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Association of *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms with risk of colorectal cancer and their interaction with environmental factors in a Chinese population

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ABSTRACT. Human colorectal cancer (CRC) is a major worldwide health concern, and its development has been shown to be associated with alcohol intake. We carried out a study to investigate the effect of the *ADH1B* Arg47His and *ALDH2* Glu487Lys genetic polymorphisms and their interaction with alcohol consumption on development of CRC. Between March 2013 and May 2015, a total of 274 CRC patients and 358 healthy controls were recruited. Genotyping of sequence variations was performed using the polymerase chain reaction-restriction fragment length polymorphism method. Under a co-dominant model, individuals with the *ADH1B* Arg47His AA genotype showed increased CRC risk compared to those carrying the GG genotype, with an adjusted odds ratio (and 95% confidence interval) of 3.37 (2.00-5.70). Moreover, under dominant and recessive models, *ADH1B* Arg47His variant genotypes were associated with greater susceptibility to CRC when

compared with the wild-type sequence. Both polymorphisms examined were positively associated with alcohol consumption in a Spearman correlation analysis of CRC risk. In conclusion, our study suggests that the *ADH1B* Arg47His polymorphism, but not the *ALDH2* Glu487Lys variation, may influence development of CRC in the Chinese population.

Key words: Colorectal cancer; *ADH1B* Arg47His; *ALDH2* Glu487Lys; Polymorphism

INTRODUCTION

Human colorectal cancer (CRC) is a major global health concern, with approximately 1.2 million new cases each year (Torre et al., 2015). It has been estimated that 663,000 men and 571,000 women suffered from this disease worldwide in 2012 (Ferlay et al., 2013). Many environmental influences are involved in CRC susceptibility, such as high fat and protein consumption, low intake of fruit, vegetables, and cereal, obesity, red and/or processed meat, alcohol, inadequate physical activity, long-term constipation, and human papilloma virus infection (Battaglia Richi et al., 2015; De Ruyck et al., 2015; Ebert and Ellison, 2015; Stefan, 2015; Blase et al., 2016). Many previous molecular studies have shown that heritable factors are involved in CRC development, including glutathione *S*-transferase pi 1 (*GSTP1*) and mu 1 (*GSTM1*), human 8-oxoguanine DNA glycosylase 1 (*hOGG1*), cytochrome P450 family 1 subfamily A member 1 (*CYP1A1*), and C-reactive protein (*CRP*) (Sun et al., 2015; Xu and Wei, 2015; Khabaz et al., 2016a,b; Geng et al., 2016).

Prior investigations have shown that alcohol intake is associated with CRC risk in several populations (Cho et al., 2015; Klarich et al., 2015; Wang et al., 2015). Ethanol metabolism involves two steps, in which the enzymes alcohol dehydrogenase 1B (ADH1B) and aldehyde dehydrogenase 2 (ALDH2) perform important functions in ethanol metabolism and acetaldehyde levels (Asakage et al., 2007; Kang et al., 2009). The polymorphisms *ADH1B* Arg47His and *ALDH2* Glu487Lys result in amino acid substitutions, thus potentially influencing (Kang et al., 2009). Previous studies have investigated the association between these variants and CRC risk (Landi et al., 2005; Matsuo et al., 2006; Yin et al., 2007; Gao et al., 2008; Chiang et al., 2012), but their results have been inconsistent. Therefore, we carried out a case-control study to evaluate the relationship between *ADH1B* Arg47His and *ALDH2* Glu487Lys and CRC in a Chinese population.

MATERIAL AND METHODS

Subjects

A hospital-based case-control design was used in this study. Between March 2013 and May 2015, a total of 274 CRC patients were consecutively recruited from the People's Hospital of Ganzhou, China. CRC was confirmed in each patient by pathological examination using colorectal colonoscopy. Patients had not received any form of anti-cancer therapy before enrollment.

During the same period, 358 healthy controls were recruited from the hospital's outpatient clinics. All control subjects were free of malignant tumors and had no history of digestive tract diseases, end-stage kidney diseases or liver cirrhosis.

Data concerning demographic and lifestyle factors of all participants were collected from medical records and a self-designed questionnaire, and included age, gender, family history of CRC, alcohol and tobacco consumption, body mass index (BMI), and physical activity. Subjects were asked to sign a consent form agreeing to participate in the study. Our investigation was performed with the permission of the People's Hospital of Ganzhou Ethics Committee.

Genotyping analysis

Genomic DNA was isolated using a QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany), following the manufacturer protocol. Genotyping of *ADH1B* Arg47His and *ALDH2* Glu487Lys was conducted utilizing the polymerase chain reaction (PCR)-restriction fragment length polymorphism technique. DNA was amplified using two different primer pairs specific for the regions containing these polymorphisms. The forward and reverse primers for *ADH1B* Arg47His were 5'-GAAGGGGGGTCACAGGTTG-3' and 5'-AATCTTTTCTGAATCTGAACAG-3', respectively, and those for *ALDH2* Glu487Lys were 5'-CCACACTCACAGTTTTGAATT-3' and 5'-GGCTACAAGAATTCGGGGAGT-3', respectively. The cycling conditions were as follows: denaturation at 95°C for 5 min, followed by 35 cycles of denaturation at 94°C for 60 s, annealing at 55°C for 60 s, and extension at 72°C for 60 s, before a final extension at 72°C for 7 min. PCR products were electrophoresed and observed under ultraviolet light.

Statistical analysis

Student *t*-tests and chi-square tests were used for analysis of demographic variables between groups. Genotypes in the patient and control populations were tested for departure from Hardy-Weinberg equilibrium (HWE) using the Pearson chi-square test with one degree of freedom. Multivariable logistic regression analysis was performed in order to determine odds ratios (ORs) and 95% confidence intervals (95%CIs) associated with CRC risk, taking the wild-type genotype as the reference group. Interactions with the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms were assessed using Spearman correlation analysis. Results were considered to be significantly different when the associated P value was lower than 0.05.

RESULTS

The demographic and lifestyle characteristics of the study subjects are presented in Table 1. Using chi-square or Student *t*-tests, we observed that patients and controls were comparable with respect to mean age ($t = 0.74$, $P = 0.23$), gender (chi-square = 1.59, $P = 0.21$), family history of cancer (chi-square = 2.87, $P = 0.09$), and tobacco smoking (chi-square = 2.34, $P = 0.13$). Patients had higher BMIs (chi-square = 68.51, $P < 0.001$), consumed more alcohol (chi-square = 5.37, $P = 0.02$), and were less physically active (chi-square = 50.84, $P < 0.001$) than control subjects.

The distributions of *ADH1B* Arg47His and *ALDH2* Glu487Lys genotypes in the two study groups are shown in Table 2. Of the patients, 85 (31.02%), 125 (45.62%), and 64 (23.36%) carried the GG, GA, and AA genotypes of *ADH1B* Arg47His, and 194 (70.80%),

67 (24.45%), and 13 (4.75%) carried the GG, GA, and AA genotypes of *ALDH2* Glu487Lys. In the control group, 152 (42.46%), 172 (48.04%), and 34 (9.50%) individuals were found to have the GG, GA, and AA genotypes of *ADH1B* Arg47His, and 270 (75.42%), 79 (22.07%), and 9 (2.51%) carried the GG, GA, and AA genotypes of *ALDH2* Glu487Lys. *ADH1B* Arg47His genotype distributions significantly differed between CRC patients and controls (chi-square = 24.84, P < 0.001), but no such difference was observed in relation to the *ALDH2* Glu487Lys variant (chi-square = 3.05, P = 0.22). Moreover, *ADH1B* Arg47His and *ALDH2* Glu487Lys genotype distributions were consistent with HWE in both patient (*ADH1B* Arg47His: chi-square = 1.85, P = 0.17; *ALDH2* Glu487Lys: chi-square = 4.80, P = 0.03) and control groups (*ADH1B* Arg47His: chi-square = 2.18, P = 0.14; *ALDH2* Glu487Lys: chi-square = 1.20, P = 0.27).

Table 1. Demographic characteristics of the investigated patients and controls.

Variable	Patients (N = 274)	%	Controls (N = 358)	%	*t* or chi-square	P
Age (years)						
Mean	57.16 ± 9.52		55.60 ± 9.25		0.74	0.23
<55	124	45.26	174	48.60		
≥55	150	54.74	184	51.40	0.69	0.40
Gender						
Female	105	38.32	155	43.30		
Male	169	61.68	203	56.70	1.59	0.21
Body mass index (kg/m^2)						
<24	111	40.51	262	73.18		
≥24	163	59.49	96	26.82	68.51	<0.001
Family history of cancer						
No	256	93.43	345	96.37		
Yes	18	6.57	13	3.63	2.87	0.09
Alcohol consumption						
Never	94	34.31	165	46.09		
Yes	162	64.97	193	53.9	5.37	0.02
Tobacco smoking						
Never	124	45.26	184	51.40		
Yes	150	54.74	174	48.6	2.34	0.13
Physical activity						
Sedentary	198	72.26	166	46.37		
Intermediate	37	13.50	133	37.15		
Active	39	14.23	59	16.48	50.84	<0.001

Table 2. Distribution of *ADH1B* Arg47His and *ALDH2* Glu487Lys genotypes between the two study groups.

Genotype	Patients	%	Controls	%	Chi-square	P	HWE (patients)		HWE (controls)	
							Chi-square	P	Chi-square	P
ADH1B Arg47His										
GG	85	31.02	152	42.46						
GA	125	45.62	172	48.04						
AA	64	23.36	34	9.50	24.84	<0.001	1.85	0.17	2.18	0.14
ALDH2 Glu487Lys										
GG	194	70.80	270	75.42						
GA	67	24.45	79	22.07						
AA	13	4.75	9	2.51	3.05	0.22	4.80	0.03	1.20	0.27

HWE = Hardy-Weinberg equilibrium.

Multivariable logistic regression revealed that individuals with the *ADH1B* Arg47His AA genotype were at increased risk of CRC compared to those carrying the GG genotype, with an adjusted OR (and 95%CI) of 3.37 (2.00-5.70; Table 3). Under a dominant model, the GA+AA genotype of this polymorphism was associated with susceptibility to CRC when

compared to the GG genotype (adjusted OR = 1.64, 95%CI = 1.16-2.32). Moreover, using a recessive model, we observed a correlation between the *ADH1B* Arg47His AA genotype and CRC, in comparison to the GG+GA genotype (adjusted OR = 3.29, 95%CI = 2.02-5.44). However, co-dominant, dominant, and recessive models suggested that the *ALDH2* Glu487Lys polymorphism does not contribute to CRC development.

Table 3. Relationship between the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms and risk of colorectal cancer.

Genotype and model	Patients	%	Controls	%	Adjusted OR (95%CI)	P
ADH1B Arg47His						
Co-dominant model						
GG	85	31.02	152	42.46	1.0 (Ref.)	-
GA	125	45.62	172	48.04	1.30 (0.90-1.88)	0.14
AA	64	23.36	34	9.50	3.37 (2.00-5.70)	<0.001
Dominant model						
GG	85	31.02	152	42.46	1.0 (Ref.)	-
GA+AA	189	68.98	206	57.54	1.64 (1.16-2.32)	0.003
Recessive model						
GG+GA	210	76.64	324	90.50	1.0 (Ref.)	-
AA	64	23.36	30	8.38	3.29 (2.02-5.44)	<0.001
ALDH2 Glu487Lys						
Co-dominant model						
GG	194	70.8	270	75.42	1.0 (Ref.)	-
GA	67	24.45	79	22.07	1.18 (0.80-1.74)	0.38
AA	13	4.74	9	2.51	2.01 (0.78-5.43)	0.11
Dominant model						
GG	194	70.8	270	75.42	1.0 (Ref.)	-
GA+AA	80	29.19	88	24.58	1.27 (0.87-1.83)	0.19
Recessive model						
GG+GA	261	95.25	349	97.49	1.0 (Ref.)	-
AA	13	4.74	9	2.51	1.93 (0.75-5.20)	0.13

OR = odds ratio, CI = confidence interval, Ref. = reference.

We observed that both variants were positively associated with alcohol consumption in determining CRC risk, with Spearman correlation coefficients for this interaction of 0.242 and 0.154 for *ADH1B* Arg47His and *ALDH2* Glu487Lys, respectively (Table 4).

Table 4. Interaction between the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms and environmental factors.

Variable	*ADH1B* Arg47His		*ALDH2* Glu487Lys	
	Spearman correlation coefficient	P	Spearman correlation coefficient	P
Age	0.041	0.27	0.036	0.37
Gender	0.038	0.29	0.021	0.42
Body mass index	0.034	0.34	0.027	0.39
Alcohol consumption	0.242	<0.001	0.154	0.03
Tobacco smoking	0.029	0.42	0.027	0.39
Physical activity	0.035	0.29	0.019	0.24

DISCUSSION

In our study, we analyzed the association between the polymorphisms *ADH1B* Arg47His and *ALDH2* Glu487Lys and CRC risk, observing that the former correlated with elevated susceptibility to this disease under all genetic models. Moreover, our results revealed an interaction between the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms and

alcohol consumption, suggesting that these variants expose drinkers to a higher risk of CRC.

Previous studies have investigated the association between these polymorphisms and risk of developing several kinds of cancer, including oral and esophageal squamous cell carcinoma, hepatocellular carcinoma (HCC), and gastric cancer (Solomon et al., 2008; Szumiło et al., 2009; Zhou et al., 2012; Wang et al., 2011, 2014; Zhang et al., 2014). Solomon et al. (2008) carried out a study in an Indian population, revealing that the *ADH1B* Arg47His genetic variation confers substantial cancer risk in heavily alcoholic patients. Wang et al. (2011) performed an investigation involving 81 Chinese women with pathologically confirmed esophageal squamous cell cancer and 162 controls, establishing that those with the *ADH1B* Arg47His and *ALDH2* Glu487Lys polymorphisms were at increased risk of this disease, as observed previously in men. In a meta-analysis of 18 case-control studies incorporating a total of 8906 esophageal cancer cases and 13,712 controls, Zhang et al. (2014) found that the *ADH1B* G48A GG genotype is associated with increased susceptibility to this condition. Likewise, Wang et al. (2014) examined seven case-control studies comprising 2563 patients and 4192 healthy controls, and reported that the *ADH1B* Arg47His and *ALDH2* Glu487Lys variants may contribute to the pathogenesis of gastric cancer. However, some authors have recorded contrasting results. For instance, Zhou et al. (2012) carried out a meta-analysis of 1231 patients and 1849 controls, in which these two polymorphisms were not found to be associated with HCC risk in East Asians.

To date, only six studies have assessed the association between *ADH1B* Arg47His and *ALDH2* Glu487Lys sequence variations and CRC development, but with inconsistent results (Landi et al., 2005; Matsuo et al., 2006; Yin et al., 2007; Gao et al., 2008; Chiang et al., 2012; Crous-Bou et al., 2013). In an investigation of a Chinese population, Gao et al. (2008) revealed that these polymorphisms are significantly correlated with CRC. Matsuo et al. (2006) carried out a study of 257 patients and 771 cancer-free controls, from which they established an association between the *ADH1B* Arg allele and increased CRC risk, but failed to detect any such relationship with the *ALDH2* Glu487Lys polymorphism. In contrast, in an assessment of 685 CRC cases and 778 healthy controls, Yin et al. (2007) found that the *ALDH2* Glu487Lys variant contributes to the likelihood of developing this malignancy, whereas the *ADH1B* Arg47His polymorphism does not. However, Crous-Bou et al. (2013) reported that *ADH1B* Arg47His is associated with CRC risk in a Spanish population. Chiang et al. (2012) carried out a study of a Taiwanese population, finding that *ADH3**1 and *ALDH2**2 allele frequencies, but not the *ADH1B* polymorphism, are significantly associated with susceptibility to CRC. Based on data from 377 patients and 326 controls, Landi et al. (2005) reported that the *ADH1B* Arg47His polymorphism does not contribute to the etiology of CRC. In the present study, this variant was found to be associated with CRC risk in a Chinese population, whereas the *ALDH2* Glu487Lys polymorphism was not. Our results are consistent with the findings of one previous study (Matsuo et al., 2006), but differ from those of four other investigations (Landi et al., 2005; Yin et al., 2007; Gao et al., 2008; Chiang et al., 2012).

One limitation should be considered in our study. Only 274 CRC cases and 358 healthy controls were included in our investigation, representing a relatively small sample size that may have reduced the statistical power of our analysis and caused a discrepancy between our results and the true values.

In conclusion, our study suggests that the *ADH1B* Arg47His polymorphism influences CRC development in the Chinese population, but the *ALDH2* Glu487Lys variant does not. Further studies with large sample sizes are greatly required to confirm our findings.

Conflicts of interest

The authors declare no conflict of interest.

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