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.

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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[5]. 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[6].

Our previous studies have shown that males with a habit of drinking are at a significantly higher risk for colorectal cancer[7]. 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’-GGGGCTTTTAGACTGAACTTGG-3’ and R: 5’-AGGGAAGAGGAACACTCTGAAA-3’ for ADH2 Arg47His, and F: 5’-TGCTATGATCTTTGGAGCC-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 holTag 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 DNASeq 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**

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 χ² 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 4.03% in controls, respectively (Table 2). The distribution of ALDH2 genotypes was significantly different in controls and patients ($\chi^2 = 7.938, P = 0.019$). 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 ($\chi^2 = 5.786, P = 0.055$). 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

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**Table 1** Background characteristics of male colorectal cancer patients and controls

| Age (yr) | Controls | | Patients | | $\chi^2_{adj}$ | $P$ |
|---|---|---|---|---|---|---|
| < 40 | 25 | 11.26 | 21 | 11.05 | 4.467 | 0.346 |
| 40-49 | 33 | 14.86 | 39 | 20.53 | 3.628 | 0.26 |
| 50-59 | 76 | 34.23 | 50 | 26.32 | 0.087 | 0.92 |
| 60-69 | 62 | 27.93 | 53 | 27.89 | 0.112 | 0.70 |
| > 70 | 26 | 11.71 | 27 | 14.21 | 0.093 | 0.76 |
| Total | 222 | 100 | 190 | 100 | | |

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

| ADH2 genotype | Controls $n$ (%) | Cases $n$ (%) | OR (95% CI) | OR (95% CI) |
|---|---|---|---|---|
| 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) |

**Crude OR, 2OR was adjusted by age and smoking status.**
**Table 3** Adjusted OR and 95% CI for colorectal cancer with reference to alcohol drinking

| Alcohol drinking status | Controls | Cases | OR^1 (CI) | OR^2 (CI) |
|-------------------------|----------|-------|-----------|-----------|
| Non-drinker             | 124      | 73    | 1.00      | 1.00      |
| Current drinker         | 91       | 99    | 1.05 (1.21-2.83) | 1.84 (1.20-2.82) |
| Former drinker          | 7        | 18    | 4.37 (1.62-12.17) | 4.19 (1.64-7.71) |
| 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) |

*Crude OR, OR^2 was adjusted for age and smoking status.

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

| Genotypes | OR^1 | 95% CI | \(\chi^2\) | \(P\) |
|-----------|------|--------|------------|------|
| ALDH2     | 1.62 | 1.06-2.47 | 5.0055     | 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 |

*Logistic regression model included age (continuous), smoking (nonsmokers, current + former), alcohol drinking (non-drinkers, current + former drinkers), ADH2 (A/A+A/A, G/G) and ADH2 genotype (G/G + G/A, A/A).

**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) |

^1OR was adjusted for age and smoking.

**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) |
| A/A + A/G | 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) |

^1OR was adjusted for age and smoking.

**ALDH2 and ADH2**

G/A 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/G 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[^13]. 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[^18] reported that Chinese alcoholic patients with **ADH2** G and **ALDH2** A alleles are more susceptible to esophageal cancer. However, Ohhira et al[^13] 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 \textit{ADH2} and \textit{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\cite{17,18}.

Our previous study showed that \textit{ADH2} and \textit{ALDH2} polymorphisms are not significantly associated with the risk of developing liver, stomach and esophageal cancer\cite{19-21}. However, those with \textit{ALDH2} G allele drinking a greater amount of alcohol significantly elevates the risk of developing HCC and those with \textit{ALDH2} G/G genotype drinking a larger amount of alcohol are at a significantly increased risk of developing gastric cancer. Matsuo \textit{et al}\cite{23} evaluated the relationship between genetic polymorphisms of \textit{ADH2} His47Arg and \textit{ALDH2} Glu487Lys and occurrence of colorectal cancer in Japan, and showed that \textit{ADH2} Arg allele is associated with an increased risk of CRC. However, no significant association was found with the \textit{ALDH2} polymorphism itself, a significant interaction between \textit{ALDH2} and \textit{ADH2} polymorphisms was observed in their study.

In the present study, \textit{ADH2} A/A and \textit{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 \textit{ADH2} and \textit{ALDH2} polymorphisms regarding colorectal cancer risk. However, further study is needed to confirm our results with a large sample size.

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