

Polymorphisms of alcohol dehydrogenase-2 and aldehyde dehydrogenase-2 and esophageal cancer risk in Southeast Chinese males

Jian-Hua Ding, Su-Ping Li, Hai-Xia Cao, Jian-Zhong Wu, Chang-Ming Gao, Ping Su, Yan-Ting Liu, Jian-Nong Zhou, Jun Chang, Gen-Hong Yao

Jian-Hua Ding, Su-Ping Li, Hai-Xia Cao, Jian-Zhong Wu, Chang-Ming Gao, Ping Su, Yan-Ting Liu, Jian-Nong Zhou, Division of Epidemiology, Jiangsu Provincial Institute of Cancer Research, 42 Baiziting, Nanjing 210009, Jiangsu Province, China

Jun Chang, Gen-Hong Yao, Taixing Center for Disease Prevention and Control, Taixing 225400, Jiangsu Province, China
Author contributions: Ding JH, Li SP, and Zhou JN designed research; Ding JH, Li SP, Cao HX, Wu JZ, Liu YT, and Su P performed research; Cao HX, Wu JZ, and Gao CM contributed new reagents/analytic tools; Li SP, and Ding JH analyzed data; Ding JH and Cao HX wrote the paper.

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Correspondence to: Jian-Hua Ding, Division of Epidemiology, Jiangsu Provincial Institute of Cancer Research, 42 Baiziting, Nanjing 210009, Jiangsu Province, China. djh_200@126.com

Telephone: +86-25-83283486 Fax: +86-25-83283487

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Abstract

AIM: To evaluate the impact of alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) polymorphisms on esophageal cancer susceptibility in Southeast Chinese males.

METHODS: Two hundred and twenty-one esophageal cancer patients and 191 healthy controls from Taixing city in Jiangsu Province were enrolled in this study. ADH2 and ALDH2 genotypes were examined by polymerase chain reaction and denaturing high-performance liquid chromatography. Unconditional logistic regression was used to calculate the odds ratios (OR) and 95% confidence interval (CI).

RESULTS: The ADH G allele carriers were more susceptible to esophageal cancer, but no association was found between ADH2 genotypes and risk of esophageal cancer when disregarding alcohol drinking status. Regardless of ADH2 genotype, ALDH2G/A or A/A carriers had significantly increased risk of developing esophageal cancer, with homozygous individuals showing higher esophageal cancer risk than

those who were heterozygous. A significant interaction between ALDH2 and drinking was detected regarding esophageal cancer risk; the OR was 3.05 (95% CI: 1.49-6.25). Compared with non-drinkers carrying both ALDH2 G/G and ADH2 A/A, drinkers carrying both ALDH2 A allele and ADH2 G allele showed a significantly higher risk of developing esophageal cancer (OR = 8.36, 95% CI: 2.98-23.46).

CONCLUSION: Both ADH2 G allele and ALDH2 A allele significantly increase the risk of esophageal cancer development in Southeast Chinese males. ALDH2 A allele significantly increases the risk of esophageal cancer development especially in alcohol drinkers. Alcohol drinkers carrying both ADH2 G allele and ALDH2 A allele have a higher risk of developing esophageal cancer.

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Peer reviewer: Satoshi Osawa, MD, First Department of Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, 431-3192, Japan

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INTRODUCTION

There is epidemiological evidence showing that alcohol intake is associated with increased esophageal cancer risk^[1]. Acetaldehyde, the oxidative metabolite of ethanol, is recognized to be carcinogenic in animals and suspected to have similar effects in humans^[2]. Ethanol is oxidized to acetaldehyde and then to acetate by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), both of which have genetic

polymorphisms. People homozygous for the ALDH2*2 allele (Glu487Lys, Lys or A allele) do not have any ALDH activity. Heterozygous individuals carrying the reference (G) and variant (A) alleles (ALDH2*1/2, or A/G) show only 1/16 of the activity seen in ALDH2*1 homozygotes (G/G)^[3-5]. ADH2*2 allele (Arg47His, His or A allele) encodes a superactive subunit of ADH2 and that superactive ADH2*2 homodimer has about a 40 times higher V_{max} than the less-active ADH2*1/2*1 form of ADH2^[3,4]. Therefore, shortly after alcohol drinking, individuals carrying both variant ADH2 and ALDH2 would accumulate a large amount of aldehyde that cannot be efficiently oxidized to the non-toxic acetic acid. Different combinations of ADH2 and ALDH2 genotypes may influence the individual susceptibility to cancer.

Taixing city, located in the middle part of Jiangsu Province, China, has relatively high incidence and mortality rates for esophageal cancer (in 2005, the age-adjusted mortality rate was 53.66 per 100 000 for esophageal cancer). Our previous study has shown that more than 40% of adult residents in Taixing drink wine and that drinking is a risk factor for esophageal cancer in this area^[6]. We have also shown relationships between ALDH2 and the risk of esophageal cancer, but no statistically significant association was found^[7]. In this study, we increased the sample size to define the individual and combined roles of ADH2, ALDH2 polymorphisms and drinking habits in the risk analysis for esophageal cancer development in Southeast Chinese males.

MATERIALS AND METHODS

Study subjects

We recruited male patients who were histopathologically diagnosed as having esophageal carcinoma from January 2005 to December 2006. Population-based male controls were recruited from healthy residents in the villages or towns where cases resided. All study subjects have completed a questionnaire administrated by a trained interviewer, covering residential, occupational, social, living style, psychological and economical factors. The interviewer then collected blood samples of subjects from a peripheral vein after obtaining their oral informed consents. The collected blood samples were shipped to the public health center within a day. Buffy coat was then separated and stored at -30°C. We defined a drinker as a person who drinks at least once per week (alcohol intake more than 40 g) and continuously drinks for at least half the year. A few patients and residents refused to participate in our study, but the overall response rate was 97% for patients and 95% for controls, respectively. The Ethics Committee of Jiangsu Provincial Institute of Cancer Research approved this study. Associations could not be assessed in women because of sparse drinking habits.

DNA extraction and genotyping of ADH2 and ALDH2

Whole blood was collected into EDTA-coated tubes

and centrifuged for 15 min. The buffy coat layer was isolated. Genomic DNA was extracted from 200 µL of buffy coat using a Qiagen QIAamp DNA blood mini kit (QIAGEN Inc., Valencia, CA). Genotyping of ADH2 and ALDH2 was determined by polymerase chain reaction (PCR) and denaturing high-performance liquid chromatography (DHPLC).

The sequences of primers used in this study are F: 5'-GGGCTTTAGACTGAATAACCTTGG-3' and R: 5'-AGGGAAAGAGGAAACTCCTGAA-3' for ADH2 Arg47His, and F: 5'-TGCTATGATGTGTTTGGAGCC-3' and R: 5'-GGCTCCGAGCCACCA-3' for ALDH2 Glu487Lys. Reactions were carried out in a total volume of 25 µL containing 20 pmol of each primer, 0.25 mmol/L each dNTPs, 2.0 mmol/L MgCl₂, 2.5 µL 10 × buffer, 1 IU hotTag polymerase and 0.5 µL genomic DNA. PCR conditions were as follows: denaturation at 95°C for 7 min, followed by 35 cycles at 95°C for 30 s, at 62°C for 30 s, at 72°C for 30 s, and a final extension at 72°C for 5 min. The products were denatured at 94°C for 4 min, and their temperature was declined to 25°C step by step according to 0.1°C/s.

Transgenomic WAVE DNA fragment analysis system (WAVE-300, Transgenomic, USA) and associated WAVEMAKER software were used for genotyping. An aliquot (5 µL) of the PCR products was directly injected into a DNasep column. The column mobile phase for sample elution consisted of a mixture of buffer A [0.1 mol/L triethylammonium acetate (TEAA)] and buffer B (0.1 mol/L TEAA with 25% acetonitrile). Samples were eluted at a linear gradient of buffer B over a 4.5-min period at a constant flow rate of 0.9 mL/min. For each DNA region, DHPLC conditions were established by a titration analysis at 1-3°C above and below the mean melting temperature predicted by software simulation. There were three genotypes: namely G/G, G/A, and A/A, for ADH2 Arg47His and ALDH2 Glu487Lys, respectively.

Statistical analysis

All analyses were done with the SAS (version 6.02) and Epi-info (version 6.04) statistical package. Odds ratios (OR) and 95% confidence intervals (CI) were adjusted by unconditional logistic regression analysis. Gene-environment interactions were evaluated by additive model and expressed in terms of synergy index (S) and attributable proportions of interaction (API)^[8]. The Mantel-Haenszel χ^2 method was used to test for significant associations between the ADH2 or ALDH2 genotype and cancer risk.

RESULTS

Four hundred and twelve Jiangsu males were enrolled in this study. Numbers of subjects were 221 cases with esophageal cancer and 191 controls (Table 1). The proportional distributions of age, occupation, education, smoking and drinking did not significantly differ between cases and controls, but the proportional distributions

Table 1 Background characteristics of cases and their controls

	Controls <i>n</i> (%)	Cases <i>n</i> (%)	χ^2 MH	<i>P</i>
Age (yr)				
<50	10 (4.53)	8 (4.19)		
50-59	57 (25.79)	60 (31.41)		
60-69	98 (44.34)	80 (41.88)		
> 70	56 (25.34)	43 (22.52)	0.91	0.341
Total	221	191		
Income (yuan/year per person)				
Ten years before	2097	3040		< 0.01
Recent years	3629	4746		< 0.01
Drinking status				
Non-drinker	96 (43.44)	94 (49.21)		
Drinker	125 (56.56)	97 (50.79)	1.38	0.24
Smoking status				
Non-smoker	70 (31.67)	58 (30.37)		
Smoker	151 (68.33)	133 (69.63)	0.78	0.08

Table 2 ORs and their 95% CIs for esophageal cancer with reference to ALDH2 and ADH2 polymorphisms

	Controls <i>n</i> (%)	Cases <i>n</i> (%)	OR ¹ (CI)	OR ² (CI)
ALDH2 genotype				
G/G	90 (40.73)	114 (59.69)	1.00	1.00
G/A	89 (40.27)	66 (34.55)	1.71 (1.10-2.66)	1.70 (1.08-2.68)
A/A	42 (19.00)	11 (5.96)	4.84 (2.25-10.61)	5.69 (2.51-12.18)
G/A+A/A	131 (59.27)	77 (40.51)	2.15 (1.43-3.26)	2.19 (1.43-3.34)
ADH2 genotype				
A/A	106 (47.96)	108 (56.54)	1.00	1.00
A/G	96 (43.44)	75 (39.27)	1.30 (0.85-1.99)	1.21 (0.79-1.86)
G/G	19 (8.60)	8 (4.19)	2.42 (1.02-5.77)	2.78 (1.06-7.29)
A/G+G/G	115 (52.04)	83 (43.46)	1.41 (0.96-2.08)	1.34 (0.89-2.04)
Allele frequencies				
ALDH2				
G	269 (60.86)	294 (76.96)	1.00	
A	173 (39.14)	88 (23.04)	2.15 (1.57-2.95)	
ADH2				
A	308 (69.68)	291 (76.18)	1.00	
G	134 (30.32)	91 (23.82)	1.39 (1.01-1.92)	

¹Crude OR; ²Adjusted odds ratios (ORs) were adjusted for income.

of income (ten years before and recent years) were significant lower in cases than in controls (4.52 and 3.64 for *T* value, *P* < 0.01).

As shown in Table 2, the frequency of ALDH2 G/G, G/A and A/A genotypes were 40.73%, 40.27% and 19.00% in cases and 59.69%, 34.55% and 5.96% in controls respectively. The distribution of the ALDH2 genotypes was significant different between controls and cases ($\chi^2 = 22.30$, *P* < 0.01). The frequency of ADH2 A/A, A/G and G/G genotypes demonstrated no significant differences between cases and controls ($\chi^2 = 4.92$, *P* = 0.085). The allelic distribution of ADH2 and ALDH2 polymorphisms was in Hardy-Weinberg equilibrium (*P* > 0.05).

As for income-adjusted odds ratio, compared with ALDH2 G/G carriers, the OR was 1.70 (95% CI: 1.08-2.68) for G/A carriers, 5.69 (95% CI: 2.51-12.18) for the A/A carriers and 2.19 (95% CI: 1.43-3.34) for the two genotypes combined. Compared with the subjects

Table 3 Interaction between ALDH2 and ADH2 genotype and the ORs for esophageal cancer

ADH2	ALDH2	Cases	Controls	OR ¹ (95% CI)	OR ² (95% CI)
A/A	G/G	44	68	1.00	1.00
G/A+G/G	G/G	46	46	1.55 (0.89-2.70)	1.46 (0.79-2.70)
A/A	G/A	40	33	1.87 (1.03-3.40)	1.93 (0.99-3.75)
G/A+G/G	G/A	49	33	2.29 (1.28-4.11)	2.10 (1.13-3.91)
A/A	A/A	22	7	4.98 (1.91-12.33)	5.28 (1.88-14.83)
G/A+G/G	A/A	20	4	7.73 (2.48-24.13)	12.22 (2.62-56.91)

¹Crude OR; ²ORs were adjusted for income.

with ADH2 A/A genotype, subjects with G/G genotypes had an increased OR of 2.78 (95% CI: 1.06-7.29). As for allelic comparison, the OR was 2.15 (95% CI: 1.57-2.95) for ALDH2 A allele and 1.39 (95% CI: 1.01-1.92) for ADH2 G allele carriers.

Regardless of ADH2 genotype, ALDH2G/A or A/A carriers were found to have significantly increased risk of developing esophageal cancer. ALDH2 A/A homozygotes have higher esophageal cancer risk than ALDH2G/A heterozygotes. As compared to the subjects with ADH2A/A and ALDH2 G/G genotypes (double wild type), those with variant alleles for both ADH2 (G allele) and ALDH2 (A allele) had a significantly increased OR. ALDH2 A/A homozygotes who were also carrying ADH2 G allele had the highest OR of 12.22 (95% CI: 2.62-56.91) (Table 3).

The ALDH2 A/A genotype alone showed a moderate increase of esophageal cancer risk in both drinkers and non-drinkers (Table 4). No significant relationship was found in analysis of ADH2 genotypes. Compared with non-drinkers with both ALDH2 G/G and ADH2 A/A genotypes, drinkers with ALDH2 A and ADH2 G alleles showed a significantly elevated risk of esophageal cancer (OR = 8.36, 95% CI: 2.98-23.46)

The OR for esophageal cancer among alcohol drinkers with ALDH2 A allele was markedly increased to 3.05 (95% CI: 1.49-6.25) compared to non-drinkers with ALDH2 G/G genotypes (Table 5). A significant gene-environment interaction between alcohol drinking and ALDH2 was observed for esophageal cancer risk (*S* = 2.93). The population attributable risk due to alcohol drinking by ALDH2 A allele carriers was estimated to be 41% for esophageal cancer (API = 0.41).

DISCUSSION

Our previous studies showed that drinking was associated with increased esophageal, stomach and liver cancer in Taixing^[6]. We also found that it was not ADH2 but ALDH2 polymorphisms that had a significant interaction with heavy alcohol consumption in the development of hepatocellular carcinoma (HCC)^[9]. In the present study, both ADH2 G allele and ALDH2 A allele significantly increased the risk of esophageal cancer development. ALDH2 A allele significantly increases the risk of esophageal cancer development

Table 4 Analysis of ALDH2 and ADH2 genotypes and risk of esophageal cancer with reference to drinking habits

Genotypes	Non-drinker			Drinker		
	Cases	Controls	OR ¹ (95% CI)	Cases	Controls	OR ¹ (95% CI)
ALDH2						
G/G	26	42	1.00	64	72	1.00
G/A	43	44	1.29 (0.65-2.55)	46	22	2.47 (1.27-4.82)
A/A	27	8	4.67 (1.63-13.38)	15	3	8.63 (2.07-35.95)
G/A+A/A	70	52	1.78 (0.94-3.37)	61	25	3.08 (1.65-5.78)
ADH2						
A/A	50	53	1.00	56	55	1.00
G/A	42	38	1.31 (0.70-2.46)	54	37	1.18 (0.64-2.16)
G/G	4	3	2.10 (0.35-12.54)	15	5	2.90 (0.85-9.90)
G/A+G/G	46	41	1.37 (0.74-2.54)	69	42	1.36 (0.76-2.43)
ALDH2 ADH2						
G/G A/A	10	28	1.00	34	40	2.02 (0.79-5.17)
G/A+A/A G/A+G/G	30	27	2.84 (1.10-7.31)	39	10	8.36 (2.98-23.46)

¹ORs were adjusted for income.

Table 5 Interaction between alcohol drinking and ALDH2 genotype and the ORs for esophageal cancer

Genotype ¹	Drinker ²	Cases	Controls	OR ¹ (95% CI)
-	-	26	42	1.00
-	+	64	72	0.92 (0.48-1.78)
+	-	70	52	1.78 (0.94-3.37)
+	+	61	25	3.05 (1.49-6.25)

¹-. ALDH2G/G; +. ALDH2G/A and A/A; ORs were adjusted for income; ²-. Non-drinker; +. Drinker.

especially in alcohol drinkers. Alcohol drinkers carrying both ADH2 G allele and ALDH2 A allele have a higher risk of developing esophageal cancer.

There is no doubt that the differences in environment exposures/lifestyle influence the genetic susceptibility to cancer. There have been a lot of papers regarding the relationship between ADH2 and ALDH2 polymorphisms and esophageal cancer susceptibility. Chao *et al*^[10] found that Chinese alcoholic patients with the ADH G and ALDH2 A allele were more susceptible to esophageal cancer. Many studies found that the inactive ALDH2 genotypes had a significantly increased risk for developing esophageal cancer and that a gene-environment interaction exists between alcohol drinking and the inactive ALDH2 genotypes^[2,11-16]. Boonyaphiphat *et al*^[17] did not find ALDH2 increased the risk significantly (OR of ALDH G/A 1.57, 95% CI: 0.89-2.76). However, the combined at risk genotypes, ADH A/A and ALDH G/A increased risk by four-fold and heavy drinkers > 60 g/d harboring ADH A/A or ALDH G/A had about an 11-fold increased risk. Our previous study showed no statistically significant association between ALDH2 and esophageal cancer susceptibility^[7]. However, in this study with a larger sample size, we found that the ALDH2 A allele showed a moderately increased risk for esophageal cancer as compared with ALDH2 G/G carriers, and significant gene-environment interactions between alcohol drinking and ALDH2 were observed regarding esophageal cancer

risk ($S = 2.93$). The population attributable risk due to alcohol drinking by ALDH2 A allele carriers was estimated to be 41% for esophageal cancer. Yokoyama *et al*^[18] also found that an extraordinarily high proportion of excessive risk for esophageal cancer in Japanese males can be attributed to drinking by persons with inactive heterozygous ALDH2 (68.5%). Aldehyde dehydrogenase-2 generates acetic acid from acetaldehyde metabolism and its activity correlates with *in vivo* acetaldehyde concentration. Thus, diminished ALDH2 enzyme activity and consequent higher concentrations of acetaldehyde can be risk factors for esophageal cancer. In this study, we, for the first time, report that ALDH2 A/A homozygotes have higher esophageal cancer risk than ALDH2 G/A homozygotes, which is consistent with the different ALDH2 enzyme activity resulting from A/A and G/G genotypes. Literature has shown that after drinking, the blood acetaldehyde concentrations in those with ALDH2 A/A and G/A were 19- and 6-fold higher than in those with G/G genotype, respectively^[19].

In this study, we found the ADH G allele carriers were more susceptible to esophageal cancer, but no association was found between ADH2 genotypes and risk of esophageal cancer when disregarding drinking status. Compared with non-drinkers carrying both ALDH2 G/G and ADH2 A/A, drinkers carrying both ALDH2 A allele and ADH2 G allele showed a significantly higher risk of developing esophageal cancer (OR = 8.36, 95% CI: 2.98-23.46). The inactive ADH2 genotype has also been demonstrated to enhance the risk of esophageal cancer among alcoholics and the general population. The inactive ALDH2 genotype and ADH2 genotype carriers have higher risk of developing esophageal cancer, especially among alcohol drinkers^[11,13-18]. These findings conflicts with those demonstrating that the enzyme activity in ADH G allele was much higher than that of A allele. Yoshihara *et al*^[20] showed that there were no significant differences in blood ethanol and acetaldehyde concentrations between volunteers with ADH2*1 and without ADH2*1. Thus, the mechanism of the ADH2 polymorphism involved

in esophageal cancer risk may be associated with, not acetaldehyde, but a direct involvement of ethanol.

In summary, this study found that polymorphisms of the ADH2 and ALDH2 genes were significantly associated with the risk of esophageal cancer in Southeast Chinese males. Significant gene-environment interactions between alcohol drinking and ALDH2 were observed in esophageal cancer risk. Significant interactions between ADH2 and ALDH2 polymorphisms were also observed. These findings can provide additional information about the role of alcohol in esophageal cancer risk in Chinese populations. For individuals with ALDH2 A/A or G/A genotypes, reducing alcohol consumption may help lower their risk for esophageal cancer.

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COMMENTS

Background

Esophageal cancer is the most common cancer in China. There is epidemiological evidence that alcohol intake is associated with an increased esophageal cancer risk. Alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) have a strong impact on alcohol metabolism. The authors' previous study has shown that more than 40% of adult residents in Taixing drink wine and that drinking is a risk factor for esophageal cancer in this area. However, no statistically significant association between ALDH2 and the risk of esophageal cancer was found. In this study, the authors increased the sample size to define the individual and combined roles of ADH2, ALDH2 polymorphisms and drinking habits in the risk for esophageal cancer development in Chinese males.

Innovations and breakthroughs

The present study showed that polymorphisms of the ALDH2 genes were significantly associated with the risk of esophageal cancer in Southeast Chinese males. Significant gene-environment interactions between alcohol drinking and ALDH2 were observed in esophageal cancer risk. Significant interactions between ADH2 and ALDH2 polymorphisms were also observed.

Applications

This research showed the genetic risk factors and the role of gene-environment interactions in identifying individuals at risk of esophageal cancer, which have certain theoretical and application values for studying the etiology of esophageal cancer and its prevention.

Terminology

ADH2: A zinc-containing enzyme which oxidizes primary and secondary alcohols or hemiacetals in the presence of NAD. In alcoholic fermentation, it catalyzes the final step of reducing aldehyde to alcohol in the presence of NADH and hydrogen. ALDH2: An enzyme that oxidizes aldehyde in the presence of NAD⁺ and water to acid and NADH. Genetic polymorphisms: The regular and simultaneous occurrence of two or more discontinuous genotypes in a single interbreeding population. The concept includes differences in genotypes ranging in size from a single nucleotide site to large nucleotide sequences visible at a chromosomal level.

Peer review

This study provides more information on the ADH2 and ALDH2 polymorphisms of esophageal cancer in Southeast Chinese males and the findings support the previous results that the risk of esophageal cancer increases in subjects carrying ADH2*1 allele (G allele) and ALDH2*2 allele (A allele) in an overall population, and especially ALDH2*2 allele (A allele) in alcohol drinkers. These epidemiological findings might help construct a prevention strategy against esophageal cancer.

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