Meta-analysis of the ADH1B and ALDH2 Polymorphisms and the Risk of Colorectal Cancer in East Asians

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Abstract

Objective  The aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase 1B (ADH1B) genes have been implicated in the development of colorectal cancer (CRC). However, the results are inconsistent. In this study, a meta-analysis was performed to assess the associations between the ALDH2 and ADH1B polymorphisms and the risk of CRC.

Methods  Relevant studies were identified using PubMed, Web of Science and CNKI up to February, 2013. The pooled odds ratio (OR) with a 95% confidence interval (CI) was calculated using the fixed- or random-effects model.

Results  A total of 11 case-controlled studies were selected. Of these, 11 studies included 2,893 cases and 3,817 controls concerning the ALDH2 Glu487Lys polymorphism and six studies included 1,864 cases and 3,502 controls concerning the ADH1B polymorphism. The results indicated that there was a statistically significant link between the ALDH2 polymorphism and the risk of CRC (Glu/Lys+Lys/Lys vs. Glu/Glu: OR=0.87, 95%CI: 0.78-0.96, p=0.10; Glu/Lys vs. Glu/Glu: OR=0.87, 95%CI: 0.77-0.97, p=0.38); however, no significant associations were observed between the ADH1B polymorphism and the risk of CRC in any of the genetic models.

Conclusion  This meta-analysis demonstrated that the ALDH2 polymorphism, but not the ADH1B polymorphism, significantly increases the risk of CRC in East Asians.

Key words:  ALDH2, ADH1B, polymorphism, colorectal cancer, meta-analysis


Introduction

Colorectal cancer (CRC) is a common digestive malignancy, the incidence of which is slightly lower than that of gastric and esophageal cancer. Although the pathogenesis of CRC is unknown, approximately 20% of cases are attributed to hereditary factors of high penetrance (1). Epidemiological studies have demonstrated the importance of a diet high in red meat and fat as a risk factor for CRC. Tobacco and alcohol consumption is also related to CRC, especially in patients with polymorphic genetic variations (2, 3). It is plausible that genes of low penetrance combined with environmental factors contribute to the pathogenesis and progression of CRC.

The metabolism of alcohol consists of two steps and involves alcohol dehydrogenase-1B (ADH1B) and aldehyde dehydrogenase-2 (ALDH2), two genes of enzymatic oxidation. Upon the consumption of an alcoholic beverage, ethanol is first catalytically oxidized into acetaldehyde, primarily by ADH1B. Acetaldehyde is subsequently metabolized into harmless acetate, chiefly by ALDH2. Therefore, genetic variants that result in functional differences in enzyme activity lead to differences in acetaldehyde exposure between drinkers. A polymorphism in the ADH1B gene, resulting in an amino acid transition from arginine (Arg) to histidine (His) at codon 47 (Arg47His) in exon 3, bestows a superactive “fast” metabolic characteristic on ethanol. An approximately 40 times greater maximum velocity has been identified for the ADH1B fast His allele than for the less active

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Received for publication June 20, 2013; Accepted for publication July 18, 2013
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Arg/Arg form (4, 5). In contrast, ALDH2 has a polymorphism that results from the substitution of glutamate (Glu) to lysine (Lys) at residue 487 (also recognized as Glu504 Lys), which encodes a catalytically inactive subunit of ALDH2 whose ALDH2 Glu/Lys genotype has only 6.25% of the normal ALDH2 Glu proteins (6). Polymorphisms in ALDH2 and ADH1B are prevalent in approximately half of East Asians but absent in Europeans and Africans (7).

To date, many studies have investigated the associations between the ADH1B and ALDH2 polymorphisms and the risk of CRC. However, the results have been inconsistent (8-18). The present comprehensive meta-analysis of currently published studies aimed to identify the relationships between the ADH1B and ALDH2 polymorphisms and the risk of CRC.

Materials and Methods

Search strategy

Literature databases, including PubMed, Web of Science and CNKI, were searched up to February, 2013 without any language restrictions. Relevant studies were identified using the terms, “aldehyde dehydrogenase 2 or ALDH2,” “alcohol dehydrogenase or ADH2 or ADH1B” and “genetic polymorphism or polymorphisms or single nucleotide polymorphism (SNP)” and “colorectal cancer/neoplasms or colon cancer/neoplasms or rectal cancer/neoplasms.” The search was restricted to studies of humans. Additional studies were identified using a hand search of references of original or review articles on this topic. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

Inclusion and exclusion criteria

The following inclusion criteria were used: 1) studies that evaluated the associations between the ALDH2 and ADH1B polymorphisms and CRC, 2) a case-controlled study design, 3) a detailed genotype frequency of cases and controls or such data that could be calculated from the article text. The major exclusion criteria were as follows: 1) case-only studies, case reports or review articles, 2) studies without the raw data of the four genotypes of ALDH2 or ADH1B, 3) studies that compared the ALDH2 and ADH1B variants in patients with familial adenomatous polyposis or colorectal adenoma.

Data extraction and quality assessment

Two investigators (Guo XF and Wang J) independently extracted the data and reached a consensus on all items. If the two investigators generated different results, they assessed the data again and had a discussion to come to an agreement. If they were unable to reach an agreement, an expert (Dong WG) was invited to the discussion. The data extracted from the selected articles included the first author’s name, year of publication, country of origin, genotyping methods, number of cases and controls and $P_{\text{HWE}}$ in control.

Statistical analysis

The risk of CRC associated with the ALDH2 and ADH1B polymorphisms was estimated for each study according to the odds ratio (OR) and 95% confidence interval (95%CI). A $\chi^2$-test-based Q statistic test was performed to assess the between-study heterogeneity (19). We also quantified the effects of heterogeneity using the $I^2$ test. When a significant Q test ($p<0.1$) or $I^2>50\%$ indicated heterogeneity across studies, either the random effects model (20) or the fixed effects model was used (21). Before estimating the effects of the ALDH2 and ADH1B polymorphisms on colorectal cancer, we tested whether the genotype frequencies of the controls were in Hardy-Weinberg equilibrium (HWE) using the $\chi^2$ test. We first estimated the risks of the heterozygote and variant homozygote compared with the wild-type homozygote, respectively, then evaluated the risks of the combined variant homozygote and heterozygote versus the wild-type homozygote and the variant homozygote versus the combined heterozygote and wild-type homozygote assuming the dominant and recessive effects of the variant allele, respectively. A sensitivity analysis was performed to evaluate the stability of the results. Publication bias was investigated using Begg's funnel plot and Egger's regression test (22, 23) ($p<0.05$ was considered to be statistically significant). The data analysis was performed using the Cochrane Collaboration RevMan 5.0 (Copenhagen, 2008) and STATA version 12.0 (Stata Corporation, College Station, Texas, USA) software package.

Results

Study characteristics

The search strategy retrieved 86 potentially relevant studies. According to the inclusion criteria and exclusion criteria, 11 studies with full text were included in the meta-analysis and 75 studies were excluded. A flow chart of the study selection process is summarized in Fig. 1. As shown
in Table, there were 11 case-controlled studies with 2,893 cancer cases and 3,817 controls concerning the ALDH2 Glu487Lys polymorphism and six case-controlled studies with 1,864 cancer cases and 3,502 controls concerning the ADH1B polymorphism. Of the 11 case-controlled studies selected for the meta-analysis, four (8-10, 16) were performed in China and seven (11-15, 17, 18) were conducted in Japan. The distribution of genotypes in the controls was consistent with the Hardy-Weinberg equilibrium in all selected studies, except for two studies (11, 18) of the ALDH2 polymorphism, the $P_{HWE}$ values of which were not available.

**Quantitative data synthesis**

**ALDH2 polymorphism**

Eleven studies reported an association between the ALDH2 polymorphism and susceptibility to CRC. The results showed that there was a statistically significant link between the ALDH2 polymorphism and the risk of CRC in dominant and heterozygote comparison models (Glu/Lys+Lys/Lys vs. Glu/Glu: $OR=0.87$, 95%CI: 0.78-0.96, $p=0.10$; Glu/Lys vs. Glu/Glu: $OR=0.87$, 95%CI: 0.77-0.97, $p=0.38$), whereas, under recessive and homozygote comparison models, no obvious associations were observed [Lys/Lys vs. Glu/Lys+Glu/Glu: $OR=1.00$, 95%CI: 0.70-1.43, $p=0.04$; Lys/Lys vs. Glu/Glu: $OR=0.96$, 95%CI: 0.66-1.39, $p=0.04$] (Fig. 2).

**ADH1B polymorphism**

Six studies reported an association between the ADH1B polymorphism and the risk of CRC. The combined results based on all studies showed that no significant associations between the ADH1B polymorphism and the risk of CRC risk were observed in any of the genetic models [Arg/Arg+Arg/His vs. His/His: $OR=1.00$, 95%CI: 0.79-1.27, $p=0.001$; Arg/Arg vs. Arg/His+His/His: $OR=1.12$, 95%CI: 0.90-1.41, $p=0.06$; Arg/His vs. His/His: $OR=0.99$, 95%CI: 0.78-1.26, $p=0.003$; Arg/Arg vs. His/His: $OR=1.13$, 95%CI: 0.90-1.42, $p=0.23$] (Fig. 3).

**Sensitivity analyses**

The influence of these studies on the pooled OR was examined by repeating the meta-analysis while excluding the study that was not in HWE. The estimated pooled odds ratio did not change, indicating that our results were statistically robust.

**Publication bias**

Begg’s funnel plot and Egger’s test were used to address potential publication bias in the available literature. As shown in Fig. 4, the shape of the funnel plots did not reveal any evidence of funnel plot asymmetry. Egger’s test also showed that there was no statistical significance for the evaluation of publication bias (ALDH2: Glu/Lys+Lys/Lys vs. Glu/Glu: $OR=0.96$, 95%CI: 0.66-1.39, $p=0.04$) (Fig. 2).
Figure 2. Forest plots for the association of ALDH2 and colorectal cancer risk. A: Glu/Lys+Lys/Lys vs. Glu/Glu, B: Lys/Lys vs. Glu/Lys+Glu/Glu, C: Glu/Lys vs. Glu/Glu, D: Lys/Lys vs. Glu/Glu.

vs. Glu/Glu p=0.487; Lys/Lys vs. Glu/Lys+Glu/Glu p=0.884; Glu/Lys vs. Glu/Glu p=0.742; Lys/Lys vs. Glu/Glu p=0.904; ADH1B: Arg/Arg+Arg/His vs. His/His p=0.104; Arg/Arg vs. Arg/His+His/His p=0.368; Arg/His vs. His/His p=0.086; Arg/Arg vs. His/His p=0.284).

Discussion

Many studies have shown that polymorphisms in a significant number of genes affect the risk of colorectal can-
In particular, ALDH2 and ADH1B polymorphisms have been extensively investigated recently. However, the associations between the ALDH2 and ADH1B polymorphisms and the risk of CRC have not been addressed conclusively. Yokoyama et al. (18) first reported an association between the ALDH2 polymorphism and the risk of CRC and suggested that the ALDH2 polymorphism plays a general role in the development of human cancers. In this study, we conducted a meta-analysis to evaluate the associations between the ALDH2 and ADH1B polymorphisms and the risk of CRC. A total of 11 case-controlled studies were selected, of which, 11 studies included 2,893 cases and 3,817 controls concerning the ALDH2 Glu487Lys polymorphism and six studies included 1,864 cases and 3,502 controls concerning the ADH1B polymorphism. We found that there was a statistically significant link between the ALDH2 polymorphism and the risk of CRC, whereas no significant associations were observed between the ADH1B polymorphism and the risk of CRC in any of the genetic models. Due to the limitations in the number of studies, the conclusions should be sensibly considered. In this meta-analysis, heterogeneity was found under recessive and homozygote comparison models in the ALDH2 polymorphism and dominant and heterozygote comparison models in the ADH1B polymorphism. Then, the sensitivity analyses were conducted by excluding the study that was...
The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We are very grateful to Mr. Hong Xia from the Key Laboratory of Hubei Province for Digestive System Disease for his valuable assistance with the data collection.

Funding
This study was supported by the Fundamental Research Funds for the Central Universities of China (No. 2012302020208). The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

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