Association between *EPHX1* polymorphism rs1051740 and the risk of ovarian cancer: a meta-analysis

Ying Jin

Department of Obstetrics and Gynecology, Beijing Friendship Hospital, Capital Medical University, Beijing, China

**ABSTRACT**

**Objective:** We carried out a meta-analysis of case-control studies to determine whether epoxide hydrolase 1 (*EPHX1*) gene polymorphism rs1051740 was related to the risk of ovarian cancer.

**Methods:** Electronic databases were searched for relevant articles published in English or Chinese language. We calculated crude odds ratios (ORs) with their 95% confidence intervals (95% CIs) to assess the relationship of *EPHX1* polymorphism rs1051740 with ovarian cancer risk. In addition, subgroup analyses were also conducted based on ethnicity and control source. Between-study heterogeneity was inspected with Q test and I² statistic.

**Results:** Five eligible studies with a total of 1919 ovarian cancer patients and 1829 controls were ultimately included in the present meta-analysis. Overall results demonstrated that the association between *EPHX1* polymorphism rs1051740 and ovarian cancer risk had no statistical significance either in total analysis or in subgroup analyses by ethnicity and source of control.

**Conclusion:** *EPHX1* polymorphism rs1051740 may have no independent effect on ovarian cancer susceptibility.

** ARTICLE HISTORY**

Received 14 January 2019
Revised 14 May 2019
Accepted 15 May 2019

**KEYWORDS**

*EPHX1*; polymorphism; ovarian cancer; meta-analysis

**Introduction**

Ovarian cancer is one of the most common malignancies in female reproductive system and a leading cause of deaths related to gynecological cancers [1,2]. It is estimated that every year, around 225,500 patients are diagnosed with this malignancy, which leads to 140,200 deaths throughout the world [3]. In early stage, ovarian cancer is asymptomatic or has non-specific symptoms, so the patients are usually diagnosed at advanced stages [4]. In addition, there is no effective screening measure for this cancer, which also contributes to extremely low 5-year survival rate [5]. With a complex process, ovarian cancer is affected by multiple aspects, such as obesity, hormonal exposure, family history, reproductive status, age of menarche and number of ovulatory cycles [6,7]. Apart from these elements, genetic factors have also been demonstrated to play a critical role in the development of this malignancy [8,9].

Epoxide hydrolase 1 (*EPHX1*) is an important phase II biotransformation enzyme in vivo, and plays a significant role in the activation and detoxification of toxins [10]. Generally, epoxides are regarded as the most toxicologically active form of drugs or environmental chemicals [11], while EPHX1 can promote the hydrolysis of epoxides into trans-dihydrodiols [12]. *EPHX1* gene, coding for this enzyme, is located at chromosome 1q42.1 with 20271 base-pairs, and is composed of 9 exons and 8 introns [13]. In this gene, more than 10 single nucleotide polymorphisms (SNPs) have been identified. Among them, the polymorphism rs1051740 leading to the substitution of tyrosine to histidine at exon 3 has been reported to reduce the enzyme activity by more than 40% *in vitro* [14]. Considering the role of EPHX1 in response to exogenous toxins, this polymorphism of the gene *EPHX1* has been proposed to be related to the risk of multiple cancers, including ovarian cancer [15], hepatocellular carcinoma [13] and colorectal cancer [14].

Only few studies discussed the association between *EPHX1* polymorphism rs1051740 and the susceptibility to ovarian cancer, but their findings were still inconsistent or even contradictory. To further understand such correlation, we performed this meta-analysis based on previously published articles involving the topic.

**Materials and methods**

**Search strategy**

In order to identify eligible publications, we conducted a comprehensive search in PubMed, EMBASE, ISI Web of Science, Wanfang and CNKI (China National Knowledge Infrastructure) databases. Studies on the correlation between *EPHX1* polymorphism rs1051740 and ovarian cancer susceptibility were retrieved using the combinations of the following keywords: “epoxide hydrolase 1 or *EPHX1* or mEH” and
“polymorphism or mutation or variant” and “ovarian cancer”. Additional articles were searched by checking the references of relevant studies.

Selection criteria
Included studies must meet the following criteria: (1) focusing on the association of EPHX1 polymorphism rs1051740 with ovarian cancer risk; (2) case-control studies; and (3) providing sufficient information on genotype frequencies in case and control groups for calculating crude odds ratios (ORs) with their 95% confidence intervals (95% CIs). Major reasons for exclusion were: (1) case-only studies; (2) based on duplicated data; and (3) review papers. If more than one study reported the same group of study objects, the one providing most information or latest published was selected.

Data extraction
Two reviewers abstracted essential data from all included studies using standardized form, and recorded data contained the following aspects: the first author’s name, year of publication, original country, ethnicity, control source, genotyping method, sample size (cases/controls), genotype distributions in cases and controls, and p values for Hardy–Weinberg equilibrium (HWE) in controls. All disagreements over extracted data were resolved through discussion between the two reviewers to reach consensus.

Statistical analysis
STATA 12.0 software (Stata Corp, College Station, TX, USA) was applied to complete all statistical analyses in this study. We calculated pooled ORs with the corresponding 95% CIs to evaluate the relationship between EPHX1 polymorphism rs1051740 and ovarian cancer risk under five genetic models of CC vs. TT, CC + TC vs. TT, CC vs. TT + TC, allele C vs. allele T and TC vs. TT. The conformity of genotype frequencies of EPHX1 polymorphism rs1051740 to HWE in controls was tested through chi-square test. We also performed subgroup analyses based on ethnicity and control source to further explore specific association. Cochran’s Q-statistic and I² test were used to evaluate between-study heterogeneity [16]. If p < .05 and I² > 50%, indicating significant heterogeneity, random-effect model was selected for calculating pooled ORs; otherwise fixed-effects model was employed. Sensitivity analysis was performed to assess the influence of each individual dataset on overall results.

Results

Study characteristics
According to the search strategy, 244 articles were initially identified. We scanned the titles and abstracts of all articles, and thus excluded 146 reports not involving our studied polymorphisms (87) or ovarian cancer (59). Then, 85 articles were further excluded during full-text examination because of reviews (7), meta-analyses (2), non-clinical studies (14) and not relevant to EPHX1 gene (62). Next, 8 additional publications were removed for lacking essential data. Finally, 5 case-control studies, including 1919 ovarian cancer patients and 1829 controls, were encompassed in this study [15,17–20]. Figure 1 describes selection process of eligible articles, and main characteristics of the included studies are presented in Table 1. Except the study by Kang and colleagues [19], genotype distribution in all included studies conformed to HWE in this meta-analysis (p > .05).

Meta-analysis results
As shown in Table 2, EPHX1 polymorphism rs1051740 was not significantly associated with the risk of ovarian cancer (Figure 2), nor was it after stratified analyses by ethnicity and control source. There was no significant heterogeneity among eligible studies under all comparison models (p > .05). Thus, we adopted the fixed-effects model to calculate pooled ORs in this meta-analysis.

Sensitivity analysis
Sensitivity analysis was carried out to detect the effect of single study on pooled ORs, through sequential omission of included studies one at a time. And such operation did not alter overall estimates qualitatively (data not shown), indicating the robustness and reliability of our results.

Discussion
Ovarian cancer is one of the most malignant tumours in female reproductive system. Without any distinct symptoms at early stage, more than 70% of the patients have already entered in advanced stage when they are first diagnosed. Five-year survival rate of ovarian cancer patients sees no marked increase despite significant improvements in diagnosis and treatment during the past two decades. Although exact pathogenesis of ovarian cancer remains unclear, the role of genetic factors has attracted increasing attentions in studies on this malignancy.

EPHX1, an important phase II biotransformation enzyme, takes part in the hydrolysis of endogenous and exogenous epoxides as well as intermediate products during phase I metabolism, and thus eliminates these epoxides from the body after transforming them into dihydrodiols, playing critical roles in maintaining internal environment and normal functions of cells [21,22]. Expressed in many tissues in the body, EPHX1 acts on a variety of substrates, including various exogenous polycyclic aromatics [23], and may participate in the metabolism of steroids [24]. Besides, documents show that polymorphisms in the gene EPHX1 can change functional activity of the enzyme through affecting the stability of its protein [25]. Over the past years, in the field of gynaecological reproduction and endocrinology, EPHX1 polymorphisms have been widely discussed in researches on
preeclampsia [26], spontaneous abortion [27] and ovarian cancer. The polymorphism rs1051740 at exon 3 of the gene EPHX1 can decrease the activity of the enzyme by approximately 50%, and has been related to individual susceptibility to ovarian cancer in some studies. For example, Goode and colleagues revealed an increasing effect of this polymorphism on the risk of invasive ovarian cancer, especially for serous subtype (OR = 1.17, 95% CI = 1.04–1.32), in their study among white non-Hispanic Caucasians [18]. Additionally, among an Australian population, Spurdle and colleagues found that the TT genotype of the polymorphism decreased the risk of invasive ovarian cancer of the endometrioid subtype (age-adjusted OR = 0.38, 95% CI = 0.17–0.87), though the distribution of genotypes did not differ significantly between total ovarian cancer patients and unaffected controls [20]. Interestingly, Lancaster and colleagues in their study demonstrated that for EPHX1 polymorphism rs1051740 in Americans, and that the frequency of the homozygous high-activity genotype (TT) was 41% in controls and 64% in patients with ovarian cancer, with an OR for the cancer of 2.6 (95% CI = 1.3–5.0) [15]. However, other two studies by Baxter et al. and Kang et al., respectively, manifested no significant difference in the frequencies of genotypes or alleles of EPHX1 polymorphism rs1051740 between ovarian cancer cases and controls [17,19]. These discrepancies between findings from previous studies might be attributed to multiple aspects, such as diverse genetic backgrounds and living surrounds,

![Figure 1. Selection process for eligible articles in this meta-analysis.](image)

Table 1. Principal characteristics of the studies included in the Meta-analysis.

| First author | Year | Country | Ethnicity | Control source | Cases/controls | No. of case | No. of control | Genotyping method | P HWE |
|--------------|------|---------|-----------|----------------|----------------|-------------|----------------|-------------------|--------|
| Lancaster    | 1996 | US      | Caucasian | H-B            | 73/75          | 47          | 17            | 9                 | .649   |
| Spurdle      | 2001 | Australia | Caucasian | P-B            | 545/287         | 255         | 233           | 57                | .265   |
| Baxter       | 2002 | UK      | Caucasian | H-B            | 291/257         | 142         | 114           | 35                | .202   |
| Kang         | 2004 | China   | Asian     | P-B            | 86/174          | 27          | 26            | 33                | <.001  |
| Goode        | 2011 | US/Australia | Caucasian | H-B            | 924/1036       | 458         | 355           | 111               | .418   |

Note. H-B: hospital-based case-control study; P-B: population-based case-control study; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HWE: Hardy–Weinberg equilibrium.
**Table 2. EPHX1 Polymorphism rs1051740 and ovarian cancer risk.**

| Comparison | Group          | OR (95% CI)     | \(P_h\) | \(I^2\) | Model for analysis |
|------------|----------------|-----------------|---------|---------|-------------------|
| CC versus TT | Ethnicity  | Caucasian | 1.13 (0.90, 1.41) | .430    | 0.0%   | FEM             |
|            | Asian         | 0.78 (0.42, 1.46) | —       | —       | —                |                |
|            | Control source | Hospital | 1.16 (0.90, 1.49) | .279    | 21.7%  | FEM             |
|            | Population    | 0.93 (0.63, 1.33) | .505    | —       | —                |                |
|            | Total         | 1.08 (0.88, 1.34) | .413    | —       | —                |                |
| CC + TC versus TT | Ethnicity  | Caucasian | 0.95 (0.73, 1.24) | .037    | 64.6%  | REM             |
|            | Asian         | 0.88 (0.50, 1.54) | —       | —       | —                |                |
|            | Control source | Hospital | 0.85 (0.57, 1.27) | .019    | 74.8%  | REM             |
|            | Population    | 1.06 (0.62, 1.73) | .466    | —       | —                |                |
|            | Total         | 1.00 (0.68, 1.44) | .069    | —       | —                |                |
| CC versus TT + TC | Ethnicity | Caucasian | 1.14 (0.92, 1.42) | .687    | 0.0%   | FEM             |
|            | Asian         | 0.77 (0.45, 1.30) | —       | —       | —                |                |
|            | Control source | Hospital | 1.20 (0.94, 1.52) | .662    | 0.0%   | FEM             |
|            | Population    | 0.87 (0.62, 1.23) | .520    | —       | —                |                |
|            | Total         | 1.08 (0.88, 1.32) | .498    | —       | —                |                |
| C versus T | Ethnicity  | Caucasian | 1.04 (0.96, 1.15) | .086    | 54.5%  | FEM             |
|            | Asian         | 0.83 (0.58, 1.20) | —       | —       | —                |                |
|            | Control source | Hospital | 0.94 (0.71, 1.24) | .038    | 69.5%  | REM             |
|            | Population    | 0.99 (0.62, 1.6) | .272    | 69.5%   | FEM             |
|            | Total         | 1.02 (0.92, 1.13) | .095    | 49.4%   | FEM             |
| TC versus TT | Ethnicity | Caucasian | 0.92 (0.69, 1.23) | .031    | 66.2%  | REM             |
|            | Asian         | 1.05 (0.54, 2.05) | —       | —       | —                |                |
|            | Control source | Hospital | 0.81 (0.53, 1.24) | .021    | 74.1%  | REM             |
|            | Population    | 1.12 (0.65, 1.78) | .824    | —       | —                |                |
|            | Total         | 0.98 (0.85, 1.13) | .063    | 55.2%   | FEM             |

**Notes.** OR: odds ratio; CI: confidence interval; \(P_h\): \(p\) values of heterogeneity test; FEM: fixed-effects model; REM: random-effect model.

**Figure 2.** Forest plot for ovarian cancer risk associated with EPHX1 polymorphism rs1051740 under CC vs. TT model stratified by ethnicity. The squares and horizontal lines correspond to study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). Diamond represents the summary OR and 95% CI.
differences in age distribution of study participants, uneven sample sizes and inadequate adjustment for confounding factors.

To abstract a more reliable conclusion on the relationship between EPHX1 polymorphism rs1051740 and ovarian cancer risk, we performed this meta-analysis to combine their inconsistent findings. After strict data syntheses, we detected no significant influence for the polymorphism on the susceptibility to ovarian cancer in total analysis; nor did we in subgroup analyses stratified by ethnicity and control source. All these results indicated that this polymorphism might not independently affect the risk of ovarian cancer. And our findings were similar to those from an earlier meta-analysis by Zhong and colleagues [28]. In their study, no stratification analysis on ethnicity or control source was performed, and such omission has been supplemented in our work.

The current study had some limitations that should be acknowledged. Firstly, only five articles were included in this meta-analysis and the sample size was small, so the comprehensiveness of our results might be limited. Secondly, due to few published studies about this topic, publication bias was not detected. Thirdly, further subgroup analyses based on age, family history or other relevant factors were not performed. Fourthly, interactions between genetic and environmental factors were not considered in the study.

Conclusion

The results of our meta-analysis demonstrated that EPHX1 polymorphism rs1051740 might be not related to the risk of ovarian cancer. However, due to the limitations mentioned above, more investigations with larger sample sizes are warranted to verify final results in future.

Disclosure statement

No potential conflict of interest was reported by the authors.

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