Relationship between genetic polymorphisms of ALDH2 and ADH1B and esophageal cancer risk: A meta-analysis

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METHODS: Nineteen articles were included by searching MEDLINE, EMBASE and the Chinese Biomedical Database, 13 on ADH1B and 18 on ALDH2. We performed a meta-analysis of case-control studies including 13 studies on ADH1B (cases/controls: 2390/7100) and 18 studies on ALDH2 (2631/6030).

RESULTS: The crude odds ratio [OR (95% confidence interval)] was 2.91 (2.04-4.14) for ADH1B*1/*1 (vs ADH1B*2/*2) and 1.32 (1.17-1.49) for ADH1B*1/*2. The crude OR for ALDH2*1/*2 (vs ALDH2*1/*1) was 2.52 (1.76-3.61). ADH1B*1/*1 increased the risk of esophageal cancer among never/rare [1.56 (0.93-2.61)], moderate [2.71 (1.37-5.35)], and heavy drinkers [3.22 (2.27-4.57)]. ADH1B*1/*2 was associated with a modest risk among moderate drinkers [1.43 (1.09-1.87)]. ALDH2*1/*2 increased the risk of esophageal cancer among never/rare [1.28 (0.91-1.80)], moderate [3.12 (1.95-5.01)], and heavy drinkers [7.12 (4.67-10.86)] and among ex-drinkers [5.64 (1.57-20.25)]. ALDH2*2/*2 increased the risk among drinkers [4.42 (1.72-11.36)]. ADH1B*1/*1 plus ALDH2*1/*2 was associated with the highest risk for heavy drinkers [12.45 (2.9-53.46)]. The results of the meta-regression analysis showed that the effects of ADH1B*1/*1 and ALDH2*1/*2 increased with the level of alcohol consumption. ALDH2*1/*2 was associated with a high risk among Taiwan Chinese and Japanese drinkers, as opposed to a moderate risk among drinkers in high-incidence regions of Mainland China. ADH1B*1/*1 in heavy drinkers and ALDH2*1/*2 in moderate-to-heavy drinkers was associated with similarly high risk among both men and women.

CONCLUSION: ADH1B/ALDH2 genotypes affect the risk of esophageal cancer, and the risk is modified by alcohol consumption, ethnicity, and gender.

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Key words: Alcohol dehydrogenase-1B; Aldehyde dehydrogenase-2; Esophageal cancer; Meta-analysis
INTRODUCTION

Esophageal cancer is a global health problem, and ranked the eighth in incidence and sixth in mortality in 2002[1]. Its incidence and mortality rates show a wide geographic variation at an international level, and there are marked differences between high-risk and low-risk areas[2-3]. Most esophageal cancer patients live in the “esophageal cancer belt”, which stretches from Northern-Central China westward through Central Asia to Northern Iran, suggesting that genetic factors and environmental factors play a role in the development of esophageal cancer[4].

The ethanol in alcohol beverages[5] and the acetaldehyde associated with alcohol consumption[6] have recently been classified as Group 1 human carcinogens by the World Health Organization (WHO) and International Agency For Research On Cancer (IARC). The ethanol consumed in alcohol beverages is primarily metabolized by alcohol dehydrogenases (ADHs), including ADH1B (previously called ADH2), to acetaldehyde, and then to acetic acid, mainly by low-Km aldehyde dehydrogenase-2 (ALDH2)[7].

The mutant ADH1B*2 allele is highly prevalent among east Asians[8]. The homodimer of ADH1B encoded by ADH1B*1/*1 has only 1/100 and 1/200 of the ethanol oxidizing capacity of the isoforms encoded by ADH1B*1/*2 and ADH1B*2/*2[9], respectively, and ADH1B1*/1* genotype carriers experience prolonged exposure to ethanol after heavy drinking[10]. The mutant ALDH2*2 allele is also prevalent in east Asians[11] and encodes a catalytically inactive subunit. The ALDH2*2 allele acts in a semidominant manner[12]. ALDH2*2 allele carriers experience unpleasant flushing responses, including facial flushing, nausea, drowsiness, and a headache, after drinking a small amount of ethanol because of severe acetaldehydeemia[13]. East Asian studies have identified that ADH1B*1 allele and ALDH2*2 allele as a strong positive factor and a strong negative risk factor, respectively, for heavy drinking[14,15], and both have been found to be a strong positive risk factor for esophageal cancer[16].

An earlier meta-analysis of ALDH2 genotype and risk of esophageal cancer included 7 case-control studies[17], and revealed only that cancer risk was reduced among ALDH2*2/*2 homozygotes because they are generally non-drinkers as a result of experiencing intense alcohol flushing responses, and that the cancer risk was higher among ALDH2*1/*2 heterozygotes. Only one case-control study has focused on the effect of the two genes in females, which showed that ALDH2*1/*2 alone is associated with a high risk of esophageal cancer among female heavy drinkers[18]. The influence of alcohol drinking on the risk of esophageal cancer varies with ethnicity, and gene polymorphisms may have different effects on cancer risk. In the present study, we conducted a comprehensive meta-analysis to clarify the effects of ADH1B and ALDH2 genotypes alone and in combination on the risk of esophageal cancer, and evaluate how the gene effects are influenced by drinking habits, gender, and ethnicity.

MATERIALS AND METHODS

Selection criteria

Only case-control studies that investigated the relationship between ADH1B and/or ALDH2 polymorphisms and esophageal cancer were included in the meta-analysis. Trials had to be original and report ADH1B and/or ALDH2 genotype frequencies in cases and controls or estimate the odds ratios (ORs). When the results of a study were published more than once, only the study that contained the most complete data was included in the analysis. Moreover, participants from high-risk populations and general populations were eligible for inclusion, and the controls were non-cancer or disease-free subjects.

Searching strategy for identification of studies

We searched MEDLINE (from January 1966 to April 2009), EMBASE (from January 1988 to April 2009), and the Chinese Biomedical Database (CBM; from January 1980 to April 2009). A comprehensive and exhaustive search strategy was formulated in an attempt to identify all relevant studies regardless of language or publication status using the following terms: “esophagus”, “oesophagus”, “carcinoma or cancer or neoplasm or tumour or tumor”, “ADH1B or ADH1 or alcohol dehydrogenase”, without any restriction on language.

Two reviewers (Yang SJ) independently examined abstracts of all candidate articles to decide whether to include or exclude them in the subsequent detailed review. We also attempted to identify additional studies by searching the reference lists of relevant trials, and scrutinized author names, location, setting, number of participants, and study data to ensure that each trial would be included only once. Of the 126 articles identified, 107 were excluded because 91 were studies regarded as animal models or studies conducted at a cellular level, 6 were reviews, 5 were not case-control studies, and 5 were duplicate publications. In addition, two articles only included part of the data since the overlapped data were excluded. Ultimately, 19 articles were included (Tables 1 and 2), 13 on ADH1B and 18 on ALDH2. The overlapping data in these studies were excluded. ADH1B and ALDH2 genotype frequencies were not reported in 8 studies. Through contacting the authors, the data missing in four of the
Information on alcohol drinking is essential in risk analysis leading to analyze the risk of esophageal cancer without confounding variable in comparing genotypes and the effect of alcohol drinking could be a strong confounding variable.

### Stratification by alcohol drinking

Information on alcohol drinking is essential in risk analysis of ADH1B and ALDH2 genotypes for two reasons. One reason is that the alcohol drinking could be a strong confounding variable in comparing genotypes and the risk of esophageal cancer because the genotypes are also related to the amount of alcohol consumed (suppressive in ALDH2*2 and facilitating in ADH1B*1[18,26,28]), thus misleading to analyze the risk of esophageal cancer without taking the alcohol consumption level into account[14].

### Table 1 Characteristics of studies of alcohol dehydrogenase-1B polymorphism and risk of esophageal cancer[15-27]

| Study ID | Country, subjects | Cases | Controls | ADH1B |
|----------|-------------------|-------|----------|-------|
|          |                   |       |          | Crude OR (95% CI) | Adjusted OR (95% CI) |
|          |                   |       |          | *1/*2 vs *2/*2 | *1/*1 vs *2/*2 |
|          |                   |       |          | *1/*2 vs *2/*2 | *1/*1 vs *2/*2 |
|          |                   |       |          | *1/*2 vs *1/*1 | *2/*2 vs *1/*1 |
|          |                   |       |          | *1/*2 vs *1/*1 | *2/*2 vs *1/*1 |
| Yokoyama et al[17], 2006 | Japan, female | 52    | 412      | 1.56 (0.56-4.35) | 2.08 (0.76-5.56) |
| Boonyaphiphat et al[18, 2002] | Thailand | 202   | 261      | NA^b   | NA |
| Ding et al[21], 2009 | China | 221   | 191      | 1.21 (0.79-1.86) | 2.78 (1.06-7.29) |
| Chao et al[22], 2000 | China (Taiwan), alcoholics | 88    | 327      | NA   | NA |
| Guo et al[23], 2008 | China, male | 80    | 480      | 2.89 (1.11-5.64) | NA |
| Li et al[24], 2008 | Africa | 220   | 241      | NA   | NA |
| Yang et al[25], 2005 | Japan | 165   | 494      | 1.57 (1.04-2.36) | 0.62 (0.22-1.72) |
| Yang et al[26], 2007 | China | 191   | 198      | 1.89 (1.13-2.22) | 1.91 (0.92-3.53) |
| Yekoyama et al[27], 2001 | Japan, alcoholic male | 112   | 526      | NA   | NA |
| Yokoyama et al[28], 2002 | Japan, male | 234   | 634      | 1.16 (0.82-1.65) | 0.98 (0.45-2.13) |
| Hori et al[29], 1997 | Japan | 94    | 130      | 1.7 (0.9-3.0) | 6.2 (2.6-14.7) |
| Lee et al[30], 2008 | China (Taiwan) | 406   | 656      | 1.3 (0.97-1.73) | 6.9 (4.07-9.23) |
| Harahbe et al[31], 2006 | Europe | 325   | 2550     | 0.64 (0.14-2.97) | 0.85 (0.19-3.79) |
| Pooled results | | 2390 | 7100 | 1.60 (1.28-2.0) | 2.17 (1.08-4.34) |
| P for heterogeneity | | | | 0.54 < 0.05 | 0.45 < 0.05 |

*The genotype frequencies among the controls differed significantly from the Hardy-Weinberg equilibrium (P < 0.05); ^a: Not available because not mentioned or calculated in the study. ADH1B: Alcohol dehydrogenase-1B; OR: Odds ratio; CI: Confidence interval.

### Table 2 Characteristics of studies of aldehyde dehydrogenase-2 polymorphism and risk of esophageal cancer[15-24,28-33]

| Study ID | Country, subjects | Cases | Controls | ALDH2 |
|----------|-------------------|-------|----------|-------|
|          |                   |       |          | Crude OR (95% CI) | Adjusted OR (95% CI) |
|          |                   |       |          | *1/*2 vs *2/*2 | *1/*1 vs *2/*2 |
|          |                   |       |          | *1/*2 vs *1/*1 | *2/*2 vs *1/*1 |
| Yokoyama et al[17], 2006 | Japan, female | 52    | 412      | 1.01 (0.54-1.87) | 1.49 (0.47-4.78) |
| Boonyaphiphat et al[18, 2002] | Thailand | 202   | 261      | 1.57 (0.89-2.56) | 0.52 (0.28-1.0) |
| Ding et al[21], 2009 | China, male | 221   | 191      | 1.71 (1.26-2.66) | 0.45 (2.25-10.16) |
| Chao et al[22], 2000 | China (Taiwan), alcoholics | 88    | 327      | NA   | NA |
| Guo et al[23], 2008 | China, male | 80    | 480      | NA   | NA |
| Li et al[24], 2008 | Africa | 237   | 268      | NA   | NA |
| Yang et al[25], 2005 | Japan | 165   | 494      | 6.43 (4.02-10.3) | 1.92 (0.23-15.7) |
| Yang et al[26], 2007 | China | 191   | 198      | 1.67 (1.02-2.72) | 0.26 (0.06-0.9) |
| Yekoyama et al[27], 2001 | Japan, alcoholic male | 112   | 526      | 13.50 (8.06-22.6) | 1.0 (NA) |
| Yekoyama et al[28], 2002 | Japan, male | 234   | 634      | 7.46 (4.71-11.81) | 0.73 (1.33-46.08) |
| Hori et al[29], 1997 | Japan | 93    | 171      | 4.4 (2.57-7.7) | 0.9 (2.3-6.3) |
| Lee et al[30], 2008 | China (Taiwan) | 406   | 656      | NA   | NA |
| Cai et al[31], 2006 | China | 205   | 394      | 0.76 (0.51-1.16) | 1.72 (0.85-3.4) |
| Ding et al[32], 2002 | China | 98    | 235      | NA   | NA |
| Igoa et al[33], 2004 | Japan, male | 74    | 241      | NA   | NA |
| Matsuo et al[34], 2001 | Japan | 102   | 241      | 3.72 (1.88-7.36) | 0.8 (0.09-6.88) |
| Yokoyama et al[35], 1996 | Japan, male | 29    | 28       | NA   | NA |
| Yokoyama et al[36], 2006 | Japan, alcoholic male | 42    | 273      | NA   | NA |
| Pooled results | | 2631  | 6030     | 2.06 (1.09-3.89) | 1.31 (0.52-3.34) |
| P for heterogeneity | | | | < 0.001 | < 0.001 |

*The genotype frequencies among the controls differed significantly from the Hardy-Weinberg equilibrium (P < 0.05); ^a: Not available; ^b: No studies were included because there were no cases and controls with ALDH2*2/*2. ALDH2: Aldehyde dehydrogenase-2; OR: Odds ratio; CI: Confidence interval.
should be noted that such a confounding effect is a unique property of alcohol-related genes. The second reason is that from the standpoint of mechanism, alcohol-related enzymes would not be expected to play a role in the development of esophageal cancer among non-drinkers, whereas the adverse roles of the inactive enzymes would be enhanced among moderate to heavy drinkers. Thus, the primary analysis was done by stratifying the data according to alcohol-drinking status (ex-drinkers, non-/rare drinkers, moderate drinkers, and heavy drinkers).

**Statistical analysis**

The STATA statistical package (version 9, STATA, College Station, TX) was used to perform the meta-analysis. The ADH1B*2/*2 group served as the control for the ADH1B*1/*2 group and the ADH1B*1/*1 group, and the ALDH2*1/*2 group served as the control for the ALDH2*1/*1 group and the ALDH2*2/*2 group. We used the ADH1B*2 and ALDH2*1/*1 group as the control for the analysis of the combined effect of ADH1B and ALDH2, because most studies have used it as the control group. The crude ORs of the studies included were calculated according to the available genotype frequencies in order to obtain pooled ORs. Overall effect was tested using Z scores with significance set at \( P < 0.05 \). Heterogeneity was tested using the \( \chi^2 \) test for goodness of fit with significance set at \( P < 0.05 \), and its possible sources were assessed by subgroup analyses as described below. A random-effect model was applied to obtain summary ORs and their 95% confidence interval (CI). The Hardy-Weinberg equilibrium in the controls in each study was assessed using the \( \chi^2 \) test, and publication bias was statistically assessed by Egger’s test. In addition, a sensitivity analysis was performed to explore whether omitting large-sample studies would greatly change or reverse the results. The influence of alcohol drinking on the relationship between the ADH1B and ALDH2 genotypes and esophageal cancer was assessed by a meta-regression analysis. A subgroup analysis in regard to ethnicity and sex to detect heterogeneity across the trials was performed. Since the number of drinkers with the ALDH2*2/*2 genotype was very small, we combined the category of moderate and heavy drinkers into a single category to analyze the effect of this genotype in drinkers.

**RESULTS**

A total of 19 case-control studies were identified, including 13 studies on the ADH1B genotype (2390 cases and 7100 controls) (Table 1) and 18 studies on the ALDH2 genotype (2631 cases and 6030 controls) (Table 2). All of the studies, except for three studies \(^{20,23,39} \) that did not mention the pathologic types, were about esophageal squamous cell carcinoma. The majority of the studies were conducted in Asian populations, except one study conducted in Europe and one in Africa. Seven studies were conducted in male populations alone, and three were conducted in alcoholics alone.

In comparison with ADH1B*2/*2, the overall crude OR (95% CI) of ADH1B*1/*2 and ADH1B*1/*1 was 1.32 (1.17-1.49) and 2.91 (2.04-4.14), respectively, and it was similar to their overall adjusted OR of 1.60 (1.28-2.0) and 2.17 (1.08-4.34) (Table 1). Significant study-heterogeneity was observed in ADH1B*1/*1 (\( P < 0.05 \)), but it disappeared after stratifying by drinking status (Figure 1). ADH1B*1/*1 increased the risk of esophageal cancer among never/rare drinkers [1.56 (0.93-2.61)], moderate drinkers [2.71 (1.37-5.35)] and heavy drinkers [3.22 (2.27-4.57)], especially among the moderate/heavy drinkers. The results of the meta-regression analysis showed that the larger the amount of alcohol consumed the greater the OR for ADH1B1/*1/*1 became (\( P = 0.043 \), Figure 1), indicating a so-called gene-environment interaction. ADH1B*1/*2 was associated with a modest but significantly increased risk of esophageal cancer among moderate drinkers [1.43 (1.09-1.87)] (Figure 2).

In comparison with ALDH2*1/*1, the overall crude OR (95% CI) of ALDH2*1/*2 was 2.52 (1.76-3.61), and it was similar to the overall adjusted OR of 2.06 (1.09-3.89) (Table 2). There was significant study-heterogeneity in ALDH2*1/*2 (\( P < 0.001 \)) and ALDH2*2/*2 (\( P < 0.001 \)). After stratifying by drinking status, the significant study-heterogeneity in ALDH2*1/*2 persisted among the moderate and heavy drinkers, and in ALDH2*2/*2 it persisted among the never/rare drinkers (Figures 3 and 4). ALDH2*1/*2 increased the risk of esophageal cancer among never/rare drinkers [1.28 (0.91-1.80)], moderate drinkers [3.12 (1.95-5.01)], heavy drinkers [7.12 (4.67-10.86)], and ex-drinkers [5.64 (1.57-20.25)], and especially among the heavy drinkers. The results of the meta-regression analysis showed that the larger the amount of alcohol consumed, the greater the OR for ALDH2*1/*2 was (\( P < 0.001 \), Figure 3), clearly demonstrating a very strong gene-environment interaction. Although the proportion of drinkers among the ALDH2*2/*2 homozygotes was very small, ALDH2*2/*2 also greatly increased the cancer risk among moderate and heavy drinkers [2.71 (1.37-5.35)] and heavy drinkers [3.22 (2.27-4.57)], especially among the moderate/heavy drinkers. The results of the meta-regression analysis showed that the larger the amount of alcohol consumed, the greater the OR for ADH1B*1/*1 became (\( P = 0.043 \), Figure 1), indicating a so-called gene-environment interaction. ADH1B*1/*2 was associated with a modest but significantly increased risk of esophageal cancer among moderate drinkers [1.43 (1.09-1.87)] (Figure 2).

The analysis of combined effects of ADH1B and ALDH2 genotypes showed that ADH1B*1/*1 plus ALDH2*2/*2 was associated with the highest risk of esophageal cancer among heavy drinkers [12.45 (2.9-53.46)] (Table 3), but no significant increase in risk was seen among never/rare drinkers.

A subgroup analysis was performed in regard to ethnicity and drinking status (Table 4). The ADH1B*1/*1 genotype was associated with a high risk of esophageal cancer in heavy drinkers among all three ethnic groups: Mainland Chinese, Taiwan Chinese, and Japanese [ORs = 3.55 (1.01-11.83), 3.36 (1.73-6.53), and 4.02 (1.83-8.80), respectively]. ALDH2*1/*2 was associated with a very high risk among Taiwan Chinese and Japanese moderate-to-heavy drinkers [ORs = 6.21 (3.78-10.22) and 4.74 (3.29-6.83)] in moderate drinkers; OR = 9.21 (5.54-15.31) and 9.75 (7.34-12.97) in heavy drinkers], but only a moderate risk among moderate drinkers in the high-incidence regions of Mainland China [OR = 1.98 (1.20-3.27)]. The analysis of the effect of ADH1B and ALDH2 genotypes on esophageal cancer risk was stratified by both...
Figure 1 Relationship between alcohol dehydrogenase-1B*1/*1 and esophageal cancer stratified by alcohol consumption status. Weights are from random effects analysis. *Ex-drinkers mean alcohol quit for more than one year; Moderate drinkers mean consumers of 1-40 g/d alcohol (Lee, 2008), > 40 g/d alcohol (Lee, 2008), > 50 g ethanol < 5 d/wk (Yang, 2001, Yokoyama, 2006; Ding, 2009); Heavy drinkers mean consumers of > 40 g/d alcohol (Lee, 2008), > 50 g ethanol ≥ 5 d/wk (Yang, 2001, Yokoyama, 2007), > 60 g/d alcohol (Chao, 2000, Yokoyama, 1996); Ex-drinkers mean alcohol quit for more than one year; and alcoholics (Yokoyama, 2001, Yokoyama, 2006). Significant trend for meta-regression from never/rare drinkers to heavy drinkers is observed (P = 0.043). ADH1B: Alcohol dehydrogenase-1B.

Table 3 Risk of esophageal cancer associated with combinations of alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 genotypes

| Genotype                  | ALDH2 *1/*1 | P for heterogeneity | ALDH2 *1/*2 | P for heterogeneity |
|---------------------------|-------------|---------------------|-------------|---------------------|
|                           | pooled OR (95% CI) |                     | pooled OR (95% CI) |                     |
| ADH1B*2/*2 or *1/*2       | 1.00 (reference) | -                   | 1.00 (reference) | -                   |
| Never/rare drinkers[21,22] | 1.00 (reference) | -                   | 1.99 (0.53-7.5) | 0.28                |
| Moderate drinkers[21,22]  | -            | -                   | 5.64 (1.74-15.3) | 0.02                |
| Heavy drinkers[21,22]     | -            | -                   | 7.56 (2.35-22.0) | 0.05                |
| ADH1B*1/*1                | 1.13 (1.22-5.7) | < 0.05              | 1.36 (0.41-4.5) | < 0.05              |
| Never/rare drinkers[21,22] | 2.37 (1.13-4.97) | < 0.05              | 9.17 (0.6-14.0) | 0.06                |
| Moderate drinkers[21,22]  | 2.43 (1.48-3.99) | 0.08                | 12.45 (2.9-53.4) | 0.08                |

ALDH2: Aldehyde dehydrogenase-2; ADH1B: Alcohol dehydrogenase-1B; OR: Odds ratio; CI: Confidence interval.

sex and drinking status (Table 4). ADH1B*1/*1 was associated with a high risk among men irrespective of drinking status [2.71 (1.13-6.51) among never/rare drinkers, 3.93 (2.43-6.36) among moderate drinkers, and 3.22 (2.16-4.83) among heavy drinkers]. ADH1B*1/*1 was associated with a high risk among heavy drinking women as well [3.55 (1.06-11.84)].

Men with ALDH2*1/*2 were highly susceptible to esophageal cancer, even among never/rare drinkers [1.92 (1.28-2.88)]. The ORs of ALDH2*1/*2 in moderate-to-heavy drinkers were similarly high in both men and women [3.53 (1.98-6.30) and 2.64 (1.24-5.68), respectively, in moderate drinkers; 7.04 (4.18-11.85) and 6.85 (1.04-44.95) in heavy drinkers]. The results of the meta-regression
| Study                      | ADH1B*1/*2 vs *2/*2 | Odds ratio (95% CI) | Weight (%) |
|---------------------------|---------------------|---------------------|------------|
| Ex-drinkers               |                     |                     |            |
| Yokoyama et al., 2002     | 1.17 (0.65-2.10)    | 0.05 (0.00-0.99)    | 0.3        |
| Yokoyama et al., 2006     | 1.41 (0.85-2.32)    | 2.00 (0.13-31.98)   | 0.3        |
| Yang et al., 2005         | 0.3                 | 1.54 (0.41-5.82)    | 1.4        |
| Subtotal (P for heterogeneity: 0.84) | 0.3                 | 0.67 (0.08-5.21)    | 2.0        |
| Never/rare drinkers       |                     |                     |            |
| Chao et al., 2000         | 1.60 (0.68-3.77)    | 1.60 (0.68-3.77)    | 3.4        |
| Lee et al., 2008          | 1.06 (0.61-1.87)    | 1.06 (0.61-1.87)    | 7.8        |
| Yang et al., 2007         | 1.22 (0.67-2.21)    | 1.22 (0.67-2.21)    | 7.0        |
| Ding et al., 2009         | 1.17 (0.65-2.10)    | 1.17 (0.65-2.10)    | 7.2        |
| Yokoyama et al., 2002     | 1.82 (0.25-13.30)   | 1.82 (0.25-13.30)   | 0.6        |
| Yokoyama et al., 2006     | 0.75 (0.30-1.88)    | 0.75 (0.30-1.88)    | 2.9        |
| Yang et al., 2005         | 0.67 (0.13-3.43)    | 0.67 (0.13-3.43)    | 0.9        |
| Excluded                  |                     |                     |            |
| Moderate drinkers         |                     |                     |            |
| Lee et al., 2008          | 1.43 (0.85-1.51)    | 1.43 (0.85-1.51)    | 29.8       |
| Yang et al., 2007         | 1.13 (0.85-1.51)    | 1.13 (0.85-1.51)    | 29.8       |
| Yokoyama et al., 2002     | 1.41 (0.85-2.32)    | 1.41 (0.85-2.32)    | 9.8        |
| Yokoyama et al., 2006     | 1.22 (0.69-2.71)    | 1.22 (0.69-2.71)    | 7.5        |
| Yang et al., 2005         | 0.80 (1.14-5.85)    | 0.80 (1.14-5.85)    | 0.7        |
| Ding et al., 2009         | 1.62 (0.88-2.97)    | 1.62 (0.88-2.97)    | 6.7        |
| Subtotal (P for heterogeneity: 0.91) | 1.43 (0.82-2.51)    | 1.43 (0.82-2.51)    | 7.9        |
| Heavy drinkers            |                     |                     |            |
| Chao et al., 2000         | 1.43 (1.09-1.87)    | 1.43 (1.09-1.87)    | 34.1       |
| Lee et al., 2008          | 1.34 (0.68-2.66)    | 1.34 (0.68-2.66)    | 5.2        |
| Yang et al., 2007         | 1.28 (0.60-2.72)    | 1.28 (0.60-2.72)    | 4.3        |
| Yokoyama et al., 2001     | 1.11 (0.51-2.41)    | 1.11 (0.51-2.41)    | 4.1        |
| Yokoyama et al., 2002     | 0.81 (0.46-1.43)    | 0.81 (0.46-1.43)    | 7.6        |
| Yokoyama et al., 2006     | 1.50 (0.82-2.73)    | 1.50 (0.82-2.73)    | 6.8        |
| Yang et al., 2005         | 23.40 (0.89-612.98) | 23.40 (0.89-612.98) | 0.2        |
| Subtotal (P for heterogeneity: 0.1) | 2.67 (1.40-5.12)    | 2.67 (1.40-5.12)    | 5.8        |
|                       |                     | 1.40 (0.96-2.04)    | 34.1       |

Figure 2 Relationship between alcohol dehydrogenase-1B*1/*2 and esophageal cancer stratified by alcohol consumption status. Weights are from random effects analysis. ADH1B: Alcohol dehydrogenase-1B.

analysis showed that the larger the amount of alcohol consumed by men, the greater the OR for ALDH2*1/*2 was (P = 0.003). Men with ALDH2*2/*2 also were at high risk of esophageal cancer among never/rare drinkers and drinkers [2.96 (1.61-5.44) and 3.47 (1.09-11.03), respectively].

**Sensitivity analysis and publication bias**

There was no evidence of publication bias in the ADH1B and ALDH2 polymorphism studies according to Egger's test, and the P values for ADH1B*1/*2, ADH1B*2/*2, ALDH2*1/*2 and ALDH2*2/*2 were 0.82, 0.21, 0.68 and 0.51, respectively. The sensitivity analysis showed that the overall ORs of the ADH1B*1/*2 genotype vs the ADH1B*2/*2 genotype did not appear to have changed greatly after excluding two large-sample studies [ORs = 1.36 (1.14-1.63)](23,26), and that the overall ORs of the ADH1B*1/*1 genotype vs the ADH1B*2/*2 genotype did not change either after removing two large-sample studies [ORs = 2.69 (1.81-3.98)](15,26). The effect of ALDH2*1/*2 and ALDH2*2/*2 vs ALDH2*1/*1 on risk of esophageal cancer was not reversed and did not change greatly after removing one large-sample study [ORs = 2.51 (1.69-3.73) and 0.72 (0.36-1.45), respectively](23,26), indicating that the finding was robust. After dropping one large-sample study, ADH1B*1/*1 combined with ALDH2*1/*2 was associated with a higher risk with an OR (95% CI) of 17.02 (2.99-96.71) in heavy drinkers than ADH1B*2 combined with ALDH2*1/*1.

**DISCUSSION**

The results of the meta-analysis in this study shed light on some aspects of the association between ALDH2 and ADH1B genotypes and the risk of esophageal cancer that had not been clarified earlier because of the smaller numbers of subjects. After drinking alcohol, people with inactive ALDH2 experience unpleasant responses, including flushing responses(11) and hangovers(24). The presence of inactive ALDH2 generally prevents East Asians from drinking heavily. Homozygotes for inactive ALDH2 are usually nondrinkers because of the very unpleasant responses they experience, and the previous meta-analysis showed that a protective effect of this genotype against esophageal carcinogenesis only resulted from non- or rare drinking. However, the inhibitory effect of ALDH2*2/*2 is not complete. In this meta-analysis, we found 24 cases and six controls who were drinkers and inactive ALDH2*2/*2 homozygotes, and confirmed that ALDH2*2/*2 greatly increased the risk of esophageal cancer.
cancer when the genotype carriers were drinkers (OR = 4.42, Figure 4). This finding is consistent with an earlier study that included only six cases and one control who were ALDH2*2/*2 drinkers[15], and it supports the hypothesis that acetaldehyde play a critical role in the development of esophageal cancer. Also, it suggested the genetic risk of esophageal cancer may be due to alcohol and genetic associations.

Although data regarding the duration of abstinence was unavailable, the results of the present study also confirmed that the strong effect of heterozygous ALDH2*1/*2 persisted in ex-drinkers (OR = 5.64, Figure 3). That may be explained by the “sick-quitter effect”, meaning that the molecular changes that predisposed the ex-drinkers to esophageal cancer may not be able to return to the healthy status. A recent pooled analysis showed that the risk of esophagus cancer and the risk of head and neck cancer only decreased by five and 10 years, respectively, after the cessation of drinking[31]. Further study is needed to evaluate the long-term effect of drinking cessation on ALDH2-associated esophageal carcinogenesis.

Another intriguing finding was the ADH1B*1-allele effect on cancer risk. The ADH1B*2 allele acts in a semidominant manner, and the homozygous ADH1B*1/*1 enzyme exhibited 100 and 200 times lower in vitro activity[7] and was associated with an 11% and 18% slower ethanol elimination rate than the heterozygous ADH1B*1/*2 enzyme and homozygous ADH1B*2/*2 enzyme, respectively[30]. Most of the case-control studies have consistently shown an increased ADH1B*1/*1-associated risk of upper aerodigestive tract cancer, but there is controversy as to whether the risk appears in a dose-dependent manner as the number of ADH1B*1 alleles increase[32]. The meta-analysis in this study showed that ADH1B*1/*1 greatly increased the risk of esophageal cancer in moderate drinkers and heavy drinkers (ORs = 2.71 and 3.22, respectively, Figure 1) and that ADH1B*1/*2 modestly but significantly increased the risk in moderate drinkers (OR = 1.43, Figure 2). These findings that the genetic risks are seen at all levels of alcohol exposure, may reveal that there is genetic risk for esophageal cancer, also show a dose-dependent relationship between the number of ADH1B*1 alleles and the risk of esophageal cancer as well. Such dose dependency has been clearly demon-
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| Study | Never/rare drinkers | Odds ratio (95% CI) | Weight (%) |
|-------|---------------------|---------------------|------------|
| Boonyaphiphit et al[22], 2002 | 0.52 (0.06-4.59) | 6.1 |
| Chao et al[19], 2000 | 0.67 (0.13-3.38) | 8.7 |
| Lee et al[17], 2008 | 2.04 (0.83-5.03) | 13.7 |
| Itoga et al[18], 2004 | 0.80 (0.04-14.89) | 4.0 |
| Yang et al[20], 2005 | 0.18 (0.02-1.80) | 5.6 |
| Yokoyama et al[21], 2002 | 2.59 (0.12-56.40) | 3.7 |
| Yokoyama et al[20], 2006 | 1.14 (0.34-3.79) | 11.5 |
| Ding et al[17], 2009 | 5.45 (2.15-13.79) | 13.5 |
| Yang et al[21], 2007 | 0.17 (0.02-1.36) | 6.5 |

Subtotal (P for heterogeneity: < 0.05)

| Drinkers (moderate and heavy drinkers) | 2.16 (0.22-21.49) | 5.7 |
| Japanese | 5.63 (1.56-20.32) | 10.9 |
| Chinese (Taiwan) | 8.55 (1.01-72.22) | 6.3 |
| Never/rare drinkers | 1.04 (0.05-21.95) | 3.7 |
| Moderate drinkers | 4.24 (1.72-11.36) | 26.6 |

Subtotal (P for heterogeneity: 0.63)

| Odds ratio | 0.02 | 1 | 56.5 |

Figure 4 Relationship between aldehyde dehydrogenase-2*2/*2 and esophageal cancer stratified by alcohol consumption status. Weights are from random effects analysis. Ex-drinkers were excluded because there were no cases and controls with the ALDH2*2/*2 for this drinking status; Moderate and heavy drinkers were combined because of the small number of ALDH2*2/*2 drinkers. ALDH2: Aldehyde dehydrogenase-2.

| Study | Never/rare drinkers | Odds ratio (95% CI) | Weight (%) |
|-------|---------------------|---------------------|------------|
| Boonyaphiphit et al[22], 2002 | 0.52 (0.06-4.59) | 6.1 |
| Chao et al[19], 2000 | 0.67 (0.13-3.38) | 8.7 |
| Lee et al[17], 2008 | 2.04 (0.83-5.03) | 13.7 |
| Itoga et al[18], 2004 | 0.80 (0.04-14.89) | 4.0 |
| Yang et al[20], 2005 | 0.18 (0.02-1.80) | 5.6 |
| Yokoyama et al[21], 2002 | 2.59 (0.12-56.40) | 3.7 |
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| Never/rare drinkers | 1.04 (0.05-21.95) | 3.7 |
| Moderate drinkers | 4.24 (1.72-11.36) | 26.6 |

Subtotal (P for heterogeneity: 0.63)

| Odds ratio | 0.02 | 1 | 56.5 |

Table 4 Risk of esophageal cancer associated with alcohol dehydrogenase-1B and aldehyde dehydrogenase-2 polymorphisms according to ethnicity or sex

| ADH1B | ALDH2*2/*2 vs *1/*1 pooled OR (95% CI) | P for heterogeneity | ALDH2 | ALDH2*2/*2 vs *1/*1 pooled OR (95% CI) | P for heterogeneity |
|-------|--------------------------------------|---------------------|-------|--------------------------------------|---------------------|
| Ethnicity | | | | | |
| Chinese (Mainland) | | | | | |
| Never/rare drinkers[17,22] | 1.20 (0.54-2.66) | 0.81 | Never/rare drinkers[17,22] | 1.75 (1.14-2.70) | 0.06 |
| Moderate drinkers[17,22] | 1.86 (0.52-6.60) | 0.22 | Moderate drinkers[17,22] | 1.98 (1.20-3.27) | 0.34 |
| Heavy drinkers[17,22] | 3.55 (1.01-11.83) | - | Heavy drinkers[17,22] | 1.31 (0.54-3.12) | - |
| Chinese (Taiwan) | | | | | |
| Never/rare drinkers[18,24] | 2.15 (0.99-4.69) | 0.51 | Never/rare drinkers[18,24] | 1.14 (0.42-3.07) | - |
| Moderate drinkers[18,24] | 3.93 (2.00-7.74) | - | Moderate drinkers[18,24] | 6.21 (3.78-10.22) | 0.67 |
| Heavy drinkers[18,24] | 3.36 (1.73-6.53) | 0.3 | Heavy drinkers[18,24] | 9.21 (5.54-15.31) | 0.76 |
| Japanese | | | | | |
| Never/rare drinkers[17,22,24] | 2.41 (1.50-11.62) | 0.31 | Never/rare drinkers[17,22,24] | 0.68 (0.33-1.42) | 0.55 |
| Moderate drinkers[17,22,24] | 2.18 (1.38-12.23) | 0.05 | Moderate drinkers[17,22,24] | 4.74 (3.29-6.83) | 0.4 |
| Heavy drinkers[17,22,24] | 4.02 (1.83-8.80) | 0.64 | Heavy drinkers[17,22,24] | 9.75 (7.34-12.97) | 0.69 |

| Sex | | | | | |
| Male | | | | | |
| Never/rare drinkers[17,22,24] | 2.71 (1.13-6.51) | 0.24 | Never/rare drinkers[17,22,24] | 1.92 (1.28-2.88) | 0.55 |
| Moderate drinkers[17,22,24] | 3.93 (2.43-6.36) | 0.39 | Moderate drinkers[17,22,24] | 3.53 (1.98-6.30) | < 0.05 |
| Heavy drinkers[17,22,24] | 3.22 (2.16-4.83) | 0.39 | Heavy drinkers[17,22,24] | 7.04 (4.18-11.85) | < 0.05 |
| Female | | | | | |
| Never/rare drinkers[17,22,24] | 1.48 (0.56-3.49) | 0.17 | Never/rare drinkers[17,22,24] | 1.55 (0.50-14.78) | 0.03 |
| Moderate drinkers[17,22,24] | 0.81 (0.21-3.15) | 0.41 | Moderate drinkers[17,22,24] | 2.64 (1.24-5.68) | 0.72 |
| Heavy drinkers[17,22,24] | 3.53 (1.06-11.84) | 0.35 | Heavy drinkers[17,22,24] | 6.85 (1.04-44.95) | 0.88 |

ALDH2: Aldehyde dehydrogenase-2; ADH1B: Alcohol dehydrogenase-1B; OR: Odds ratio; CI: Confidence interval.

Stratified in the effect of the ADH1B*1 allele on the risk of alcoholism[21,33]. Stratification according to status of alcohol consumption is essential to accurate assessment of the effects of ALDH2 and ADH1B genotypes on cancer risk. The ALDH2*2 allele plays a suppressive role in alcohol drinking, whereas ADH1B*1 plays a facilitating role. Without stratification, the OR associated with the ALDH2*2 allele is underestimated, and the OR associated with the ADH1B*1 allele is overestimated[21]. That is why the crude pooled OR is larger for ADH1B*1/*1 (OR = 2.91) than for ALDH2*1/*2 (OR = 2.52), while the alcohol-stratified OR for ALDH2*1/*2 in the moderate-to-heavy drinkers (OR = 3.12-7.12, Figure 3) is larger than for ADH1B*1/*1 (OR = 2.71-3.22, Figure 1). Moreover, the significant study-heterogeneity in ADH1B*1/*1, ALDH2*1/*2 and ALDH2*2/*2 disappeared or greatly decreased after stratification by alcohol consumption, indicating that alcohol consumption plays an important role on the effects of the two genes on cancer risk. The meta-analysis in this study demonstrated that the combination of ALDH2*1/*2 and ADH1B*1/*1 was
associated with the highest risk of esophageal cancer in heavy drinkers (OR = 12.45, Table 3).

The mechanism underlying the ALDH2*1/*2-associated increase in risk of esophageal cancer is straightforward. The WHO and IARC have concluded that the aldehyde associated with alcohol beverages is carcinogenic for humans (Group 1 carcinogen) and causes cancer of the esophagus and head and neck [3]. The extended tissue exposure to ethanol and acetaldehyde in persons with the ADH1B*1/*1 genotype is a plausible explanation for the high risk of esophageal cancer [4]. The distinctly high tissue exposure to, and accumulation of acetaldehyde in ALDH2*1/*2 carriers may increase the risk of esophageal cancer more greatly than, and synergistically with the prolonged tissue exposure to ethanol and acetaldehyde in the ADH1B*1 allele carriers.

Only one case-control study has focused on the cancer risk in women, and it showed a weaker increasing effect of ALDH2*1/*2 on the risk of esophageal cancer in female moderate drinkers than in male moderate drinkers and a markedly increasing effect in female heavy drinkers [5]. The small sample size in that study hampered the assessment of the effect of the ADH1B genotype in women. The meta-analysis in our study demonstrated that ALDH2*1/*2 affected the risk of esophageal cancer in a similar manner in both women and men who were moderate drinkers (ORs = 2.64 and 3.53, respectively, Table 4) or heavy drinkers (ORs = 6.85 and 7.04, respectively, Table 4). Two earlier meta-analyses showed that the magnitude of the ALDH2-effect on the risk of esophageal cancer and head and neck cancer was greater in heavy drinkers than in moderate drinkers [6,8,14], and the results of the present study demonstrated this phenomenon in both women and men. We also observed a significant increase in cancer risk by ALDH2*1/*2 and ALDH2*2/*2 in male never/rare drinkers alone (ORs = 1.92 and 2.96, respectively, Table 4), suggesting that the ALDH2-related susceptibility to esophageal cancer extends to very low dose or frequency levels of alcohol consumption in men. Similar effects of ADH1B*1/*1 on cancer risk were observed in both female and male heavy drinkers (ORs = 3.55 and 3.22, respectively, Table 4). These results are consistent with the results of a meta-analysis demonstrating a similarly high risk of esophageal cancer in women who consume alcohol at the same dose levels as men [10].

The magnitude of the ALDH2-associated risk depends on the strength of the association between the esophageal cancer and alcohol consumption evaluated. The incidence rate of esophageal cancer in the high-incidence regions in Mainland China is extremely high, e.g. 65/100000 population in Taixing City [9], and alcohol drinking plays a less important role in esophageal carcinogenesis there than in Taiwan or Japan. The incidence rates in Taiwan and Japan are approximately 9/100000 men and extremely low among women [17]. The four case-control studies conducted in the high-incidence regions in Mainland China showed a moderate-to-modest positive association [19,20,23] or no association [28] between heterozygous ALDH2 and esophageal cancer risk. The ALDH2*1/*2-associated risks in these Chinese studies were higher where the impact of alcohol consumption on esophageal cancer was greater and/or when only male populations were evaluated. The subgroup analysis in regard to ethnicity demonstrated that the ALDH2*1/*2 genotype was associated with a similarly very high risk of esophageal cancer among Taiwan Chinese and Japanese drinkers (OR = 4.74-6.21 in moderate drinkers, 9.21-9.75 in heavy drinkers, Table 4), but the OR of ALDH2*1/*2 in the high incidence regions of Mainland China was not so high in moderate-to-heavy drinkers (OR = 1.98 in moderate drinkers, OR = 1.31 in heavy drinkers, Table 4). However, it is possible to prevent a large number of esophageal cancer deaths by preventive strategies that include public education about high-risk drinking in Mainland China, because the incidence rates of esophageal cancer there are extremely high. Over the past 40 years, there has been a 9-fold increase in per capita alcohol consumption in Mainland China and a 2-fold increase in Japan [39]. It will be probably continue to increase in China, because current Chinese consumption is still comparable to Japanese consumption in the 1970s. The inhibitory effect of inactive heterozygous ALDH2 on heavy drinking is influenced by socio-cultural factors. Among Japanese alcoholics, the proportion of inactive ALDH2 heterozygotes has dramatically increased from 2.5% to 13% among Japanese alcoholics since the 1970s [40], and this change partially explains the alarming rate of increase in the prevalence of multiple upper aerodigestive tract cancers among Japanese esophageal cancer patients during the same period [41]. The proportion among Han Chinese alcoholics in Taiwan also increased from 10% to 18% during the 1990s [22]. Alcohol-related esophageal cancer will be an important problem in Mainland Chinese in the future.

Several limitations of this study should be considered. There was heterogeneity between the studies of ALDH2 polymorphisms, and some heterogeneity still existed after performing the subgroup analysis, suggesting that other factors should have been taken into account in the analysis. Smoking presents a critical risk factor for esophageal cancer, and drinkers also tends to smoke, and may influence the risk of drinking for esophageal cancer, but the further subgroup analysis on smoking would have been limited by the missing information in most of these studies. Five control samples were not in Hardy-Weinberg equilibrium. The disequilibrium in the controls suggests that the samples were not representative of the expected distribution of the genotypes and thus may have distorted the findings. Alcohol consumption measurement was defined by different criteria across the studies, which would have resulted in overestimation or underestimation of the ORs, but the ORs did not change greatly or reverse according to the sensitivity analysis, indicating that the results in the drinking categories are robust. Finally, some subgroups were included in only one study, and that may have lowered the power to identify the true effect. However, we did attempt to contact the authors, but some data were still unavailable because the data were missing or there was no response from the authors.
Based on the results of our meta-analysis, we concluded that the ADH1B*1-allele and ALDH2*2 allele increase the risk of esophageal cancer at all levels of exposure to ethanol and acetaldehyde after drinking and that these effects are modified by alcohol consumption, ethnicity, and gender. These findings broaden the concept of high-risk drinking and may provide a new strategic approach to the prevention of esophageal cancer.

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