GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Quantitative assessment of the effects of the *EPHX1* Tyr113His polymorphism on lung and breast cancer

X. Tan[1]*, Y.Y. Wang[1]*, X.Y. Chen[2]*, L. Xian[1], J.J. Guo[1], G.B. Liang[1] and M.W. Chen[1]

[1]Department of Cardiothoracic Surgery, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China
[2]Department of Oncology, First Affiliated Hospital, Guangxi Medical University, Nanning, Guangxi, China

*These authors contributed equally to this study.
Corresponding author: M.W. Chen
E-mail: chen535@126.com

Genet. Mol. Res. 13 (3): 7437-7446 (2014)
Received July 12, 2013
Accepted March 9, 2014
Published September 12, 2014
DOI http://dx.doi.org/10.4238/2014.September.12.10

ABSTRACT. The association between the microsomal epoxide hydrolase 1 gene (*EPHX1*) Tyr113His polymorphism and lung cancer and breast cancer risk has been reported in many recent studies, but there is no consensus among the results. Thus, we examined the association between the *EPHX1* Tyr113His polymorphism and lung cancer through a meta-analysis. A comprehensive literature search was performed using the Pubmed and Embase databases. Odds ratios with 95% confidence intervals were used to assess the strength of associations. Our meta-analysis suggested that the Tyr113His polymorphism was associated with lung cancer risk in Asians under 3 genetic models, including a C *vs* T, CC *vs* TT, and recessive model. However, the risk was decreased in Caucasians under the genetic models, including a C *vs* T, CC *vs* TT, or CT *vs* TT, dominant, and recessive model. In contrast, there was no association with breast cancer risk for any of the genetic models. Our meta-analysis suggested that the *EPHX1* Tyr113His polymorphism may be a risk factor for lung cancer in Asians, whereas it may

be a decreased risk factor among Caucasians. However, this polymorphism was not found to be associated with breast cancer.

Key words: EPHX1; Polymorphism; Lung cancer; Breast cancer; Meta-analysis

INTRODUCTION

Among human cancers, lung cancer, with a 5-year survival rate less than 14% for males and less than 18% for females in most countries (Youlden et al., 2008), is regarded as one of the most common lethal malignancies worldwide. Breast cancer is the most common cancer and the leading cause of death among females, accounting for 23% of total cancer in females and 14% of cancer deaths (Jemal et al., 2011). It is well-known that cigarette smoking contributes to an increased risk of lung cancer. In addition, other environmental carcinogens, such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons (PAH), may also be considered risk factors for lung cancer and breast cancer (Sangrajrang et al., 2009; Jemal et al., 2011). However, not all exposed individuals develop lung and breast cancers, suggesting that genetic factors play a role in these conditions. Microsomal epoxide hydrolase (mEH) is an important metabolic biotransformation enzyme that catalyzes epoxidation intermediate hydrolysis to trans-dihydrodiols, which can be conjugated and excreted from the body. In certain conditions, trans-dihydrodiols generated from chemical carcinogens, such as PAHs, are highly toxic and mutagenic. Thus, mEH has a dual effect in the detoxification and activation of procarcinogens, and its role in carcinogenesis may depend on exposure to different environmental substrates (Zhang et al., 2003). The tyrosine to histidine (T→C) replacement in exon 3 (Tyr113His) of the EPHX1enzyme decreased activity by approximately 50% (Hassett et al., 1994), suggesting that mutations in this gene may lead to cancer.

The *EPHX1* gene, which is located on chromosome 1q42.1, has several known variations. These polymorphisms may be associated with prostate cancer, colorectal cancer, and bladder cancer (Mittal and Srivastava, 2007; Liu et al., 2012; Zhang et al., 2012). Previous studies have suggested that the *EPHX1* Tyr113His polymorphisms associated with the risk for lung cancer and breast cancer. However, the results were unclear. Thus, we performed a meta-analysis to investigate the association between the *EPHX1* Tyr113His polymorphism and susceptibility to lung cancer and breast cancer.

MATERIAL AND METHODS

Search strategy and selection criteria

All case-control studies were systematically researched from the Pubmed and Embase databases for all medical publications until February 2013 with the following terms: microsomal epoxide hydrolase 1, mEH, EPHX1, EPOX, HYL1, Tyr113His, exon 3, codon113, T113C, rs1051740, polymorphism, variant, and "lung" combined with "carcinoma", "cancer", or "breast", "mammary" combined with "cancer", and "carcinoma". All human studies included in our meta-analysis met the following criteria: full-text articles, case-control design, evaluated the association between the *EPHX1* Tyr113His polymorphism and lung cancer or breast cancer risk, odds ratio (OR) with 95% confidence interval (95%CI) with sufficient data for estimating, genotype associations, and the dis-

tribution of genotypes complied with Hardy-Weinberg equilibrium (HWE) in controls.

Data extraction

As inclusion criteria, all eligible studies were carefully identified by 2 investigators (X. Tan and Y.Y. Wang) independently. In case of disagreement, a third investigator (M.W. Chen) evaluated the data. Data items included: first author's name, year of publication, country, ethnicity, genotyping method, source of controls, and different genotype numbers in all studies.

Statistical analysis

The pooled risk (OR) and 95%CI were used to assess the strength of the association between the *EPHX1* Tyr113His polymorphism and lung cancer or breast cancer for each study. To avoid assuming only one "incorrect" genetic model, there were at least 3 possible genotypes to examine in our meta-analysis. We estimated the OR for the co-dominant model (CC *vs* TT, CT *vs* TT), dominant model (CC+CT *vs* TT), and recessive model (CC *vs* CT+TT), respectively.

Between-study heterogeneity was assessed by using the chi-square statistic based on the Q statistical test and its associated P value (Higgins et al., 2003). A P value > 0.1 or I^2 < 25% indicated no heterogeneity, which was estimated by the fixed effects model with Mantel-Haenszel's method for the overall gene effect (Mantel and Haenszel, 1959). When P < 0.1 or I^2 > 50%, the heterogeneity was considered to be significant, and the random effects model with the DerSimonian-Laird method was performed (Lau et al., 1997). Sensitivity analysis was conducted to exclude 1 study at a time. HWE was determined by using the Pearson statistic (P > 0.05) for each study (Bosco et al., 2012). Potential publication bias was estimated by Begg's test and Egger's test (P < 0.05 was considered to be statistically significant) (Peters et al., 2006). Owing to geographical and ethnic differences, to evaluate the effects of covariance, subgroup analyses were performed. Ethnic subgroups were divided into Caucasian and Asian. Our analysis was performed using the Stata software version 11.1 (StataCorp; College Station, TX, USA). All P values were 2-sided, with values less than 0.05 considered to be statistically significant.

RESULTS

Characteristics of relevant studies

Using our search strategy and inclusion criteria, 9 studies were excluded because they deviated from HWE. A total of 14 studies (Benhamou et al., 1998; Persson et al., 1999; London et al., 2000; To-Figueras et al., 2001; Wu et al., 2001; Yin et al., 2001; Cajas-Salazar et al., 2003; Gsur et al., 2003; Harms et al., 2004; Liang et al., 2004; Voho et al., 2006; Timofeeva et al., 2010; Ihsan et al., 2011; Tilak et al., 2011) that included full-text articles and complied with HWE demonstrated an association between the *EPHX*1 Tyr113His polymorphism and lung cancer (Table 1). Among the studies included, 2 included 2 ethnicity types (London et al., 2000; Wu et al., 2001), and the data was collected separately and served as independent studies in our meta-analyses. A total of 16 studies, including 2399 cases and 5623 controls, examined the *EPHX1* Tyr113His polymorphism (Table 1). In order to evaluate the effects of covariance, subgroup analyses were performed. Because smoking status and histopathology data were insufficient, we performed subgroup analyses by ethnicity.

There were 5 studies involving Asians (Persson et al., 1999; Yin et al., 2001; Liang et al., 2004; Ihsan et al., 2011; Tilak et al., 2011), 7 studies on Caucasians (Benhamou et al., 1998; London et al., 2000; To-Figueras et al., 2001; Gsur et al., 2003; Harms et al., 2004; Voho et al., 2006; Timofeeva et al., 2010), and 3 studies on African subjects (London et al., 2000; Wu et al., 2001; Cajas-Salazar et al., 2003). For breast cancer, 1study was excluded because there was not sufficient genotype data (de Assis et al., 2002), and therefore 5 studies (Sarmanová et al., 2004; Spurdle et al., 2007; Khedhaier et al., 2008; Justenhoven et al., 2008; Sangrajrang et al., 2009) including a total of 2943 cases and 2314 controls that examined the association between the *EPHX1* Tyr113His polymorphism and breast cancer were included into our meta-analysis (Table 2). In the subgroup analyses by ethnicity, there were 4 studies on Caucasians (Sarmanová et al., 2004; Spurdle et al., 2007; Khedhaier et al., 2008; Justenhoven et al., 2008), whereas there was 1 study on Asians (Sangrajrang et al., 2009).

Table 1. Studies summary of *EPHX1* Tyr113His polymorphism with lung cancer.

Investigator	Year	Race	Country	Case			Control			P[a]	Control source	Methods
				CC	CT	TT	CC	CT	TT			
Tilak et al.	2011	Asian	India	28	85	62	31	157	134	0.12	HB	PCR
Ihsan et al.	2011	Asian	India	55	51	82	63	133	94	0.21	PB	PCR-RFLP
Timofeeva et al.	2010	Caucasian	Germany	57	238	316	119	520	627	0.45	PB	MALDI-TOFMS
Voho et al.	2006	Caucasian	Finland	13	81	133	189	865	1029	0.70	PB	PCR-RFLP
Liang et al.	2004	Asian	China	29	87	36	28	76	48	0.82	HB	PCR
Harms et al.	2004	Caucasian	USA	6	37	67	5	52	62	0.14	HB	PCR
Gsur et al.	2003	Caucasian	Austria	16	114	147	54	218	224	0.92	HB	PCR
Cajas-Salazar et al.	2003	African	American	6	37	67	5	52	62	0.14	HB	PCR
Yin et al.	2001	Asian	China	15	54	15	14	46	24	0.30	HB	PCR
Wu et al.	2001	Mixed	USA	5	26	20	7	29	28	0.90	PB	PCR
Wu et al.	2001	African	USA	3	22	40	4	20	38	0.54	PB	PCR
To-Figueras et al.	2001	Caucasian	Spain	8	70	97	15	85	87	0.35	PB	PCR
London et al.	2000	Caucasian	USA	15	82	85	37	184	237	0.87	PB	PCR
London et al.	2000	African	USA	1	48	106	12	77	153	0.56	PB	PCR
Persson et al.	1999	Asian	China	20	33	21	22	59	41	0.92	PB	PCR
Benhamou et al.	1998	Caucasian	France	22	46	82	31	77	64	0.35	HB	PCR

P[a] for Hardy-Weinberg equilibrium in control group; HB = hospital-based; PB = population-based; PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction restriction fragment length polymorphism; MALDI-TOFMS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Table 2. Studies summary of *EPHX1* Tyr113His polymorphism with breast cancer.

Investigator	Year	Race	Country	Case			Control			Control source	Methods
				CC	CT	TT	CC	CT	TT		
Sarmanová et al.	2004	Caucasian	Czech Republic	45	77	115	39	124	148	HB	PCR-RFLP
Spurdle et al.	2007	Caucasian	Australian	103	496	639	85	262	316	PB	PCR
Khedhaier et al.	2008	Caucasian	Tunisia	38	119	149	16	115	113	PB	PCR-RFLP
Justenhoven et al.	2008	Caucasian	Germany	63	246	296	45	269	295	PB	MALDI-TOF MS
Sangrajrang et al.	2009	Asian	Thailand	128	286	143	115	247	125	HB	PCR

HB = hospital-based; PB = population-based; PCR = polymerase chain reaction; PCR-RFLP = polymerase chain reaction restriction fragment length polymorphism; MALDI-TOFMS = matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

Meta-analysis results

The main results of the meta-analysis regarding the association between the *EPHX1* Tyr113His polymorphism and breast cancer risk are shown in Table 3. Results for lung cancer are shown in Table 4. When all studies were pooled, we performed analyses using fixed-effects models if the *Q*-test for heterogeneity was not considered to be significant; otherwise, we used random-effects models.

Table 3. Main result of the meta-analysis *EPHX1* Tyr113His relation with breast cancer.

Variable	N	His/His *vs* Tyr/Tyr			His/Tyr *vs* Tyr/Tyr			Dominant model			Recessive model		
		OR (95%CI)	P^a	P^b	OR (95%CI)	P^a	P^b	OR (95%CI)	P^a	P^b	OR (95%CI)	P^a	P^b
Total	5	1.122 (0.750-1.677)	0.575	0.001	0.908 (0.805-1.024)	0.115	0.789	0.926 (0.827-1.037)	0.184	0.858	1.184 (0.785-1.787)	0.421	0
Ethnicity													
Caucasian	4	1.185 (0.683-2.055)	0.546	0	0.888 (0.779-1.013)	0.078	0.781	0.912 (0.806-1.033)	0.146	0.808	1.276 (0.714-2.280)	0.411	0
Asian	1	0.973 (0.687-1.378)	0.877	0	1.012 (0.754-1.358)	0.936	0	1 (0.757-1.321)	0.998	0	0.965 (0.724-1.287)	0.809	0

N = number of studies in each analysis; dominant model, His/His+His/Tyr *vs* Tyr/Tyr; recessive model, His/His *vs* His/Tyr+Tyr/Tyr; OR = odds ratio; CI = confidence interval; [a]pool P value; [b]P value for heterogeneity test.

Our meta-analysis showed no evidence for an association between the *EPHX1* Tyr113His polymorphism and lung cancer risk in overall studies (Table 4). To determine covariance effects, ethnicity was examined in subgroup analyses. We detected no significant genetic models for African and mixed race populations (Table 4). Interestingly, significant evidence was found for Asians, showing that the low-activity allele (C) of *EPHX1* Tyr113His was associated with an increased risk of lung cancer (C *vs* T, OR = 1.159, 95%CI = 1.006-1.335, P = 0.042). In addition, 2 other genetic models revealed a risk relationship with lung cancer in Asians (CC *vs* TT, OR = 1.391, 95%CI = 1.046-1.850, P = 0.023; CC *vs* CT+TT, OR = 1.421, 95%CI = 1.103-1.829, P = 0.006) (Figure 1, Table 4). However, we obtained opposite results showing that the *EPHX1* Tyr113His polymorphism may be a decreased risk factor in Caucasians for all genetic models examined (Figure 2, Table 4).

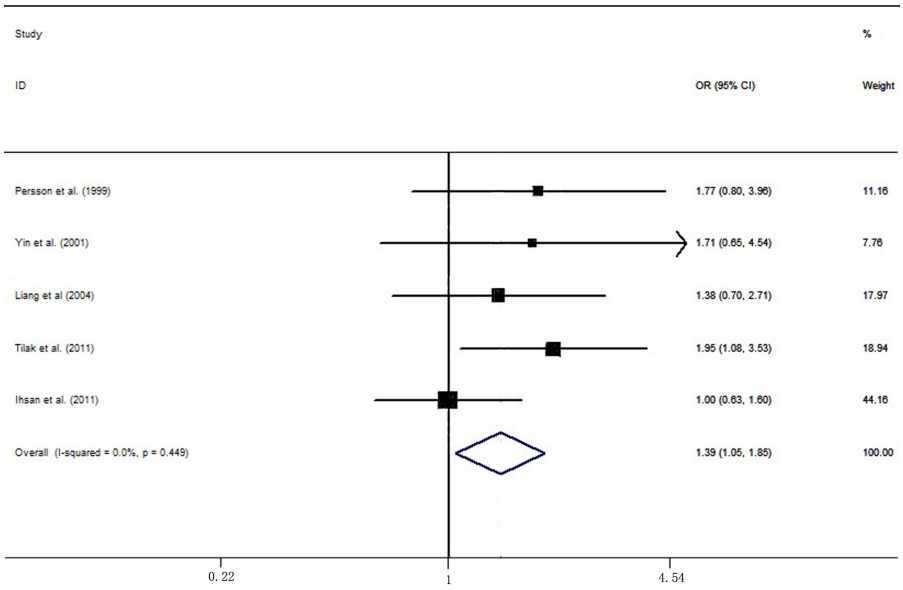

Figure 1. Forest plots for the *EPHX1* Tyr113His polymorphism and risk of lung cancer in Asian using the fixed-effect co-dominant model (CC *vs* TT).

In the overall analysis, no association of *EPHX1* Tyr113His with risk for breast cancer was found (CC *vs* TT, OR = 1.122, 95%CI = 0.750-1.677, P = 0.575; CT *vs* TT, OR = 0.908, 95%CI = 0.805-1.024, P = 0.115; dominant model, OR = 0.926, 95%CI = 0.827-1.037, P = 0.184; recessive model, OR = 1.184, 95%CI = 0.785-1.787, P = 0.421) (Figure 3, Table 3). Similarly, there was no association for the risk of breast cancer in Caucasians and Asians (Table 3).

Sensitive analysis and test for publication bias

Sensitivity analysis was performed in our meta-analysis. Upon omitting studies one at a time, the results of reanalyses for the *EPHX1* Tyr113His polymorphism and lung cancer and breast cancer became stable, indicating that our meta-analysis results were reliable and robust (data not shown).

Table 4. Main result of the meta-analysis Tyr113His relation with lung cancer.

Contrast Model	Studies	Odds ratio		P[b]	I^2 (%)	Model
		OR (95%CI)	P[a]			
Total studies						
C *vs* T	16	0.920 (0.818-1.036)	0.169	0.003	56.20%	Random[c]
CC *vs* TT	16	0.888 (0.753-1.047)	0.158	0.013	49.50%	Fixed[d]
CT *vs* TT	16	0.865 (0.730-1.025)	0.095	0.002	58.10%	Random
CC+TC *vs* TT	16	0.876 (0.748-1.027)	0.103	0.003	57.00%	Random
CC *vs* TC+TT	16	0.973 (0.834-1.136)	0.729	0.044	41.10%	Fixed
Caucasians						
C *vs* T	7	0.815 (0.702-0.946)	0.007	0.03	56.90%	Random
CC *vs* TT	7	0.720 (0.580-0.895)	0.003	0.141	37.80%	Fixed
CT *vs* TT	7	0.794 (0.656-0.962)	0.018	0.047	53.00%	Random
CC+TC *vs* TT	7	0.774 (0.638-0.940)	0.01	0.025	58.50%	Random
CC *vs* TC+TT	7	0.793 (0.643-0.978)	0.03	0.329	13.20%	Fixed
Asians						
C *vs* T	5	1.159 (1.006-1.335)	0.042	0.38	4.80%	Fixed
CC *vs* TT	5	1.391 (1.046-1.850)	0.023	0.449	0.00%	Fixed
CT *vs* TT	5	1.066 (0.631-1.801)	0.812	0.001	79.20%	Random
CC+TC *vs* TT	5	1.177 (0.788-1.760)	0.426	0.011	69.20%	Random
CC *vs* TC+TT	5	1.421 (1.103-1.829)	0.006	0.647	0.00%	Fixed
Africans						
C *vs* T	3	0.793 (0.615-1.023)	0.074	0.768	0.00%	Fixed
CC *vs* TT	3	0.509 (0.229-1.134)	0.099	0.165	44.40%	Fixed
CT *vs* TT	3	0.834 (0.612-1.137)	0.251	0.553	0.00%	Fixed
CC+TC *vs* TT	3	0.792 (0.586-1.069)	0.128	0.743	0.00%	Fixed
CC *vs* TC+TT	3	0.594 (0.164-2.153)	0.428	0.131	50.80%	Random

[a]Pooled P value; [b]P value for heterogeneity test; [c]random-effects model; [d]fixed-effects model.

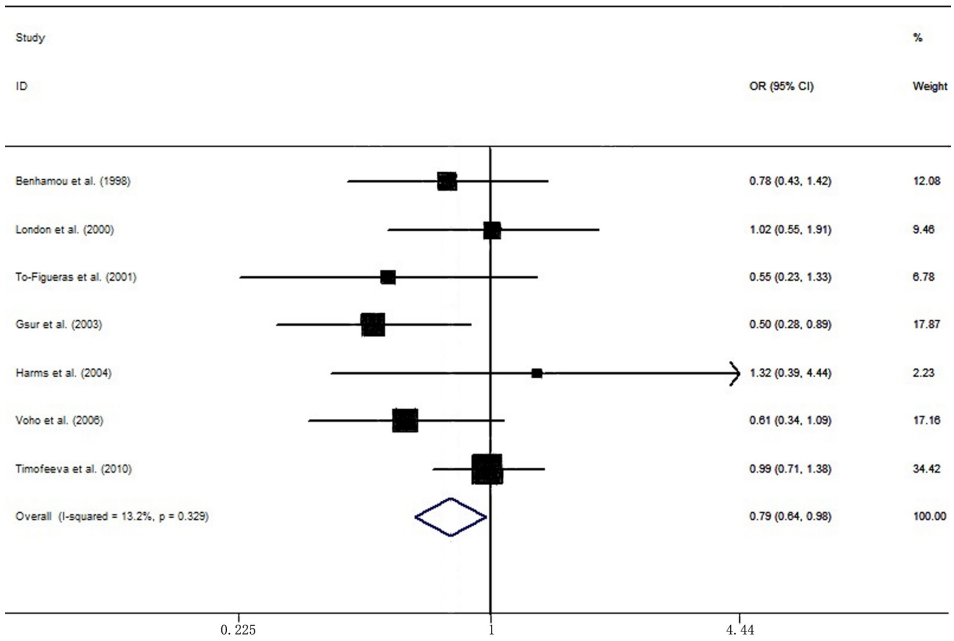

Figure 2. Forest plots for the *EPHX1* Tyr113His polymorphism and risk of lung cancer in Caucasians using the fixed-effect recessive model (CC *vs* CT+TT).

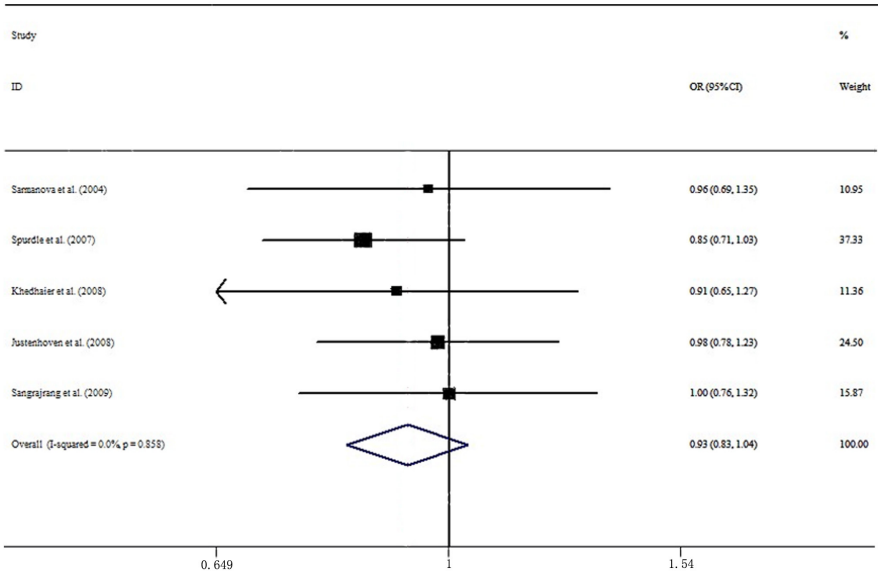

Figure 3. Forest plots for the *EPHX1* Tyr113His polymorphism and risk of breast cancer in all studies using the fixed-effect dominant model (CC+CT *vs* TT).

Estimation of publication bias was determined using the Begg and Egger tests. For all studies, the Egger test indicated no evidence of publication bias for lung cancer (CC *vs* TT Egger's test, P = 0.691; CT *vs* TT Egger's test, P = 0.734; recessive model, Egger's test, P = 0.579; dominant model, Egger's test, P = 0.975) or for breast cancer (CC *vs* TT Egger's test, P = 0.065; CT *vs* TT Egger's test, P = 0.263; recessive model, Egger's test, P = 0.090; dominant model, Egger's test, P = 0.369) (Begg's data not shown).

DISCUSSION

EPHX1 is a crucial enzyme in xenobiotic metabolism, which plays an important role in both the activation and detoxification of PAHs and aromatic amines (Liu et al., 2012). The *EPHX1* Tyr113His mutation may modify the susceptibility to lung and breast cancers.

The overall OR for the pooled studies revealed no statistically significant association between the Tyr113His polymorphism and lung cancer. Stratified analyses were performed by ethnicity, and no significant association with lung cancer was found for the *EPHX1* Tyr113His polymorphism in Africans and mixed ethnicity subjects. However, our meta-analysis indicated that the Tyr113His polymorphism increases the risk of lung cancer in Asians, but decreases the risk in Caucasians. A recent meta-analysis showed similar results (Wang et al., 2013), although some studies were excluded because they deviated from HWE. Lee et al. (2002) suggested a decreased risk for lung cancer with the exon 3 His/His genotype, which was partially consistent with our results. However, the results remain controversial and inconclusive. This may be due to gene-gene interactions that show significant differences for various ethnicities. Furthermore, gene-environment interactions may play an important role in the susceptibility to lung cancer. PAH and tobacco-specific nitrosamines or other substrates have been suggested to be associ-

ated with the genotype His113His. An imbalance in carcinogen metabolism may increase the susceptibility to lung cancer (Tilak et al., 2011). In contrast, low activity of the His113 allele because of conversion is decreased, decreasing lung cancer susceptibility (Voho et al., 2006).

For breast cancer, this is the first systematic review to investigate the association between the *EPHX1* Tyr113His polymorphism and breast cancer. No significant association was observed between these factors under any of the genetic models examined. de Assis et al. (2002) first reported that there was no significant association between the *EPHX1* Tyr113His polymorphism and breast cancer with menopausal or smoking status. Spurdle et al. (2007) suggested that there was a decreased risk associated with the *EPHX1* CC genotype. However, Khedhaier et al. (2008) showed that the *EPHX1* Tyr113His homozygous mutant genotype was significantly associated with breast cancer, particularly in premenopausal patients. This may have been due to low sample size or some other potentially confounding factors such as smoking status, menopausal status, occupation, or lifestyle. Overall, the carcinogenic mechanism is not completely clear.

The Begg and Egger tests did not reveal any publication bias in this meta-analysis, indicating that our meta-analysis conclusions are credible. Heterogeneity significantly affects the results of meta-analysis, and therefore exploring the source of heterogeneity is very important. When we performed stratified analyses by ethnicity, heterogeneity was clearly decreased. This may be an important source of heterogeneity.

Several limitations should be noted for our meta-analysis. First, our results were based on unadjusted estimates, and a well-designed study should be adjusted by age, smoking status, occupation, and lifestyle, among other factors. Insufficient information can cause serious confounding bias. Second, the sample size in our study was very small, and therefore the results should be interpreted with caution. Future studies involving larger samples are recommended to clarify the association. Third, different genotyping methods, such as matrix-assisted laser desorption ionization-time-of-flight mass spectrometry and polymerase chain reaction-restriction fragment length polymorphism, may affect the results. Finally, we did not conduct further studies regarding gene-gene and gene-environment interactions, which may play an important role in lung cancer and breast cancer susceptibility.

In conclusion, this meta-analysis indicated that the *EPHX1* Tyr113His polymorphism is associated with an increased risk of lung cancer in Asians, whereas it is associated with a decreased risk in Caucasians. In addition, we found no evidence for an association between the *EPHX1* Tyr113His polymorphism and breast cancer risk. Because our data is limited, a larger sample size should be examined using case-control studies for further confirmation.

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