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Association Between NAT2 Polymorphisms and Lung Cancer Susceptibility

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Abstract: To further investigate the association between *NAT2* polymorphisms and lung cancer susceptibility.

In terms of phenotypes, we investigated the acetylator status of *NAT2* polymorphisms associated with lung cancer risk. Additionally, in view of genotypes, we mainly analyzed 5 single nucleotide polymorphisms (SNPs) in *NAT2* gene, namely C282T, A803G, C481T, G590A, and G857A. Twenty-six eligible studies were included in our meta-analysis by searching PubMed, Embase, and CNKI databases. We used odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to evaluate the susceptibility to lung cancer associated with *NAT2* polymorphisms.

Overall, based on phenotypes, the pooled ORs showed no significant association between *NAT2* polymorphisms and lung cancer susceptibility. In the subgroup analyses by ethnicity and source of control, there was still no significant association. In terms of genotypes, overall, no obvious relationship was observed between *NAT2* polymorphisms and lung cancer risk. But increased risk of lung cancer was found in association with *NAT2* C282T polymorphism (TT vs. CC + TC: OR = 1.58, 95% CI = 1.11–2.25).

Our meta-analysis demonstrates that TT genotype in *NAT2* C282T polymorphism may be a risk factor for lung cancer susceptibility. Additionally, the acetylator status of 5 SNPs in *NAT2* gene may not be associated with lung cancer risk.

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Abbreviations: CI = confidence intervals, HWE = Hardy–Weinberg equilibrium, NAT2 = N-acetyltransferase 2, OR = odds ratios, PCR = polymerase chain reaction, PCR-RFLP = PCR-restriction fragment length polymorphism, SNP = single nucleotide polymorphism, TaqMan = TaqManSNP.

INTRODUCTION

Lung cancer is the most common cancer and the leading cause of cancer death in the world.[1,2] It consists of 3 major histological subtypes, adenocarcinoma, squamous cell carcinoma, and small cell carcinoma. The exposure to tobacco smoke is known as a crucial cause of lung cancer.[3] Additionally, genetic factors are considered to play an important role in lung cancer risk.[4,5]

N-acetyltransferase 2 (*NAT2*) gene, located on the short arm of chromosome 8 (8q22), encodes a phase II xenobiotic-metabolizing enzyme.[6,7] *NAT2* gene is essentially involved in the metabolism of aromatic, heterocyclic amines, and hydrazines.[8,9] Five known polymorphisms in *NAT2* gene, namely C282T, A803G, C481T, G590A, and G857A, are associated with decreased enzyme activity and variable stability, leading to imbalance of the process of xenobiotics detoxification and consequently affecting lung cancer susceptibility.[10]

The alteration of NAT2 acetylator status caused by polymorphisms in *NAT2* gene may lead to decreased enzyme activity and absence of efficiency in detoxification, and further contribute to elevated cancer risk.[11] There are 2 major NAT2 phenotypes, including rapid acetylator phenotype and slow acetylator phenotype. Wild-type homozygotes and heterozygotes in *NAT2* gene are categorized into rapid acetylator phenotype whereas mutant homozygotes are categorized into slow acetylator phenotype.[12] The rapid acetylator phenotype was reported to increase the risk of bladder, colon, and prostate cancers.[13–15] Whereas slow acetylator phenotype was in association with increased risk of bladder cancer and decreased risk of colon cancer.[16,17]

In 1995, Martinez et al first explored *NAT2* polymorphisms in malignancies among Caucasians. However, no significant association was observed.[18] Since then, several phenotyping studies have investigated the association between acetylator status of *NAT2* polymorphisms and lung cancer risk.[12,19–38] However, the results were inconclusive. With respect to genotypes, quite a few studies focused on the relationship between genetic polymorphisms in *NAT2* gene and lung cancer susceptibility.[39–42] Therefore, we conducted this meta-analysis to gain more precise evidence for the association from genotype and phenotype aspects.

METHODS

Search Strategy

We searched PubMed, Embase, and CNKI databases using the terms ''NAT2,'' ''polymorphism,'' and ''lung cancer.'' The reference lists of the selected papers were also screened for other potential articles. The following inclusion criteria were used to select the eligible studies for this meta-analysis: case–control studies; enough data for estimating odds ratio (OR) with 95% confidence interval (CI). Additionally, when the same data were included in several publications, only the largest or most recent study was selected in our meta-analysis. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

TABLE 1. Principle Characteristics of the Studies Included in the Meta-Analysis Based on Phenotypes of *NAT2* Polymorphisms

Publish Time	Writer	Ethnicity	State	Genotyping Means	Source
2005	Belogubova	Caucasian	Russia	PCR-RFLP	Hospital based
2006	Borlak	Caucasian	UK	PCR-RFLP	Population based
1998	Bouchardy	Caucasian	France	PCR-RFLP	Hospital based
1996	Cascorbi	Caucasian	Germany	PCR-RFLP	Population based
2006	Chen	Asian	China	PCR-RFLP	Population based
2005	Chiou	Asian	China	PCR-RFLP	Population based
2005	Habalova	Caucasian	Slovak	PCR-RFLP	Hospital based
2000	Hou	Caucasian	Norway	PCR-RFLP	Population based
2009	Lee	Asian	China	PCR-RFLP	Population based
2012	Mahasneh	Asian	Jordan	PCR-RFLP	Hospital based
1995	Martinez	Caucasian	Spain	PCR-RFLP	Hospital based
1998	Nyberg	Caucasian	Sweden	PCR-RFLP	Population based
2007	Osawa	Asian	Japan	PCR-RFLP	Hospital based
1997	Oyama	Asian	Japan	PCR-RFLP	Population based
2000	Saarikoski	Caucasian	Finland	PCR-RFLP	Population based
1999	Seow	Asian	Singapore	PCR-RFLP	Hospital based
2005	Skuladottir	Caucasian	Denmark	PCR-RFLP	Population based
2009	Sobti	Asian	India	PCR-RFLP	Hospital based
2005	Sorensen	Caucasian	Denmark	TaqMan/PCR-RFLP	Nest
2001	Wikman	Caucasian	Germany	PCR-RFLP	Hospital based
2002	Zhou	Caucasian	America	PCR-RFLP	Population based
2009	Zupa	Caucasian	Italy	PCR-RFLP	Hospital based

PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; TaqMan = TaqManSNP.

Data Extraction

All the following data were independently extracted from each study by 2 investigators: single nucleotide polymorphisms (SNPs), first author, publication date, country of origin, ethnicity, source of controls, genotyping method, total cases and controls, and *P*-value for Hardy–Weinberg equilibrium (HWE), as shown in Tables 1 and 2. Inconsistent results were settled generally through discussion.

Statistical Analysis

Crude ORs with 95% CIs were calculated to assess the strength of association between *NAT2* polymorphisms and lung cancer susceptibility. In terms of phenotypes, subgroup analyses were based on ethnicity and source of control. The Chi-square based Q-test was performed to evaluate heterogeneity. $P < 0.05$ indicates significant heterogeneity among studies, thus the pooled OR was calculated using random-effects model; otherwise, the fixed-effects model was used. Sensitivity analysis was performed to assess the stability of results. The potential publication bias was estimated by Egger test and Begg funnel plot. HWE was checked by χ^2 test. Statistical analyses were conducted using the STATA software (version 12.0, Stata Corporation, College Station, TX).

TABLE 2. Principle Characteristics of the Studies Included in the Meta-Analysis Based on Genotypes of *NAT2* Polymorphisms

Publish Time	Locus	Writer	Ethnicity	State	Genotyping Means	Source	Total Case Number	Total Control Number
2008	C282T	Zienolddiny	Caucasian	Norway	Arrayed primer extension	PB	321	715
2007		Nikishina	Caucasian	Russia	Polymerase chain reaction	NA	122	243
2010	A803G	Zheng	Asian	China	TaqManSNP	PB	266	172
2007		Nikishina	Caucasian	Russia	Polymerase chain reaction	NA	122	278
2007	C481T	Nikishina	Caucasian	Russia	Polymerase chain reaction	NA	122	197
2014	G590A	Tian	Asian	China	TaqManSNP	HB	259	208
2010		Zheng	Asian	China	TaqManSNP	PB	266	167
2007		Nikishina	Caucasian	Russia	Polymerase chain reaction	NA	122	375
2010	G857A	Zheng	Asian	China	TaqManSNP	PB	266	119
2007		Nikishina	Caucasian	Russia	Polymerase chain reaction	NA	122	99

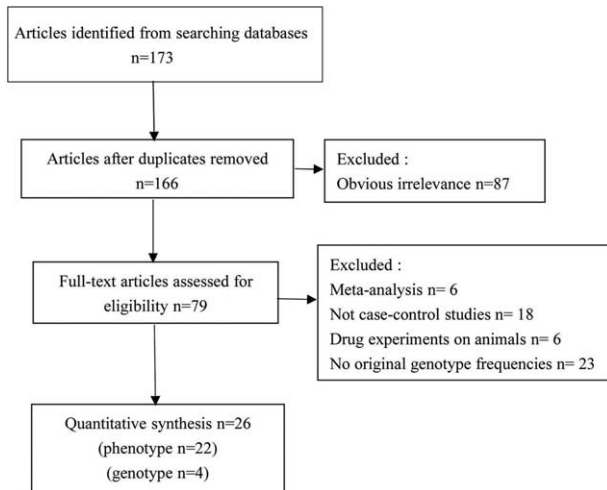HB = hospital based; NA = not available; PB = population based.

FIGURE 1. Flow diagram of included studies for the meta-analysis.

RESULTS

Study Characteristics

As displayed in Figure 1, a total of 173 studies were selected through databases in which 7 articles were excluded for duplicates and 87 articles were excluded for obvious irrelevance and finally 79 full-text articles were assessed for eligibility. Among these 79 full-text articles, 53 articles were excluded for only meta-analysis and drug experiments on animals and without case-control and original genotype frequencies, finally 26 eligible studies on the association between *NAT2* polymorphisms and lung cancer risk were included in our meta-analysis. Twenty-two studies involved phenotypes[11,12,18–21,23–26,29–38,43,44] and 4 studies discussed about genotypes.[39–42] Diverse genotyping methods were used, including polymerase chain reaction (PCR), PCR-restriction fragment length polymorphism (PCR-RFLP), TaqManSNP (TaqMan), arrayed primer extension.

Meta-Analysis

The main results are shown in Tables 3 and 4. Overall, with respect to phenotypes, the pooled ORs showed no significant association of *NAT2* polymorphisms with lung cancer susceptibility. In the subgroup analyses by ethnicity and source

of control, there was still no significant association. In terms of genotypes, no obvious relationship was found between 5 SNPs in *NAT2* gene and lung cancer susceptibility. But increased risk of lung cancer was found in association with *NAT2* C282T polymorphism (TT vs. CC + TC: OR = 1.58, 95% CI = 1.11–2.25), as displayed in Figure 2.

Sensitivity Analysis

Sensitivity analysis was carried out to evaluate the influence of each individual study on the pooled ORs. The recalculated ORs were not materially altered, suggesting our results were statistically steady.

Publication Bias

Egger test and Begg funnel plot were performed to estimate the publication bias. The shape of the funnel plot did not indicate obvious asymmetry, as displayed in Figure 3. Additionally, result of Egger test did not show statistical evidence for bias ($P = 0.805$). Thus, there was no obvious publication bias and the results were credible.

DISCUSSION

Both environmental and genetic factors are considered crucial in the etiology of lung cancer. The risk of lung cancer correlated with exposure to exogenous xenobiotics or endogenous substances may be modified by the genetic variation in metabolic detoxication activities. Thus, the relevance of the *NAT2* polymorphisms to lung cancer risk is of particular importance.[45]

So far, the role of NAT2 acetylator status in lung cancer risk is unclear. Some epidemiological studies demonstrated that lung cancer susceptibility was not associated with NAT2 acetylator status.[18,25,28,30,35] However, some investigators held the opinion that slow acetylator phenotype of *NAT2* polymorphisms was associated with increased risk of lung cancer.[20,24] In our meta-analysis, there was no significant association between slow acetylator phenotype of *NAT2* polymorphisms and lung cancer risk. The disagreement may underlie differences in study population. Specifically, our study was based on Asians and Caucasians, whereas the studies of Sobti et al and Oyama et al were respectively performed in the North Indian population and Japanese population. With respect to rapid acetylator phenotype, Sorensen et al pointed out the NAT2 rapid acetylator phenotype seemed to be protective against lung cancer in light smokers but not among heavy smokers.[34] Nevertheless, several

TABLE 3. *NAT2* Polymorphisms With Phenotypes and Lung Cancer Risk

NAT2 Polymorphisms	Rapid vs. Slow			Slow vs. Rapid		
	P Heterogeneity	OR	95% CI	*P* Heterogeneity	OR	95% CI
Race subgroup						
Caucasian	0.978	0.97	0.89–1.05	0.993	1.02	0.95–1.10
Asian	0.659	1.01	0.90–1.14	0.012	0.99	0.82–1.20
Source subgroup						
Hospital based	0.806	0.92	0.81–1.04	0.401	1.15	1.00–1.33
Population based	0.982	1.02	0.93–1.12	0.473	0.97	0.89–1.06
Hospital based–population based	0.485	1.03	0.81–1.32	0.554	0.98	0.78–1.23
Nested case–control	0.000	0.85	0.62–1.16	0.000	1.13	0.85–1.50
Total value	0.977	0.98	0.92–1.05	0.411	1.02	0.95–1.09

CI = confidence interval; OR = odds ratios.

TABLE 4. *NAT2* Polymorphisms With Genotypes and Lung Cancer Risk

NAT2 Polymorphisms	22 vs. 11			22 + 12 vs. 11			22 + 12 vs. 11			22 + 12 vs. 11			22 + 12 vs. 11		
	P-Value	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value	OR	95% CI
C282T	0.365	1.45	1.00−2.10	0.953	1.07	0.86−1.33	0.170	1.58	1.11−2.25	0.463	1.17	0.98−1.39	0.731	1.01	0.79−1.30
A803G	0.000	0.74	0.37−1.50	0.515	0.79	0.57−1.09	0.000	0.88	0.45−1.71	0.479	0.81	0.61−1.07	0.585	0.76	0.54−1.09
C481T	0.000	0.84	0.41−1.71	0.000	1.05	0.73−1.52	0.000	0.71	0.36−1.38	0.000	0.98	0.72−1.33	0.000	1.11	0.74−1.67
G590A	0.714	0.96	0.64−1.44	0.964	0.95	0.80−1.14	0.616	1.02	0.69−1.51	0.949	0.96	0.82−1.12	0.912	0.94	0.78−1.14
G857A	0.000	0.49	0.17−1.41	0.907	0.97	0.69−1.36	0.000	0.48	0.17−1.38	0.998	0.91	0.67−1.24	0.825	1.02	0.72−1.45
Total value	0.352	1.05	0.83−1.32	0.961	0.97	0.87−1.09	0.122	1.11	0.89−1.38	0.647	0.99	0.90−1.09	0.962	0.96	0.85−1.08

P: *P*-value in the heterogeneity examination; 22: rare homozygote; 11: wide homozygote; 12: heterozygote.
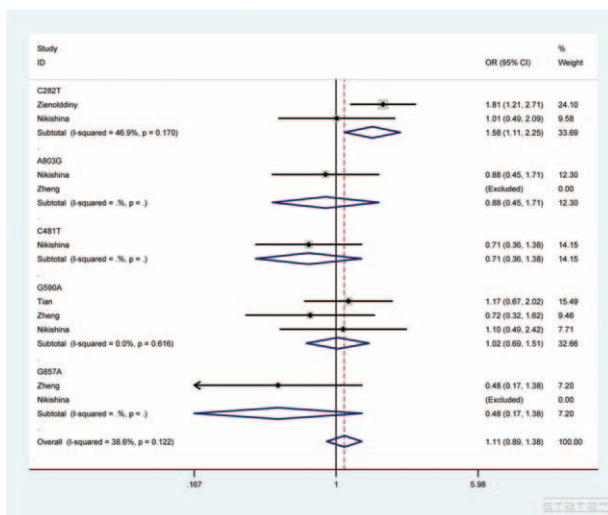CI = confidence interval; OR = odds ratios.

FIGURE 2. Forest plot of lung cancer susceptibility associated with *NAT2* C282T polymorphism under TT versus CC + TC genetic model. For each study, the estimates of OR and its 95% CI are plotted with square and a horizontal line. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
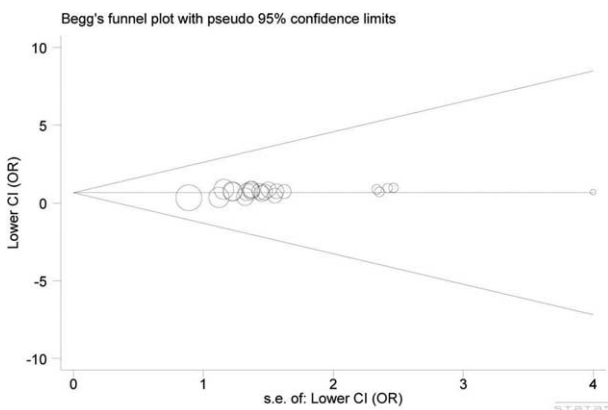

FIGURE 3. Begg funnel plot of publication bias test. Each point represents a separate study for the indicated association. Log(OR), natural logarithm of OR. Horizontal line, mean effect size.

research indicated rapid acetylator phenotype may contribute to increased risk of lung cancer.[23,36,37]

From the perspective of genotypes, to our knowledge, this is the second study definitely clarifying the association of *NAT2* C282T polymorphism with increased risk of lung cancer, which is not in accordance with Nikishina et al.[39] The inconsistency may be on account of study population and sample size. In detail, our study included 1988 cases and 2411 controls among Asians and Caucasians, while the study of Nikishina et al was performed in only 122 cases and 167 controls among Caucasians living in Novosibirsk.

Some limitations in our study should be pointed out. First, in the subgroup analysis by ethnicity, our study was based on Asians and Caucasians, not considering other ethnic groups. Second, our study was not stratified by smoking status which is an important cause of lung cancer. Finally, lacking some original data of genotypes, the comprehensiveness and precision of association between *NAT2* polymorphisms and lung cancer may be influenced.

In conclusion, our meta-analysis demonstrated that TT genotype in C282T polymorphism among 5 SNPs in *NAT2* gene was a susceptibility factor for lung cancer. Additionally, the acetylator status of *NAT2* polymorphisms was not in association with lung cancer susceptibility. In the future, well-designed studies are required to give more comprehensive understanding of the association.

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