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Original Article

Association between CYP2D6 polymorphisms and lung cancer risk: an up-date meta-analysis

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Abstract: Background: Genetic variants in metabolic enzymes of CYP2D6 have been shown to be associated with the pathogenesis of lung cancer. However, the results remain inconsistent. The aim of the present study was to explore the exact role of CYP2D6 polymorphisms in lung cancer risk. Methods: Online electronic databases were searched to retrieve related articles published between 2000 and 2014. The odds ratio (OR) with its 95% confidence interval (CI) were employed to assess these associations. Results: A total of 11 case-control studies were screened out, including 1634 cases and 1626 healthy controls. No significant heterogeneity was found between studies. Our results found that the T allele and TT genotype of C188T polymorphism, the C allele and CC genotype of G4268C variant, were associated with increased the risk of lung cancer. Subgroup analysis by hyphology of lung cancer showed that TT genotype of C188T polymorphism was significantly associated with adenocarcinoma risk. No relationship was found between G1934A polymorphism and lung cancer. Conclusions: Our results found that polymorphisms of C188T and G4268C in CYP2D6 gene were associated with increased the risk of lung cancer. Further large-scale studies concerning the interaction of gene-gene or gene-environment are needed.

Keywords: Lung cancer, CYP2D6, polymorphism, meta-analysis

Introduction

Lung cancer is currently one of the more frequently diagnosed cancer types, and the leading cause of cancer death worldwide [1]. An estimated 224210 new cases and 159260 deaths are expected to occur in the United States in 2014 according to cancer statistics [2]. Smoking is a major risk factor to morbidity and mortality, directly accounting for 85% of all lung cancer cases [3]. Although National Lung Screening Trial found that screening significantly reduced lung cancer mortality [4], recent study showed opposite result [5]. Genetic factors are shown to contribute to the progression of lung cancer [6], and may influence the relationship between cigarette smoking and cancer risk [7]. Future evolvement in comprehending and treating lung cancer will be based on genetic analysis. Thus, identification of genes involved in the pathogenesis of lung cancer may contribute to further understanding of the underlying mechanism, and provide more specific values for the development of prevention strategies and treatment therapies.

Genetic susceptibility factors are identified to play a vital role in developing lung cancer risk [8], and be associated with clinical outcome measures [9]. Gene variants might affect susceptibility to cancer. Cytochrome P450s (CYPs) are the most important enzymes in phase I oxidative metabolism responsible for the oxidation of endobionts and xenobiotics [10]. CYP2D6, one member of CYPs gene families, located on human chromosome 22q13. It combined with 2CP, 3A4 are in charge of most of the CYP mediated oxidations [11] and mediate over 90% of human drug oxidations [12]. CYP2D6 exhibits a highly polymorphic property, and its spectrum involves over 100 allele variants. Among them, C188T polymorphism on exon 1, leading a proline to serine substitution at position 34; G4268C variant on exon 9, leading a serine to threonine substitution at position 486; G1934A mutation on the junction of intron 3 and exon 4, resulting in an incorrectly spliced transcript, are three of the most studied drug metabolizing enzymes in humans. These substitutions result in lower CYP2D6 stability, and thus decrease enzymatic activity [13] which associated with

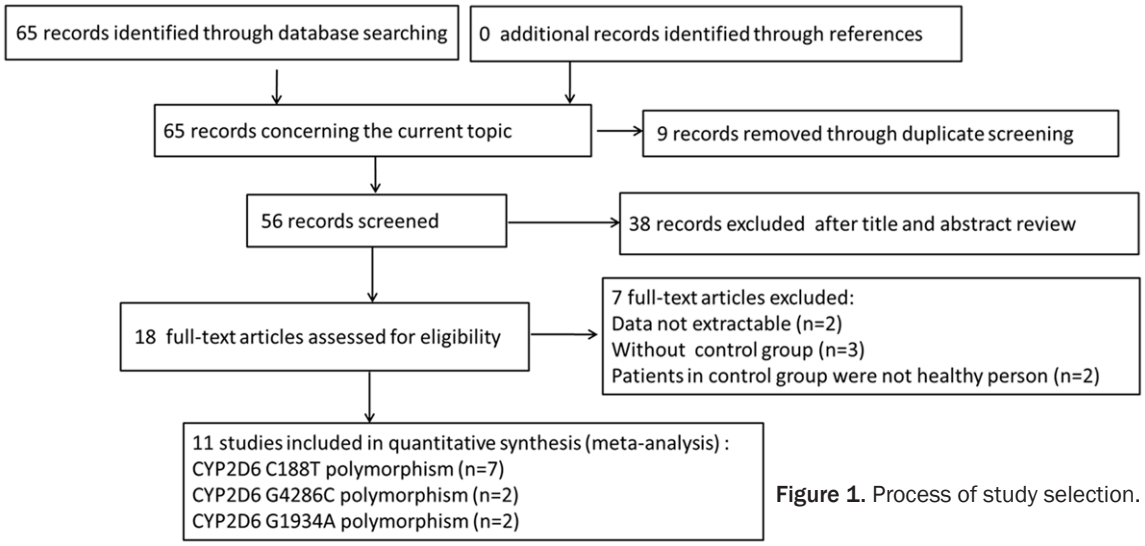

Figure 1. Process of study selection.

numerous cancer risk and drug treatment response. Han et al. suggested that the C allele of C188T polymorphism was a favorable factor in escitalopram treatment for major depressive disorder, and might be a good genetic marker for predicting escitalopram treatment outcomes [14]. Klyotani et al. demonstrated that CYP2D6 polymorphism was important predictors for the prognosis of patients with breast cancer treated with tamoxifen [15]. Khlifi et al. identified that CYP2D6 variant might significantly associate with head and neck cancer in the Tunisian population [16].

Although several case-control studies have investigated the role of CYP2D6 variants in lung cancer risk, the results remain inconclusive. Moreover, allele frequency of CYP2D6 polymorphisms has been shown to vary amongst racial/ethnic groups [17]. Therefore, we conducted this meta-analysis to systematic review published studies to explore the related roles in total populations.

Materials and methods

Search strategy

Online literature libraries of PubMed, Medline, CNKI (Chinese National Knowledge Infrastructure) and Wanfang were searched to retrieve related articles published between January 2000 and November 2014. The following MeSH terms: "lung cancer or carcinoma or neoplasms", "CYP2D6 or cytochrome P450", and "polymorphism or mutation or variant" as well as their combinations were employed as the searching key words. We manually searched the references of retrieved articles to obtain more related studies. All included studies should be conducted in humans and published only in English or Chinese languages.

Inclusion and exclusion criteria

The included articles should meet the following criteria: 1) case-control studies; 2) evaluating the association between polymorphisms in CYP2D6 gene and lung cancer risk; 3) the patients should be histopathology confirmed, the controls should be age-, sex- matched healthy participants; 4) the genotype information was available to extract, and the results presented in odds ratio (OR) with its corresponding 95% confidence interval (CI); and 5) the genotype distribution in controls should be in Hardy-Weinberg equilibrium (HWE).

Data extraction

Two experts independently assessed the quality of related studies and reached a consensus on each item. The following information was extracted from each individual study: first-author name, published year, ethnicity, total number of cases and controls, genotype methods and distribution.

Statistical analysis

The pooled ORs with its 95% CI were employed to assess the strength of association between

Table 1. Main characteristics and genotype distribution of included studies

First author	Year	Sample size		Cases					Controls				
		Cases	Controls										
C188T				CC	CT	TT	C	T	CC	CT	TT	C	T
Chen SQ	2004	50	50	17	15	18	49	51	12	13	25	37	63
Guo ZL	2005	150	152	34	71	45	139	161	28	64	60	120	184
Yan Z	2008	118	118	27	56	35	110	126	22	46	50	90	146
Zhang JJ	2010	200	200	42	99	59	183	217	37	78	85	152	248
Zhou JL	2011	86	86	26	33	27	85	87	19	29	38	67	105
Li WY	2012	217	198	63	64	90	190	244	48	52	98	148	248
Huang FM	2013	168	201	25	88	55	138	198	43	99	59	185	217
G4268C				GG	GC	CC	G	C	GG	GC	CC	G	C
Yan Z	2007	118	118	1	70	47	72	164	4	51	63	59	177
Kang H	2011	200	200	3	116	81	122	278	5	88	107	98	302
G1934A				GG	GA	AA	G	A	GG	GA	AA	G	A
Sobti RC	2003	100	76	75	25	0	175	25	62	14	0	138	14
Liang GY	2005	227	227	221	5	1	447	7	225	2	0	452	2

Table 2. Meta-analysis of association between C188T polymorphism and lung cancer risk in total cases and subgroup analysis by tissue distribution

C188T	Comparisons	OR (95% CI)	P	PH	I^2	Model
Total	T vs. C	0.80 (0.70, 0.90)	0.0004	0.09	45%	F
	TT vs. CC	0.71 (0.56, 0.90)	0.004	0.19	31%	F
	CT vs. CC	1.04 (0.82, 1.32)	0.73	0.85	0%	F
	TT+CT vs. CC	0.86 (0.69, 1.06)	0.15	0.40	4%	F
	TT vs. CT+CC	0.70 (0.58, 0.84)	0.0001	0.28	20%	F
Adenocarcinoma	TT vs. CT+CC	0.61 (0.41, 0.91)	0.01	0.25	29%	F
Squamous cell carcinoma	TT vs. CT+CC	0.69 (0.38, 1.25)	0.22	0.11	55%	R

OR, odds ration; 95% CI, 95% confidence interval; P, *p*-value of the association; PH, I^2, between-study heterogeneity; F, fixed-effect model; R, random-effect model.

CYP2D6 polymorphisms and lung cancer risk. A *P*-value of Z test which was used to determine the significance of OR less than 0.05 was considered statistically significant. For each polymorphism, the allelic model, the homozygous model, the heterozygous model, the dominant model and the recessive model were calculated in this study to evaluate the risk. Between-study heterogeneity was assessed by Q test. Fixed-effects model was used when it was homogenous (the *P*-value of Q-test more than 0.1), otherwise, random-effects model was selected when it was heterogenous. Both funnel plot and Egger's test were used to assess the publication bias (P<0.01 was considered statistical significance). All statistical analyses were performed using Review Manage 5.2 (Oxford, England) as described by Deeks et al. [18].

Results

Characteristics of included studies

The literature search firstly identified 65 articles. After applying for the inclusion criteria, only eleven articles were finally screened out, including 1634 lung cancer patients and 1626 healthy controls. The process of selection was shown in **Figure 1**. Among the eleven studies, seven articles (two in English [19, 20] and five in Chinese [21-25]) concerned the C188T polymorphism involving 989 patients and 1005 controls, two (Chinese articles) [26, 27] concerned G4268C variant involving 318 patients and 318 controls, the other two (one in English [28] and one in Chinese [29]) concerned the G1934A mutation involving 327 patients and 303 controls. One study conducted in Indian

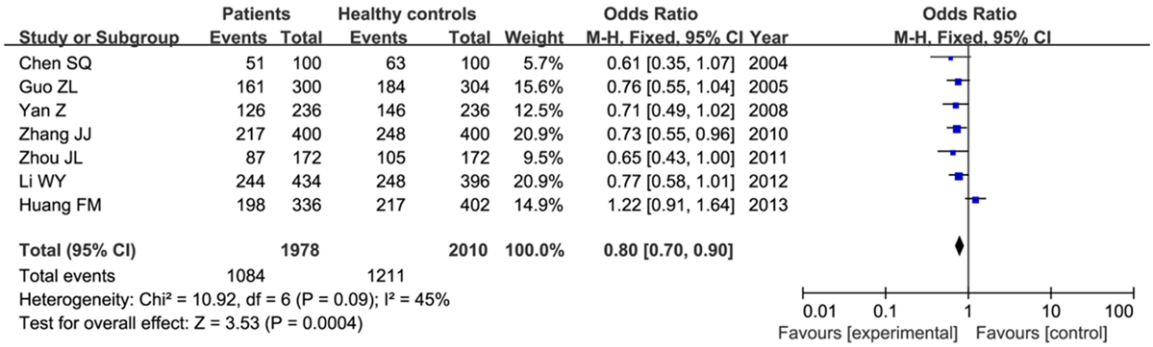

Figure 2. Meta-analysis of the association between CYP2D6 C188T variant and lung cancer risk under the allele model (T vs. C) in a fixed-effect model.

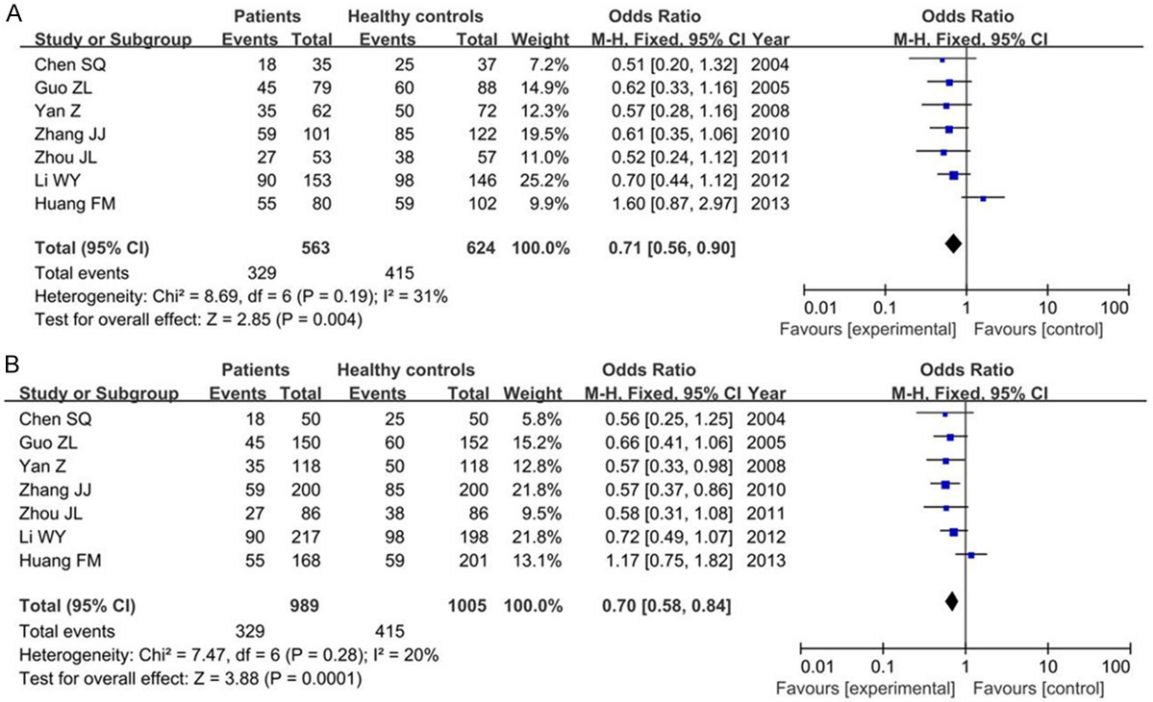

Figure 3. Forest plot of TT genotype in C188T variant and lung cancer risk in the homozygous model (A) and the recessive model (B).

population, and ten in Chinese population. Three articles assessed the relationship between genetic polymorphism of CYP2D6 C188T and susceptibility to lung cancer by different histology. The sample size ranged from 100 to 454. **Table 1** listed the main characteristics and genotype distribution of included studies.

Association between CYP2D6 C188T polymorphism and lung cancer risk

Table 2 presented the results of the strength of association between C188T variant and lung cancer risk. No significant heterogeneity was found between studies (P>0.01, I^2<50%), and the fixed-effect model was used. Overall, our results found that the T allele of CYP2D6 C188T polymorphism was associated with increased the risk of lung cancer (T vs. C: OR=0.80, 95% CI=0.70-0.90, P=0.0004) as shown in **Figure 2**. This significant association was also found in the homozygous model (TT vs. CC: OR=0.71, 95% CI=0.56-0.90, P=0.004) and the recessive model (TT vs. CT+CC: OR=0.70, 95% CI= 0.58-0.84, P=0.0001) as shown in **Figure 3**.

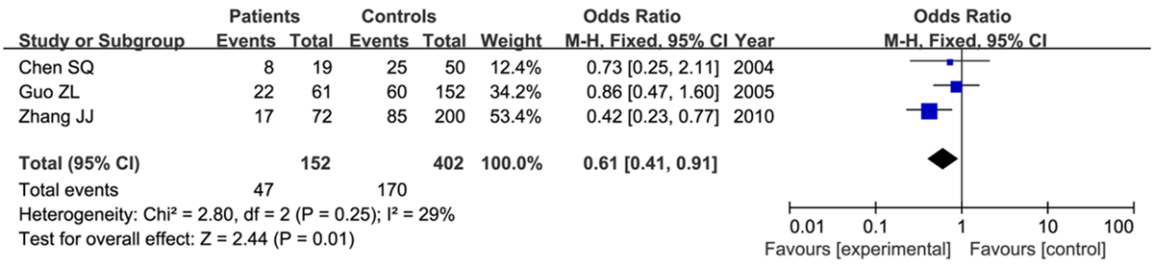

Figure 4. Association between C188T variant and adenocarcinoma risk under the recessive model (TT vs. CT+CC).

Table 3. Results of G4286C and G1934A polymorphisms in lung cancer risk

Comparisons	OR (95% CI)	P	PH	I^2	Model
G4268C					
C vs. G	0.75 (0.58, 0.96)	0.02	0.92	0%	F
CC vs. GG	1.69 (0.51, 5.62)	0.39	0.52	0%	F
GC vs. GG	3.00 (0.91, 9.95)	0.07	0.50	0%	F
CC+GC vs. GG	2.28 (0.70, 7.49)	0.17	0.51	0%	F
CC vs. GC+GG	0.59 (0.43, 0.80)	0.0009	0.94	0%	F
G1934A					
A vs. G	1.67 (0.89, 3.13)	0.11	0.29	10%	F
GA vs. GG	1.63 (0.83, 3.18)	0.15	0.55	0%	F
AA+GA vs. GG	1.70 (0.87, 3.30)	0.12	0.42	0%	F

OR, odds ration; 95% CI, 95% confidence interval; P, *p*-value of the association; PH, I^2, between-study heterogeneity; F, fixed-effect model.

However, no relationship was found between C188T variant and lung cancer risk in the heterozygous model (CT vs. CC: OR=1.04, 95% CI=0.82-1.32, P=0.73) and the dominant model (TT+CT vs. CC: OR=0.86, 95% CI=0.69-1.06, P=0.15).

In subgroup analysis by different histology of lung cancer, we found that the TT genotype in the recessive model was significantly associated with adenocarcinoma risk (TT vs. CT+CC: OR=0.61, 95% CI=0.41-0.91, P=0.01) in a fixed effect model as shown in **Figure 4**. However, no association was found between C188T variant and squamous cell carcinoma in the recessive model (OR=0.69, 95% CI=0.38-1.25, P=0.22) in a random-effect model.

Association between CYP2D6 G4268C polymorphism and lung cancer risk

Table 3 presented the results of G4268C variant with lung cancer risk. Our results found that G4268C variant was associated with lung cancer risk under the allele model (C vs. G: OR=0.75, 95% CI=0.58-0.96, P=0.02) and the recessive model (CC vs. GC+GG: OR=0.59, 95% CI=0.43-0.80, P=0.0009) as shown in **Figure 5**. While no significant association was found under the homozygous model (CC vs. GG: OR=1.69, 95% CI=0.51-5.62, P=0.39), the heterozygous model (GC vs. GG: OR=3.00, 95% CI=0.91-9.95, P=0.07) and the dominant model (CC+GC vs. GG: OR=2.28, 95% CI=0.70-7.49, P=0.17).

Association between CYP2D6 G1934A polymorphism and lung cancer risk

As shown in **Table 3**, our results found that G1934A was not related with increased the susceptibility of lung cancer under any studied genetic models (A vs. G: OR=1.67, 95% CI=0.89-3.13, P=0.11; GA vs. GG: OR=1.63, 95% CI=0.83-3.18, P=0.15; AA+GA vs. GG: OR=1.70, 95% CI=0.87-3.30, P=0.12) in a fixed-effect model.

Publication bias

The funnel plot is presented in **Figure 6**. No publication bias was detected (P=0.126 for Egger's test). These results indicated that there was no possible publication bias in the current study.

Discussion

In this meta-analysis, we evaluated the association between C188T, G4268C and G1934A polymorphisms in CYP2D6 gene and lung cancer risk. Our results found that C188T variant was associated with lung cancer risk in the allele model, the homozygous model and the recessive model; G4268C variant was related with increased the susceptibility of lung cancer in the allele model and the recessive model.

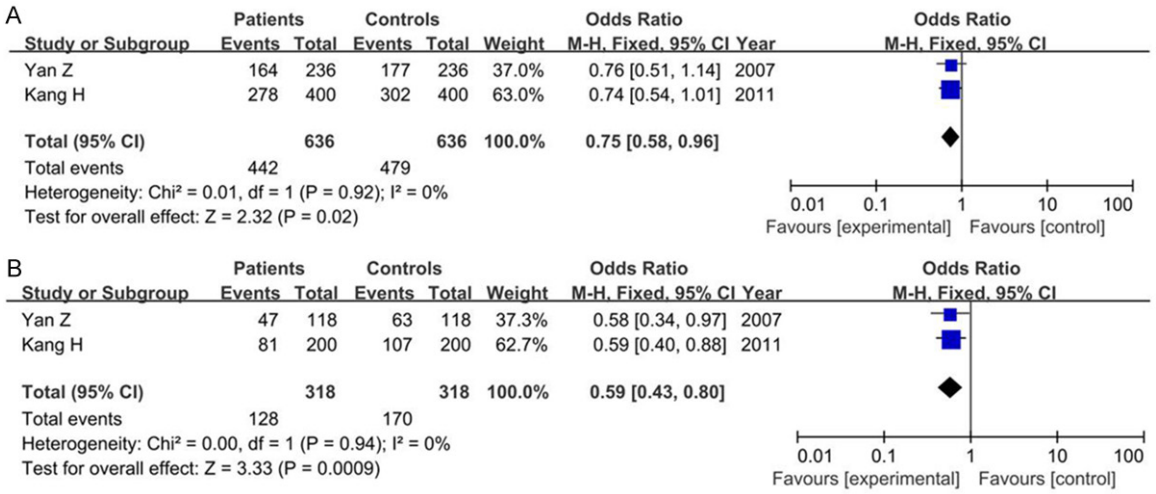

Figure 5. Forest plot of G4268C variant and lung cancer risk in the allele model (A) and recessive model (B).

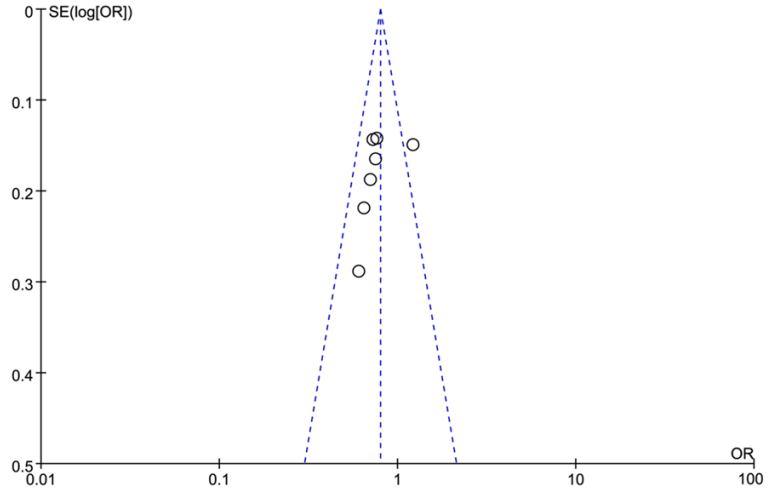

Figure 6. Funnel plot of the association between CYP2D6 C188T variant and lung cancer under the allele model.

However, no significant relationship was found between G1934A polymorphism and lung cancer. Subgroup analysis by tissue distribution showed that TT genotype was significantly associated with adenocarcinoma risk. Our results were consistent with previous meta-analysis which supported the positive association of CYP2D6 T188C variant with lung cancer in the Chinese.

CYP2D6 encodes the phase I enzyme debrisoquine-4-hydroxylase, and is shown to be involved in the metabolism of drugs and environmental chemicals [30]. Its expression was presented in human lung, liver and central nervous system, playing a functional role [31]. CYP2D6 expression is regulated by polymorphisms that affect splicing and transcription [32], and the spatial structure and function of CYP2D6 can be changed by gene mutation [33]. Variants in CYP2D6 gene are currently used as biomarkers to predict its activity. Studies have shown that CYP2D6 polymorphisms could reduce CYP2D6 enzyme activity and hence resulted in lower plasma concentrations of clinically active metabolite of tamoxifen [34]. CYP2D6 variants were found to be associated with response to vinorelbine in patients with non-small-cell lung cancer [35]. Moreover, these polymorphisms contribute to inter-individual and interethnic variation in drug metabolism which may lead to differences in drug response. CYP2D6 polymorphisms for drug response and/or adverse drug reactions is clinical importance because many different drug substrates in this enzyme can be either inactivated or activated [36]. There are significant differences in CYP2D6 allele and genotype frequencies in different populations leading to differential estimates of EM and IM, suggesting the importance of delivering pharmacotherapeutic regimes for patients on the basis of their genetic profile [37].

The CYP2D6 genetic polymorphism represents one of the most diverse and best studied genetic polymorphisms of drug metabolizing enzymes in humans. CYP2D6 variants may explain the differences of individuals in drug efficacy and safety through individual variation in treatment response. The mutant protein of C188T polymorphism in CYP2D6 gene was proven to be more unstable than the wild-type protein for gene mutation can change the spatial structure and function of CYP2D6, thus decreased activity of the enzyme [33]. CYP2D6 polymorphism may affect the basic brain function which are relevant to psychiatric practice [38]. Bakken et al. demonstrated that genetic variability in CYP2D6 contributed to the interindividual variability in steady-state serum concentrations of N-desalkylquetiapine in psychiatric patients [39]. Stingl et al. found that genetic variation in CYP2D6 impacted the neural activation during cognitive tasks in humans [40]. Genotyping of CYP2D6 was clinically relevant in post-menopausal women with early breast cancer [41], and determined estrogen receptor activity of the major infertility drug clomiphene via its active metabolites [42]. Wu et al. demonstrates that the CYP2D6*10 allele plays an important role in the pharmacokinetics of the O-demethylated metabolites of codeine after oral administration [43].

CYP2D6 polymorphism was also associated with other human diseases. Zhong et al. found that the allele (*10) of CYP2D6 gene may respond better to donepezil than those with wild allele (*1) in patients with Alzheimer's Disease [44]. Lu et al. demonstrated that the poor metabolizer phenotype of CYP2D6 conferred a significant genetic susceptibility to Parkinson's disease in Caucasians [45]. Han et al. showed that CYP2D6 polymorphisms was associated with susceptibility to both development and progression of head and neck squamous cell carcinoma [46]. Ahmad et al. identified a significant association between the poor metabolizer CYP2D6 (TT) and progression towards higher pathological stage of renal cell carcinoma [47]. Penas-Lledo et al. suggested an association between CYP2D6 and eating disorder [48]. Ali et al. found that CYP2D6 polymorphism was positively associated with hypertensive cardiac complications as well as hypertensive obese cases [49].

There were several limitations in our study. Firstly, the number of included studies for G4268C and G1934A polymorphisms was small, which may influence the reliability of the results. Secondly, most of the retrieved articles were conducted among Chinese population, while other populations should be considered due to the difference of the frequency of T188C variant among ethnics. Thirdly, other genetic polymorphisms of CYP, which may interact with CYP2D6 in exerting their role should be analyzed. Huang et al. found a interaction between CYP1A1, CYP2A6, and CYP2D6 polymorphisms in lung cancer risk [20]. Lastly, environmental factors which may be affected by genetic polymorphisms of CYP1D6 should obtain attention. Studies have shown that environment factors might affect the variation of CYP2D6 gene, resulting in an increase of the frequency of alleles which are associated with a slower rate of metabolism [50]. Genetic polymorphism of CYP genes, alone or in combination, might act as a risk modifier of tobacco-related cancers [51].

Conclusion

In conclusion, our results showed that polymorphisms of C188T and G4268C in CYP2D6 gene were significantly associated with increased the risk of lung cancer. Subgroup analysis showed that TT genotype of CYP2D6 C188T variant was associated with adenocarcinoma risk. Further large-scale studies concerning other ethnicities are needed to explore the exact role in total population.

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Disclosure of conflict of interest

None.

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