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Single Nucleotide Polymorphisms of *ADH1B*, *ADH1C* and *ALDH2* Genes and Esophageal Cancer: A Population-Based Case-Control Study in China

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Abstract

Alcohol drinking is a major risk factor for esophageal cancer (EC) and the metabolism of ethanol has been suggested to play an important role in esophageal carcinogenesis. Epidemiologic studies, including genome-wide association studies (GWAS), have identified single nucleotide polymorphisms (SNPs) in alcohol dehydrogenases (ADHs) and aldehyde dehydrogenases (ALDHs) to be associated with esophageal cancer. Using a population-based case-control study with 858 EC cases and 1,081 controls conducted in Jiangsu Province, China, we aimed to provide further information on the association of *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms with esophageal cancer in a Chinese population. Results showed that *ADH1B* (rs1229984) was associated with EC with odds ratios (ORs) of 1.34 (95% confidence interval: 1.08-1.66) for G-allele carriers compared to A/A homozygotes. No heterogeneity was detected on this association across different strata of alcohol drinking and tobacco smoking. Statistical interactions between *ALDH2* (rs671) and alcohol drinking on EC susceptibility in both additive and multiplicative scales were observed. Compared to G/G homozygotes, A-allele carriers were positively associated with EC among moderate/heavy drinkers (OR=1.64, 1.12-2.40) and inversely associated with EC among never/light drinks (OR=0.75, 0.54-1.03). In addition, statistical interaction between *ALDH2* and *ADH1B* polymorphisms on EC susceptibility among never/light drinkers was indicated. We did not observe association of *ADH1C* polymorphism with EC. In conclusion, our findings indicated that *ADH1B* (rs1229984) was associated with esophageal cancer independent of alcohol drinking and tobacco smoking status and alcohol

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drinking interacted with *ALDH2* (rs671) on esophageal cancer susceptibility in this high-risk Chinese population.

Keywords

alcohol dehydrogenase (ADH); aldehyde dehydrogenase (ALDH); alcohol; single nucleotide polymorphism (SNP); esophageal cancer

Introduction

Alcohol consumption has been established as a major risk factor for esophageal cancer (EC), which remains one of the most common and fatal malignancies worldwide [1-2]. Around 26% of deaths from EC could be attributed to alcohol use worldwide with attributable fractions ranging from 24% in low and middle income countries to 41% in high-income countries[3]. Although the biological mechanisms underlying alcohol-induced carcinogenesis have not been fully understood, the metabolism of ethanol has been suggested to play an important role in the development of EC [4-5]. In alcohol metabolism, alcohol dehydrogenases (ADHs) oxidize alcohol to acetaldehyde, which was classified as a Group I human carcinogen by the International Agency of Research on Cancer (IARC) [6]. When further oxidized, acetaldehyde produces less toxic acetic acid by aldehyde dehydrogenases (ALDHs) [7].

Single-nucleotide polymorphisms (SNPs) of ADH- and ALDH-related genes can lead to structural and functional changes of the enzymes which would influence acetaldehyde levels and may predispose people to cancers[8-9]. Among them, three functional SNPs, rs1229984 in *ADH1B*, rs698 in *ADH1C*, and rs671 in *ALDH2* have been frequently studied on their roles in alcoholism and carcinogenesis[8,9]. The *ADH1B* (rs1229984) A/A homodimer has been found to have a 40-fold higher enzyme activity than the G/G form[10]. Enzymes encoded by *ADH1C* (rs698) A allele have been shown to have a 2.5-times higher capacity oxidizing ethanol compared to those encoded by the G allele[10]. The *ALDH2* rs671 A allele encoded an inactive subunit with restrained ability to metabolize acetaldehyde. Blood acetaldehyde concentrations after consuming alcoholic beverages in individuals carrying *ALDH2* A/A and A/G genotype was 6-19 times higher than in those with the G/G genotype[11].

Epidemiologic studies, including genome-wide association studies (GWAS), have associated genetic variations in *ADHs* and *ALDHs* with EC susceptibility[12-16]. However, most studies had relatively small sample sizes which can suffer from limited statistical precision to detect interactions. In addition, few studies have investigated *ADH1C* and EC association among Asian populations. The primary aim of this large case-control study was to replicate the associations between esophageal cancer and genetic polymorphisms of *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) in a Chinese population. The joint effects and interactions between these polymorphisms and alcohol consumption and tobacco smoking status on EC susceptibility were also evaluated.

Materials and Methods

Study population

Study design has been previously described in detail[17-18]. In brief, this population-based case-control study was conducted from 2003 to 2007 in two counties, Dafeng and Ganyu, in Jiangsu province, one of the areas with the highest esophageal cancer mortality in South East China[19]. The annual average age-standardized incidence of EC was 36 and 24 per 100,000 in Dafeng and Ganyu during 2006-2008, respectively.

Eligible subjects were restricted to local residents who have lived in the study area for at least 5 years. Newly diagnosed primary esophageal cancer patients were recruited as cases, using the information from local population-based cancer registries. From 2003-2007, 68% and 75% of eligible cases were recruited and interviewed in Dafeng and Ganyu, respectively. Because of the low proportion of histologically confirmed cases in rural areas (39%), patients who were diagnosed by endoscopic examination (40%) or radiology (11%) were also included. Controls were randomly selected from the same county as cases in the county demographic database. Cases and controls were frequency matched by gender and age (±5 years). The response rate of controls was 87% in Dafeng and 85% in Ganyu.

This study was approved by the Institutional Review Board of Jiangsu Provincial Health Department. With written informed consent, epidemiological data were obtained by face-to-face interviews using a standardized questionnaire. The questionnaire collected information on demographic characteristics, socioeconomic status, living environment, smoking history, and dietary history. Lifetime alcohol consumption was also collected, including age started drinking, drinking frequency, years of drinking, weekly consumption (frequency and amount) on type-specific alcoholic beverages, and alcohol drinking cessation. A 5 ml non-fasting blood sample was collected during interview for both cases and controls.

Laboratory analysis

DNA was isolated from blood clots using phenol-chloroform method. SNPs were genotyped using the Taqman platform (Applied Biosystems [ABI], Foster City, CA) as previously described[20]. Genotype detection was performed on an ABI 7900HT sequence detection system with SDS2.3 software. Around 10% of the samples were randomly repeated for quality control. Call rates were above 95% and reproducibility was observed at 99.3%.

Statistical analysis

Data were entered into an Epidata 3.0 (EpiData Association, Odense, Denmark) database and cleaned and analyzed using SAS v9.1 (SAS Institute, Inc., Cary, NC, USA). Ever smokers were defined as those we have smoked for more than 100 cigarettes in their lifetime. Ever alcohol drinkers were defined as those who drank at least once per month. Average weekly consumption of ethanol (ml) was converted from weekly intake of six mostly consumed type-specific alcoholic beverages in Jiangsu area (high degree liquor, low degree liquor, beer, wheat liquor, rice liquor, and wine) according to average frequency and amount of drinking. We used median levels in the control group by gender to impute for 53

(4.4%) alcohol drinkers with missing values on weekly ethanol intake and 185 smokers (14%) with missing values on pack-years of smoking.

We used Pearson χ^2 test and student's t test to compare difference of distributions of selected demographic factors among cases and controls. Unconditional logistic regression models were applied for estimating the associations with odds ratios (ORs) and 95% confidence intervals (CIs). Potential confounders were selected based on prior knowledge, including age, sex (Male/Female), education level (Illiteracy, Primary school, Middle school & above), previous income (continuous), body mass index (BMI, continuous), smoking pack-years (continuous), family history of esophageal cancer (any malignancy in first-degree relatives) and study site (Ganyu, Dafeng). To minimize age confounding and to account for age matching, we used fine categories of age (under 50, 50-51, 52-53, 54-55, 56-57, 58-59, 60-61, 62-63, 64-65, 66-67, 68-69, 70-71, 72-73, 74-75, 76-77, 78-79, 80 and over) in the adjusted models.

Effect modifications were evaluated by stratified analyses. Gene-environmental and gene-gene interactions were assessed at both additive and multiplicative scales. The stratum with the lowest risk in joint effect models was used as the reference category in interaction analyses as suggested by Knol et al[21]. The multiplicative interaction was assessed by including both the main effect variables and their product terms in the logistic regression models. Three additive interaction measurements suggested by Knol, et al.[22], relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) were calculated. The 95% CI of RERI, AP, and SI were estimated by the delta method[23-24]. In the absence of an additive interaction, RERI and AP amount to 0 and SI amounts to 1.

Results

From 2003 to 2007, 1,520 cases and 1,683 controls were recruited in this study. However, because the quality of DNA samples was greatly improved after 2004, genotyping was only performed among those recruited after 2004. We did not observe difference between those who recruited before and after 2004 on basic demographic characteristics. A total of 846 EC cases and 1,079 controls were included in this analysis. Compared to population controls, cases had lower levels of education, previous income, and BMI (Table 1). More cases were males, smokers, and had family history of EC than controls.

Ever alcohol drinking was associated with increased risk of EC with OR of 1.43 (95% CI: 1.12-1.84), after adjusting for potential confounders (Table 2). Positive dose-response relationships were observed with increased frequency and amount of alcohol drinking (*P* for trend <0.001). Compared to never alcohol drinkers, the ORs for consuming ethanol for 250-500 ml/week and for at least 500 ml/week were 1.62 (95% CI: 1.16 -2.26) and 1.72 (95% CI: 1.28-2.32), respectively. We found similar results using imputed weekly ethanol consumption.

Genotype distributions of *ADH1B* (rs1229984), *ADH1C* (rs698) and *ALDH2* (rs671) among controls were all in agreement with Hardy-Weinberg equilibrium (P>0.05). After adjusting

for potential confounders, the inactive *ADH1B* (rs1229984) G-allele was positively associated with EC with ORs of 1.88 (95% CI: 1.34-2.64) for G/G homozygotes and 1.19 (95% CI: 0.94-1.51) for A/G heterozygotes, as compared to individuals with the A/A genotype (Table 3). The OR was 1.34 (95% CI: 1.08-1.66) in dominant model. We did not observe strong main effects of *ADH1C* (rs698) and *ALDH2* (rs671) polymorphisms on EC susceptibility.

ADH1B (rs1229984) G-allele carriers had consistent 30% increased odds of having EC compared to A/A homozygotes across different strata of alcohol drinking and tobacco smoking (Table 4 and Table 5). In join-effect analysis, the highest odds were observed among moderate/heavy drinkers (consumed 250 ml ethanol or more per week) with the G/G genotype (OR=3.58, 95% CI: 2.20, 5.84) as compared to never/light drinkers (consumed less than 250 ml ethanol per week) with the A/A genotype, and among smokers with the G/G genotype (OR=3.62, 95% CI: 2.23, 5.87) as compared to never smokers with the A/A genotype. *ALDH2* (rs671) A-allele carriers were associated with increased odds of EC among moderate/heavy drinkers and reduced odds of EC among never/light drinkers, while compared to G/G homozygotes. Statistical interactions were detected between *ALDH2* (rs671) and alcohol drinking on esophageal cancer susceptibility in both additive and multiplicative scales. Moderate/heavy drinkers with the *ALDH2* A/G genotype had the highest risk of EC (OR=2.34, 95% CI: 1.52-3.61) in joint-effect analysis, as compared to never/light drinkers with the G/G genotype.

Although gene-gene interaction was not detected, among moderate/heavy drinkers, the joint effect of *ALDH2* and *ADHs* polymorphisms showed that the highest odds of EC was observed among those carrying *ALDH2* A and *ADHs* G alleles (OR=2.35, 95% CI: 1.40-3.94 for *ADH1B*; OR=1.96, 95% CI: 0.94-4.09 for *ADH1C*), as compared to those with *ALDH2* G/G and *ADHs* A/A genotype (Table 6). Among never/light drinkers, statistical interactions between *ALDH2* and *ADH1B* were observed in both additive and multiplicative scales.

Discussion

In this population-based case-control study among Chinese population, we reported that *ADH1B* (rs1229984) polymorphism was associated with esophageal cancer and this association was consistently seen across different strata of alcohol drinking and tobacco smoking behaviours. We observed statistical interaction between alcohol drinking and *ALDH2* (rs671) polymorphism on EC susceptibility, with positive association among moderate/heavy drinkers and inverse association among never/light drinkers. In addition, we found statistical interaction between *ALDH2* (rs671) and *ADH1B* (rs1229984) on EC susceptibility among never/light drinkers. Although gene-gene interaction was not detected among moderate/heavy drinkers, the highest odds of EC were observed among those carrying *ALDH2* A allele and *ADHs* G allele.

Our results on *ADH1B* (rs1229984) were in accordance with previous studies[12, 14, 16]. In a meta-analysis across Chinese and Japanese populations, the ORs for those with *ADH1B* A/G and G/G genotype compared to the A/A genotype were 1.60 (95% CI: 1.25-2.00) and 2.17

(95% CI: 1.08-4.34), respectively[16]. In recent GWASs, *ADH1B* (rs1229984) has also been identified to be associated with EC with ORs of 1.79 (95% CI: 1.69-1.88) for the G allele in Japanese populations[12] and 0.38 (95% CI: 0.24-0.59) for the A allele in European populations[14]. Several reasons could contribute to the excess risk of the G allele. First, in contrast with the less active G allele, the fast-metabolizing A allele may prevent people from heavy drinking because of higher concentration of acetaldehyde after drinking which results in ethanol intolerance at low doses. Several studies have reported that G allele was associated with increased intensity of alcohol drinking[25-26]. However, we consistently observed the association across different strata of alcohol drinking. Second, G allele carriers may experience longer exposure time to both ethanol and acetaldehyde after drinking than A allele carriers. Yokoyama et al. have demonstrated that the salivary and blood ethanol and acetaldehyde levels were higher in G allele carriers than those carry the A allele[27]. Increased salivary acetaldehyde production could result from oral microorganism overgrowth due to prolonged ethanol exposure resulted from less ADH1B activity.

The inactive *ALDH2* (rs671) A allele is rare in Western populations, but is highly prevalent and mostly studied among Eastern Asians on its association with cancer, especially among Chinese and Japanese[8, 12-13, 15-16, 28]. In agreement with most studies, we detected statistical interaction between *ALDH2* (rs671) and EC and observed that while compared to those with the G/G genotype, A allele carriers were associated with increased odds of EC among moderate/heavy drinkers, but not among never/light drinkers. A Chinese GWAS indicated multiplicative interaction between alcohol drinking and rs11066015 of *ACAD10* (in high linkage disequilibrium [LD] with rs671, r^2=0.79) on esophageal squamous cell carcinoma (ESCC) risk, with more pronounced risk enhancement seen in drinkers (interaction $P = 4.54 \times 10^{-34}$)[15]. In a meta-analysis including 18 studies[16], increased risk was found among moderate/heavy drinkers, while no clear association observed among never/rare drinkers. The increased risk of A-allele carriers among moderate/heavy drinkers was biologically relevant, indicating the harmful effect of accumulated acetaldehyde after alcohol drinking[9]. The reduced risk among never/light drinkers, however, were in agreement with some studies[29-30] and in disagreement with some others[31-33] and warrants further studies. A Japanese GWA study suggested a reduced risk of EC for A/A homozygotes compared to G/G homozygotes (OR = 0.47, 95% CI: 0.28-0.78)[12]. Prevention of alcohol drinking among A/A homozygotes because of severe alcohol flush responses has been proposed as one of the mechanisms for the risk reduction[12]. In this study, we observed similar inverse association among A/A homozygotes. However, the small sample size of the A/A homozygotes make the effect estimates vulnerable to shifts and further elucidation of this association is needed.

Alcohol drinking could mediate the association of *ADHs* and *ALDHs* SNPs with EC and we found that subjects with the fast genotype of *ADH1B* (A/A) and the slow genotype of *ALDH2* (A/A) drank less, even within strata of alcohol drinking intensity (Supplementary Table S1 and S2). To examine effect of SNPs on EC not mediated through alcohol drinking, we further adjusted on weekly ethanol intake for the main- and stratified-association of *ADH1B* (rs1229984) and *ALDH2* (rs671) on EC and did not find much difference of the results with and without the adjustment (data not shown). Furthermore, we found both polymorphisms to be associated with EC among never alcohol drinkers ($OR_{A/G+G/G \text{ vs. } A/A}$

= 1.41, 95% CI: 1.00-2.01 for *ADH1B*; $OR_{A/G+A/A \text{ vs. } G/G}$ = 0.69, 95% CI: 0.48-1.00 for *ALDH2*; data not shown), which suggested that *ADH1B* and *ALDH2* may be associated with EC through pathways in addition to alcohol drinking.

Although we did not detect gene-gene interaction between *ALDH2* (rs671) and *ADH1B* (rs1229984) on EC among moderate/heavy drinkers, the highest risk of esophageal cancer was found on those carrying *ALDH2* A allele and *ADHs* G allele. Similar associations have been reported by several studies[12, 16, 30-31, 33-36]. In a meta-analysis, the highest risk of esophageal cancer was observed among heavy drinkers with *ADH1B* G/G and *ALDH2* A/G genotype (OR=12.45, 95% CI: 2.9-53.46), as compared to those with *ADH1B* any A and *ALDH2* G/G genotype[16]. In the Japanese GWAS which identified both rs671 and rs1229984 as risk loci for esophageal cancer, individuals with *ADH1B* G/G and *ALDH2* A/G genotype had a remarkably higher risk (OR=16.17, 95% CI: 11.55-22.65) than those with *ADH1B* any A and *ALDH2* A/A or G/G genotype[12]. Interestingly, statistical interaction of *ALDH2* and *ADH1B* on EC was indicated among never/light drinkers in our study, with the highest risk observed among those with *ALDH2* G/G and *ADH1B* any G genotype. This association may need further investigation.

We did not observe association of *ADH1C* (rs698) with EC in this study. Different from *ADH1B* and *ALDH2*, *ADH1C* (rs698) polymorphism is the rate-limiting factor in alcohol metabolism among Western populations and studies from European origins have associated *ADH1C* polymorphism with EC[14, 37]. *ADH1B* and *ADH1C* genes are closely located in the short arm of chromosome 4, and strong LD (D′ >0.75) has been reported by previous studies including Asians[26, 37-40]. The role of *ADH1C* in esophageal carcinogenesis independent of *ADH1B* has been observed to be controversial. A Japanese study reported the association between *ADH1C* and EC disappeared after the adjustment on *ALDH2* and *ADH1B* genotypes in multiple logistic models[41]. However, a study in Europe indicated that *ADH1B* and *ADH1C* had independent association with upper aerodigestive tract (UADT) cancers, despite of their strong LD[37]. Linkage disequilibrium between *ADH1B* (rs1229984) and *ADH1C* (rs698) in our study was minor (r^2=0.16, D'=0.41) and could possibly explain the lack of association between *ADH1C* (rs698) and EC. Results on *ADH1C* (rs698) polymorphism and EC remain sparse and inconsistent, and need to be further elucidated.

There are several limitations in this present analysis. First, 4.4% of alcohol drinkers had missing information on weekly ethanol intake and 14.4% of smokers had missing information on pack-years of smoking. Instead of using medians in controls for missing imputation, we also performed multiple imputations in SAS with the Proc MI and the Proc Mianalyze procedures and only found limited differences between the results. Second, although the questionnaire had been tested in previous studies, the self-reported exposure level of alcohol drinking may be vulnerable to subjective judgement and recall bias which could cause misclassification of exposures. However, the strength of the associations for EC with alcohol consumption, particularly the dose-response trend indicates good validity and sensitivity of our study. Third, cases were in mixed histology in this population-based study because of the low proportion of pathological examinations in less developed rural areas. However, previous reports have indicated that more than 95% of esophageal cancers in China are ESCC[42]. And last, only subjects recruited after 2004 were involved in this study.

However, no major difference on basic characteristics between this study population and the complete population has been found.

In conclusion, *ADH1B* (rs1229984) polymorphism was associated with esophageal cancer in this high-risk Chinese population. Gene-environment interaction between alcohol drinking and *ALDH2* (rs671) polymorphism on esophageal cancer susceptibility was observed. Moderate/heavy drinkers carrying *ALDH2* A allele and *ADHs* G allele had the highest risk of esophageal cancer. Genetic predispositions, together with lifestyle factors may ultimately determine individual's risk of esophageal cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

EC	Esophageal cancer
ADHs	alcohol dehydrogenases
IARC	International Agency of Research on Cancer
ALDHs	aldehyde dehydrogenases
SNPs	single-nucleotide polymorphisms
GWAS	genome-wide association studies
ABI	Applied Biosystems
ORs	odds ratios
CIs	confidence intervals
BMI	body mass index
RERI	relative excess risk due to interaction
AP	attributable proportion due to interaction
SI	synergy index
LD	linkage disequilibrium
ESCC	esophageal squamous cell carcinoma
UADT	upper aerodigestive tract

Novelty & Impact

In this large population-based case-control study in China, we reported an association of *ADH1B* (rs1229984) with esophageal cancer independent of alcohol drinking and tobacco smoking status. Multiplicative interactions between alcohol drinking and *ALDH2* (rs671) and between *ADH1B* (rs1229984) and *ALDH2* (rs671) among never/light drinkers were detected. The results from this study provide further evidence on effect modification of alcohol drinking on the association of *ADHs* and *ALDHs* polymorphisms with esophageal cancer in Chinese population.

Table 1

Distributions of selected demographic characteristics among cases and controls[1]

	Cases (%) (N=846)	Controls (%) (N=1079)	*P*-Value[3]
Gender*			
Male	663 (78.4)	782 (72.5)	0.003
Female	183 (21.6)	297 (27.5)	
Age*			
Mean±SD (years)	63.7±9.4	63.7±10.3	0.939
<50	59 (7.0)	101 (9.4)	
50-60	217 (25.7)	229 (21.2)	
60-70	335 (39.6)	426 (39.5)	0.087
70-80	201 (23.8)	273(25.3)	
≥80	34 (4.0)	50 (4.6)	
Education level			
Illiteracy	481 (56.9)	494 (45.8)	
Primary school	264 (31.2)	387 (35.9)	<0.001
Middle school & above	101 (11.9)	198 (18.4)	
Previous income (RMB)			
<1000	196 (23.5)	164 (15.3)	
1000-1500	162 (19.4)	195 (18.2)	<0.001
15002500	149 (17.8)	154 (14.4)	
≥2500	328 (39.3)	559 (52.2)	
Body Mass Index (BMI)[2]			
Mean±SD	21.5±3.6	22.7±7.4	<0.001
Low (<18.5)	138 (16.3)	84 (7.8)	
Normal (18.5-23.9)	569 (67.3)	693 (64.3)	
Overweight (24-27.9)	111 (13.1)	250 (23.2)	<0.001
Obesity (≥28)	27 (3.2)	51 (4.7)	
Smoking, packyears			
Mean±SD (years)	36.4±22.2	33.8±23.7	0.0564
Never	212 (30.0)	419 (40.5)	
<30	197 (27.9)	300 (29.0)	<0.001
≥30	297 (42.1)	315 (30.5)	
Family history of esophageal caner			
No	676 (80.3)	904 (84.0)	0.033
Yes	166 (19.7)	172 (16.0)	

[1] Missing data were excluded from analysis;

[2] Chinese recommend standard was used for the cut-off points for overweight and obesity;

[3] P-value from the Pearson χ^2 test (for categorical variables) and student's t test (for continuous variables) comparing cases and controls.

* Matching variable.

Table 2
Association between alcohol drinking and the risk of esophageal cancer

	Case (%) (N=846)	Control (%) (N=1,079)	OR (95% CI)[1]	OR (95% CI)[2]
Alcohol consumption				
Never	264 (31.2)	456 (42.3)	1.00	1.00
Ever	582 (68.8)	623 (57.7)	1.52 (1.20, 1.93)	1.43 (1.12, 1.84)
Drinking frequency				
Never	264 (31.2)	456 (42.3)	1.00	1.00
Occasional	135 (16.0)	168 (15.6)	1.23 (0.89, 1.70)	1.28 (0.92, 1.79)
Often	156 (18.4)	137 (12.7)	1.59 (1.15, 2.21)	1.45 (1.03, 2.04)
Everyday	291 (34.4)	317 (29.4)	1.69 (1.29, 2.22)	1.54 (1.15, 2.06)
P for trend			<0.001	0.0031
Average ethanol intake (ml/week)				
Never	264 (32.7)	456 (42.9)	1.00	1.00
1-250	85 (10.5)	165 (15.5)	1.03 (0.74, 1.44)	0.96 (0.68, 1.37)
250-500	157 (19.4)	170 (16.0)	1.63 (1.19, 2.24)	1.62 (1.16, 2.26)
≥500	302 (37.4)	273 (25.7)	1.84 (1.39, 2.44)	1.72 (1.28, 2.32)
P for trend			<0.001	<0.001
Average ethanol intake (ml/week) (Imputed)*				
Never	264 (31.2)	456 (42.3)	1.00	1.00
1-250	87 (10.3)	166 (15.4)	1.04 (0.74, 1.45)	0.97 (0.68, 1.38)
250-500	193 (22.8)	184 (17.1)	1.69 (1.24, 2.30)	1.68 (1.22, 2.32)
≥500	302 (35.7)	273 (25.3)	1.84 (1.39, 2.45)	1.71 (1.27, 2.30)
P for trend			<0.001	<0.001

[1] Adjusted on age, gender and study area;

[2] Further adjusted on education, previous income, BMI, smoking pack-years, and family history of esophageal cancer.

* The medians of the ethanol intake in the control group by gender were used for imputation.

Table 3

Distribution of ADH1B, ADH1C and ALDH2 polymorphisms and their associations with esophageal cancer

	Case (%) (N=858)	Control (%) (N=1,081)	OR (95% CI)[1]	OR (95% CI) [2]
ADH1B (rs1229984)				
A/A (fast)	355 (44.3)	510 (50.0)	1.00	1.00
A/G	309 (38.5)	410 (40.2)	1.18 (0.94, 1.47)	1.19 (0.94, 1.51)
G/G (slow)	138 (17.2)	101 (9.9)	1.89 (1.37, 2.61)	1.88 (1.34, 2.64)
P for trend			<0.001	0.0005
A/G+GG	447 (55.7)	511 (50.0)	1.32 (1.08, 1.63)	1.34 (1.08, 1.66)
ADH1C (rs698)				
A/A (fast)	671 (83.0)	844 (82.3)	1.00	1.00
A/G	124 (15.4)	171 (16.7)	0.97 (0.73, 1.28)	0.97 (0.72, 1.30)
G/G (slow)	13 (1.6)	10 (1.0)	1.21 (0.47, 3.11)	1.08 (0.39, 2.97)
P for trend			0.9962	0.9002
A/G+GG	137 (17.0)	181 (17.7)	0.99 (0.75, 1.29)	0.97 (0.73, 1.29)
ALDH2 (rs671)				
G/G (fast)	523 (65.3)	645 (62.8)	1.00	1.00
A/G	245 (30.6)	337 (32.8)	0.95 (0.76, 1.18)	0.92 (0.73, 1.17)
A/A (slow)	33 (4.1)	45 (4.4)	0.71 (0.42, 1.21)	0.68 (0.39, 1.19)
P for trend			0.2699	0.1954
A/G+A/A	278 (34.7)	382 (37.2)	0.92 (0.74, 1.14)	0.89 (0.71, 1.12)

[1] Adjusted on age, gender and study area;

[2] Further adjusted on education level, previous income, BMI, smoking pack-years, and family history of esophageal cancer.

Table 4

Joint effects between ADH1B, ADH1C and ALDH2 polymorphisms and alcohol drinking on esophageal cancer

Genotype	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
	Alcohol Drinking Amount (ml ethanol/week)			
	Never/light (< 250ml/wk)		Moderate/heavy (≥ 250ml/wk)	
ADH1B (rs1229984)				
A/A (fast)	146/305	1.00 (referent)	195/199	1.67 (1.18, 2.37)
A/G	142/232	1.28 (0.92, 1.77)	154/170	1.88 (1.31, 2.70)
G/G (slow)	42/54	1.39 (0.84, 2.31)	87/46	3.58 (2.20, 5.84)
Stratified analysis				
A/A		1.00 (referent)		1.00 (referent)
A/G+G/G		1.31 (0.96, 1.78)		1.37 (1.00, 1.89)
Interaction				
A/A		1.00 (referent)		1.67 (1.18, 2.36)
A/G+G/G		1.30 (0.96, 1.77)		2.25 (1.61, 3.15)
Additive		RERI = 0.28 (-0.42, 0.98)		
		AP = 0.13 (-0.18, 0.43)		
		S = 1.29 (0.65, 2.57)		
Multiplicative		ROR = 1.04 (0.67, 1.61)		
ADH1C (rs698)				
A/A (fast)	274/482	1.00 (referent)	365/349	1.59 (1.21, 2.09)
A/G	54/106	0.82 (0.54, 1.23)	66/63	1.92 (1.22, 3.02)
G/G(slow)	4/6	0.65 (0.15, 2.81)	8/4	2.65 (0.62, 11.27)
Stratified analysis				
A/A		1.00 (referent)		1.00 (referent)
A/G+G/G		0.81 (0.54, 1.21)		1.24 (0.81, 1.91)
Interaction				
A/A		1.24 (0.83, 1.84)		1.97 (1.30, 3.00)
A/G+G/G		1.00 (referent)		2.44 (1.42, 4.20)
Additive		RERI = -0.71 (-1.90, 0.49)		
		AP = -0.36 (-0.93, 0.22)		
		S = 0.58 (0.29, 1.15)		
Multiplicative		ROR = 0.65 (0.37-1.17)		
ALDH2 (rs671)				
G/G (fast)	191/301	1.00 (referent)	310/336	1.35 (0.99, 1.85)
A/G	112/254	0.74 (0.53, 1.02)	120/77	2.34 (1.52, 3.61)
A/A (Slow)	22/38	0.84 (0.44, 1.59)	10/6	0.91 (0.28, 2.96)
Stratified analysis				
G/G		1.00 (referent)		1.00 (referent)
A/G+A/A		0.75 (0.54, 1.03)		1.64 (1.12, 2.40)

Genotype	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
	Alcohol Drinking Amount (ml ethanol/week)			
	Never/light (< 250ml/wk)		Moderate/heavy (≥ 250ml/wk)	
Interaction				
G/G		1.33 (0.97, 1.83)		1.80 (1.33, 2.45)
A/G+A/A		1.00 (referent)		2.92 (1.93, 4.43)
Additive		RERI = -1.46 (-2.65, -0.26)		
		AP = -0.81 (-1.46, -0.16)		
		S = 0.36 (0.19, 0.65)		
Multiplicative		ROR = 0.46 (0.28, 0.75)		

* ORs were adjusted on age, gender, study area, education level, previous income, BMI, smoking pack-years, and family history of esophageal cancer.

Table 5

Joint effects between ADH1B, ADH1C and ALDH2 polymorphisms and tobacco smoking on esophageal cancer

Genotype	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
		Tobacco Smoking		
		Never		Ever
ADH1B (rs1229984)				
A/A (fast))	82/198	1.00 (referent)	273/312	1.75 (1.22, 2.51)
A/G	86/160	1.30 (0.85, 1.97)	223/250	1.95 (1.34, 2.84)
G/G (slow)	32/45	1.62 (0.89, 2.96)	106/56	3.62 (2.23, 5.87)
Stratified analysis				
A/A		1.00 (referent)		1.00 (referent)
A/G+G/G		1.38 (0.94, 2.03)		1.28 (0.98, 1.67)
Interaction				
A/A		1.00 (referent)		1.75 (1.22, 2.52)
A/G+G/G		1.37 (0.93, 2.03)		2.28 (1.59, 3.27)
Additive		RERI = 0.15 (-0.53, 0.84)		
		AP = 0.07 (-0.23, 0.37)		
		S = 1.14 (0.62, 2.10)		
Multiplicative		OR = 0.94 (0.59, 1.52)		
ADH1C (rs698)				
A/A (fast)	166/322	1.00 (referent)	505/522	1.66 (1.25, 2.19)
A/G	31/78	0.78 (0.46, 1.32)	93/93	1.76 (1.18, 2.64)
G/G(slow)	2/5	1.09 (0.16, 7.25)	11/5	1.88 (0.56, 6.28)
Stratified analysis				
A/A		1.00 (referent)		1.00 (referent)
A/G+G/G		0.81 (0.49, 1.34)		1.07 (0.75, 1.52)
Interaction				
A/A		1.26 (0.75, 2.09)		2.08 (1.27, 3.41)
A/G+G/G		1.00 (referent)		2.23 (1.26, 3.93)
Additive		RERI = -0.40 (-1.44, 0.63)		
		AP = -0.19 (-0.65, 0.26)		
		S = 0.73 (0.40, 1.34)		
Multiplicative		OR = 0.74 (0.40, 1.38)		
ALDH2 (rs671)				
G/G (fast)	134/247	1.00 (referent)	389/398	1.65 (1.21, 2.25)
A/G	54/134	0.87 (0.56, 1.34)	191/203	1.58 (1.11, 2.24)
A/A (Slow)	9/21	0.71 (0.27, 1.83)	24/24	1.13 (0.55, 2.31)
Stratified analysis				
G/G		1.00 (referent)		1.00 (referent)
A/G+A/A		0.84 (0.56, 1.26)		0.91 (0.69, 1.20)

Genotype	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
		Tobacco Smoking		
		Never		**Ever**
Interaction				
G/G		1.19 (0.78, 1.79)		1.95 (1.33, 2.87)
A/G+A/A		1.00 (referent)		1.81 (1.20, 2.73)
Additive		RERI = -0.04 (-0.72, 0.64)		
		AP = -0.02 (-0.37, 0.32)		
		S = 0.96 (0.49, 1.88)		
Multiplicative		OR = 0.91 (0.56, 1.49)		

* ORs were adjusted on age, gender, study area, education level, previous income, BMI, and family history of esophageal cancer.

Table 6

Joint effects between ALDH2 and ADHs polymorphisms on esophageal cancer, stratified on alcohol drinking status

SNP1	SNP2	Case/Control	OR (95% CI)	Case/Control	OR (95% CI)
		Alcohol Drinking Amount (ml ethanol/week)			
		Never/light (<250ml/week)		Moderate/heavy (≥250ml/week)	
ALDH2	**ADH1B**				
G/G	A/A	75/160	1.03 (0.65, 1.63)	141/165	1.00 (referent)
G/G	A/G+G/G	109/134	1.92 (1.23, 2.99)	160/168	1.33 (0.92, 1.92)
A/G+A/A	A/A	65/142	1.16 (0.73, 1.84)	49/33	1.50 (0.83, 2.72)
A/G+A/A	A/G+G/G	69/148	1.00 (referent)	77/46	2.35 (1.40, 3.94)
Interction					
Additive		RERI = -1.05 (-2.05, -0.04)		RERI = 0.52 (-0.82, 1.87)	
		AP = -1.02 (-1.99, -0.05)		AP = 0.22 (-0.29, 0.73)	
		S = 0.03 (0.00, 328532.89)		S = 1.63 (0.42, 6.35)	
Multiplicative		OR = 0.46 (0.25-0.87)		OR = 1.18 (0.55, 2.56)	
ALDH2	**ADH1C**				
G/G	A/A	149/243	1.98 (1.05, 3.72)	255/283	1.00 (referent)
G/G	A/G+G/G	40/53	1.96 (0.93, 4.16)	47/48	1.22 (0.73, 2.05)
A/G+A/A	A/A	113/233	1.56 (0.82, 2.95)	103/63	1.62 (1.06, 2.49)
A/G+A/A	A/G+G/G	18/58	1.00 (referent)	26/18	1.96 (0.94, 4.09)
Interction					
Additive		RERI = -0.55 (-1.97, 0.88)		RERI = 0.11 (-1.51, 1.74)	
		AP = -0.28 (-0.93, 0.38)		AP = 0.06 (-0.74, 0.85)	
		S = 0.64 (0.28, 1.47)		S = 1.13 (0.19, 6.65)	
Multiplicative		OR = 0.65 (0.28, 1.47)		OR = 0.99 (0.38, 2.55)	

*ORs were adjusted on age, gender, study area, education level, previous income, BMI, smoking pack-years, and family history of esophageal cancer.