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Original Article

Association between *EPHX1* rs1051740 and lung cancer susceptibility: a meta-analysis

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Abstract: Background: Microsomal epoxide hydrolase 1 (EPHX1) may play an important role in epigenetic change and DNA repair concerned with lung cancer. Several studies have investigated the association between *EPHX1* rs1051740 and lung cancer risk, but there is no consensus. Therefore, we performed a meta-analysis to further identify the relationship. Methods: The Pubmed and Embase databases were searched for eligible studies. An odds ratio (OR) with 95% confidence intervals (CIs) was used to assess the correlation between *EPHX1* rs1051740 polymorphism and lung cancer risk through a meta-analysis. Results: Overall, no significant relationship was found between *EPHX1* rs1051740 and lung cancer risk (CC vs. TT: OR=1.10, 95% CI=0.88-1.36; CC+CT vs. TT: OR=1.02, 95% CI=0.88-1.18; CC vs. TT+CT: OR=1.08, 95% CI=0.91-1.27; C vs. T: OR=1.04, 95% CI=0.93-1.17; CT vs. TT: OR=0.98, 95% CI=0.85-1.13). Nevertheless, further subgroup analysis by ethnicity demonstrated that EPHX1 rs1051740 with CC genotype or C allele was an increased risk for lung cancer in Asians (CC vs. TT: OR=1.54, 95% CI=1.23-1.94; CC vs. TT+CT: OR=1.43, 95% CI=1.20-1.71; C vs. T: OR=1.26, 95% CI=1.08-1.47). Conclusions: This meta-analysis indicates that *EPHX1* rs1051740 with CC genotype or C allele may be a risk factor in Asians.

Keywords: *EPHX1*, polymorphism, lung cancer

Introduction

Lung cancer, the leading cause of mortality, is considered as a public health problem [1-3]. Every year about 1,180,000 people die from this cancer all over the world. Common symptoms of lung cancer are weight loss, breath shortness, cough and chest pains. The vast majority (80-90%) of lung cancer cases are due to long-term exposure to tobacco smoke [4], whereas about 10-15% of cases occur in non-smokers [5]. In addition to environmental factors, genetic background has also been recently considered as a risk factor for lung cancer susceptibility [6].

Microsomal epoxide hydrolase 1 (*EPHX1*), an important metabolic biotransformation enzyme, catalyzes the hydrolysis of epoxides from polycyclic aromatic hydrocarbons and aromatic amines of cigarette smoking, which can be conjugated and excreted from the body [7, 8]. Previous studies have shown that two common polymorphic sites in *EPHX1* gene located on chromosome 1q42 with 9 exons and 8 introns could affect EPHX1 enzyme activity. The tyrosine to histidine substitution in exon 3 (rs1051740) sharply decreases the enzyme activity about 40%-50%, whereas the histidine to arginine substitution in exon 4 (rs2234922) could increase the enzyme activity by approximately 25% [9, 10]. Among these two polymorphic sites, the mostly studied one is rs1051740.

Molecular epidemiological studies have broadly investigated the association between rs1051740 and lung cancer risk [11-13]. Whereas the results are conflicting rather than conclusive, probably due to different ethnic or environmental backgrounds and sample sizes. Thus, a comprehensive meta-analysis including 5232 cases and 9522 controls was performed to further identify the association between rs1051740 and LC risk.

Methods

Search strategy

The Pubmed and Embase databases were systematically searched using the key words “EPHX1”, “polymorphism”, “lung cancer”. Addi-

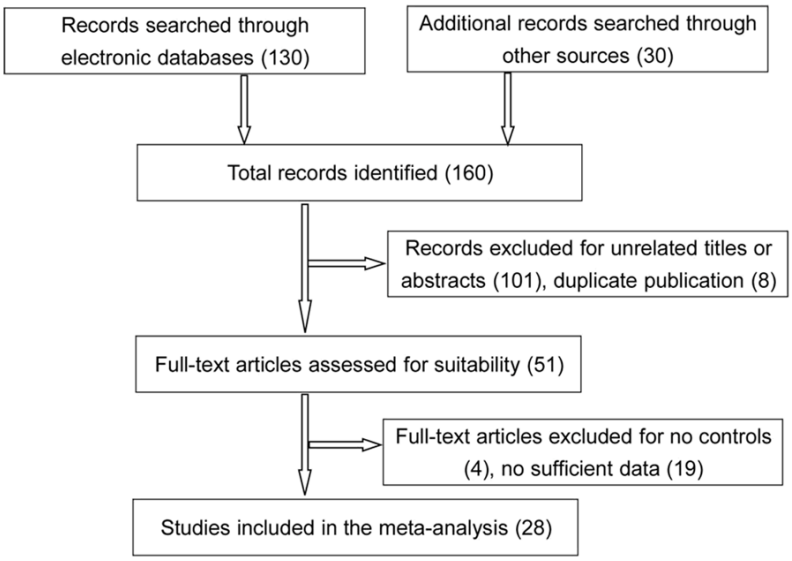

Figure 1. Flow diagram of the study selection process for the meta-analysis.

tional useful articles were also retrieved in reference lists of previously searched publications by hand.

Inclusion and exclusion criteria

All included studies had to meet the following criteria: (1) with a case-control design; (2) evaluating the association between *EPHX1* rs1051740 polymorphism and lung cancer risk; (3) providing sufficient data for calculating the odds ratios (ORs) with 95% confidence intervals (95% CIs). When numerous publications covered the same or overlapping data, we selected the largest or most recent publication.

Data extraction

According to the inclusion and exclusion criteria, two independent reviewers completed the data extraction. The extracted data included: the name of first author, publication date, ethnicity, country of origin, number of cases and controls, genotyping method, genotype frequencies, and Hardy-Weinberg equilibrium (HWE). And inconsistent results were settled by the third reviewer.

Quality assessment

To assess the quality of all included studies, two reviewers independently scored each study according to the Newcastle-Ottawa Scale (NOS) [14]. The NOS, with eight items, ranges from zero to nine scores, and in our meta-analysis, high-quality was conferred to studies which got five scores or more. The third reviewer would be consulted if the discussion about the scores between the first two reviewers failed to reach a consensus.

Statistical analysis

We used the pooled ORs with 95% CIs to identify the strength of the relationship between *EPHX1* rs10517-40 and lung cancer risk. The pooled ORs were performed for CC vs. TT, CC+CT vs. TT, CC vs. TT+CT, C vs. T, CT vs. TT genetic models. In the subgroups, statistical analyses would be performed based on ethnicity, source of control, quality assessment score and HWE in control group, if appropriate. Z test was used to evaluate whether the pooled ORs were significant. $P<0.05$ was considered statistically significant. Heterogeneity assumption was testified by Q test. The pooled ORs were calculated by the fixed-effects model when P (heterogeneity) >0.05. Otherwise, the random-effects model was used. The potential publication bias was assessed via Begg's funnel plots and Egger's test. HWE was checked by χ^2 test. Statistical analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

As performed in **Figure 1**, we first identified 160 articles according to the search strategy, and 8 studies were excepted for duplicate publications, 101 studies were excluded by screening the titles and abstracts, 4 studies were precluded for no controls, and 19 studies were eliminated for insufficient data. Ultimately, 28 studies were considered acceptable and included into our meta-analysis (**Table 1**). The above method for scoring showed that all included studies were high-quality (**Table 1**).

Table 1. Principle characteristics of the studies included in the meta-analysis

First author/Year	Country	Ethnicity	Control source	Genotyping method	Case/Control			HWE	Score
					TT	TC	CC		
Benhamou/1998	France	Caucasian	HB	PCR	82/64	46/77	22/31	0.36	6
Cajas-Salazar/2003	America	African	HB	PCR	67/62	37/52	6/5	0.14	6
Erkisi/2010	Turkey	Caucasian	PB	PCR-RFLP	6/22	26/12	26/7	0.04	7
Fathy/2014	Egypt	African	PB	PCR-RFLP	28/78	14/18	8/4	0.04	6
Gemignani/2007	Mixed	Caucasian	HB	Kit	136/151	83/82	31/27	0.00	8
Graziano/2009	Italy	Caucasian	PB	PCR	26/40	14/32	2/0	0.02	7
Gsur/2003	Australia	Caucasian	HB	PCR	147/224	114/218	16/54	0.93	5
Ihsan/2011	India	Asian	PB	PCR-RFLP	82/94	51/133	55/63	0.22	7
Liang/2004	China	Asian	HB	PCR	36/48	87/76	29/28	0.83	5
London/2000	USA	Caucasian	PB	PCR	85/237	82/184	15/37	0.88	6
London/2000	USA	African	PB	PCR	106/153	48/77	1/12	0.57	6
Park/2005	USA	Mixed	PB	PCR-RFLP	81/138	72/147	25/80	0.01	7
Perez-Morales/2014	Mexico	Mixed	PB	RFLP	61/128	64/134	65/120	0.94	5
Persson/1999	China	Asian	PB	PCR	21/41	33/59	20/22	0.92	5
Rosenberger/2008	Germany	Caucasian	PB	MALDI-TOFMS	55/49	38/43	7/8	0.74	6
Smith/1997	UK	Caucasian	PB	PCR	25/91	20/99	5/13	0.04	5
Sun/2007	China	Asian	PB	PCR	38/61	40/38	144/123	0.97	8
Tilak/2011	India	Asian	HB	PCR	62/134	85/157	28/31	0.12	6
Timofeeva/2010	Germany	Caucasian	PB	MALDI-TOFMS	316/627	238/520	57/119	0.46	8
To-Figueras/2001	Spain	Caucasian	PB	PCR	97/87	70/85	8/15	0.36	7
Voho/2006	Finland	Caucasian	PB	PCR-RFLP	133/1029	81/865	13/189	0.71	6
Wang/2012	China	Asian	PB	PCR-RFLP	54/97	70/82	85/77	0.96	5
Wu/2001	USA	Mixed	PB	PCR	20/28	26/29	5/7	0.90	5
Wu/2001	USA	African	PB	PCR	40/38	22/20	3/4	0.54	5
Yin/2001	China	Asian	HB	PCR	15/24	54/46	15/14	0.31	7
Yoshikawa/2000	Japan	Asian	PB	PCR	24/35	35/51	12/21	0.76	5
Zhao/2002	USA	Caucasian	PB	PCR-RFLP	86/77	56/54	20/22	0.02	7
Zhou/2001	USA	Caucasian	PB	PCR	465/581	332/355	177/206	0.97	6

PCR: polymerase chain reaction; PCR-RFLP: PCR-restriction fragment length polymorphism; MALDI-TOFMS: matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; HWE: Hardy-Weinberg equilibrium.

Quantitative synthesis

As shown in **Table 2**, no significant relationship was found between *EPHX1* rs1051740 and LC risk (CC vs. TT: OR=1.10, 95% CI=0.88-1.36; CC+CT vs. TT: OR=1.02, 95% CI=0.88-1.18; CC vs. TT+CT: OR=1.08, 95% CI=0.91-1.27; C vs. T: OR=1.04, 95% CI=0.93-1.17; CT vs. TT: OR=0.98, 95% CI=0.85-1.13). Additionally, subgroup analyses by source of control and HWE in controls revealed no significant association between the two sides either. However, further subgroup analysis by ethnicity demonstrated that *EPHX1* rs1051740 with CC genotype or C allele was an increased risk for LC in Asians (CC vs. TT: OR=1.54, 95% CI=1.23-1.94; CC vs. TT+CT: OR=1.43, 95% CI=1.20-1.71; C vs. T: OR=1.26, 95% CI=1.08-1.47) (**Figures 2** and **3**).

Sensitivity analysis

The sensitivity analysis was executed repeatedly by precluding a single study at a time. The overall results were not drastically altered when any individual study was excluded, suggesting our meta-analysis results were of high stability (data not shown).

Publication bias

Begg's funnel plot and Egger's test were adopted to evaluate the publication bias of literature (**Figure 4**). The shape of the funnel plot seemed symmetrical. Additionally, no significant publication bias was detected by Egger's test in the meta-analysis (P=0.97). Therefore, there existed no apparent publication bias influencing the overall results.

Table 2. *EPHX1* rs1051740 polymorphism and lung cancer risk

		CC versus TT		CC+CT versus TT		CC versus TT+CT		C versus T		CT versus TT	
		OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*	OR (95% CI)	*Ph*
Ethnicity	Caucasian	0.93 [0.68, 1.27]	0.0002	0.91 [0.75, 1.11]	0.000	0.94 [0.75, 1.17]	0.04	0.95 [0.81, 1.11]	0.000	0.91 [0.75, 1.09]	0.0003
	African	0.98 [0.23, 4.16]	0.01	1.06 [0.62, 1.81]	0.02	1.00 [0.26, 3.82]	0.02	1.09 [0.63, 1.90]	0.001	0.99 [0.65, 1.51]	0.13
	Asian	1.54 [1.23, 1.94]	0.34	1.29 [0.96, 1.74]	0.004	1.43 [1.20, 1.71]	0.70	1.26 [1.08, 1.47]	0.07	1.17 [0.82, 1.67]	0.0010
	Mixed	0.82 [0.46, 1.46]	0.09	0.92 [0.68, 1.24]	0.26	0.84 [0.51, 1.40]	0.10	0.92 [0.68, 1.26]	0.06	0.94 [0.72, 1.24]	0.62
Source of control	Population	1.12 [0.87, 1.44]	0.000	1.04 [0.88, 1.23]	0.000	1.10 [0.91, 1.34]	0.002	1.06 [0.93, 1.22]	0.000	0.99 [0.84, 1.16]	0.0002
	Hospital	1.05 [0.66, 1.66]	0.007	0.97 [0.71, 1.34]	0.0009	1.02 [0.73, 1.42]	0.08	0.98 [0.78, 1.23]	0.001	0.96 [0.70, 1.30]	0.004
HWE in controls	Conform	1.03 [0.84, 1.27]	0.000	0.98 [0.84, 1.13]	0.000	1.06 [0.90, 1.24]	0.03	1.00 [0.89, 1.12]	0.000	0.95 [0.82, 1.10]	0.000
	Not conform	1.86 [0.84, 4.10]	0.000	1.28 [0.81, 2.04]	0.000	1.51 [0.82, 2.76]	0.002	1.30 [0.87, 1.95]	0.000	1.15 [0.77, 1.72]	0.004
Total		1.10 [0.88, 1.36]	0.000	1.02 [0.88, 1.18]	0.000	1.08 [0.91, 1.27]	0.001	1.04 [0.93, 1.17]	0.000	0.98 [0.85, 1.13]	0.000

Ph: *P*-value of heterogeneity test.

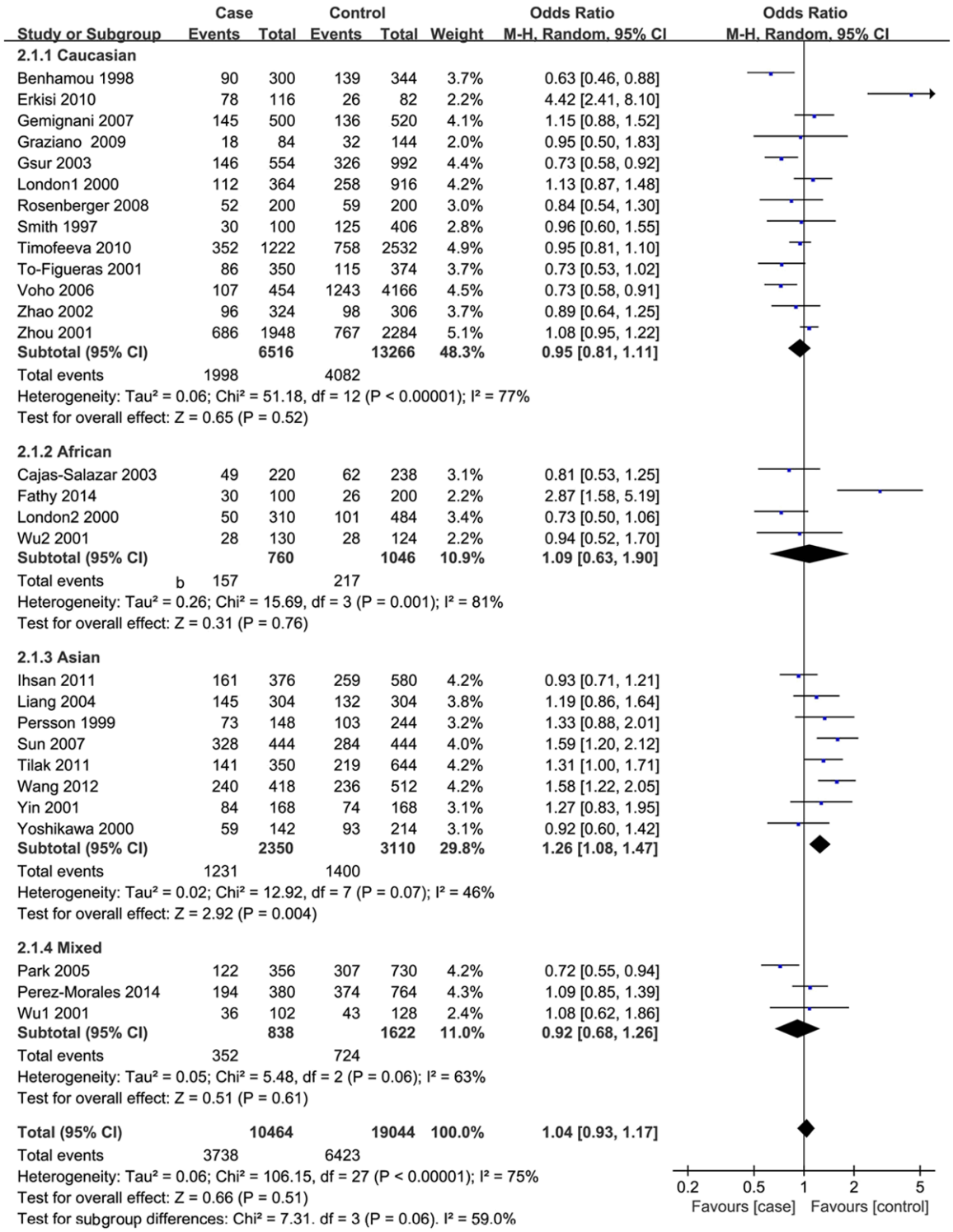

Figure 2. Forest plot of lung cancer risk associated with *EPHX1* rs1051740 polymorphism under C vs. T genetic model by ethnicity.

Discussion

Lung cancer, with a five-year survival rate of less than 14% for males and less than 18% for females in most countries, is considered as one of the most common lethal malignancies worldwide [15-18]. The incidence of lung cancer is increasing obviously in Asian countries,

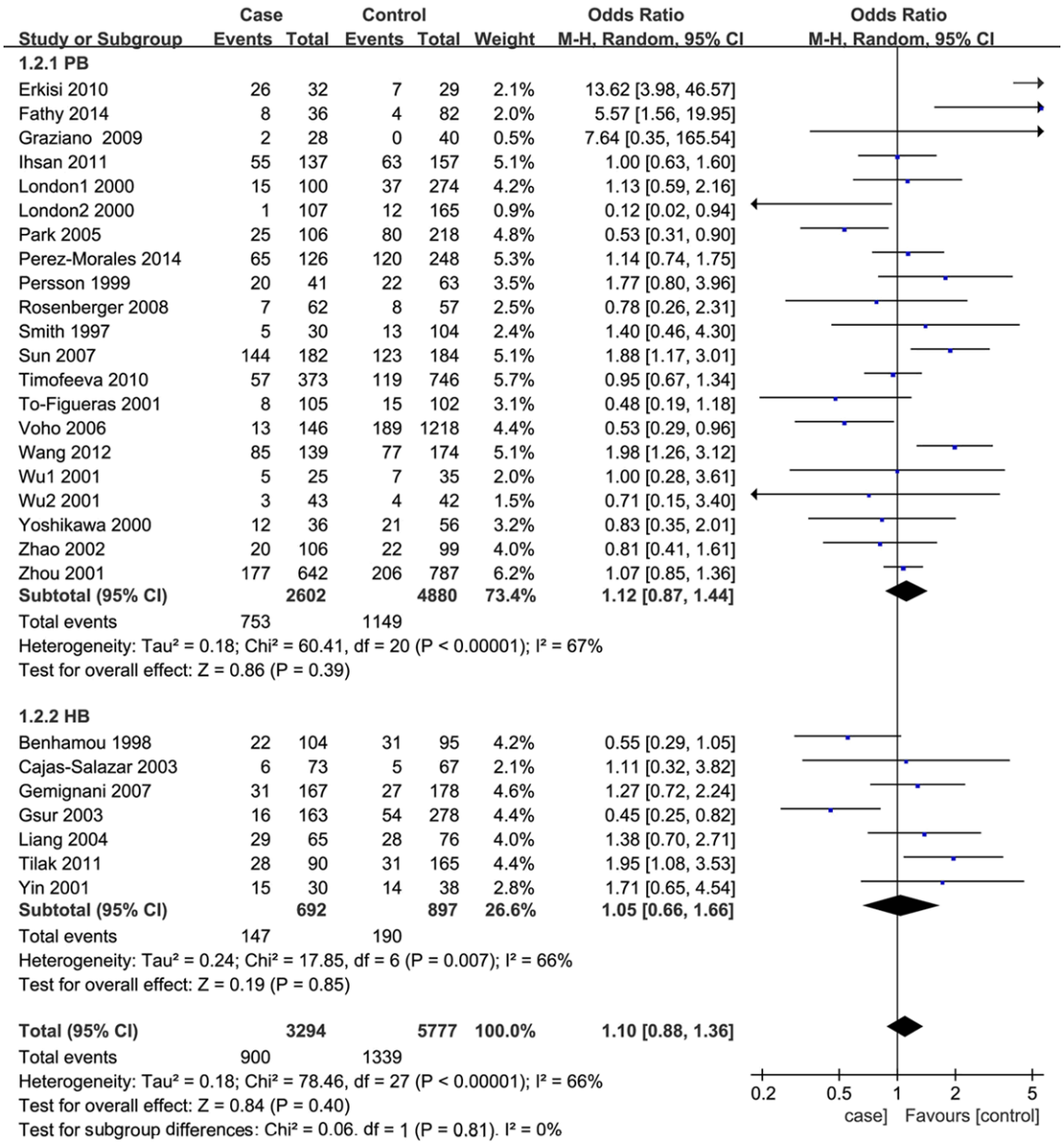

Figure 3. Forest plot of lung cancer risk associated with *EPHX1* rs1051740 polymorphism under CC vs. TT genetic model by source of control.

especially in China. Although some measures have been taken to improve the diagnosis and treatment, the prognosis is still imperfect due to unclear etiology [19-23].

Besides environmental factors, the effects of genetic background on lung cancer risk cannot be ignored. Polymorphic variations in genes associated with carcinogen metabolism, DNA repair, and cell-cycle disregulation may influence the development of lung cancer [24].

EPHX1 is a kind of metabolic biotransformation enzyme in metabolizing some exogenous carcinogens, and it plays an important role in both the activation and detoxification of aromatic amines [25]. *EPHX1* rs2234922 has been identified as a risk factor for lower white blood cell and colorectal cancer [26, 27]. There are also studies investigating the association between rs1051740 polymorphism and several cancers, such as prostate cancer, colorectal cancer, bladder cancer, and breast cancer [27-36]. And

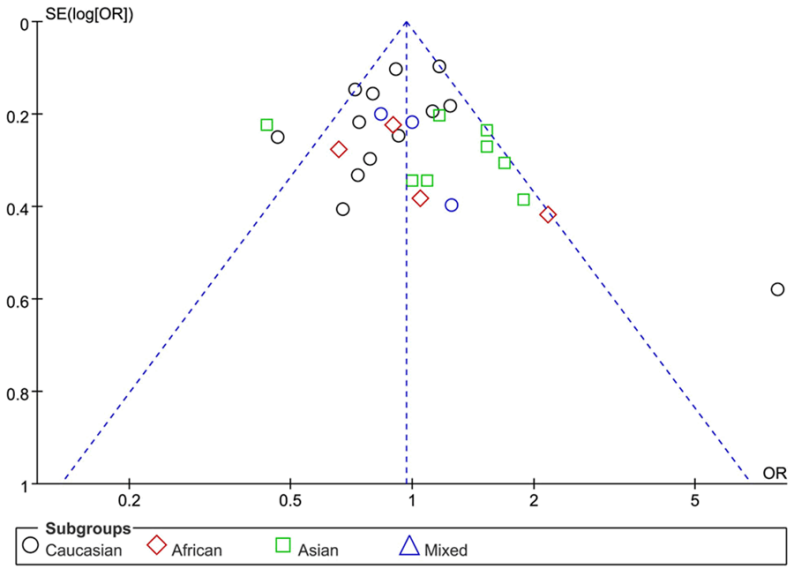

Figure 4. Begg's funnel plot of publication bias test. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR. Horizontal line, mean effect size.

the relationship between *EPHX1* rs1051740 and lung cancer was widely researched as well. Wang S et al. observed no relationship between *EPHX1* rs1051740 and lung cancer generally in the meta-analysis, but significantly increased lung cancer risk among Asians and decreased risk in Caucasians in the subgroup analysis by ethnicity [37]. A large-scale study conducted by Erkisi Z et al. drew the same conclusion [11]. However, consistent with our findings, a study designed by Tilak AR et al. demonstrated the same increased risk in Asians, whereas no association in Caucasians [38]. The reasons for the divergent results in Caucasians were likely to be caused by either different genders of Caucasians studied or lack of sufficient original data.

Although the statistical evidence in the meta-analysis was adequate and robust, there also existed some limitations which should be addressed. First, our meta-analysis was stratified by ethnicity and source of control, not reflecting the influence of gender on lung cancer risk. Second, the absence of original data of studies affected the validity of association. Third, the possible critical role of CC genotype or C allele of rs1051740 polymorphism in lung cancer was not specially discussed. Finally, not considering the effects of other genetic or environmental factors might make our results biased to a large extent.

Overall, despite the limitations, our meta-analysis indicated that *EPHX1* rs1051740 with CC genotype or C allele may be an increased factor in Asians. Further well-designed investigations performed in larger scales are wanted to clarify this point of view.

Disclosure of conflict of interest

None.

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