RESEARCH COMMUNICATION

Meta-analysis of ALDH2 Variants and Esophageal Cancer in Asians

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Abstract

Alcohol drinking is considered a risk factor for esophageal cancer, and exposure to high levels of acetaldehyde, the principal metabolite of alcohol, may be responsible. Individuals homozygous for the *2 variant allele of aldehyde dehydrogenase 2 (ALDH2) are unable to metabolize acetaldehyde, which prevents them from alcohol drinking, whereas those with *1/*2 have a 6-fold higher blood acetaldehyde concentration postalcohol consumption with respect to *1*1. We carried out a meta-analysis of ALDH2 and esophageal cancer searching for relevant studies on Asians in Medline and EMbase up to May 2011, and investigated the association between this genotype variation and esophageal cancer risk. A total of 2,697 cases and ,6344 controls were retained for the analysis. The pooled OR (95% CI) for ALDH2*1/*2 was 2.47 (95%CI: 1.76-3.46) compared with ALDH2*1/*1. ALDH2*2/*2 showed a non-significant decreased risk for esophageal cancer with OR of 0.6 (0.26-1.38). ALDH2*1/*2 individuals showed a higher risk of esophageal cancer among moderate and heavy alcohol users [2.17(1.95-2.43) and 3.20(2.78-3.70), respectively]. Moderate drinkers with ALDH2*2/*2 showed strong esophageal cancer risk [OR(95%CI)=8.52(3.81-19.04)] compared with ALDH2*1/*1 carriers among heavy drinkers than non-drinkers and moderate drinkers (OR=7.05). Our finding showed that ALDH2*1/*2 genotype increases the risk of esophageal cancer, while the ALDH2*2/*2 genotype reduces the risk, presumably preventing people from consumption due to discomfort. Drinking clearly modifies the effect of ALDH2 on esophageal cancer risk in Asians.

Keywords: Esophageal cancer - ALDH2 - variants - meta-analysis

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Introduction

Esophageal cancer is a global health problem, ranking eighth in terms of incidence and sixth in terms of mortality in 2002 (Parkin, et al., 2005; Ferlay et al., 2004). Genetic factors as well as environmental factors play a role in the development of esophageal cancer (Coeley and Buffler, 2001; Hiyama et al., 2003). Individual variations in cancer risk have been associated with specific variant alleles (polymorphisms) of different genes that are present in a significant proportion of the normal population. Alcohol consumption has been classified as a risk factor for esophageal cancer according to data from epidemiologic studies (Xing et al., 2003).

Alcohol in humans is oxidized to acetaldehyde, which in turn is oxidized by aldehyde dehydrogenases (ALDH) to acetate (Erikson 1984). ALDH2 is the major enzyme responsible for acetaldehyde elimination, and its polymorphic variants determine blood acetaldehyde concentrations after drinking. A single point mutation in the ALDH2 gene results in the ALDH2*2 allele, bearing a lysine amino acid at residue 487 instead of glutgamic acid and characterized by a reduced ability tometabolize acetaldehyde (Yoshida et al., 1984). Half of the Japanese are heterozygotes or homozygotes for the *2 allele of ALDH2, showing respectively peak blood acetaldehyde concentrations postalcohol consumption 6- and 19-fold higher than homozygous wide-type individuals (Mizoi et al., 1994). As a result, ALDH2*2/*2 homozygtes show facial flusing and nausea after alcohol consumption that prevent them from alcohol drinking, whereas heterozygotes exhibit less severe reactions (Mizoi et al., 1994). It would therefore be expected that the ALDH2 genotype influences diseases known to be related to alcohol consumption because of its strong influence on the propensity to alcohol drinking, and in fact the ALDH2*2/*2 genotype was found to lower the risk of liver cirrhosis and esophageal cancer (Chao et al., 1994; Lewis and Smith, 2005).

The aim of this study was to quantify the association between ALDH2 genotype and esophageal cancer via a meta-analysis of published studies, exploring the hypotheses: (a) ALDH2*2/*2 should have a reduced esophageal cancer risk predicted by very low alcohol

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consumption; (b) if acetaldehyde plays a carcinogenic role in esophageal cancer cancer it is expected that ALDH2*1/*2 heterozygote are at increased risk compared with ALDH2*1/*1, given a similar level of alcohol intake.

Materials and Methods

Selection criteria and search strategy

Identification of relevant studies was to carried out through a search of Medline and EMbase up to May 2011 using the following terms without any restriction on language: 1. esophag$. ab, ti.2. oesophag$. ab, ti.3. 1 or 24. (carcino$ or cancer$ or neoplasm$ or tumour$ or tumor$). ab, ti.5. adenocarcinoma$. ab, ti.6. or/4-57. 3 and 68. (or ALDH2 or aldehyde dehydrogenase). ab, ti.9. 7 and 8

The search produced 56 articles. A cited reference search of the retrieved articles was carried out, and publications were also identified by reviewing the bibliographies of the retrieved articles. Eligible studies were those reporting the frequency of the ALDH2 polymorphism among esophageal cancer cases and controls according to the three variant genotypes (ALDH2*2/*2, ALDH2*2/*1, and ALDH2*1/*1). If more than one article was published from the same case series, we included the paper where the most individuals were reported in the analysis. Of the 56 articles retrieved, 16 studies were eligible for the meta-analysis. Totally, 2697 cases and 6344 controls were retained for the analysis. A description of the studies is given in Table 1.

Statistical analysis

Two of the authors extracted the data from each article using a structured sheet and entered them into a database. The followings items were considered: year and location of the study, characteristics of the case and control group, and number of cases and controls homozygous and heterozygous for the ALDH2 variant alleles. The STATA statistical package (version 9, STATA, College Station, TX) was used for meta-analysis. ALDH2*1/*1 was used as the reference group for ALDH2*1/*2 and ALDH2*2/*2. The crude ORs of the included studies were calculated according to the available genotype frequencies to get the pooled ORs. Overall effect should be tested by using Z score with significance being set at $p < 0.05$. Heterogeneity should be tested for using the Chi-square test of goodness of fit with significance being set at $p < 0.05$ and I2 test. A random-effect model was applied to obtain summary ORs and their 95% CI since the results with fixed effect model was the same as with random effect models if there is no heterogeneity across the studies. Hardy-Weinberg equilibrium in controls of each included study was assessed by Chi-square test. Due to detecting heterogeneity across the trials, we performed a subgroup analysis regarding the alcoholic status among participants. A funnel plot was also used to present the publication bias. A sensitivity analysis was performed to explore robustness of the results by excluding the large sample study and studies which did not have controls in HWE.

Results

A total of 16 case-control studies were identified in our review. In none of the studies did the genotype frequencies among controls deviate from values predicted from Hardy-Weinberg equilibrium ($p \geq 0.05$). The overall ORs from the meta-analysis were 2.47 (95%CI: 1.76-3.46) and 0.6(0.26-1.38) for the risk of esophageal cancer among ALDH2*1/*2 compared with ALDH2*1/*1 (2697 cases and 6344 controls, Figure 1). There was significant evidence of between-study heterogeneity for studies in terms of ALDH2*1/*2 ($p<0.001$) and ALDH2*1/*1 ($p<0.001$).

The overall OR for esophageal cancer due to moderate and heavy alcohol intake among ALDH2*1/*2 individuals was 2.17(1.95-2.43) and 3.20(2.78-3.70) compared with never/rare drinkers with ALDH2*1/*1 genotype (Figure 3). The heterogeneity among alcohol strata was reduced compared with the overall estimated, with p for

Table 1. Studies of ALDH2 Polymorphism and Esophageal Cancer

First author year	Country	Study design	Cases Mean age	Controls Mean age	Cases	Controls	Case/Control 2*1/*1	2*1/*2	2*2/*2
Cai 2006	China	Hospital-based	NA	NA	205	394	119/214	61/160	25/20
Chao 2000	China	Population-based	NA	NA	88	327	40/240	46/78	2/9
Ding 2002	China	Hospital-based	31-83	30-81	98	235	55/119	41/98	2/18
Ding 2009	China	Population-based	NA	NA	221	191	90/114	89/66	42/11
Guo 2008	China	Population-based	60.2±8.9	59.7+9.7	80	480	37/252	43/195	0/33
Itoga 2004	Japan	Population-based	65.5+9.5	51.1±9.3	74	241	30/143	42/88	2/10
Lee 2008	China	Multicenter	NA	NA	406	656	111/325	281/286	14/45
Matsuo 2001	Japan	Population-based	61	58	102	241	35/126	66/96	1/19
Yang 2005	Japan	Population-based	61.4	61.4	165	494	38/254	126/195	1/45
Yang 2007	China	Hospital-based	58.3	52.8	191	198	90/108	98/76	3/14
Yokoyama 1996	Japan	Population-based	55±7	56±4	69	83	8/23	21/5	0/0
Yokoyama 2001	Japan	Population-based	56±7	53±8	112	526	50/476	62/50	0/0
Yokoyama 2002	Japan	Hospital-based	61.7±7.9	58.8±7.1	234	634	63/341	169/250	2/43
Yokoyama 2006	Japan	Hospital-based	63±8.8	58.7±7.6	52	412	26/223	22/167	4/22
Wu 2005	China	Hospital-based	58.9±12.6	57.8±11.8	134	237	18/249	24/24	0/0
Chen 2006	China	Hospital-based	59.5±11.8	58.8±11.2	330	592	92/294	228/257	10/41
Total					2697	6344	934/3621	1518/2196	111/621

NA, not available

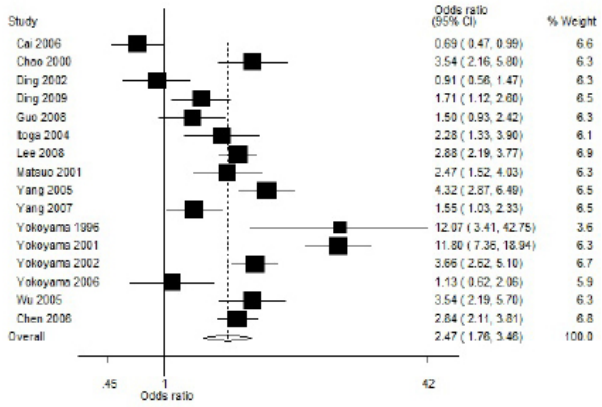

Figure 1. ALDH2*1/*2 and Esophageal Cancer Risk

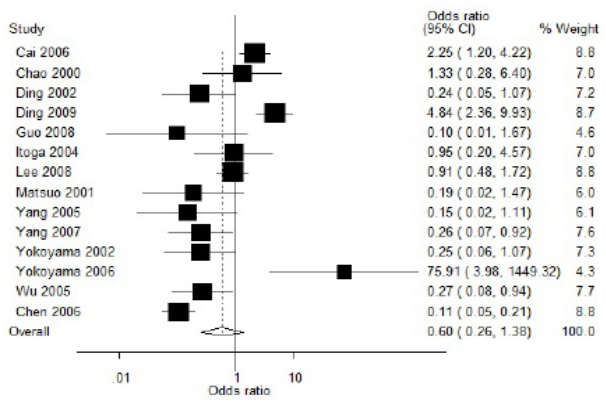

Figure 2. ALDH2*2/*2 and Esophageal Cancer Risk

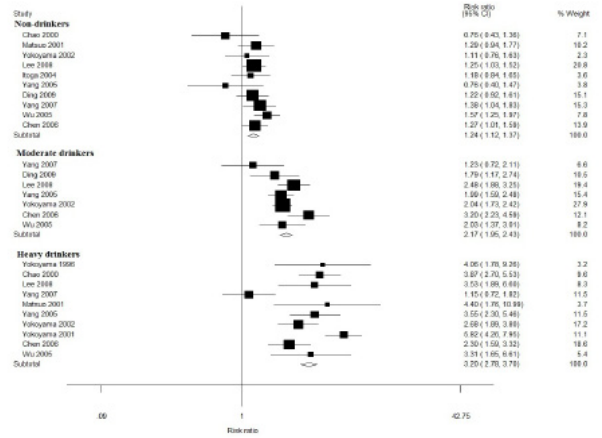

Figure 3. ALDH2*1/*2 and Esophageal Cancer Risk by Drinking

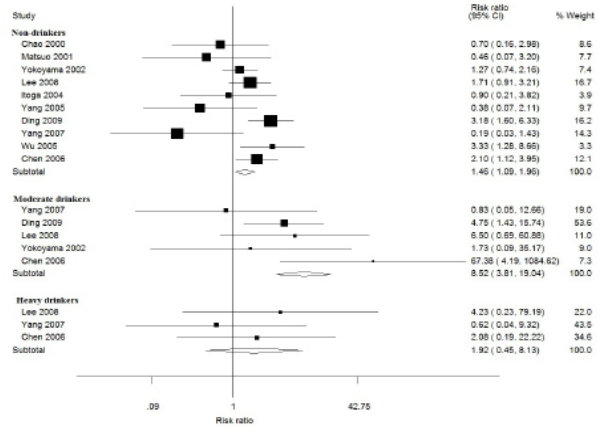

Figure 4. ALDH2*2/*2 and Esophageal Cancer Risk by Drinking

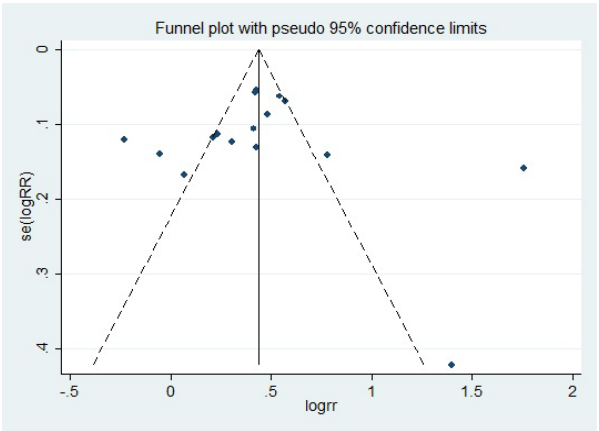

Figure 5. Funnel Plot for ALDH2*1/*2

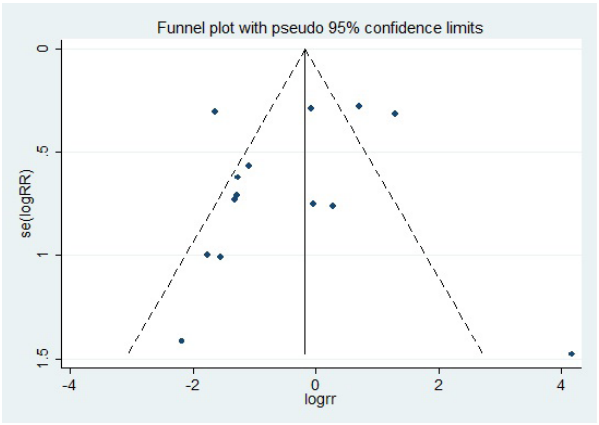

Figure 6. Funnel Plot for ALDH2*2/*2

heterogeneity =0.32 and 0.073 among non-drinkers and moderate drinkers with ALDH2*1/*2 genotype, however, a persisted among heavy drinkers (p<0.05).

The adjusted OR for moderate drinkers individuals with ALDH2*2/*2 compared with ALDH2*1/*1 carriers was 8.52(3.81-19.04), with no evidence of between-study heterogeneity (p>0.05). Among heavy drinkers, there was no evidence for increased risk for ALDH2*2/*2 versus ALDH2*1/*1 individuals (OR=1.92, 95% CI=0.45-8.13). The heterogeneity of studies regarding ALDH2*2/*2 was significantly reduced in moderate and heavy drinkers with p for heterogeneity =0.09 and 0.62, respectively, while heterogeneity still existed in non-drinkers (p=0.02).

A symmetry funnel plot also showed no existence of publication bias of ALDH2*1/*2 (Figure 5), but a significant publication bias of ALDH2*2/*2 was found (Figure 6). A sensitivity analysis indicated the overall crude ORs for ALDH2*1/*2 and ALDH2*2/*2 did not greatly changed after excluding two large sample study [ALDH2*1/*2 and ALDH2*2/*2 were 2.60 (95% CI: 1.80-3.77) and 0.51(0.21-1.21), respectively].

Discussion

The present meta-analysis showed that the ALDH2*1/*2 genotype increased the risk of esophageal

cancer by almost 147%, and this risk was seemed to be reduced among ALDH2*2/*2 compared with versus ALDH2*1/*1 individuals (Figure 2). The ALDH*1/*2 showed higher cancer risk in heavy drinkers. Subjects with ALDH2*2/*2 showed non-significant protective effect on esophageal cancer. However, individuals bearing the ALDH2*2/*2 genotype showed high esophageal cancer risk after intake of moderate amounts of alcohol.

Acetaldehyde is a very active intermediate, it showed cytoxic effects in vitro and in vivo (Wickramasinghe et al., 1986), and its concentrations after drinking alcohol are mainly dependent on the enzyme active of ALDH2 (Yokoyama et al., 2002; Wu et al., 2005). It is reported that the blood acetaldehyde concentrations in ALDH2*1/*2 and ALDH2*2/*2 subjects after consumption of alcohol were 6 and 19 folds higher than the concentrations in ALDH2*1/*1 subjects (Mizoi et al., 1994). Our results indicated that individuals with ALDH2*1/*2 had an increased risk of esophageal cancer, especially among heavy drinkers, which could prove the inactive ALDH2 fails to metabolize acetaldehyde rapidly, leading to excessive accumulation of acetaldehyde in blood and repeated high exposure to acetaldehyde after drinking, thus contributing to the development of esophageal cancer. Yang's meta-analysis (Yang et al., 2010) showed the effect of ALDH2*1/*2 versus ALDH2*1/*1 had a non-significantly increased risk for esophageal cancer among non-drinkers, but our study showed a non-significantly decreased risk for esophageal cancer. Our results also showed that the magnitude of the ALDH2-associated risk depended on the extent of the association between the esophageal cancer and alcohol consumption and the proportion of alcohol drinkers with inactive ALDH2.

Our study showed that ALDH2*2/*2 had a non-significantly increased risk for esophageal cancer compared with ALDH2*1/*1. The possible reason might be ALDH2*2/*2 subjects can develop intense facial flushing responses with nausea, drowsiness, headache and other unpleasant symptoms due to high blood acetaldehyde levels after drinking alcohol (Enomoto et al., 1991). This unpleasant discomfort may prevent people from consuming beverage and may keep them from developing alcoholism (Crabb et al., 1989; Thomasson et al., 1991), which may decrease the risk for esophageal cancer. This finding is also proved our study, that is, our study indicated the ALDH2*2/*2 had small amount of heavy drinkers.

There are several limitation of our study. Firstly, our study found a publication bias on studies regarding ALDH2*2/*2, which showed further studies should reported more unsatisfied results. Secondly, there was heterogeneity between studies of ALDH2 polymorphisms, and heterogeneity still existed in heavy drinkers with ALDH2*1/*2 and non-drinkers with ALDH2*2/*2 after we performed subgroup analysis regarding drinking status. Therefore, other confounding factors must be considered into analysis, but most of studies did not inquire other important risk factors such as smoking. Thirdly, most studies were conducted in Japan and China, and other high risk areas of esophageal cancer did not explore the relationship between ALDH2 and this cancer, such as Iran. Therefore, further studies are warranted in other high risk areas.

In conclusion, the finding of this meta-analysis showed that ALDH2*1/*2 genotype increased the risk of esophageal cancer, and ALDH2*2*2 genotype reduced the risk of esophageal cancer and this might be seem to be due to prevention people from consuming beverage by the unpleasant discomfort symptom of ALDH2*2/*2 carries. Drinking could modified the effect of ALDH2 on esophageal cancer risk. Our study provides more information on prevention of esophageal cancer.

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