Research Article

Association of ADH1B Arg47His polymorphism with the risk of cancer: a meta-analysis

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Alcohol consumption has been established to be a major factor in the development and progress of cancer. Genetic polymorphisms of alcohol-metabolism genes result in differences between individuals in exposure to acetaldehyde, leading to possible carcinogenic effects. Arg47His (rs1229984 G > A) in ADH1B have been frequently studied for its potential effect on carcinogenesis. However, the findings are as yet inconclusive. To gain a more precise estimate of this potential association, we conducted a meta-analysis including 66 studies from 64 articles with 31999 cases and 50964 controls. The pooled results indicated that ADH1B Arg47His polymorphism is significantly associated with the decreased risk of overall cancer (homozygous model, odds ratio (OR) = 0.62, 95% confidence interval (CI) = 0.49–0.77; heterozygous model, OR = 0.71, 95% CI = 0.60–0.84; recessive model, OR = 0.83, 95% CI = 0.76–0.91; dominant model, OR = 0.62, 95% CI = 0.53–0.72; and allele comparison, OR = 0.82, 95% CI = 0.75–0.89). Stratified analysis by cancer type and ethnicity showed that a decreased risk was associated with esophageal cancer and head and neck cancer amongst Asians. In conclusion, our meta-analysis suggested that ADH1B Arg47His polymorphism was significantly associated with decreased overall cancer risk. These findings need further validation in large multicenter investigations.

Introduction

Cancer is a major public health problem worldwide. According to GLOBOCAN worldwide estimates, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012 [1]. In addition, the incidence of cancer is predicted to reach 25 million worldwide by 2032 [2]. This growing cancer burden is expected as populations expand and age. Meanwhile, certain lifestyles, such as alcohol consumption, are likely to further boost the burden [1–3].

Alcohol consumption is the third-largest risk factor for global health burden [4]. Approximately 3.3 million deaths, almost 5.9% of total deaths worldwide in 2012, were attributable to alcohol consumption [5]. As early as 2002, approximately 3.6% of all cancers and 3.5% of all cancer deaths were reported due to alcohol consumption [3]. It is well established that alcohol is first catalytically oxidized to acetaldehyde, mainly by alcohol dehydrogenases (ADH), and then to harmless acetate by aldehyde dehydrogenases (ALDH) [6,7]. Acetaldehyde may stimulate carcinogenesis by disrupting DNA synthesis and repair, inhibiting DNA methylation, and by interacting with retinoid metabolism [8,9]. Genetic polymorphisms of alcohol-metabolism genes result in differences between individuals in exposure to acetaldehyde, leading to possible carcinogenic effects [10]. Amongst them, Arg47His (rs1229984 G > A) in ADH1B have been frequently studied for its potential effect on the carcinogenesis. Compared with the Arg/Arg individuals, the His/His individuals have a 40-fold higher enzyme activity oxidized alcohol to toxic acetaldehyde [7].

Epidemiologic studies have extensively explored the association between ADH1B Arg47His polymorphism and cancer risk. However, the findings are as yet inconclusive. Several meta-analyses published before 2016 associated this polymorphism only with esophageal, head and neck, gastric, colorectal, and...
upper aerodigestive tract cancer [11–16]. However, no meta-analyses have ever investigated the association between \textit{ADH1B} Arg47His polymorphism and overall cancer risk, including other types of cancer. In addition, several more studies with larger sample size were published since 2016 [17–24]. Therefore, we performed an updated meta-analysis including the most recent and relevant studies to clarify the association between \textit{ADH1B} Arg47His polymorphism and the overall cancer risk, involving 66 studies with 31999 cases and 50964 controls [17–80].

\section*{Methods}
\subsection*{Identification of relevant studies}

A systematic literature search was conducted in the following electronic databases: Medline and Embase database up to 1 July 2018. The following search terms were used: 'ADH1B or ADH2' or 'polymorphism or variant' or 'cancer or carcinoma or tumor'. In addition, reviews and references lists of eligible studies were manually searched to identify additional relevant articles.

\subsection*{Inclusion and exclusion criteria}

The eligible articles must meet the following criteria. The inclusion criteria were as follows: (i) studies evaluating the association between \textit{ADH1B} Arg47His polymorphism and overall cancer risk; (ii) case–control studies; (iii) studies with sufficient information to calculate the odds ratio (OR) and its 95\% confidence interval (CI). The major exclusion criteria were as follows: (i) no control group; (ii) duplicate publication; (iii) reviews, meta-analyses, conference reports, or editorial articles; (iv) no available data.

\subsection*{Data extraction}

Investigators independently extracted the relevant information from all eligible studies according to the inclusion and exclusion criteria listed above. A final consensus was achieved regarding each selected study. The following information was extracted from each study: first author's surname, publication year, country, ethnicity, cancer type, control source, genotyping method, number of cases and controls with different genotypes, and Hardy–Weinberg equilibrium (HWE) of genotypes in controls.
### Table 1: Main characteristics of included studies in our meta-analysis

| Author       | Year | Country | Ethnicity | Cancer type       | Control source | Genotyping method | Number of cases | Number of controls | HWE     |
|--------------|------|---------|-----------|-------------------|----------------|-------------------|-----------------|-------------------|---------|
| Zhong        | 2016 | China   | Asian     | Colorectal        | HB             | PCR-RFLP          | 85              | 152               | Yes     |
| Masaoka      | 2016 | Japan   | Asian     | Bladder           | HB             | TaqMan            | 3               | 27                | 44      |
| Liu          | 2016 | China   | Asian     | Hepatocellular    | HB             | Affymetrix        | 48              | 236               | 1748 Yes|
| Kagimoto     | 2016 | Japan   | Asian     | Esophageal        | PB             | Multiplex PCR     | 31              | 60                | 676 Yes |
| Chen         | 2016 | China   | Asian     | Gastric           | HB             | PCR-RFLP          | 83              | 104               | 45     |
| Ji           | 2015 | Korea   | Asian     | Head and neck     | HB             | TaqMan            | 26              | 15                | 190     |
| Hitaka       | 2015 | Japan   | Asian     | Gastric           | PB             | TaqMan            | 32              | 35                | 254     |
| Bediaga      | 2015 | Spain   | Caucasian | Head and neck    | PB             | TaqMan            | 78              | 203               | NA     |
| Ye           | 2014 | China   | Asian     | Head and neck     | HB             | TaqMan            | 47              | 25                | 268     |
| Chung        | 2014 | China   | Asian     | UADT              | HB             | MassARRAY         | 68              | 25                | 111     |
| Yuan         | 2013 | China   | Asian     | Head and neck     | PB             | TaqMan            | 42              | 72                | 455     |
| Wu           | 2013 | China   | Asian     | Esophageal        | PB             | TaqMan            | 138             | 101               | 510     |
| Bediaga      | 2015 | Spain   | Caucasian | Head and neck    | PB             | TaqMan            | 326             | 406               | 0       |
| Crous-Bou    | 2013 | Spain   | Caucasian | Colorectal       | PB             | Illumina          | 457             | 513               | 54      |
| Liang        | 2012 | Island  | Mixed     | Head and neck     | PB             | TaqMan            | 530             | 590               | 15     |
| Gu           | 2012 | China   | Asian     | Esophageal        | HB             | MassArray         | 1129            | 1300              | 182     |
| Ferrari      | 2012 | France  | Caucasian | Colorectal       | PB             | TaqMan            | 317             | 1133              | 6       |
| Duell        | 2012 | Spain   | Caucasian | Gastric          | PB             | Illumina          | 7               | 43                | 297     |
| Chiang       | 2012 | China   | Asian     | Colorectal        | PB             | PCR-RFLP          | 25              | 71                | 588     |
| Yin          | 2011 | Japan   | Asian     | Colorectal        | PB             | PCR-RFLP          | 15              | 20               | 78      |
| Wang         | 2011 | China   | Asian     | Esophageal        | PB             | PCR-CPP           | 5               | 17                | 78      |
| McKay        | 2011 | France  | Caucasian | UADT             | PB             | Illumina          | 6776            | 7742              | 50      |
| Marichalar-Mendia | 2011 | Spain  | Caucasian | Head and neck   | PB             | TaqMan            | 80              | 203               | NA     |
| Ji           | 2011 | Korea   | Asian     | Head and neck     | PB             | TaqMan            | 30              | 15                | 174     |
| Hakeneserhew | 2011 | U.S.A.  | Mixed     | Head and neck     | PB             | Illumina          | 1192            | 1243              | 79      |
| Wei          | 2010 | U.S.A.  | Caucasian | Head and neck   | PB             | TaqMan            | 1059            | 1075              | 2       |
| Tanaka       | 2010 | Japan   | Asian     | Esophageal        | PB             | Affymetrix        | 151             | 44                | 776     |
| Soucek       | 2010 | Czech   | Caucasian | Head and neck    | PB             | TaqMan            | 101             | 111               | 1       |
| Mohelnikova-Duchonova | 2010 | Czech | Caucasian | Pancreatic       | PB             | TaqMan            | 213             | 242               | 1       |
| Garcia       | 2010 | Brazil  | Mixed     | Head and neck     | PB             | PCR-RFLP          | 195             | 213               | 2       |
| Cao          | 2010 | China   | Asian     | Gastric           | PB             | DHPLC             | 40              | 29                | 193     |
| Yang         | 2009 | China   | Asian     | Colorectal        | HB             | SNPllex           | 39              | 62                | 370     |
| Oze          | 2009 | Japan   | Asian     | UADT              | HB             | TaqMan            | 71              | 53                | 709     |
| Kawase       | 2009 | Japan   | Asian     | Breast            | HB             | TaqMan            | 25              | 47                | 539     |
| Kanda        | 2009 | Japan   | Asian     | Pancreatic        | HB             | TaqMan            | 4               | 74                | 975     |
| Ding         | 2009 | China   | Asian     | Esophageal        | PB             | DHPLC             | 8               | 19                | 106     |
| Cui          | 2009 | Japan   | Asian     | Esophageal        | PB             | Illumina          | 194             | 151               | 1628    |
| Akbari       | 2009 | Iran    | Asian     | Esophageal        | PB             | MassARRAY         | 21              | 73                | 827     |
| Solomon      | 2008 | India   | Asian     | Head and neck     | HB             | PCR-RFLP          | 13              | 8                 | 54      |
| Lee          | 2008 | China   | Asian     | Esophageal        | HB             | PCR-RFLP          | 117             | 46                | 335     |
| Guo          | 2008 | China   | Asian     | Esophageal        | HB             | PCR-RFLP          | 17              | 24                | 288     |
| Gao          | 2008 | China   | Asian     | Gastric           | PB             | DHPLC             | 15              | 20                | 93      |
| Ding         | 2008 | China   | Asian     | Hepatocellular    | PB             | PCR-RFLP          | 21              | 26                | 84      |
| Zhang        | 2007 | U.S.A.  | Caucasian | Gastric          | PB             | TaqMan            | 261             | 352               | 1       |
| Yin          | 2007 | Japan   | Asian     | Colorectal        | PB             | PCR-RFLP          | 40              | 37                | 452     |
| Yang         | 2007 | China   | Asian     | Esophageal        | PB             | PCR-CPP           | 33              | 22                | 100     |
| Hiraki       | 2007 | Japan   | Asian     | Head and neck     | HB             | TaqMan            | 26              | 31                | 471     |
| Asakage      | 2007 | Japan   | Asian     | Head and neck     | PB             | PCR-RFLP          | 31              | 19                | 49      |
| Sakamoto     | 2006 | Japan   | Asian     | Colorectal        | HB             | PCR-CPP           | 12              | 13                | 159     |
| Matsuo       | 2006 | Japan   | Asian     | Colorectal        | HB             | PCR-CPP           | 19              | 36                | 473     |
| Hashibe      | 2006 | France  | Caucasian | Head and neck    | HB             | TaqMan            | 719             | 877               | 108     |
| Hashibe      | 2006 | France  | Caucasian | Esophageal       | HB             | TaqMan            | 163             | 792               | NA     |

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Table 1 Main characteristics of included studies in our meta-analysis (Continued)

| Author | Year | Country | Ethnicity | Cancer type | Control source | Genotyping method | Number of cases | Number of controls | HWE |
|--------|------|---------|-----------|-------------|----------------|------------------|----------------|-------------------|-----|
| Chen   | 2006 | China   | Asian     | Esophageal  | HB             | PCR-RFLP         | 88             | 117, 125          | Yes |
| Yang   | 2005 | China   | Asian     | Esophageal  | HB             | PCR-CTPP         | 6              | 85, 74            | 22  | 168, 304 Yes |
| Wu     | 2005 | China   | Asian     | Esophageal  | PB             | PCR-RFLP         | 39             | 49, 46            | 16  | 191, 130 No  |
| Landi  | 2005 | France  | Caucasian | Colorectal  | HB             | Millipore        | 292            | 54, 2             | 263 | 48, 3 Yes    |
| Risch  | 2003 | Germany | Caucasian | Head and neck | PB             | PCR-RFLP         | 227            | 18, 0             | 227 | 24, 0 Yes    |
| Chao   | 2003 | China   | Asian     | Esophageal  | HB             | PCR-RFLP         | 19             | 41, 28            | 7   | 43, 55 Yes   |
| Yokoyama | 2002 | Japan   | Asian     | Esophageal  | PB             | PCR-RFLP         | 51             | 73, 110           | 31  | 220, 383 Yes |
| Boonyaphiphat | 2002 | Thailand | Asian     | Esophageal  | HB             | APLP             | 15             | 86, 101           | 28  | 139, 94 No   |
| Yokoyama | 2001 | Japan   | Asian     | Esophageal  | PB             | PCR-RFLP         | 56             | 56^1, 56^1       | 145 | 381^1, 381^1 |
| Yokoyama | 2001 | Japan   | Asian     | Gastric     | PB             | PCR-RFLP         | 28             | 10^1, 10^1       | 145 | 381^1, 381^1 |
| Takeshita | 2000 | Japan   | Asian     | Hepatocellular | PB             | PCR-RFLP         | 3              | 36, 63            | 8   | 43, 74 Yes   |
| Hori   | 1997 | Japan   | Asian     | Esophageal  | HB             | PCR-RFLP         | 20             | 31, 40            | 5   | 20, 43 Yes   |

Abbreviations: APLP, amplified product length polymorphism; DHPLC, denaturing high-performance liquid chromatography; HB, hospital-based, NA, not applicable; PB, population-based; PCR-CTPP, PCR with the confronting-two-pair primer; PCR-RFLP, PCR-restriction fragment length polymorphism; UADT, upper aerodigestive tract.

The number of GA + AA.

Statistical analysis

The strength of the association between ADH1B Arg47His polymorphism and overall cancer risk was evaluated by calculating ORs and 95% CIs. The pooled ORs were also estimated using homozygous model (His/His vs. Arg/Arg), heterozygous model (Arg/His vs. Arg/Arg), recessive model [His/His vs. (Arg/Arg + Arg/Arg)], dominant model [(Arg/His + His/His) vs. Arg/Arg], as well as allele comparison (His vs. Arg). Stratification analyses were further conducted according to ethnicity, cancer type, control source, and HWE. Chi square-based Q-test was applied to assess between-study heterogeneity. If no heterogeneity ($P > 0.10$) was found, the fixed-effect model (Mantel–Haenszel method) was performed [81]. Otherwise, the random-effect model (DerSimonian and Laird method) was used [82]. Sensitivity analysis was carried out to assess the stability of the results, and potential publication bias was assessed with Begg’s funnel plot and Egger’s linear regression test [83]. All the statistical analyses were calculated using STATA software (version 11.0, Stata Corporation, College Station, TX). A $P$-value less than 0.05 was considered statistically significant.

Results

Study characteristics

As listed in Figure 1, a total of 432 potential records were initially identified from Medline and Embase using the search terms listed above. After a screening of the titles and abstracts, 146 publications were subjected for further evaluation. Of them, 59 articles were excluded for irrelevant information, 13 for only meta-analysis, 12 for no sufficient data, and 1 was excluded for duplicate study. In addition, three studies were manually identified from reviews and references lists of the eligible studies. Ultimately, 64 articles investigating the association between ADH1B Arg47His polymorphism and cancer risk were included in the final meta-analysis [17–80].

Overall, 66 studies from 64 articles with 31999 cases and 50964 controls were finally included in our meta-analysis. As shown in Table 1, there were 48 studies conducted amongst Asians, 15 amongst Caucasians, and 3 amongst mixed ethnic group. With respect to cancer type, 23 studies addressed esophageal cancer, 16 head and neck cancer, 10 colorectal cancer, 6 gastric cancer, 4 hepatocellular, 3 upper aerodigestive tract cancer, 2 pancreatic and 1 bladder and breast cancer. Regarding control source, 34 studies were hospital-based and 32 studies were population-based. With respect to HWE, 52 met HWE, 5 departed from HWE, and 9 had not enough information.

Meta-analysis results

The main results for the association between ADH1B Arg47His polymorphism and cancer risk are shown in Table 2 and Figure 2. We found that ADH1B Arg47His polymorphism significantly associated with the decreased risk of overall cancer under all the five genetic models: homozygous model, OR = 0.62, 95% CI = 0.49–0.77; heterozygous
model, OR = 0.71, 95% CI = 0.60–0.84; recessive model, OR = 0.83, 95% CI = 0.76–0.91; dominant model, OR = 0.62, 95% CI = 0.53–0.72; and allele comparison, OR = 0.82, 95% CI = 0.75–0.89.

Regarding the stratified analysis by ethnicity, a decreased cancer risk was also detected amongst Asians under all the genetic models: homozygous model, OR = 0.60, 95% CI = 0.48–0.76; heterozygous model, OR = 0.66, 95% CI = 0.53–0.81; recessive model, OR = 0.82, 95% CI = 0.75–0.91; dominant model, OR = 0.58, 95% CI = 0.47–0.72; and allele comparison, OR = 0.82, 95% CI = 0.75–0.89; and amongst mixed ethnic group: homozygous model, OR = 0.35, 95% CI = 0.30–0.40; heterozygous model, OR = 0.53, 95% CI = 0.47–0.60; recessive model, OR = 0.76, 95% CI = 0.70–0.83; and allele comparison, OR = 0.50, 95% CI = 0.45–0.55. However, an increased risk of cancer was detected amongst Caucasians under homozygous model (OR = 1.45, 95% CI = 1.05–2.02) and recessive model (OR = 1.45, 95% CI = 1.05–2.00).

Regarding the stratified analysis by cancer type, the ADH1B Arg47His polymorphism significantly decreased the risk of esophageal cancer: homozygous model, OR = 0.39, 95% CI = 0.28–0.55; heterozygous model, OR = 0.50, 95% CI = 0.34–0.66; recessive model, OR = 0.58, 95% CI = 0.47–0.72; dominant model, OR = 0.50, 95% CI = 0.36–0.68; and allele comparison, OR = 0.46, 95% CI = 0.30–0.60; and amongst mixed ethnic group: homozygous model, OR = 0.66, 95% CI = 0.54–0.85; heterozygous model, OR = 0.75, 95% CI = 0.62–0.92; recessive model, OR = 0.78, 95% CI = 0.68–0.87; and allele comparison, OR = 0.80, 95% CI = 0.74–0.88.

### Table 2 Meta-analysis of the association between the ADH1B Arg47His and cancer risk

| Variables          | Sample size Case/control | Homozygous | Heterozygous | Recessive | Dominant | Allele comparison |
|--------------------|--------------------------|------------|--------------|-----------|----------|-------------------|
|                    |                          | His/His vs. Arg/Arg | Arg/His vs. Arg/Arg | His/His vs. (Arg/His + Arg/Arg) | Arg/His vs. Arg/Arg | His vs. Arg |
|                    |                          | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Ethnicity          |                          | phet       | phet         | phet       | phet      | phet             |
| Asian              | 17067/31885              | 0.60       | <0.001       | 0.66       | <0.001    | 0.62             |
|                    |                          | (0.46–0.76) | (0.53–0.81)  | (0.53–0.81) | (0.53–0.81) | (0.53–0.72)     |
| Caucasian          | 12970/16906              | 1.45       | <0.001       | 1.45       | <0.001    | 1.03             |
|                    |                          | (1.05–2.02) | (1.05–2.00)  | (1.05–2.00) | (1.05–2.00) | (0.88–1.21)     |
| Mixed              | 1972/2171                | 0.35       | <0.001       | 0.37       | <0.001    | 0.66             |
|                    |                          | (0.13–0.93) | (0.14–0.98)  | (0.14–0.98) | (0.14–0.98) | (0.54–0.85)     |
| Cancer type        |                          |            |              |            |           |                  |
| Colorectal         | 4821/7697                | 1.19       | <0.001       | 1.19       | <0.001    | 1.03             |
|                    |                          | (0.82–1.72) | (0.91–1.55)  | (0.91–1.55) | (0.91–1.55) | (0.88–1.21)     |
| Hepatocellular     | 1111/3820                | 0.84       | <0.001       | 0.81       | <0.001    | 0.98             |
|                    |                          | (0.64–1.10) | (0.81–1.08)  | (0.81–1.08) | (0.81–1.08) | (0.76–1.28)     |
| Esophageal         | 9117/15930               | 0.39       | <0.001       | 0.72       | <0.001    | 0.86             |
|                    |                          | (0.28–0.55) | (0.62–0.83)  | (0.62–0.83) | (0.62–0.83) | (0.51–0.87)     |
| Gastric            | 1770/2090                | 1.02       | <0.001       | 1.02       | <0.001    | 1.03             |
|                    |                          | (0.86–1.36) | (0.96–1.22)  | (0.96–1.22) | (0.96–1.22) | (0.88–1.23)     |
| Head and neck      | 6646/7901                | 0.55       | <0.001       | 0.78       | <0.001    | 0.77             |
|                    |                          | (0.31–0.97) | (0.66–0.93)  | (0.66–0.93) | (0.66–0.93) | (0.47–0.87)     |
| UADT               | 7613/9173                | 0.31       | <0.001       | 0.70       | <0.001    | 0.64             |
|                    |                          | (0.23–0.42) | (0.57–0.86)  | (0.57–0.86) | (0.57–0.86) | (0.28–0.58)     |
| Pancreatic         | 395/1865                 | 1.65       | <0.001       | 1.09       | <0.001    | 1.26             |
|                    |                          | (0.62–4.38) | (0.78–2.15)  | (0.78–2.15) | (0.78–2.15) | (0.75–2.13)     |
| Control source     |                          |            |              |            |           |                  |
| HB                 | 10660/20932              | 0.53       | <0.001       | 0.79       | <0.001    | 0.56             |
|                    |                          | (0.40–0.71) | (0.69–0.90)  | (0.69–0.90) | (0.69–0.90) | (0.44–0.72)     |
| PB                 | 21439/30032              | 0.75       | <0.001       | 0.89       | <0.001    | 0.68             |
|                    |                          | (0.52–1.07) | (0.78–1.02)  | (0.78–1.02) | (0.78–1.02) | (0.54–0.85)     |
| HWE                |                          |            |              |            |           |                  |
| YES                | 20769/37678              | 0.60       | <0.001       | 0.81       | <0.001    | 0.67             |
|                    |                          | (0.46–0.76) | (0.74–0.89)  | (0.74–0.89) | (0.74–0.89) | (0.56–0.81)     |
| NO                 | 1987/1982                | 0.72       | <0.001       | 0.72       | <0.001    | 0.72             |
|                    |                          | (0.22–2.65) | (0.76–2.59)  | (0.76–2.59) | (0.76–2.59) | (0.25–2.09)     |

Abbreviations: HB, hospital-based; PB, population-based; UADT, upper aerodigestive tract. Values in bold indicate P<0.05.
CI = 0.57–0.86; dominant model, OR = 0.39, 95% CI = 0.26–0.58; and allele comparison, OR = 0.62, 95% CI = 0.54–0.71; and head and neck cancer: homozygous model, OR = 0.55, 95% CI = 0.31–0.97; recessive model, OR = 0.78, 95% CI = 0.66–0.93; dominant model, OR = 0.64, 95% CI = 0.47–0.87; and allele comparison, OR = 0.80, 95% CI = 0.66–0.96.

Regarding the stratified analysis by control source and HWE, a decreased cancer risk was detected in hospital-based studies: homozygous model, OR = 0.53, 95% CI = 0.40–0.71; heterozygous model, OR = 0.64, 95% CI = 0.51–0.81; recessive model, OR = 0.79, 95% CI = 0.69–0.90; dominant model, OR = 0.56, 95% CI = 0.44–0.72; and allele comparison, OR = 0.77, 95% CI = 0.68–0.87; population-based studies: dominant model, OR = 0.68, 95% CI = 0.54–0.85; and allele comparison, OR = 0.87, 95% CI = 0.76–0.99; and also the studies in agreement with HWE: homozygous model, OR = 0.60, 95% CI = 0.48–0.76; heterozygous model, OR = 0.71, 95% CI = 0.60–0.84; recessive model, OR = 0.81, 95% CI = 0.74–0.89; dominant model, OR = 0.67, 95% CI = 0.56–0.81; and allele comparison, OR = 0.81, 95% CI = 0.74–0.88.
Figure 3. Funnel plot analysis to detect publication bias for ADH1B Arg47His polymorphism under the allele comparison model

**Sensitivity analysis and publication bias**

Substantial heterogeneities were found under all the five genetic models ($P<0.001$). Therefore, the random-effect model was adopted to assess the ORs and 95% CIs. Furthermore, the leave-one-out sensitivity analyses indicated that no single study could change the pooled ORs. The results of the Begg's funnel plot and Egger's linear regression test showed no evidence of publication bias (homozygous model, $P=0.227$; heterozygous model, $P=0.697$; recessive model, $P=0.663$; dominant model, $P=0.599$; and allele comparison $P=0.342$, see Figure 3).

**Discussion**

Alcohol consumption has been established to be a major factor in the development and progress of cancer [13]. Alcohol is first catalytically oxidized to acetaldehyde, mainly by ADH, and then to harmless acetate by ALDH [6,7]. Acetaldehyde, a Group I human carcinogen classified by the International Agency for Research on Cancer (IARC), may stimulate carcinogenesis by disrupting DNA synthesis and repair [8,9,84]. Therefore, to reduce the risk of cancer, it is important to modulate exposure levels to acetaldehyde in the liver. ADH1B gene, also known as ADH2, is located on chromosome 4q22 and is the locus responsible for the majority of activities of ADH function [25]. Arg47His (rs1229984 G > A) in ADH1B led to a single amino acid substitution of arginine (Arg) for histidine (His) at codon 47. Compared with the Arg/Arg individuals, the His/His individuals have a 40-fold higher enzyme activity oxidized alcohol to toxic acetaldehyde, thereby inducing tumorigenesis [25,85].

To the best of our knowledge, this is the first meta-analysis investigating the association between $ADH1B$ Arg47His polymorphism and the overall cancer risk. A total of 66 studies from 64 articles with 31999 cases and 50964 controls were included, and the large sample size provided adequate power to detect this association. Overall, $ADH1B$ Arg47His polymorphism was associated with a decreased risk of overall cancer under all the five genetic models. Stratified analysis by ethnicity revealed that $ADH1B$ Arg47His polymorphism reduced cancer risk amongst Asians and mixed ethnicity group but increased risk amongst Caucasians. Stratified analysis by cancer type revealed that $ADH1B$ Arg47His polymorphism reduced risk in esophageal cancer, upper aerodigestive tract cancer, and head and neck cancer, while no effect was found on colorectal, hepatocellular, gastric and pancreatic cancer. In stratified analysis by control source and HWE, a decreased cancer risk was detected in hospital-based studies, population-based studies, and also the studies in agreement with HWE.

There were several meta-analyses focussed on $ADH1B$ Arg47His polymorphism and only one particular type of cancer risk, such as esophageal, head and neck, gastric and colorectal cancer [11–15]. For esophageal cancer, Mao et al. [11] found that the 47His allele was significantly associated with the reduced risk of this cancer when compared
with the 47Arg allele. And these findings were replicated in our meta-analysis. For head and neck cancer, the 47His allele was also found to be associated with decreased risk of head and neck cancer amongst Asians only under the dominant model [12]. However, similar results were found under the other three models in our analysis, which may be attributed to a larger sample size including eight more studies. Interestingly, Chen et al. [15] found that ADH1B Arg47His polymorphism was associated with decreased risk of colorectal cancer supported by four studies. However, this decreased risk was not present in the current one including six more studies. It was noteworthy that we found that ADH1B Arg47His polymorphism was associated with decreased cancer risk amongst Asians while increased cancer risk amongst Caucasians. In Caucasian population, the A allele was found to associate with an increased risk of colorectal cancer [32]. The opposite findings may result from the difference of ethnicity with the 47His allele occupied more than 90% amongst Asians but fewer than 20% amongst Caucasians [7]. Furthermore, we re-analyzed the ethnic groups of Asian and Caucasian people. Amongst Asians, a decreased cancer risk was also detected in esophageal cancer and head and neck cancer. While in Caucasians, we did not repeat the results, but an increased cancer risk was detected in colorectal cancer (homozygous model, OR = 1.55, 95% CI = 1.10–2.20 and recessive model, OR = 1.55, 95% CI = 1.11–2.18).

Several limitations in the current meta-analysis should be addressed. First, a number of studies adopted in our meta-analysis had relatively small sample size for each cancer type, like bladder and breast cancer. Second, because of the absence of original data, our analyses were based on unadjusted estimates of ORs without adjustment for other confounding factors. Third, there were substantial heterogeneities in all the five genetic models, hence the random-effect model was adopted and might present unstable results. Overall, due to these limitations, the findings in the current meta-analysis should be interpreted with caution.

In conclusion, our meta-analysis suggested that ADH1B Arg47His polymorphism was significantly associated with the decreased overall cancer risk, especially for esophageal cancer and head and neck cancer amongst Asians.

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Competing interests
The authors declare that there are no competing interests associated with the manuscript.

Author contribution
All authors contributed significantly to this work. B.T. designed the research study. B.T. and N.N. performed the research study, analyzed the data, and wrote the paper. Both the authors reviewed the paper.

Abbreviations
ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; CI, confidence interval; HWE, Hardy–Weinberg equilibrium; OR, odds ratio.

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