RESEARCH COMMUNICATION

Alcohol Dehydrogenase-2 and Aldehyde Dehydrogenase-2 Genotypes, Alcohol Drinking and the Risk for Stomach Cancer in Chinese Males

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Abstract

Objective: To investigate the relationship among alcohol dehydrogenase-2 (ADH2) and aldehyde dehydrogenase-2 (ALDH2) genetic polymorphisms, alcohol consumption, and the susceptibility of stomach cancer in Chinese males. Methods: Three hundred and eighty-two stomach cancer patients and 382 healthy controls from Taixing and Changshu city of Jiangsu province were enrolled in this study. ADH2 and ALDH2 genotypes were examined by PCR and denaturing high-performance liquid chromatography (DHPLC). Unconditional logistic regression was used to calculate the odds ratios (OR) and 95% confidence intervals (95% CI). Results: (1) In no drinkers, compared with ALDH2G/G carriers, ALDH2 G/A (OR=1.67, 95%CI: 1.01-2.78) carriers showed a significantly elevated risk of developing stomach cancer. No association was found between ADH2 genotypes and risk of stomach cancer. (2) ALDH2 A allele carriers with cumulative amount of alcohol consumption ≥2.5 (Kg * years) were at a higher risk of developing stomach cancer compared with those with cumulative amount of alcohol consumption <2.5Kg (Kg * years) (OR=2.72, 95%CI:0.89-8.31) and ALDH2 G/G carriers with cumulative amount of alcohol consumption <2.5 (Kg * years) (OR=2.46, 95%CI=0.90-6.72) or ≥2.5 (Kg * years) (OR=2.53, 95%CI=0.86-7.49). (3) Compared with individuals with ADH2 A/A and ALDH2 G/G genotypes, ADH2 G and ALDH2 A allele carriers were not at a high risk of developing stomach cancer, with regard to the status of alcohol consumption, and even cumulative amount of alcohol consumption ≥1.5 (Kg * years) (OR =1.65, 95%CI:0.56-4.82). Conclusion: ADH2 and ALDH2 polymorphisms and alcohol drinking may not play an important role in the development of stomach cancer in Chinese males.

Keywords: Stomach cancer - alcohol drinking - ADH2 - ALDH2 - case-control study

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Introduction

Ethanol is oxidized first to acetaldehyde and then to acetate by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) in the liver. Acetaldehyde is recognized to be carcinogenic in animals and suspected to have similar effects on human beings (Matsuo et al., 2001). Since acetaldehyde accumulates in the blood causing uncomfortable symptoms of facial flushing, palpitation and headache, even when a small amount of alcohol is consumed, greater alcohol consumption is often limited in sensitive individuals. Most of the acetaldehyde generated during alcohol metabolism in vivo is promptly eliminated by ALDH2, a low-Km mitochondrial ALDH (Bosron and Li, 1986). The gene for the homotetrameric enzyme ALDH2 has a polymorphism and its mutant ALDH2 *2 allele (Glu487Lys, Lys or A allele) encodes a catalytically inactive subunit (Yoshida et al., 1991). ADH2 is also polymorphic and its mutant ADH2*2 allele (Arg47His) encodes a superactive subunit of ADH2 (Bosron and Li, 1986; Yoshida et al., 1991). Inactive ALDH2 and superactive ADH2 are considered to contribute to alcohol flushing and prevent people from developing alcoholism (Harada et al., 1982; Thomasson et al., 1991; Chen et al., 1998).

Stomach cancer is the fourth most common cancer and the second most common cause of cancer death in the world. There is little epidemiologic evidence that alcoholic beverages play a causal role in stomach cancer (Freedman et al., 2007). However, in animal model, alcohol drinking causes DNA damage in stomach, which was ALDH2 genotype-dependent (Nagayoshi et al., 2009). It suggests that heavy-alcohol drinking and ALDH2 deficiency might be risk factors of stomach cancer.

A meta analysis showed that drinking is a risk factor of stomach cancer in Chinese (Zhou et al., 2006). Jiangsu province is one of the highest incidence rates for stomach cancer in China. The mortality rates for gastric cancer is 34.92 per 100,000 and is 16% of the rates for cancers (Zhou et al., 2008). Our previous screen also have found

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that drinking was associated with increased stomach cancer in this area (Ding et al., 2001). We have studied the association between polymorphisms of the ADH2 and ALDH2 and esophageal, liver and colorectal cancer susceptibility in previous studies (Gao et al., 2008; Ding et al., 2008; 2009; 2010). In this study, we attempted to define the role of ADH2 and ALDH2 polymorphisms and drinking habit in the development of stomach cancer in Jiangsu males.

Materials and Methods

Study Subjects

We recruited 382 patients who were histopathologically diagnosed as having stomach cancer from January 2005 to December 2006. Population-based 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 factor, information of alcohol drinking included whether the subject had been an alcoholic in his lifetime, what year the subject started and quitted, the duration of consumption and the daily amount consumed, and type of alcoholic beverage consumed. The interviewer then collected the 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. A few patients and residents refused to participate in our study, but the overall response rate was 96% for patients and controls. 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

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).[13] 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 and 95% confidence intervals were adjusted by unconditional logistic regression analysis. The Mantel-Haenszel χ^2 method was used to test for significant associations between the ADH2 or ALDH2 genotype and cancer risk. We defined a drinker as a person who drinks at least once per week (absolute ethanol intake more than 40 g) and continuously drinks at least half a year. Lifetime consumption of alcoholic beverage was calculated by multiplying the concentration of alcohol in the consumed beverage by the amount consumed per day by the number of years consumed, resulting in number (cumulative amounts of alcohol consumption) designated as kilogram (Kg) *year. One "kg * year" was defined as drinking absolute ethanol one kg per day and continuously drinking for one year.

Results

The proportional distributions of age, smoking and drinking were not significantly differ in cases and controls, but distributions of occupation, education were significant differ (P<0.01) (Table 1). The proportional distribution of income (ten years before) were significant lower in cases than in controls (P=0.02).

As shown in Table 2, the frequency of the ALDH2 and ADH2 genotypes demonstrated no significant differences between cases and controls. The allelic distribution of ADH2 and ALDH2 polymorphism was in Hardy-Weinberg equilibrium (P>0.05).

In no drinkers, compared with ALDH2G/G carriers,

Table 1. Background Characteristics of Cases and Their Controls

	Controls		Cases		χ^2_{MH}	P
	No.	%	No.	%		
Age (years)						
<50	21	5.50	24	6.28		
50-59	105	27.49	105	27.49		
60-69	147	38.48	137	35.86		
>70	109	28.53	116	30.37	0.77	0.86
Income(yuan/year/person)*						
Ten years before	3153		2719			0.02
Recent years	5655		5638			0.97
Drinking status						
Nondrinker	184	48.17	178	46.60		
Drinker	198	51.83	204	53.40	0.19	0.66
Education						
Junior and before	248	64.92	290	75.92		
After Junior	134	35.08	92	24.08	11.08	<0.01
Occupation						
Farmer	215	56.28	257	67.28		
Others	167	43.72	125	32.72	9.78	<0.01

*T-test result

Table 2. Adjusted Odds Ratios (ORs) and Their 95% Confidence Intervals (CIs) for Stomach Cancer with Reference to ALDH2 and ADH2 Polymorphisms

	Controls (%)	Cases (%)	ORa (95%CI)	ORb (95%CI)
ALDH2 genotype				
G/G	206 (53.93)	196 (51.31)	1.00	1.00
G/A	155 (40.58)	161 (42.15)	1.09 (0.81-1.47)	1.13 (0.83-1.53)
A/A	21 (5.49)	25 (6.54)	1.25 (0.68-2.30)	1.15 (0.60-2.17)
G/A+A/A	176 (46.07)	186 (48.69)	1.11 (0.84-1.48)	1.13 (0.84-1.52)
ADH2 genotype				
A/A	193 (50.52)	194 (50.79)	1.00	1.00
G/A	160 (41.88)	148 (38.74)	0.92 (0.68-1.24)	0.84 (0.61-1.15)
G/G	29 (7.60)	40 (10.47)	1.37 (0.82-2.30)	1.49 (0.86-2.56)
G/A+G/G	189 (49.48)	188 (49.21)	0.99 (0.75-1.31)	0.93 (0.69-1.26)

aCrude OR; bORs was adjusted for occupation, education and income (ten years before)

Table 3. Analysis of ALDH2 and ADH2 Genotypes and Risk of Stomach Cancer with Reference to Drinking Habits

Genotypes		No drinker			Drinker		
		cases	controls	ORa(95%CI)	cases	controls	ORa(95%CI)
ALDH2							
G/G		50	65	1.00	146	141	1.00
G/A		105	101	1.67 (1.01-2.78)	56	54	1.03 (0.65-1.62)
A/A		23	18	1.61 (0.73-3.54)	2	3	0.43 (0.04-4.33)
G/A+A/A		128	119	1.69 (1.03-2.75)	58	57	1.00 (0.63-1.57)
ADH2							
A/A		96	97	1.00	98	96	1.00
G/A		60	74	0.76 (0.48-1.23)	88	86	0.88 (0.57-1.35)
G/G		22	13	1.87 (0.85-4.09)	18	16	1.19 (0.59-2.63)
G/A+G/G		82	87	0.92 (0.59-1.42)	106	102	0.92 (0.61-1.39)
ALDH2	ADH2						
G/G	A/A	31	40	1.00	74	72	1.00
G/A+A/A	G/A+G/G	63	62	1.36 (0.72-2.60)	32	30	0.92 (0.49-1.74)

[a]ORs were adjusted for occupation, education and income (ten years before)

Table 4. Drinking Habit, ADH2 or ALDH2 Polymorphism and Stomach Cancer Risk

Drinking status	ALDH2					ADH2				
	(G/A + A/A)		(G/G)			(G/A + G/G)		(A/A)		
	case	control	case	control	OR (95%CI)	case	control	case	control	OR (95%CI)
Drinking	58	57	146	141	0.99 (0.63-1.57)	106	102	98	96	0.92 (0.61-1.39)
Never	128	119	50	65	1.69 (1.03-2.75)	82	87	96	97	0.92 (0.59-1.42)
OR(95%CI)	1.00 (0.63-1.60)		1.60 (1.00-2.56)		1.70 (0.95-3.07)	1.20(0.78-1.83)		1.20(0.78-1.84)		1.09 (0.72-1.64)
Started drinking age										
≤25	31	28	93	84	0.97 (0.52-1.80)	63	58	61	54	0.89 (0.52-1.54)
>25	27	29	53	57	1.07 (0.54-2.10)	43	44	37	42	0.91 (0.48-1.73)
OR(95%CI)	0.89(0.38-2.05)		1.13(0.69-1.86)		1.06 (0.55-2.06)	1.16(0.65-2.07)		1.07(0.58-1.98)		1.16 (0.63-2.11)
Duration of alcohol consumption history (years)										
>30	23	26	85	84	0.87 (0.45-1.70)	53	63	55	47	0.61 (0.35-1.08)
≤30	35	31	61	57	1.05 (0.55-1.99)	53	39	43	49	1.52 (0.82-2.82)
OR(95%CI)	0.47 (0.19-1.17)		0.75 (0.45-1.23)		0.63 (0.31-1.29)	0.51(0.28-0.92)		1.08(0.58-2.02)		0.80 (0.43-1.49)
Times of drinking per month										
>30	10	10	38	47	1.36 (0.49-3.76)	27	30	21	27	0.94 (0.41-2.16)
≤30	48	47	108	94	0.89 (0.53-1.48)	79	72	77	69	0.86 (0.53-1.39)
OR(95%CI)	1.46 (0.51-4.17)		0.71 (0.42-1.20)		0.97 (0.38-2.49)	0.87(0.46-1.63)		0.67(0.32-1.37)		0.80 (0.41-1.55)
Amount of alcohol consumption every time(g)										
>60	34	27	113	112	1.37 (0.75-2.49)	78	73	69	66	0.90 (0.55-1.47)
≤60	24	30	33	29	0.61 (0.27-1.36)	28	29	29	30	0.90 (0.41-1.97)
OR(95%CI)	2.00 (0.87-4.60)		0.93 (0.52-1.67)		1.16 (0.54-2.48)	1.22(0.65-2.28)		1.12(0.58-2.15)		1.07 (0.58-2.00)
Cumulative amounts of alcohol consumption(kg* year)										
≥2.5	15	6	50	51	2.53 (0.86-7.49)	30	31	35	26	0.56 (0.26-1.21)
<2.5	43	51	96	90	0.82 (0.49-1.38)	76	71	63	70	1.10 (0.67-1.79)
OR(95%CI)	2.72 (0.89-8.31)		0.98 (0.59-1.62)		2.46 (0.90-6.72)	0.94 (0.51-1.73)		1.72 (0.88-3.37)		1.02 (0.54-1.95)

ORs were adjusted for occupation, education and income (ten years before)

Table 5. Interactive Effect between the Cumulative Amount of Alcohol Consumption and ADH2 and ALDH2 Genotypes on Stomach Cancer Risk

ADH2	ALDH2	Alcohol consumption	case	control	P value	ORa (95%CI)
A/A	G/G	-	31	40		1.00
G/G+ G/A	G/G	-	19	25	0.99	1.01 (0.41-2.51)
A/A	G/A+ A/A	-	65	57	0.08	1.81 (0.94-3.48)
G/G+ G/A	G/A+ A/A	-	63	62	0.35	1.36 (0.72-2.60)
A/A	G/G	≤1.5	35	33	0.18	1.64 (0.80-3.40)
A/A	G/A+ A/A	≤1.5	33	28	0.17	1.71 (0.80-3.66)
G/G+ G/A	G/G	≤1.5	19	21	0.37	1.54 (0.60-3.94)
G/G+ G/A	G/A+ A/A	≤1.5	22	20	0.31	1.55 (0.67-3.60)
A/A	G/G	>1.5	37	36	0.22	1.60 (0.76-3.31)
A/A	G/A+ A/A	>1.5	41	43	0.40	1.35 (0.68-2.69)
G/G+ G/A	G/G	>1.5	7	6	0.65	1.39 (0.34-5.60)
G/G+ G/A	G/A+ A/A	>1.5	10	10	0.37	1.65 (0.56-4.82)

aORs were adjusted for occupation, education and income (ten years before)

ALDH2 G/A (OR=1.67, 95%CI: 1.01-2.78) carriers showed a significantly elevated risk of developing stomach cancer (Table 3). No association was found between ADH2 genotypes and risk of stomach cancer.

As for the relationship among ADH2 genotype, ALDH2 genotype, drinking habit and stomach cancer risk, our results demonstrated that drinking status was not a risk modifier among people with the same genotype, nor was genotype among people with the same drinking status (Table 4). ALDH2 A allele carriers with cumulative amount of alcohol consumption ≥2.5 (Kg * years) were at a higher risk of developing stomach cancer compared with those with cumulative amount of alcohol consumption <2.5Kg (Kg * years) (OR=2.72, 95% CI:0.89-8.31) and ALDH2 G/G carriers with cumulative amount of alcohol consumption <2.5 (Kg * years) (OR=2.46, 95% CI=0.90-6.72) or ≥2.5 (Kg * years) (OR=2.53, 95% CI=0.86-7.49).

Next, we investigated the combination of ALDH2 and ADH2 genotypes in conjunction with cumulative amount of alcohol consumption. Compared with individuals with ADH2 A/A and ALDH2 G/G genotypes, ADH2 G and ALDH2 A allele carriers were not at a high risk of developing stomach cancer, with regard to the status of alcohol consumption, and even cumulative amount of alcohol consumption ≥1.5 (Kg * years) (OR =1.65, 95%CI:0.56-4.82) (Table 5).

Discussion

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 do not have any ALDH activity. Even those heterozygous for the normal and variant alleles (ALDH2*1/2) show only 1/16 of the activity in homozygotes of ALDH2*1 allele(Bosron and Li, 1986; Bosron et al., 1988; Enomoto et al., 1991). Some studies found 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 (Mizoi et al., 1994). ADH2*2 allele encodes a superactive subunit of ADH2 and that superactive ADH2*2 homodimer has about a 40 times higher Vmax than the less-active ADH2*1/2*1 form of ADH2 (Bosron and Li, 1986; Bosron et al., 1988). 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. The different combinations of genotypes of ADH2 and ALDH2 are possible to influence the individual susceptibility to cancer.

Up to this date there is only one paper addressing the relationship between ALDH2 genetic polymorphisms and stomach cancer susceptibility (Zhang et al., 2007). However it is Ex1+82 A>G polymorphism (rs 886205) in the 5' untranslated region of ALDH2 gene. In the present study, we examined the associations of stomach cancer with ALDH2 Glu487Lys and ADH2 Arg47His genetic polymorphisms. We found that, in no drinkers, ALDH2 G/A carriers showed a significantly elevated risk of developing stomach cancer when compared with ALDH2 G/G carriers. Yokoyama et al (Yokoyama et al., 2001) also found that stomach cancer has a relatively weak but significant association with ALDH2 G/A genotype. It was observed not for patients with stomach cancer alone but those who also had oropharynyolaryngeal and/or esophageal cancer. They suggested that the pathogenesis of these stomach cancers were associated with acetaldehyde exposure. Dipadova C et al (DiPadova et al., 1987) found that a significant fraction of ingested alcohol undergo first-pass metabolism in humans but reduced in alcoholics and by fasting. Chinese drinkers tend to drink alcohol fastly at parties. These may explain that stomach cancer had no significant association with ALDH2 G/A genotype in drinkers.

There is no doubt that the differences in environment exposures/lifestyle influence the genetic susceptibility to cancer. In studies of cancer risk from alcohol exposure, it is necessary to investigate not only alcohol metabolism, which is mainly decided by the genetic variations of ADH and ALDH, but also drinking habits. Thus, investigation of ADH and ALDH polymorphisms combined with alcohol consumption will benefit many people by identifying their risk of gastric cancer. Our previous studies have examined the associations of primary hepatocellular carcinoma and esophageal cancer with ALDH2 and ADH2 genetic polymorphisms in conjunction with alcohol drinking habits

in Chinese males (Ding et al., 2008; 2010). Our result suggests that to help lower their risk for cancer, persons with ALDH2 A/A or G/A genotypes should be encouraged to reduce their consumption of alcohol beverages. In this study, we also analysis the associations of stomach cancer with ADH2 and /or ALDH2 polymorphism combined with drinking habit. ALDH2 A allele carriers with cumulative amount of alcohol consumption ≥2.5 (Kg * years) were at a higher risk of developing stomach cancer compared with those with cumulative amount of alcohol consumption <2.5Kg (Kg * years) (OR=2.72, 95%CI:0.89-8.31) and ALDH2 G/G carriers with cumulative amount of alcohol consumption <2.5 (Kg * years) (OR=2.46, 95%CI=0.90-6.72) or ≥2.5 (Kg * years) (OR=2.53, 95% CI=0.86-7.49), but these did not reach statistical significance. Yin SJ et al (Yin et al., 1993) showed that the esophageal ADH activity was approximately 4-fold and the ALDH activity 20% that of the stomach. Because the presence of lower activity ADH as well as high-activity ALDH were found in human gastric mucosa, little intracellular acetaldehyde may be exist in gastric mucosa during alcohol ingestion. Thus, the roles of alcohol metabolic enzyme polymorphisms and alcohol drinking are weak on stomach cancer risk.

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