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RAPID COMMUNICATION

Polymorphisms of alcohol dehydrogenase 2 and aldehyde dehydrogenase 2 and colorectal cancer risk in Chinese males

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Abstract

AIM: To evaluate the relationship between drinking and polymorphisms of alcohol dehydrogenase 2 (*ADH2*) and/or aldehyde dehydrogenase 2 (*ALDH2*) for risk of colorectal cancer (CRC) in Chinese males.

METHODS: A case-control study was conducted in 190 cases and 223 population-based controls. *ADH2* Arg47His (G-A) and *ALDH2* Glu487Lys (G-A) genotypes were identified by PCR and denaturing high-performance liquid chromatography (DHPLC). Information on smoking and drinking was collected and odds ratio (OR) was estimated.

RESULTS: The *ADH2* A/A and *ALDH2* G/G genotypes showed moderately increased CRC risk. The age- and smoking-adjusted OR for *ADH2* A/A relative to G/A and G/G was 1.60 (95% CI=1.08-2.36), and the adjusted OR for *ALDH2* G/G relative to G/A and A/A was 1.79 (95% CI=1.19-2.69). Significant interactions between *ADH2*, *ALDH2* and drinking were observed. As compared to the subjects with *ADH2* G and *ALDH2* A alleles, those with *ADH2* A/A and *ALDH2* G/G genotypes had a significantly increased OR (3.05, 95% CI= 1.67-5.57). The OR for CRC among drinkers with the *ADH2* A/A genotype was increased to 3.44 (95% CI= 1.84-6.42) compared with non-drinkers with the *ADH2* G allele. The OR for CRC among drinkers with the *ALDH2* G/G genotype was also increased to 2.70 (95% CI= 1.57-4.66) compared with non-drinkers with the *ALDH2* A allele.

CONCLUSION: Polymorphisms of the *ADH2* and *ALDH2* genes are significantly associated with CRC risk. There are also significant gene-gene and gene-environment interactions between drinking and *ADH2* and *ALDH2* polymorphisms regarding CRC risk in Chinese males.

Key words: Alcohol dehydrogenase 2; Aldehyde dehydrogenase 2; Gene polymorphisms; Alcohol drinking; Colorectal cancer

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INTRODUCTION

There is epidemiological evidence that alcohol intake is associated with increased colorectal cancer risk[1]. The oxidative metabolites of ethanol, acetaldehyde, is recognized to be carcinogenic in animals and suspected to have similar effects on human beings[2]. 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.

Ethanol is oxidized to acetaldehyde and then to acetate by alcohol dehydrogenase (*ADH*) and aldehyde dehydrogenase (*ALDH*) in the liver. Most of the acetaldehyde generated during alcohol metabolism *in vivo* is promptly eliminated by *ALDH2*, a low-Km mitochondrial *ALDH*[3]. 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[4]. *ADH2* is also polymorphic and its mutant *ADH2*2* allele (Arg47His) encodes a superactive subunit of *ADH2*[3,4]. The *ALDH2* Glu487Lys and *ADH2* His47Arg polymorphisms thus have a strong impact on alcohol metabolism. Inactive *ALDH2* and superactive *ADH2* are considered to contribute to alcohol flushing and prevent people from developing alcoholism[5-7].

Our previous studies have shown that males with a habit of drinking are at a significantly higher risk for colorectal cancer[8,9]. In this study, we attempted to define the role of *ADH2* and *ALDH2* polymorphisms and drinking habit in the development of colorectal cancer.

MATERIALS AND METHODS

Study subjects

We recruited colorectal cancer patients from the Cancer Registries in Huian and Jintan Cities of Jiangsu Province of China, and also recruited patients who visited Jiangsu Provincial Cancer Hospital from August 2000 to September 2002. All patients were histopathologically diagnosed as having a primary colorectal cancer. Physicians at the hospital asked eligible patients to participate in our study, and doctors or nurses interviewed the subjects and collected blood samples from a peripheral vein after obtaining informed consent. Population-based controls were selected from healthy residents in eight villages or towns of Huian and Jintan Cities. Doctors of the public health centers randomly selected one or two controls for each patient, after matching for ethnicity, sex and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation. Interviews and blood collection were performed as for the cancer patients. A few patients and residents refused to participate in our study, but the response rate was 97% for patients and 93% 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.

Environmental factors

Smoking and drinking habits were covered in our questionnaire. Each subject was asked whether he had ever smoked at least one cigarette per day for six months or longer. If he answered yes, he was further asked about the age at which he started to smoke cigarettes regularly, the average number of cigarettes smoked per day, and the number of years he had smoked. If the subject had quit smoking at least one year ago, the age at which he stopped smoking was recorded. Each subject was asked whether he had ever drunk alcoholic beverages at least once a month for one year or longer. If his answer was yes, he was asked to provide the age at which he started to drink regularly, frequency and usual amount of hot wine, beer and grape wine consumed separately every time. If the subject had quit his drinking habit at least one year ago, the age at which he stopped drinking was recorded. Consumption of ethanol every month was calculated according to 25 g/100 g of hot wine, 3.5 g/100 g of beer and 12 g/100 g of grape wine. In the present study, smoking status was categorized as never and ever-smokers (including both current and former smokers) and alcohol consumption as drinkers/non-drinkers (the latter including individuals whose alcohol intake was less than 30 g/mo).

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). 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 $MgCl_2$, 2.5 μL 10 × buffer, 1 IU hotTag polymerase and 0.5 μL genomic DNA. PCR conditions were as follows: denaturation at 95℃ for 7 min, followed by 35 cycles at 95℃ for 30 s, at 62℃ for 30 s, at 72℃ for 30 s, and a final extension at 72℃ for 5 min. The products were denatured at 94℃ for 4 min, and their temperature was declined to 25℃ step by step according to 0.1℃/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℃ 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

Associations between the *ADH2* and *ALDH2* polymorphisms and colorectal cancer risk were estimated by OR, using the unconditional logistic regression model. The procedure LOGISTIC from the statistical package SAS was employed for the calculations. The probability of Hardy-Weinberg equilibrium was assessed by the χ^2 test.

RESULTS

The numbers of 190 patients with colorectal cancer and 222 controls are listed in Table 1. The proportional distributions of age and smoking did not significantly differ in patients and controls, but the proportional distributions of alcohol drinkers (including current and former drinkers) were significantly higher in colorectal cancer patients than in controls.

The frequencies of *ALDH2* G/G, G/A and A/A genotypes were 68.95%, 28.42% and 2.63% in patients and 55.41%, 40.54% and 4.05% in controls, respectively (Table 2). The distribution of *ALDH2* genotypes was significantly different in controls and patients (χ^2=7.938, P = 0.019). The frequencies of *ADH2* A/A, A/G and G/G genotypes were 53.68%, 38.42% and 7.89% in patients and 41.89%, 49.10% and 9.01% in controls, with no significant difference (χ^2=5.786, P = 0.055). The allelic distribution of *ADH2* and *ALDH2* polymorphisms in controls was in the Hardy-Weinberg equilibrium (P > 0.05). Therefore, the controls from the general population could be considered as a representative.

The *ADH2* A/A and *ALDH2* G/G genotypes showed a moderately increased risk for colorectal cancer. The age- and smoking-adjusted OR relative to G/A and G/G was 1.60 (95% CI=1.08-2.36), and the adjusted OR for *ALDH2* G/G relative to G/A and A/A was 1.79 (95% CI= 1.19-2.69).

The ORs and 95% CIs for association of alcohol drinking with colorectal cancer risk are shown in Table 3. Compared with non-drinkers, the age-adjusted and smoking-adjusted OR for colorectal cancer among alcohol drinkers was 2.04 (95% CI=1.36-3.08). Furthermore, a significant increase trend in the risk of colorectal cancer with amount of alcohol intake was also observed (P = 0.0001).

The results of multivariant analysis of smoking, alcohol drinking, *ALDH2* and *ADH2* genotypes and risk of colorectal cancer are shown in Table 4. After adjustment of all these variables for each other, *ADH2* A/A, *ALDH2* G/G genotypes and alcohol drinking were associated with an increased risk for colorectal cancer, but smoking was not.

As compared to the subjects with *ADH2* G and *ALDH2* A alleles, those with *ADH2* A/A and *ALDH2* G/G genotypes had a significantly increased OR (3.05, 95% CI=1.67-5.57, Table 5). The OR for CRC among alcohol drinkers with *ADH2* A/A genotype was markedly increased to 3.44 (95% CI=1.84-6.42) compared to non-drinkers with *ADH2* G allele. The OR for colorectal cancer among alcohol drinkers with

Table 1 Background characteristics of male colorectal cancer patients and controls

	Controls		Patients		χ^2_{MH}	*P*
	No.	%	No.	%		
Age (yr)						
< 40	25	11.26	21	11.05	4.467	0.346
40-49	33	14.86	39	20.53		
50-59	76	34.23	50	26.32		
60-69	62	27.93	53	27.89		
> 70	26	11.71	27	14.21		
Total	222		190			
Smoking status						
Nonsmoker	87	39.19	67	35.26	3.794	0.150
Current smoker	122	54.95	102	53.68		
Former smoker	13	5.86	21	11.05		
Drinking status						
Nondrinker	124	55.86	73	38.42	15.952	0.001
Current drinker	91	40.99	99	52.11		
Former drinker	7	3.15	18	9.47		
Kinds of alcoholic beverage						
Hot wine	68	69.39	77	40.53	3.453	0.327
Beer	0	0	2	1.05		
Wine	3	3.06	1	0.53		
All kinds	27	27.55	37	31.62		
Alcohol consumption (g/mo)						
0-29	124	55.86	73	38.42	15.437	0.001
30-299	20	9.01	14	7.37		
300-599	17	7.66	20	10.53		
⩾ 600	61	27.46	83	43.68		

Table 2 Adjusted odds ratio (OR) and 95% confidence interval (CI) for colorectal cancer with reference to *ALDH2* and *ADH2* polymorphisms

	Controls *n* (%)	Cases *n* (%)	OR[1] (95% CI)	OR[2] (95% CI)
ALDH2 genotype				
G/G	123 (55.41)	131 (68.95)	1.00	1.00
G/A	90 (40.54)	54 (28.42)	0.56 (0.37-0.86)	0.56 (0.37-0.86)
A/A	9 (4.05)	5 (2.63)	0.52 (0.15-1.76)	0.52 (0.17-1.60)
G/A + A/A	99 (44.59)	59 (31.05)	0.56 (0.37-0.86)	0.56 (0.37-0.84)
A/A + A/G	99 (44.59)	59 (31.05)	1.00	1.00
G/G	123 (55.41)	131 (68.95)	1.79 (1.19-2.68)	1.79 (1.19-2.69)
ADH2 genotype				
A/A	93 (41.89)	102 (53.68)	1.00	1.00
A/G	109 (49.10)	73 (38.42)	0.61 (0.41-0.92)	0.62 (0.41-0.93)
G/G	20 (9.01)	15 (7.89)	0.68 (0.33-1.41)	0.68 (0.33-1.40)
A/G + G/G	129 (58.11)	88 (46.32)	0.62 (0.41-0.94)	0.63 (0.42-0.93)
G/G + G/A	129 (58.11)	88 (46.32)	1.00	1.00
A/A	93 (41.89)	102 (53.68)	1.61 (1.09-2.38)	1.60 (1.08-2.36)

[1]Crude OR, [2]OR was adjusted by age and smoking status.

Table 3 Adjusted OR and 95% CI for colorectal cancer with reference to alcohol drinking

	Controls	Cases	OR[1] (CI)	OR[2] (CI)
Alcohol drinking status				
Non-drinker	124	73	1.00	1.00
Current drinker	91	99	1.85 (1.21-2.83)	1.84 (1.20 -2.82)
Former drinker	7	18	4.37 (1.62-12.17)	4.19 (1.64-0.71)
Current and former	98	107	2.03 (1.37-3.01)	2.04 (1.36-3.08)
Alcohol consumption (g/mo)				
0-29	124	73	1.00	1.00
30-299	20	14	1.19 (0.53-2.65)	1.22 (0.58-2.58)
300-599	17	20	2.00 (0.93-4.30)	1.98 (0.96-4.09)
⩾ 600	61	83	2.31 (1.46-3.68)	2.33 (1.47-3.71)
			P for trend = 0.0001	

[1]Crude OR, [2]OR was adjusted for age and smoking status.

Table 4 Multivariant analysis of smoking, alcohol drinking, *ALDH2* and *ADH2* genotypes and risk of colorectal cancer

	OR[1]	95% CI	χ^2	*P*
ALDH2	1.62	1.06-2.47	5.0035	0.0253
ADH2	1.73	1.15-2.58	7.0548	0.0079
Smokers	0.97	0.63-1.50	0.0138	0.9063
Alcohol drinkers	1.95	1.27-2.98	9.3884	0.0022

[1]Logistic regression model included age (continuous), smoking (nonsmokers, current + former), alcohol drinking (nondrinkers, current + former drinkers), *ALDH2* (A/A+A/G, G/G) and *ADH2* genotype (G/G + G/A, A/A).

ALDH2 G/G genotype was markedly increased to 2.70 (95% CI=1.57-4.66) compared to non-drinkers with *ALDH2* A allele (Table 6).

DISCUSSION

Our previous studies showed that drinking is associated with increased colorectal cancer risk[8-10]. We also found that a polymorphism of cytochrome P450 2E1 (*CYP2E1*), an alcohol metabolizing enzyme, could influence susceptibility to colorectal cancer and *CYP2E1* C2/C2 genotype and alcohol drinking have a coordinated effect on the development of colorectal cancer[9]. In the present study, polymorphisms of the *ADH2* and *ALDH2* genes were significantly associated with the risk of colorectal cancer in Chinese males. Significant gene-gene and gene-environment interactions were also found between alcohol drinking and *ADH2* and *ALDH2* polymorphisms.

Colorectal carcinogenesis, as with other cancers, is complex and due to the coordinated effects of environmental and genetic factors. Thus, the exposure dosage to chemical carcinogens could vary with enzyme activity. In theory, when *ADH2* activity is increased or *ALDH2* activity is decreased, the blood acetaldehyde level also increases in drinkers, thus increasing the risk of developing colorectal cancer. However, inconsistent results have been reported in many studies on the relation between *ADH2* and *ALDH2* gene polymorphisms and cancer susceptibility[11-18]. Yokoyama *et al*[11] found *ALDH2* G/A genotype encoding inactive

Table 5 Interaction between *ALDH2* and *ADH2* genotypes and OR for colorectal cancer

ALDH2	*ADH2*	Controls	Cases	OR[1] (95% CI)
A/A + A/G	G/G + G/A	55	25	1.00
A/A + A/G	A/A	44	34	1.64 (0.85-3.18)
G/G	G/G + G/A	74	63	1.87 (1.05-3.35)
G/G	A/A	49	68	3.05 (1.67-5.57)

[1]OR was adjusted for age and smoking in a logistic regression model.

Table 6 Interaction between alcohol drinking and polymorphisms of the *ALDH2* and *ADH2* genes, and the odds ratio (OR) for colorectal cancer

Genotypes	Drinker	Controls	Cases	OR[1] (95% CI)
ALDH2				
A/A + A/G	No	64	32	1.00
G/G	No	60	41	1.36 (0.76-2.43)
A/A + A/G	Yes	35	27	1.39 (0.69-2.81)
G/G	Yes	63	90	2.70 (1.57-4.66)
ADH2				
G/G + G/A	No	65	34	1.00
A/A	No	59	39	1.27 (0.71-2.26)
G/G + G/A	Yes	64	54	1.65 (0.94-2.91)
A/A	Yes	34	63	3.44 (1.84-6.42)

[1]OR was adjusted for age and smoking status.

ALDH2 and *ADH2* G/G genotype encoding the low-activity form of *ADH2* can enhance the risk of esophageal cancer in Japanese alcoholics. For those individuals with both *ALDH2* G/A and *ADH2* G/G genotypes, the risk of esophageal cancer is increased in a multiplicative fashion. It was reported that after adjustment for age, daily alcohol consumption and amount of cigarette smoking, the risk of developing oropharyngolaryngeal, esophageal, stomach, colon, lung and multiple primary cancers is significantly increased in the presence of *ALDH2* A allele[12]. In a study on the association between genetic polymorphisms of tobacco- and alcohol-related metabolizing enzymes and esophageal squamous cell carcinoma susceptibility, Hori *et al*[13] showed that there is a significant difference in the distribution of *ADH2* and *ALDH2* genotypes between healthy controls and esophageal cancer patients, and that *ADH2* G/G and *ALDH2* G/A genotypes are significantly higher in esophageal cancer patients than in healthy controls. Furthermore, persons with combined genotypes of *ADH2* G/G and *ALDH2* G/A are at a high risk of developing esophageal squamous cell carcinoma. Chao *et al*[14] reported that Chinese alcoholic patients with *ADH2* G and *ALDH2* A alleles are more susceptible to esophageal cancer. However, Ohhira *et al*[15] showed that 10 patients with hepatocellular carcinoma (HCC) associated with pure alcoholic liver disease all have *ALDH2* G/G genotype. Takeshita *et al*[16] also examined associations between *ADH2* and *ALDH2* polymorphisms, alcohol drinking and HCC development in Japanese, and showed that a greater cumulative amount of alcohol consumption is significantly associated with HCC development but

not with *ADH2* and *ALDH2* genotypes, indicating that ethanol is directly involved in the development of HCC rather than acetaldehyde. The latest evaluation in 2007 by the International Agency for Research on Cancer (IARC) confirmed that alcoholic beverages are carcinogenic to human beings (Group 1), thus increasing the occurrence of cancer in many sites, such as oral cavity, pharynx, larynx esophagus, liver, colorectum and female breast[17,18].

Our previous study showed that *ADH2* and *ALDH2* polymorphisms are not significantly associated with the risk of developing liver, stomach and esophageal cancer[19-21]. However, those with *ALDH2* G allele drinking a greater amount of alcohol significantly elevates the risk of developing HCC and those with *ALDH2* G/G genotype drinking a larger amount of alcohol are at a significantly increased risk of developing gastric cancer. Matsuo *et al*[22] evaluated the relationship between genetic polymorphisms of *ADH2* His47Arg and *ALDH2* Glu487Lys and occurrence of colorectal cancer in Japan, and showed that *ADH2* Arg allele is associated with an increased risk of CRC. However, no significant association was found with the *ALDH2* polymorphism itself, a significant interaction between *ALDH2* and *ADH2* polymorphisms was observed in their study.

In the present study, *ADH2* A/A and *ALDH2* G/G genotypes moderately increased the risk of developing colorectal cancer in Chinese males. Significant gene-gene and gene-environment interactions were also observed between alcohol drinking and *ADH2* and *ALDH2* polymorphisms regarding colorectal cancer risk. However, further study is needed to confirm our results with a large sample size.

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COMMENTS

Background

Colorectal cancer (CRC) is the fifth most common cancer in China. There is epidemiological evidence that alcohol intake is associated with an increased CRC risk. Alcohol dehydrogenase 2 (*ADH2*) and aldehyde dehydrogenase 2 (*ALDH2*) have a strong impact on alcohol metabolism. To evaluate the relationship between habitual drinking and genetic polymorphisms of *ADH2* and *ALDH2* with reference to the risk of CRC in Chinese males, we conducted a population based case-control study of CRC in Jiangsu Province of China.

Research frontiers

Susceptibility to cancer is generally thought to be the sum of complex interactions between environmental and genetic factors. Therefore, interaction between environmental and genetic factors is a hotspot of cancer epidemiology. We studied interactions between *ADH2* and/or *ALDH2* and habitual alcohol drinking in CRC development.

Innovations and breakthroughs

The present study showed that *ADH2* A/A and *ALDH2* G/G genotypes were correlated with the increased risk of CRC. Furthermore, a significant cooperative role of *ADH2* A/A and/or *ALDH2* G/G genotypes and alcohol consumption was also observed in the development of CRC.

Applications

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

Peer review

The correlation between habitual drinking and genetic polymorphisms of *ADH2* and *ALDH2* was studied with reference to the risk of CRC in Chinese males. Furthermore, significant gene-gene and gene-environment interactions between alcohol drinking and *ADH2* and *ALDH2* polymorphisms were also found regarding the CRC risk. The experiments contained appropriate controls and data about the age, smoking status and alcohol consumption. This research also reported the genetic risk factors and the role of gene-environment interactions in identifying patients at risk of developing colorectal cancer in Chinese males.

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