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RESEARCH

A critical Analysis of the Relationship Between *Aldehyde dehydrogenases-2* Glu487Lys Polymorphism and Colorectal Cancer Susceptibility

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Abstract Studies investigating the association between genetic polymorphism of *aldehyde dehydrogenases-2* (*ALDH-2*) Glu487Lys and colorectal cancer (CRC) risk have reported conflicting results. Given this uncertainty, we carried out a critical analysis of published case-control studies to derive a more precise estimation of this relationship. Published literature from PubMed, EMBASE and China Knowledge Resource Integrated Database were retrieved, and the literature search was updated in June 2014. Eleven studies comprising 6965 subjects were selected (2300 cases and 4665 controls). Overall, our study showed no statistical significance for CRC risk associated with any of the genetic models of *ALDH-2* Glu487Lys polymorphism. When studies were stratified for control source, a decreased risk of CRC for participants with Lys/Lys was observed in population based case-control studies [Lys/Lys vs. (Glu/Lys + Glu/Glu): odds ratio (OR)=0.57, 95% confidence interval (CI)=0.38–0.87]. Furthermore, we also confirmed the significant correlation between Glu487Lys polymorphism and the influence on the risk of rectal cancer in males [Glu/Glu vs. (Glu/Lys + Lys/Lys): OR=1.52, 95%CI= 1.10–2.08]. The combined effects of the two gene polymorphisms [*ALDH-2* and *alcohol dehydrogenase 1B* (*ADH-1B*)] were also studied. Compared with subjects having *ALDH*-2 Lys+ with *ADH-1B* His/His, ORs and 95%CIs for those with *ALDH-2* Glu/Glu and *ADH-1B* His/His was 3.42(0.57–20.38). Similar trends were observed for the other two types of comparisons. Our study supports that *ALDH*-2 Glu487Lys polymorphism is associated with significant reduced risks of CRC in population-based samples, and of rectal cancer in males.

Keywords Colorectal cancer · *Aldehyde dehydrogenases-2* · *ALDH-2* · Polymorphism · Risk factor

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Introduction

Colorectal cancer (CRC) is the second most common cause of cancer-related mortality in western countries and the fourth most abundant type of cancer in the world [1, 2]. Now, it is widely accepted that the colorectal carcinogenesis is a complex and multilevel process, and human CRC is caused by both genetic and environmental influences, including dietary and lifestyle factors [3, 4].

In humans, the relationship between alcohol consumption and CRC risk has been long debated due to numerous conflicting epidemiological studies [5]. Nevertheless, the positive association between alcohol and CRC has not only been observed in some regions of Europe and North America [6–8], but also in some Asian countries [9, 10], with few exceptions [11]. Finally, during 2007–2009, the International Agency for Research on Cancer have completely classified chronic alcohol consumption as a risk factor for CRC [12, 13]. However, uncertainty remains as to the biological mechanisms for the relationship between alcohol consumption and CRC.

Ethanol is first oxidized to acetaldehyde by alcohol dehydrogenase(ADH), and acetaldehyde is further metabolized to acetate by aldehyde dehydrogenases (ALDH). ALDH-2 is a major enzyme involved in the alcohol-metabolizing pathways, and its encoding gene *ALDH-2* has

a functional polymorphism (Glu487Lys, also named rs671), which associated with low enzyme activity. Human *ALDH-2* gene is located on chromosome 12q24.2 and composed of 13 exons [14]. The single nucleotide polymorphism(SNP) Glu487Lys leads to the substitution of glutamate(Glu, corresponding to G or *1 allele) by lysine (Lys, corresponding to A or *2 allele), which is highly prevalent among Asians [15, 16]. Genetic variant in *ALDH-2* gene may be closely associated with the inhibition of acetaldehyde oxidation, conducing to the accumulation of acetaldehyde [17]. Therefore, it is hypothesized that *ALDH-2* Glu487Lys polymorphism may be strongly correlated with the susceptibility to CRC.

Over the past two decades, numerous case-control studies have focused on the association of this common *ALDH-2* polymorphism and CRC susceptibility. During 2013–2014, Zhao et al.[18] and Guo et al.[19] have firstly published two system reviews of the association between *ALDH-2* Glu487Lys polymorphism and CRC susceptibility. Unfortunately, there is considerable evidence that many mistakes have been made in their studies. The accurate and reliable conclusion, therefore, may be different when updated data are re-analyzed in an appropriate way.

Materials and Methods

Identification and Eligibility of Relevant Studies

Search was applied to the following electronic databases: PubMed (1950 to June 2014), EMBASE (1950 to June 2014), and China National Knowledge Infrastructure (1979 to June 2014). The following key words were used: ("aldehyde dehydrogenase" OR "ALDH*" OR "Glu487Lys" OR "rs671" OR "alcohol metaboli*" OR "aldehyde metaboli*" OR "alcohol consumption" OR "alcohol drinking" OR "alcohol intake") AND ("adenocarcinoma" OR "carcinoma" OR "cancer" OR "tumour" OR "tumor" OR "neoplasm" OR "malignancy") AND ("colorectal" OR "colon" OR "rectal" OR "gastrointestinal" OR "digestive tract") AND ("variant" OR "polymorphism" OR "mutation"). The search was conducted without restriction on language. We also checked the reference list of all papers of interest, as well as that of some reviews on the issue, to retrieve other relevant publications. If more than one article was published by the same author using the same case series, we selected the research with higher sample size.

Papers met the following criteria were included in this meta-analysis:(1) independent case-control studies for human; (2) evaluating the association between the *ALDH-2* Glu487Lys polymorphism and CRC risk; (3) genotype data for both patients and control populations were given to calculate the combined odds ratio(OR) with 95% confidence interval(CI). The reasons for exclusion of studies were: (1) duplicate publications; (2) abstract, comment and review.

Data Extraction

Data were extracted from each study by two researchers independently, and then decided by the research team. Finally, the efforts to resolve the disagreement between authors were viewed in retrospect. The following data were extracted: the first author name, publication year, country, ethnicity of the population, source of controls [hospital-based case-control study (HCC) and population-based case-control study (PCC)], the number of cases and controls with different genotypes.

Statistical Analysis

All statistical analyses were conducted by use of STATA 12.0 (Stata-Corp LP, College Station, TX, USA) and Review Manager 5.0 (Cochrane Collaboration, Oxford, UK). We considered a P value<0.05 to be statistically significant. Pooled estimates were tested for heterogeneity by use of the chi-squared test. The crude odds ratios (OR) were pooled using the random-effects model when statistical heterogeneity was found. Otherwise, we used the fixed-effects model. To establish the effect of clinical heterogeneity between researches on the results of the systematic review, subgroup analyses were conducted on the basis of source of control, country, gender and tumor location. The Begg's rank correlation method and the Egger's weighted regression method were used to statistically assess publication bias (P value<0.05 was considered representative of statistically significant publication bias). The Galbraith plot was used to detect the potential sources of heterogeneity, and re-analyses were performed when the studies possibly causing the heterogeneity were excluded.

Results

Characteristics of Studies

The search terms resulted in 366 studies. Three hundred and fifty-five were excluded because they did not report outcomes of interest (n=292), did not have primary data for CRC (n=47), and duplicate data (n=16). Figure 1 describes the study selection process in this meta-analysis. Eleven studies (2300 cases and 4665 controls) were included according to the inclusion criteria [20–30]. Among them, eight studies were carried out in Japan (1561 cases and 2897 controls) and three in China (739 cases and 1,768 controls).

Meta-analysis Results

Overall, our study showed no statistical significance for CRC risk associated with any of the genetic models of

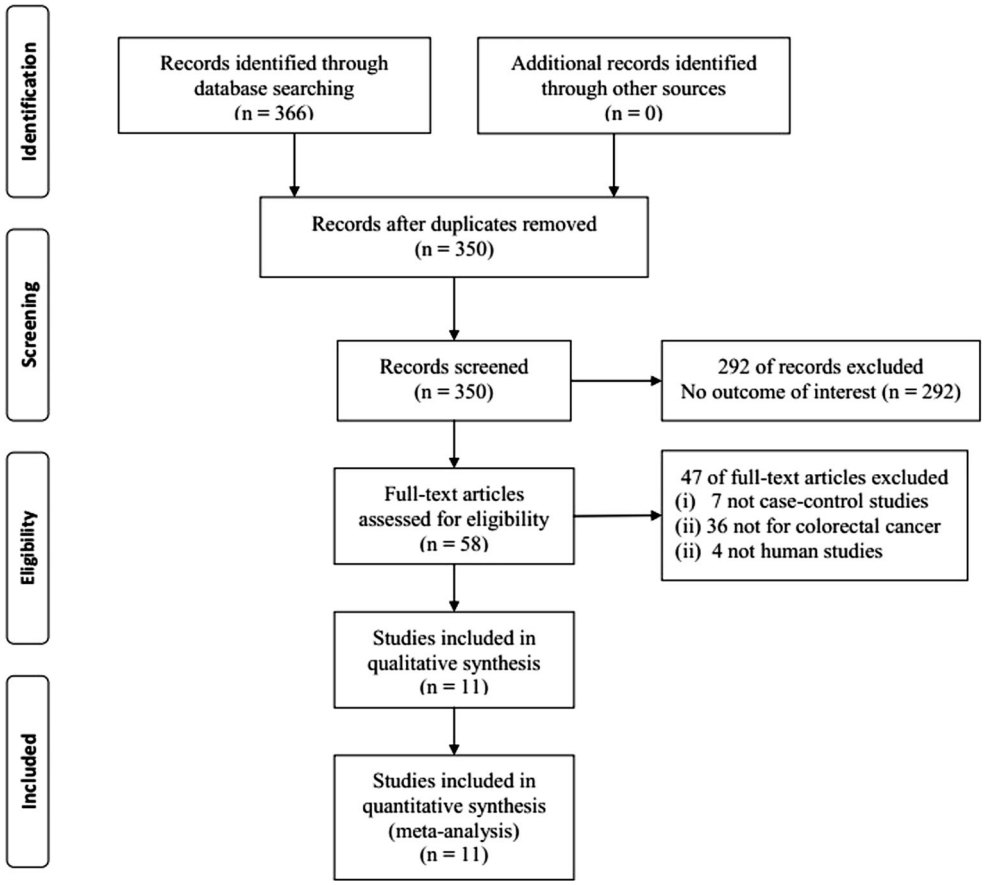

Fig. 1 Flow diagram of the study selection process

ALDH-2 Glu487Lys polymorphism(Glu vs. Lys: OR= 0.98, 95%CI=0.83–1.15; Glu/Glu vs. Lys/Lys: OR= 0.97, 95%CI=0.64–1.46) (Table 1, Fig. 2). Additionally, sensitivity analyses excluding data from studies reporting allele frequencies not in Hardy–Weinberg equilibrium (HWE) gave similar results (Glu vs. Lys: OR=1.02, 95%CI=0.86–1.19, P=0.85; Glu/Glu vs. Lys/Lys: OR=1.02, 95%CI=0.65–1.61, P=0.92).

When studies were stratified for control source, a decreased risk of CRC for participants with Lys/Lys was observed in PCC studies[Lys/Lys vs. (Glu/Lys + Glu/Glu): OR=0.57, 95%CI=0.38–0.87, P=0.009]. Furthermore, we also observed significant association between Glu487Lys polymorphism and the decreased risk of rectal cancer in males [Glu/Glu vs. (Glu/Lys + Lys/Lys): OR=1.52, 95%CI=1.10–2.08, P=0.01] (Table 1).

The combined effects of the two gene polymorphisms [*ALDH-2* and *alcohol dehydrogenase 1B* (*ADH-1B*)] were also studied. Compared with subjects having *ALDH*-2 Lys + with *ADH-1B* His/His, ORs and 95%CIs for those with *ALDH-2* Glu/Glu and *ADH-1B* His/His, *ALDH-2* Glu/Glu and *ADH-1B* Arg+, and *ALDH-2* Lys + and *ADH-1B* Arg + were, 3.42(0.57–20.38), 1.07(0.70–1.62), and 3.19(0.22–47.13), respectively.

Detection for Heterogeneity

The Galbraith plot was also used to detect the possible source of heterogeneity, and re-analyses were carried out when the studies possibly causing the heterogeneity were excluded [31]. The results were persistent, which suggested that our results were credible[1.09(0.99–1.19) for Glu vs. Lys, 1.00(0.73–1.36) for Glu/Glu vs. Lys/Lys, and 1.01(0.74–1.36) for Lys/Lys vs. (Glu/Lys + Glu/Glu)].

Publication Bias

Begg's rank correlation method and Egger's weighted regression method were used to assess publication bias. No publication bias was detected in either analysis [Glu/Glu vs. Lys/Lys: P_{Begg}=0.72, P_{Egger}=0.54; Glu/Glu vs. (Glu/Lys + Lys/Lys) : P_{Begg}=0.09, P_{Egger}=0.10].

Discussion

In humans, the major enzymes involved in the alcohol metabolizing pathways are ADH-1B and ALDH-2. Metabolism of

Table 1 Meta-analyses of the association between *ALDH-2* Glu487Lys polymorphism and the risk of colorectal cancer

Meta-analysis models	Overall OR(95%CI) *P* value (Model[a])	HCC OR(95%CI) *P* value (Model[a])	PCC OR(95%CI) *P* value (Model[a])	Male OR(95%CI) *P* value (Model[a])	Female OR(95%CI) *P* value (Model[a])	China OR(95%CI) *P* value (Model[a])	Japan OR(95%CI) *P* value (Model[a])
Colorectal cancer							
Glu/Glu vs. Glu/Lys	1.01 [0.85–1.20] 0.92 R	0.93 [0.75–1.16] 0.53 R	1.20 [0.99–1.44] 0.06 F	1.11 [0.64–1.90] 0.72 R	0.87 [0.55–1.39] 0.57 F	1.00 [0.64–1.56] 0.99 R	1.05 [0.92–1.21] 0.46 F
Glu/Lys vs. Lys/Lys	0.94 [0.65–1.36] 0.73 R	0.77 [0.58–1.02] 0.07 F	1.57 [1.02–2.43] 0.04 F	0.97 [0.47–2.02] 0.94 F	1.36 [0.44–4.19] 0.59 F	0.77 [0.39–1.55] 0.47 R	1.14 [0.85–1.52] 0.38 F
Glu/Glu vs. Lys/Lys	0.97 [0.64–1.46] 0.88 R	0.79 [0.60–1.04] 0.09 F	1.87 [1.23–2.86] 0.004 F	1.39 [0.69–2.77] 0.36 F	1.16 [0.38–3.56] 0.79 F	0.80 [0.36–1.77] 0.58 R	1.11 [0.70–1.76] 0.65 R
Glu vs. Lys	0.98 [0.83–1.15] 0.77 R	0.90 [0.76–1.06] 0.22 R	1.26 [1.09–1.46] 0.002 F	1.06 [0.65–1.71] 0.83 R	0.96 [0.66–1.38] 0.80 F	0.96 [0.67–1.37] 0.82 R	0.99 [0.82–1.20] 0.91 R
Lys/Lys vs. (Glu/Lys + Glu/Glu)	1.04 [0.71–1.54] 0.83 R	1.27 [0.98–1.66] 0.08 F	0.57 [0.38–0.87] 0.009 F	0.82 [0.41–1.63] 0.57 F	0.79 [0.27–2.37] 0.68 F	1.24 [0.61–2.54] 0.55 R	0.85 [0.64–1.12] 0.24 F
Glu/Glu vs. (Glu/Lys + Lys/Lys)	0.99 [0.83–1.19] 0.93 R	0.90 [0.73–1.12] 0.35 R	1.26 [1.06–1.51] 0.01 F	1.09 [0.63–1.91] 0.75 R	0.90 [0.57–1.40] 0.63 F	0.97 [0.62–1.51] 0.89 R	1.07 [0.94–1.23] 0.30 F
Colon cancer							
Glu/Glu vs. Glu/Lys	0.91 [0.54–1.55] 0.74 R	0.91 [0.54–1.55] 0.74 R	NA	0.89 [0.36–2.18] 0.79 R	0.93 [0.55–1.60] 0.80 F	NA	0.91 [0.54–1.55] 0.74 R
Glu/Lys vs. Lys/Lys	0.82 [0.40–1.67] 0.59 F	0.82 [0.40–1.67] 0.59 F	NA	0.75 [0.23–2.39] 0.62 F	1.13 [0.28–4.56] 0.86 F	NA	0.82 [0.40–1.67] 0.59 F
Glu/Glu vs. Lys/Lys	0.83 [0.20–3.32] 0.79 R	0.83 [0.20–3.32] 0.79 R	NA	1.07 [0.08–13.73] 0.96 R	1.14 [0.30–4.28] 0.84 F	NA	0.83 [0.20–3.32] 0.79 R
Glu vs. Lys	0.85 [0.50–1.43] 0.53 R	0.85 [0.50–1.43] 0.53 R	NA	0.86 [0.35–2.13] 0.75 R	0.98 [0.63–1.51] 0.92 F	NA	0.85 [0.50–1.43] 0.53 R
Lys/Lys vs. (Glu/Lys + Glu/Glu)	1.29 [0.36–4.62] 0.70 R	1.29 [0.36–4.62] 0.70 R	NA	1.02 [0.11–9.50] 0.98 R	0.87 [0.23–3.26] 0.84 F	NA	1.29 [0.36–4.62] 0.70 R
Glu/Glu vs. (Glu/Lys + Lys/Lys)	0.88 [0.50–1.57] 0.67 R	0.88 [0.50–1.57] 0.67 R	NA	0.88 [0.33–2.31] 0.79 R	0.95 [0.56–1.60] 0.83 F	NA	0.88 [0.50–1.57] 0.67 R
Rectal cancer							
Glu/Glu vs. Glu/Lys	1.19 [0.91–1.55] 0.21 F	1.05 [0.70–1.55] 0.82 F	1.31 [0.92–1.88] 0.14 F	1.52 [1.10–2.11] 0.01 F	0.84 [0.46–1.53] 0.56 F	1.31 [0.92–1.88] 0.14 F	1.05 [0.70–1.55] 0.82 F
Glu/LYS vs. Lys/Lys	1.31 [0.69–2.50] 0.41 F	1.10 [0.45–2.69] 0.83 F	1.57 [0.61–4.04] 0.35 F	1.00 [0.45–2.25] 0.99 F	1.55 [0.36–6.62] 0.55 F	1.57 [0.61–4.04] 0.35 F	1.10 [0.45–2.69] 0.83 F
Glu/Glu vs. Lys/Lys	1.49 [0.79–2.81] 0.22 F	1.04 [0.42–2.56] 0.93 F	2.06 [0.82–5.18] 0.12 NA	1.44 [0.65–3.19] 0.37 F	1.08 [0.25–4.67] 0.92 F	2.06 [0.82–5.18] 0.12 F	1.04 [0.42–2.56] 0.93 F
Glu vs. Lys	1.20 [0.97–1.49] 0.09 F	1.05 [0.76–1.43] 0.78 F	1.36 [1.01–1.83] 0.04 F	1.38 [1.06–1.80] 0.02 F	0.95 [0.59–1.54] 0.84 F	1.36 [1.01–1.83] 0.04 F	1.05 [0.76–1.43] 0.78 F
Lys/Lys vs. (Glu/Lys + Glu/Glu)	0.69 [0.37–1.30] 0.25 F	0.92 [0.38–2.19] 0.84 F	0.53 [0.21–1.32] 0.17 F	0.79 [0.36–1.72] 0.55 F	0.77 [0.19–3.17] 0.72 F	0.53 [0.21–1.32] 0.17 F	0.92 [0.38–2.19] 0.84 F
Glu/Glu vs. (Glu/Lys + Lys/Lys)	1.22 [0.94–1.58] 0.13 F	1.05 [0.72–1.54] 0.80 F	1.38 [0.97–1.95] 0.07 F	1.52 [1.10–2.08] 0.01 F	0.87 [0.48–1.58] 0.65 F	1.38 [0.97–1.95] 0.07 F	1.05 [0.72–1.54] 0.80 F

CI Confidence intervals, *DTC* Digestive tract cancers, *F* Fixed effects model, *HCC/PCC* Hospital/population based case–control studies, *NA* Not applicable, *OR* Odds ratios, *R* Random effects model

[a] If the results of the studies were heterogeneous, the random effects model was used for meta-analysis; Otherwise, the fixed-effects model was used

ethanol with ADH produces acetaldehyde, a highly reactive and toxic byproduct that may contribute to tissue damage. Several isozymes of ALDH have been identified, but only the cytosolic ALDH-1 and the mitochondrial ALDH-2 metabolize acetaldehyde [32]. There is one significant SNP of *ALDH-2*, resulting in a Glu-487 → Lys change, which shows virtually inactive. This variant is found mainly in Chinese and Japanese populations and is best known for its role in protecting against the development of alcohol dependence. Human who have one or especially two copies of the *ALDH-2* 487Lys mutation show increased acetaldehyde levels after alcohol intake and therefore experience negative physiological responses to alcohol [32, 33].

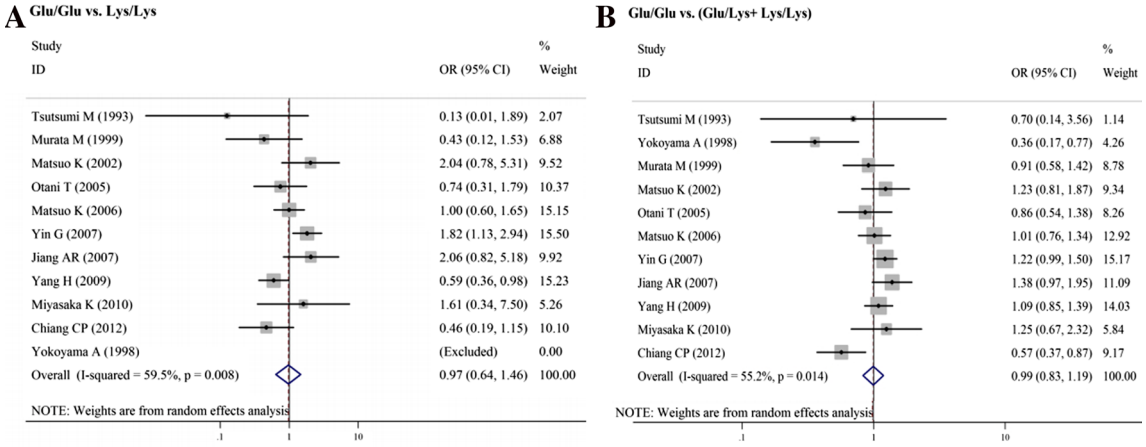

Fig. 2 Forest plots of the association between *ALDH-2* Glu487Lys polymorphism and colorectal cancer risk. **a**. Glu/Glu vs. Lys/Lys analysis; **b**. Glu/Glu vs. (Glu/Lys + Lys/Lys) analysis

This genetic polymorphism in *ALDH-2* gene is responsible for different activity and expression levels of ALDH as well as the subsequent metabolites influenced by this enzyme. Previous studies argued that *ALDH-2* 487Lys polymorphism could affect the concentration of acetaldehyde and reactive oxygen species formed during the metabolic reaction in the body, altering the effects of alcohol, and potentially leading to tumorigenesis [15, 17, 28, 34]. According to this theoretical point of view, the Glu/Lys and Lys/Lys polymorphisms should be risk factors for CRC.

However, this meta-analysis and subgroup analyses showed the opposite results. We observed that there was a statistically significant relationship between the *ALDH-2* Glu487Lys polymorphism and the decreased risk of CRC(including rectal cancer) in the PCC subgroup analysis, whereas no obvious association was found between this gene mutation and CRC risk in any of the genetic models in overall analysis. The sensitivity analyses were performed by excluding the studies that were not in HWE or possibly causing the heterogeneity, and the qualitative conclusions remained unchanged, strengthening the results of our meta-analysis. Thus, the Lys variant may be a protective factor for CRC susceptibility in some, but not all, populations.

In general, in people with *ALDH-2* Glu/Lys or Lys/Lys variants, the blood level of acetaldehyde may maintain high. This can cause a "flushing response" to alcohol consumption characterized by increased blood flow, sweating, elevated heart rate, dizziness, and nausea. Individuals who flush are protected by its unpleasantness from consuming alcohol and ultimately alcoholism [35]. Therefore, these people have less chance to expose normal tissue to higher levels of acetaldehyde, which may reduce the CRC susceptibility [18]. The protective role of *ALDH-2* 487Lys variant may be attributed to decreasing of alcohol consumption.

Usually, conclusions of meta-analyses depend on control selection procedures. The results for studies with hospital-based controls (HBC) and population-based controls (PBC) might be dissimilar. In subgroup analysis stratified on the basis of different study designs, we found that use of PBC resulted in a significantly stronger association between *ALDH-2* polymorphism and decreased CRC risk than did use of HBC. In fact, HBC are not likely to be representative of the source population that produced the CRC cases. On the other hand, HBC are often selected from patients with noncancer illnesses, and thus a real association of the exposure with CRC might be missed. However, due to the limitation in the number of PCC studies available, more data is needed to confirm our findings.

Some limitations of our study are: (1) The evidence on gene-environment (e.g., alcohol consumption, supplement use and dietary behavior) interaction might interpret the results of this study more strongly. However, due to lack of consistency of original data reporting, further meta-analysis was not conducted; (2) As carcinogenesis is influenced by a wide variety of genes and gene interactions, any SNP affecting CRC risk is expected to make a small contribution at the level of the individual. (3) Our meta-analysis is based on unadjusted estimates, while a more precise analysis could be conducted if the individual study data and records were available. (4). Lacking of the original data limited our further evaluation of the association between *ALDH-2* polymorphism and CRC risk in non-Asians.

In conclusion, our current study demonstrates that *ALDH-2* Glu487Lys polymorphism is associated with significant reduced risks of CRC in PBC, and of rectal cancer in males. Because of the relatively small sample size in some subgroup analyses, additional well-designed, high-quality epidemiological studies with larger PBC are needed.

Conflict of Interest The Authors declare that there is no conflict of interest.

Authors' Contribution BC, KWH carried out the literature search, and draft the manuscript. JWZ and ZJW performed the statistical analysis. MMX, XLM conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript. MMX accepts full responsibility for the work and has accessed to the data, and overseen the decision to publish.

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