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Quantitative assessment of the influence of EPHX1 gene polymorphisms and cancer risk: a meta-analysis with 94,213 subjects

Xiaoqin Yang[1*], Yubing Wang[1] and Guiping Wang[2*]

Abstract

Purpose: Previous studies investigating the association between EPHX1 polymorphisms (Tyr113His and His139Arg) and cancer risk have yielded inconsistent results. This meta-analysis was performed to derive a more precise estimation of relationship between two EPHX1 polymorphisms and risk of different types of cancer.

Methods: Data were extracted from relevant studies detected by a systematic literature search. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association between EPHX1 polymorphisms and cancer risk.

Results: This meta-analysis carefully collected 99 studies on these two polymorphisms and cancer risk published up to March 2014, consisting of 45 studies (20,091 cases and 27,396 controls) for Tyr113His and 54 studies (19,437 cases and 27,289 controls) for His139Arg. The results in overall population did not show any significant association between these two polymorphisms and cancer risk for all genetic models. However, EPHX1 Tyr113His homozygote individuals have a significantly increased risk of cancer among Asians (homozygote model: OR =1.46, 95% CI=1.05–2.03; recessive model: OR =1.39, 95% CI =1.10–1.76) and mixed population (homozygote model: OR =1.17, 95% CI =1.02–1.34; recessive model: OR =1.17, 95% CI =1.02–1.33), but not Caucasians.

Conclusion: His/His genotype of EPHX1 Tyr113His polymorphism is a risk factor for developing caner for Asian and mixed population, while no evidence was found for the association between the EPHX1 His139Arg polymorphism and increased cancer risk.

Keywords: EPHX1 polymorphisms, Meta-analysis, Cancer risk

Background

Xenobiotic catalytic pathway is an important defense mechanism against carcinogenesis [1]. As a critical biotransformation enzyme of this pathway, microsomal epoxide hydrolase (EPHX1) plays a key role in the detoxification of potential carcinogens from endogenous compounds as well as exogenous chemicals, which ultimately convert them into less toxic metabolites [2-5].

The EPHX1 gene is located on chromosome 1q42 with 9 exons and 8 introns. Functional studies have shown that two common polymorphic sites in the gene affecting EPHX1 enzyme activity. The tyrosine to histidine substitution in exon 3 (Tyr113His, site: T337C, dbSNP: rs1051740) sharply decreases its enzyme activity by nearly 40%, whereas the histidine to arginine substitution in exon 4 (His139Arg, site: A415G, dbSNP: rs2234922) could increase the enzyme activity by approximately 25% [6]. Given the significance of EPHX1 in eliminating carcinogenicity of toxic compounds like epoxides, it could be proposed that these two functional polymorphisms may lead to individual variations of xenobiotic detoxification and further influence susceptibility to chemical carcinogen-induced cancers.

Over the past two decades, a number of studies have been conducted to investigate the relationship between EPHX1 polymorphisms and cancer in different populations. However, the results of these studies are conflicting rather than conclusive. Several previous meta-analyses were flawed in their lack of sufficient data or there were

* Correspondence: sirxqyang@gmail.com; docgpwang@163.com
[1]Department of bioinformatics, School of Life Science and Technology, Tongji University, Shanghai 200092, People's Republic of China
[2]Department of Pharmacy, College of Health sciences, Guangzhou Medical University, Guangzhou 510180, People's Republic of China

methodological problems. One meta-analysis by Li et al. found that no significant association between EPHX1 polymorphisms (Tyr113His and His139Arg) and increased risk of cancers [7]. However, several studies [8-10] included in this meta-analysis were incorrectly classified according to source of controls, which may lead to an inaccurate result. Some recent studies did not evaluate the deviations from Hardy–Weinberg equilibrium (HWE) in control subjects [11-13], which could bias the estimates of genetic effects in genetic association studies and meta-analysis [14]. Since that date, several more studies have emerged to assess the relationship between the Tyr113His and/or His139Arg polymorphisms of the EPHX1 gene and susceptibility to a variety of cancers. Given the new information, we systematically evaluated the effect of these two polymorphisms on cancer risk in an updated meta-analysis with increased statistical power in order to get a more precise and reliable assessment of the association.

Materials and methods

Search strategy

A comprehensive literature search was performed using PubMed database for relevant articles published (last search: March 14, 2014) with the following terms: ((“epoxide hydrolase 1”) OR EPHX1) AND (((polymorphism) OR (SNP)) OR variant)) AND ((((neoplasm) OR cancer) OR carcinoma) OR leukemia). All the references of retrieved articles and supplementary data were checked when key information relevant to the meta-analysis was missing.

Inclusion criteria

All studies were included if they met the following criteria: (1) case–control study; (2) studies to evaluate the association between EPHX1 gene polymorphisms (Tyr113His and His139Arg) and risk of cancer; (3) sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI); (4) full-text in English available and (5) more than 100 patients. When the same population was included in several publications, only the most complete one was included in this meta-analysis.

Data extraction

Data were carefully evaluated and extracted from the eligible studies by two investigators independently according to the inclusion criteria listed above. The following characters were collected from eligible studies: first author’s name, year of publication, ethnicity (categorized as Asian, Caucasian, African, or mixed), source of control groups (population-based [PB], hospital-based [HB], family-based [FB] or unknown), genotype frequency of cases and controls, and the results of Hardy-Weinberg equilibrium (HWE) test. When it came to discrepancy between two investigators, another investigator was invited to discuss and check the data until a consensus was reached.

Statistical analysis

The departure from the Hardy-Weinberg equilibrium for the control group in each study was assessed with Pearson's goodness-of-fit Chi-square test with 1 degree of freedom by a web-based program (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) and the violation of HWE was determined with a threshold of $p < 0.05$. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the EPHX1 gene polymorphisms and cancer susceptibility. Pooled ORs were performed for dominant model (aa + Aa vs. AA, a was for the minor allele and A was for the major allele), recessive model (aa vs. Aa + AA), homozygote comparison (aa vs. AA), heterozygote comparison (Aa vs. AA), and additive model (a vs. A), respectively. Heterogeneity among pooled studies were evaluated by the Chi-square-based Cochran’s Q test [15] and I^2 statistics [16]. To be more conservative, heterogeneity was considered to be present when the Cochran’s Q-test P-value was less than 0.1, then random-effects model (the DerSimonian and Laird method) [17] was utilized, otherwise, fixed-effects model was used (the Mantel-Haenszel method) [18]. In addition, inconsistency across studies was quantified by means of I^2 statistic, with $I^2 < 25\%$, 25-75%, and >75% considered to represent low, moderate and high degree of heterogeneity, respectively [16]. Stratification analyses were performed to test the effects of cancer types, source of control, ethnicity and smoking status, respectively. To explore the source of heterogeneity among the studies of this meta-analysis, a multivariate meta-regression analysis subjected to 10,000 permutations was undertaken to explore the possible sources of heterogeneity. The following study characteristics were included as covariates in the meta-regression analysis: ethnicity, source of control, cancer types. Sensitivity analysis was carried out through omitting individual study in turn to check the consistency of the results. Publication bias was evaluated by visual inspection of the Begg’s funnel plots [19] and the Egger’s linear regression ($P < 0.05$ was considered a significant publication bias) [20]. All statistical tests were performed with metafor [21] and meta (http://cran.r-project.org/web/packages/meta/) packages of R (version 3.0.1), using two-sided p-values.

This meta-analysis followed the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [22] (Additional file 1: Table S1).

Results

Study characteristics

The initial literature search through PubMed database yielded 192 published articles. Totally, when reviewed in full-text, 4 were not concerned with Tyr113His or His139Arg polymorphisms in EPHX1 gene, 37 were not cancer risk studies, 1 was not published in English, 1 was not provided in full text, 7 were not case–control studies, 30 were no usable reported data, and 19 were meta-analysis or reviews; all these publications were excluded. Among the remaining 87 articles, studies presented separate OR by different polymorphisms, cancer types or ethnicity, and each of them was considered separately for pooling analysis. Furthermore, 32 studies not in HWE and 39 with less 100 patients were also deleted. Hence, 45 studies [8-10,23-63] for Tyr113His polymorphism (20,091 cases and 27,396 controls) and 54 studies [8-10,24-26,28,29,32,34-45,47-51,53,55-61,63-81] for His139Arg polymorphism (19,437 cases and 27,289 controls) were included eventually. Genotype distributions in the controls of all selected studies are in agreement with HWE. The flow of study selection was shown in Figure 1, and the main characteristics of eligible studies were summarized (Additional file 2: Table S2 and Additional file 3: Table S3).

Quantitative synthesis

The pooled results of meta-analysis for the association between EPHX1 polymorphisms (Tyr113His and His139Arg) and cancer susceptibility are shown in Tables 1 and 2. Heterogeneity across studies must be considered because it may affect the strengths of the meta-analysis. Significant heterogeneity was observed in some comparisons for both EPHX1 Tyr113His and His139Arg polymorphisms. Thus, random-effect model was used when heterogeneity identified.

For Tyr113His polymorphism, overall, no significantly elevated cancer risk could be observed in all genetic models (Table 1. homozygote model: OR = 1.05, 95% CI = 0.95–1.16; heterozygote model: OR = 0.94, 95% CI = 0.88–1.01; additive model: OR = 1.00, 95% CI = 0.95–1.05; dominant model: OR = 0.96, 95% CI = 0.90–1.03, Figure 2; recessive model: OR = 1.08, 95% CI = 0.99–1.18). When stratified by ethnicity, the significantly increased cancer risks were found among Asian population (homozygote model: OR = 1.46, 95% CI = 1.05–2.03; recessive model: OR = 1.39, 95% CI = 1.10–1.76) and Mixed population (homozygote model: OR = 1.17, 95% CI = 1.02–1.34; recessive model: OR = 1.17, 95% CI = 1.02–1.33). Stratified analyses by cancer types, smoking status and source of controls indicated no evidence of significant association between Tyr113-His polymorphism and the cancer risk. Furthermore, individuals carrying Tyr/His or His/His genotype have a significantly reduced risk of lung cancer (heterozygote model: OR = 0.80, 95% CI = 0.65-0.98; dominant model: OR = 0.81, 95% CI = 0.68–0.98).

With respect to His139Arg polymorphism, similarly, the combined results did not show any association with the elevated risk of cancer for all genetic models (homozygote model: OR = 1.05, 95% CI = 0.93–1.18; heterozygote model: OR = 0.96; 95% CI = 0.91–1.01; additive model: OR = 0.99, 95% CI = 0.94–1.04; dominant model: OR = 0.97, 95% CI = 0.92–1.03, Figure 3; recessive model: OR = 1.02, 95% CI = 0.93–1.13). When stratified according to cancer types, no significant association with increased cancer risk was demonstrated in all subgroups for overall population. However, the result suggested a decreased risk for blood cancers (additive model: OR = 0.91, 95% CI = 0.83–0.99; dominant model: OR = 0.90, 95% CI = 0.81–0.99) and colorectal cancer (heterozygote model: OR = 0.92; 95% CI = 0.85–0.99). In the subgroup analysis by source of controls, smoking status and ethnicity, no significant association with cancer risk was observed in all subgroups (Table 2).

Meta-regression and sensitivity analyses

Heterogeneity is a potential issue that may affect the interpretation of the results. As for Tyr113His polymorphism,

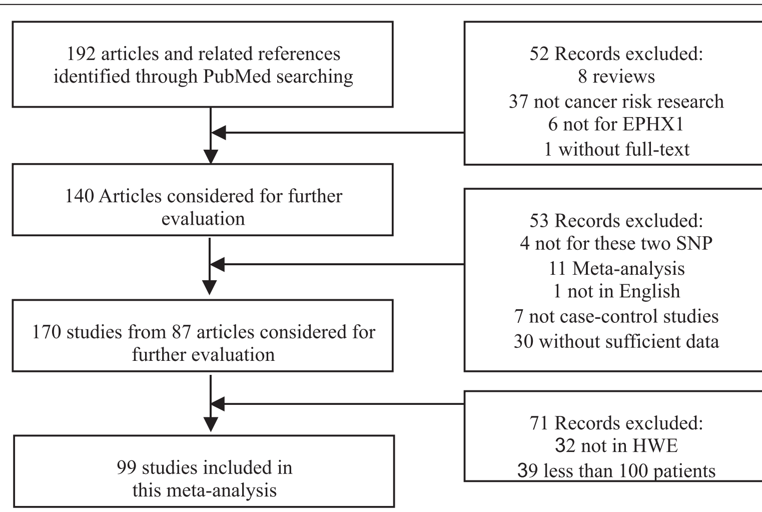

Figure 1 The flow diagram of the literature search and the study selection.

Table 1 Overall and stratified meta-analyses of the association between the EPHX1 Tyr113His polymorphism and cancer risk

Variables	No[a]	Case/control	Homozygote comparison			Heterozygote comparison			Dominant model			Recessive model			Additive model		
			OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)
Total	45	20091/27396	1.05(0.95 ~ 1.16)	0.37	0.00(50.8)	0.94(0.88 ~ 1.01)	0.08	0.0(54.0)	0.96(0.90 ~ 1.03)	0.26	0.0(56.8)	1.08(0.99 ~ 1.18)	0.08	0.0(37.4)	1.00(0.95 ~ 1.05)	0.94	0.0(57.7)
Cancer type																	
Blood	7	2419/2319	1.05(0.76 ~ 1.46)	0.76	0.03(56.1)	0.89(0.73 ~ 1.01)	0.24	0.06(49.8)	0.92(0.75 ~ 1.13)	0.42	0.02(60.3)	**1.17(0.96 ~ 1.41)**	**0.12**	**0.14(37.3)**	0.97(0.82 ~ 1.15)	0.76	0.01(65.9)
Prostate	3	1706/1192	1.54(0.57 ~ 4.16)	0.86	0.00(88.9)	1.31(0.82 ~ 2.01)	0.26	0.00(79.7)	1.39(0.80 ~ 2.41)	0.24	0.00(87.1)	1.29(0.62 ~ 2.65)	0.50	0.0(82.2)	1.27(0.81 ~ 1.97)	0.30	0.00(89.7)
Esophageal	3	593/1086	**1.09(0.78 ~ 1.51)**	**0.63**	**0.19(40.5)**	1.01(0.52 ~ 1.93)	0.99	0.00(86.0)	1.08(0.63 ~ 1.84)	0.79	0.00(81.6)	**1.16(0.85 ~ 1.58)**	**0.34**	**0.20(38.4)**	1.09(0.84 ~ 1.41)	0.51	0.07(61.9)
Colorectal	9	5512/6787	**0.98(0.86 ~ 1.11)**	**0.75**	**0.85(0.0)**	**1.00(0.93 ~ 1.08)**	**0.98**	**0.79(0.0)**	**0.99(0.93 ~ 1.07)**	**0.98**	**0.80(0.0)**	**0.98(0.87 ~ 1.11)**	**0.76**	**0.87(0.0)**	**1.00(0.94 ~ 1.05)**	**0.87**	**0.84(0.0)**
Other	7	2425/2872	1.20(0.90 ~ 1.59)	0.22	0.06(50.4)	1.00(0.81 ~ 1.24)	0.99	0.01(66.7)	1.04(0.84 ~ 1.29)	0.74	0.00(69.4)	**1.18(0.98 ~ 1.42)**	**0.08**	**0.40(2.8)**	1.06(0.91 ~ 1.23)	0.45	0.01(65.5)
Lung	9	2065/5429	0.80(0.57 ~ 1.12)	0.20	0.00(62.5)	0.80(0.65 ~ 0.98)	0.03	0.00(65.0)	0.81(0.68 ~ 0.98)	0.03	0.01(62.5)	0.91(0.66 ~ 1.25)	0.57	0.01(61.7)	0.87(0.75 ~ 1.01)	0.08	0.0(65.5)
Head and neck	3	825/821	**1.04(0.74 ~ 1.47)**	**0.81**	**0.98(0.0)**	**0.87(0.71 ~ 1.07)**	**0.19**	**0.82(0.0)**	**0.90(0.74 ~ 1.10)**	**0.30**	**0.85(0.0)**	**1.11(0.80 ~ 1.54)**	**0.53**	**0.99(0.0)**	**0.96(0.83 ~ 1.12)**	**0.61**	**0.91(0.0)**
Breast cancer	4	4546/6890	**1.02(0.90 ~ 1.17)**	**0.73**	**0.15(43.0)**	**0.99(0.91 ~ 1.07)**	**0.73**	**0.60(0.0)**	**0.99(0.92 ~ 1.07)**	**0.35**	**0.99(0.0)**	1.14(0.89 ~ 1.46)	0.31	0.05(62.6)	**1.00(0.97 ~ 1.03)**	**0.93**	**0.68(0.0)**
Source of control																	
PB	31	16035/23111	1.03(0.93 ~ 1.14)	0.54	0.06(29.7)	0.97(0.92 ~ 1.03)	0.28	0.10(25.1)	0.98(0.93 ~ 1.04)	0.45	0.06(30.4)	**1.03(0.96 ~ 1.11)**	**0.38**	**0.14(21.9)**	1.00(0.95 ~ 1.04)	0.91	0.03(34.7)
HB	11	3517/3627	0.94(0.77 ~ 1.15)	0.56	0.08(40.9)	0.81(0.69 ~ 0.96)	0.01	0.00(59.4)	0.85(0.74 ~ 0.98)	0.03	0.03(49.4)	1.05(0.86 ~ 1.27)	0.66	0.05(45.7)	0.93(0.84 ~ 1.03)	0.16	0.05(45.3)
Ethnicity																	
Caucasian	26	11757/18447	**0.94(0.87 ~ 1.03)**	**0.17**	**0.29(11.7)**	**0.93(0.87 ~ 1.00)**	0.04	0.09(28.7)	0.93(0.87 ~ 1.00)	0.04	0.06(31.7)	**0.97(0.89 ~ 1.05)**	**0.45**	**0.49(0.0)**	0.96(0.91 ~ 1.00)	0.07	0.08(29.6)
Mixed	7	5645/5502	**1.17(1.02 ~ 1.34)**	**0.03**	**0.42(0.7)**	**1.00(0.93 ~ 1.09)**	**0.96**	**0.57(0.0)**	**1.03(0.96 ~ 1.11)**	**0.44**	**0.53(0.0)**	**1.17(1.02 ~ 1.33)**	**0.02**	**0.44(0.0)**	**1.05(0.99 ~ 1.11)**	**0.11**	**0.43(0.0)**
Asian	11	2534/3205	1.46(1.05 ~ 2.03)	0.04	0.00(75.1)	1.04(0.77 ~ 1.40)	0.81	0.00(81.7)	1.16(0.88 ~ 1.53)	0.30	0.00(56.8)	1.39(1.10 ~ 1.76)	0.01	0.01(60.7)	1.19(0.99 ~ 1.42)	0.05	0.0(79.4)
Smoking status																	
Smoker	9	1786/2114	**0.99(0.80 ~ 1.23)**	**0.95**	**0.42(1.4)**	0.85(0.66 ~ 1.10)	0.21	0.03(52.1)	0.89(0.71-1.11)	0.30	0.05(47.8)	**1.07(0.87 ~ 1.31)**	**0.56**	**0.43(0.5)**	**0.97(0.88 ~ 1.08)**	**0.60**	**0.13(36.7)**
Non-smoker	8	1357/1947	1.45(0.89 ~ 2.37)	0.14	0.00(71.4)	1.19(0.88 ~ 1.60)	0.27	0.01(63.6)	1.27(0.92 ~ 1.74)	0.14	0.00(71.7)	1.29(0.92~1.82)	0.14	0.05(50.0)	1.23(0.97 ~ 1.57)	0.09	0.00(75.8)

PB: population based; HB: hospital based. P^b: P-values for heterogeneity from Q test; I^2 refers to the proportion of total variation owing to between-study heterogeneity.
Bold font marks where fixed effect model used.

Table 2 Overall and stratified meta-analyses of the association between the EPHX1 His139Arg polymorphism and cancer risk

Variables	No[a]	Case/control	Homozygote comparison			Heterozygote comparison			Dominant model			Recessive model			Additive model		
			OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)	OR (95% CI)	P	P^b (I^2)
Total	54	19437/27289	1.05(0.93 ~ 1.18)	0.73	0.09(21.3)	0.96(0.91 ~ 1.01)	0.15	0.02(31.5)	0.97(0.92 ~ 1.03)	0.30	0.00(40.1)	**1.02(0.93 ~ 1.13)**	**0.66**	**0.23(12.0)**	0.99(0.94 ~ 1.04)	0.57	0.00(44.9)
Cancer type																	
Other	11	3160/4581	**0.94(0.75 ~ 1.20)**	**0.64**	**0.53(0.0)**	**0.97(0.87 ~ 1.10)**	**0.51**	**0.56(0.0)**	**0.97(0.87 ~ 1.06)**	**0.47**	**0.53(0.0)**	**0.96(0.76 ~ 1.21)**	**0.71**	**0.53(0.0)**	**0.97(0.89 ~ 1.05)**	**0.50**	**0.46(0.0)**
Blood	9	2929/3629	**0.87(0.67 ~ 1.13)**	**0.29**	**0.90(0.0)**	**0.90(0.81 ~ 1.00)**	**0.05**	**0.25(21.4)**	**0.90(0.81 ~ 0.99)**	**0.04**	**0.47(0.0)**	**0.90(0.70 ~ 1.17)**	**0.44**	**0.82(0.0)**	**0.91(0.83 ~ 0.99)**	**0.04**	**0.80(0.0)**
Esophageal	3	593/1081	1.30(0.50 ~ 3.38)	0.59	0.07(61.8)	1.02(0.65 ~ 1.62)	0.92	0.03(72.6)	1.06(0.66 ~ 1.73)	0.80	0.01(77.3)	1.30(0.54 ~ 3.13)	0.56	0.10(56.5)	1.10(0.71 ~ 1.69)	0.67	0.01(79.2)
Colorectal	10	5552/7089	1.14(0.85 ~ 1.53)	0.39	0.02(53.5)	**0.92(0.85 ~ 0.99)**	**0.03**	**0.97(0.0)**	**0.94(0.87 ~ 1.01)**	**0.09**	**0.73(0.0)**	1.17(0.87 ~ 1.58)	0.29	0.02(54.0)	**0.97(0.91 ~ 1.03)**	**0.28**	**0.11(36.8)**
Lung	14	4767/8411	1.14(0.83 ~ 1.56)	0.42	0.02(49.3)	1.10(0.94 ~ 1.27)	0.24	0.00(63.4)	1.10(0.93 ~ 1.29)	0.27	0.00(71.9)	**0.97(0.80 ~ 1.17)**	**0.76**	**0.16(27.2)**	1.07(0.93 ~ 1.24)	0.36	0.00(74.1)
Head and neck	4	1035/1075	**1.28(0.81 ~ 2.02)**	**0.30**	**0.99(0.0)**	**0.84(0.70 ~ 1.01)**	**0.06**	**0.69(0.0)**	**0.88(0.73 ~ 1.05)**	**0.14**	**0.70(0.0)**	**1.35(0.85 ~ 2.13)**	**0.20**	**1.0(0.0)**	**0.94(0.81 ~ 1.01)**	**0.41**	**0.78(0.0)**
Breast cancer	3	1401/1423	**1.04(0.69 ~ 1.59)**	**0.85**	**0.49(0.0)**	**0.91(0.77 ~ 1.07)**	**0.04**	**0.66(0.0)**	**0.92(0.79 ~ 1.08)**	**0.30**	**0.67(0.0)**	**1.09(0.93 ~ 1.13)**	**0.70**	**0.49(0.0)**	**0.95(0.83 ~ 1.09)**	**0.44**	**0.66(0.0)**
Source of control																	
HB	16	5010/5638	**1.14(0.93 ~ 1.41)**	**0.21**	**0.99(0.0)**	**0.96(0.88 ~ 1.05)**	**0.37**	**0.20(22.7)**	**0.98(0.90 ~ 1.06)**	**0.63**	**0.32(11.4)**	**1.17(0.95 ~ 1.44)**	**0.15**	**0.99(0.0)**	**1.00(0.94 ~ 1.08)**	**0.94**	**0.66(0.0)**
PB	36	14191/21351	1.04(0.89 ~ 1.22)	0.61	0.01(39.4)	0.96(0.90 ~ 1.03)	0.22	0.01(39.4)	0.97(0.90 ~ 1.04)	0.40	0.00(50.7)	1.04(0.90 ~ 1.21)	0.56	0.05(30.0)	0.99(0.92 ~ 1.05)	0.64	0.00(57.2)
Ethnicity																	
Asian	13	2957/3770	**0.97(0.75 ~ 1.27)**	**0.84**	**0.51(0.0)**	**0.99(0.89 ~ 1.11)**	**0.90**	**0.26(18.6)**	**0.99(0.89 ~ 1.10)**	**0.88**	**0.14(30.6)**	**0.98(0.76 ~ 1.28)**	**0.90**	**0.59(0.0)**	1.01(0.90 ~ 1.13)	0.90	0.09(37.1)
Caucasian	32	12294/17831	1.10(0.93 ~ 1.30)	0.26	0.03(34.8)	0.95(0.88 ~ 1.02)	0.18	0.01(44.0)	0.97(0.89 ~ 1.04)	0.39	0.00(52.8)	**1.07(0.95 ~ 1.21)**	**0.27**	**0.11(24.4)**	0.99(0.92 ~ 1.06)	0.71	0.00(57.3)
Mixed	7	3921/5262	**0.90(0.73 ~ 1.12)**	**0.35**	**0.81(0.0)**	**0.94(0.86 ~ 1.04)**	**0.22**	**0.43(0.0)**	**0.94(0.86 ~ 1.03)**	**0.16**	**0.69(0.0)**	**0.92(0.74 ~ 1.14)**	**0.45**	**0.71(0.0)**	**0.95(0.88 ~ 1.02)**	**0.15**	**0.93(0.0)**
African	2	265/426	0.81(0.22 ~ 2.96)	0.75	0.08(21.3)	**1.09(0.79 ~ 1.50)**	**0.60**	**0.78(0.0)**	**1.06(0.78 ~ 1.45)**	**0.69**	**0.46(0.0)**	0.78(0.23 ~ 2.73)	0.70	0.08(66.6)	**1.03(0.94 ~ 1.01)**	**0.84**	**0.22(34.7)**
Smoking status																	
Smoker	9	2331/2542	1.08(0.64 ~ 1.83)	0.77	0.01(61.5)	1.19(0.88 ~ 1.60)	0.27	0.00(76.6)	1.16(0.85 ~ 1.58)	0.35	0.00(79.9)	1.04(0.68~1.60)	0.86	0.06(46.8)	1.09(0.84 ~ 1.41)	0.52	0.00(80.1)
Non-smoker	8	1498/2336	**1.25(0.90 ~ 1.75)**	**0.19**	**0.67(0.0)**	**1.05(0.91 ~ 1.21)**	**0.49**	**0.78(0.0)**	**1.08(0.94 ~ 1.23)**	**0.30**	**0.71(0.0)**	**1.24(0.89 ~ 1.72)**	**0.21**	**0.71(0.0)**	**1.08(0.96 ~ 1.22)**	**0.19**	**0.60(0.0)**

PB: population based; HB: hospital based. P^b: P-values for heterogeneity from Q test; I^2 refers to the proportion of total variation owing to between-study heterogeneity.
Bold font marks where fixed effect model used.

Study	Case Events	Case Total	Control Events	Control Total	OR	95%−CI	W(random)
Benhamou 1998	68	150	108	172	0.49	[0.31; 0.77]	1.4%
London 2000	97	182	221	458	1.22	[0.87; 1.73]	2.0%
London 2000	49	155	89	242	0.79	[0.52; 1.22]	1.5%
Spurdle 2001	290	545	145	287	1.11	[0.84; 1.48]	2.4%
Soucek 2002	52	112	129	203	0.50	[0.31; 0.79]	1.3%
To−Figueras 2002	98	204	110	203	0.78	[0.53; 1.15]	1.7%
Gsur 2003	130	277	272	496	0.73	[0.54; 0.98]	2.4%
Wenghoefer 2003	138	280	153	289	0.86	[0.62; 1.20]	2.1%
Sarmanov.. 2004	122	237	163	311	0.96	[0.69; 1.35]	2.0%
Clavel 2005	98	218	56	105	0.71	[0.45; 1.14]	1.3%
Landi 2005	186	363	155	323	1.14	[0.84; 1.54]	2.3%
Tranah 2005	224	443	452	891	0.99	[0.79; 1.25]	2.9%
Robien 2005	804	1593	969	1960	1.04	[0.91; 1.19]	3.9%
De Roos 2006	575	1103	452	921	1.13	[0.95; 1.35]	3.5%
De Roos 2006	282	595	259	527	0.93	[0.74; 1.18]	2.9%
van der Logt 2006	180	365	197	391	0.96	[0.72; 1.27]	2.4%
Voho 2006	94	227	1054	2083	0.69	[0.52; 0.91]	2.5%
Skjelbred 2007	50	102	167	299	0.76	[0.48; 1.19]	1.4%
Mittal 2007	104	130	78	140	3.18	[1.85; 5.48]	1.1%
Jain 2008	79	107	187	320	2.01	[1.24; 3.26]	1.3%
Lacko 2008	223	429	223	419	0.95	[0.73; 1.25]	2.6%
Rosenberger 2008	45	100	51	100	0.79	[0.45; 1.37]	1.0%
Srivastava 2008	80	106	82	160	2.93	[1.71; 5.02]	1.1%
Justenhoven 2008	309	605	314	609	0.98	[0.78; 1.23]	3.0%
Sangrajrang 2009	414	557	362	487	1.00	[0.76; 1.32]	2.5%
Ockenga 2009	200	367	375	679	0.97	[0.75; 1.25]	2.7%
Cleary 2010	602	1163	667	1292	1.01	[0.86; 1.18]	3.6%
Hlavata 2010	274	495	264	495	1.08	[0.84; 1.39]	2.7%
Ihsan 2010	87	142	130	185	0.67	[0.42; 1.06]	1.4%
Soucek 2010	56	116	60	113	0.82	[0.49; 1.39]	1.2%
Timofeeva 2010	295	611	639	1266	0.92	[0.76; 1.11]	3.3%
MARIE−GENICA Consortium 2010	1612	3147	2812	5483	1.00	[0.91; 1.09]	4.3%
Ihsan 2011	106	188	196	290	0.62	[0.42; 0.91]	1.8%
Bonaventure 2011	238	493	222	485	1.11	[0.86; 1.42]	2.7%
Tilak 2011	113	175	188	322	1.30	[0.89; 1.90]	1.8%
Balaji 2011	86	157	83	132	0.72	[0.45; 1.15]	1.3%
Chauhan 2011	70	120	125	202	0.86	[0.54; 1.37]	1.4%
Catsburg 2012	666	1382	347	747	1.07	[0.90; 1.28]	3.4%
Dura 2012	166	344	286	581	0.96	[0.74; 1.26]	2.6%
Jang 2012	234	451	452	884	1.03	[0.82; 1.29]	2.9%
Sivonova 2012	108	194	176	305	0.92	[0.64; 1.32]	1.9%
Tumer 2012	78	167	79	189	1.22	[0.80; 1.86]	1.6%
Wang 2012	136	303	170	358	0.90	[0.66; 1.22]	2.3%
Conesa−Zamora 2013	88	206	101	214	0.83	[0.57; 1.23]	1.7%
Nisa 2013	457	685	539	778	0.89	[0.71; 1.11]	3.0%
Random effects model		**20091**		**27396**	**0.96**	**[0.90; 1.03]**	**100%**

Heterogeneity: I−squared=56.8%, tau−squared=0.023, p<0.0001

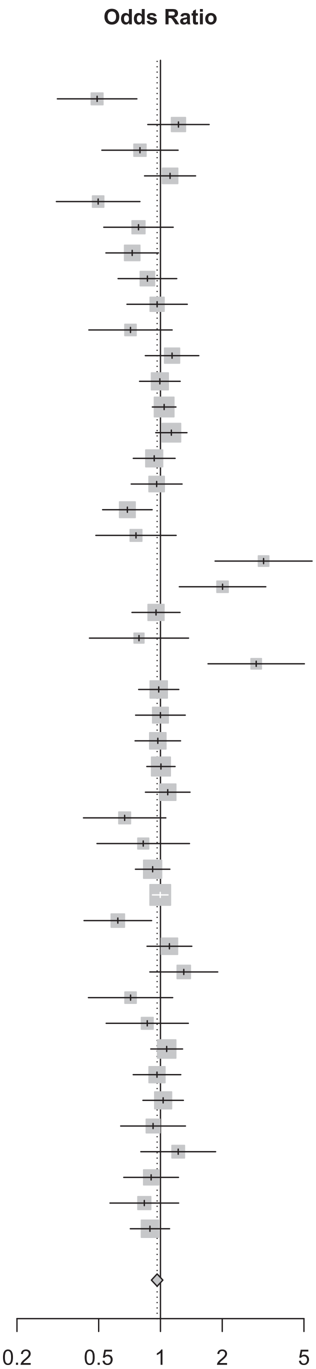

Figure 2 Forest plot for association of EPHX1 Tyr113His polymorphism and cancer risk (dominant model, CT + CC vs. TT).

the heterogeneity was observed in all genetic models and the detailed data are shown in Table 1. With respect to His139Arg polymorphism (Table 2), the heterogeneity was detected in homozygote comparison, heterozygote model, dominant model and additive model. We therefore explored the source of heterogeneity by cancer type, ethnicity, and source of control by meta-regression in all comparisons with significant heterogeneity. As a result, for Tyr113His polymorphism, source of control may be the major source of heterogeneity in homozygote model (P = 0.024), heterozygote model (P = 0.000), dominant model (P = 0.002) and additive model (P = 0.005), but not recessive model. However, for His139Arg polymorphism, none of these variables showed statistically significant

Study	Case Events	Case Total	Control Events	Control Total	OR	95%−CI	W(random)
Benhamou 1998	56	150	51	172	1.41	[0.89; 2.25]	1.1%
Harrison 1999	25	101	56	203	0.86	[0.50; 1.49]	0.9%
London 2000	57	182	156	458	0.88	[0.61; 1.28]	1.6%
London 2000	85	155	123	242	1.17	[0.78; 1.76]	1.4%
To−Figueras 2001	56	175	61	187	0.97	[0.63; 1.51]	1.2%
Tiemersma 2001	47	110	82	184	0.93	[0.58; 1.49]	1.1%
Sarmanov.. 2001	71	224	163	453	0.83	[0.59; 1.16]	1.8%
To−Figueras 2002	59	204	69	203	0.79	[0.52; 1.20]	1.3%
Zhao 2002	72	166	52	157	1.55	[0.98; 2.43]	1.2%
Baxter 2002	98	291	105	257	0.74	[0.52; 1.04]	1.7%
Gsur 2003	91	277	160	496	1.03	[0.75; 1.41]	2.0%
Wenghoefer 2003	103	280	115	289	0.88	[0.63; 1.23]	1.8%
Sarmanov.. 2004	91	238	130	310	0.86	[0.61; 1.21]	1.7%
Tranah 2004	317	901	446	1235	0.96	[0.80; 1.15]	3.4%
Clavel 2005	78	219	43	105	0.80	[0.49; 1.29]	1.1%
Landi 2005	111	361	96	321	1.04	[0.75; 1.44]	1.9%
Tranah 2005	130	444	303	884	0.79	[0.62; 1.02]	2.6%
Park 2005	61	182	129	363	0.91	[0.63; 1.33]	1.5%
Robien 2005	542	1593	693	1960	0.94	[0.82; 1.08]	4.0%
Agudo 2006	86	242	329	944	1.03	[0.77; 1.38]	2.1%
De Roos 2006	386	1091	345	916	0.91	[0.76; 1.09]	3.4%
van der Logt 2006	130	371	145	414	1.00	[0.75; 1.34]	2.1%
Voho 2006	48	227	670	2078	0.56	[0.40; 0.79]	1.8%
Skjelbred 2007	45	101	109	299	1.40	[0.89; 2.21]	1.1%
Mittal 2007	56	130	62	140	0.95	[0.59; 1.54]	1.1%
Kiss 2007	163	500	171	500	0.93	[0.72; 1.21]	2.4%
Figueroa 2008	367	1087	349	1011	0.97	[0.81; 1.16]	3.4%
Jain 2008	36	107	133	320	0.71	[0.45; 1.13]	1.1%
Lacko 2008	143	429	150	419	0.90	[0.68; 1.19]	2.2%
Rosenberger 2008	33	101	30	99	1.12	[0.61; 2.03]	0.7%
Zienolddiny 2008	198	318	160	361	2.07	[1.52; 2.82]	2.0%
Srivastava 2008	40	106	68	160	0.82	[0.50; 1.36]	1.0%
Boccia 2008	66	210	94	245	0.74	[0.50; 1.09]	1.5%
Justenhoven 2008	210	601	236	624	0.88	[0.70; 1.11]	2.7%
Gold 2009	95	260	284	736	0.92	[0.68; 1.23]	2.1%
Silveira 2009	47	125	90	300	1.41	[0.91; 2.18]	1.2%
Rotunno 2009	618	1858	710	2026	0.92	[0.81; 1.05]	4.0%
Sangrajrang 2009	158	562	136	489	1.02	[0.77; 1.33]	2.3%
Hlavata 2010	198	495	205	495	0.94	[0.73; 1.22]	2.5%
Ihsan 2010	55	142	47	185	1.86	[1.16; 2.98]	1.1%
Soucek 2010	45	116	45	122	1.08	[0.64; 1.83]	0.9%
Timofeeva 2010	235	613	406	1160	1.15	[0.94; 1.41]	3.1%
Ihsan 2011	67	188	78	290	1.50	[1.01; 2.24]	1.4%
Bonaventure 2011	153	493	197	528	0.76	[0.58; 0.98]	2.4%
Tilak 2011	72	175	135	322	0.97	[0.67; 1.41]	1.6%
Balaji 2011	66	157	55	132	1.02	[0.64; 1.62]	1.1%
Chauhan 2011	45	120	87	202	0.79	[0.50; 1.26]	1.1%
Chauhan 2012	89	230	72	199	1.11	[0.75; 1.65]	1.4%
Dura 2012	122	344	212	576	0.94	[0.71; 1.25]	2.3%
Jang 2012	155	451	316	882	0.94	[0.74; 1.19]	2.7%
Sivonova 2012	70	194	85	305	1.46	[0.99; 2.15]	1.5%
Turner 2012	47	167	59	190	0.87	[0.55; 1.37]	1.2%
Chung 2013	42	188	73	363	1.14	[0.74; 1.75]	1.3%
Nisa 2013	200	685	253	778	0.86	[0.68; 1.07]	2.8%
Random effects model		**19437**		**27289**	**0.97**	**[0.92; 1.03]**	**100%**

Heterogeneity: I−squared=40.1%, tau−squared=0.0152, p=0.0016

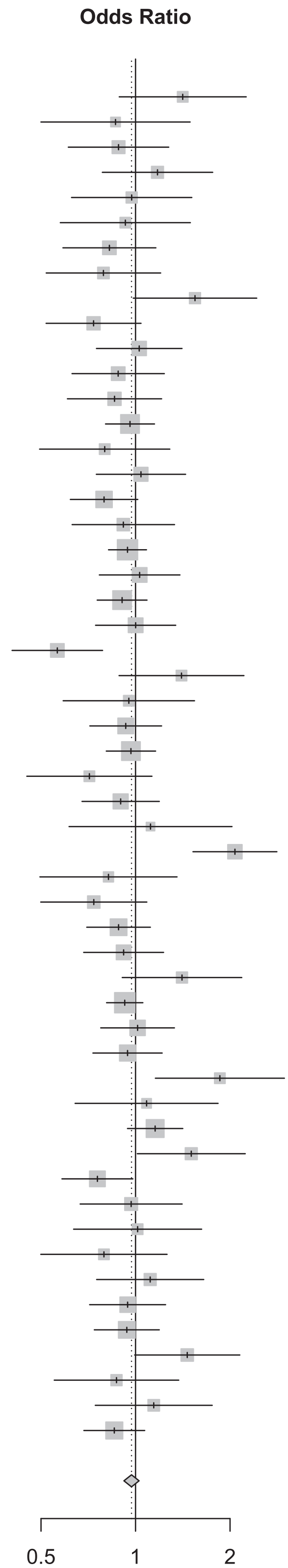

Figure 3 **Forest plot for association of EPHX1 His139Arg polymorphism and cancer risk (dominant model, GA + GG vs. AA).**

associations in multivariate meta-regression model ($P > 0.05$), suggesting factors mentioned above could not explain the heterogeneity among studies.

The influences of each individual study on the overall ORs for Tyr113His/His139Arg polymorphisms were evaluated. The results showed the pooled ORs of these two polymorphisms were not materially altered by the omission of any individual study, suggesting credibility for the conclusions (Additional file 4: Figure S1 and Additional file 5: Figure S2).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of funnel plots (Figures 4 and 5) did not reveal any evidence of asymmetry. The statistical results of Egger's test still did not show publication bias for Tyr113His polymorphism (additive model: $P = 0.146$; homozygote comparison: $P = 0.620$; heterozygote model: $P = 0.189$; dominant model: $P = 0.054$; recessive model: $P = 0.915$) and His139Arg polymorphism (additive model: $P = 0.125$; homozygote comparison: $P = 0.847$; heterozygote model: $P = 0.255$; dominant model: $P = 0.111$; recessive model: $P = 0.153$).

Discussion

With increased knowledge of human gene functions and the architecture of genetic variations, it has become clear that individual variation in genetic backgrounds, such as single nucleotide polymorphism, could substantially influence cancer risk with specific environmental exposure. However, evidences from studies of genetic epidemiology were usually too conflicting to draw conclusions. Meta-analysis shed light on objective and

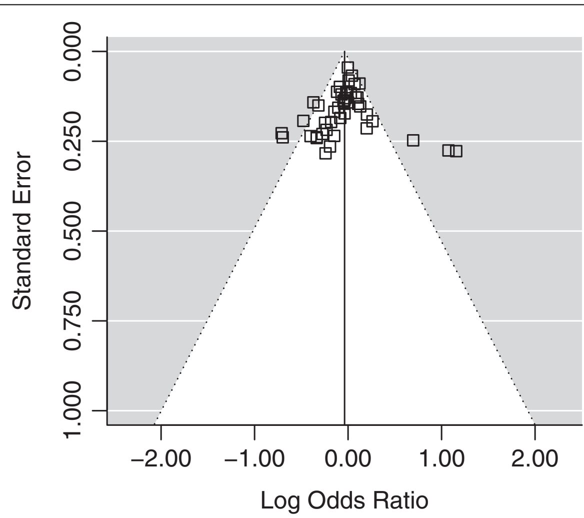

Figure 4 **Begg's funnel plot for publication bias in studies on EPHX1 Tyr113His polymorphism and cancer (dominant model, CT + CC vs. TT).**

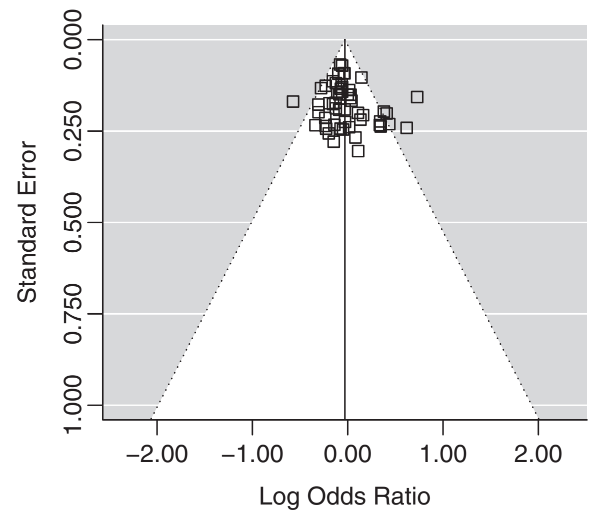

Figure 5 **Begg's funnel plot for publication bias in studies on EPHX1 His139Arg polymorphism and cancer (dominant model, GA + GG vs. AA).**

comprehensive assessment of the associations between polymorphisms and cancer risks. Several single nucleotide polymorphisms were identified as cancer risk factors for specific populations by means of meta-analysis [82-84].

The genetic polymorphisms of EPHX1, Tyr113His and His139Arg, may affect enzyme activity involved in general oxidative defenses against a number of environmental substances [6]. Variations in the expression and activity level of EPHX1 as a result of such polymorphisms could cause individual variations of detoxifying capability, then further influence the risk of chemical carcinogen-induced cancers [85]. The findings from some previous studies suggested that genetic polymorphism in EPHX1 has important roles in the development of cancers [55,86-88]. However, others reported no association of EPHX1 polymorphisms with risk of cancers [24,26,34,45]. This inconsistency may be due to tremendous difference in sample size, diverse ethnic background, sampling bias, publication bias, or inadequate statistical power. The benefits of meta-analysis include a larger number of participants, different geographic locations, and the possibility of inclusion of a wider range of population groups, all of which could derive a more precise estimation and further increase the generalizability of the results.

In this meta-analysis, 99 eligible case–control studies including 39,528 cases and 54,685 controls were included to provide a comprehensive assessment of the relationship between EPHX1 polymorphisms and cancer risk. The results revealed that neither EPHX1 Tyr113His polymorphism, nor His139Arg polymorphism have significant association with the cancer susceptibility for all comparing models when all studies were accumulated together. Further stratified analysis according to cancer types, smoking status, or source of controls did not suggest a significantly increased risk. Moreover, His139Arg polymorphism might play a potentially protective role in the development of blood cancer based on dominant model and additive model, and colorectal cancer by heterozygous model. Meanwhile Tyr113His polymorphism showed possible protective effect on risk for lung cancer by heterozygote model and dominant model.

Stratified analysis by ethnicity allowed for assessing the ethnic differences in the association of cancer risk. As for His139Arg polymorphism, no significant associations were found in any genetic model among all populations. However, with respect to the Tyr113His polymorphism, an increased risk of cancer based on homozygote and recessive model could be observed in Asian and mixed population, indicating there is an obvious race-specific effect in the association. It was consistent with the results from two recent meta-analyses for hepatocellular cancer [89] and lung cancer [90]. Further subgroup analysis by the cancer types in Asian and Mixed population was not performed due to the limited data for individual cancer type according to our inclusion criteria.

Heterogeneity between studies should be noted because it may potentially affect the strengths of the meta-analysis. In the current meta-analysis, significance heterogeneity was observed for both EPHX1 Tyr113His and His139Arg polymorphisms. Thus, random-effect models were used if significant heterogeneity was identified. Furthermore, multivariate meta-regression analysis involving covariates, such as source of control, cancer type, ethnicity, was performed to explore the source of heterogeneity. The results from meta-regression emphasized that the heterogeneity of polymorphism Tyr113His was associated with source of control in homozygote model, heterozygote model, dominant model and additive model, but not recessive model. Neither cancer type, nor ethnicity was found to be the source of heterogeneity. However, as for His139Arg, results indicated none of these three covariates could be the main source of the between-study heterogeneity. It suggested that some other confounding factors, such as environmental exposures, gene-gene interaction, and lifestyle might lead to the heterogeneity. Large studies for both polymorphisms with comprehensive classification information are needed to facilitate the subgroup analysis according to these factors, which is unavailable for present meta-analysis because of inadequate information from our original data sources.

Although our result is suggestive, there are still some limitations inherited from the published studies and our analysis strategies. First, the present conclusion was drawn based on unadjusted estimates, while a more precise analysis with the necessary adjustment by other covariates including age, lifestyle, gene–gene interactions and environmental factors should be conducted when more detailed individual data were available. Second, although some results were significant, the p–values were on the borderline, i.e. slightly less than 0.05. Further large and well-designed studies are required for confirmation. Finally, most studies were from Caucasian population, it is critical that larger and well-designed multi-centric studies based on Asians and other racial-ethnic groups should be performed to re-evaluate the association. In spite of these, our meta-analysis also had some advantages. First, the quality of case–control studies included in current meta-analysis was satisfactory and met our inclusion criterion, ensuring the quality of our results. Second, the sensitivity analysis showed that no individual study materially altered the pooled ORs indicating statistical stableness and robustness of the current meta-analysis. In addition, no publication bias for the association between these two polymorphisms and cancer risk could be observed, which further confirmed the credibility.

In conclusion, our investigations suggested that the EPHX1 His139Arg polymorphism might not contribute to the susceptibility of all cancer types for overall population, whereas Tyr113His polymorphism might be associated with increased risk of cancer in the Asian and mixed population. Larger well-designed epidemiological studies with different cancer types, ethnically diverse populations and functional evaluations are warranted to confirm our findings.

Additional files

Additional file 1: Table S1. PRISMA Checklist for this meta-analysis.

Additional file 2: Table S2. Principal characteristics of the studies included on EPHX1 Tyr113His polymorphism.

Additional file 3: Table S3. Principal characteristics of the studies included on EPHX1 His139Arg polymorphism.

Additional file 4: Figure S1. Sensitivity analysis of the summary OR of the association between EPHX1 Tyr113His polymorphism and cancer susceptibility in dominant model. Results were computed by omitting each study in turn. Random-effects model was used. The two ends of the dotted lines represent the 95% confidence interval.

Additional file 5: Figure S2. Sensitivity analysis of the summary OR of the association between EPHX1 His139Arg polymorphism and cancer susceptibility in dominant model. Results were computed by omitting each study in turn. Random-effects model was used. The two ends of the dotted lines represent the 95% confidence interval.

Abbreviations

HWE: Hardy–Weinberg equilibrium; EPHX1: Epoxide hydrolase 1; SNP: Single nucleotide polymorphism; OR: Odds ratio; CI: Confidence interval.

Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

YXQ and WGP conceived and designed the study, YXQ, WYB and WGP participated in selecting study, extracting data and performing the statistical analysis. YXQ and WGP were involved in drafting and revising the manuscript. All authors read and approved the final manuscript.

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