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Original Article

Association between the COMT 158 G/A polymorphism and lung cancer risk: a meta-analysis

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Abstract: Catechol-O-methyltransferase (COMT) 158 G/A gene polymorphism seem to associate with lung cancer, but the results are inconclusive. This meta-analysis aims to investigate the association between COMT 158 G/A gene polymorphism and lung cancer susceptibility. We searched PubMed, Embase, China National Knowledge Infrastructure (CNKI), VIP Chinese science and technology periodical database (VIP) and Wanfang databases up to March 25, 2015 for articles on the connection between the COMT 158 G/A polymorphism and the risk of lung cancer. Pooled odds ratio (OR) and corresponding 95% confidence interval (CI) were used to estimate the connection. STATA (Version 12.0) was adopted for data analysis. Overall, 6 articles of 7 studies including 2,293 cases and 2,768 controls were included in our meta-analysis. In general analysis, no significant association was found between COMT 158 G/A polymorphism and the risk of lung cancer (AA + AG vs. GG: OR 1.14, 95% CI 0.90-1.44, P=0.28). However, in subgroup analysis of different method of genotyping, we found significant increase of lung cancer risk (OR 1.30, 95% CI 1.04-1.62, I^2=61.5%, P=0.02), also there was significant association between COMT 158 G/A polymorphism and the risk of lung cancer in Chinese non-smoker women of unsorted cancer type (OR 1.48, 95% CI 1.24-1.77, I^2=0%, P=0.00). The study indicates that COMT 158 G/A G->A gene transition might contribute to lung cancer, especially in Chinese non-smoker women.

Keywords: COMT, lung cancer, meta-analysis, polymorphism

Introduction

Lung cancer is the most frequently diagnosed cancer in males, second frequently diagnosed cancer in females, and the leading cause of death from cancer over the world [1]. The incidence is one of the highest, while the 5-year survival rate is approximately 15.9%, one of the lowest among all cancers [1], this disease has been a great threat to human health career, while few cost-effective drug is available. Several decades of research on the etiology and pathogenesis has proved that smoking is the most predominant risk factor of lung cancer [2]. There are other causes including racial differences and socioeconomic disparities, diet, physical activity, pollutants, infections and genetic factors [3]. In cellular levels, some independent studies have pointed out that estrogen, estrogen receptor and genetic polymorphisms of estrogen metabolism-related genes, albeit controversial, may affect the onset age and the prognosis of lung cancer [4-7]. Epidemical studies have revealed that there are more lung adenocarcinomas in female, suggesting that estrogen, estrogen receptor or estrogen metabolism-related genes might be responsible for this gender discrepancy [1, 8].

Catechol-O-methyltransferase (COMT), an estrogen-metabolizing enzyme, is responsible for inactivating catechol estrogens (CE) by transforming them into nongenotoxic metabolites. However, a single G to A base pair transition at codon 158 of COMT gene, resulting in a substitution of methionine for valine, will cause 3- to 4-fold activity reduction of COMT [9, 10]. This change leads to the accumulation of CE, which is responsible for oxidative DNA damages [11, 12], and the production of quinines. Quinines are genetic poisoning, while combined with DNA damages, they can initiate and promote tumorigenesis [13, 14]. Therefore, theo-

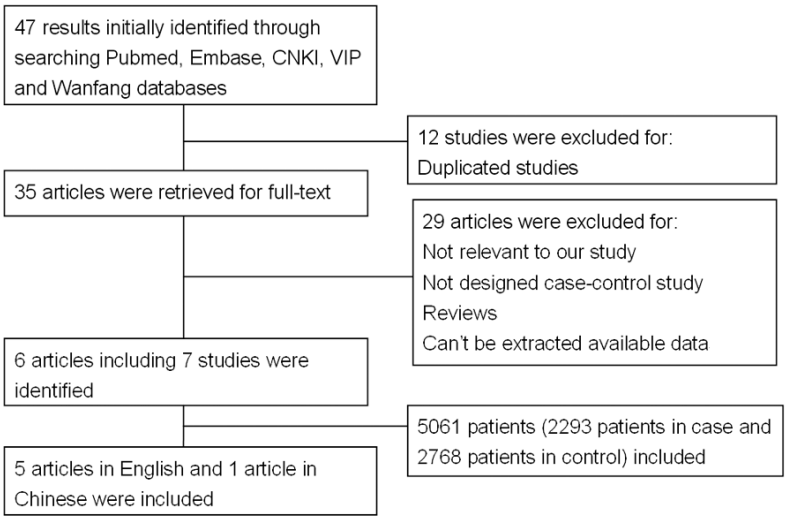

Figure 1. Flow diagram of included and excluded studies.

retically COMT 158 G/A G->A mutation can increase risk of cancer.

Recently, there are some researches showing relationship between COMT 158 G/A polymorphism and the risk of lung cancer [15-20]. Zienolddiny and his colleagues concluded from their study that COMT 158 G/A G->A mutation can increase the risk of lung cancer in Norwegian Non-small cell lung cancer (NSCLC) smokers [15]. Cote et al. reported no association between individual COMT 158 G/A polymorphism and the risk of lung cancer in NSCLC, ignoring racial disparities or smoking status [16]. However, Zhang et al. declaimed an evidence of protection effect of COMT 158 G/A G->A mutation in Chinese for NSCLC, especially adenocarcinoma, which is very different from the other studies [17]. To conclude, to date, there is no validated evidence about the connection of COMT 158 G/A G->A mutation and lung cancer. And we mean to perform this meta-analysis to investigate the connection between the COMT 158 G/A polymorphism and the risk of lung cancer.

Materials and methods

Study selection

Two reviewers (Shifeng Peng, Xiang Tong) independently searched PubMed, Embase, China National Knowledge Infrastructure (CNKI), VIP Chinese science and technology periodical database (VIP) and Wanfang databases up to March 25, 2015 for articles on the association between the COMT 158 G/A polymorphism and the risk of lung cancer. The following search terms were introduced: 'COMT' or 'Catechol-O-Methyltransferase' or 'Catechol O Methyltransferase' or 'Catechol Methyltransferase', and 'polymorphism' or 'variant' or 'mutation', and 'lung' or 'pulmonary' or 'respiratory', and 'neoplasm' or 'cancer' or 'carcinoma' or 'leukemia' or 'lymphoma' or 'sarcoma'. There was no language restriction. The inclusion criteria are as following: (1) case-control study; (2) evaluation of the relationship between COMT polymorphism and the risk of lung cancer; (3) availability of data on genotype distributions in both cases and controls; (4) the genotype distributions of control cohorts should be accord with Hardy-Weinberg equilibrium (HWE). Exclusion criteria were: (1) abstract or review article; (2) no data regarding genotype frequency; and (3) duplicates or overlapping studies.

Data extraction

Two reviewers (Shifeng Peng, Xiang Tong) extracted the data independently according to the inclusion and exclusion criteria, when there was a disagreement, a third author (Sitong Liu) would get involved to assess the article. We collected the following information in the articles: first author's name, year, country, ethnicity, gender, histological types, smoking history, number of case/control, genotype distributions of case and control, method of genotyping, HWE for control. Data was collected with Excel (Version 2007).

Statistical analysis

Data analysis was performed using the STATA (Version 12.0). The association between COMT 158G/A and the risk of lung cancer was estimated by pooled odds ratio (OR) and corresponding 95% confidence interval (CI). The significance of the pooled OR was determined by the Z-test, and *P* value less than 0.05 was considered as statistically different. Five genetic models (AA + AG vs. GG, AA vs. AG + GG, AA vs. GG, AG vs. GG and A vs. G) were introduced to assess the OR from different dimensions. The

Table 1. Basic information about the studies included in the meta-analysis

Author	Year	Country	Ethnicity	Gender	Histological[a]	Smoking[b]	Method[c]
Gemignan	2007	Europe	Caucasian	both sex	all types[d]	both	MicroARRAY[e]
Cote	2009	USA	Caucasian	women	NSCLC	both	TaqMan PCR[f]
Zienolddiny	2008	Norwegian	Caucasian	both sex	NSCLC	smoker	TaqMan PCR
Lim	2011	Singapore	Chinese	women	all types	non-smoker	TaqMan PCR
Lim	2011	Singapore	Chinese	women	all types	smoker	TaqMan PCR
Wu	2014	China	Chinese	women	all types	non-smoker	TaqMan PCR
Zhang	2013	China	Chinese	both sex	NSCLC	non-smoker	MassARRAY[g]

[a]Histological types; [b]smoking history; [c]method of genotyping; [d]unsorted cancer type; [e]MicroARRAY technique; [f]polymerase chain reaction; [g]SEQUENOM MassARRAY matrix-assisted laser desorption/ionization-time of flight mass spectrometry platform (Sequenom, San Diego, CA).

Table 2. Genotype distribution of *COMT 158 G/A* gene in case and control

Author	Case/Control[a]	Case			Control			HWE[b]
		AA	AG	GG	AA	AG	GG	
Gemignan	286/302	59	144	83	75	146	81	0.57
Cote	497/523	112	251	134	128	244	151	0.14
Zienolddiny	257/270	32	62	163	8	60	202	0.18
Lim	340/847	25	148	167	56	303	488	0.34
Lim	203/118	14	72	117	7	50	61	0.43
Wu	510/508	35	220	255	31	168	309	0.21
Zhang	200/200	11	69	120	19	78	103	0.45

[a]Number of case/control; [b]Hardy-Weinberg equilibrium.

subgroup analysis was performed considering different ethnicity (Caucasian, Chinese), gender (women, both sex), histological types of cancer (NSCLC, unsorted lung cancer type), smoking history (smoker, nonsmoker, both) and method of genotyping (TapMan, MicroARRAY, MassARRAY). The χ^2 based Q-test and I-squared (I^2) statistics test was used to examine the heterogeneity. If the I^2>50% and P<0.10, the heterogeneity was considered statistically significant, and the pooled OR should be calculated by the random-effect model, otherwise the fixed-effect model was applied for OR calculation. In addition, the possible publication bias was tested by visual inspection of asymmetry in funnel plots, the Begger's and Egger's test. The Hardy-Weinberg equilibrium for the control group in each study was calculated before the meta-analysis.

Results

Study characteristics

After removing duplicates, 35 articles were initially selected to be in line with the searching strategy, 29 of which were further excluded for not meeting the inclusion criteria. Then 6 articles were figured out to be eligible for further study (**Figure 1**) [15-20]. At last 7 studies were included in our pooled analysis. The detailed information of the eligible articles is summarized in **Tables 1** and **2**.

Meta-analysis results

In total, 2,293 cases and 2,768 controls were included in the meta-analysis of the connection between COMT 158 G/A gene polymorphism and risk of lung cancer. After the Q-test and I^2 statistics test, we found significant heterogeneity in these studies, so pooled calculation was conducted under the random-effects model. No significant association was found between COMT 158 G/A and the risk of lung cancer when analyzing the AA + AG vs. GG model (OR 1.14, 95% CI 0.90-1.44, I^2=73%, P=0.28) (**Figure 2**). The results were the same with the other genetic models (**Table 3**). No publication bias was found in the funnel plot, with Begger's test (P=0.07) and Egger's test (P=0.11) (**Figure 3**).

We perform subgroup analysis for ethnicity (Caucasian, Chinese), gender (women, both sex), histological types of cancer (NSCLC, unsorted lung cancer type), smoking history (smoker, nonsmoker, both) and method of genotyping (TapMan, MicroARRAY, MassARRAY). Interestingly, we found significant increase of lung cancer risk by COMT 158 G/A mutation in TapMan genotyping group (OR 1.30, 95% CI 1.04-1.62, I^2=61.5%, P=0.02) (**Figure 4**). But we found no significant association between COMT 158 G/A polymorphism

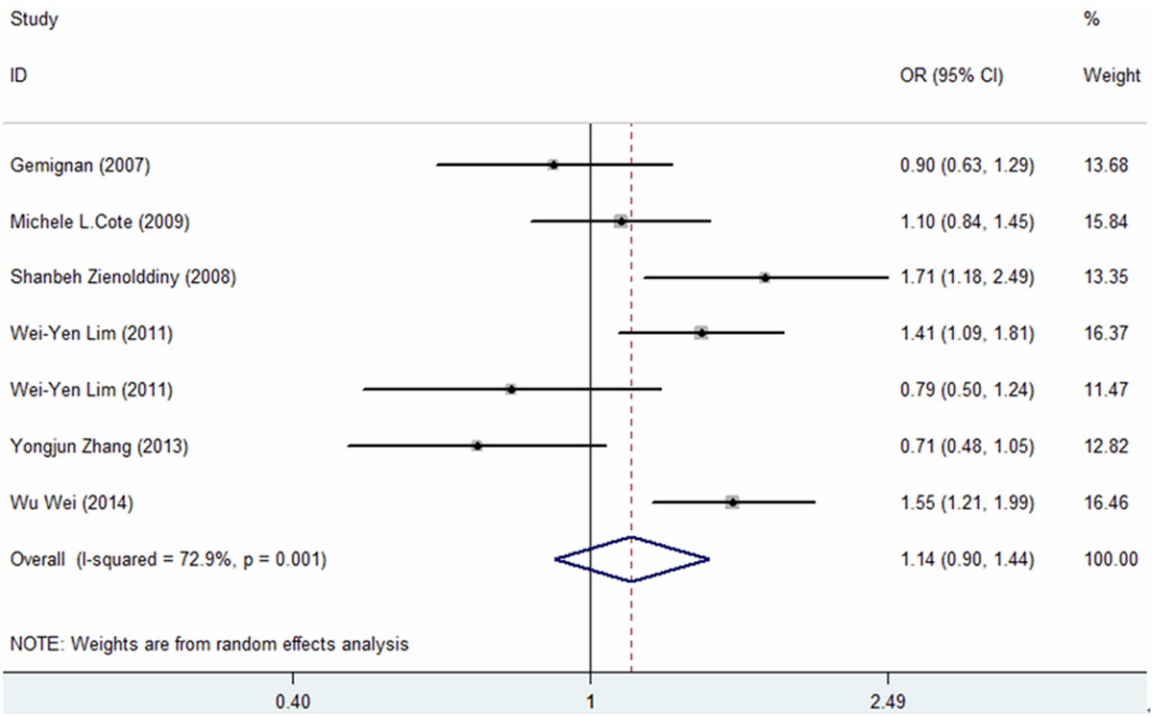

Figure 2. Meta-analysis with a random-effects model for the association between the *COMT 158 G/A* polymorphism and the risk of lung cancer (AA + AG vs GG). OR, odds ratio; CI, confidence interval; I-squared, measure to quantify the degree of heterogeneity in meta-analyses.

and the risk of lung cancer in Chinese group (OR 1.09, 95% CI 0.75-1.57, I^2=81%, P=0.65), Caucasian group (OR 1.18, 95% CI 0.84-1.66, I^2=81%, P=0.34), women group (OR 1.23, 95% CI 0.96-1.57, I^2=64%, P=0.101), both sex group (OR 1.03, 95% CI 0.62-1.72, I^2=82%, P=0.90), NSCLC group (OR 1.10, 95% CI 0.71-1.73, I^2=80%, P=0.66), unsorted lung cancer type group (OR 1.16, 95% CI 0.86-1.57, I^2=73%, P=0.33), and non-smoker group (OR 1.19, 95% CI 0.80-1.78, I^2=82%, P=0.40) in AA + AG vs. GG model. No significant results were obtained when testing the AA vs. AG + GG, AA vs. GG, AG vs. GG and A vs. G model in subgroup analysis.

At last, we want to mention that we found significant association between COMT 158 G/A polymorphism and the risk of lung cancer in Chinese non-smoker women with unsorted lung cancer type when we limited the analysis to researches on women subjects (OR 1.48, 95% CI 1.24-1.77, I^2=0%, P=0.00) (**Figure 5**).

Discussion

Lung cancer is one of the most common cancers around the world, with an estimated 224,210 new cases and 159,260 deaths in America in 2014 [1, 21]. The risky causes have been suggested to be smoking, radiation therapy, environmental toxins, pulmonary fibrosis, HIV infection, genetic factors and diet [3, 22-26]. Recently, COMT (an estrogen-metabolizing enzyme) gene was reported to be related to lung cancer susceptibility, which still has disputes [15-19]. Therefore, we have conducted this meta-analysis to investigate into the association of the COMT 158 G/A polymorphism and the risk of lung cancer.

This meta-analysis included 7 case-control studies (2,293 cases and 2,768 controls), and in general analysis, we found no associations between COMT 158 G/A polymorphism and the risk of lung cancer in either of the genetic models (AA + AG vs. GG, AA vs. AG + GG, AA vs. GG, AG vs. GG and A vs. G) with big heterogeneity among all the studies. In subgroup analysis, we found no significant association between COMT 158 G/A polymorphism and the risk of lung cancer in Chinese group, Caucasian group, women group, both sex group, NSCLC group, unsorted histology types group, and non-smok-

Table 3. Summary of the results for each genetic model

Variables	AA + AG vs. GG			AA vs. AG + GG			AA vs. GG			AG vs. GG			A vs. G		
	OR[a]	95% CI[b]	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Total	1.14	0.90-1.44	0.28	1.10	0.77-1.58	0.59	1.16	0.78-1.74	0.32	1.14	0.92-1.40	0.24	1.10	0.89-1.36	0.37
Subgroups TapMan	1.30	1.04-1.62	0.02	1.22	0.70-2.13	0.47	1.26	0.69-2.26	0.45	1.08	0.84-1.39	0.55	1.10	0.83-1.47	0.50
Chinese	1.09	0.75-1.57	0.65	1.03	0.77-1.40	0.83*	1.11	0.81-1.51	0.52*	1.11	0.77-1.60	0.57	1.05	0.80-1.39	0.72
Caucasian	1.18	0.84-1.66	0.34	1.34	0.64-2.77	0.44	1.43	0.63-3.28	0.39	1.13	0.92-1.38	0.24*	1.18	0.79-1.77	0.42
Women	1.23	0.96-1.57	0.10	1.10	0.81-1.25	0.96*	1.13	0.89-1.44	0.31*	1.25	0.96-1.62	0.09	1.14	0.95-1.36	0.17
Both sex	1.03	0.62-1.72	0.90	1.24	0.40-3.79	0.71	1.22	0.36-4.14	0.76	0.98	0.78-1.24	0.86*	1.08	0.61-1.89	0.80
NCSCLC	1.10	0.71-1.73	0.66	1.29	0.46-3.63	0.63	1.32	0.44-3.96	0.62	1.07	0.87-1.32	0.51*	1.12	0.68-1.85	0.65
Unsorted cancer types	1.16	0.86-1.57	0.33	0.99	0.77-1.27	0.92*	1.08	0.82-1.41	0.60*	1.19	0.87-1.61	0.27	1.10	0.88-1.88	0.42
Non-smoker	1.19	0.80-1.78	0.40	1.02	0.74-1.40	0.91*	1.04	0.61-1.78	0.89	1.24	0.85-1.80	0.26	1.10	0.80-1.52	0.56

[a]Odds ratio; [b]95% confidence interval; *fixed effect model.

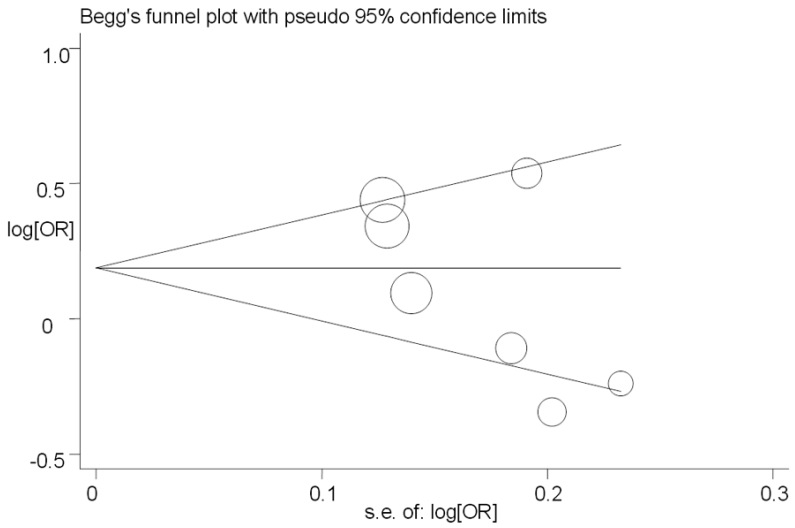

Figure 3. Funnel plot for evaluation of publication bias in the selection of studies on the association between the COMT 158 G/A polymorphism and the risk of lung cancer (AA + AG vs GG). OR, odds ratio; s.e., standard error.

er group in each of the AA + AG vs. GG, AA vs. AG + GG, AA vs. GG, AG vs. GG and A vs. G model. However, when we focused on study using unified TapMan genotyping method, the heterogeneity was decreased and there was a positive relationship between COMT 158 G/A and lung cancer risk. We also found that in Chinese non-smoker women population who were uniformly genotyped with TapMan method, there was a significant link between COMT 158 G/A mutation and risk of lung cancer of unsorted histology type.

To conclude, our meta-analysis found neither a significant harm nor significant protection effect of COMT 158 G/A G->A mutation on lung cancer, which seems to be a compromise of the existing studies [15-19]. And the result is in consistent with Xiang Tan et al's report, in their meta-analysis, no significant association between the COMT 158 G/A polymorphism and lung cancer risk was found [27]. However, when focusing on data using unified TapMan genotyping method, we found that COMT 158 G/A G->A mutation was a significant risk factor for lung cancer. We assume that different methods of genotyping have different sensitivity and accuracy for gene detection result, and this may cause different deviations in the recognition of genotype. And this may have affected the results of the studies we have included in our research. In Xiang Tan et al's reports, they found that the 158 G/A G->A mutation was a risk factor to lung cancer among women, but we didn't observe this result in women subgroup analysis. However, we found that in Chinese non-smoker women population, COMT 158 G/A polymorphism was associated with an increase risk of unsorted-type lung cancer. We assume that this positive result should attribute to the similar method, the same background information of population, and the same group of cancer type. And owing to all these homogeneity, we think this result is more convincing. Thus we concluded that COMT 158 G/A G->A mutation was a significant risk factor for lung cancer, especially for Chinese non-smoker women. However, this result must be warranted by further studies.

Lung cancer is a complicated disease with multidimensional and interacting patho-physiological, genetic and environmental factors. The total analysis shows COMT 158 G/A G->A mutation isn't an independent factor to lung cancer, however, we assume that different combinations of background information have caused big heterogeneity to lung cancer researches, and the real effect of COMT 158 G/A G->A mutation might be covered by all kinds of interacting factors. And after the heterogeneity adjusted, when we limiting the analysis to unified TapMan genotyping method, the result shows that COMT 158 G/A G->A mutation is an independent risk factor to lung cancer. Besides, among Chinese non-smoker women of unsorted cancer type, the heterogeneity is low and the result is positive. Anyway, lung cancer is a complicated disease, we need to do more research of different combination of background information, and more information should be taken into consideration in the future. For example, some studies noted that estrogen might interact with epidermal growth factor receptor gene (EGFR), which might be the key driver of lung cancer among never smokers [28, 29], so we assume that COMT 158 G/A gene may act on lung cancer together

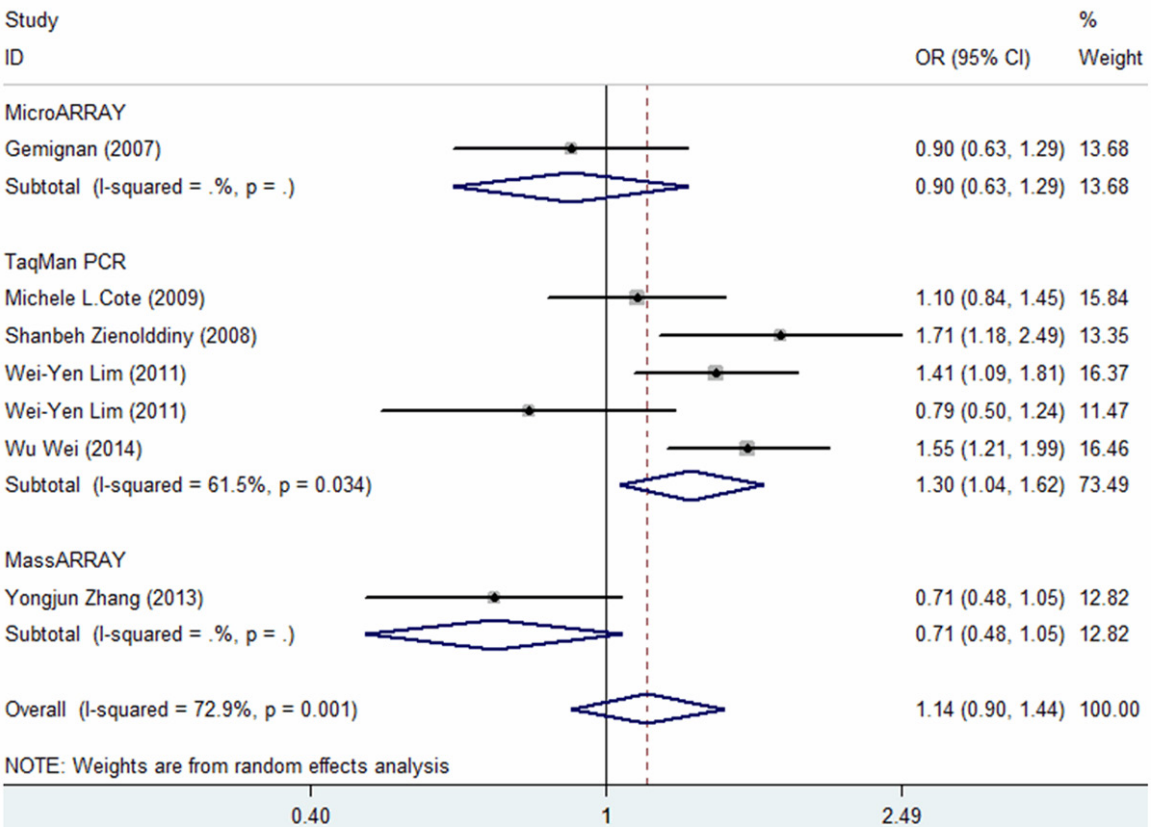

Figure 4. Subgroup analysis for the association between the *COMT 158 G/A* polymorphism and the risk of lung cancer according to genotyping method (AA + AG vs GG). OR, odds ratio; CI, confidence interval; I-squared, measure to quantify the degree of heterogeneity in meta-analyses.

with EGFR gene, and we suggest future studies to combine the two genes together. Unfortunately, we lack these data for meta-analysis in our articles.

There are limitations in this meta-analysis. Firstly, only published articles were extracted from a few datebases, so a publication bias might have occurred. Secondly, a small number of studies were included in our meta-analsysis to investigate the connection between COMT 158 G/A polymorphism and lung cancer, so we must be cautious when referring to the pooled results. Besides, we failed to perform subgroup analysis for different combinations of background information of the patients because of the limited studies. Since the baseline information may interact with each other when it comes to lung cancer, such a complicated multifactorial disease, we suggest the results for subgroup analysis should be viewed carefully. Moreover, significant heterogeneity was found for the total analysis. This should owe to the different genotyping methods, small amount of population in each study and the different combinations of baseline information, ect. So we chose random-effect model for analysis and we perform the subgroup analysis. Despite of these limitations, we minimized the likelihood of bias through the whole process by creating a detailed protocol and carefully performing study selection, data collection and statistical analysis. Anyway, the reliability of the result is guaranteed.

In conclusion, our meta-analysis suggests that there might be an association between COMT 158 G/A polymorphism and the risk of lung cancer, especially in Chinese non-smoker women. We assume that COMT may have some important role in the pathogenesis of lung cancer, while further research is needed to confirm the result based on larger study population of different combinations of ethnicity, gender, histological types of cancer, smoking history, related genes. And related pathogenesis research is highly wanted.

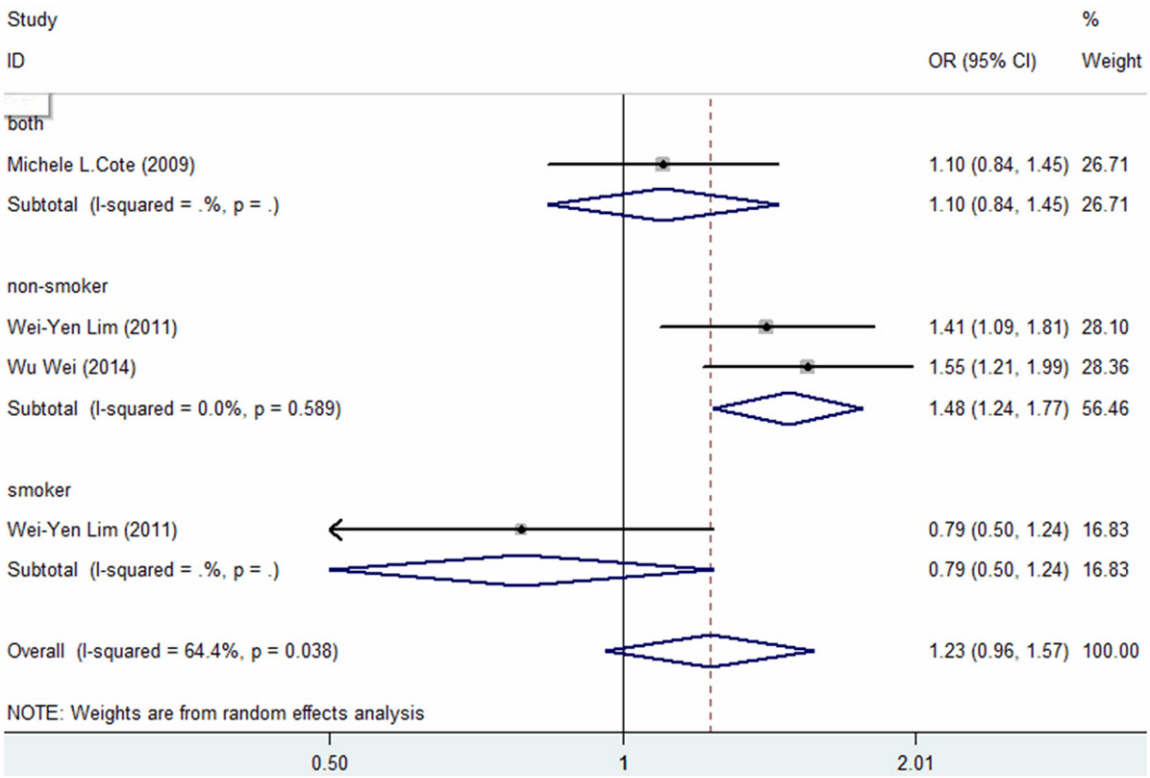

Figure 5. Analysis of association between the *COMT 158 G/A* polymorphism and the risk of lung cancer in Chinese women non-smoker population of unsorted lung cancer type. OR, odds ratio; CI, confidence interval; I-squared, measure to quantify the degree of heterogeneity in meta-analyses.

Disclosure of conflict of interest

None.

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