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EPHX1 Tyr113His and His139Arg polymorphisms in esophageal cancer risk: a meta-analysis

X. Tan[1]*, W.W. He[1]*, Y.Y. Wang[1], L.J. Shi[2] and M.W. Chen[1]

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

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ABSTRACT. Microsomal epoxide hydrolase 1 (EPHX1) is an important biological phase II metabolic enzyme that is extensively involved in the metabolism of diverse environmental carcinogens such as polycyclic aromatic hydrocarbons and heterocyclic amines. Many articles have reported the association between EPHX1 (Tyr113His and His139Arg) polymorphisms and esophageal cancer risk, but the results are controversial. This study aimed to identify the association between EPHX1 (Tyr113His and His139Arg) polymorphisms and esophageal cancer risk by meta-analysis. The odds ratio (OR) with 95% confidence interval (95%CI) was used to evaluate the strength of the associations. Heterogeneity was estimated by the chi-square-based Q-statistic test and the P value. Meanwhile, the random-effect or fixed-effect model was used according to the between-study heterogeneity. Begg's funnel plot and the Egger test were performed to assess the publication bias of articles. Finally, 8 case-control studies involving 1158 cases and 1868 controls

for the Tyr113His polymorphism and 7 case-control studies involving 901 cases and 1615 controls for the His139Arg polymorphism were included in this meta-analysis. Meta-analysis showed that the Tyr113His polymorphism was a stronger power trend towards risk for esophageal cancer using a recessive model (CC versus CT+TT, OR = 1.204, 95%CI = 1.001-1.450, P = 0.049). However, no significant associated risk was found between the His139Arg polymorphism and esophageal cancer. These findings suggest that the Tyr113His polymorphism might be a stronger power trend towards risk for esophageal cancer. However, no evidence was found for the association between the EPHX1 His139Arg polymorphism and esophageal cancer risk.

Key words: EPHX1; Polymorphism; Esophageal cancer; Meta-analysis

INTRODUCTION

Among human cancers, esophageal cancer (EC), with a 5-year survival rate of less than 20%, is regarded as one of the most common lethal malignancies worldwide. In particular, in the "esophageal cancer belt", which stretches from North Central China westward through Central Asia to northern Iran, the incidence is quite high (Akbari et al., 2006). The incidence and mortality of EC have been listed as eighth and sixth, respectively, of all cancers (Jemal et al., 2008, 2011). The main histological subtypes are squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). The epidemiology is different; ESCC is widely distributed in Southern Russia and Southeastern Africa and Asia, and adenocarcinoma is widely distributed in Western Europe, Australia, and North America. In the "esophageal cancer belt", the most common histology of the squamous cell cancer has even reached 90% (Wheeler and Reed, 2012). Alcohol, smoking, age, gender, racial or ethnic group, areca chewing, and gastroesophageal reflux disease may be risk factors of EC (Yu et al., 1988; Farrow et al., 2000). However, not all exposed persons develop EC, suggesting that genetic factors may play a role in the development of EC.

Human carcinogens first pass Phase I metabolism enzyme activation to produce widely and highly active intermediates. Next, the active intermediates are subjected to detoxification by Phase II enzymes. Microsomal epoxide hydrolase (EPHX1) is the phase-II xenobiotic biotransformation enzyme that plays a dual effect in the detoxification and activation of procarcinogens (Casson et al., 2006). The Tyr113His (exon 3) and His139Arg (exon 4) EPHX1 variants have been identified in the protein sequences. These mutations correspond to 2 genetic polymorphisms of T/C (Tyr113His) in exon 3 and A/G (His139Arg) in exon 4, respectively (Hassett et al., 1994). In exon 3, the 113His allele of the enzyme results in a decrease in the activity of approximately 50% (slow allele), whereas the exon 4 Arg139 allele causes an increase in the activity of 25% (fast allele) (Hassett et al., 1994; Pinarbasi et al., 2010). The variations of the EPHX1 enzyme activity may lead to inter-individual variations in the susceptibility to mutagenic, carcinogenic, or teratogenic processes.

The EPHX1 gene is located in the long arm of chromosome 1 and is extensively expressed in the lungs, upper gastrointestinal tract, and other organs (Voho et al., 2006). Given the know variations of the EPHX1 gene, the polymorphisms may strongly affect cancer risk,

such as lung cancer, colorectal cancer, upper aerodigestive tract cancers, and ovarian cancer (Harrison et al., 1999; Jourenkova-Mironova et al., 2000; Spurdle et al., 2001; Park et al., 2005).

Recent studies have suggested that T113C and A139G polymorphisms might clarify the causes and events correlated with EC, but the results were conflicting and inconclusive. Therefore, a meta-analysis was conducted to investigate the relationship between T113C and A139G polymorphisms and susceptibility to EC.

MATERIAL AND METHODS

Search strategy and selection criteria

A comprehensive systematic bibliographic search was performed using PubMed, Embase, and Cochrane for all medical publications until November 1, 2012, with the following terms: microsomal epoxide hydrolase 1, mEH, EPHX1, Tyr113His, exon 3, codon 113, T113C, rs1051740, His139Arg, exon4, codon 139, A139G, rs2234922, polymorphism, variant; and "esophagus" or "esophageal" combined with "carcinoma", "cancer", "squamous cell", or "adenocarcinoma". All human studies fulfilled the following criteria: 1) full-text articles, 2) using case-control study, 3) investigation of EPHX1 Tyr113His and His139Arg polymorphisms and esophageal cancer, 4) sufficient data for estimating an odds ratio (OR) with a 95% confidence interval (95%CI), 5) sufficient genotype data can be obtained, 6) and report written in English.

Data extraction

Study selection and data extraction were performed independently by 2 investigators (X. Tan and W.W. He). Cases of disagreement were discussed and then resolved. If the 2 investigators could not resolve the case, a third investigator (M.W. Chen) made the decision. The data items included first author, year of publication, country, ethnicity, sample size, diagnostic criteria, source of controls, study design, genotyping method, and different genotype counts in all studies.

Statistical analysis

The pooled risk OR and 95%CI of EC associated with Tyr113His and His139Arg polymorphisms were calculated for each study. To avoid using a specific genetic model and thus outcome bias, at least 3 possible genotypes were compared in the meta-analysis of genetic associations. For example, for Tyr113His, we estimated the OR of a cancer associated with a codominant model (CC versus TT, CT versus TT), dominant model (CC+CT versus TT), and recessive model (CC versus CT+TT).

Between-study heterogeneity was estimated by the chi-square-based Q-statistic test and the P value (Higgins et al., 2003). If $P > 0.1$ and $I^2 < 25\%$, study heterogeneity did not exist. If there was no heterogeneity, the overall gene effect was evaluated by the fixed-effect model according to the Mantel-Haenszel method (Mantel and Haenszel, 1959). When $I^2 > 50\%$ or $P < 0.1$, the heterogeneity was considered to be statistically significant, and sensitivity analysis was used for excluding studies that had potential bias; the random-effect model according to the DerSimonian and Laird method was applied if heterogeneity still existed (Lau et al., 1997).

Potential publication bias was investigated by Begg's funnel plot, and the unweighted funnel plot was applied using a regression test (Peters et al., 2006). To evaluate the effects of covariance subgroup analyses were performed due to geographical and ethnic differences as well as the pathological type of EC. Ethnic subgroups were divided into Caucasian and Asian, while pathological subgroups were categorized into ESCC and EAC. All analyses were performed using Stata version 11.1 (StataCorp., College Station, TX, USA). All of the P values were two-sided, and $P < 0.05$ was considered to be statistically significant.

RESULTS

Characteristics of relevant studies

Our search strategy and inclusion criteria (the publication selection process is shown in Figure 1), 8 studies were identified with full-text articles that remained with association between EPHX 1 (Tyr113His and His139Arg) polymorphisms and EC (Zhang et al., 2003; Wang et al., 2003; Casson et al., 2003, 2006; Lin et al., 2006; Jain et al., 2008; Ihsan et al., 2010; Dura et al., 2012). Among the included articles, 7 articles provided separate data for the EPHX1 Tyr113His and EPHX1 His139Arg polymorphisms (Wang et al., 2003; Casson et al., 2003, 2006; Lin et al., 2006; Jain et al., 2008; Ihsan et al., 2010; Dura et al., 2012), which were treated as 2 separate studies. Finally, 8 articles including a total of 1158 cases and 1868 controls included studies of the Tyr113His polymorphism, whereas 7 articles including 901 cases and 1615 controls included studies of the His139Arg polymorphism.

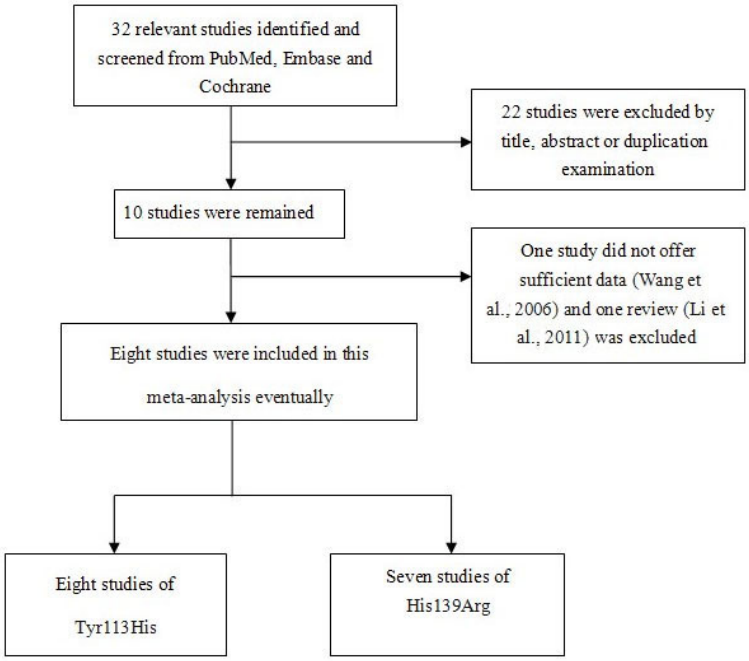

Figure 1. Publication selection process of this meta-analysis.

To evaluate the effects of covariance, subgroup analyses were performed. For 1 study (Dura et al., 2012), including 2 pathologic types, ESCC and EAC, the data were collected separately and served as independent studies in the subgroup analyses. Thus, there were 9 studies on the Tyr113His polymorphism and 8 studies on the His139Arg polymorphism for ESCC and EAC. However, in the ethnic subgroup analysis, there were 5 studies in Asian (Zhang et al., 2003; Wang et al., 2003; Lin et al., 2006; Jain et al., 2008; Ihsan et al., 2010) and 3 studies in Caucasian (Casson et al., 2003, 2006; Dura et al., 2012). Among the 8 studies, a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay was performed in 5 studies (Zhang et al., 2003; Wang et al., 2003; Lin et al., 2006; Jain et al., 2008; Ihsan et al., 2010). The remaining 3 studies used PCR (Casson et al., 2003, 2006; Dura et al., 2012). The source of the controls are hospital-based, and the diagnostic criteria are listed in Table 1. The genotype distributions of all studies are shown in Table 2.

Meta-analysis results

The main results of the meta-analysis of the association between Tyr113His and His139Arg polymorphisms and EC risk are shown in Tables 3 and 4, respectively.

For the Tyr113His polymorphism, although the statistical significance was not obvious, we found a stronger power trend towards risk for EC (C versus T, OR = 1.139, 95%CI = 0.942-1.377, P = 0.178; CC versus TT, OR = 1.073, 95%CI = 0.867-1.329, P = 0.516; CT versus TT, OR = 0.934, 95%CI = 0.642-1.358, P = 0.720; recessive model CC versus CT+TT, OR = 1.204, 95%CI = 1.001-1.450, P = 0.049; dominant model CC+CT versus TT, OR = 1.066, 95%CI = 0.773-1.468, P = 0.697). To assess the covariance effects, ethnicity and histological typing were performed by subgroup analyses. However, in the ethnic subgroup analysis, no significant risk association was found for any genetic models between the EPHX1 Tyr113His polymorphism and Caucasian and Asian populations. We also did not detect any significant simultaneously association between the EPHX1 Tyr113His polymorphism and ESCC and EAC in the subgroup histological type analysis (Table 3).

Overall, the EPHX1 His139Arg polymorphism was not significantly associated with an increased risk of EC (G versus A, OR = 1.059, 95%CI = 0.908-1.236, P = 0.464; GG versus AA, OR = 1.340, 95%CI = 0.848-2.117, P = 0.210; AG versus AA, OR = 1.174, 95%CI = 0.806-1.712, P = 0.403; recessive model GG versus AG+AA, OR = 1.047, 95%CI = 0.727-1.506, P = 0.345; dominant model GG+AG versus AA, OR = 1.174, 95%CI = 0.821-1.679, P = 0.379). Similarly, in subgroup analyses for the His139Arg polymorphism, risk associated with EC was not found for either ethnicity (Caucasian and Asian) or histological type (ESCC and EAC) (Table 4).

Tests for heterogeneity, sensitivity, and publication bias

Using the recessive model, there was no obvious between-study heterogeneity observed for EPHX1. In contrast, using the codominant and dominant models, heterogeneity was obvious. Sensitivity analysis was performed in our meta-analysis. When we omitted every study at each time, the reanalysis results for the EPHX1 His139Arg polymorphism were stable; for the EPHX1 Tyr113His polymorphism, the result fluctuated somewhat, but there was still a risk for EC (data not show).

Table 1. Summary of the EPHX1 (Tyr113His and His139Arg) polymorphism with esophageal cancer (EC).

Investigator	Country	Race	Tyr113His		His139Arg		Characteristics		Source of controls	Method
			Case	Control	Case	Control	Case	Control		
Dura et al., 2012	Dutch	Caucasian	344	581	344	576	Only patients with a diagnosis of EC, as confirmed by a pathologist, were included in the study	Caucasian healthy controls were recruited from the same geographical area of the Netherlands after advertisement in local papers as described earlier. Controls were matched with the EC patients for age, ethnicity and gender	Population-based	PCR
Ihsan et al., 2010	India	Asian	142	185	142	185	Histopathologically confirmed patients with EC, from Dr. B. Borooah Cancer Institute (BBCI), Assam, India	A total of 185 unrelated, healthy controls were also included. The controls were recruited in the study if they did not have any disease or malignancy	Population-based	PCR-RFLP
Jain et al., 2008	India	Asian	107	320	107	320	Histopathologically confirmed subjects with EC, from Department of Gastroenterology and Radiotherapy, Sanjay Gandhi Post-Graduate Institute of Medical Sciences (SGPGIMS)	The controls were recruited in the study if they did not have any disease or malignancy. The patients and controls were mean matched for age and proportion matched for gender	Population-based	PCR-RFLP
Lin et al., 2006	Taiwan	Asian	145	352	145	352	One hundred and forty-five patients from three medical centers in Taiwan diagnosed with pathologically proven ESCC	Healthy controls from the preventive medicine department at each center on the same date	Hospital-based	PCR-RFLP
Casson et al., 2006	Canada	Caucasian	56	95	56	95	All cases underwent diagnostic esophago-gastroscopy with biopsy to confirm the diagnosis of esophageal adenocarcinoma	Controls were screened for GERD-related symptoms, a history of hiatus hernia, dyspepsia, antiacid use, previous malignancy or upper gastrointestinal surgery, and if negative, were asked to participate as controls	Hospital-based	PCR
Zhang et al., 2003	China	Asian	257	252			This study included patients with histologically confirmed esophageal squamous cell carcinomas	Two hundred and fifty-two healthy individuals without overt cancer, from the same hospital for physical examination in the same period	Hospital-based	PCR-RFLP
Wang et al., 2003	China	Asian	62	38	62	38	Sixty-two cases of esophageal squamous cell carcinoma, who were histopathologically confirmed in 1999	Thirty-eight subjects with matched age and gender frequencies were randomly selected as the control group from the same region during the field surveys between 1998 and 1999	Population-based	PCR-RFLP
Casson et al., 2003	Canada	Caucasian	45	45	45	49	1) Barrett's epithelium; 2) >75% tumor mass involving the tubular esophagus; 3) direct invasion of periesophageal tissues; 4) minimal gastric involvement; 5) clinical symptoms of esophageal obstruction (i.e., dysphagia)	Healthy volunteers from the same geographic region (southern Ontario). All controls remained tumor-free as of July 2002	Population-based	PCR

PCR = polymerase chain reaction; RFLP = restriction fragment length polymorphism.

Table 2. Genotype distribution of all studies in this meta-analysis.

Investigator	Tyr113His (case/control)			His139Arg (case/control)		
	CC	TC	TT	GG	AG	AA
Dura et al., 2012	30/58	136/228	178/295	11/25	111/187	222/364
Ihsan et al., 2010	38/34	49/96	55/55	7/2	48/45	87/138
Jain et al., 2008	13/31	66/156	28/133	7/17	29/116	71/187
Lin et al., 2006	42/105	51/140	52/107	0/0	28/65	117/287
Casson et al., 2006	34/42	16/34	6/19	35/55	20/33	1/7
Zhang et al., 2003	115/105	58/71	84/76	NA	NA	NA
Wang et al., 2003	17/5	22/10	23/23	1/1	11/5	50/32
Casson et al., 2003	26/21	10/20	9/4	28/34	16/8	1/7

NA = not available.

Table 3. Main results of the meta-analysis EPHX1 Tyr113His relationship with esophageal 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	8	1.073 (0.867-1.329)	0.092	0.516	0.934 (0.642-1.358)	0.001	0.720	1.066 (0.773-1.468)	0.002	0.697	1.204 (1.001-1.450)	0.286	0.049
Ethnicity													
Caucasian	3	0.994 (0.666-1.483)	0.108	0.977	0.814 (0.366-1.809)	0.088	0.613	0.990 (0.505-1.940)	0.115	0.976	1.185 (0.843-1.664)	0.201	0.328
Asian	5	1.107 (0.86-1.424)	0.107	0.432	0.991 (0.582-1.688)	0.001	0.973	1.118 (0.712-1.756)	0.001	0.627	1.213 (0.972-1.513)	0.286	0.087
Histopathology													
ESCC	6	1.081 (0.851-1.375)	0.160	0.523	0.956 (0.624-1.466)	0.002	0.838	1.057 (0.731-1.529)	0.003	0.767	1.188 (0.961-1.468)	0.465	0.111
EAC	3	1.014 (0.66-1.558)	0.111	0.948	0.829 (0.365-1.880)	0.082	0.653	1.011 (0.515-1.985)	0.118	0.975	1.213 (0.848-1.734)	0.121	0.290

EPHX1 Tyr113His; 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; 95%CI = 95% confidence interval; [a]P value for heterogeneity test; [b]the pool P value; ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma.

Table 4. Main results of the meta-analysis EPHX1 His139Arg relationship with esophageal cancer.

Variable	N	Arg/Arg *vs* His/His			Arg/His *vs* His/His			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	7	1.340 (0.848-2.117)	0.099	0.210	1.174 (0.806-1.712)	0.026	0.403	1.174 (0.821-1.679)	0.030	0.379	1.047 (0.727-1.506)	0.345	0.806
Ethnicity													
Caucasian	3	1.177 (0.650-2.132)	0.144	0.590	2.905 (0.521-16.215)	0.031	0.224	2.262 (0.535-9.563)	0.066	0.267	0.890 (0.583-1.359)	0.519	0.589
Asian	4	1.629 (0.796-3.334)	0.179	0.182	1.093 (0.691-1.727)	0.060	0.704	1.136 (0.712-1.811)	0.042	0.593	1.708 (0.833-3.503)	0.276	0.144
Histopathology													
ESCC	5	1.287 (0.705-2.347)	0.214	0.411	0.990 (0.671-1.46)	0.051	0.959	1.021 (0.683-1.527)	0.028	0.918	1.374 (0.753-2.509)	0.323	0.301
EAC	3	1.273 (0.674-2.406)	0.080	0.457	2.961 (0.577-15.195)	0.042	0.193	2.284 (0.589-8.865)	0.088	0.233	0.894 (0.576-1.385)	0.514	0.615

EPHX1 His139Arg; N = number of studies in each analysis; Dominant model = Arg/Arg + Arg/His *vs* His/His; Recessive model = Arg/Arg *vs* Arg/His + His/His; OR = odds ratio; 95%CI = 95% confidence interval; [a]P value for heterogeneity test; [b]the pool P value; ESCC = esophageal squamous cell carcinoma; EAC = esophageal adenocarcinoma.

Begg's funnel plot and the Egger test were performed to assess the publication bias of the articles. The results of both Begg and Egger tests did not show any evidence of publication bias (Tyr113His: CC *vs* TT Egger test, P = 0.134; TC *vs* TT Egger test, P = 0.937; recessive model, Egger test, P = 0.050, dominant model, Egger test, P = 0.525; His139Arg: GG *vs* AA Egger test, P = 0.125; TC *vs* TT Egger test, P = 0.123; recessive model, Egger test, P = 0.532, dominant model, Egger test, P = 0.141) (Begg test; data not show).

DISCUSSION

Our meta-analysis included 8 studies with a total of 1158 cases and 1868 controls that were used to evaluate the association between the Tyr113His polymorphism and EC; 7 studies including 901 cases and 1615 controls were used for the His139Arg polymorphism. Although the sample size is not sufficiently large, this is to our knowledge the first systematic review that has independently evaluated the relationship between the EPHX1 (Tyr113His and His139Arg) polymorphisms and EC. Our meta-analysis provided evidence that the Tyr113His polymorphism might play an important role in EC under a recessive model (OR = 1.204, 95%CI = 1.001-1.450, P = 0.049 < 0.05) (Figure 2). However, we found that the His139Arg polymorphism was not significantly associated with EC risk in the codominant, dominant, and recessive models (dominant model as show in Figure 3). No publication bias was revealed by the funnel plots, supporting our meta-analysis conclusions.

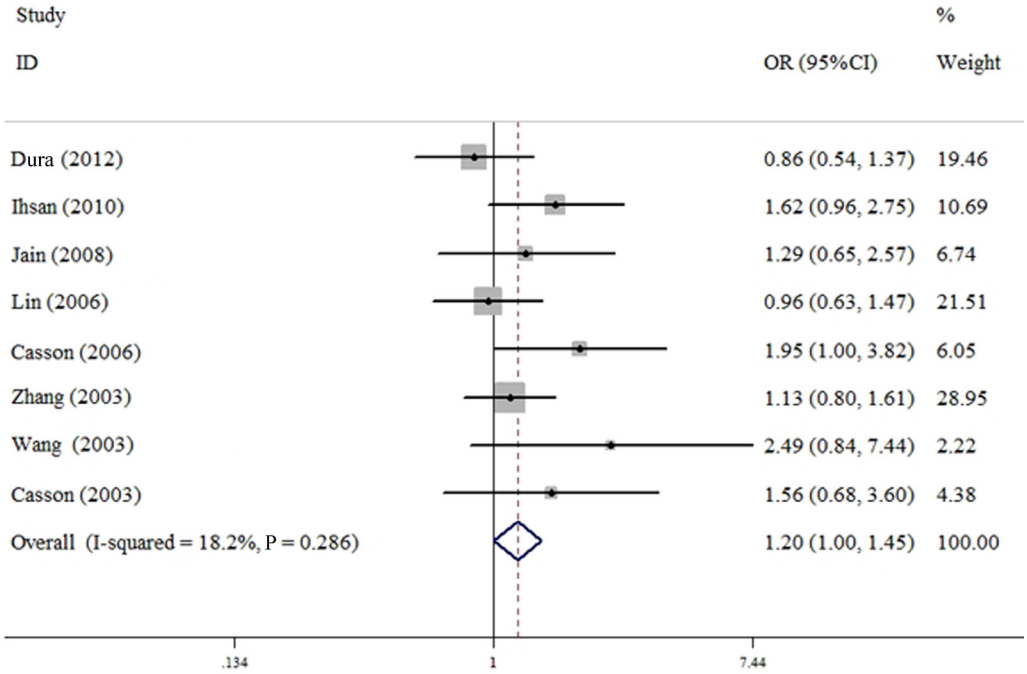

Figure 2. Forest plot describing the meta-analysis with a fixed-effect recessive model (CC *vs* TC+TT) for the association of the EPHX1 Tyr113His polymorphism with esophageal cancer. Each study is depicted with size inversely proportional to its variance, accompanied by the respective 95% confidence intervals.

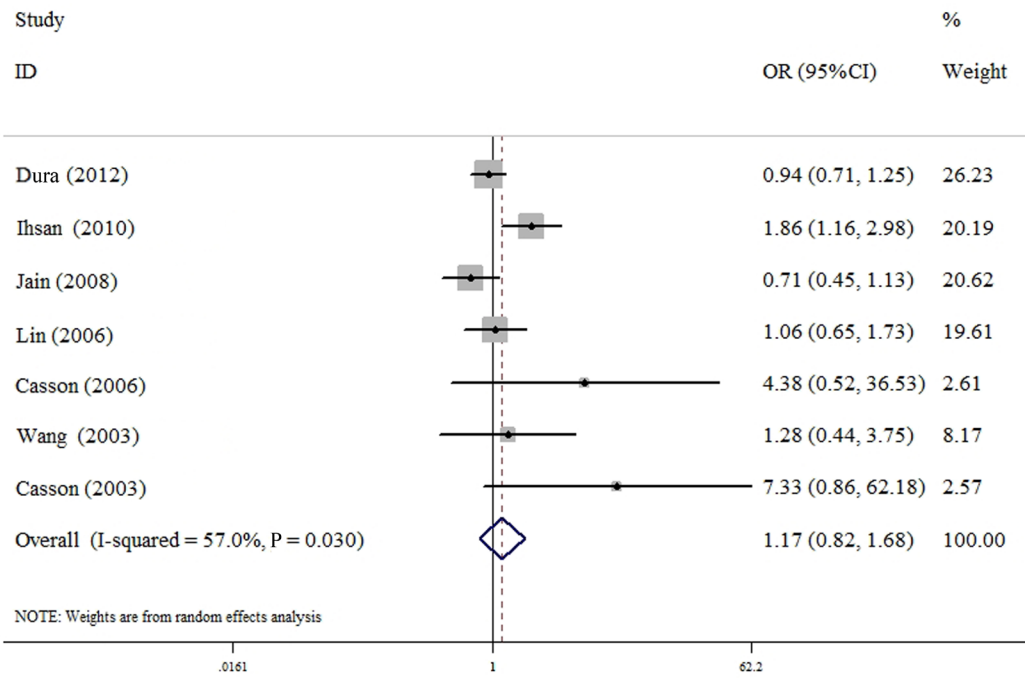

Figure 3. Forest plot describing the meta-analysis with a random-effect dominant model (GG+AG *vs* AA) for the association of the EPHX1 His139Arg polymorphism with esophageal cancer. Each study is depicted with size inversely proportional to its variance, accompanied by the respective 95% confidence interval.

EPHX1 is a crucial biotransformation enzyme, catalyzing the conversion of a series of xenobiotic epoxide substrates to more polar diol metabolites (Omiecinski et al., 2000). Because of the EPHX1 Tyr113His polymorphism, a slow 113His allele of the enzyme decreases the activity, which might decrease the detoxification of carcinogens, resulting in highly reactive intermediates and carcinogen-induced cancer (Kiyohara et al., 2006; Sivonova et al., 2012). Two studies (Wang et al., 2003; Jain et al., 2008) showed risk for association between the Tyr113His polymorphism and EC, whereas the others (Zhang et al., 2003; Casson et al., 2003, 2006; Lin et al., 2006; Ihsan et al., 2010; Dura et al., 2012) did not show any significant difference of developing EC. In addition, Ihsan et al. (2010) reported that the Tyr113His genotype was a protective factor in the Indian population. Our results indicated a correlation between the Tyr113His polymorphism and risk of EC.

In contrast to the Tyr113His polymorphism, His139Arg leads to an increased enzyme activity, which might promote more rapid detoxification of exogenous carcinogens. Three articles (Casson et al., 2003; Jain et al., 2008; Ihsan et al., 2010) indicated that the His139Arg polymorphism is associated with EC, whereas 4 studies revealed a contradictory result (Wang et al., 2003; Casson et al., 2006; Lin et al., 2006; Dura et al., 2012). According to our findings, this meta-analysis did not indicate a significant effect of the His139Arg polymorphism.

To prevent excessive evaluation of the true effect between the EPHX1 polymorphism and EC, we conducted subgroup analyses by ethnicity and histological type. We similarly found that EPHX1 (Tyr113His and His139Arg) polymorphism had no statistically significant

relationship with EC based on ethnicity and histological type. This lack of significant relationship may be due to the low sample size or some other potentially suspected factors such as smoking status, alcohol consumption, history of gastroesophageal reflux disease, and lifestyle, which influence our research. Although we did not find any such associations, we cannot eliminate the possibility that an association exists in certain subgroups of individuals.

Although we made considerable efforts to collect all available data to study EPHX1 (Tyr113His and His139Arg) polymorphism correlation with EC risk, some limitations existed. First, present research articles describing associations between EPHX1 polymorphisms and EC risk are few, and therefore, the sample of participants included in our meta-analysis is comparatively small. Second, the source of the controls did not differ. Healthy controls recruited from the same geographical area acted as the reference group for some studies, whereas other studies selected hospital patients without organic EC as the reference group. Furthermore, age, gender, smoking status, cancer type, and ethnicity were not consistent in all studied subjects. As stated above, these factors may be sources of heterogeneity. Finally, the EPHX1 gene might influence susceptibility to EC with other factors, but we did not conduct relative research, such as the gene-gene and gene-environment interactions.

In conclusion, this meta-analysis did not find any evidence for the association between the EPHX1 His139Arg polymorphism and EC risk in the overall studies. However, we found that although statistical significance was barely observed, there was a stronger power trend towards risk for the Tyr113His polymorphism and EC. Meanwhile, gene-gene and gene-environmental interactions on EC risk may be involved because most data were insufficient; therefore, further studies with larger sample size and well-designed and high-quality case-control studies are required to investigate the associations between EPHX1 polymorphisms and EC.

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