Current evidence on the relationship between CYP1B1 polymorphisms and lung cancer risk: a meta-analysis

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Abstract The association between single-nucleotide polymorphisms (SNPs) of the CYP1B1 gene and lung cancer risk is still ambiguous. In this meta analysis, we assessed 10 case–control studies included 7,067 cases and 9,374 controls of the association between CYP1B1 SNPs of Leu432Val (rs1056836, 432C>G), Asn453Ser (rs1800440, 453A>G), Ala119Ser (rs1056827, 119G>T), Arg48Gly (rs10012, 48C>G) and the risk of lung cancer. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of association between the polymorphism and lung cancer risk under codominant model, dominant model and additive model respectively. Although there were limitations, this meta analysis indicated that individuals with 432GG genotype had a 39.7% higher risk of having lung cancer than those with the 432CC genotype, and individuals with the 432G allele had a 26.3% increased risk as well. An increased risk of lung cancer of 2.13 fold was observed in individuals with 119TT genotype. For Arg48Gly, individuals with 48GG genotype had a significantly increased risk of lung cancer compared with individuals with 48CC (OR 3.859; 95% CI 2.536–5.87). Elevated risk of lung cancer were observed in dominant model (OR 2.115; 95% CI 1.653–2.705) as well. The risk of lung cancer was elevated as the frequency of G allele increased in additive model ($P = 0.000$). For individuals with the polymorphism at codon 453, no evidence of such association was observed. Furthermore, a possible association between the CYP1B1 polymorphism at codon 432 and the lung cancer could be detected in individuals of Caucasian origin, while a negative association was suggested in Asians and African-Americans. An increased lung cancer risk was also found in women with polymorphism at codon 453. These results are supportive for the hypothesis that the CYP1B1 432GG, 119TT and 48GG genotypes are low-penetrance risk factors for developing lung cancer, and further studies are needed to validate these associations.

Introduction

Lung cancer is the leading cause of death in the world, with an estimated death of 1,178,918 cases and an estimated new case of 1,332,132 worldwide in 2002 [1]. The exact mechanism of lung carcinogenesis is still under investigation. It has been well documented that tobacco smoking as well as environmental tobacco smoke exposure in life-long time is the most important etiological factor for developing lung cancer [2, 3], the risk of lung cancer in smokers is at least 15 times higher than non-smokers [4, 5]. Carcinogens such as polycyclic aromatic hydrocarbons (PAHs), arylamines and quinones are found to be present in the tobacco smoke. However, only 10–15% of lifelong smokers develop lung cancer, this implies that genetic factors are associated with lung cancer susceptibility as well [6, 7].

Carcinogens present in tobacco smoke are mainly metabolized by phase I and phase II xenobiotic metabolizing enzymes. Recently accumulating studies regarding the role of genes encoding these enzymes in the lung

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cancer susceptibility have been done. Evidences indicate that genetic polymorphisms of these genes can interfere with the balance between metabolic detoxication and activation of some toxicants, and thus they are relevant to individual susceptibility to lung cancer. A highly studied phase I gene is cytochrome P450 1B1 (CYP1B1). It plays a significant role in the oxidation of variety of carcinogens, including PAHs and arylamines in the lung tissue [8]. Studies demonstrated that CYP1B1 is expressed constitutively in extrahepatic tissues such as lung and is in significantly higher levels within the peripheral leukocytes of lung cancer patients versus controls [9, 10].

CYP1B1 gene is located on chr2p22-p21 and there are at least 179 different polymorphism sites in the gene (http://ncbi.nlm.nih.gov/dbSNP). Of the most studied single-nucleotide polymorphisms (SNP), four are reported to result in amino acid substitutions, they are rs10012 (Arg48Gly), rs1056827 (Ala119Ser), rs1056836 (Leu432Val) and rs1800440 (Asn453Ser). To date, no prospective studies have been done to evaluate the relationship between the CYP1B1 polymorphisms and the risk of lung cancer. Some case–control studies have been conducted. Schoket et al. showed that the CYP1B1 Leu432Val variant was associated with higher levels of DNA adducts within white blood cells [11], and another population-based study reported that non-smoking Caucasians with CYP1B1 Leu432Val polymorphism had increased lung cancer risk [12]. However, the results of these studies are confusing rather than conclusive. In order to get a decisive conclusion, we performed this meta-analysis and evaluate the relationship between the polymorphism of CYP1B1 and the risk of lung cancer.

Methods

Publication search

We conducted a search in the Pubmed (last updated to Feb, 16th, 2010) using the following search terms: ("CYP1B1" or "P4501B1") and ("genetic variant" or "polymorphism") and "lung cancer", trying to cover all papers published. All the searched studies were retrieved, and their references were checked as well for other relevant publications. Review articles were also searched to find additional eligible studies. Only studies published in English with full text available were included. For overlapping studies, only the first published one was selected; for republished studies, only the one with the largest sample numbers was included.

Study identification criteria

The following criteria were followed for study identification: (1) describing the diagnoses of lung cancer; (2)

evaluating the association between CYP1B1 genotype and the risk of lung cancer in either a case–control study or a cohort study; (3) supplying the specific number of homozygous and heterozygous carriers in cases and controls, odds ratios (ORs), 95% confidence intervals (CIs) or the information that can lead to the results; (4) fulfilling the Hardy–Weinberg equilibrium in the controls ($P > 0.01$ was eligible); (5) statistically acceptable methods were mentioned for data collection and analysis; (6) only studies published in English.

Data extraction

Following data were collected if available: first author's surname, publication year, ethnicity (categorized as Caucasian, Asian, African American), demographics, numbers of cases and controls of different genotypes respectively. We did not define any minimum number of patients to include a study in this meta-analysis. Information was carefully extracted from all eligible publications independently by two of the authors (Xu Wenhuan and Zhou Yunhai).

Statistical methods

Crude ORs of lung cancer associated with CYP1B1 polymorphism were evaluated for every study. We first estimated the risk between rare homozygous and common homozygous carriers. Then we calculated the risk using the dominant model (rare allele carriers vs. common homozygous carriers) and additive model. Heterogeneity assumption was checked by the Q-test and heterogeneity was considered significant for $P < 0.10$. We combined the data using a fixed-effects model (the Mantel–Haenszel method) or a random-effects model (the DerSimonian and Laird method) according to the heterogeneity. In the absence of heterogeneity, these two methods yield identical results. Random effects are more appropriate when heterogeneity is present. The potential publication bias was examined visually in a funnel plot, and the degree of asymmetry was tested using Egger's test ($P < 0.05$ considered representative of statistical significance). Finally we also performed sensitivity analysis by omitting each study to find potential outliers. All the calculations were performed using Stata/SE version 10.0 (Stata Corporation, College Station, TX, USA). All P values are two-sided.

Results

Selected studies

The details of all the studies included were listed in Table 1. We assessed the association between the CYP1B1

Table 1 Characteristics of all the association studies regarding polymorphisms in the CYP1B1 gene and lung cancer risk

Author	Year	Ethnicity	Cases	Controls	Polymorphism
Watanabe	2000	Asian	330	324	rs1056836
			326	361	rs1056827
Wenzlaff	2005	Caucasian	129	138	rs1056836
		African-American	30	30	rs1056836
Sorensen	2005	Caucasian	256	269	rs1056836
Zienolddiny	2008	Caucasian	327	368	rs10012
			233	291	rs1800440
Liang	2005	Asian	227	227	rs1056836
Yoon	2008	Asian	213	213	rs1056836
Shah	2008	Asian	200	200	rs10012, rs1056827, rs1056836 rs1800440
Timofeeva	2009	Caucasian	638	1,300	rs1056827, rs1056836, rs1800440, rs2567206, rs10916
Cote	2009	Caucasian African-American	504	527	rs1056836
Rotunno	2009	Caucasian	1,865	2,032	rs1800440

Table 2 Distribution of CYP1B1 genotype among lung cancer cases and controls included in the meta-analysis

	Author	Ethnicity	Year	Cases			Controls			HWE	MAF
				AA	Aa[a]	aa	AA	Aa	aa		
rs1056836	Wenzlaff	Caucasian	2005	25	62	42	63	58	27	0.042	0.378
Leu432Val, 432C>G	Sorensen	Caucasian	2005	40	128	88	56	126	87	0.407	0.558
	Timofeeva	Caucasian	2009	183	303	129	424	604	234	0.465	0.425
	Cote	Caucasian	2009	119	190	76	136	195	74	0.779	0.423
	Watanabe	Asian	2000	247	75	8	230	88	6	0.465	0.154
	Yoon	Asian	2008	165	45	3	179	31	3	0.229	0.087
	Shah	Asian	2008	108	76	16	124	67	9	0.989	0.212
	Liang	Asian	2005	158	66	3	154	69	4	0.233	0.170
	Wenzlaff	African-Americans	2005	2	11	17	1	9	20	0.992	0.817
	Cote	African-Americans	2009	1	44	69	8	45	68	0.88	0.748
rs1800440	Zienolddiny	Caucasian	2008	197	26	10	222	60	9	0.057	0.134
Asn453Ser, 453A>G	Shah	Asian	2008	124	66	10	134	59	7	0.872	0.183
	Timofeeva	Caucasian	2009	409	184	24	845	376	47	0.521	0.185
	Rotunno	Caucasian	2009	1,188	580	97	1,296	654	82	0.964	0.201
rs1056827	Watanabe	Asian	2000	233	83	10	280	77	4	0.611	0.118
Ala119Ser, 119G>T	Shah	Asian	2008	52	107	41	90	88	22	0.944	0.33
	Timofeeva	Caucasian	2009	300	238	62	613	543	99	0.159	0.295
rs10012	Zienolddiny	Caucasian	2008	152	123	52	234	116	18	0.463	0.207
Arg48Gly, 48C>G	Shah	Asian	2008	52	107	41	90	88	22	0.944	0.33

HWE Hardy–Weinberg equilibrium, *MAF* minor allele frequency

[a] "A" denotes a common allele; "a" denotes a rare allele

polymorphism and the risk of lung cancer via searching the Pubmed. A total of 12 case–control studies [10, 12–22] published as original papers were initially included. Among these reports, six SNPs were analyzed, they were rs10012 (Arg48Gly, 48C>G), rs1056827 (Ala119Ser, 119G>T), rs1056836 (Leu432Val, 432C>G), rs1800440 (Asn453Ser, 453A>G), rs2567206 and rs10916. Since only one study [21] concentrated on rs2567206 and rs10916, we did not perform further analysis about these two

polymorphisms. The study from Wu et al. [10] failed to provide details of rare homozygous and heterozygous and therefore was excluded. Cote et al. had published two studies [14, 18] based on subjects enrolled into the same program, therefore we only included the one with the larger number [14]. So a total of 10 publications [12–17, 19–22] including 7,067 cases and 9,374 controls entered the following meta-analysis. Table 2 listed the frequency distribution of the CYP1B1 SNPs Leu432Val, Asn453Ser,

Ala119Ser and Arg48Gly. Of those, eight studies [12, 14, 15, 17, 19–22] containing 2,499 cases and 3,199 controls were with regard to the association between the polymorphism of Leu432Val and lung cancer. Four studies [13, 15, 16, 21] with 2,915 cases and 3,791 controls focused on Asn453Ser. With regard to Ala119Ser, three studies [15, 20, 21] with 1,126 cases and 1,816 controls were included. For Arg48Gly, two studies [15, 16] with 527 cases and 568 controls were included. All studies indicated that the distribution of genotypes in controls were consistent with Hardy–Weinberg equilibrium at a significant level of 0.01.

Combined analysis

Table 3 showed the main results on lung cancer risk associated with the CYP1B1 polymorphism of Leu432Val, Asn453Ser, Ala119Ser and Arg48Gly. For Leu432Val, individuals with rare homozygous had a significantly increased risk of lung cancer compared with individuals with common homozygous (OR 1.397; 95% CI 1.172–1.666, $P = 0.261$ for heterogeneity). The ORs on lung cancer associated with the rare homozygous carriers compared with the common homozygous carriers in individual studies are indicated in Fig. 1. In addition, elevated risk of lung cancer were observed in dominant model (OR 1.263; 95% CI 1.027–1.552, $P = 0.011$ for heterogeneity). And the risk of lung cancer was elevated as the frequency of G allele increased in additive model ($P = 0.000$). In terms of SNP Asn453Ser with 2,915 cases and 3,791 controls, no evidence of significant association were observed with the risk of lung cancer in either codominant or dominant model. Elevated risk of lung cancer was found as the frequency of G allele increased in additive model ($P = 0.000$). With regard to the CYP1B1 SNP Ala119Ser, the eligible studies included 1,126 cases and 1,816 controls. An significant increased risk of lung cancer was found in rare homozygous carriers versus common homozygous carriers (OR 2.130; 95% CI 1.032–4.398, $P = 0.023$ for heterogeneity) (Fig. 2), while no such association was observed in dominant model (OR 1.414; 95% CI 0.857–2.332, $P = 0.000$ for heterogeneity). For

Arg48Gly, individuals with rare homozygous had a significantly increased risk of lung cancer compared with individuals with common homozygous (OR 3.859; 95% CI 2.536–5.872, $P = 0.456$ for heterogeneity). Elevated risk of lung cancer were observed in dominant model (OR 2.115; 95% CI 1.653–2.705, $P = 0.579$ for heterogeneity). All these results were based on pooling data from all the studies regardless of gender, smoking status and ethnicity.

We also stratified the most studied SNP Leu432Val by descent and details were listed in Table 4. Significantly increased risks of lung cancer were found among Caucasian (1,385 cases and 2,084 controls) rare homozygote carriers (OR 1.570; 95% CI 1.049–2.350; $P = 0.017$ for heterogeneity), while no such association was observed in dominant model (OR 1.400, 95% CI 0.947–2.068; $P = 0.002$ for heterogeneity). The risk of lung cancer was elevated as the frequency of G allele increased in additive model ($P = 0.000$). For the Asians with 970 cases and 964 controls, no evidence of significant association were observed with the risk of lung cancer in either codominant or dominant model. There were only two studies dealt with African-Americans and only a total of 144 cases and 151 controls were included. Rare allele carriers seemed not to be associated with lung cancer risk in any model (codominant, dominant, additive model). In addition, we analyzed the influence of gender on the overall OR. In the subgroup of women, the risk of having lung cancer was 37.8% higher in the rare homozygous carriers than the common homozygous carriers (95% CI 1.053–1.803, $P = 0.426$ for heterogeneity), and the same tendency was observed in dominant model (OR 1.469,95% CI 1.203–1.794, $P = 0.565$ for heterogeneity) and increased risk of lung cancer was found as the frequency of G allele increased in additive model ($P = 0.000$).

Sensitivity analysis and publication bias

In addition, we analyzed the influence of individual study on the overall OR of the CYP1B1 SNP Leu432Val (Fig. 3a). We calculated the pooled OR by omitting one

Table 3 Main results of pooled OR with CI of the four SNPs

	Number of cases/ controls	Codominant (rare homozygous carriers vs. common homozygous carriers)			Dominant (rare allele carriers vs. common homozygous carriers)			Additive model P
		OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	
Leu432Val (432C>G)	2,499/3,199	1.397 (1.172–1.666)	0.000	0.261	1.263 (1.027–1.552)	0.027	0.011	0.000
Asn453Ser (453A>G)	2,915/3,791	1.243 (0.975–1.584)	0.079	0.886	0.970 (0.803–1.170)	0.018	0.088	0.000
Ala119Ser (119G>T)	1,126/1,816	2.130 (1.032–4.398)	0.041	0.023	1.414 (0.857–2.332)	0.175	0.000	0.000
Arg48Gly (48C>G)	527/568	3.859 (2.536–5.872)	0.000	0.456	2.115 (1.653–2.705)	0.000	0.579	0.000
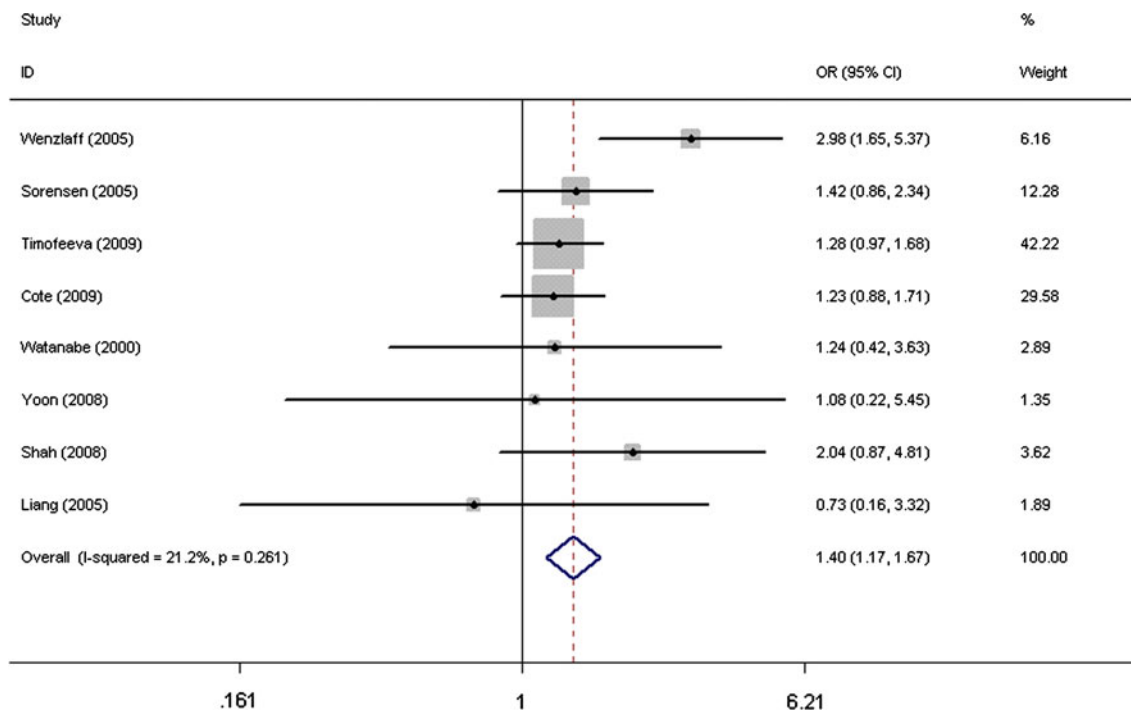
Fig. 1 OR on lung cancer associated with CYP1B1 Leu432Val for the GG genotype compared with the CC genotype
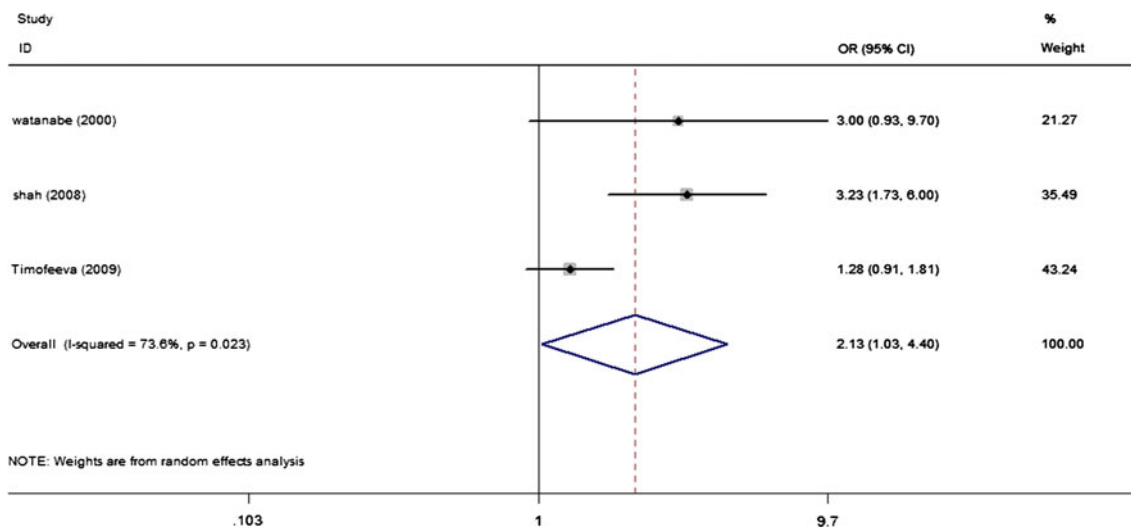
Fig. 2 OR on lung cancer associated with CYP1B1 Ala119Ser for the TT genotype compared with the GG genotype

single study each time, and no materially huge difference was made. This indicated that there was no individual study affecting the overall OR dominantly. Moreover, we evaluated the publication bias of literatures with Begg's funnel plot (Fig. 3b). The shape of the funnel plot seems approximately symmetrical, suggesting that publication bias may be neglected. Furthermore, we used the Egger's test to provide statistical evidence of the symmetry. The

Egger's test is based on a linear regression of the standard normal deviate against its precision, and the intercept value of linear regression measures the symmetry of the funnel plot—the more it deviated from zero, the more pronounced the asymmetry. For the CYP1B1 Leu432Val polymorphism, the egger's test indicated $P = 0.688$. This provided evidence that publication bias had no significant effect on the results of our meta-analysis.

**Table 4** Main results of pooled OR with CI of SNP Leu432Val

	Number of cases/controls	Codominant (rare homozygous carriers vs. common homozygous carriers)			Dominant (rare allele carriers vs. common homozygous carriers)			Additive model
		OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	P
Total	2,499/3,199	1.397 (1.172–1.666)	0.000	0.261	1.263 (1.027–1.552)	0.027	0.011	0.000
Caucasian	1,385/2,084	1.570 (1.049–2.350)	0.028	0.017	1.400 (0.947–2.068)	0.091	0.002	0.000
Asian	970/964	1.417 (0.805–2.494)	0.227	0.660	1.099 (0.817–1.479)	0.532	0.089	0.006
African-Americans	144/151	2.004 (0.109–36.851)	0.64	0.073	2.118 (0.132–33.951)	0.596	0.085	0.381
Women	937/1,218	1.378 (1.053–1.803)	0.019	0.426	1.469 (1.203–1.794)	0.000	0.565	0.000

Discussion

Lung cancer is the leading frequent and lethal malignant tumor worldwide. For most sporadic lung cancers, a substantial component of risk may be determined by the interaction of multiple low-penetrance susceptibility genes and the exposure to tobacco smoke. It has been accepted that polymorphism of genes involved in the metabolism of tobacco carcinogen are candidate loci for lung cancer susceptibility. Accumulating studies regarding gene variants in the carcinogen metabolism pathway have been performed.

CYP1B1 has been widely studied as a gene encoding phase I metabolizing enzyme. However, evidences of the association between the polymorphism of CYP1B1 and the risk of lung cancer are rather confusing than conclusive. In this meta-analysis, we included 10 publications with a total of 7,067 cases and 9,374 controls. Our result indicated that individuals with the CYP1B1 polymorphisms may contribute to the risk of lung cancer. For SNP Leu432Val, individuals with rare homozygous had a 39.7% higher risk of having lung cancer than those with common homozygous, and increased risk of lung cancer was found in dominant and additive model as well. In addition, for Ala119Ser, a 2.13 fold increased risk of lung cancer was found comparing the rare homozygous carriers with the common homozygous carriers, while no such association was found in dominant model. The risk of lung cancer was elevated as the frequency of T allele increased in the additive model ($P = 0.000$). For Arg48Gly, an increased risk of lung cancer was found in codominant, dominant and additive model. In addition for SNP Asn453Ser, no evidence of such association was observed in codominant and dominant models.

The exact reason for the correlation between SNPs of CYP1B1 and the risk of lung cancer needs further exploring. Published studies on the structure and functions of the CYP1B1 gene together with their genetic variants
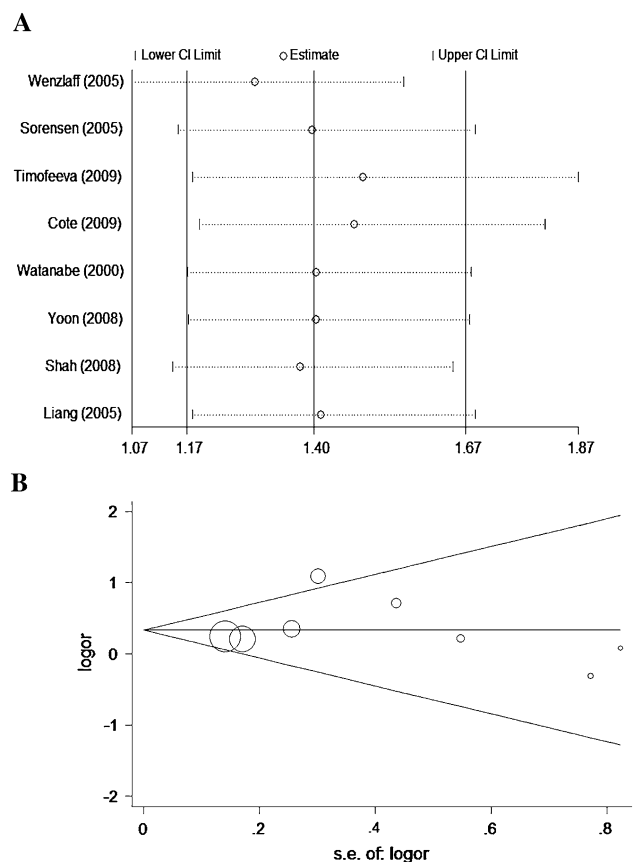
Fig. 3 Outlier analysis and publication bias analysis for the CYP1B1 Leu432Val polymorphism. **a** Shows the influence of individual studies on the summary OR. The *vertical axis* indicates the overall OR and the *two vertical axes* indicate its 95% CI. *Every hollow round* indicates the pooled OR when the left study is omitted in this meta-analysis. The two ends of every *broken line* represent the respective 95% CI. **b** Shows the Begg's funnel plot of studies included in the meta-analysis. The *vertical axis* represents log [OR] and the *horizontal axis* means the standard error of log [OR]. *Horizontal line* and *sloping lines* in funnel plot represent fixed-effects summary OR and expected 95% CI for a given standard error, respectively. Area of each *circle* represents contribution of the study to the pooled OR the Begg's funnel plot of studies concerning Leu432Val included in the meta-analysis

may help us understand the potential roles of these polymorphisms. CYP1B1 gene locates on chromosome 2p22-p21 and takes part in the oxidation of procarcinogens, such as PAHs, arylamines [23, 24]. The gene has three exons and two introns [25]. The entire coding sequence is contained in exons 2 and 3, exon 3 has a domain for heme-binding. It is reasonable to conceive that CYP1B1 may affect the metabolism of environmental carcinogens and alter susceptibility to lung cancer. The SNP Ala119Ser is located on exon 2, the putative substrate recognition site 1 [26], and this polymorphism might affect the catalytic activity mediated by CYP1B1 in different individuals. Watanabe et al. reported that the SNP Ala119Ser was associated with the incidence of squamous cell carcinoma of the lung [20]. Jaworowska reported that this polymorphism significantly increase the risk of breast as well as laryngeal cancers in Polish individuals [27]. For the polymorphism Leu432Val at codon 432 of exon 3, it was reported that the 432G allele increased the mutation of p53 [28]. Previous reports demonstrated increased risk of malignant tumors correlated with this polymorphism [29–31]. Consistent with earlier reports on breast cancer [32, 33], individuals with CYP1B1 polymorphism Asn453Ser was not found with increased lung cancer risk in our study.

CYP1B1, in addition to activating procarcinogens in the metabolism of tobacco smoke, is also thought to take part in the hydroxylation of 17β-estradiol. Furthermore, the Leu-Val transition at codon 432 of CYP1B1, which is located in the heme-binding domain of exon 3, causes the enzyme display a higher 4-hydroxylation of estradiol. This leads to the formation of carcinogenic estradiol-3,4-semiquinones and quinones. It is possible that the CYP1B1 is involved in lung carcinogenesis through the estrogenic activity of the 4-OH-E2 [8, 34, 35]. There is possibility that CYP1B1 polymorphism may be associated with lung cancer in woman, since this enzyme is responsible for the oxidizing of procarcinogens in tobacco smoke as well as the formation of carcinogenic metabolic product of estradiol. In our meta-analysis, we found an elevated risk of lung cancer in women carrying the 432 rare allele (OR 1.469; 95% CI 1.203–1.794, $P = 0.565$ for heterogeneity) as well as the rare homozygous (OR 1.378; 95% CI 1.053–1.803, $P = 0.426$ for heterogeneity) compared with women carrying common homozygous. Due to the limited number of cases and controls and the lack of detailed information of individuals, we cannot make further analysis according to the menopausal status of women.

For SNP Leu432Val (432C>G), we stratified the result with descent as well. Results indicated that Caucasians with CYP1B1 432GG genotype had significantly increased risk of lung cancer compared with individuals with the CC genotype (OR 1.570, 95% CI 1.049–2.350, $P = 0.017$ for heterogeneity), while no association was observed in a

dominant model (OR 1.400, 95% CI 0.947–2.068, $P = 0.002$ for heterogeneity). The risk of lung cancer was elevated as the frequency of G allele increased in additive model ($P = 0.000$). However, the same risk was seen in neither Asians nor African-Americans, indicating that polymorphism of CYP1B1 may be important for individuals with specific ethnicity. Genetic variances in different populations may partially explain this phenomenon. The frequency of 432G allele was varied from 0.378 to 0.558 in Caucasians [12, 14, 19, 21], and it was only 0.087–0.23 in Asians [15, 17, 20, 36]. It was quite surprising that in African-Americans, with the frequency of 432G allele from 0.75 to 0.817 [12, 14, 31], no significant effect was observed with lung cancer risk in codominant, dominant or additive model. This may be due to the limited number of study subjects in these two studies [12, 14].

There are some limitations of this meta analysis. The overall result was based on the crude ORs from pooling of individual unadjusted studies. A more specific result shall be concluded if adjusted by potential suspected factors, such as age and gender. Second, the available data on the polymorphisms were relatively limited, with approximately 2,500 cases and 3,200 controls for Leu432Val, 2,915 cases and 3,791 controls focused on Asn453Ser, 1,126 cases and 1,816 controls for Ala119Ser as well as 527 cases and 568 controls focused on Arg48Gly. This made it quite difficult to perform subgroup analysis. The majority of the subjects presented in our study were cases with lung adenocarcinoma, so the result we concluded may not be representative of all NSCLC's histological types. There were differences in the original study designs. Most of the studies included were case–control studies while the study by Sorensen et al. [19] was a population based case-cohort one. However, the test of sensitivity did not show materially huge difference while omitting this study. Finally, we did not have detailed individual information on these four SNPs, and this made it impossible to make detailed analyses of linkage disequilibrium and the combined effect of various genetic polymorphisms and lung cancer susceptibility. Furthermore, it is well known that combinations of certain genotypes may be more prominent risk factors compared with single genotype, and large studies including multiple important SNPs of the genes related with the phase I and phase II xenobiotic metabolizing enzymes.

Despite the limitations of this meta-analysis, the overall result of our study suggested that the 432GG genotype, 432G allele, 119TT genotype, 48GG genotype and 48G allele were low-penetrance risk factors for developing lung cancer, while neither T allele at codon 453 nor T allele at codon 119 might alter the individual susceptibility of lung cancer. Furthermore, a possible association between the CYP1B1 Leu432Val polymorphism and the lung cancer could be detected in individuals of Caucasian origin, while

a negative association was suggested in Asians and African-Americans. In addition an increased risk of lung cancer was seen in women. However, there is a need for case–control studies and cohort studies to validate the effects of polymorphism at CYP1B1 codon 432, 453, 119 and 48 on metabolizing tobacco smoke carcinogenes in different ethnic groups, different gender and in premenopausal together with postmenopausal women.

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