% CI=0.72-1.24). In subgroup analysis of control source, *ALDH2* 487G/A polymorphism was also not related to risk of HCC. Conclusion: The study demonstrated *ALDH2* 487G/A polymorphism may not be a risk factor for HCC. Further well-designed studies with larger sample sizes are needed to verify this result.

Keywords: *ALDH2*, hepatocellular carcinoma, polymorphism, meta-analysis

Introduction

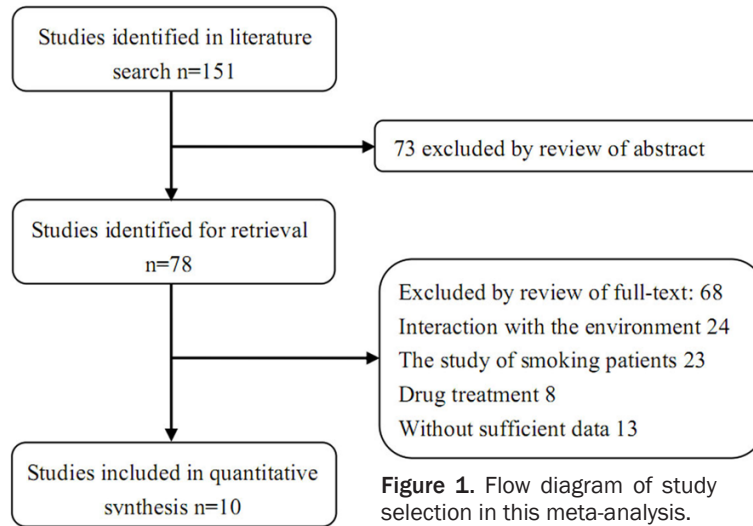
Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor and the third fatal cancer worldwide [1, 2]. With a long-term, multi-step process, the highest incidence rate of HCC (>20 per 100,000) is reported to occur in countries in sub-Saharan Africa and Southeast Asia [3]. Hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol intake, independent on chronic viral infection have been identified to play important roles in the development of HCC [4-8]. But only a minority of people who exposed to these factors develops HCC. It is obviously that genetic factors are indispensable for the occurrence of HCC.

Aldehyde dehydrogenase 2 (*ALDH2*), encoded by *ALDH2* located on the chromosome 12q24, is the second enzyme of the major oxidative pathway in alcohol metabolism, which is asso-

ciated with more than 60% of acetaldehyde metabolism [9]. *ALDH2* contains a polymorphism of G487A [10], and there are two alleles in *ALDH2* G487A polymorphism: wild allele G (*ALDH2* *1) that indicates normal enzyme activity and variant A (*ALDH2* *2) which inactivates catalytic capability. The mutation from G (for guanine) to A (for adenine) at exon12 or the substitution of Glu to Lys leads to molecular structure aberrations and the inactivity of *ALDH2* enzyme [11, 12]. Several publications have reported that *ALDH2* G487A polymorphism is related to various diseases, such as tuberculosis [13], colorectal cancer [14], coronary heart disease [15], esophageal cancer [16], essential hypertension [17], and liver cancer [18].

Previous studies have investigated the association between *ALDH2* G487A polymorphism and HCC risk. However, the results were inconsistent [18-20]. The discrepancy may result from

Association between *ALDH2* 487G/A polymorphism and HCC risk



different ethnicity, study sample sizes and other environmental factors. Therefore, a meta-analysis was performed to explore whether *ALDH2* gene 487G/A polymorphism was associated with the risk of HCC.

Materials and methods

Literature search strategy

The databases of PubMed, ELSEVIER, and China National Knowledge Infrastructure (CNKI) were searched for all eligible studies which were limited to English and Chinese language and human subjects. The search terms were: “*ALDH2*” or “aldehyde dehydrogenase 2”, “Glu-487Lys” or “rs671”, “polymorphism” or “genetic variations” or “mutation” and “hepatocellular carcinoma” or “HCC” or “hepatic tumor”. Eligible studies were selected according to the following inclusion criteria: (1) Assessing the association between *ALDH2* 487G/A polymorphism and HCC risk; (2) Sufficient data were contained for the computation of odds ratios (ORs) with 95% confidence intervals (CIs); (3) The data of genotype frequencies were given in detail; (4) Case-control studies. The following exclusion criteria were used: (1) The design and the definition of the experiments were obviously different from those of the selected papers. (2) Not offering the source of cases and controls and other essential information. (1) Reviews and repeated literature were also excluded. If more than one article were published using the same patient population, only the most recent study

with the largest number of participants would be included in this meta-analysis.

Data extraction

Data extraction of eligible articles based on the inclusion criteria was carried out independently by two investigators. The following information was extracted from each study: first author’s name, publication year, country, ethnicity, source of control, genotyping method, the frequency of genotypes and Hardy-Weinberg equilibrium (HWE)

of controls. Discrepancies were adjudicated by a third investigator until a consensus was achieved.

Statistical methods

Statistical analysis was undertaken using STATA 12.0 software. The distributions of genotypes in the controls were tested by HWE. The strength of association between *ALDH2* 487G/A polymorphism and HCC risk was assessed by the pooled odds ratios (ORs) with 95% confidence intervals (CIs). Moreover, Q and I^2 test were used to evaluate heterogeneity among studies. $P < 0.05$ and $I^2 > 50\%$ indicated significant heterogeneity [21] and then the random-effects model was used to calculate the pooled ORs with 95% CIs [22], or else, the fixed-effects model was employed [23]. Publication bias was estimated using Begg’s funnel plot and Egger’s linear regression test [24, 25]. Sensitivity analysis was performed to test the stability of the results by omitting one study at a time.

Results

Selection of the included studies

According to the inclusion criteria listed above, a total of 151 relevant publications were systematically identified through PubMed, ELSEVIER and CNKI, but only 78 studies were preliminarily identified for further evaluation. Of them, we excluded 68 studies, of which there were 24 studies with gene-environment inter-

Association between *ALDH2* 487G/A polymorphism and HCC risk

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

First author/ Country	Publica- tion date	Genotyping method	HWE	Case size	Control size	Control source
Ding/China	2008	Polymerase chain reaction-restriction fragment length polymorphism	0.025	208	207	Population based
Kato/Japan	2003	Polymerase chain reaction-restriction fragment length polymorphism	NA	94	133	Hospital based
Koide/Japan	2000	NA	0.652	84	84	Population based
Munaka/Japan	2003	Polymerase chain reaction-restriction fragment length polymorphism	NA	78	138	Hospital based
Sakamoto/Japan	2006	Two-pair primers	0.700	209	275	Hospital based
Takeshita (M)/Japan	2000	Restriction fragment length polymorphism	0.539	85	101	Hospital based
Takeshita (F)/Japan	2000	Restriction fragment length polymorphism	0.744	17	24	Hospital based
Tomoda/Japan	2012	Sequenom MassARRAY	0.121	264	199	Hospital based
Yamagishi/Japan	2004	Polymerase chain Reaction-restriction fragment length polymorphism	0.251	24	461	Population based
Ye/China	2010	Polymerase chain reaction-restriction fragment length polymorphism	0.727	300	292	Population based
Yu/China	2002	Polymerase chain reaction	0.489	132	134	Population based

Table 2. *ALDH2* 487G/A polymorphism and hepatocellular carcinoma risk

Contrast	Control source	OR (95% CI)	<i>P</i> value for heterogeneity test	Method for OR calculation
*2*2 vs. *1*1	Population based	1.17 (0.82, 1.69)	0.203	
	Hospital based	0.90 (0.57, 1.42)	0.122	
	Total evaluation	1.06 (0.80, 1.40)	0.131	Fixed
*2*2 + *1*2 vs. *1*1	Population based	0.87 (0.60, 1.27)	0.026	
	Hospital based	0.95 (0.56, 1.61)	0.008	
	Total evaluation	0.92 (0.69, 1.23)	0.003	Random
*2*2 vs. *1*1 + *1*2	Population based	1.23 (0.82, 1.83)	0.342	
	Hospital based	1.25 (0.64, 2.43)	0.009	
	Total evaluation	1.22 (0.83, 1.79)	0.029	Random
*2 vs. *1	Population based	0.93 (0.67, 1.28)	0.011	
	Hospital based	0.91 (0.59, 1.40)	0.007	
	Total evaluation	0.93 (0.73, 1.19)	0.002	Random
*1*2 vs. *1*1	Population based	0.88 (0.63, 1.22)	0.100	
	Hospital based	1.03 (0.62, 1.70)	0.021	
	Total evaluation	0.95 (0.72, 1.24)	0.015	Random

actions, 23 studies with smoking patients, 8 studies for drug treatment and 13 studies without sufficient data. Finally, as shown in **Figure 1**, a total of 10 eligible studies matched our inclusion criteria, including 1,495 cases and 2,048 controls [18-20, 26-32]. The characteristics of every study are listed in **Table 1**.

Meta-analysis results

In **Table 2**, the overall result showed that no significant association between *ALDH2* 487G/A polymorphism and HCC risk was observed under genetic models including *2*2 vs. *1*1 (OR=1.06, 95% CI=0.80-1.40), *2*2 + *1*2 vs. *1*1 (OR=0.92, 95% CI=0.69-1.23, *2*2 vs. *1*2 + *1*1 (OR=1.22, 95% CI=0.83-1.79), *2 vs. *1 (OR=0.93, 95% CI=0.73-1.19) and

*1*2 vs. *1*1 (OR=0.95, 95% CI=0.72-1.24). In subgroup analysis for source of control, no remarkable relationship of 487G/A with HCC was observed in either population-based (PB) or hospital-based (HB) group (**Figure 2**).

Sensitivity analysis

Sensitivity analysis was conducted to assess the influence of each study on the pooled ORs by omitting each single study. The stable pooled ORs showed the robustness of current results (data not shown).

Publication bias

Begg's funnel plot and modified Egger's test were performed to estimate the publication

Association between *ALDH2* 487G/A polymorphism and HCC risk

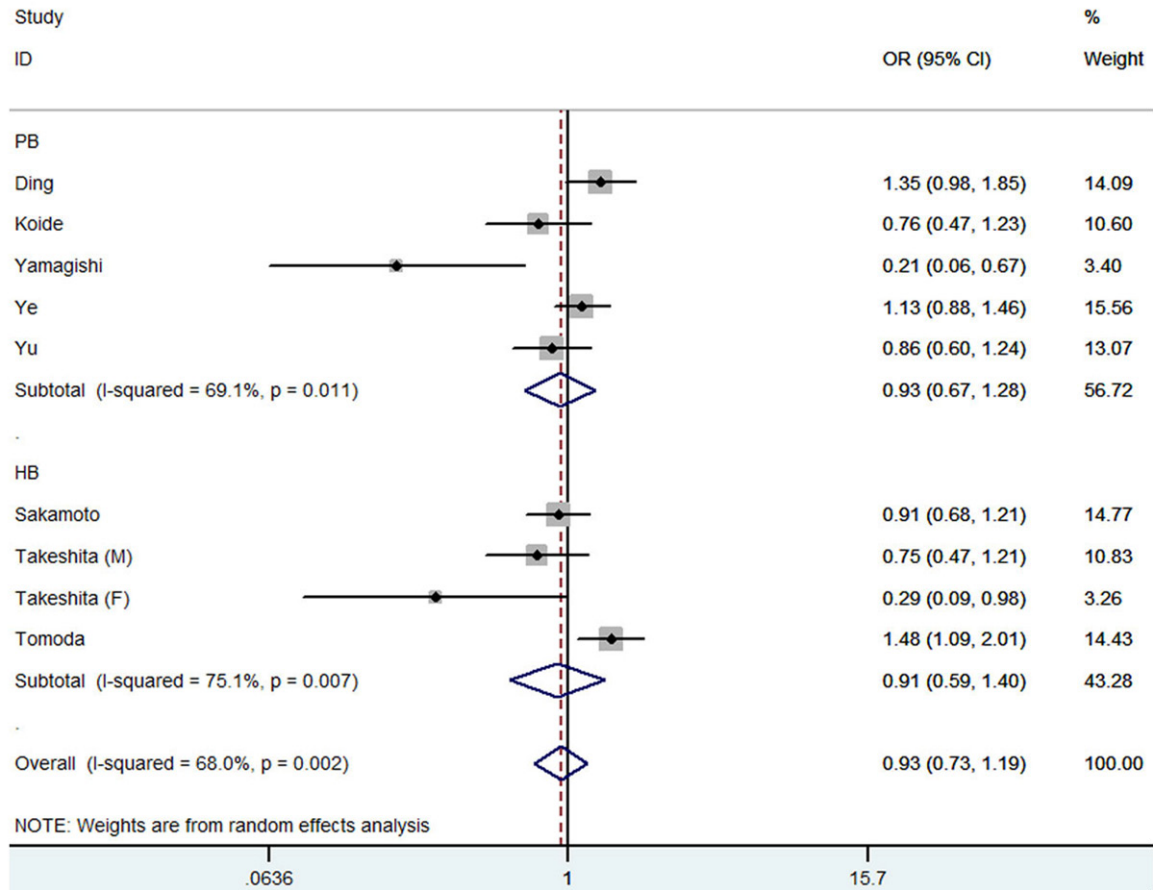


Figure 2. Forest plot of HCC and *ALDH2* 487G/A under the model of *2 vs. *1.

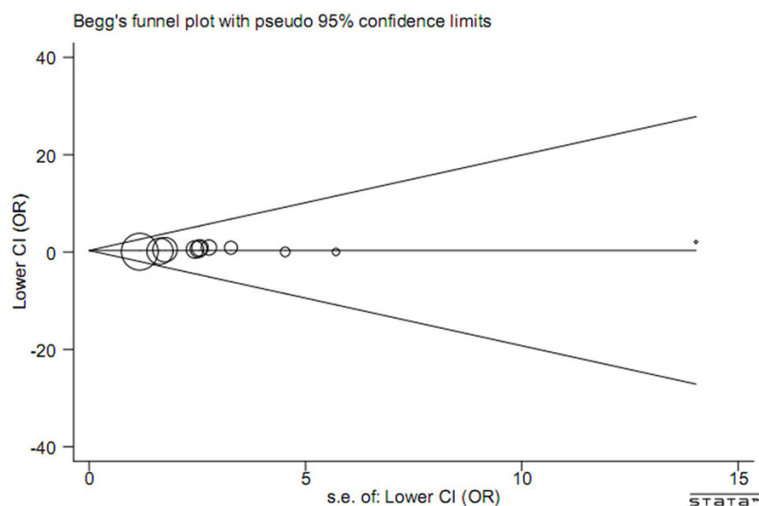


Figure 3. Begg's funnel plot of association between *ALDH2* 487G/A polymorphism and HCC risk.

bias of literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry for all genetic models in the overall meta-analysis (**Figure 3**). The results of Egger's test

also did not present any obvious evidence of publication bias (data not shown).

Discussion

ALDH2 is a polymorphic enzyme which is the most important for aldehyde oxidation. It is expressed in many tissues of the body, especially in the liver with the highest concentration [9]. *ALDH2* gene was reported to contain abundant genetic polymorphisms and these polymorphisms have been found to be related to the occurrence of cancers. A meta-analysis of Matsuo et al. suggested that *ALDH2* Glu-

504Lys polymorphism, interacting with alcohol drinking, was a risk factor for stomach cancer [33]. In the study of Wang et al., there was significant association between *ALDH2* genetic

polymorphisms and increased risk of gastric cancer [34]. In contrast, significantly decreased risk for colorectal cancer was found in *ALDH2* Glu487Lys polymorphism by Zhao et al. [35].

HCC is one of the most common malignant tumors in human with a poor prognosis worldwide [36]. Rapid progression and lack of effective early diagnosis are the major obstacles for the treatment of HCC [37]. So it is necessary to find a reliable gene biomarker for early diagnosis and treatment timely. As we all known, like the other cancers, the onset of HCC attributes to the synergetic role of the environmental and genetic factors, but the inheritance is always dominant, which accounts for that only a part people who expose to the same circumstance suffer from HCC. Given this, a mass of scholars devote to studying the effect of the genetic factors on HCC, especially the genetic variant. Zheng et al. explored the role of interleukin-6 (IL6) gene polymorphisms in HCC, two selected polymorphisms both showed the correlation with HCC susceptibility [38]. *TGF-β1* 509C>T polymorphism was found to increase the susceptibility to HCC in HCV-infected patients [39]. Meanwhile, *XRCC1*, *TNF-α*, *P53*, *IL-23R*, *Cyclin D1* gene polymorphisms are also proved to involve in the generation of HCC.

The association between *ALDH2* polymorphism and risk of HCC was also reported in many previous studies. Kato et al. have demonstrated that *ALDH2* polymorphism may promote the development of HCC [27]. Munaka et al. and Sakamoto et al. also have the similar results [20, 29]. However, according to the study of Zhou et al., *ALDH2* polymorphism is not significantly associated with HCC risk in East Asians [40]. The results do not support a contribution of *ALDH2* 487G/A polymorphism to risk of HCC by Takeshita et al. [18]. The previous results were inconsistent, so a meta-analysis was performed to confirm the correlation between the two.

In our present study, a total of 1,495 cases and 2,048 controls were employed. The overall data showed that *ALDH2* 487G/A polymorphism had no significant association with risk of HCC. The result was similar in the subgroup analysis by control of source. Several limitations must be pointed out in this meta-analysis. First of all, some environmental factors have influences on the development of HCC, such as

HBV, HCV, and alcohol drinking [7], so the effects of gene-environment interactions should be addressed. Secondly, some studies in our meta-analysis were not large enough in sample size for an eligible analysis.

In conclusion, *ALDH2* 487G/A polymorphism is not significantly associated with risk of HCC. Further studies with a large scale and considering gene-gene and gene-environment interactions should be conducted to investigate the association.

Disclosure of conflict of interest

None.

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Association between *ALDH2* 487G/A polymorphism and HCC risk

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Association between *ALDH2* 487G/A polymorphism and HCC risk

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