# A Novel Polymorphism rs1329149 of *CYP2E1* and a Known Polymorphism rs671 of *ALDH2* of Alcohol Metabolizing Enzymes Are Associated with Colorectal Cancer in a Southwestern Chinese Population

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## Abstract

Background: **To screen for tagging single nucleotide polymorphisms (tagSNP) in the major alcohol metabolizing enzymes: ADH1B, ALDH2, and CYP2E1, and to evaluate the association between these tagSNPs and colorectal cancer (CRC) in a southwestern Chinese population.**

Methods: **A hospital-based case-control study of 440 CRC patients and 800 cancer-free controls was conducted. Personal information was collected by a Semi-Quantitative Food Frequency Questionnaire. The tagSNPs were screened in the HapMap with Haploview by setting the minor allele frequency at 0.03 with the highest score of $r^2$ form each block. Genotypes were identified by using the SNPLex System. Both crude and adjusted odds ratio (OR) and 95% confidence interval (CI) were used to evaluate the risk of each SNP.**

Results: **Sixteen tagSNPs were selected, and 13 were successfully genotyped. A novel *CYP2E1* locus rs1329149 and a known *ALDH2* locus rs671 were found to be significantly associated with CRC risk. The adjusted OR was 1.86 (95% CI, 1.12-3.09) for the rs671 A/A genotype and 4.04 for the rs1329149 T/T genotype (95% CI, 2.44-6.70), compared with their common homozygous genotypes. Interaction was found between alcohol consumption and gene polymorphisms on CRC, the adjusted OR was 7.17 (95% CI, 2.01-25.53) for drinking habits combined with rs671 A/A or rs1329149 T/T genotype.**

Conclusion: **The results of this study suggest that rs671 A/A and the first reported locus rs1329149 T/T genotypes increase the susceptibility to CRC, and gene-environmental interaction between the two loci and alcohol use existed for CRC in Southwestern Chinese. Larger studies are warranted to verify our findings.** (Cancer Epidemiol Biomarkers Prev 2009; 18(9):2522–7)

## Introduction

Studies have shown that 3.6% of cancers of the upper digestive tract, liver, colorectum, and breast could be attributed to chronic alcohol consumption worldwide (1) and this association is strong in colorectal cancer (CRC; refs. 2-5). The risk of CRC was increased at the level of 1.07- to 3.50-fold in western countries and 1.42- to 2.19-fold in Asian populations (Japanese and Koreans) among drinkers (4, 5). Furthermore, meta-analyses also suggested a positive dose-response relationship between alcohol consumption and CRC (6, 7). In China, as in other countries, alcoholism is a serious social and health problem, and it is becoming widespread, with the frequent consumption and abuse of alcohol (8). Our previous epidemiologic study revealed that alcohol consumption was associated with CRC in a Southwestern Chinese population, leading to a 7.77-fold increased risk for colon cancer and 1.73-fold increase in the risk of rectal cancer (9).

After alcohol is absorbed, the concentration of alcohol in the colon is as high as that is found in the blood. The primary metabolite of alcohol in humans is acetaldehyde, which is known as a carcinogen. In animal experiments, it has been shown that the acetaldehyde concentration can exceed 250 and 500 μmol/L in the mucosa of large intestine in piglets and rats, respectively, after 2.5 grams/kg bw i.v. alcohol administration for piglets and 1.5 grams/kg bw i.p. alcohol administration for rats (10, 11). Acetaldehyde concentrations above 50 to 100 μmol/L are considered to be mutagenetic, and the high levels of acetaldehyde resulting from alcohol metabolism have been implicated in alcohol-associated carcinogenesis of the gastrointestinal tract (12). It has been shown that when aldehyde dehydrogenase (ALDH) activity was inhibited, tumorigenesis was observed in the colon of rats (13). Additionally, bacteria in the large intestine can also metabolize alcohol into

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acetaldehyde, but bacteria do not metabolize acetaldehyde to acetic acid for detoxification (13, 14).

In humans, alcohol is mainly metabolized by the alcohol dehydrogenase pathway, microsomal ethanol-oxidizing system, and to a lesser extent, by catalase. Any of these pathways can metabolize alcohol into acetaldehyde then into acetic acid (15). In humans, the major enzymes involved in the alcohol metabolizing pathways are alcohol dehydrogenase IB (ADH1B), aldehyde dehydrogenase-2 (ALDH2), and cytochrome P450 2E1 (CYP2E1). Although these enzymes are expressed mainly in the liver, they are also present in the gastrointestinal tract (16). ADH1B and CYP2E1 can both metabolize alcohol into acetaldehyde, the latter also leading to increased generation of reactive oxygen species (15), whereas ALDH2 can metabolize acetaldehyde into acetic acid for detoxification (13). CYP2E1 can be induced by drugs, such as pyrazole (17), and low molecular weight compounds such as alcohol (17-19). In humans, the induction of CYP2E1 was observed in subjects who consumed 40 grams of alcohol daily for just 1 week, with even greater induction after 4 weeks of daily alcohol consumption (20). However, this increase varies between individuals, indicating that heritage may be responsible for differences in the expression and activity as well as the subsequent metabolites generated by the enzyme (20).

Polymorphisms in genes responsible for these pathways can affect the amount of acetaldehyde and reactive oxygen species generated during the metabolic process, altering the effects of alcohol, potentially leading to carcinogenesis (21-23). Moreover, a recent study reported that the activity of alcohol dehydrogenase and ALDH in CRC patients differed from that in healthy controls and that the increased enzymes activities were due to the enzymes released by CRC cells or metastatic CRC cells (24).

Several studies have reported associations between polymorphisms of alcohol metabolizing enzymes and CRC risk in Japanese, Korean, and Eastern Chinese population (21-23, 25-27). The most frequently reported loci are *ADH1B* Arg47His (because the activity of ADH1B decreased by 40-fold in *ADH1B* His/His individuals), *ALDH2* Glu487Lys (equally to rs671, which affects the $K_m$ of this enzyme for alcohol with loss of the enzyme activity in individuals with the *ALDH2* Lys/Lys phenotype), and *CYP2E1 Rsa* $^1$(rs2031920) and *Dra*$^1$ (rs6413432; because rs2031920 affects the transcription and rs6413432 affects the activity of the enzyme; ref. 26). However, all these studies were focused on the functional loci reported in other diseases but there is no reported comprehensive study that investigated novel loci that have not been reported.

The genome-wide haplotype structure in Chinese Han people has been described in the International HapMap Consortium. It is known that there are ~10 millions of single nucleotide polymorphisms (SNP) in the whole-genome, and we cannot assess all SNPs in the entire genome for each subject. However, representative information abstracted from the whole genome according to the linkage disequilibrium theory can help resolve this problem. By selecting a small fraction of tagging SNPs (tagSNP) for mapping purposes, we can significantly reduce the need for extensive genotyping without much loss of power, because haplotype tagSNPs can represent strong linkage disequilibrium blocks without much information loss (28, 29).

Because there is no reported tagSNP-based association study on CRC, we conducted a tagSNP-based research on the association between genes encoding major alcohol metabolizing enzymes and CRC, as a part of the Japan, Korea, and China Colorectal Cancer collaboration study. We obtained SNP information of the genes coding *ADH1B, ALDH2*, and *CYP2E1* in Chinese Han population from HapMap project and applied the software Haploview for screening of the tagSNPs. We then examined whether the selected tagSNPs in these three genes are associated with CRC risk.

## Materials and Methods

**Subject Recruiting.** A total of 478 CRC patients and 838 controls between ages 30 and 80 y were recruited between 2001 and 2003 from the three largest hospitals in Chongqing, the biggest city in southwest China. Most patients were from Chongqing, the others were from parts of Sichuan, Yunnan, and Guizhou provinces in southwest China, adjacent to Chongqing. The recruitment followed the Japan, Korea, and China Colorectal Cancer collaboration Group guidelines. As such, all of the patients were required to have lived in the study area continuously for >15 y, or for >30 y in total with no >5 y spent in another district. All CRC cases were histopathologically diagnosed as primary CRC, but ileocecal junction tumors and anal canal tumor were excluded. The patients were newly diagnosed in 6 mo, and had not been treated by any medical treatments. Patients were excluded who were suffering from: (*a*) recurrence of CRC; (*b*) familial adenomatous polyposis; (*c*) hereditary nonpolyposis CRC; (*d*) other tumors; (*e*) severe digestive tract diseases over 2 y; and (*f*) diabetes, fatty liver, hepatic cirrhosis, metabolism syndrome, and severe cardiovascular diseases. Having provided a written informed consent, each patient donated a 5-mL peripheral venous blood sample and completed a Semiquantitative Food Frequency Questionnaire, with assistance from study interviewers, which collected demographic information as well as information about dietary, smoking, and alcohol habits. For each eligible case, one or two control patients, matched by age within 5 y, sex, and residence, were recruited from the Departments of General Surgery, Orthopedics, or Trauma who were admitted for trauma, bone fracture, appendicitis, arthritis, or varicose vein. Control patients with (*a*) tumors; (*b*) severe digestive tract diseases over 2 y; (*c*) diabetes, fatty liver, hepatic cirrhosis, metabolism syndrome, and severe cardiovascular diseases were excluded. All controls also provided their written informed consent, Semiquantitative Food Frequency Questionnaire, and blood samples as the CRC patients group. In this study, we excluded patients and controls whose drinking habits were absent, as a result, a sample of 440 patients and 800 controls were studied.

**Drinking Habits.** Data about drinking habits was collected by Semiquantitative Food Frequency Questionnaire, and the population was divided into two groups by their average daily alcohol consumption under or above 15 grams, the recommended level of daily alcohol consumption suggested by China Health Care Association (8). Additionally, our previous study showed a significant increase in CRC susceptibility, when average alcohol consumption exceeded 15 grams/d.

**Table 1. TagSNPs screened from the *ADH1B*, *ALDH2*, and *CYP4502E1* genes**

| Gene | Total no. of reported SNPs | tagSNPs* |
|---|---|---|
| *ADH1B* | 30 | rs2075633, rs17033, rs1229984 |
| *ALDH2* | 33 | rs440, rs4767939, rs4767944, rs671, rs16941669, rs886205, rs7296651 |
| *CYP4502E1* | 62 | rs1329149, rs2249695, rs2480259, rs8192772, rs8192775, rs915908 |

*Sixteen loci screened from the three genes that were related to alcohol metabolism.

**Screening for Candidate SNPs in Genes Related to Alcohol Metabolism.** The SNP information for the Chinese Han population of full-length genes plus 2,000 bp in the upper stream of each candidate gene was obtained from the HapMap (version 33). After setting the minor allele frequency at 0.03, the Haploview software was used to screen for the tag-SNPs from *ADH1B, ALDH2*, and *CYP2E1* (Table 1). Only one SNP was selected in each of linkage disequilibrium blocks. As a result, a total of 16 tagSNPs from the 127 reported SNPs of the three major genes metabolizing alcohol.

**Genotyping of Selected TagSNPs.** DNA was extracted from 2.5-mL whole blood with a Promega DNA Purification Wizard kit according to the manufacturer's instructions and diluted to 37 ng/μL by Tris-EDTA, and then aliquoted into sealed 96-well plates and stored at −20°C. The identified 16 tagSNPs were genotyped by SNPLex (Applied Biosystems Incorporated). Loci were submitted online to ABI, probes were designed and synthesized by ABI. The OLA, purification, and PCR reactions were done on an Eppendorf 5333 Mastercycler, and allele inspection was done on an ABI 3130xl Gene Analyzer. All the steps were carried out as the recommendation in the SNPlex Genotyping System 48-plex User Guide. The main reagents used in reactions and allele inspection were provided by ABI in the SNPlex Genotyping System 48-plex kit. After the information was collected, 10% of the samples were randomly repeated to verify the results. The information about the SNPs was collected using Data Collection Software version 3.0, and the genotypes were analyzed by GeneMapper Software version 4.0. One locus (rs2480259) failed in probe synthesis due to the SNPLex technological limitation, and another locus (rs440) could not be genotyped in the reactions, as a result, 13 loci were successfully genotyped and analyzed.

**Statistical Analysis.** Genotype frequencies were determined by direct counting, and Hardy-Weinberg equilibrium in control group was assessed by $\chi^2$ test. Associations between polymorphisms and CRC were estimated by odds ratios (OR) with 95% confidence interval (CI), using an unconditional logistic regression model. The ORs were adjusted for age, sex, smoking, and alcohol consumption. The population was divided into two subgroups based on their average daily alcohol consumption, with those who drank no >15 grams/d considered "nondrinkers," and the rest considered "drinkers." All calculations were carried out using Statistical Analysis System (version 9.0; SAS Institute, Inc.).

## Results

**Subject Characteristics.** As shown in Table 2, a total of 1,220 including 788 controls and 432 cases were successfully genotyped in this study. In both of the groups, male was more than female, but no significant difference in sex existed between the two groups ($P > 0.05$), suggesting the matching was adequate. The average age of the studied population was 56 y, and the subjects were divided into five age groups by an interval of 10 y; however, there was significant difference in age between control and CRC patients ($P < 0.01$), suggesting the matching was not adequate, which needs additional adjustment in later multivariate analysis. Considering the people consuming no >15 grams of pure alcohol per day as nondrinkers and the rest as drinkers, the study population was divided into two groups, i.e., the drinking and nondrinking group, which distributed differently between cases and controls ($P < 0.01$). No difference was observed for smoking status ($P > 0.05$).

**TagSNPs Genotyping and Association with CRC Risk.** Within the control group, all tested loci were in Hardy-Weignberg equilibrium except for rs915908 (Table 3). By setting the ancestral allele defined in dbSNP database or common allele (no ancestral allele is defined for rs1329149 in the dbSNP database) as the reference allele, two (rs671 and rs1329149) of the 13 loci were found to be significantly associated with CRC risk (Table 3).

In the CRC associated loci, the rs671 A/A genotype was associated with an increase risk for CRC risk with age-, sex-, smoking-, and alcohol consumption–adjusted OR of 1.86 (95% CI, 1.12-3.09), and the rs1329149 T/T genotype was associated with moderately increased risk of CRC with age-, sex-, smoking-, and alcohol consumption–adjusted OR of 4.04 (95% CI, 2.44-6.70).

When the recessive model was assumed, we found that the rs671 A/A genotype was associated with an increased risk of CRC (OR, 1.95; 95% CI, 1.19-3.21), compared with A/G and G/G genotypes and that the rs1329149 T/T genotype was associated with an increased risk of CRC (OR, 4.09; 95% CI, 2.48-6.74) compared with C/T and C/C genotypes (Table 4).

**Table 2. Demographic distributions in a hospital-based case-control study in Southwestern China**

| Characteristics | CRC patients (%) | Controls (%) | *P* |
|---|---|---|---|
| Total | 432 (100) | 788 (100) | |
| Gender | | | 0.808 |
| Male | 237 (54.86) | 438 (55.58) | |
| Female | 195 (45.14) | 350 (44.42) | |
| Age in years | | | 0.009 |
| <40 | 81 (18.75) | 150 (19.04) | |
| 40-50 | 65 (15.05) | 152 (19.29) | |
| 50-60 | 129 (29.86) | 263 (33.38) | |
| 60-70 | 116 (26.85) | 183 (23.22) | |
| ≥70 | 41 (9.49) | 40 (5.08) | |
| Alcohol use* | | | 0.009 |
| No (=15 grams/d) | 321 (74.31) | 636 (80.71) | |
| Yes (>15 grams/d) | 111 (25.69) | 152 (19.29) | |
| Smoking | | | 0.591 |
| No | 258 (59.72) | 483 (61.29) | |
| Yes | 174 (40.28) | 305 (38.71) | |

*The level to define drinking or not drinking based on the recommended level of China Health Care Association.

**Gene-Gene Interaction.** We combined the loci reported in Table 4 to analyze the interaction between *ALDH2* rs671 and *CYP2E1* rs1329149 polymorphisms on CRC risk. However, no significant interaction was found between the two loci, and only the increased risk trend was found in the number of A and T allele combination.

**Gene-Alcohol Consumption Interaction.** In the recessive model, an interaction between alcohol consumption and rs671 or rs1329149 was found. After dividing the population into two groups by drinking or not drinking, compared with the reference genotype (rs671 G/G+A/G and rs1329149 C/C+C/T), we found a 7.2-fold increased risk (95% CI, 2.01-25.53) of CRC in drinkers but only 2.5-fold increased risk (95% CI, 1.70-3.81) of CRC in nondrinkers (Table 5).

## Discussion

Chronic alcohol consumption has been reported by many studies to be associated with various cancers (1). In China, a recent investigation covered 25 provinces including Chongqing indicated that 15.2% adolescents started drinking alcohol before age 18 years, and up to 65.39% of these young drinkers drank frequently and/or excessively, with an average consumption of 41.04 grams pure alcohol per instance (8), which exceeded the 20 grams defined as the safe drinking level by International Center for Alcohol Policies (30), and also the 15-gram level suggested as the safe drinking level by China Health Care Association (8). In Chinese drinking population, the average drinking frequency was 0.6 times per day, with >36% of drinkers consuming alcohol more than once per day (8). Thus, excessive alcohol consumption is a serious and worsening social problem that is likely to lead to severe health problems in the Chinese population.

Our previous study showed that alcohol consumption was associated with an increased risk of CRC (9). In this study, we investigated genetic variants in the three genes encoding the major alcohol metabolizing enzymes (ADH1B, ALDH2, and CYP2E1). To our knowledge, this is the first report on the association between tag SNPs in

**Table 3. Distributions of screened SNPs loci in case and control groups**

| SNPs | Genotype* | Cases | Controls | *P* for genotypes' distributions | *P* for H-W equilibrium |
|---|---|---|---|---|---|
| rs2075633 | AA | 13 | 24 | 0.99 | 0.43 |
| | AG | 130 | 241 | | |
| | GG | 273 | 498 | | |
| rs17033 | AA | 347 | 628 | 0.95 | 0.74 |
| | AG | 75 | 132 | | |
| | GG | 4 | 6 | | |
| rs1229984 | GG | 39 | 62 | 0.85 | 0.56 |
| | GA | 181 | 319 | | |
| | AA | 205 | 370 | | |
| rs4767939 | GG | 333 | 607 | 0.97 | 0.67 |
| | GA | 89 | 159 | | |
| | AA | 6 | 12 | | |
| rs4767944 | CC | 60 | 97 | 0.75 | 0.8 |
| | CT | 191 | 356 | | |
| | TT | 176 | 314 | | |
| rs671 | GG | 274 | 489 | 0.02* | 0.98 |
| | GA | 119 | 261 | | |
| | AA | 33 | 35 | | |
| rs16941669 | TT | 394 | 690 | 0.96 | 0.66 |
| | TG | 34 | 63 | | |
| | GG | 1 | 2 | | |
| rs886205 | CC | 325 | 590 | 0.67 | 0.29 |
| | CT | 94 | 154 | | |
| | TT | 6 | 14 | | |
| rs7296651 | GG | 316 | 529 | 0.76 | 0.8 |
| | GC | 93 | 139 | | |
| | CC | 6 | 10 | | |
| rs1329149 | TT | 263 | 520 | <0.001† | 0.61 |
| | TC | 103 | 214 | | |
| | CC | 51 | 25 | | |
| rs2249695 | TT | 68 | 125 | 0.77 | 0.38 |
| | TC | 222 | 388 | | |
| | CC | 137 | 264 | | |
| rs8192772 | TT | 244 | 473 | 0.12 | 0.37 |
| | TC | 164 | 254 | | |
| | CC | 17 | 41 | | |
| rs8192775 | GG | 245 | 436 | 0.72 | 0.86 |
| | GA | 165 | 288 | | |
| | AA | 21 | 46 | | |
| rs915908 | GG | 303 | 513 | 0.09 | 0.01 |
| | GA | 115 | 255 | | |
| | AA | 12 | 16 | | |

NOTE: The total number for each tagSNP was less than the total number of the study population due to some missing genotyping data.
*The reference allele was determined following the ancestral allele defined in dbSNP, except for rs1329149 that was not defined in the database. The common allele in locus rs1329149 was defined as reference allele.
†The distributions of the genotypes were significantly different between controls and patients.

**Table 4. Association between CRC risk and the two tagSNPs (rs671 and rs1329149)**

| Locus | Genotype | Cases *n* (%) | Controls *n* (%) | Adjusted OR (95% CI)* | *P* |
|---|---|---|---|---|---|
| rs671 | GG | 274 (64.32) | 489 (62.29) | 1.00 | Reference |
| | AG | 119 (27.93) | 261 (33.25) | 0.87 (0.67-1.14) | 0.33 |
| | AA | 33 (7.75) | 35 (4.46) | 1.86 (1.12-3.09) | 0.02† |
| | AG+GG | 393 (92.25) | 750 (95.54) | 1.00 | Reference |
| | AA | 33 (7.75) | 35 (4.46) | 1.95 (1.19-3.21) | 0.01† |
| rs1329149 | CC | 263 (63.07) | 520 (68.51) | 1.00 | Reference |
| | CT | 103 (24.70) | 214 (28.19) | 0.96 (0.72-1.27) | 0.75 |
| | TT | 51 (12.23) | 25 (3.29) | 4.04 (2.44-6.70) | <0.001‡ |
| | CT+CC | 366 (87.77) | 734 (96.71) | 1.00 | Reference |
| | TT | 51 (12.23) | 25 (3.29) | 4.09 (2.48-6.74) | <0.001‡ |

*Adjusted for age, sex, smoking, and alcohol consumption.
†$P < 0.05$.
‡$P < 0.01$.

these alcohol metabolizing enzymes and CRC risk in Chinese populations. Among the 127 reported SNPs, 16 tagSNPs were selected by the Haploview software, of which two loci, rs671 in *ALDH2* and rs1329149 in *CYP2E1ADH1B*, were found to be significantly associated with CRC risk.

The rs671 G > A base change causes a glutamic acid change to lysine, and the A allele encodes a lysine subunit which is catalytically inactive, often described as ALDH2*2 (15).Theoretically, when ALDH2 activity is decreased, the blood acetaldehyde level should increase in the mucosa of the large intestine as well as in the blood, which would result in an increased risk of CRC. However, previously published studies have generated some inconsistent results. The A allele showed risk effects in some studies but protective effects in some other studies. In a recent study in a Chinese Han male population of 190 CRC cases and 222 controls, Gao CM et al. (22) found that rs671 A/G and A/A genotypes were both protective against CRC risk, but our results showed an opposite effect. As ALDH2 is the major enzyme metabolizing acetaldehyde, its inactivation (with an A allele in the gene) brings the accumulation of acetaldehyde, which may cause a series of symptoms that may prevent someone from drinking. According to a survey, drinking habits between the two populations were different, the percentage of drinkers who continue drinking even they had symptoms of alcohol intoxication is higher in southwestern population than that in Gao's study population (8). This behavioral difference may partially explain why the results were opposite in different geographic populations in Chinese Han population.

*CYP2E1* has been extensively studied in alcohol-related diseases. *CYP2E1* is a well-conserved gene encoding an enzyme that metabolizes a broad range of organic solvents, such as N-nitroso-dimethylamine, vinyl chloride, benzene, and alcohol. Many of the substrates exert a high affinity for the enzyme (31). In both humans and animals, a 10- to 20-fold increase in hepatic CYP2E1 was observed after chronic alcohol consumption (32). Alcohol metabolized by CYP2E1 leads to the formation of reactive oxygen species, which causes oxidative injury leading to various diseases, including cancer (16). In animal experiments, the induction of CYP2E1 correlates with increased NADPH oxidase activity, the generation of HER, lipid peroxidation, and the severity of hepatic injury, all of which could be prevented by chlormethiazole, a CYP2E1 inhibitor (33). These indicate that CYP2E1 may play an important role in alcohol-mediated liver pathology and cancer development. The most frequently studied SNPs in *CYP2E1* were rs2031920 in the 5′-flanking region and rs6413432 in intron 6, and to a less extent, the rs2070676 in intron 7. Although no association was found between *CYP2E1* SNPs and esophageal cancer (34) or hepatic cancer (35), in meta-analyses, the *CYP2E1* rs2031920 T allele was associated with a decreased risk of rectal cancer (OR, 0.71) in a Japanese population (36). In contrast, Gao et al. (22) reported that the T allele was a risk factor for CRC (OR, 1.55; genotype T/T versusC/C) in Chinese males.

We genotyped six *CYP2E1* tagSNPs and found that rs1329149 was significantly associated with CRC risk. This locus was in the block consisting of 19 loci. Locus rs1329149 is located in intron 6,766 bp from the nearest exon (exon 7) and is characterized by a C>T base change. However, no other information was available in the literature about this locus, nor its functional study or association with cancers. In this block, several loci (including rs2070676, rs2070677, and rs2515641) were recorded in the SNP500 Cancer Project. The nearest locus to rs1329149 is rs2070676, which is located in intron 7, and exon 7 is located between these two loci. Thus, it is likely that the observed association between rs1329149 and CRC

**Table 5. Analysis of genotypes and combined with alcohol consumption**

| Alcohol | Combined genotypes* | Cases (%) | Controls (%) | Adjusted OR (95% CI)† | *P* |
|---|---|---|---|---|---|
| Yes | 1 | 95 (85.59) | 142 (97.93) | 1.00 | Reference |
| | 2 | 16 (14.41) | 3 (2.07) | 7.17 (2.01-25.53) | 0.002‡ |
| No | 1 | 243 (80.46) | 559 (91.34) | 1.00 | Reference |
| | 2 | 59 (19.54) | 53 (8.66) | 2.55 (1.70-3.81) | <0.001§ |

*Combined genotypes: 1 = rs671 AG+GG and rs1329149 CT+CC and 2 = rs671 AA and rs1329149 CT+CC, or rs671 GG+AG and rs1329149 TT, or rs671 AA and rs1329149 TT.
†Adjusted for age, sex, and smoking.
‡$P < 0.01$.
§$P < 0.001$.

may be related to rs2070676. We genotyped rs2070676 in the same population and found rs2070676 G allele were at higher risk of developing CRC, the OR was 2.60, and 95% CI was 1.06 to 6.39 ($P = 0.04$), which indicated the polymorphisms in this block may associated with CRC development and rs1329149 was a representitive SNP. Further studies are needed to explore the mechanism underlying the association between rs1329149 and CRC.

In summary, a novel locus *CYP2E1* rs1329149 and a known locus *ALDH2* rs671 were found to be associated with a moderate increase in the risk of developing CRC in a population from southwest China. However, further studies in different populations and with a larger sample size are needed to confirm the association between these loci and CRC, especially for locus rs1329149.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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