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*RAPID COMMUNICATION*

# Genetic polymorphisms in cytochrome P4502E1, alcohol and aldehyde dehydrogenases and the risk of esophageal squamous cell carcinoma in Gansu Chinese males

Yan-Mei Guo, Qin Wang, Yan-Zhen Liu, Huei-Min Chen, Zhi Qi, Qing-Hong Guo

Yan-Mei Guo, Yan-Zhen Liu, Department of Clinical Medicine, Gansu College of Traditional Chinese Medicine, Lanzhou 730000, Gansu Province, China
Qin Wang, Zhi Qi, Qing-Hong Guo, Department of Gastroenterology, First Hospital of Lanzhou University, Lanzhou 730000, Gansu Province, China
Huei-Min Chen, Matheson Library, Library, Monash University, Victoria 3800, Australia
Author contributions: Guo YM, Wang Q, Qi Z, Guo QH, Chen HM, and Liu YZ designed the research; Guo YM, Qi Z, and Guo QH performed the research; Chen HM contributed new reagents/analytic tools; Guo YM, Chen HM and Liu YZ analyzed the data; and Guo YM, Wang Q, Qi Z and Chen HM wrote the paper.
Correspondence to: Yan-Mei Guo, Department of Clinical Medicine, Gansu College of Traditional Chinese Medicine, Lanzhou 730000, Gansu Province, China. guoyanmei100@126.com
Telephone: +86-931-8278294 Fax: +86-931-8625200
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## Abstract

**AIM:** To evaluate the association between genetic polymorphisms in *CYP2E1*, *ALDH2* and *ADH1B* and the risk of esophageal squamous cell carcinoma (ESCC) in a high risk area of Gansu Province, in Chinese males.

**METHODS:** A case-control study was conducted to investigate the genetic polymorphisms of these enzymes (*CYP2E1**c1/*c2, *ALDH2**1/*2 and *ADH1B* *1/*1 genotypes). A total of 80 esophageal cancer cases and 480 controls were recruited.

**RESULTS:** Compared with controls, cases had a greater prevalence of heavier alcohol consumption (53.8% *vs* 16.2%) and a higher proportion of alcohol drinkers with > 30 drink-years (28.8% *vs* 13.5%). Heavier alcohol consumption and alcohol drinking with > 30 drink-years increased the risk of ESCC, with ORs (95% CI) of 3.20 (1.32-9.65) and 1.68 (0.96-3.21). *CYP2E1* (*c1/*c1), *ALDH2* (*1/*2) and *ADH1B* (*1/*1) genotype frequencies were higher among patients with squamous cell carcinomas, at a level close to statistical significance ($P$ = 0.014; $P$ = 0.094; $P$ = 0.0001 respectively). There were synergistic interactions among alcohol drinking and *ALDH2*, *ADH1B* and *CYP2E1* genotypes. The risk of the ESCC in moderate-to-heavy drinkers with an inactive *ALDH2* encoded by *ALDH2**1/*2 as well as *ADH1B* encoded by *ADH1B* *1/*1 and *CYP2E1* encoded by *CYP2E1* *c1/*c1 was higher than that in the never/rare-to-light drinkers with an active *ALDH2* (*1/*1 genotype) as well as *ADH1B* (*1/*2 + *2/*2) and *CYP2E1* (*c1/*c2 + *c2/*c2) genotypes, with a statistically significant difference; ORs (95% CI) of 8.58 (3.28-22.68), 27.12 (8.52-70.19) and 7.64 (2.82-11.31) respectively. The risk of the ESCC in moderate-to-heavy drinkers with *ALDH2* (*1/*2) combined the *ADH1B* (*1/*1) genotype or *ALDH2* (*1/*2) combined the *CYP2E1* (*c1/*c1) genotype leads to synergistic interactions, higher than drinkers with *ALDH2* (*1/*1) + *ADH1B* (*1/*2 + *2/*2), *ALDH2* (*1/*1) + *CYP2E1* (*c1/*c2 + *c2/*c2) respectively , ORs (95% CI) of 7.46 (3.28-18.32) and 6.82 (1.44-9.76) respectively. Individuals with the *ADH1B* combined the *CYP2E1* genotype showed no synergistic interaction.

**CONCLUSION:** In our study, we found that alcohol consumption and polymorphisms in the *CYP2E1*, *ADH1B* and *ALDH2* genes are important risk factors for ESCC, and that there was a synergistic interaction among polymorphisms in the *CYP2E1*, *ALDH2* and *ADH1B* genes and heavy alcohol drinking, in Chinese males living in Gansu Province, China.



**Key words:** Esophageal squamous cell carcinoma; Cytochromes P4502E1; Alcohol dehydrogenases; Aldehyde dehydrogenases; Genetic polymorphisms

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## INTRODUCTION

Esophageal carcinoma is the seventh leading cause of cancer deaths worldwide[1]. It is a devastating disease with very few patients cured once diagnosed. Esophageal squamous cell carcinoma (ESCC) is one of the most

common malignancies in Gansu province, China. There is great geographic variation in the occurrence of this tumor type in China, including exceptionally high-risk areas such as Gansu Province in the Northwest of China. Within high-risk regions in China, there is a strong tendency toward alcohol drinking, suggesting that genetic susceptibility, in conjunction with alcohol consumption, plays a role in the etiology of ESCC.

Epidemiologic studies have demonstrated that drinking alcoholic beverages is causally related to the development of ESCC[2,3]. Genetic polymorphisms in the genes encoding cytochrome P4502E1 (*CYP2E1*)[4-7], aldehyde dehydrogenase-2 (*ALDH2*) and alcohol dehydrogenase-1B (*ADH1B*; previously called ADH2) affect the metabolism of alcohol[8-12]. There have been some studies on the roles of alcohol and polymorphisms in the *CYP2E1*, *ALDH2* and ADH2 genes in ESCC[13-15]. However, their results were conflicting.

To provide further data on this issue, we evaluated the susceptibility to ESCC conferred by *CYP2E1*, *ALDH2* and *ADH1B* genetic polymorphisms, and defined the individual and combined roles of these genes and alcohol consumption in a high risk area for ESCC in Chinese males.

## MATERIALS AND METHODS

The case participants in this study were 80 Gansu males with ESCC treated at the Department of Gastroenterology, First Hospital of Lanzhou University and the Department of Gastroenterology, Affiliated Hospital of Gansu College of Traditional Chinese Medicine. All were registered between September 2004 and March 2007.

The 480 age-and-gender matching controls consisted of cancer-free men who received annual health checkups at two Lanzhou clinics between September 2004 and March 2007. Gansu was the ancestral home for all.

Each participant independently completed a structured questionnaire concerning his alcohol drinking habits, and those with cancer were instructed to report their habits before they were diagnosed with cancer. Each participant was asked to classify himself as a drinker or non-drinker, and to report alcohol intake as the frequency of consumption and usual amount(s) and type(s) of alcoholic beverage(s) consumed. The subjects were classified as never drinks alcohol, or drinkers who consumed 200 g/wk (light drinkers), 200-400 g/wk (moderate drinkers) or 400+ g/wk (heavy drinkers).

Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) methods or a PCR method were performed on lymphocyte DNA samples from all participants, without any knowledge of their cancer status, to determine their P4502E1, *ALDH2* and *ADH1B* genotypes (Tables 1 and 2).

The Rsa I and Pst I linkage disequilibrium polymorphisms of the P4502E1 gene were determined according to the method of Hayashi *et al*[16] with some modification. The final mixture (50 μL) was prepared containing 0.3 μg of DNA, 0.2 μmol/L of dNTP, 0.3 μmol/L of each of the primers, 1.5 μmol/L of $MgCl_2$, 5 μL of 10 × buffer, and 2 U of Taq polymerase. Briefly, the samples were denatured at 94℃ for 2 min and submitted to 40 cycles of 1 min at 94℃ (denaturation), 50 s at 50℃ (annealing) and 50 s at 72℃ (extension), with a final extension at 72℃ for 10 min. PCR products (15 μL) were digested by Pst I or Rsa I restriction enzymes (1 μL of a 10 U/μL preparation) for 18 h at 37℃. Fragments were separated on 40 g/L low melting point agarose gels, and stained with ethidium bromide.

*ALDH2* and *ADH1B*[17] polymorphisms were determined by PCR-RFLP as previously described. Each PCR analysis was performed twice, double blindly.

The allele frequency was determined by direct counting. Deviation of the genotype distribution from Hardy-Weinberg equilibrium was analyzed by the exact test. Fisher's exact test was used for comparing group statistics. The Spearman rank-correlation analysis was used as a nonparametric test for trend. All *P*-values were obtained from 2-sided tests. Associations between genotypes or other potential risk factors and ESCC are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) adjusted for the effects of several possible confounders using a multiple logistic regression model and the STEPWISE method.

**Table 1 Polymorphisms in the *CYP2E1*, *ALDH2* and *ADH1B* genes**

| Locus /protein | Gene | Subunit | Nucleotide change | Effect | RFLP |
|---|---|---|---|---|---|
| *ADH1B* | *ADH2**1 | β1 | | Wild-type | |
| | *ADH2**2 | β2 | 48G>A | His48; (earlier as His47) | |
| *ALDH2* | *ALDH2**1 | | | Wild-type | |
| | *ALDH2**2 | | 1510G>A | Lys487 | |
| *CYP2E1* | *CYP2E1**1A | | None | Wild type | Pst I-/Rsa I + (c1allele) |
| | *CYP2E1**5B | | -1293G>C; -1053C>T | | Pst I+/Rsa I - (c2 allele) |

*CYP2E1* allele nomenclature, http://www.imm.ki.se; NIAAA publications, http://pubs.niaaa.nih.gov.

**Table 2 Primer sequences and lengths of PCR products**

| Gene | Primer | Size of PCR product (bp) | Chromosomal location |
|---|---|---|---|
| *CYP2E1* | 5'-CCAGTCGAGTCTACATTGTCA-3'<br>5'-TTCATTCTGTCTTCTAACTGG-3' | 410 | 10q24.3-qter |
| *ALDH2* | 5'-CCCTTTGGTGGCTAGAAGATG-3'<br>5'-CCACACTCACAGTTTTCTCTT-3' | 91 | 12q24.2 |
| *ADH1B* | 5'-ATTCTGTAGATGGTGGCTGT-3'<br>5'-GAAGGGGGGTCACCAGGTTG-3' | 76 | 4q22 |

## RESULTS

Five hundred and sixty males were enrolled in this study. The cancer cases were age-and-gender matched with cancer-free control subjects. The mean age of the patients was 60.2 ± 8.9, ranging from 49 to 75 years of age. The mean age of the controls was 59.7 ± 9.7, ranging from 49 to 73 years of age.

**Table 3 Alcohol drinking in esophageal cancer cases and control subjects**

| Alcohol drinking | Cases (*n* = 80) % | Controls (*n* = 480) % | *P* | OR | 95% CI |
|---|---|---|---|---|---|
| Status | | | | | |
| Never | 4 (5.0) | 132 (27.5) | | | |
| Former | 46 (7.5) | 36 (7.5) | | | |
| Current | 20 (87.5) | 312 (65.0) | 0.17 | | |
| Dose | | | | | |
| Non-drinker | 4 (5.0) | 132 (27.5) | | 1 | |
| Light | 10 (12.5) | 153 (31.9) | | 0.16 | 0.03-0.24 |
| Moderate | 23 (28.7) | 117 (24.4) | | 0.85 | 0.54-1.07 |
| Heavy | 43 (53.8) | 78 (16.2) | < 0.0001 | 3.20 | 1.32-9.65 |
| Total years of drinking | | | | | |
| Never | 40 (50.0) | 243 (50.6) | | 1 | |
| ≤ 30 | 17 (21.2) | 172 (35.8) | | 0.69 | 0.36-0.98 |
| > 30 | 23 (28.8) | 65 (13.5) | 0.009 | 1.68 | 0.96-3.21 |

**Table 4 Genotypes of *ALDH2*, *ADH2* and *P4502E1*, *n* (%)**

| Genotype | Cases (*n* = 80) | Controls (*n* = 480) | *P* | OR | 95% CI |
|---|---|---|---|---|---|
| *ALDH2* genotype | | | | | |
| 1/1 | 37 (46.3) | 252 (52.5) | | 1 | |
| 1/2 | 43 (53.7) | 195 (40.6) | 0.094 | 2.89 | 1.11-5.64 |
| 2/2 | 0 (0.0) | 33 (6.9) | | | |
| *ADH1B* genotype | | | | | |
| 1/1 | 17 (21.3) | 24 (5.0) | | 1 | |
| 1/ 2 | 25 (31.3) | 168 (35.0) | < 0.0001 | 3.67 | 1.26-8.73 |
| 2/2 | 38 (47.5) | 288 (60.0) | < 0.0001 | 1.46 | 0.71-2.59 |
| *CYP2E1* Pst I/Rsa I | | | | | |
| c2/c2 | 7 (8. 8) | 75 (15.6) | | 1 | |
| c1/c2 | 16 (20.0) | 180 (37.5) | 0.918 | | |
| c1/c1 | 57 (71.3) | 225 (46.9) | 0.014 | 2.82 | 1.23-6.55 |

Table 3 shows alcohol drinking in esophageal cancer cases and control subjects. We observed that, compared with controls, cases had a greater prevalence of heavier alcohol consumption (53.8% *vs* 16.2%) and a higher proportion of alcohol drinkers with > 30 drink-years (28.8% *vs* 13.5%). Heavier alcohol consumption and alcohol drinking with > 30 drink-years increased the risk of ESCC, with ORs (95% CI) of 3.20 (1.32-9.65) and 1.68 (0.96-3.21).

Table 4 shows the distributions of *ALDH2*, *ADH1B* and *CYP2E1* genotypes. Cases and controls differed significantly in the distributions of these genotypes. These genotypes significantly deviated from the Hardy-Weinberg equilibrium (HWE) in ESCC cases, but among controls, all genotypes were in HWE.

There are two *ALDH2* alleles (*1 and *2) and three genotypes: *1/*1 (GG, typical homozygote), *1/*2 (GA, heterozygote) and *2/*2 (AA, atypical homozygote), and the distributions of these genotypes were significantly different between the esophageal cancer group and the control group ($\chi^2$ = 2.89, $P < 0.1$). The prevalence of the inactive *ALDH2* encoded by *ALDH2**1/*2 was correlated with susceptibility to esophageal cancer, with an OR (95% CI) of 2.89 (1.11-5.64).

There are three *ADH1B* genotypes: The wild-type genotype (*1/*1), heterozygote (*1/*2) and homozygote (*2/*2) genotypes. The prevalence of the less-active *ADH1B* encoded by *ADH1B* *1/*1 increase the risk of esophageal cancer. ($\chi^2$ = 18.664, $P < 0.0001$), OR (95% CI) of 3.67 (1.26-8.73).

There are three *CYP2E1* genotypes: wild homozygote (*c1/*c1), heterozygote (*c1/*c2) and mutated homozygote (*c2/*c2) genotypes. A significant difference in the distributions of the three Pst I/Rsa I genotypes of *CYP2E1* was found between the esophageal cancer group and the control group ($\chi^2$ = 5.977, $P < 0.05$). The c1/c1 genotype was correlated with susceptibility to esophageal cancer, with an OR (95% CI) of 2.82 (1.23-6.55).

Tables 5 and 6 show the frequency distributions and ORs for each combination of alcohol drinking habits and *ALDH2*, *ADH1B* and *CYP2E1* genotypes.

The risk of ESCC was 8.58-fold higher in moderate-to-heavy drinkers with inactive *ALDH2* (encoded by

**Table 5 Probability ratios for the combinations of *ALDH2*, *ADH2* and *CYP2E1* genotypes and the amount of alcohol consumed, *n* (%)**

| Alcohol drinking | Genotype | Cases (*n* = 80) | Controls (*n* = 480) | OR (95% CI) | OR (95% CI) |
|---|---|---|---|---|---|
| *ALDH2* | | | | | |
| Never/rare | 1/1 | 7 (8.8) | 72 (15.0) | 1 | |
| -to-light | 1/2 | 7 (8.8) | 180 (37.5) | 0.56 (0.20-1.59) | |
| | 2/2 | 0 (0.0) | 33 (6.9) | 0.00 (NC) | |
| Moderate | 1/1 | 30 (37.5) | 180 (37.5) | 2.29 (0.94-5.57) | |
| -to-heavy | 1/2 | 36 (45.0) | 15 (3.1) | 8.58 (3.28-22.68) | 3.12 (1.86-6.58) |
| *ADH1B* | | | | | |
| Never/rare | 1/2+2/2 | 13 (16.3) | 273 (56.9) | 1 | |
| -to-light | 1/1 | 1 (1.3) | 12 (2.5) | 1.00 (0.18-9.22) | |
| Moderate | 1/2+2/2 | 50 (62.5) | 183 (38.1) | 4.75 (2.53-9.38) | |
| -to-heavy | 1/1 | 16 (20.0) | 12 (2.5) | 27.12 (8.52-70.19) | 5.48 (1.98-14.55) |
| *CYP2E1* | | | | | |
| Never/rare | | 5 (6.3) | 189 (39.4) | 1 | |
| -to-light | c1/c1 | 9 (11.3) | 96 (20.0) | 0.56 (0.20-1.59) | |
| Moderate | c1/c2+ | 18 (22.5) | 96 (20.0) | 1.93 (0.43-2.41) | |
| -to-heavy | c2/c2 | | | | |
| | c1/c1 | 48 (60.0) | 99 (20.6) | 7.64 (2.82-11.31) | 5.32 (1.62-9.28) |

**Table 6 Probability ratios for the combinations of *ADH1B*, *CYP2E1* and *ALDH2* genotypes among moderate-to-heavy drinkers, *n* (%)**

| Combined genotypes | Genotype | Cases (*n* = 80) | Controls (*n* = 480) | OR | 95% CI |
|---|---|---|---|---|---|
| *ALDH2* + *ADH1B* | *ALDH2**1/1 + *ADH1B**1/2 + 2/2 | 28 (35.0) | 144 (30.0) | 1 | |
| | *ALDH2**1/2 + *ADH1B**1/1 | 15 (18.8) | 27 (1.9) | 7.46 | 3.28-18.32 |
| *ALDH2* + *CYP2E1* | *ALDH2**1/1 + *CYP2E1**c1/c2 + c2/c2 | 10 (12.5) | 60 (12.5) | 1 | |
| | *ALDH2**1/2 + *CYP2E1**c1/c1 | 32 (40.0) | 15 (3.1) | 6.82 | 1.44-9.76 |
| *ADH1B* + *CYP2E1* | *ADH1B**1/2 + 2/2 + *CYP2E1**c1/c2 + c2/c2 | 12 (15.0) | 36 (2.5) | 1 | |
| | *ADH1B**1/1 + *CYP2E1**c1/c1 | 14 (17.5) | 66 (13.8) | 6 | |

*ALDH2**1/*2) than in the never/rare-to-light drinkers with an active *ALDH2* (encoded by *ALDH2**1/*1).

When the ORs were compared within each alcohol drinking category, the risk of the ESCC associated with *ALDH2* (*1/*2) versus *ALDH2* (*1/*1) was 3.12-fold greater among moderate-to-heavy drinkers, whereas no significant increase in risk was observed with *ALDH2* *1/*2 *versus* ALDH2 *1/*1 among never/rare-to-light drinkers.

The results for the *ADH1B* genotype showed that only among moderate-to-heavy drinkers did the less-active *ADH1B* *1/*1 genotype significantly increase the risk of cancer, with an OR (95% CI) 5.48 (1.98-14.55). Thus, the risk of the cancer in moderate-to-heavy drinkers with the *ADH1B* (1/1) genotype was markedly higher (by 27.12-fold) than that in never/rare-to-light drinkers with a super-active *ADH1B* encoded by *ADH1B* *1/*2 and *ADH1B* *2/*2.

The results for the *CYP2E1* genotype showed that, among moderate-to-heavy drinkers, the *CYP2E1* (*c1/*c1) genotype significantly increased the risk of cancer, with an OR (95% CI) of 5.32 (1.98-14.55). Thus, the risk of the cancer in moderate-to-heavy drinkers with *CYP2E1* (*c1/*c1) was markedly higher (by 7.64-fold) than that in never/rare-to-light drinkers with a super-active *CYP2E1* (genotypes *c1/*c2 + *c2/*c2).

The results of our analysis of *ALDH2* and *ADH1B* genotypes showed that among moderate-to-heavy drinkers, the combination of *ALDH2* (*1/*2) and *ADH1B* (*1/*1) genes synergistically increased the risk of cancer, to 7.46-fold higher than that in drinkers with an *ALDH2* (*1/*1) + ADH1B (*1/*2 + *2/*2) genotype.

The results of an analysis of the effects of combinations of *ALDH2* and *CYP2E1* genotypes showed that among moderate-to-heavy drinkers, the combination of *ALDH2* (*1/*2) and *CYP2E1* (*c1/*c1) genes synergistically increased the risk of cancer, to 6.82-fold higher than that in drinkers with an *ALDH2* (*1/*1) + *CYP2E1* (*c1/*c2 + *c2/*c2) genotype.

There was no combinatorial effect of *ADH1B* and *CYP2E1* genotypes.

## DISCUSSION

In the present study, we examined the associations of ESCC with *ALDH2*, ADH2 and *CYP2E1* genetic polymorphisms in conjunction with alcohol drinking habits among a population at high risk of esophageal cancer. The study was conducted in Gansu province, an area of China with a relatively high alcohol consumption rate.

We found that alcohol intake was associated with ESCC, and that polymorphisms in *CYP2E1*, as well as in the genes encoding alcohol and aldehyde dehydrogenases (*ADH1B* and *ALDH2*) are important risk factors for ESCC in Chinese men living in this high risk area.

We found that heavier alcohol consumption and alcohol drinking for > 30 drink-years could increase the risk of ESCC, with ORs (95% CI) of 3.20 (1.32-9.65) and 1.68 (0.96-3.21), respectively. There is substantial evidence that drinking alcohol increases the risk of ESCC. Alcohol can be considered to induce DNA damage and result in the modification of nucleotides. Our risk estimates were consistent with those of previous studies[18]. This study confirms that alcohol consumption contributes to the etiology of ESCC.

It has been reported that individual differences in cytochrome P450 (CYP) gene expression may contribute to a person's individual susceptibility to pro-carcinogens and, subsequently, to the development of malignancies. CYP plays a central role in the metabolism of carcinogens by activating oxidation reactions, and may be expressed in esophageal mucosa.

*CYP2E1* metabolizes ethanol to acetaldehyde and is primarily responsible for the metabolic activation of many low molecular weight carcinogens, including certain nitrosamines, which may be involved in carcinogenesis of the esophagus. This enzyme is also believed to participate in the oxidation of other compounds, such as ethanol, to produce reactive free radicals that may initiate lipid peroxidation and consequently influence carcinogenesis. In addition, it effectively reduces dioxygen to give rise to radical species, thus contributing to lipid peroxidation and oxidative inhibition. Individuals with the variant Pst I/Rsa I allele (*c1/*c2 or *c2/*c2) have a lower basal *CYP2E1* activity. Two studies found an association between the *CYP2E1* Pst I /Rsa I variant allele and a decreased risk of ESCC[19]. The results of our study indicated that the *CYP2E1* *c1/*c1 or c1 allele increased the susceptibility to ESCC in a Gansu population ($P = 0.014$), and that there are synergistic interactions between *CYP2E1* (*c1/*c1) and alcohol drinking; the risk of ESCC in moderate-to-heavy drinkers with the *CYP2E1* (*c1/*c1) genotype was markedly higher, by 7.64-fold, than in never/rare-to-light drinkers with a super-active *CYP2E1* (genotypes *c1/*c2 + *c2/*c2).

The genetic polymorphisms of alcohol and aldehyde dehydrogenases affect the metabolism of alcohol. Aldehyde dehydrogenase-2 (*ALDH2*) is the key enzyme for elimination of acetaldehyde. Acetaldehyde, a recognized animal carcinogen derived from alcohol, may play an important role in the pathogenesis of alcohol-related cancers, such as esophageal cancer. In persons with inactive *ALDH2* encoded by *ALDH2**1/*2, the body fails to metabolize acetaldehyde rapidly, leading to excessive accumulation of acetaldehyde.

Polymorphisms in the *ADH1B* and *ALDH2* genes associated with the risk of esophageal cancer have been described in several studies[20-24]. *ADH1B* (*1/*1) has also been demonstrated to enhance the risk of esophageal cancer, and the combination of *ALDH2* (*1/*2) and *ADH1B* (*1/*1) increased the risk of esophageal cancer[8].

In our study, we found that polymorphisms in the genes encoding alcohol and aldehyde dehydrogenases (*ADH1B* and *ALDH2*) are important risk factors for ESCC in a Gansu population, and individuals with the *ADH1B* (*1/*1) genotype had a 5.32-fold risk (1.98-14.55) of developing esophageal cancer compared with those with the *ADH1B* (*2/*2) genotype.

Individuals with the *ALDH2* (*1/*2) genotype had a 3.12-fold higher risk (1.86-6.58) of developing esophageal cancer than those with the *ALDH2* (*1/*1) genotype, among male Chinese moderate-to-heavy drinkers. We also

found that individuals with a combined *ALDH2* (*1/*2) and *ADH1B* (*1/*1) genotype showed a dramatically increased risk of ESCC, with an OR (95% CI) 7.46 (3.28-18.32), which is higher than those due to the respective genotypes. These findings indicate the *ALDH2* (*1/*2) genotype has synergistic interactions with the *ADH1B* (*1/*1) genotype, contributing to the development of ESCC. Our study confirmed the findings of Tetsuji[8].

The significant finding in this study was the interaction between the *CYP2E1* and *ALDH2* genotypes and heavy alcohol drinking, using a case-control study design. Previous studies have not examined this issue in detail and, to our knowledge, this is the first study to show a significant interaction between the *CYP2E1* and *ALDH2* genotypes and alcohol drinking. In our study, we found synergistic interactions among polymorphisms in the *CYP2E1* and *ALDH2* genotypes and heavy alcohol drinking; individuals with a combined *ALDH2* (*1/*2) and *CYP2E1* (*c1/*c1) genotype showed a dramatically increased risk of ESCC, with an OR (95% CI) of 6.82 (1.44-9.76), which is higher than those due to the respective genotypes.

Conflicting results from studies[25-28] in different countries and areas show the complexity of the biological mechanisms underlying ESCC. The susceptibility to ESCC may be correlated with genes, environment, area, race or other factors. The results of this study demonstrate that *CYP2E1* (*c1/*c1), *ALDH2* (*1/*2) and *ADH1B* (*1/*1) genotypes are associated with esophageal cancer risk among moderate-to-heavy drinking Chinese males in Gansu province. In addition, this study also showed *ALDH2* (*1/*2) and *CYP2E1* (*c1/*c1) carriers, and *ALDH2* (*1/*2) and *ADH1B* (*1/*1) carriers have a much higher risk of developing esophageal cancer, especially among alcohol drinkers. Future studies are needed to examine the biological mechanisms involved, and to evaluate the contribution of gene and environment interactions to the risk of ESCC.

## COMMENTS

### Background

Worldwide, cancer of the esophagus ranks among the 10 most common cancers. Epidemiological studies have demonstrated that drinking alcoholic beverages is causally related to the development of esophageal squamous cell carcinoma (ESCC). Genetic polymorphisms in the P4502E1 (*CYP2E1*), *ALDH2* and *ADH1B* genes affect the metabolism of alcohol. There have been some studies on the roles of alcohol and the *CYP2E1*, *ALDH2* and ADH2 genes in ESCC. However, their results were conflicting. Therefore, the aim of the present study was to evaluate the susceptibility to ESCC conferred by *CYP2E1*, *ALDH2* and *ADH1B* genetic polymorphisms, and to define the individual and combined roles of these genes and alcohol consumption in a high risk area for ESCC, among Chinese males.

### Research frontiers

Accumulating evidence from prior epidemiologic studies suggests an association between esophageal cancer and the use of alcohol. The genetic polymorphisms of alcohol and aldehyde dehydrogenases affect the metabolism of alcohol. *ALDH2* is the key enzyme involved in the elimination of acetaldehyde. Polymorphisms in the *ADH1B* and *ALDH2* genes are associated with the risk of esophageal cancer.

### Innovations and breakthroughs

To our knowledge, this is the first study to show significant interactions among the *CYP2E1* and *ALDH2* genotypes and alcohol drinking. We found synergistic interactions among polymorphisms in the *CYP2E1* and *ALDH2* genes and heavy alcohol drinking: Individuals with a combined *ALDH2* (*1/*2) and *CYP2E1* (*c1/*c1) genotype showed a dramatically increased risk of ESCC, which is higher than the risk of ESCC due to the respective genotypes.

### Applications

The detection of *ALDH2*, *ADH1B* and *CYP2E1* genotypes may become a useful index for esophageal cancer, and also help clinicians to diagnose esophageal cancer earlier.

### Terminology

Esophageal squamous cell carcinoma: The most common types of esophageal cancer are squamous cell carcinoma and adenocarcinoma. Squamous cell carcinoma develops in flat cells that line the esophagus. Approximately 60% of squamous cell carcinomas develop in the middle third of the organ, 30% occur in the lower third, and 10% occur in the upper third. Adenocarcinoma develops in the lining of the esophagus and is associated with a condition called Barrett's esophagus. This type usually occurs in the lower third of the esophagus. Genetic polymorphisms: The occurrence together in the same population of more than one allele or genetic marker at the same locus, with the least frequent allele or marker occurring more frequently than can be accounted for by mutation alone. Genetic polymorphisms provide us with the ability to predict inter-individual differences in susceptibility to clinical disease. Biomarkers of susceptibility include polymorphisms in carcinogen metabolism, DNA repair capacity and genes that control cell growth.

### Peer review

This is an interesting study on the etiology of esophageal squamous cell cancer in China. They confirm a synergy between alcohol consumption and the phenotype of inactive enzymes.

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