

Association between ALDH₂ Glu504Lys polymorphism and colorectal cancer risk: a meta-analysis.

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Abstract

Background: The findings from studies on the relationship between aldehyde dehydrogenases(ALDH) gene Glu504Lys polymorphism and colorectal cancer(CRC) were inconsistent.

Objectives: The aim of this meta-analysis was to assess ALDH gene Glu504Lys polymorphism and CRC risk.

Methods: All of the relevant studies were identified from PubMed and Embase database. Statistical analyses were conducted with STATA 12.0 software.Odds ratio (OR) with 95% confidence interval (CI) values were applied to evaluate the strength of the association. Nine studies with 2779 cases and 4533 controls were included.

Results: No significant variation in CRC risk was detected in any of the genetic models overall. To explore the sources of heterogeneity,we performed further sub-group analyses by ethnicity and quality assessment of these studies.In the sub-group analysis by race,significant associations between ALDH gene Glu504Lys polymorphism and CRC risk were found in China(Glu/Lys vs Glu/Glu: OR = 0.70, 95%CI = 0.57–0.85; the dominant model: OR =0.69, 95%CI =0.48–0.98) and Japan(Lys/Lys vs Glu/Glu:OR =0.72, 95%CI =0.55–0.95).

Conclusion: This meta-analysis suggests that the ALDH₂ Glu504Lys polymorphism may be associated with susceptibility to CRC. Furthermore, large and well-designed studies are needed to confirm these conclusions.

Keywords: Aldehyde dehydrogenases, colorectal cancer, polymorphism, susceptibility.

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Introduction

Colorectal cancer (CRC) is one of the most prevailing cancers occurring in the digestive system,and it is ranked as the third worldwide primary cancer-causing death worldwide¹. The highest morbidity of CRC is discovered in Australia, Europe, and North America. In addition, the morbidity of CRC is rapidly increasing in many countries within Eastern Asia². CRC is a multi-step process and multiple factors are involved. Although etiology of CRC is still not fully understood, cumulative evidence demonstrates that the environment, life style, diet habit,and other environmental factors contribute to the pathogenesis of CRC in different degrees³. In recent years,molecular epidemiological studies have manifested that single nucleotide polymorphisms (SNPs) in genes play a key role in CRC development and progression⁴. Genome-wide asso-

ciation studies (GWASs) have showed that genetic factors accounted for 33% of CRC cases in the world^{5,6}.

The primary enzymes involved in alcohol metabolism are alcohol dehydrogenases (ADH) and aldehyde dehydrogenases(ALDH)⁷. ALDH₂ is the key enzyme responsible for acetaldehyde elimination, and its polymorphic variants determine blood acetaldehyde concentrations after drinking. Therefore, genetic variants that result in functional differences in enzyme activity lead to differences in acetaldehyde exposure between drinkers.Human ALDH₂ gene is located on chromosome 12q24.2 and composed of 13 exons, spanning 46,031 bp⁸. A common SNP is at exon 12 results from the substitution of glutamate(-Glu) to lysine (Lys) at residue 487 appropriately named Glu504Lys(NCBI ID: rs671), which encodes a catalytically inactive subunit of ALDH₂.The variant 504lys allele decreases the activity of ALDH₂⁹, and ALDH₂ Glu/Lys genotype has only 6.25% of the normal ALDH₂ Glu proteins¹⁰. Previous meta-analysis suggested that ALDH₂ Glu504Lys polymorphism may play crucial roles in the pathogenesis of gastric cancer¹¹.

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To date, many studies have investigated the interrelation between ALDH₂ Glu504Lys polymorphism and CRC risk. However, the results have been inconsistent. One of the most potential reasons is that the statistical power is limited for the individual studies. The present comprehensive meta-analysis of currently published studies aimed to identify the relationships between the ALDH₂ Glu504Lys polymorphism and the risk of CRC.

Materials and methods

Search strategy

Extensive literature was retrieved using the PubMed and EMBASE databases for relevant studies published (the last search update was June 15, 2016) with the following key words: (colorectal cancer odds ratio [OR] colorectal carcinoma) AND (ALDH or aldehyde dehydrogenases) AND (polymorphisms OR variant). The search was not limited to language. We contacted the corresponding author for specific raw data if the data presented in the article were not sufficient. When overlapping data existed, only the latest study with the largest sample was searched for this meta-analysis.

Inclusion criteria

The included studies met all the following inclusion criteria: (a) evaluated the associations of ALDH₂ Glu504Lys polymorphism and CRC risk; (b) used case-control or co-

hort design; and (c) provide sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). In addition, the following exclusion criteria were also used: (a) no usable data reported; (b) the study only involved a case population; (c) not concerned with CRC risk; and (d) duplicate publications.

Data extraction

The following information was extracted from each study: name of the first author; year of publication; country of origin; ethnicity; number of subjects in each category, and the counts of persons with different genotypes in cases and controls. Information on the Hardy-Weinberg equilibrium test (HWE) was also calculated.

Quality assessment

The quality of these articles was also evaluated independently by the two investigators according to the predefined quality assessment rules in Table 1¹². The criteria cover the representativeness of patients, source of controls, ascertainment of cancer, total sample size, quality control of genotyping methods, and Hardy-Weinberg equilibrium (HWE) in the control population. Disagreements were resolved by consensus. The total score ranged from 0 (worst) to 15 (best). Papers scoring <10 were classified as “low quality” and those scoring ≥10 as “high quality.”

Table 1. Scale for quality assessment

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathological archives, but without a description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens obtained from patients to determine genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
≥ 1000	3
≥ 500 but < 1000	2
≥ 200 but < 500	1
> 0 but < 200	0

Statistical analysis

All the data was analyzed using Stata 12.0 software (Stata Corp., LP, <http://www.stata.com>; Stata Corporation, College Station, TX). The association strength between ALDH₂ Glu504Lys polymorphism and CRC risks was

measured by OR with 95%CI. We examined ALDH₂ Glu504Lys polymorphism using the homozygote comparison (Lys/Lys vs Glu/Glu), heterozygote comparison (Glu/Lys vs Glu/Glu), dominant (Lys/Lys+Glu/Lys vs Glu/Glu) and recessive (Lys/Lys vs Glu/Lys+Glu/Glu)

models. We also quantified the effects of heterogeneity using the I² test. When a significant I² > 50% indicated heterogeneity across studies, either the random effects model or the fixed effects model was performed¹³. Subgroup analyses were performed by ethnicity and quality assessment. A sensitivity analysis was used to evaluate the stability of the results. Publication bias was investigated using Begg's funnel plot and Egger's regression test ($p < 0.05$ was considered to be statistically significant).

Results

Study characteristics

The search strategy searched 36 potentially relevant articles. According to the inclusion criteria and exclusion criteria, nine studies with full text were included in the meta-analysis and 27 studies were excluded¹⁴⁻²². These 9 case-control studies selected included a total of 2779 cases and 4533 healthy controls. A flow chart of the study selection process is summarized in Figure 1.

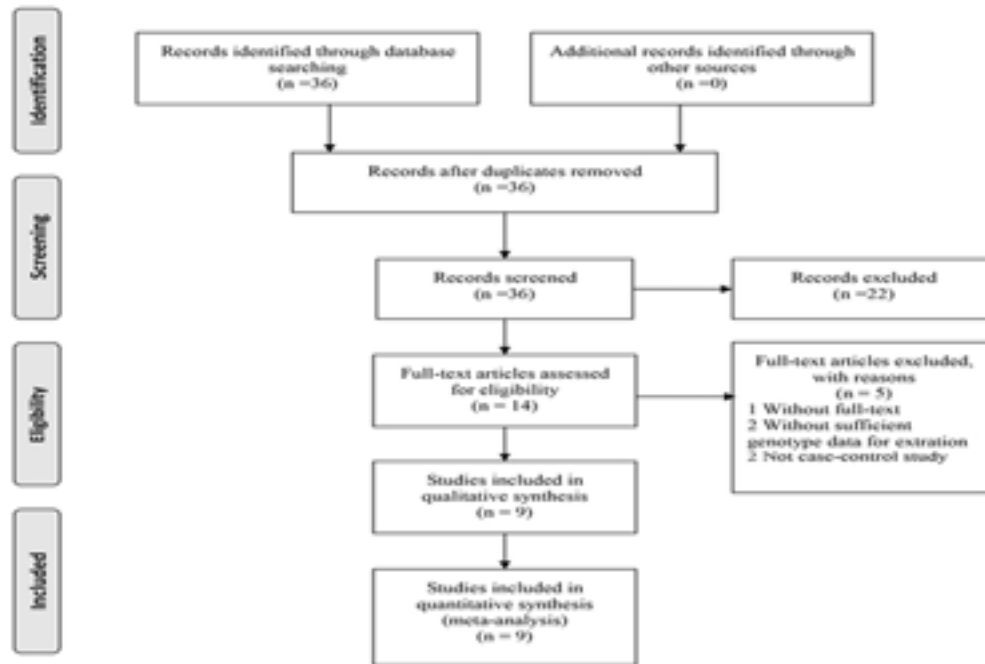


Figure 1 PRISMA Flow Diagram of the meta-analysis.

The publication years ranged from 1998 to 2012. All the studies were published in English. The genotype distributions in the controls of all studies were in agreement with

HWE. General characteristics and the allele and genotype distributions in the published articles included in this meta-analysis are shown in Table 2.

Table 2. Characteristics of the included studies for meta-analysis

Study	Area	Cases/ Controls	Genotypes for cases			Genotypes for controls			HWE test	Quality scores
			Glu/Glu Lys/Lys	Glu/Lys	Lys/Lys	Glu/Glu	Glu/Lys	Lys/Lys		
Chiang 2012	China	545/103	304	218	23	43	53	7	0.08	11
Yang 2009	China	426/785	274	119	33	489	261	35	0.98	12
Gao 2008	China	190/222	131	54	5	123	90	9	0.13	12
Yin 2007	Japan	685/778	400	257	28	416	309	53	0.67	13
Matsuo 2006	Japan	257/768	129	104	24	383	314	71	0.57	12
Otani 2005	Japan	106/ 224	61	36	9	137	72	15	0.20	10
Kuriki 2005	Japan	72 /116	45	24	3	64	44	8	0.91	9
Hirose 2005	Japan	452/1050	299	137	16	605	390	55	0.44	12
Yokoyama 1998	Japan	46/487	36	10	0	443	44	0	0.30	11

Meta-analysis

A summary of the meta-analysis findings of the association between ALDH₂ Glu504Lys polymorphism and CRC risk is shown in Figure 2-4 and Table 3. When all eligible studies were pooled into one dataset for the meta-analysis, we found no statistical association between the ALDH₂ Glu504Lys polymorphism and CRC risk (Lys/

Lys vs Glu/Glu: OR = 0.80, 95%CI = 0.55–1.16; Glu/Lys vs Glu/Glu: OR = 0.84, 95%CI = 0.69–1.01; the dominant model: OR = 0.84, 95%CI = 0.69–1.02; the recessive model: OR = 0.87, 95%CI = 0.62–1.23). Sensitivity analyses were performed by altering the statistic models. No material alteration was detected, indicating that our results were statistically robust.

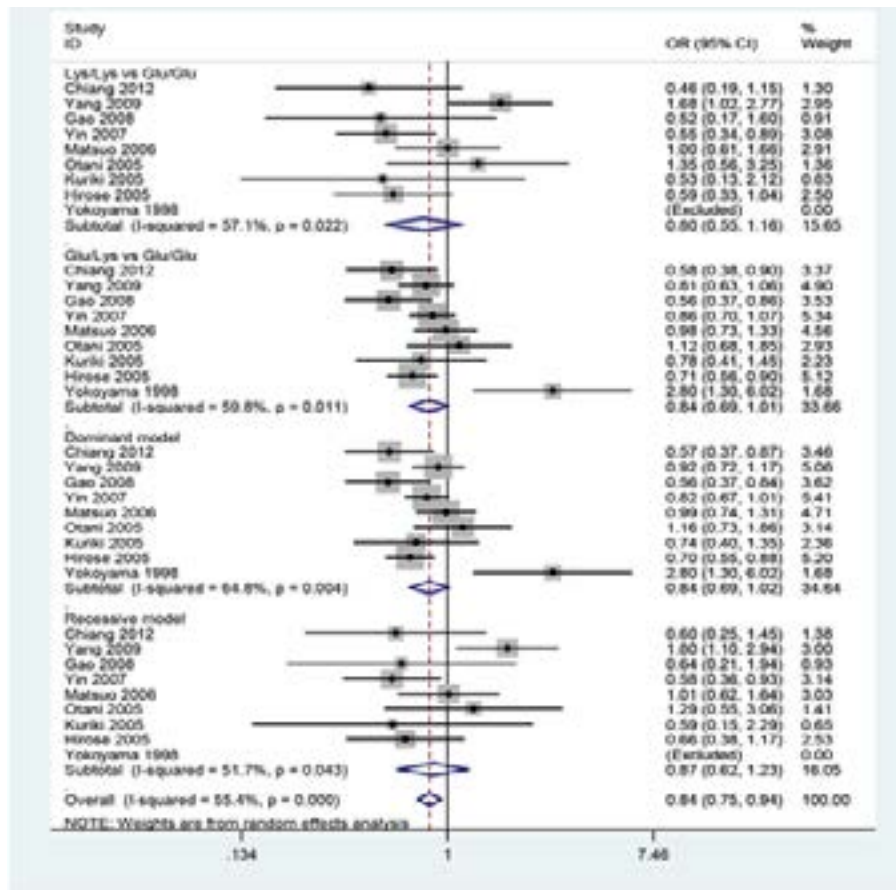


Figure 2 Forest plot of CRC risk associated with ALDH₂ Glu504Lys polymorphism in the total population.

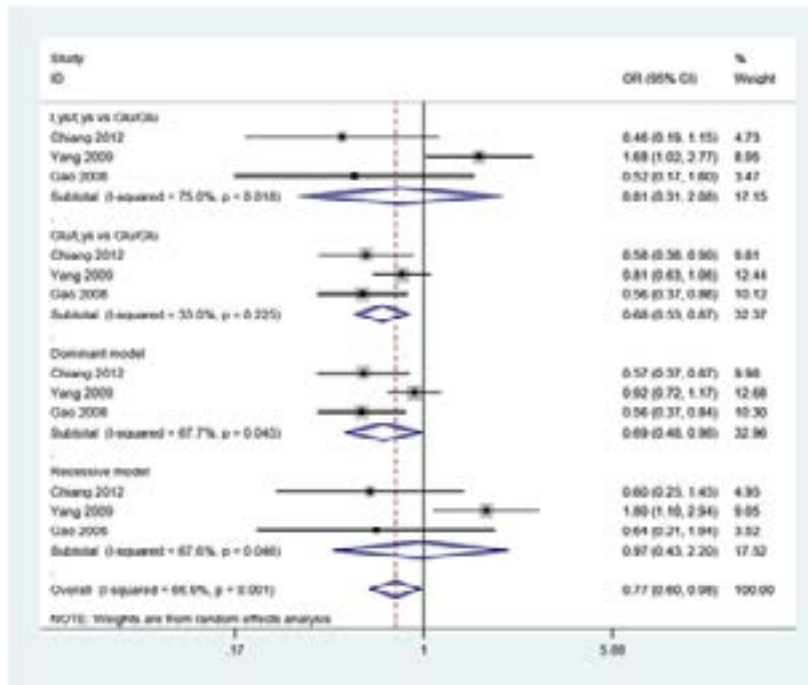


Figure 3 Forest plot of CRC risk associated with ALDH2 Glu504Lys polymorphism in China.

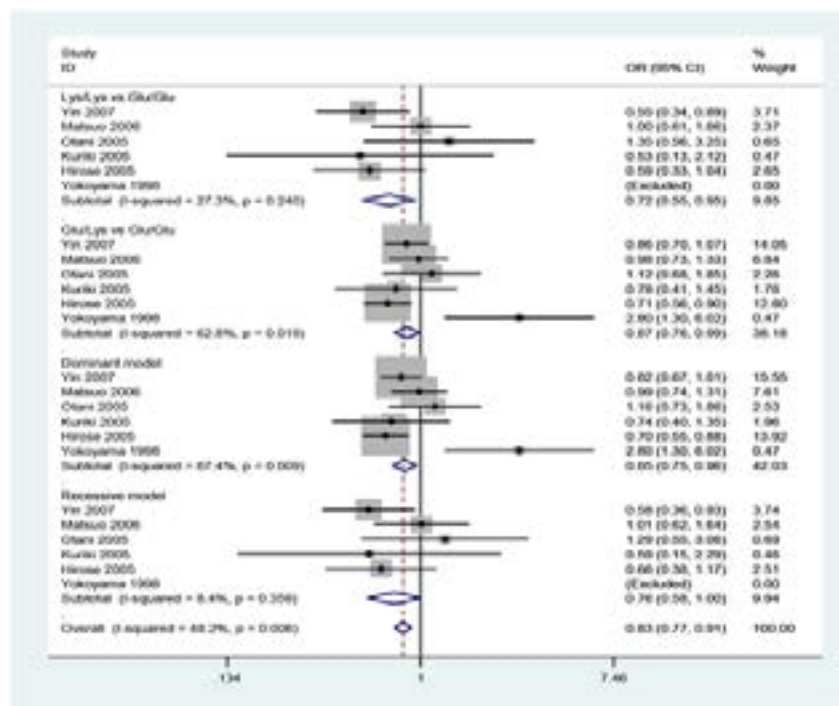


Figure 4 Forest plot of CRC risk associated with ALDH2 Glu504Lys polymorphism in Japan

To explore the sources of heterogeneity, we performed further sub-group analyses by ethnicity and quality assessment of included studies. In sub-group analysis by ethnicity, the studies included were divided into China and Japan, and significant association was found between ALDH₂ Glu504Lys polymorphism and CRC in China (-

Glu/Lys vs Glu/Glu: OR = 0.70, 95%CI = 0.57–0.85; the dominant model: OR = 0.69, 95%CI = 0.48–0.98) and Japan (Lys/Lys vs Glu/Glu: OR = 0.72, 95%CI = 0.55–0.95). When stratified according to high-quality studies, ALDH₂ Glu504Lys polymorphism was not associated with CRC (Table 3).

Table 3 Summary ORs and 95%CI of ALDH2 Glu504Lys polymorphism with colorectal cancer risk.

Variables	N ^a	Lys/Lys vs Glu/Glu		Glu/Lys vs Glu/Glu		Dominant model		Recessive model	
		OR(95%CI)	I ² (%)	OR(95%CI)	I ² (%)	OR(95%CI)	I ² (%)	OR(95%CI)	I ² (%)
Total	9	0.80(0.55–1.16)	57.1	0.84(0.69–1.01)	59.8	0.84(0.69–1.02)	64.8	0.87(0.62–1.23)	51.7
Ethnicity									
China	3	0.81(0.31-2.08)	75.0	0.70(0.57-0.85)	33.0	0.69(0.48-0.98)	67.7	0.97(0.43-2.20)	67.6
Japan	6	0.72(0.55-0.95)	27.3	0.95(0.74-1.21)	62.8	0.94(0.73-1.20)	67.4	0.76(0.58-1.00)	8.4
Quality									
High-quality	8	0.81(0.55-1.21)	62.3	0.84(0.69-1.03)	64.8	0.85(0.69-1.04)	69.1	0.89(0.61-1.28)	57.4
Low-quality	1	/		/		/		/	

^a Number of comparisons.

Publication bias

The Begg's funnel plot was performed to assess the publication bias in the reports included for meta-analysis. The

shapes of the funnel plots in all genetic models did not reveal any evidence of obvious asymmetry (Figure 5). And Egger's line regression test indicated no significant publication bias ($P > 0.05$).

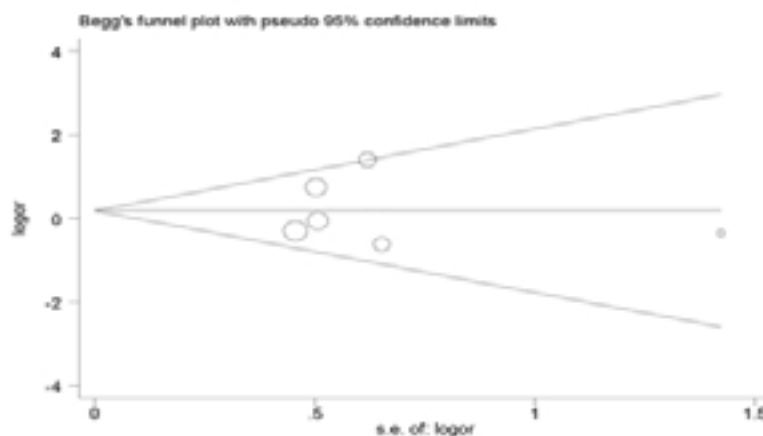


Figure 5 Begg's funnel plot for evaluation of publication bias.

Discussion

CRC is one of the most common malignancies and represents a significant cause of morbidity and mortality worldwide. Previous epidemiological evidence demonstrated that alcohol intake is associated with increased CRC risk²³. After alcohol is absorbed, the concentration of alcohol in the colon is as high as that found in the blood²⁴. Most of the acetaldehyde generated during alcohol metabolism is promptly eliminated by ALDH. Previous animal experiments have shown that when ALDH activity was inhibited, tumorigenesis was observed in the colon of rats²⁵. Yokoyama et al. first examined the association between ALDH₂ Glu504Lys and colon cancer among Japanese alcoholics and reported a 3-fold increased risk among heterozygotes²². Later, several studies, but not all, showed an association of ALDH₂ Glu504Lys polymorphism with increased risk for CRC. Furthermore, these results above were based on a small

sample size, it is possible that the observed associations reflect chance observations rather than true associations. To help resolve these conflicting results, we conducted this meta-analysis to get a more authentic result.

The aim of our meta-analysis was to combine the same kind of studies to increase the sample size and statistical power, and thereby get a more authentic result. Finally, 9 case-control studies were included and assessed, involving a total of 2779 cases and 4533 healthy controls. Eventually, the results of the present meta-analysis revealed that ALDH₂ Glu504Lys polymorphism is not associated with increased or decreased risk of CRC in the overall population. Nevertheless, considering that other potential confounding factors would influence the result, we further conducted several sub-group analyses. In the stratified analysis by ethnicity, results showed significant association in both China and Japan. This might account

for ethnic differences and diverse live environment. The mechanism by which the Glu504Lys polymorphism affects CRC risk is currently unclear. As with other diseases, the development of CRC is due to the joint effect of multiple genes and gene-environment interactions. Matsuo et al. found that heavier drinking, risk genotypes (ADH₂ 47His and ALDH₂ 487Lys), and low folate consumption might synergistic increase the risk of CRC¹⁸. As the eligible study number was limited in the meta-analysis, these results still need further investigation.

Limitations

Some limitations of our meta-analysis should be addressed. First of all, studies included in the present meta-analysis mainly provided data towards Asians, other ethnicities including Caucasian, and others should be investigated in future studies. Second, most of the men had a high frequency of drinking, while the majority of women had a low frequency of drinking, which may affect the final results. Further stratification analysis should aim at gender. Third, the existence of gene-gene and gene-environment interactions may affect the accuracy of our results. Lack of the relevant data limited our further analysis of potential interactions among gene-gene and gene-environment.

Conclusion

This meta-analysis suggested that the ALDH₂ Glu504Lys polymorphism may be associated with CRC risk. Large-scale case-control and population-based association studies are warranted to validate the risk identified in the current meta-analysis and investigate the potential gene-gene and gene-environment interactions on CRC risk.

Conflict of interest

None to declare.

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