Relationship of ALDH2 rs671 and CYP2E1 rs2031920 with hepatocellular carcinoma susceptibility in East Asians: a meta-analysis

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**Abstract**

**Background:** Aldehyde dehydrogenase 2 (ALDH2) and cytochrome p450 2E1 (CYP2E1) are important alcohol-metabolizing enzymes. The aim of this meta-analysis was to evaluate the association of ALDH2 rs671 and CYP2E1 rs2031920 polymorphisms with hepatocellular carcinoma (HCC) susceptibility in East Asians.

**Methods:** A systematic search strategy was implemented in MEDLINE, PubMed, Scopus, Embase, and China Academic Journals databases. Nineteen case-control studies were selected for inclusion. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated through random-effects or fixed-effects models. Subgroup analysis, meta-regression, sensitivity analysis, cumulative meta-analysis, and evaluation of publication bias were performed.

**Results:** The overall meta-analysis did not find a significant association of ALDH2 rs671 and CYP2E1 rs2031920 genotypes with HCC susceptibility in East Asians. In addition, stratified analysis by country, Hardy-Weinberg equilibrium status, and source of controls also did not identify any association.

**Conclusion:** The ALDH2 rs671 and CYP2E1 rs2031920 polymorphisms are not associated with HCC susceptibility in East Asians.

**Keywords:** ALDH2, CYP2E1, Hepatocellular carcinoma, Polymorphism

**Introduction**

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and is the third most common cause of cancer-related death. In sub-Saharan Africa and some parts of Asia, it is the leading cause of cancer death. HCC most commonly develops in chronic liver disease patients, the etiology of which includes hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, alcohol, aflatoxin exposure, hemachromatosis, and α1-antitrypsin deficiency [1]. It is likely that HCC arises as a consequence of complex interactions between genetic risk factors and environmental exposures. Candidate gene and genome-wide association studies have started to explore this area, but the role of genetic factors in HCC development remains poorly understood.

Aldehyde dehydrogenase 2 (ALDH2) is a mitochondrial enzyme, which is known for its role in alcohol detoxification. It has the highest affinity for acetaldehyde (ACE) and mediates the rate-limiting step of metabolizing ACE to acetic acid. In addition, ALDH2 metabolizes other aldehydes generated during oxidative stress such as 4-hydroxy-2-nonenal (4-HNE), protecting against oxidative stress [2]. In the human ALDH2 gene, there is a G-to-A point mutation at exon 12, resulting in a glutamic acid-to-lysine substitution at residue 487 (rs671, Glu>Lys) of the ALDH2 protein (designated ALDH2*2) [3]. The rs671 polymorphism is found in nearly 35–50% of East Asian populations but has not been found in Africans or Caucasians [4]. It is associated with a reduction in the ALDH2 enzymatic activity by 70 and 98% in heterozygotes and homozygotes, respectively [5]. There are multiple association studies assessing the relationship between ALDH2 rs671 and HCC risk in East Asians. The study by Takeshita et al. was the first study to...
evaluate the association of ALDH2 rs671 with HCC susceptibility, finding no association of the ALDH2 genotypes with HCC development [6]. Their results were supported by several other studies including the study by Liu et al. which was based on a large sample size (600 cases and 3221 controls) [7]. However, the study by Sakamoto et al. suggested that ALDH2 rs671 might modify the risk for developing HCC [8]. The discrepancies among these studies may be due to the modest effect of the polymorphism, variation in ethnic background, and different sample sizes these studies used. Because the findings remain controversial, a quantitative analysis is needed to assess the evidence.

Cytochrome p450 2E1 (CYP2E1) is also one of the important alcohol-metabolizing enzymes. It is strongly expressed in the liver but can also be found in extrahepatic organs such as the brain and kidneys [9]. Hepatic CYP2E1 levels can be induced by chronic alcohol consumption. CYP2E1 metabolizes ethanol and numerous chemicals including environmental pollutants and clinical drugs. Its highly uncoupled NADPH oxidase activity generates high levels of reactive oxygen species, leading to hepatic lipid peroxidation, cell stress, and apoptosis [10]. Human CYP2E1 is located on chromosome 10q26.3 and consists of nine exons and eight introns. It is shown that a restriction fragment length polymorphism (rs2031920, Pst I/Rsa) in the 5′-transcriptional region may modify the CYP2E1 enzyme function or mRNA expression levels [11]. Although several studies from East Asia evaluated the possible association of

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Fig. 1 Flow chart of the study selection
rs2031920 with HCC susceptibility, the results have been conflicting.

In this study, we aim to perform a meta-analysis to assess the relationship of ALDH2 rs671 and CYP2E1 rs2031920 with HCC susceptibility in East Asian populations.

### Table 1 Characteristics of the studies assessing ALDH2 rs671 and HCC susceptibility

| Author  | Country | Year | Cases  | Controls | HWE | Genotyping method | Virus infection | Quality score |
|---------|---------|------|--------|----------|-----|--------------------|-----------------|---------------|
| Takeshita | Japan | 2000 | 102 | 62 | 38 | 12 | 65 | 49 | 11 | Yes | PCR-RFLP | HbsAg (+), 0%; HCV antibody (+), 0% | 7 |
| Koide | Japan | 2000 | 84 | 48 | 32 | 4 | 84 | 43 | 33 | 8 | Yes | PCR-RFLP | HbsAg (+), 14.5%; anti-HCV (+), 81.9% | 6 |
| Yu | China | 2002 | 132 | 67 | 51 | 14 | 134 | 58 | 63 | 13 | Yes | PCR | HbsAg (+), 67.9%; anti-HCV (+), 5.2% | 8 |
| Munaka | Japan | 2003 | 78 | 34 | 44 (GA + AA) | 138 | 76 | 62 (GA + AA) | Yes | PCR | HbsAg (+), 17.9%; anti-HCV (+), 69.2% | 8 |
| Kato | Japan | 2003 | 94 | 75 (GG + GA) | 19 | 133 | 127 (GG + GA) | 6 | Yes | PCR-RFLP | HbsAg (+), not reported; anti-HCV (+), 100% | 7 |
| Sakamoto | Japan | 2006 | 209 | 117 | 77 | 15 | 275 | 146 | 107 | 22 | Yes | PCR-CTPP | HbsAg (+), 9.1%; anti-HCV (+), 85.6% | 8 |
| Ding | China | 2008 | 208 | 120 | 64 | 24 | 207 | 133 | 59 | 15 | No | PCR-RFLP | HbsAg (+), 72.1%; anti-HCV (+), not reported | 8 |
| Tomoda | Japan | 2012 | 264 | 132 | 111 | 21 | 199 | 126 | 60 | 13 | Yes | PCR | HbsAg (+), 0%; anti-HCV (+), 100% | 6 |
| Abe | Japan | 2015 | 67 | 51 | 16 | 0 | 67 | 62 | 5 | 0 | Yes | PCR-CTPP | HbsAg (+), 0%; anti-HCV (+), 0% | 8 |
| Liu | China | 2016 | 600 | 303 | 248 | 49 | 3221 | 1617 | 1354 | 250 | Yes | PCR | HbsAg (+), 100%; anti-HCV (+), 0% | 7 |
| Ye | China | 2018 | 300 | 149 | 121 | 30 | 292 | 152 | 119 | 21 | Yes | PCR-RFLP | HbsAg (+), 85.0%; anti-HCV (+), not reported | 8 |

For ALDH2 rs671, the G allele is the wild-type allele

CTPP confronting two-pair primers, HWE Hardy-Weinberg equilibrium, NOS Newcastle Ottawa Scale, PCR polymerase chain reaction, RFLP restriction fragment length polymorphism

### Methods

#### Databases and search strategy

Searches were performed in MEDLINE, PubMed, Scopus, Embase, and China Academic Journals databases from inception to July 8, 2019, by two independent authors (Additional file 1). Searches were built around
the keywords: “hepatocellular carcinoma,” “liver cancer,” “aldehyde dehydrogenase 2,” “ALDH2,” “cytochrome p450 2E1,” “CYP2E1,” “polymorphism,” “genetic variant,” “susceptibility,” and “development.” No restrictions on language or setting were applied. Titles and abstracts were screened against the inclusion and exclusion criteria. Full texts of potentially eligible studies were screened. Reference lists of all included studies and relevant reviews were hand-searched to identify additional eligible studies. The design and report of our meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12].

### Inclusion and exclusion criteria

After the removal of duplicates from different databases, the titles and abstracts of the citations were carefully screened. Irrelevant papers were excluded, leaving potential studies for further full-text evaluation. The inclusion and exclusion criteria for the studies were as follows: (1) case-control studies of unrelated individuals using a population or hospital-based design, (2) evaluation of the relation of ALDH2 and CYP2E1 polymorphisms with susceptibility to HCC, and (3) sufficient data for pooling the odds ratio (OR) and 95% confidence interval (CI). Exclusion criteria were studies in languages other than English and Chinese, review articles, meeting abstracts, editorials, and animal studies.

### Table 2 Characteristics of the studies analyzing CYP2E1 rs2031920 and HCC susceptibility

| Author  | Country | Year | Cases | Controls | HWE Genotyping method | Virus infection | Quality score |
|---------|---------|------|-------|----------|-----------------------|----------------|--------------|
| Yu      | China   | 1995 | 30    | 25 5 0   | PCR-RFLP             | HbsAg (+), 96.7%; anti-HCV (+), 16.7% | 7             |
| Lee     | Korea   | 1997 | 108   | 67 36 5 | PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), not reported | 8             |
| Liu     | China   | 2000 | 84    | 60 22 2 | PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), not reported | 7             |
| Yu      | China   | 2002 | 131   | 83 41 7 | PCR-RFLP             | HbsAg (+), 67.9%; anti-HCV (+), 5.2% | 8             |
| Kato    | Japan   | 2003 | 93    | 57 36   | PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), 100% | 7             |
| Munaka  | Japan   | 2003 | 77    | 45 32   | PCR-RFLP             | HbsAg (+), 17.9%; anti-HCV (+), 69.2% | 8             |
| Meng    | China   | 2003 | 21    | 1 19 1  | PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), not reported | 6             |
| Jiang   | China   | 2004 | 207   | 122 76 9| PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), not reported | 6             |
| Wu      | China   | 2007 | 63    | 43 17 3 | PCR-RFLP             | HbsAg (+), not reported; anti-HCV (+), not reported | 8             |
| Imaizumi| Japan   | 2009 | 209   | 127 73 9| PCR-RFLP             | HbsAg (+), 9.1%; anti-HCV (+), 85.6% | 6             |
| Di      | China   | 2013 | 95    | 80 15 0 | PCR-RFLP             | HbsAg (+), 85.0%; anti-HCV (+), not reported | 8             |
| Ye      | China   | 2018 | 300   | 203 87 10| PCR-RFLP             | HbsAg (+), 10.3%; anti-HCV (+), not reported | 8             |

For CYP2E1 rs2031920, the C allele is the wild-type allele

HWE Hardy-Weinberg equilibrium, NOS Newcastle Ottawa Scale, PCR-RFLP polymerase chain reaction-restriction fragment length polymorphism

**Data extraction and quality assessment**

Two authors extracted data from the eligible studies using a standardized template. Data were collected on first author, country of study, year, number of HCC patients and controls, demographics of HCC patients, source of controls, matching criteria, genotyping methods, and counts of genotypes and alleles (ALDH2
rs671 and CYP2E1 rs2031920). The quality of the included studies was evaluated according to the Newcastle Ottawa Scale (NOS) (www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

**Data analysis**

Since all meta-analyses conducted involved the use of dichotomous data, summary OR with 95% CIs were presented as the effect measure. The minor allele was considered the at-risk allele. ORs were pooled according to fixed- or random-effects models. The analyses were stratified according to country, Hardy-Weinberg equilibrium status, and source of controls. Heterogeneity was evaluated using the $I^2$ statistic, with values higher than 50% indicating substantial heterogeneity [13]. We performed a sensitivity analysis to ensure that the effect sizes of our meta-analysis were not driven by any one study. We used sensitivity analysis, meta-regression, and Galbraith plot to identify the main contributors to between-study heterogeneity. A cumulative meta-analysis was performed to explore the trend in the effect sizes. Egger’s test and funnel plots were applied to assess publication bias. All statistical analyses were conducted using STATA 13.0 (Stata, College Station, TX, USA).

**Results**

**Summary of included studies**

A total of 182 studies were identified after the removal of duplicates from different databases. Twenty-seven articles passed title and abstract screening and underwent full-text review. Nineteen studies met the inclusion criteria and were included in the final analysis. A PRISMA flow chart showing the selection of studies for this meta-analysis is presented in Fig. 1. Eleven studies with 2138 cases and 4875 controls analyzed the ALDH2 rs671 polymorphism.
[6–8, 14–21], while 12 studies including 1418 cases and 1701 controls assessed the CYP2E1 rs2031920 polymorphism [11, 15–17, 21–28]. The quality score of the eligible studies ranged from 6 to 8 points. The characteristics of the included studies are summarized in Tables 1 and 2.

Quantitative synthesis
The ALDH2 rs671 polymorphism was evaluated in Chinese and Japanese populations. The overall meta-analysis did not suggest any association between ALDH2 rs671 and HCC susceptibility for AA + GA genotype vs. GG genotype (OR = 1.10, P = 0.369), AA genotype vs. GA + GG genotype (OR = 1.19, P = 0.357), AA genotype vs. GG genotype (OR = 1.08, P = 0.509), and GA genotype vs. GG genotype (OR = 1.06, P = 0.569; Fig. 2 and Table 3). The sensitivity analysis revealed that omitting the study by Ding et al. which deviated from Hardy-Weinberg equilibrium had no effect on the overall

| Genotype and subgroup | Number of studies | Test of association | Test of heterogeneity | P of Egger’s test |
|-----------------------|-------------------|---------------------|-----------------------|------------------|
|                       |                   | OR (95% CI)         | Z (P value)           | I² (%)           | Phet |
| AA + GA vs. GG        | Overall           | 10                  | 1.10 (0.90–1.35)      | 0.369            | 59.6 | 0.008 | 0.430 |
|                       | HWE (yes)         | 9                   | 1.08 (0.86–1.35)      | 0.527            | 62.0 | 0.007 |
|                       | HWE (no)          | 1                   | 1.32 (0.89–1.96)      | 0.171            | NA   | NA    |
|                       | Chinese           | 4                   | 1.03 (0.87–1.21)      | 0.770            | 17.7 | 0.303 |
|                       | Japanese          | 6                   | 1.21 (0.81–1.80)      | 0.362            | 71.5 | 0.004 |
|                       | Population-based studies | 4   | 0.98 (0.80–1.20)      | 0.859            | 24.1 | 0.267 |
|                       | Hospital-based studies | 6   | 1.24 (0.88–1.75)      | 0.210            | 68.9 | 0.007 |
| AA vs. GA + GG        | Overall           | 9                   | 1.19 (0.82–1.73)      | 0.357            | 58.2 | 0.014 | 0.866 |
|                       | HWE (yes)         | 8                   | 1.13 (0.75–1.71)      | 0.562            | 61.2 | 0.012 |
|                       | HWE (no)          | 1                   | 1.67 (0.85–3.28)      | 0.137            | NA   | NA    |
|                       | Chinese           | 4                   | 1.19 (0.93–1.52)      | 0.165            | 0    | 0.589 |
|                       | Japanese          | 5                   | 1.00 (0.41–2.42)      | 1.000            | 76.8 | 0.002 |
|                       | Population-based studies | 4   | 1.10 (0.82–1.49)      | 0.521            | 8.6  | 0.350 |
|                       | Hospital-based studies | 5   | 1.26 (0.62–2.56)      | 0.526            | 73.7 | 0.004 |
| AA vs. GG             | Overall           | 8                   | 1.08 (0.87–1.34)      | 0.509            | 37.1 | 0.133 |
|                       | HWE (yes)         | 7                   | 1.02 (0.81–1.28)      | 0.892            | 33.6 | 0.171 |
|                       | HWE (no)          | 1                   | 1.77 (0.89–3.54)      | 0.104            | NA   | NA    |
|                       | Chinese           | 4                   | 1.18 (0.92–1.52)      | 0.191            | 0    | 0.452 |
|                       | Japanese          | 4                   | 0.82 (0.54–1.26)      | 0.373            | 58.0 | 0.067 |
|                       | Population-based studies | 4   | 1.08 (0.74–1.57)      | 0.690            | 24.7 | 0.263 |
|                       | Hospital-based studies | 4   | 1.00 (0.54–1.85)      | 0.992            | 58.1 | 0.067 |
| GA vs. GG             | Overall           | 9                   | 1.06 (0.86–1.31)      | 0.569            | 54.2 | 0.026 | 0.464 |
|                       | HWE (yes)         | 8                   | 1.05 (0.83–1.32)      | 0.697            | 58.7 | 0.018 |
|                       | HWE (no)          | 1                   | 1.20 (0.78–1.85)      | 0.403            | NA   | NA    |
|                       | Chinese           | 4                   | 0.99 (0.85–1.14)      | 0.833            | 0    | 0.452 |
|                       | Japanese          | 5                   | 1.21 (0.78–1.89)      | 0.395            | 70.0 | 0.010 |
|                       | Population-based studies | 4   | 0.97 (0.83–1.13)      | 0.669            | 0    | 0.452 |
|                       | Hospital-based studies | 5   | 1.22 (0.83–1.78)      | 0.305            | 69.2 | 0.011 |

For ALDH2 rs671, the G allele is the wild-type allele.

CI confidence interval, NA not applicable, OR odds ratio.
outcome of disease risk [18] (Table 3). Through sub-
group analyses by country, no significant associations
were found in Chinese or Japanese (Fig. 2 and Table 3).
A subgroup analysis by source of controls (population-
based and hospital-based) also did not identify any asso-
ciation (Table 3).

The CYP2E1 rs2031920 polymorphism was assessed in
Chinese, Japanese, and Korean populations. There was
no association between the polymorphism and HCC sus-
ceptibility when combining the results from all eligible
studies (OR = 0.82, P = 0.358 for TT + CT vs. CC; OR =
0.72, P = 0.096 for TT vs. CT + CC; OR = 0.54, P = 0.079
for TT vs. CC; OR = 0.97, P = 0.886 for CT vs. CC; Fig. 3
and Table 4). All studies conformed to Hardy-Weinberg
equilibrium. In the subgroup analysis by country, we did
not find any association of CYP2E1 rs2031920 with
HCC susceptibility in Chinese (Fig. 3 and Table 4), Japa-
nese, and Koreans. When the included studies were sub-
grouped according to the source of controls, the
analyses did not show any statistically significant results
(Table 4).

**Heterogeneity and meta-regression**

Significant heterogeneity was found among the studies
evaluating rs671 and rs2031920 (Tables 3 and 4). We per-
formed a meta-regression analysis to explore the potential
modifiers contributing to the heterogeneity between the
studies that assessed rs671. Year of publication, country,
source of controls, and sample size were considered. How-
ever, the results showed that these factors were not the
sources of heterogeneity (P = 0.101 for year of publication;
P = 0.606 for country; P = 0.366 for source of controls; P =
0.212 for sample size). The meta-regression results for rs2031920 were similar. Next, we conducted the Galbraith plot and accordingly singled out the studies of Tomoda et al. [19] and Abe et al. [20] as the main sources of heterogeneity for rs671 (graph not shown). Removing these studies decreased heterogeneity ($P_{\text{het}} = 0.247$, $I^2 = 22.9\%$), without significantly influencing the pooled ORs. For rs2031920, removing the studies by Meng et al. [24] and Jiang et al. [25] significantly reduced between-study heterogeneity ($P_{\text{het}} = 0.096$, $I^2 = 39.4\%$) but did not alter the corresponding pooled ORs.

### Table 4: Meta-analysis results for CYP2E1 rs2031920

| Genotype and subgroup | Number of studies | Test of association OR (95% CI) | Z (P value) | Test of heterogeneity $I^2$ (%) | $P_{\text{het}}$ | $P$ of Egger's test |
|-----------------------|------------------|---------------------------------|-------------|---------------------------------|----------------|-------------------|
| **CT + TT vs. CC**    |                  |                                 |             |                                 |                |                   |
| Overall               | 12               | 0.82 (0.53–1.26)                | 0.358       | 83.2                            | 0.000          | 0.843             |
| Chinese               | 8                | 0.69 (0.37–1.31)                | 0.259       | 87.0                            | 0.000          |                   |
| Japanese              | 3                | 1.08 (0.82–1.42)                | 0.587       | 0                               | 0.698          |                   |
| Korean                | 1                | 1.76 (0.72–4.30)                | 0.215       | NA                              | NA             |                   |
| Population-based studies | 2           | 0.31 (0.05–1.98)                | 0.214       | 95.2                            | 0.000          |                   |
| Hospital-based studies | 10              | 0.97 (0.68–1.39)                | 0.871       | 68.7                            | 0.001          |                   |
| **TT vs. CT + CC**    |                  |                                 |             |                                 |                |                   |
| Overall               | 9                | 0.72 (0.49–1.06)                | 0.096       | 0                               | 0.921          | 0.714             |
| Chinese               | 7                | 0.69 (0.44–1.08)                | 0.107       | NA                              | 0.803          |                   |
| Japanese              | 1                | 0.84 (0.35–2.01)                | 0.697       | NA                              | NA             |                   |
| Korean                | 1                | 0.70 (0.13–3.82)                | 0.684       | NA                              | NA             |                   |
| Population-based studies | 2           | 0.80 (0.41–1.57)                | 0.520       | 0                               | 0.717          |                   |
| Hospital-based studies | 7                | 0.68 (0.43–1.10)                | 0.115       | 0                               | 0.818          |                   |
| **TT vs. CC**         |                  |                                 |             |                                 |                |                   |
| Overall               | 9                | 0.54 (0.27–1.08)                | 0.079       | 59.0                            | 0.012          | 0.523             |
| Chinese               | 7                | 0.47 (0.19–1.16)                | 0.102       | 65.1                            | 0.009          |                   |
| Japanese              | 1                | 0.87 (0.36–2.11)                | 0.761       | NA                              | NA             |                   |
| Korean                | 1                | 0.86 (0.16–4.73)                | 0.861       | NA                              | NA             |                   |
| Population-based studies | 2           | 0.25 (0.04–1.67)                | 0.153       | 84.9                            | 0.010          |                   |
| Hospital-based studies | 7                | 0.70 (0.37–1.31)                | 0.266       | 27.2                            | 0.221          |                   |
| **CT vs. CC**         |                  |                                 |             |                                 |                |                   |
| Overall               | 9                | 0.97 (0.67–1.41)                | 0.886       | 70.6                            | 0.001          | 0.595             |
| Chinese               | 7                | 0.89 (0.56–1.42)                | 0.624       | 75.2                            | 0.000          |                   |
| Japanese              | 1                | 1.11 (0.75–1.64)                | 0.607       | NA                              | NA             |                   |
| Korean                | 1                | 2.06 (0.77–5.52)                | 0.151       | NA                              | NA             |                   |
| Population-based studies | 2           | 1.03 (0.69–1.52)                | 0.899       | 31.4                            | 0.227          |                   |
| Hospital-based studies | 7                | 1.00 (0.59–1.68)                | 0.994       | 76.6                            | 0.000          |                   |

For CYP2E1 rs2031920, the C allele is the wild-type allele.

CI: confidence interval, NA: not applicable, OR: odds ratio

### Discussion

HCC is the major cause of cancer mortality in some parts of Asia. The poor prognosis of HCC accentuates the need to develop novel genetic markers and therapeutic approaches. Over the past two decades, the relationship of ALDH2 rs671 and CYP2E1 rs2031920 with HCC susceptibility has been extensively studied among...
East Asian populations, but there are inconsistencies in the results. In the present study, we reviewed the available literature and performed a meta-analysis regarding these associations. Our results showed no significant effect of \textit{ALDH2} rs671 and \textit{CYP2E1} rs2031920 on susceptibility to HCC in East Asians under various genetic models.

This is the largest and most comprehensive meta-analysis on the relationship of \textit{ALDH2} rs671 and \textit{CYP2E1} rs2031920 with HCC susceptibility in East Asians. The evaluation of \textit{ALDH2} rs671 was based on 11 studies with 2138 cases and 4875 controls, whereas 12 studies including 1418 cases and 1701 controls were reviewed for \textit{CYP2E1} rs2031920. In addition to the overall meta-analyses, we performed subgroup analyses by country (Chinese, Japanese, and Koreans), Hardy-Weinberg equilibrium status, and source of controls. Moreover, we conducted a cumulative meta-analysis to see how the evidence had shifted over time. These efforts did not identify any association of \textit{ALDH2} rs671 and \textit{CYP2E1} rs2031920 with HCC susceptibility. Our findings were supported by most of the included studies.

Among the 11 studies evaluating \textit{ALDH2} rs671, 8 reported no association with HCC, including the study by Liu et al. which had the largest sample size (600 cases and 3221 controls) [7]. Concerning \textit{CYP2E1} rs2031920, 9 studies did not observe any association. Yu et al. evaluated the association between \textit{CYP2E1} rs2031920 and HCC susceptibility in a Chinese population for the first time; they found no association for the \textit{CYP2E1} polymorphism [11]. Null association between \textit{CYP2E1} rs2031920 and HCC susceptibility was also reported in several Japanese and Korean studies [16, 17, 22, 27]. The findings of the published case-control studies, together with the outcomes from this meta-analysis, suggested that \textit{ALDH2} rs671 and \textit{CYP2E1} rs2031920 were unlikely to be major contributors to HCC susceptibility in East Asian populations.

There was significant heterogeneity between the included studies. For exploring the potential modifiers contributing to heterogeneity, we conducted a meta-regression analysis. We showed that year of publication, country, source of controls, and sample size were not the main contributors to heterogeneity. We did not take
into account other factors such as sex ratio, HBV/HCV status, and drinking habits, because not all studies reported the information. It was suggested that meta-regression was not always effective in explaining between-study heterogeneity [29]. In addition to meta-regression, we conducted the Galbraith plot to explore heterogeneity, finding that the studies of Tomoda et al. [19] and Abe et al. [20] were the sources of heterogeneity for ALDH2 rs671. When these studies were omitted from the overall meta-analysis, the heterogeneity dropped down to 22.9% ($I^2_{het} = 0.247$), without significantly affecting the pooled ORs. Concerning CYP2E1 rs2031920, Galbraith’s test showed that the studies of Meng et al. [24] and Jiang et al. [25] were the main contributors to heterogeneity; removing them did not alter the overall estimation. Thus, we ensured that the meta-analytic results were robust.

A previous meta-analysis by Zhou et al. reported no association between ALDH2 rs671 and the risk of HCC in East Asians with a total of 1231 cases and 1849 controls [30]. Using a larger sample size (2138 cases and 4875 controls), our study confirmed their findings and provided more information through subgroup analysis and cumulative meta-analysis. In addition, we explored the source of heterogeneity, but Zhou et al. did not perform any analyses for it [30]. For CYP2E1 rs2031920, our results contrasted with those of the meta-analysis by Tian et al. which reported an association between rs2031920 and HCC susceptibility in East Asians [31]. Tian and colleagues’ results may be false positive, because they included studies deviating from Hardy-Weinberg equilibrium and pooled overlapping data from the same research group. Two other meta-analyses evaluated the association of rs2031920 with HCC susceptibility using Asian, Caucasian, and Hispanic populations together, but did not find any significant association [32, 33].

Our meta-analysis suggested a lack of association between ALDH2 rs671 and HCC susceptibility, but we could not exclude the possibility that an interaction between ALDH2 rs671 and alcohol drinking may have a role in the development of HCC. Abe et al. found that the profile of alcohol consumption and ALDH2 rs671 had a close relation, and ALDH2 rs671 and the consumptive period affected HCC development in patients with alcoholic liver cirrhosis [20]. In addition, the study by Liu et al. suggested that the association between ALDH2 rs671 and HCC might be significantly mediated by habitual alcohol consumption [7]. However, a principal limitation of these studies was the definition of alcohol drinking, which may cause selection bias. Another limitation was that viral infection was not taken into account. It is known that chronic HBV or HCV infection is common in the Asian continent; adjustment for viral infection may be necessary to clarify whether potential
interactions between ALDH2 rs671 and alcohol drinking contribute to HCC susceptibility.

Some limitations of our meta-analysis should be considered. First, the eligible studies in our meta-analysis were mainly from Chinese and Japanese. There was only one study from Koreans [22]. Chronic infection with HBV is the predominant risk factor for HCC in China and Japan, while chronic HCV infection is the risk factor for HCC in Japan [34]. A subgroup analysis was performed to evaluate the association of these polymorphisms with HCC in different countries. Second, most of the included studies were hospital based. The controls may not reflect the representative element of the source population. Third, although Egger’s test and funnel plots did not suggest publication bias, selection bias might have occurred, because we included only studies written in English and Chinese. Fourth, owing to the insufficient information, we did not perform a subgroup analysis by gender.

In conclusion, the results of our meta-analysis suggest that ALDH2 rs671 and CYP2E1 rs2031920 are not associated with susceptibility to HCC in East Asians. Further, well-designed and population-based studies are needed to evaluate the potential interaction between these polymorphisms and alcohol drinking in HCC susceptibility.

Supplementary information
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Additional file 1: Table S1. Database search strategy.

Abbreviations
ACE: Acetaldehyde; ALDH2: Aldehyde dehydrogenase 2; CI: Confidence interval; CYP2E1: Cytochrome p450 2E1; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; NOS: Newcastle Ottawa Scale; OR: Odds ratio; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Authors’ contributions
KL contributed to the conception and design of the study. JC, WP, YC, and KL searched the aimed studies, extracted the corresponding data, and performed the statistical analysis. JC, WP, YC, LJ, and KL contributed to the discussion. JC and KL wrote the draft of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

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Not applicable.

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Competing interests
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