RESEARCH ARTICLE

N-Acetyltransferase 2 Gene Polymorphisms are Associated with Susceptibility to Cancer: a Meta-analysis

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Abstract

N-acetyltransferase 2 (NAT2) is a polymorphic enzyme that plays an important role in the metabolism of various potential carcinogens. In recent years, a number of studies have been carried out to investigate the relationship between the rs1799930 and rs1799931 polymorphism in NAT2 and cancer risk in multiple populations for different types of cancer. However, the results were not consistent. Therefore, we performed a meta-analysis to further explore the relationship between NAT2 polymorphism and the risk of cancer. A total of 21 studies involving 15, 450 subjects for rs1799930 and 13, 011 subjects for rs1799931 were included in this meta-analysis. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess strength of associations. We also evaluated the publication bias and performed a sensitivity analysis. Overall, our results showed an apparent significant association between the NAT2 rs1799930 polymorphism and cancer susceptibility in Asians (GA vs. GG: OR=1.22, 95% CI=1.03-1.45; dominant model: OR=1.22, 95% CI=1.03-1.43) and population-based controls (GA vs. GG: OR=1.10, 95% CI=1.01-1.19; dominant model: OR=1.09, 95% CI=1.01-1.18). In contrast, a significant association was observed between the NAT2 rs1799931 G>A polymorphism and decreased cancer susceptibility in overall meta-analysis (AA vs. GG: OR=0.55, 95% CI=0.33-0.93; GA vs. GG: OR=1.00, 95% CI=0.88-1.14; dominant model: OR=0.97, 95% CI=0.86-1.10; recessive model: OR=0.56, 95% CI=0.34-0.94) and the Asian group (AA vs. GG: OR=0.50, 95% CI=0.26-0.94; recessive model, OR=0.50, 95% CI=0.27-0.94). We found that the NAT2 rs1799930 may be a risk factor, while the NAT2 rs1799931 polymorphism is associated with a decreased risk of cancer and is likely a protective factor against cancer development.

Keywords: NAT2 - polymorphism - association - cancer susceptibility - meta-analysis

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Introduction

N-acetyltransferase 2 (NAT2) gene, located in chromosomal region 8p21.3-23.1, encodes a phase II xenobiotic metabolizing enzyme (Blum et al., 1990; Hickman et al., 1998). As one of the phase II metabolizing enzymes, it played a essential part in the metabolism of aromatic, heterocyclic amines and hydrazines via N-acetylation and O-acetylation which was significant ultimate carcinogens involved in the initiation process of cancer (Hein et al., 1993; De Stefani et al., 1998).

In recent years, some studies have reported the association NAT2 variants such as the polymorphism rs1799930 (G590A) and rs1799931 (G857A) with risk of several types of cancer, including colorectal cancer, lung cancer, breast cancer and acute lymphoblastic leukemia. However, the results of these studies have still been discordant Kown et al (Kown et al., 2013) have conducted a study which showed that Asian Americans experienced disproportionate incidence and mortality rates of certain cancers, for example, liver cancer and stomach cancer were perceived as higher cancer risks among Asian Americans than among the general population. Our study was a meta-analysis of all relevant studies published up to May 2013. It presented the more precise estimation on the relationship between NAT2 G590A and G857A and susceptibility to the development of cancer.

Materials and Methods

Literature search

Databases of Medline, PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) were performed (between January 2005 and May 2013). The following search words and their combinations were used: ("genetic polymorphism" or "polymorphism" or "SNP" or "gene mutation" or "genetic variants") and ("cancer" or "lymphocytic leukemia" or "carcinoma" or "malignancy") and ("NAT2" or "G590A" or "rs1799930" or "G857A" or "rs1799931"). All searched studies were retrieved, and their bibliographies were checked for the other relevant publications. For overlapping and

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Table 1. Characteristics of Included Studies in This Meta-analysis

Study	Year	Ethnicity	Type of cancer	Source of control	rs1799930 (case/control) GG	GA	AA	P value	rs1799931 (case/control) GG	GA	AA	*P* value
Landi	2005	Caucasian	Colorectal cancer	HB	179/150	135/122	24/21	0.572	337/294	14/13	0/0	0.705
Osian	2006	Caucasian	Colorectal cancer	HB	24/13	28/15	18/12	0.115				
Nikishina	2006	Caucasian	Lung cancer	PB	59/72	51/80	12/15	0.275	116/158	6/9	0/0	0.720
Majumdar	2007	Asian	Acute myeloid leukemia	PB	32/80	55/53	23/11	0.593	93/115	16/26	1/3	0.302
Gemignani	2007	Caucasian	Lung cancer	HB	141/156	106/106	18/24	0.326	244/258	15/12	0/0	0.709
Al-Moundhri	2007	Asian	Gastric cancer	PB	49/42	44/46	7/12	0.912	87/83	10/17	1/0	0.353
Eichholzer	2008	Caucasian	Colorectal cancer	HB	211/418	177/337	39/71	0.792	387/745	24/44	0/1	0.678
Demokan	2009	Caucasian	Head and neck cancer	PB	46/51	45/31	4/11	0.079	76/62	19/30	0/1	0.202
Cotterchio	2009	Caucasian	Colorectal cancer	PB	410/644	365/505	60/98	0.942	788/1191	44/57	0/0	0.409
Zheng	2010	Asian	Lung cancer	HB	156/176	100/115	10/16	0.617	195/223	66/72	5/12	0.052
Delort	2010	Caucasian	Breast cancer	PB	428/475	399/429	82/91	0.677				
Cleary	2010	Caucasian	Colorectal cancer	PB	577/662	502/529	87/99	0.637	1105/1233	58/58	2/1	0.710
Zanrosso	2011	Mix	Acute myeloid leukemia and Acute lymphoblastic leukemia	HB	115/159	92/105	21/25	0.206	169/178	34/52	3/7	0.192
Hou	2011	Asian	Oral and pharyngeal carcinoma	PB	88/97	68/63	16/10	0.957	126/122	42/44	4/4	0.989
Wang	2012	Asian	Renal cell carcinoma	PB	106/138	84/78	17/20	0.068	146/155	59/72	2/9	0.860
Silveira	2012	Mix	Acute lymphoblastic leukemia	HB	111/198	62/133	14/30	0.259	174/328	13/32	0/1	0.815
Balaji	2012	Asian	Oral cancer	PB	57/55	78/61	22/16	0.885	136/119	21/12	0/1	0.276
Muthusamy	2012	Asian	Glioma	PB					7/9	5/3	0/1	0.354
Jang	2012	Caucasian	Pancreatic cancer	PB	236/450	174/360	41/71	0.933	415/849	31/40	1/1	0.463
Zgheib	2013	Asian	Breast cancer	HB	107/47	100/38	20/13	0.241				
Agudo	2013	Caucasian	Gastric adenocarcinoma	HB	124/444	100/396	16/83	0.692	226/874	16/41	0/0	0.488

*P value for the result of Chi-square test of Hardy-Weinberg equilibrium; PB, population based; HB, hospital based

republished studies, only the most recent or the largest sample size was selected in this meta-analysis.

Inclusion and exclusion criteria

Studies selected in the meta-analysis need to meet all the following criteria: a) studies focused on associations between NAT2 rs1799930 and rs1799931 polymorphism and cancer susceptibility; b) case-control studies; c) sufficient published data for expressing an odds ratio (OR) with 95% confidence interval (CI); d) the studies included detailed genotyping data. Major reasons for exclusion of studies were: a) no control population; b) duplicate of earlier publication; c) no available data for case and control; d) genotype distributions of polymorphism were inconsistent with Hardy-Weinberg Equilibrium (HWE).

Data extraction

Two investigators independently collected the data from all eligible publications according to the criteria of inclusion and exclusion. Whenever disagreements occurred, the third investigator was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were extracted from each study: the first author's last name, publication year, ethnicity, study design, cancer type, controls source and numbers of cases and controls with the NAT2 rs1799930 and rs1799931.

Statistical analysis

In our meta-analysis, we investigated the association between NAT2 rs1799930 and rs1799931 polymorphism and cancer risk according to pooled OR with corresponding 95% CI. For rs1799930, we estimated cancer risk associated with the co-dominant (AA versus GG; GA versus GG), dominant model (AA+GA versus GG) and recessive model (AA versus GA+GG) ; for rs1799931, we also applied co-dominant (AA versus GG; GA versus GG), dominant model (AA+GA versus GG) and recessive model (AA versus GA+GG) to evaluate cancer risks. Stratification analysis was performed by ethnicity, type of cancer and source of controls. The significance of the pooled ORs was determined by the Z test and $p<0.05$ was considered as statistically significant.

In our study, HWE was tested using the chi-squared goodness-of-fit test. The heterogeneity of studies was examined through the Q-test and the I2 test (Colditz et al., 1995; Higgins et al., 2002). If between-study heterogeneity was significant ($p<0.05$ for the Q-test and I2>50%), we used a random-effects model (DerSimonian-Laird method) (DerSimonian et al., 1986). Otherwise, the fixed-effects model (Mantel–Haenszel's method) was used (Mantel et al., 1959). Sensitivity was performed by omitting individual studies, in order to determine the stability of results in this meta-analysis. To assess the potential publication bias, Begg's funnel plot was generated as the visual inspection to detect bias (Begg et al., 1994), besides Egger's test was also conducted to analyze the publication bias statistically (Egger et al., 1997). All the p-values were two-sided. All analyses were calculated using STATA Version 11.0 software (Stata Corporation, College Station, TX, USA).

Results

Characteristics of included studies

By searching the databases, 474 abstracts were collected according to the search criteria. Of these 474 articles, 303 were excluded after reviewing the title

Table 2. Results of Meta-Analysis for NAT2 rs1799930 Polymorphism and Cancer Risk

NAT2 rs1799930	AA vs. GG OR (95% CI)	P_h	GA VS. GG OR (95% CI)	P_h	Dominant model OR (95% CI)	P_h	Recessive model OR (95% CI)	P_h
Total Ethnicity	1.01 (0.89, 1.14)	0.120	1.06 (0.99, 1.14)	0.250	1.05 (0.99, 1.12)	0.086	0.97 (0.87, 1.10)	0.370
Caucasian	0.96 (0.84, 1.11)	0.924	1.04 (0.96, 1.12)	0.731	1.03 (0.95, 1.10)	0.895	0.95 (0.83, 1.08)	0.824
Asian	1.23 (0.91, 1.65)	0.003	1.22 (1.03, 1.45)	0.092	1.22 (1.03, 1.43)	0.008	1.10 (0.83, 1.46)	0.033
Type of cancer								
Colorectal cancer	1.00 (0.82, 1.20)	0.983	1.08 (0.97, 1.19)	0.873	1.06 (0.96, 1.17)	0.905	0.96 (0.80, 1.16)	0.970
Lung cancer	0.83 (0.54, 1.28)	0.862	0.98 (0.79, 1.22)	0.522	0.96 (0.78, 1.18)	0.663	0.84 (0.55, 1.29)	0.723
Breast cancer	0.94 (0.70, 1.28)	0.362	1.05 (0.88, 1.25)	0.682	1.03 (0.87, 1.22)	0.979	0.92 (0.69, 1.23)	0.280
Gastric cancer	0.64 (0.39, 1.06)	0.588	0.89 (0.68, 1.15)	0.769	0.84 (0.65, 1.09)	0.661	0.68 (0.42, 1.10)	0.638
Other cancer	1.12 (0.84, 1.50)	0.399	1.11 (0.94, 1.31)	0.255	1.11 (0.95, 1.30)	0.455	1.07 (0.81, 1.42)	0.272
Source of controls								
Population-based	1.07 (0.92, 1.24)	0.020	1.10 (1.01, 1.19)	0.057	1.09 (1.01, 1.18)	0.015	1.03 (0.89, 1.18)	0.099
Hospital-based	0.89 (0.72, 1.09)	0.916	1.00 (0.89, 1.13)	0.912	0.98 (0.88, 1.10)	0.895	0.88 (0.72, 1.08)	0.930

*OR, odds ratios; 95%CI, 95% confidence interval ;P_h P values for heterogeneity for Q-test

Table 3. Results of Meta-Analysis for NAT2 rs1799931 Polymorphism and Cancer Risk

NAT2 rs1799931	AA VS. GG OR (95% CI)	P_h	GA VS. GG OR (95% CI)	P_h	Dominant model OR (95% CI)	P_h	Recessive model OR (95% CI)	P_h
Total Ethnicity	0.55 (0.33, 0.93)	0.938	1.00 (0.88, 1.14)	0.357	0.97 (0.86, 1.10)	0.284	0.56 (0.34, 0.94)	0.940
Caucasian	1.07 (0.29, 4.00)	0.714	1.13 (0.94, 1.35)	0.363	1.13 (0.94, 1.35)	0.306	1.10 (0.29, 4.15)	0.759
Asian	0.50 (0.26, 0.94)	0.804	0.95 (0.77, 1.17)	0.575	0.90 (0.73, 1.10)	0.723	0.50 (0.27, 0.94)	0.788
Type of cancer								
Colorectal cancer	1.40 (0.23, 8.53)	0.541	1.10 (0.87, 1.39)	0.964	1.10 (0.88, 1.39)	0.952	1.40 (0.23, 8.50)	0.541
Lung cancer	0.48 (0.16, 1.38)	-	1.08 (0.78, 1.50)	0.825	1.01 (0.74, 1.39)	0.759	0.47 (0.16, 1.35)	0.349
Gastric cancer	2.86 (0.12, 71.27)	-	1.05 (0.64, 1.71)	0.059	1.08 (0.66, 1.75)	0.082	3.09 (0.12, 76.83)	0.000
Other cancer	0.49 (0.22, 1.12)	0.699	1.01 (0.81, 1.28)	0.082	0.97 (0.78, 1.22)	0.066	0.50 (0.22, 1.13)	0.711
Source of controls								
Population-based	0.61 (0.31, 1.22)	0.736	1.01 (0.86, 1.19)	0.216	0.99 (0.84, 1.17)	0.188	0.62 (0.31, 1.24)	0.741
Hospital-based	0.48 (0.22, 1.06)	0.996	0.99 (0.80, 1.21)	0.498	0.94 (0.77, 1.16)	0.422	0.49 (0.23, 1.08)	0.996

*OR, odds ratios; 95%CI, 95% confidence interval ;P_h,P values for heterogeneity for Q-test

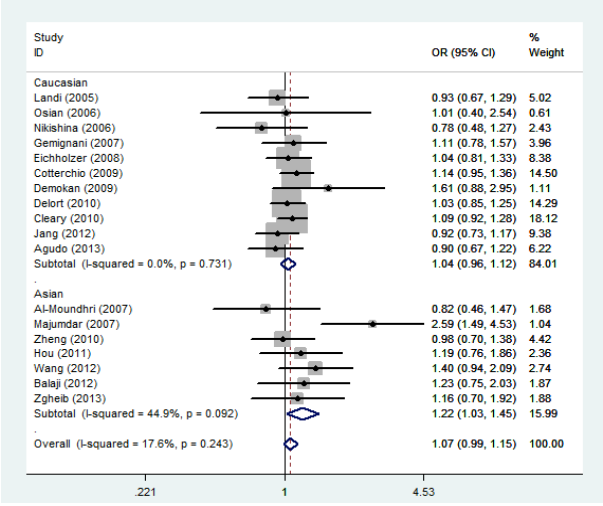

Figure 1. Forest Plot of Cancer Risk Associated with NAT2 rs1799930 Polymorphism in Caucasian and Asian (The genetic model is GA versus GG)

and abstract. Another 150 studies were excluded after reviewing full texts. Conclusively, 21 case-control studies about the association NAT2 rs1799930 and rs1799931 polymorphism with cancer susceptibility were included in this meta-analysis. The characteristics of all the studies were summarized in Table 1. Among the 21 eligible studies (Landi et al., 2005; Osian et al., 2006; Al-Moundhri et al., 2007; Gemignani et al., 2007; Nikishina et al., 2007; Cotterchio et al., 2008; Majumdar et al., 2008; Cleary et al., 2010; Delort et al., 2010; Demokan et al., 2010; Zheng et al., 2010; Hou et al., 2011; Balaji et al., 2012; Eichholzer et al., 2012; Jang et al., 2012; Muthusamy et al., 2012; Silveira et al., 2012; Wang et al., 2012; Zanrosso et al., 2012; Agudo et al., 2013; Zgheib et al., 2013), 20 studies were included in the meta-analysis with 6, 572 cases and 8, 878 controls for rs1799930 polymorphism and 18 studies with 5, 339 cases and 7, 672 controls for rs1799931 polymorphism.

Meta-analysis results

NAT2 rs1799930 By pooling genotype datum from all 20 studies, the meta-analysis results of NAT2 rs1799930 were listed in Table 2. Overall, The combined results based on all studies showed that no significant association was found between the NAT2 rs1799930 polymorphism and cancer risk (AA vs. GG: OR=1.01, 95% CI=0.89-1.14; GA vs. GG: OR=1.06, 95% CI=0.99-1.14; dominant model: OR=1.05, 95% CI=0.99-1.12; recessive model: OR=0.97, 95% CI=0.87-1.10).

Several stratified analyses were performed according to the ethnicity, type of cancer and source of controls (Table 2). Subgroup analyses for the different ethnic groups were therefore conducted. There was significant association with the risk of cancer in Asian (GA vs. GG: OR=1.22, 95% CI=1.03-1.45, Figure 1; dominant model: OR=1.22, 95% CI=1.03-1.43) but not in Caucasian. The result of subgroup analyses in different source of controls showed that rs1799930 G>A polymorphism increased the cancer risk in population-based control (GA vs. GG: OR=1.10, 95% CI=1.01-1.19, Figure 2; dominant model:

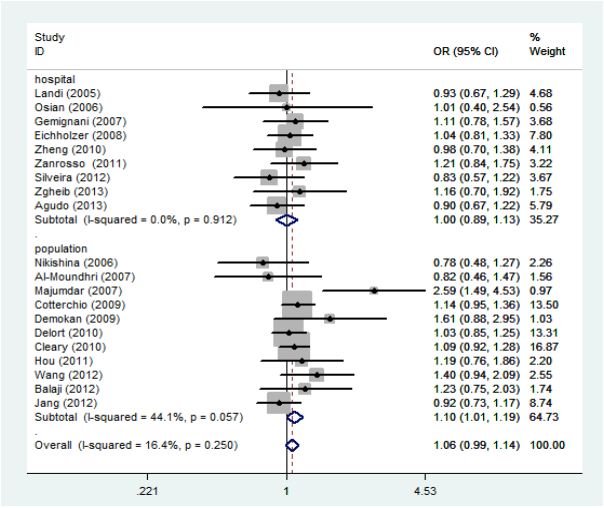

Figure 2. Forest Plot of Cancer Risk Associated with NAT2 rs1799930 Polymorphism for Population-based and Hospital-based Control (The genetic model is GA versus GG)

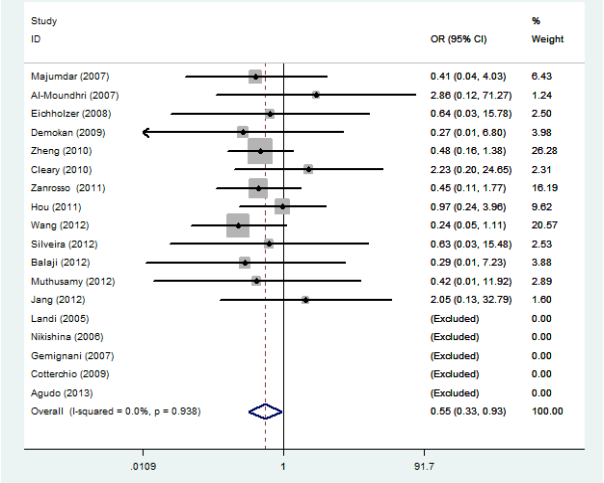

Figure 3. Forest Plot of Cancer Risk Associated with NAT2 rs1799931 Polymorphism (The Genetic Model is AA Versus GG)

OR=1.09, 95% CI=1.01-1.18) but not in hospital-based control. Subgroup analyses in the different type of cancer were also performed, however, no statistically significantly increased risk was found in all solid tumors.

NAT2 rs1799931 Table 3 showed 18 case-control studies reported the association between NAT2 rs1799931 polymorphism and cancer risk. A significant association was observed between the NAT2 rs1799931 G>A polymorphism and decreased cancer susceptibility in our meta-analysis (AA vs. GG: OR=0.55, 95% CI=0.33-0.93, Figure 3.; GA vs. GG: OR=1.00, 95% CI=0.88-1.14; dominant model: OR=0.97, 95% CI=0.86-1.10; recessive model: OR=0.56, 95% CI=0.34-0.94).

In the subgroup analysis by ethnicity, the same association was discovered in Asian (AA vs. GG: OR=0.50, 95% CI=0.26-0.94, Figure 4.; recessive model, OR=0.50, 95% CI=0.27-0.94) but not in Caucasians. We didn't observe any significant association among other subgroups (cancer type and source of control). The results of subgroup analysis were shown in Table 3.

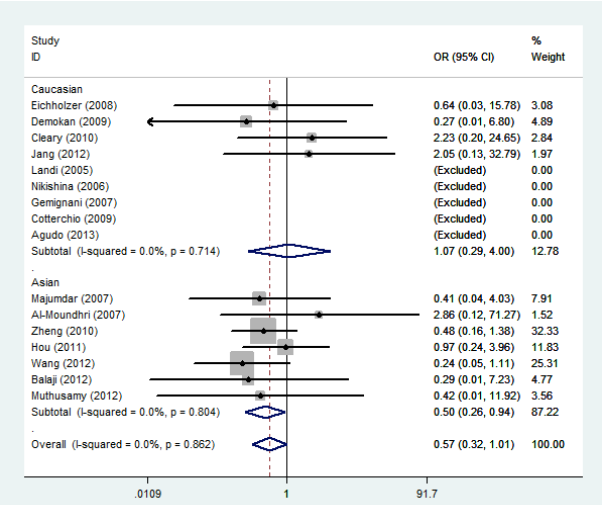

Figure 4. Forest Plot of Cancer Risk Associated with NAT2 rs1799931 Polymorphism in Caucasian and Asian (The genetic model is AA versus GG)

Sensitivity analysis and publication bias

An independent study involved in this meta-analysis was performed to evaluate the influence of the individual data set on the pooled ORs each time. The results were not substantially altered, indicating that our results were stable and robust. Begg's funnel plots were conducted to assess publication bias, and the shapes revealed no evidence of obvious asymmetry. Egger's test was based on linear regression of the standard normal deviate against its precision, which was performed to test the existence of publication bias. The results did not show any evidence of publication bias for NAT2 rs1799930 (t=-0.24, p=0.815 for AA vs. GG; t=0.80, p=0.433 for GA vs. GG). Meanwhile, the results indicated publication bias for NAT2 rs1799931 (t=0.89, p=0.394 for AA vs. GG; t=-0.31, p=0.763 for GA vs. GG).

Discussion

NAT2 mainly encoded drug phase-IImetabolic enzyme, namely N-acetyltransferase 2, which was most frequently present in the liver and the intestinal mucosa. Allelic polymorphism of the NAT2 enzyme has been investigated for a long time, first detected phenotypically, based on enzyme activity distribution in healthy subjects, and later these activity differences were bound to an allelic polymorphism (Le Marchand et al., 1996). Probst Hensch et al. reported an inverse association between NAT2 rapid genotypes and colorectal adenomas among African Americans, but an increased risk among whites (Probst-Hensch et al., 1995). Other studies found that NAT2 rapid genotypes played a great role in susceptibility of colorectal cancer (Osian et al., 2006), but not in susceptibility of lung cancer (Borlak et al., 2006). Currently available data were not concordant due to ethnic differences and differences in types of cancer.

NAT2 catalyzed the reaction in which environment carcinogens (such as aromatic, heterocyclic amines, hydrazines) combined with some strong polar groups (such as methyl and acetyl) can be metabolized out of the body (Windmill et al., 2000; Pande et al., 2003; Yamada

et al., 2009). There were some sites of mutation in NAT2 gene polymorphism, G590A and G857A of which were high-profile (Hickman et al., 1992). At the 590 position a G>A substitution resulted in the arginine 197 to glutamine substitution. A G>A substitution at position 857 produced replacement of glycine by gluta in the 286th amino acid of the protein (Hein et al., 1988). The locus mutation directly caused to change activity of metabolic enzyme, which affected the metabolism of some drugs and carcinogens inactivation or activation and made incidence of cancer increase or decrease. Although, the markedly association between NAT2 rs1799930 and rs1799931 polymorphism and cancer risk was found in some publications (Majumdar et al., 2008; Zanrosso et al., 2012), while some other studies indicated that rs1799930 and rs1799931 had no any correlation with the risk of cancer (Gemignani et al., 2007; Al-Moundhri et al., 2007). In order to resolve this contradiction, we performed a meta-analysis involving in 21 eligible studies to understand if the rs1799930 and rs1799931 polymorphism were significantly associated with risk of cancer in ethnicity, types of cancer and source of controls.

For rs1799930 G>A, the result of this meta-analysis indicated that there was a weak association with risk of cancer in Asian and population-based control, but not in Caucasian and hospital-based control, which indicated that the differences in genetic backgrounds might be a critical factor on the effects of the association between NAT2 rs1799930 G>A polymorphism and the risk of cancer.

For rs1799931 G>A, a negative association with cancer susceptibility was found, which showed a protective effect of the rs1799931 against cancer development. In the subgroup analysis by ethnicity, rs1799931 might decrease the risk of cancer in the Asian population, but not in the Caucasian population, while it was not associated with cancer risk in other subgroups. Those results indicated that the different ethnicity may influence cancer susceptibility by different genetic back-grounds and environmental exposures through gene-gene and gene-environmental interactions.

Our meta-analysis also had many advantages compared with others' work. Firstly, sufficient date was extracted form well-selected studies, providing stable and robust power for this meta-analysis. Secondly, all of studies we included didn't show obvious publication bias, according to Begg and Egger's formal statistical test. Besides, the results were consistent with Hardy-Weinberg equilibrium in control population of all the studies.

Some limitations of this study should be acknowledged and taken into consideration. First, detailed information, such as the mean age and sex of the case and control populations, was not available in all of the selected studies. Secondly, the controls were not uniformly defined. Some of the controls may potentially have benign disease. In addition, our results were based on unadjusted estimates without adjustment for other risk factors such as age, smoking status, drinking status, obesity, environmental factors and so on.

In conclusion, our meta-analysis indicated that the NAT2 rs1799930 had an association with risk of cancer in Asian and population-based control while NAT2 rs1799931 polymorphism was associated with a decreased risk of cancer and was likely a protective factor against cancer development. Whereas it is necessary to conduct large sample studies so that improving statistical power and overcoming the limitations of individual studies. Furthermore, gene-gene and gene-environment interactions should also be considered in the analysis. Further studies will take these factors into account to evaluate the association between NAT2 rs1799931 and rs1799930 polymorphism and cancer susceptibility more precisely.

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