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Association Between CYP2C19 Polymorphisms and Esophageal Squamous Cell Carcinoma Risk in Asian Populations: A Systematic Review and Meta-analysis

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Abstract

Background: This meta-analysis was performed to evaluate the association between CYP2C19 gene polymorphisms and ESCC risk in Asian populations.

Methods: A literature search was performed in main medical publication databases for the association between CYP2C19 gene polymorphisms and ESCC risk, up to May 2020. A random/fixed-effects model was used to calculate the pooled odds ratios (OR) and 95% confidence intervals (CI) to evaluate the associations, considering multiple genetic models. And people were classified into three groups according to metabolizer phenotypes: (i) extensive metabolizers (EMs: *1/*1, *1/*2, *1/*3); (ii) intermediate metabolizers (IMs: *1/*2, *1/*3) and (iii) poor metabolizers (PMs: *2/*2, *2/*3, *3/*3).

Results: Eight studies with 1955 cases and 2754 controls were ultimately included that showed that individuals carrying the "A" allele of CYP2C19*2 G681A and AA genotype of CYP2C19*3 G636A were significantly associated with an increased ESCC risk (CYP2C19*2 A vs. G: OR = 1.823, 95% CI = 1.616-2.056; CYP2C19*3 AA vs. AG + GG: OR = 2.992, 95% CI = 1.122-7.981). In the analysis of metabolizer phenotypes, PMs and IMs groups were associated with ESCC risk compared to EMs (IMs vs. EMs: OR = 1.673, 95% CI = 1.281-2.186; PMs vs. EMs: OR = 2.605, 95% CI = 1.945-3.489). And PMs showed a stronger correlation (PMs vs. IMs + EMs: OR = 2.220, 95% CI = 1.705-2.891).

Results: Eight studies with 1955 cases and 2754 controls were ultimately included that showed that individuals carrying the "A" allele of CYP2C19*2 G861A and AA genotype of CYP2C19*3 G636A were significantly associated with an increased ESCC risk (CYP2C19*2 A vs. G: OR = 1.823, 95% CI = 1.616-2.056; CYP2C19*3 AA vs. AG + GG: OR = 2.992, 95% CI = 1.122-7.981). In the analysis of metabolizer phenotypes, PMs and IMs groups were associated with ESCC risk compared to EMs (IMs vs. EMs: OR = 1.673, 95% CI = 1.281-2.186; PMs vs. EMs: OR = 2.605, 95% CI = 1.945-3.489). And PMs showed a stronger correlation (PMs vs. IMs + EMs: OR = 2.220, 95% CI = 1.705-2.891).

Conclusions: Our meta-analysis revealed that "A" allele (AA+AG) ofCYP2C19*2 and AA genotype of CYP2C19*3 polymorphism are significantly associated with ESCC risk. In metabolizer phenotypes, PMs and IMs are associated with an increased risk of ESCC in Asian populations.

Background

Esophageal carcinoma (EC) is one of the most aggressive cancers, with high mortality and low 5 years survival rate ranging from 4–40% [1]. According to GLOBOCAN 2018, EC is the ninth most common cancer and sixth leading cause of cancer death worldwide, with about 572,034 new cases and 508,584 deaths each year [2].There are clear geographic variations of EC in both incidence and histological types. Esophageal adenocarcinoma (EADC) and esophageal squamous cell cancer (ESCC) are the two main histological types. EADC is more prevalent in western developed countries; ESCC is more common in Eastern Asia, Central Asia and Southern Africa which called "the esophageal cancer belt", where nearly 90% of EC are ESCC [1, 3]. As early symptoms of ESCC may be subtle and nonspecific, most ESCC patients had been the advanced stage at diagnosis, lead to a poor prognosis. It's worth confirming pathogenesis and risk factors for ESCC.

Several exposures were related to the process of ESCC, including tobacco smoking, hot food and beverages, lack of vegetables and fruits, and HPV infection [4]. However, more evidences indicated that genetic predisposition, especially single-nucleotide polymorphisms, plays an important role in the development and progression of ESCC [5]. As a member of cytochrome P450 (CYP) superfamily, CYP2C19, also known as S-mephenytoin hydroxylase, is an important phase I metabolic enzyme. Cytochrome P450 2C19 (CYP2C19) is located on chromosome 10q24 and consists of 490 amine acids [6, 7]. There are at least 14 mutants and 18 alleles in CYP2C19 gene. CYP2C19*2 and CYP2C19*3 are the two commonest mutations, causing 99% people in Eastern countries to have poor metabolism [8, 9]. The mechanism of CYP2C19*2 mutation is a 681 substitution of guanine to adenine (G > A) in the exon 5, which lead to a 40 base pair fragment containing a SmaI restriction endonuclease site to be lost in the initial segment of exon 5 during transcription, causing an inactive

enzyme. The CYP2C19*3 polymorphism is a 636 substitution of guanine to adenine (G > A) in the exon 4, causing the codon of tryptophan changing to a stop codon, which lead to a premature termination of protein synthesis and a lack of connective zone of the substrate and the hemochrome [10]. According to metabolic capacity, CYP2C19 can be divided into three phenotypes: extensive metabolizers (EMs), intermediate metabolizers (IMs), and poor metabolizers (PMs). Individuals with homozygous are EMs (*1/*1), which have efficient enzyme to metabolize CYP2C19 substrates [11, 12]. Individuals with heterozygous are IMs (*1/*2, *1/*3), which have intermediate enzyme to metabolize CYP2C19 substrates. Individuals with mutant CYP2C19 alleles are PMs (*2/*2, *3/*3 or *2/*3), which have a reduced capacity to metabolize CYP2C19 substrates [13]. The study intended to investigate the association of gene polymorphisms and metabolizer phenotypes of CYP2C19 with ESCC risk in Asian populations.

Materials And Methods

Literature search and selection criteria

We conducted a systematic literature search in PubMed, Web of Science, EMBASE, and China National Knowledge Internet (CNKI) databases. The search covered all publications before May, 2020. The used search terms included: “esophageal cancer” or “esophageal squamous cell carcinoma” or “ESCC” or “esophageal carcinoma” and “polymorphisms” or “SNP” or “variation” or “genetic” and “CYP2C19” or “Cytochrome P450 2C19” or “CYP 2C19” or “Cytochrome P2C19” or “rs4244285” or “rs4986893”. References from retrieved articles were searched manually for additional studies [14].

Inclusion and exclusion criteria

The inclusion criteria had to meet the following conditions: (1) case–control or retrospective cohort studies that evaluated the association between CYP2C19 polymorphisms and ESCC risk, (2) patients with pathologically or histologically confirmed diagnosis of ESCC, (3) independent genotype information of CYP2C19*1, CYP2C19*2 and CYP2C19*3 polymorphisms, and (4) sufficient data that could evaluate odds ratio (OR) with 95% confidence interval [15].

In addition, the following exclusion criteria were used: (1) lack of sufficient data to extract the necessary information; (2) EADC studies or samples mixed with EADC, making it impossible to extract sufficient information, (3) Studies about other CYP2C19 genotypes (ie, CYP2C19*17), and (4) reviews, meta-analyses, case reports, in vitro cell line studies, and animal experiment studies. For each study, general characteristics including authors, year of publication, ethnicity, sample size, genotype, and allele frequencies were collected (Fig. 1).

Statistical analysis

In this study, a detailed meta-analysis was performed to reveal the association between CYP2C19*1 (G/G), CYP2C19*2 (G681A), CYP2C19*3 (G636A) polymorphisms and ESCC risk. Subgroup and metabolizer phenotypes analyses were performed on the original date to explore the potential heterogeneity among studies. Associations of CYP2C19*2 and *3 gene polymorphisms with ESCC risk were estimated by five contrasts: dominant genetic model, recessive genetic model, allele genetic mode, homozygote genetic model and heterozygote genetic model.

A formal Q statistical test, as well as I^2, was used to judge the heterogeneity among studies. A $P < 0.10$ or $I^2 > 50\%$ was considered to be a fixed-effect model; otherwise, a random-effect model was conducted [16]. Depending on the heterogeneity results, the pooled ORs with 95%CIs were calculated in a fixed-effect or random-effect model to evaluate the association of CYP2C19 polymorphisms with ESCC risk. A $P < 0.05$ was considered statistically significant. Sensitivity analysis was conducted to validate the stability of results by sequential omission of each study. Publication bias was evaluated by both Egger’s regression test and Begg’s adjusted rank correlation test of funnel plot. All tests in this meta-analysis were performed using STATA version 11.0 software (STATA Corporation, College Station, TX, USA).

Results

A total of 320 studies were identified from the database search. After carefully screening of titles or abstracts, 277 studies were excluded. Then, 31 studies were excluded based on the exclusion criteria. Finally, 8 studies were involved in this meta-analysis (Fig. 1). Among the 8 studies, data were available from 6 studies on the CYP2C19*2 genotype (970 cases and 1415 controls) and 6 studies on the CYP2C19*3 genotype (757 cases and 1164 controls). The information and characteristics of the included 8 studies were listed in Tables 1.

The quality of the included studies was evaluated using the Newcastle–Ottawa Scale (NOS). It is designed to assess studies in three components: the selection of the study groups (0–4 points), the comparability of the groups (0–2 points) and the determination of either the exposure or the outcome of interest (0–3 points) [17]. A perfect NOS score is 9. In this meta-analysis, two studies scored 9 [18, 19]; four studies scored 8 [20–23]; two studies scored 7 [24, 25].

CYP2C19*2 (G681A) polymorphism and ESCC risk

A meta-analysis of CYP2C19*2 polymorphism and ESCC risk was conducted in all genetic models, which enrolled six studies and 2385 individuals. The detailed results were shown in Table 2. The pooled meta-analysis showed that compared to controls, an increased ESCC risk was observed in all genetic models: dominant model, AA + AG vs. GG (OR = 2.406, 95% CI = 2.013–2.876) (Fig. 2); recessive model, AA vs. AG + GG (OR = 1.934, 95% CI = 1.533–2.439); allele model, A vs. G (OR = 1.823, 95% CI = 1.616–2.056); homozygous model, AA vs. GG (OR = 4.467, 95% CI = 3.320–6.011); and heterozygous model, GA vs. GG (OR = 1.309, 95% CI = 1.073–1.596). According to the heterogeneity study, three genetic models (allele model: I^2 = 0.0%, P = 0.694; recessive model: I^2 = 23.2%, P = 0.260; dominant model: I^2 = 30.3%, P = 0.208) used the fixed-effect model and two genetic models (heterozygous model: I^2 = 92.2%, P = 0.000; homozygous model: I^2 = 97.2%, P = 0.000) used random-effect model.

CYP2C19*3 (G636A) polymorphism and ESCC risk

Six studies including 757 cases and 1164 controls described the association between the CYP2C19*3 polymorphism and ESCC risk. The pooled meta-analysis showed that there was a significant association between AA genotype of CYP2C19*3 polymorphism and ESCC risk under recessive model (AA vs. AG + GG: OR = 2.992, 95% CI = 1.122–7.981) (Fig. 3) and homozygote model (AA vs. GG: OR = 2.889, 95% CI = 1.073–7.776); but not in dominant, heterozygote and allele models (Table 2). For the zero events of CYP2C19*3 AA genotype in 2 studies included, only 4 studies including 545 cases and 694 controls were calculated in the recessive and homozygote models finally [26]. Heterogeneity assessment showed significant inter-study variation existed in three genetic models (dominant model: I^2 = 69.3%, P = 0.006; heterozygote model: I^2 = 85.1%, P = 0.000; allele model: I^2 = 70.7%, P = 0.004) and a random-effect model was used; no variation in two genetic models (recessive model: I^2 = 49.9%, P = 0.112; homozygous model: I^2 = 48.0%, P = 0.123) used random-effect model and a fixed-effect model was used (Table 2).

Metabolizer phenotypes and ESCC risk

Based on metabolizer phenotype, individuals including 1955 cases and 2602 controls were divided into three groups: EMs (*1/*1); IMs (*1/*2, *1/*3); and PMs (*2/*2, *3/*3 and *2/*3). As shown in Table 3, the results of the meta-analysis showed that there were significant differences in the risk of ESCC in the following comparisons: between IMs group and EMs group (OR = 1.673, 95% CI = 1.281–2.186), between PMs group and EMs group (OR = 2.605, 95% CI = 1.945–3.489), between PMs group and IMs group (OR = 1.685, 95% CI = 1.154–2.459), between PMs group and EMs group + IMs group (OR = 2.220, 95% CI = 1.705–2.891) (Fig. 4). Heterogeneity analysis showed significant inter-study variation in two comparisons (IMs vs. EMs: I^2 = 56.4%, P = 0.032; PMs vs. IMs + EMs: I^2 = 52.4%, P = 0.161).

Publication bias

Figure 5 (A and B) showed the funnel plots for association between CYP2C19*2, CYP2C19*3 polymorphisms and ESCC risk, which reveal no visually significant publication bias. The *P*-values for both Begg's and Egger's tests (CYP2C19*2: *P*Begg = 0.452 and *P*Egger = 0.406; CYP2C19*3: *P*Begg = 1.000 and *P*Egger = 0.822) indicated no publication bias, respectively. Figure 5 (C) shows the funnel plots for the association between the metabolizer phenotypes and ESCC risk. No publication bias was fund in IMs and EMs group (*P*Begg = 1.000, *P*Egger = 0.760). Three groups (PMs and EMs: *P*Begg = 0.368, *P*Egger = 0.053; PMs and IMs: *P*Begg = 0.368, *P*Egger = 0.075; PMs and EMs + IMs: *P*Begg = 0.368, *P*Egger = 0.083) showed significant publication bias.

Sensitivity analysis

The sensitivity analysis was carried out by repeating the analysis after sequentially omitting each study to investigate the causes for heterogeneity. As a result, no significant effect was shown in ORs of CYP2C19*2, CYP2C19*3 genotypes and metabolizer phenotypes (Fig. 6).

Discussion

Previous studies regarding the association between CYP2C19 gene polymorphisms and the risk of ESCC remain inconsistent and inconclusive. This meta-analysis aimed to explore the association between CYP2C19 gene polymorphisms and ESCC risk. Among the results, people carrying the CYP2C19*2 gene A allele had a high ESCC risk compared to people carrying the G allele (OR = 1.823, 95% CI = 1.616–2.056). In previous study, the result was inconsistent in CYP2C19*3 gene polymorphism. Wei *et al.* found that there was no association between CYP2C19*3 gene polymorphism and ESCC risk in 2004 [22], whereas Yun *et al.* reported that CYP2C19*3 gene A allele showed significantly more prevalent in ESCC patients in 2012 [19]. This meta-analysis combined the results of 6 associated studies and found that AA genotype of CYP2C19*3 polymorphism was related to ESCC risk (OR = 2.992, 95% CI = 1.122–7.981). CYP2C19*2 G681A and CYP2C19*3 G636A genes have single base mutations, resulting in reduced CYP2C19 enzyme activity and slowed metabolism of the carcinogens, which accumulate in the body as exposed time and dose increase, contributing to the susceptibility to ESCC [27]. CYP2C19 can be divided into EMs, IMs and PMs phenotypes by metabolic capacity. The results confirmed that IMs had a higher risk of ESCC than EMs (OR = 1.673, 95% CI = 1.281–2.186); PMs had a higher risk of ESCC than IMs (OR = 1.685, 95% CI = 1.154–2.459). And PMs was associated with a higher risk than EMs + PMs (OR = 2.220, 95% CI = 1.705–2.891). This meta-analysis suggested that the lower CYP2C19 enzyme active, the higher ESCC risk.

CYP2C19 is a member of the cytochrome P450 superfamily which acts on substances from drugs or environment. Previous studies indicated that CYP2C19 may affect the occurrence of tumors by participating both in activation of procarcinogen and detoxification of carcinogens. Wei *et al.* used the ASA-PCR method to perform CYP2C19 allele analysis on 372 healthy controls and patients with 212 lung cancer, 148 gastric cancer, 135 esophageal cancer and 112 bladder cancer [22]. The results suggested CYP2C19 PMs had a high incidence of ESCC, lung cancer and stomach cancer. In contrast, PMs had a low incidence of bladder cancer. In 2014, Li *et al.* conducted a study in Han population and founded that individuals with variant genotypes of CYP2C19 (*2/*2, *2/*3, *3/*3) have increased risk of getting primary liver cancer [28]. Anna *et al.* reported a significant association of CYP2C19 deletion allele with triple-negative breast cancer in Finnish population [29] and Jabir *et al.* found the association of CYP2C19 polymorphism with breast cancer in Iraqi population [30], whereas Laith *et al.* found no association with breast cancer in Japanese people [31]. The above results suggested poor metabolism in CYP2C19 increases the risk of EC, gastric cancer, lung cancer, and liver cancer. On the other hand, CYP2C19 PMs can reduce the risk of bladder cancer.

To our knowledge, this is the first meta-analysis to assess the association between the CYP2C19 polymorphisms and phenotypes with the risk of ESCC in Asian. But there are some limitations in this study. First, only 8 articles were included in

the analysis. Small sample size may affect our results. Second, 3 of the included studies were PhD thesis and only 6 studies were available for each CYP2C19 genotypes analysis, which may affect our statistical power [32]. We conducted a sensitivity analysis and no impact on the results were shown. Third, the included populations were mainly concentrated in Asian populations (ie, Chinese and Indian), and no studies were from Caucasian or African populations [33]. To obtain more accurate conclusions, the inclusion of ethnic groups should be expanded, and subgroup analyses should be performed. We plan to follow up the research and expand the sample size to improve the results next.

Conclusions

In conclusion, our meta-analysis demonstrated that “A” allele of CYP2C19*2 G681A and AA genotype of CYP2C19*3 G636A polymorphism are significantly associated with the risk of ESCC. In metabolizer phenotypes, PMs and IMs groups may be associated with an increased ESCC risk. The results should be confirmed by collecting more case–control studies.

Abbreviations

CYP2C19
Cytochrome P450 2C19; EC:esophageal carcinoma; ESCC:esophageal squamous cell cancer; EADC:Esophageal adenocarcinoma; EMs:extensive metabolizers; IMs:intermediate metabolizers; PMs:poor metabolizers; CNKI:China National Knowledge Internet; OR:odds ratio; CI:confidence interval; NOS:Newcastle-Ottawa scale; PCR:polymerase chain reaction; RFLP:restriction fragment length polymorphism; ASA, allele specific amplification; *P*h:*P*-value of the heterogeneity test.

Declarations

Authors’ contributions

XH G designed the study. XH G, GG W, ZK, YQ Wand JQ Z performed the literature search, data collection, statistical analysis and data Interpretation. XH G, LL and SQ L drafted the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

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Ethics approval and consent to participate

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Tables

Table 1
Characteristics of studies included in the systematic review and meta-analysis.

Author	Year	Country	Sample Size	No. of case/control	Male (%)	Age (case/control)	Genotype alleles tested	Genotyping method	NOS
Gulzar Ahmad Bhat	2017	India	984	492/492	56	60.2±11.25/ 61.57±11.17	CYP2C19*1, *2 CYP2D6	PCR-RFLP	9
Xian-E Peng	2015	China	1710	570/1140	59	59.67±9.83/ 59.71±9.84	CYP2C19*1, *2,*3	PCR-RFLP	8
Yun Shi	2012	China	700	350/350	60	59.4±12.5/ 60.7±12.4	CYP2C19*1, *3	PCR-RFLP	9
Hua-F Chen	2006	China	776	258/518	61	59.78/59.79	CYP2C19*1, *2,*3	PCR-RFLP	8
Li-W Zhang	2006	China	160	88/72	59	55.77±8.85/ 55.52±9.15	MTHFR CYP2C19*1, *2,*3	PCR-RFLP	8
Lin Zhang	2004	China	62	12/50	NS	NS/31.50±8.45	CYP2C19*1, *2,*3	PCR-RFLP	7
Wei-X Shi	2004	China	507	135/32	NS	NS	CYP2C19*1, *2,*3	ASA-PCR	8
Wei-P Zhao	2000	China	150	50/100	NS	NS	CYP2C19*1, *2,*3	PCR-RFLP	7

NS, not specified; NOS, Newcastle-Ottawa scale;PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism;ASA, allele specific amplification.

Table 2
Meta-analysis of associations between CYP2C19*2 and CYP2C19*3 polymorphisms and ESCC risk.

Model	Genotype	OR with 95% CI	Heterogeneity			Publication bias	
			χ2	*P*h	I^2	Begg	Egger
CYP2C19*2							
Dominant	**AA+AG vs. GG**	**2.406 (2.013-2.876)**	**7.71**	**0.208**	**30.3%**	**0.452**	**0.406**
Recessive	**AA vs. AG+GG**	**1.934 (1.533-2.439)**	**6.51**	**0.260**	**23.2%**	**0.009**	**0.019**
Homozygote	**AA vs. GG**	**4.467 (3.320-6.011)***	**63.92**	**<0.001**	**92.2%**	**0.707**	**0.727**
Heterozygote	**GA vs. GG**	**1.308 (1.073-1.596)***	**177.22**	**<0.001**	**97.2%**	**1.000**	**0.801**
Allele	**A vs. G**	**1.823 (1.616-2.056)**	**3.04**	**0.694**	**0.0%**	**0.452**	**0.512**
CYP2C19*3							
Dominant	AA+AG vs. GG	1.206 (0.637-2.284)*	16.27	0.006	69.3%	0.707	0.760
Recessive	**AA vs. AG + GG**	**2.992 (1.122-7.981)**	**5.99**	**0.112**	**49.9%**	**0.308**	**0.556**
Homozygote	**AA vs. GG**	**2.889 (1.073-7.776)**	**5.77**	**0.123**	**48.0%**	**0.308**	**0.626**
Heterozygote	GA vs. GG	1.699 (0.685-4.213)*	33.62	<0.001	85.1%	0.452	0.354
Allele	A vs. G	1.259 (0.690-2.295)*	17.07	0.004	70.7%	1.000	0.822

OR, odds ratio; 95% CI, 95% confidence interval,χ^2: chi-square; I^2, I-squared; *P*h, *P*-value of the heterogeneity test. * A random-effects model was constructed.

Table 3
Meta-analysis of associations between CYP2C19 metabolizer phenotypes and ESCC risk.

Metabolizer phenotype	OR with 95% CI	Heterogeneity			Publication bias	
		χ2	*P*h	I^2	Begg	Egger
IMs vs. EMs	1.673 (1.281-2.186)*	13.76	0.032	56.4%	1.000	0.760
PMs vs. EMs	2.605 (1.945-3.489)	8.15	0.227	26.4%	0.368	0.053
PMs vs. IMs	1.685 (1.154-2.459)	11.23	0.161	46.6%	0.368	0.075
PMs vs. IMs + EMs	2.220 (1.705-2.891)*	10.52	0.161	52.4%	0.386	0.083

OR – odds ratio; 95% CI – 95% confidence interval;χ^2 – chi-square; I^2 – I-squared; *P*h – *P*-value of the heterogeneity test. * A random-effects model was constructed.

Figures

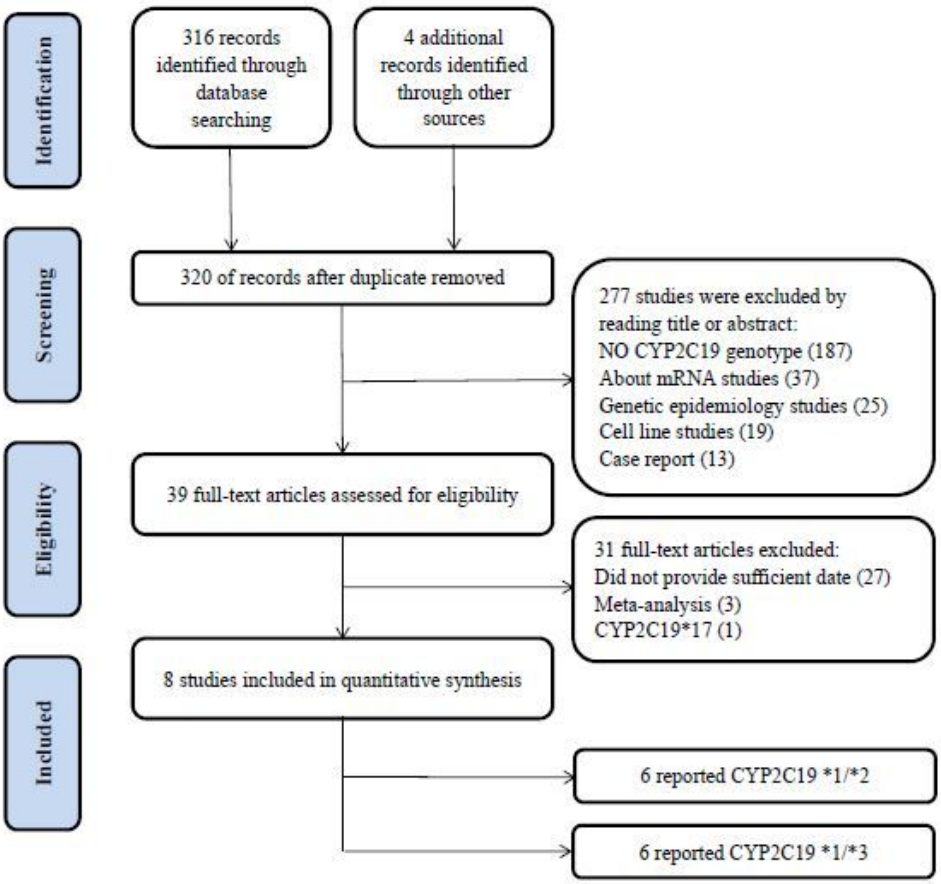

Figure 1

Flowchart for inclusion of eligible studies.

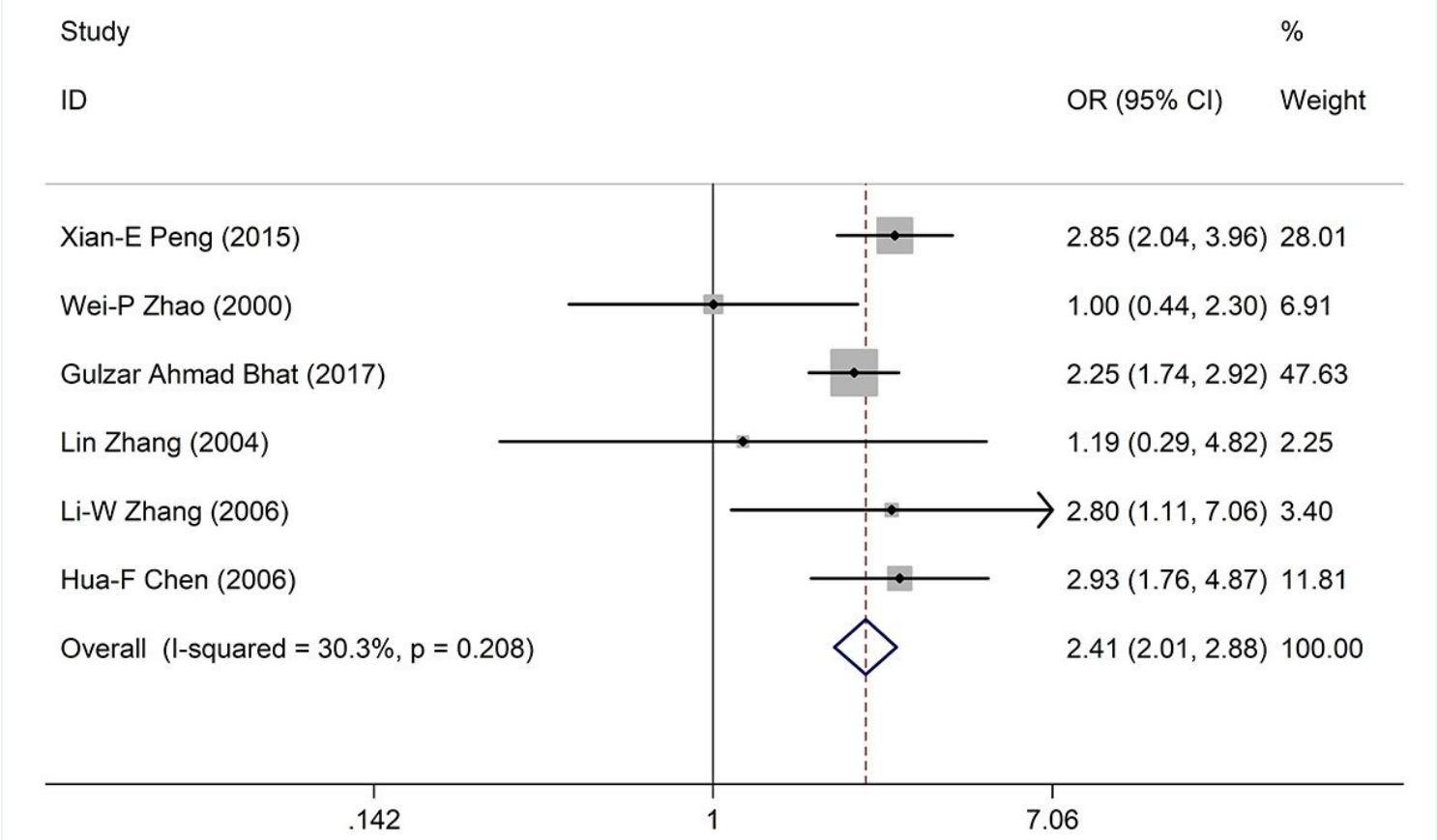

Figure 2

Meta-analysis for CYP2C19*2 polymorphism and ESCC risk under the dominant model.The squares and horizontal lines represent OR and 95% CI, respectively. The area of the squares represents the study-specific weight.

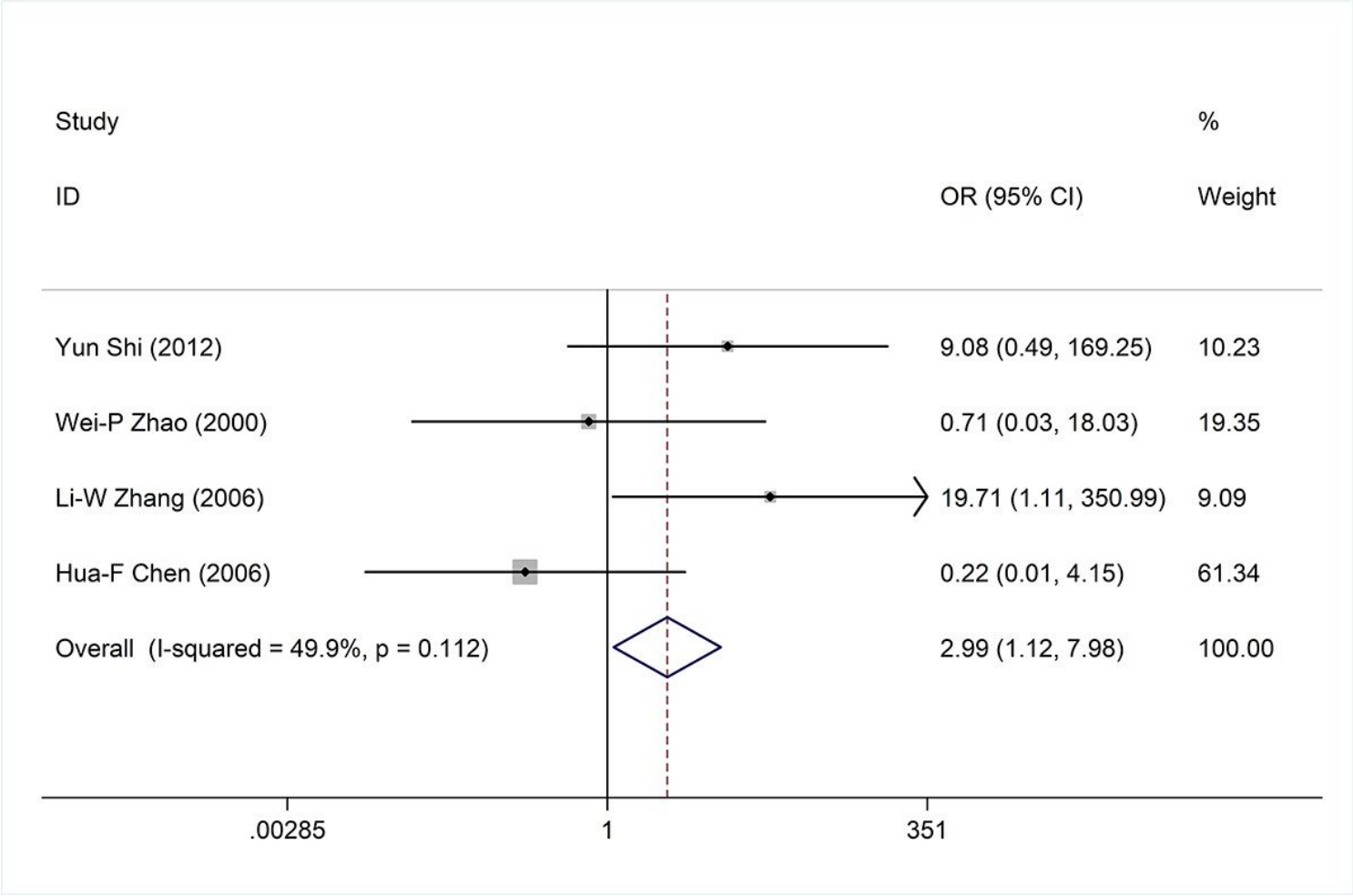

Figure 3

Meta-analysis for CYP2C19*3 polymorphism and ESCC risk under the recessive model.

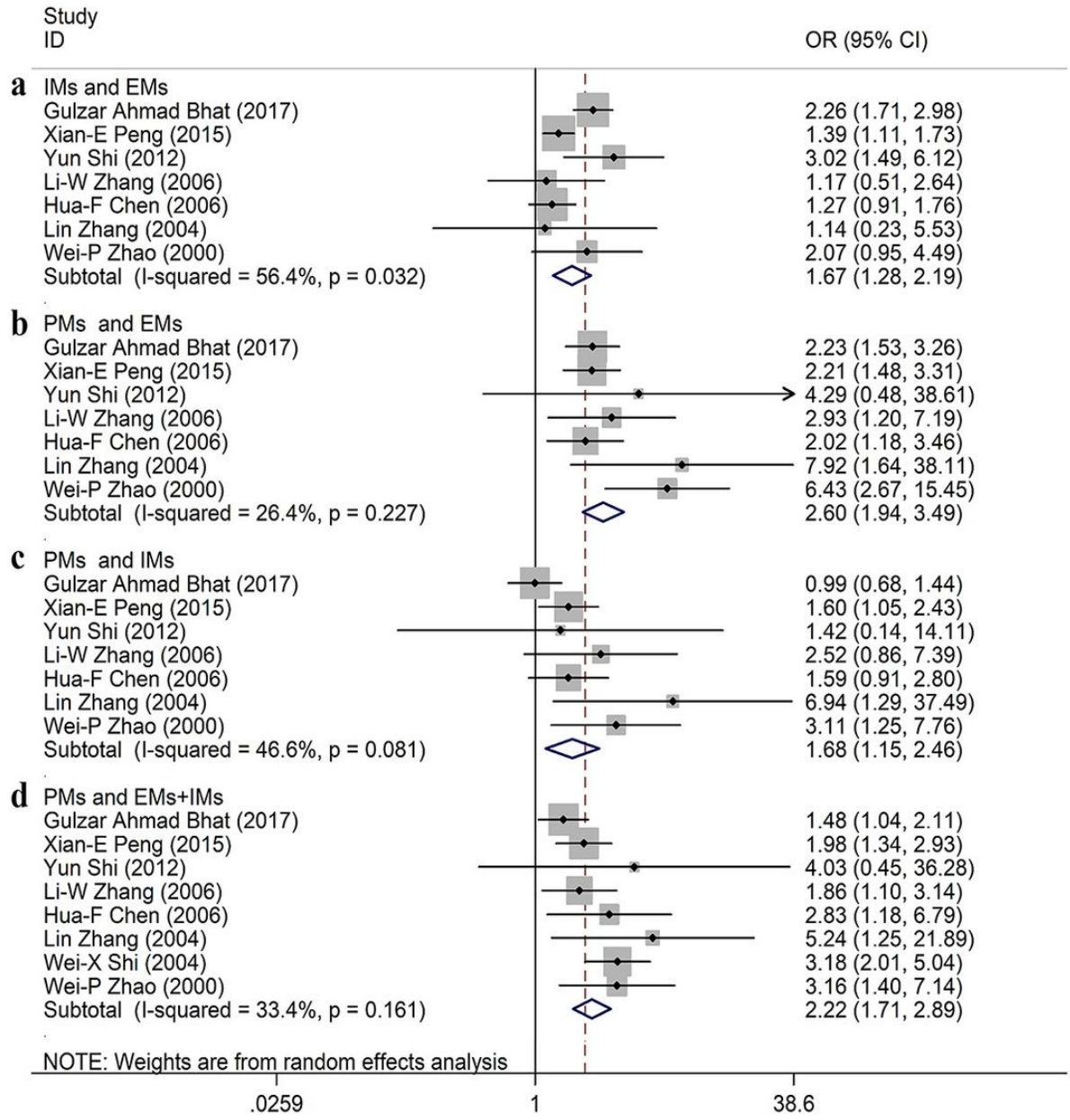

Figure 4

Forest plots of CYP2C19 metabolizer phenotypes and ESCC risk. a IMs and EMs; b PMs and EMs; c PMs and IMs; d PMs and EMs + IMs.

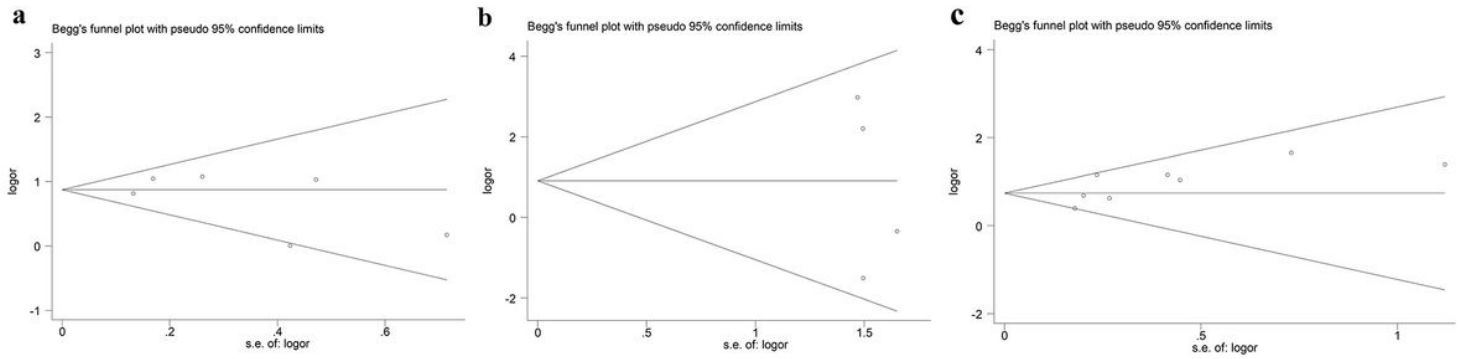

Figure 5

Funnel plots of publication bias of CYP2C19 gene polymorphisms. a CYP2C19*2 dominant model; b CYP2C19*3 recessive model; c PMs and EMs + IMs phenotype.

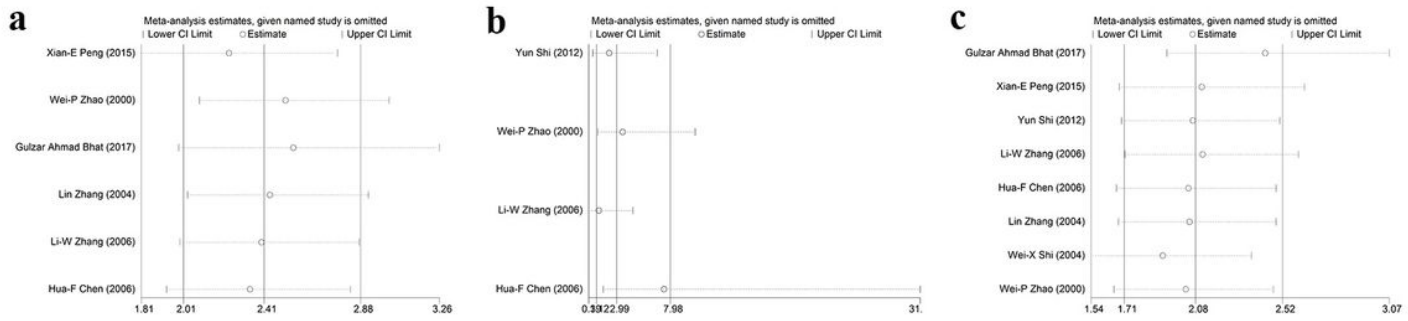

Figure 6

Sensitivity analysis of the associations between CYP2C19 polymorphisms with ESCC risk. a CYP2C19*2; b CYP2C19*3; c PMs and EMs + IMs.