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Association between aldehyde dehydrogenase 2 (*ALDH2*) Glu504Lys polymorphism and susceptibility to colorectal cancer: a meta-analysis

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ABSTRACT. Numerous studies have evaluated the association between Glu504Lys polymorphism in the aldehyde dehydrogenase 2 (ALDH2) gene and colorectal cancer (CRC) risk. However, the specific association remains controversial. To assess the relationship between the *ALDH2* Glu504Lys polymorphism and CRC, we conducted a comprehensive meta-analysis of five case-control studies comprising 1664 patients with CRC and 2777 controls. The results of this meta-analysis showed that the *ALDH2* Glu504Lys polymorphism was associated with a significantly reduced risk of CRC [Lys/Lys *vs* Glu/Glu: odds ratio (OR) = 0.95, 95% confidence interval (CI) = 0.58-1.54; Glu/Lys *vs* Glu/Glu: OR = 0.85, 95%CI = 0.75-0.97; dominant model: OR = 0.86, 95%CI = 0.76-0.98; recessive model: OR = 1.00, 95%CI = 0.62-1.61]. No significant heterogeneity or publication bias

was observed in our meta-analysis. Based on the statistical data, our meta-analysis indicates that the *ALDH2* Glu504Lys polymorphism is associated with reduced risk of developing CRC.

Key words: ALDH; Gene polymorphism; CRC; Meta-analysis

INTRODUCTION

Colorectal cancer (CRC) is a common type of cancer that is the third leading cause of cancer-related deaths worldwide (Jemal et al., 2010). There has been an increase in the incidence of CRC over the past few years due to demographical changes and the implementation of a Western lifestyle in developing countries (Andersen and Vogel, 2014). It is a multifactorial disease resulting from complex interactions between genetic, epigenetic, and environmental factors. However, the exact cellular and molecular mechanisms of CRC remain unclear. Factors that contribute to CRC incidence include alcohol consumption, tobacco usage, physical inactivity, and obesity (Ward et al., 2004; Fedirko et al., 2011). However, approximately 25% of the cases are attributable to a family history of CRC (Chen et al., 2006), indicating the prominent role played by genetic factors in colorectal carcinogenesis.

Ethanol is mainly metabolized in the liver through two rate-limiting reactions: conversion of ethanol into acetaldehyde by alcohol dehydrogenase (ADH), and the subsequent conversion of acetaldehyde to acetate by aldehyde dehydrogenase (ALDH) (Ehlers et al., 2012). To date, 18 genes have been identified in the ALDH gene superfamily, among which ALDH2 is the most widely studied. The *ALDH2* gene is located on chromosome 12q24.2 and is composed of 13 exons, spanning 46,031 bp (Yoshida et al., 1998). A G-to-A missense mutation occurs in exon 12, where glutamate at position 504 is replaced by lysine (Glu504Lys). This polymorphism is believed to decrease the activity of the ALDH2 enzyme, leading to higher levels of acetaldehyde in the blood (Jo et al., 2007). Previous meta-analyses have suggested that the *ALDH2* Glu504Lys polymorphism could be strongly correlated with an increased risk of gastric cancer (Wang et al., 2014).

Several recent studies have evaluated the association between the *ALDH2* Glu504Lys polymorphism and CRC risk (Otani et al., 2005; Matsuo et al., 2006; Yin et al., 2007; Gao et al., 2008; Yang et al., 2009). Meta-analysis is a useful tool for the detection and manipulation of potential inconsistencies between combined datasets, especially in those evaluating rare allele frequency polymorphisms (Attia et al., 2003; Kavvoura and Ioannidis, 2008). Therefore, in this study, we have performed a quantitative meta-analysis of all eligible studies reporting a correlation between the *ALDH2* Glu504Lys polymorphism and CRC risk.

MATERIAL AND METHODS

Literature search

All studies assessing the associations between the *ALDH2* Glu504Lys polymorphism and CRC were retrieved by an intensive search of the PubMed and Embase databases using the following retrieval terms: “colorectal cancer”, “alcohol dehydrogenase” or “ALDH”, and “polymorphism” or “allele” or “genetic variant” or “variants”. The latest search was conducted on May 2015 without any language restriction. In addition, this search was supplemented by reviewing the reference lists of all retrieved publications and identifying additional relevant articles.

Inclusion and exclusion criteria

The studies had to meet the following criteria for inclusion in the meta-analysis: i) case-control studies evaluating the association between the Glu504Lys polymorphism in the *ALDH2* gene and risk of CRC; ii) studies with sufficient genotype data for the calculation of odds ratios (ORs) and 95% confidence intervals (CIs); and iii) papers clearly describing the sources of cases and controls. Reviews, meta-analyses, and case reports were excluded from the analysis. Moreover, studies lacking key information were excluded from the analysis.

Data extraction

The data were independently extracted by two investigators. Differences in results were resolved by a second evaluation, followed by a discussion, by the investigators. The following information was extracted from each study: first author's last name, publication year, country of origin, ethnicity, number of cases and controls, polymorphisms, genotype frequency, and evidence of conformance with the Hardy-Weinberg Equilibrium (HWE) in controls.

Statistical analysis

The association between the Glu504Lys polymorphism in the *ALDH2* gene and risk of CRC was analyzed by calculating the pooled ORs and the associated 95%CIs. The ORs between different groups were calculated using the co-dominant (Lys/Lys *vs* Glu/Glu, Glu/Lys *vs* Glu/Glu), dominant (Lys/Lys + Glu/Lys *vs* Glu/Glu), and recessive (Lys/Lys *vs* Glu/Lys + Glu/Glu) models (Sun et al., 2014). Heterogeneity among studies was assessed by the I^2 statistic, which described the proportion of total variation attributable to between-study differences or heterogeneity, as opposed to random error or chance. The random-effect model was used to pool data when $I^2 > 50\%$; in all other cases, the fixed-effect model was used. Sensitivity analysis was performed by omitting one study at a time to determine its magnitude of influence on the overall summary estimate (Crump et al., 2004). Publication bias was examined using the Begg funnel plot. $P < 0.05$ was considered statistically significant. Data were analyzed using the STATA V.12.0 (Stata Corporation, College Station, TX, USA) software package.

RESULTS

Study characteristics

The literature search retrieved 205 potentially relevant studies. Five of these studies (full-text) that conformed to all inclusion and exclusion criteria were included in the meta-analysis, while the remaining studies were discarded (Otani et al., 2005; Matsuo et al., 2006; Yin et al., 2007; Gao et al., 2008; Yang et al., 2009). The studies published between 2005 and 2010 were included. The study selection process is summarized in a flow chart (Figure 1). A total of 4441 subjects, including 1664 patients with CRC and 2777 healthy controls, were included in this meta-analysis. The conformance of the genotype distribution of the controls in all 11 studies to the HWE was tested. None of the studies deviated from the HWE (all had $P > 0.05$). The characteristics and methodological qualities of the included studies are summarized in Table 1.

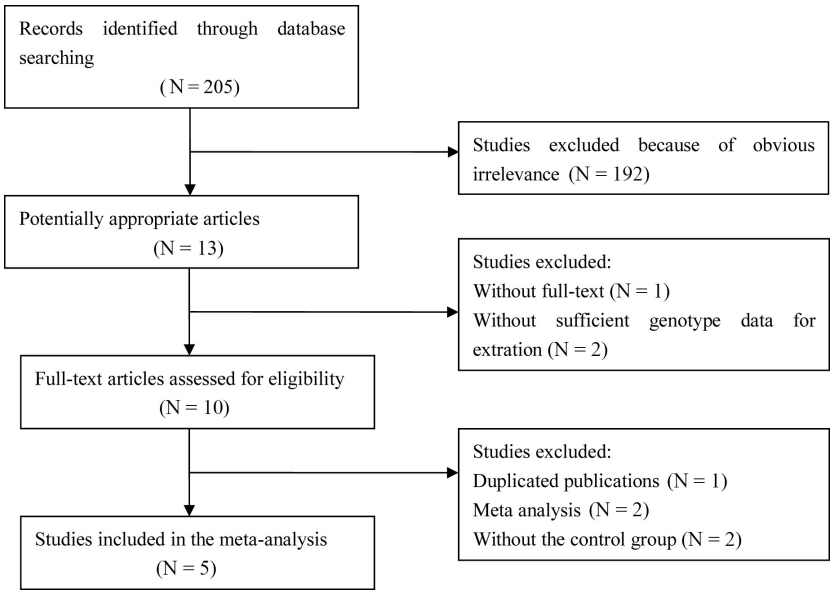

Figure 1. Flow chart depicting the study selection.

Table 1. Characteristics of the studies included in the meta-analysis.

First author of each included study	Year	Area	Race	Cases/controls	Genotypes for cases			Genotypes for controls			HWE test
					Glu/Glu	Glu/Lys	Lys/Lys	Glu/Glu	Glu/Lys	Lys/Lys	
Otani	2005	Japan	Asian	106/224	61	36	9	137	72	15	0.20
Matsuo	2006	Japan	Asian	257/768	129	104	24	383	314	71	0.57
Yin	2007	Japan	Asian	685/778	400	257	28	416	309	53	0.67
Gao	2008	China	Asian	190/222	131	54	5	123	90	9	0.13
Yang	2009	China	Asian	426/785	274	119	33	489	261	35	0.98

HWE = Hardy-Weinberg equilibrium.

Meta-analysis

Power analysis was performed using the statistical program PS: Power and sample size calculation (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) (Yao et al., 2015). Single studies are known to have insufficient power because of the small sample sizes, leading to inconclusive study results. The results of the heterogeneity test and the meta-analysis of the association between the *ALDH2* Glu504Lys polymorphism and CRC risk are presented in Figures 2-5 and Table 2. The combined results summarized in Figures 3 and 4 show an association between this variant and reduced risk of CRC (Lys/Lys *vs* Glu/Glu: OR = 0.95, 95%CI = 0.58-1.54; Glu/Lys *vs* Glu/Glu: OR = 0.85, 95%CI = 0.75-0.97; dominant model: OR = 0.86, 95%CI = 0.76-0.98; recessive model: OR = 1.00, 95%CI = 0.62-1.61). One-way sensitivity analysis was performed to assess the stability of the meta-analysis (Crump et al., 2004). The statistical significances of the overall results did not change when individual studies were omitted, indicating that the results of this meta-analysis were statistically significant (Figure 6).

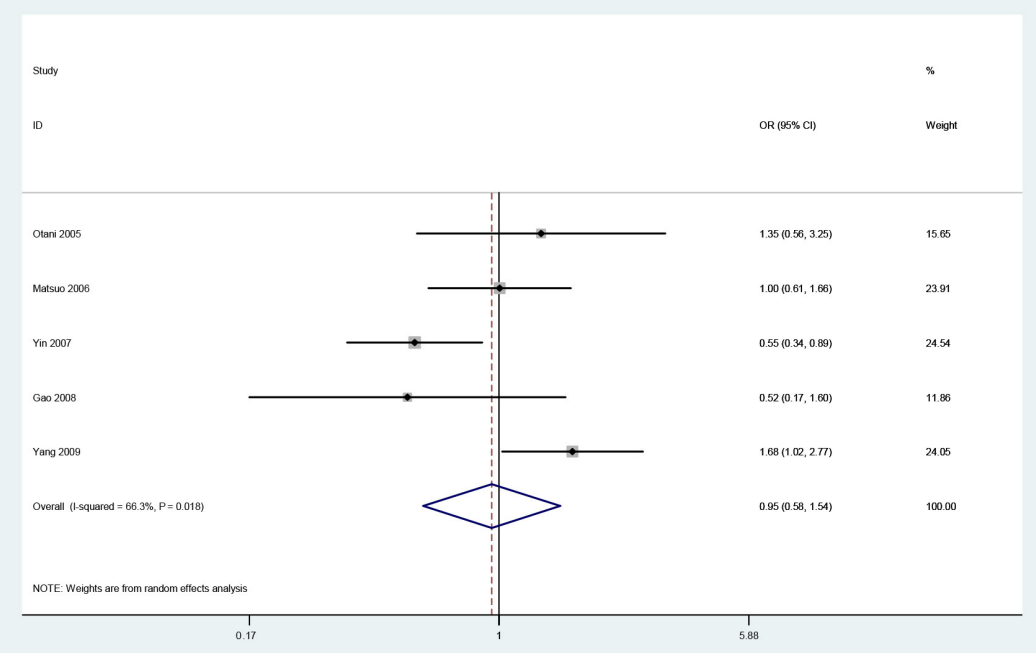

Figure 2. Forest plot of colorectal cancer associated with *ALDH2* Glu504Lys polymorphism (Lys/Lys *vs* Glu/Glu).

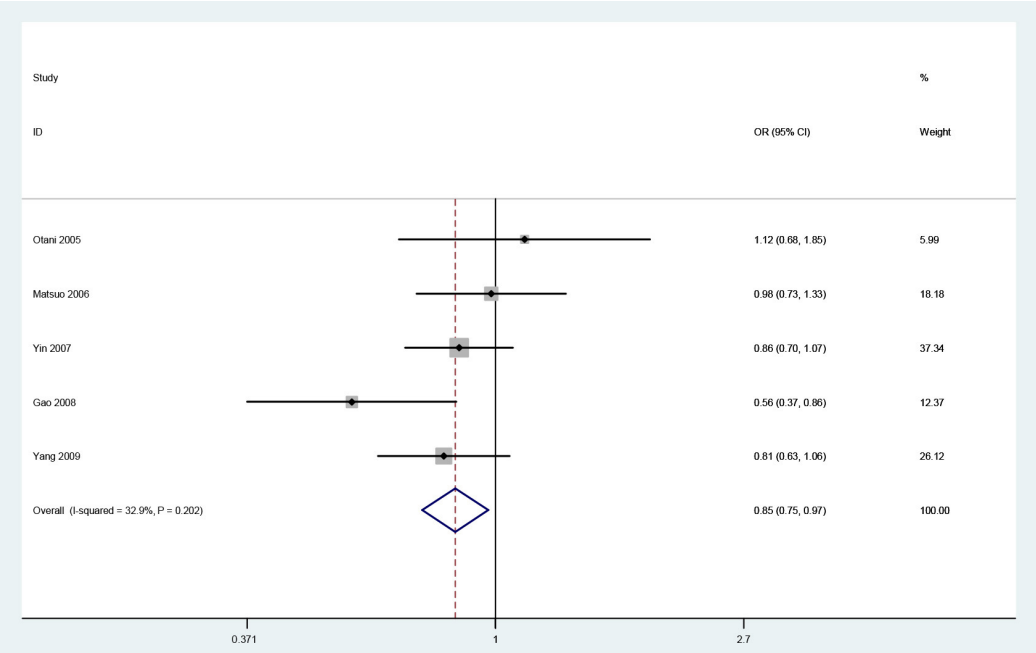

Figure 3. Forest plot of colorectal cancer associated with *ALDH2* Glu504Lys polymorphism (Glu/Lys *vs* Glu/Glu).

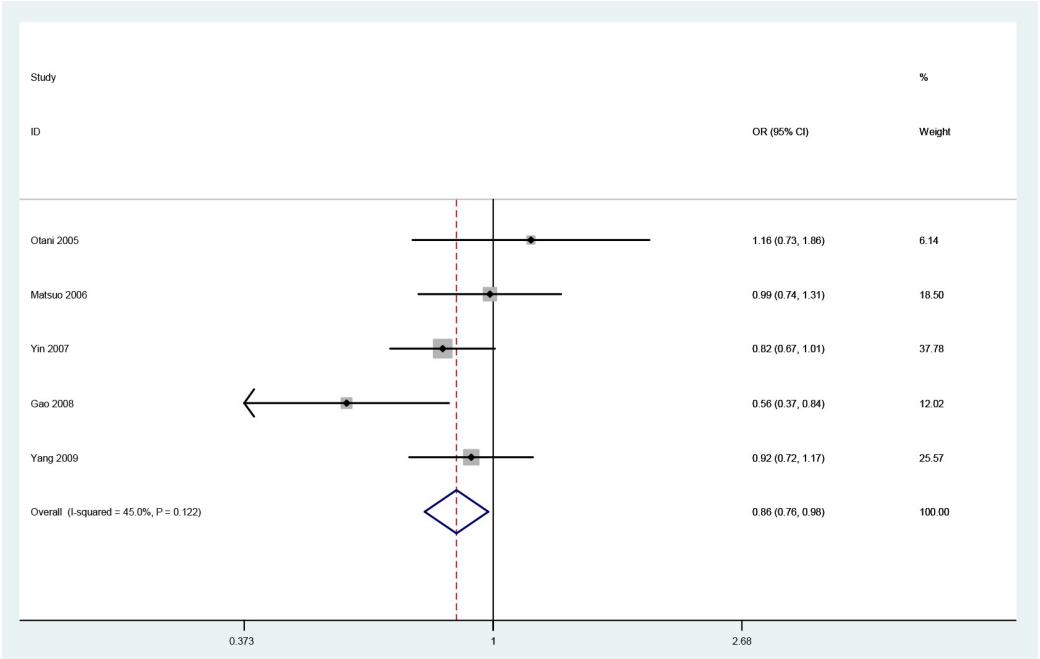

Figure 4. Forest plot of colorectal cancer associated with *ALDH2* Glu504Lys polymorphism (dominant model).

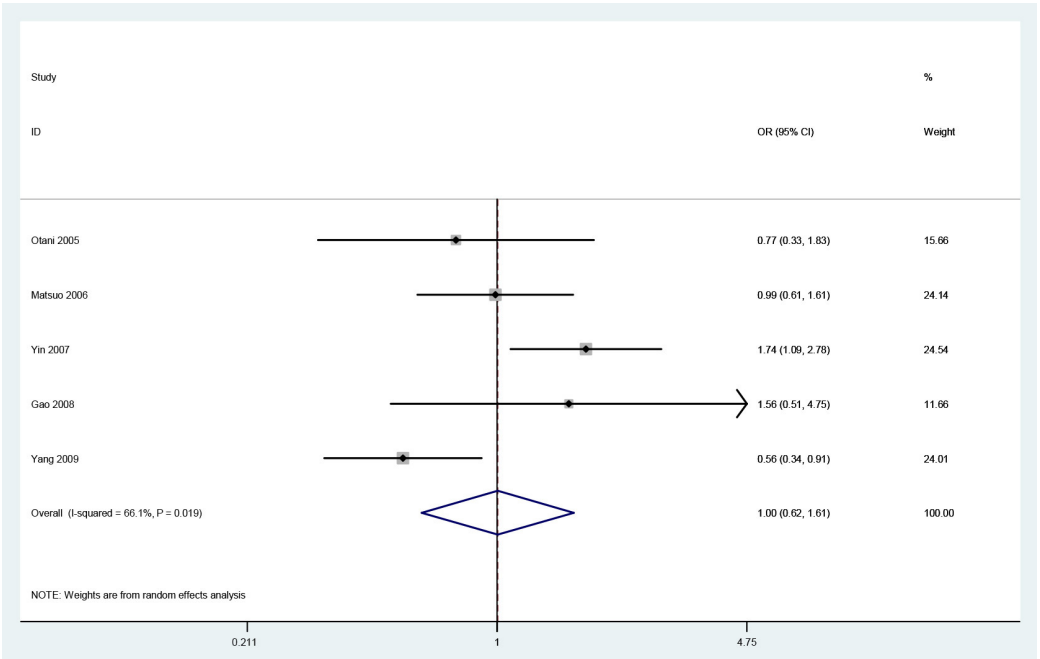

Figure 5. Forest plot of colorectal cancer associated with *ALDH2* Glu504Lys polymorphism (recessive model).

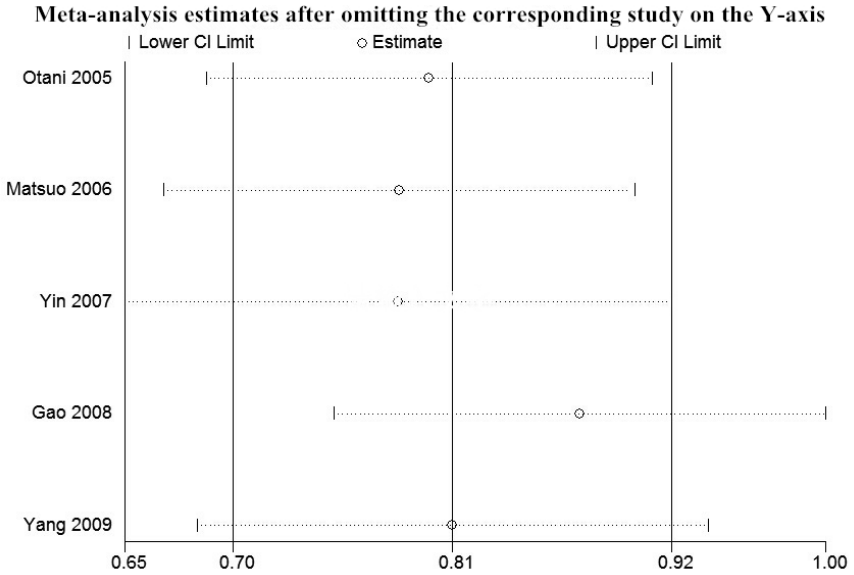

Figure 6. One-way sensitivity analysis of the pooled odds ratios and 95% confidence intervals for *ALDH2* Glu504Lys polymorphism, omitting each dataset in the meta-analysis.

Table 2. Summary of odds ratios (OR) and 95% confidence intervals (95%CI) of *ALDH2* Glu504Lys polymorphism and colorectal cancer risk.

Genetic model	Type of model	Test of heterogeneity		Test of association	
		I^2	P	OR	95%CI
Lys/Lys *vs* Glu/Glu	Random	66.3%	0.02	0.95	0.58-1.54
Glu/Lys *vs* Glu/Glu	Fixed	32.9%	0.20	0.85	0.75-0.97
Dominant model	Fixed	45.0%	0.12	0.86	0.76-0.98
Recessive model	Random	66.1%	0.02	1.00	0.62-1.61

Publication bias

The Begg funnel plot was constructed to assess the potential publication bias in the available literature. The shape of the funnel plots did not reveal any evidence of asymmetry (Figure 7).

DISCUSSION

Studies have documented the increase in incidence of CRC over the past few years (Parkin et al., 2005). Epidemiological studies have consistently demonstrated that the development of CRC is determined by a complex interaction between environmental and genetic factors. However, CRC is a multifactorial disease and its pathogenesis is not yet fully understood. The latest evaluation in 2007 by the International Agency for Research on Cancer confirmed that alcohol consumption has been related to an increased risk of CRC (Gao et al., 2008). The key enzymes involved in the alcohol metabolism pathways in humans are ADH and

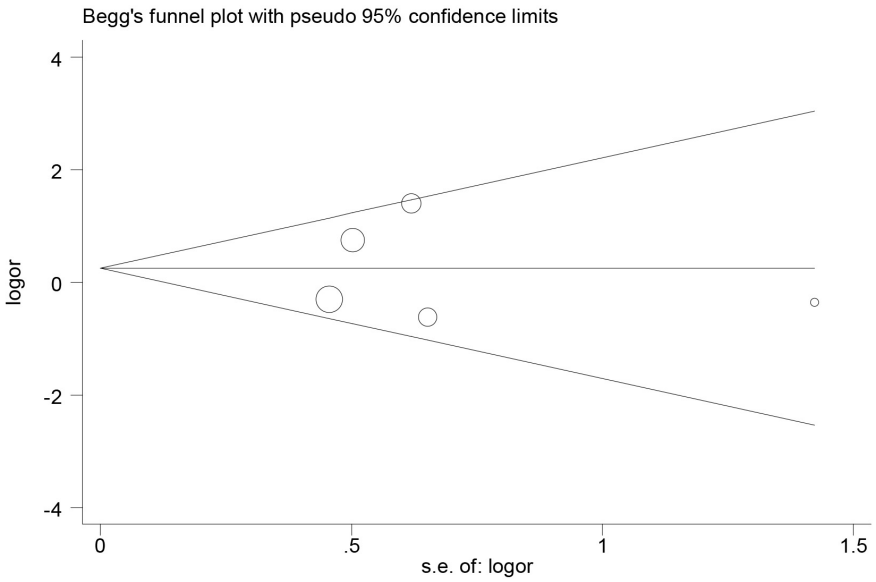

Figure 7. Begg's funnel plot for the publication bias test.

ALDH. Glu504Lys is a novel polymorphism that has been recently identified in the *ALDH2* gene. The variant 504Lys allele decreases the activity of ALDH2, which may contribute to the development of cancer (Wang et al., 2002). Therefore, several recent studies have focused on the association between the *ALDH2* Glu504Lys polymorphism and CRC. However, the results are controversial. In view of the conflicting evidence and controversy, we have conducted this meta-analysis of all published data to evaluate the association between the *ALDH2* Glu504Lys polymorphism and CRC.

This meta-analysis included five independent case-control studies comprising 4441 subjects (1664 patients with CRC and 2777 healthy controls). Pooling of all eligible studies into the meta-analysis revealed a possible association between the *ALDH2* Glu504Lys polymorphism and a decreased risk of CRC. Individuals with the *ALDH2* Glu/Lys genotype express very little (only 6.25%) normal ALDH2 487Glu protein (Crabb et al., 1989). Theoretically, a decrease in ALDH2 activity leads to a corresponding increase in the blood acetaldehyde level in drinkers, which leads to an increased risk of CRC. However, the statistically significant decrease in the risk of CRC associated with the Glu/Lys genotype remains to be elucidated. In fact, previous *in vitro* studies contain no relevant data. A possible reason for this may be that *ALDH2* is a major acetaldehyde-metabolizing enzyme, and its inactivation because of the Glu/Lys genotype leads to acetaldehyde accumulation, which in turn could lead to a series of symptoms that may prevent alcohol consumption (Yang et al., 2009). In addition, the potential function of the *ALDH2* Glu504Lys polymorphism could be affected by gene-gene and gene-environment interactions (Singh et al., 2015). Therefore, caution should be exercised when considering this conclusion.

This meta-analysis has some limitations. First, there are only five articles included in this meta-analysis; therefore, the statistical power of this meta-analysis, conducted using the power

and sample size calculation (http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize) statistical program, may not be sufficient. Therefore, further studies with a larger sample size are required. Second, although *ALDH2* Glu504Lys polymorphism is common in Asians (30-50%), it is rare in Caucasians (<5%) (Tan et al., 2012). In fact, all studies included in this review were conducted in Asian populations. Therefore, this polymorphism must be further investigated in Caucasian populations. Finally, as only studies published in English were included in this study, potential publication and language bias may occur (Jin et al., 2015).

In conclusion, our meta-analysis indicates that the *ALDH2* Glu504Lys polymorphism might be associated with decreased risk of CRC. However, more detailed and well-designed studies are warranted to confirm these findings.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

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