Association study between polymorphisms of XRCC1, hOGG1 in DNA repair gene and the risk of endometrial carcinoma: a meta-analysis

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huang wen huangwen90@163.com
First Affiliated Hospital of University of science and technology of china
Corresponding Author
ORCiD: 0000-0003-2776-365X

Zhou xiaosi
First Affiliated Hospital of University of science and technology of china

yi li
First Affiliated Hospital of University of science and technology of china

zhihao wang
First Affiliated Hospital of University of science and technology of china

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Abstract

Objective

The association of DNA repair gene XRCC1, hOGG1 polymorphisms with susceptibility to endometrial carcinoma (EC) have been extensively studied with inconsistent results. The objective of this study was to clarify this issue by a comprehensive review and meta-analysis.

Methods

English (PubMed, Medline, Embase) and Chinese (CNKI, wanfang) electric databases were searched to collect a case-control study on the association between XRCC1 or hOGG1 gene polymorphisms and endometrial carcinoma. The retrieval time was from the database until May 1th, 2019. According to inclusion and exclusion criteria, relevant data of the final included literature were extracted and STATA 11.0 software was used for meta analysis.

Results

A total of 8 references meeting the inclusion criteria were included for analysis from the 243 retrieved literatures. The Arg399Gln polymorphism at the XRCC1 gene was associated with increased susceptibility to endometrial carcinoma (OR=1.36, 95%CI=1.23~1.51, P<0.001) in the overall population, the same results were shown in the subgroup analysis of Caucasians (OR=1.44, 95%CI=1.29~1.61, P<0.001). Ser326Cys polymorphism of the hOGG1 gene also increases the risk of endometrial carcinoma in Caucasians (OR=1.54, 95%CI=1.34~1.76, P=0.001). No publication bias was detected in this meta-analysis.

Conclusions

This meta-analysis provided evidence that the Arg399Gln polymorphism of DNA repair gene XRCC1 may increase risk of endometrial carcinoma, especially in the Caucasian. Moreover, Ser326Cys polymorphism of hOGG1 increase endometrial carcinoma risk in the Caucasian.
Background

Endometrial carcinoma (EC) is one of the three most common malignancies in the female reproductive system. The incidence of EC is on the rise in recent years, and it has become a gynecological tumor that threatens women's health after breast cancer and ovarian cancer[1,2]. The pathogenesis of EC has not been fully elucidated, and it is generally believed that the occurrence and development of EC is a complex process with multiple genes, multiple pathways and multiple stages[3]. On the one hand, the occurrence of tumor is related to the repeated stimulation of external carcinogenic factors; on the other hand, it is also inseparable from the genetic background of individuals[4,5]. DNA damage is caused by endogenous and exogenous mutagens and carcinogens. If the damage of body's DNA cannot be effectively repaired, the damage will be fixed as mutation after one cell cycle, which may eventually lead to increased risk of tumor[6].

The human oxoguanine glycosylase 1 (hOGG1) is a key enzyme in the repair of oxidative damage in human cells and plays an important role in the repair of oxidative damage[7]. The functional single nucleotide polymorphisms may change the repair ability, thus leading to the increased risk of cancer[8]. X-ray repair cross-complementing 1 (XRCC1) is the first isolated gene involved in the repair of DNA damage caused by ionizing radiation [9, 10]. It plays a key role in the repair of base excision and DNA single strand fracture. At present, many studies have found that single nucleotide polymorphisms (SNP) of hOGG1 and XRCC1 may be involved in the development of EC [11-18]. However, the conclusions are inconsistent. In this study, the associations between Arg399Gln of XRCC1 gene and Ser326Cys of hOGG1 gene and the EC risk was systematically evaluated by a meta-analysis.

Materials And Methods
Retrieval strategy

The case-control study on the relationship between XRCC1 Arg399Gln, hOGG1 Ser326Cys gene polymorphisms and the EC risk published before Jan, 2019 was searched in PubMed, Medline, Web of Science, Embase, Chinese National Knowledge Infrastructure (CNKI) and wanfang databases. The two researchers independently performed a search using the following terms: “X-ray repair cross complementing protein 1”, “Human 8-oxoguanine DNA glycosylase”, “XRCC1” “Arg399Gln”, “hOGG1”, “Ser326Cys”, “Polymorphism”, “variant”, “SNP”, “Endometrial Neoplasms”, “Endometrial Cancer”. Relevant references were also retrieved manually to prevent omission of relevant study in the above databases.

Inclusion and exclusion criteria

Inclusion criteria: (1) Published case-control studies; (2) The patients in the case group were confirmed by cytology or pathology, and the control group were persons without cancer or healthy volunteers; (3) study on the association of the XRCC1 Arg399Gln, hOGG1 Ser326Cys gene polymorphisms and endometrial carcinoma; (4) The frequency distribution of each genotype of the case and control groups can be provided, and the odd ratio (OR) and its 95% confidence interval (95%CI) can be calculated.

Exclusion criteria: (1) Literature type was summary, review or case report; (2) The frequency distribution of each genotype in the case and control groups could not be obtained; (3) The genotype distribution of control group is not compatible with the Hardy-Weinberg equilibrium test (HWE).

Literature quality evaluation

All the included studies were case-control design, and the Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of each study [19]. Literature evaluation was conducted from 8 items in 3 aspects with scores of 0 to 9, and if the study acquired scores of more than 6, we consider that it was high-quality study.
Data obtaining

Two evaluators independently screened the retrieval literatures and then they compare them to each other. The irrelevant literature was initially removed through the title and abstract, and then the rest of literature was read in full reference to the preliminary criteria of inclusion and exclusion. If the data of genotype and allele frequency cannot be obtained, it will be deleted in the final included studies. Two researchers carefully extracted the relevant data from the included literatures, and differences were resolved by discussion together. If consensus could not be reached, the third researcher was invited to evaluate ultimately. The content of data extraction is as follows: the sure name of first author, publication year, the country of study conducted, sample size of case and control groups, ethnicity, and genotype distribution in case and control groups.

Statistical analysis

Pooled odds ratios (ORs) with its 95% confidence intervals (CIs) were calculated to evaluate the strength of associations between the gene polymorphisms of XRCC1 Arg399Gln, hOGG1 Ser326Cys and risk for endometrial carcinoma. Three genetic models included allele, dominant and recessive were used to assess the association of above gene polymorphisms with endometrial carcinoma. Z test was used to test the statistical significance of OR and 95%CI in meta analysis results. Subgroup analysis was performed according to ethnicity. The Cochran Q test was used to evaluate the heterogeneity among the included studies, and the corresponding effect model (fixed- or random- model) was selected for meta analysis according to the heterogeneity test results. When the heterogeneity test result of $P$-value of the Cochran Q test was > 0.10, the heterogeneity was considered not significant, then fixed effect model was used in meta analysis. Otherwise, meta-analy results of random effect model were choosed. The heterogeneity of across studies was quantitatively assessed using $I^2$ test, and it was considered that mild
heterogeneity existed when $I^2$ value was less than 25%, moderate heterogeneity existed when $I^2$ value was between 25% and 50%, and high heterogeneity existed when $I^2$ value was more than 50%. The HWE was tested by chi-square test in the control group, and $P > 0.05$ was consistent with the HWE. Sensitivity analysis was conducted by excluding studies one by one to determine the robustness of the meta-results. Publication bias in present study were evaluated by Begg's funnel plot and Egger's linear regression method [20,21]. Meta-analyses were performed by mean of the Stata version 11.0 software (Stata Corporation, College Station, TX, USA). All statistical evaluations were made assuming a 2-sided test with the significance level of 0.05.

### Availability of data and materials

No additional data are available.

### Results

#### Basic information of the included literature

The literature retrieval results and the screening process are shown in Figure 1. A total of 243 literatures were initially retrieved through the database search. Of these, 168 literatures were excluded after reading the titles and abstracts, among which 106 were not consistent with the research purpose, 15 were reviews, and 47 were non-human subjects. After further reading, 19 literatures were excluded, among which 4 did not have a control group, 8 were repeatedly published, and 7 could not provide complete data. Finally, a total of 8 references meeting the inclusion criteria were included for analysis from the 243 retrieved literatures. Of these studies, 7 articles were related to XRCC1-Arg399Gln polymorphism, including 1613 cases and 1703 controls, 5 articles were related to HOGG1-Ser326Cys polymorphisms, including 988 cases and 1062 controls. NOS scores indicated that the 8 literatures were of high quality. The basic information of the final
included literatures in this meta-analysis are shown in Table 1.

**XRCC1-Arg399Gln and susceptibility to EC**

The detailed results of the meta-analysis for XRCC1-Arg399Gln polymorphism and risk of EC are shown in Table 2. The heterogeneity analysis of XRCC1-Arg399Gln showed significant heterogeneity in the overall population, but it was reduced partially by subgroup analysis according to ethnicity. There was a significant associations between XRCC1-Arg399Gln and susceptibility for EC finded in the overall population (allelic model OR=1.36, 95%CI=1.23~1.51, \( P<0.001 \); dominant model OR =1.36, 95%CI=1.13~1.58, \( P=0.001 \); recessive model OR=1.53, 95% CI=1.31~1.78, \( P<0.001 \)). Stratified by ethnicity, we found a significant association between XRCC1-Arg399Gln genotype and risk to EC in the Caucasian population (allelic model OR=1.44, 95%CI=1.29~1.61, \( P<0.001 \); dominant model OR =1.36, 95%CI=1.14~1.61, \( P=0.001 \); recessive model OR=1.72, 95% CI=1.45~2.04, \( P<0.001 \)) (Figure 2), but not in the Asian population.

**hOGG1-Ser326Cys and susceptibility to EC**

The detailed results of the meta-analysis for hOGG1-Ser326Cys genotype and risk of EC are shown in Table 2. There is a significant association between hOGG1-Ser326Cys and susceptibility to EC in the Caucasian population (allelic model OR=1.54, 95%CI=1.34~1.76, \( P=0.001 \); dominant model OR =1.38, 95%CI=1.14~1.66, \( P=0.001 \); recessive model OR=2.03, 95% CI=1.63~2.53, \( P=0.001 \)) (Figure 3).

**Sensitivity analysis**

For evaluate the influence of single study on the results of meta analysis, excluding one of the included literature was conducted for sensitivity analysis. The results showed that there was no significant change in meta analysis results after excluding any literature (Figure 4).

**Publication Bias**
Funnel plot was used in this study to assess publication bias in the included literature. The funnel plots of the two gene loci were roughly symmetrical, indicating that there was no publication bias exist in this meta-analysis (Figure 5).

Discussion

Under the action of various endogenous and exogenous carcinogenic factors, endogenous intermediates, for example reactive oxygen intermediates (ROI) or substances oxidized by ROI will be generated in our organism. These substances may damage the DNA structure and cause point or chromosomal mutations. Some of these mutations lead to cell neoplastic transformation and in consequence to neoplasm development [22]. There are five main repair mechanisms for DNA damage in the human cells: direct reversal, mismatch repair, single-strand and double-strand DNA repair, base excision repair (BER), and nucleotide excision repair (NER) [23]. DNA repair system can repair DNA damage of the organism and play an important role in maintaining the integrity of the human gene [24]. DNA repair system gene mutation may change DNA repair ability, and there is a the certain relationship in the occurrence and development of cancer [25]. Literatures have shown that the gene polymorphisms of XRCC1 and hOGG1 in the DNA base excision repair (BER) mechanism are associated with the occurrence of multiple malignant tumors, however, its association with endometrial carcinoma has not been determined. Therefore, on the premise of a comprehensive search of relevant literatures, this study conducted a quantitative and systematic comprehensive evaluation on the correlation between XRCC1 Arg399Gln and hOGG1 Ser326Cys single nucleotide polymorphism and the incidence of endometrial carcinoma using the meta analysis method.

A total of 8 case-control trials involving 1643 EC patients and 1733 normal controls were included for pool analysis. The results indicated that the 399Gln allele for XRCC1 was associated with an increased risk of endometrial carcinoma compared to 399Arg in the
overall analysis, which is related to endometrial carcinoma susceptibility, especially the risk of endometrial carcinoma in patients with Gln/Gln genotype is significantly higher than that of Arg/Arg genotype. Inter-study heterogeneity decreased in subgroup analyses of the Caucasian populations and the the same results were showed in the Caucasian populations. These suggests that the Arg399Gln polymorphism of XRCC1 gene is associated with susceptibility to endometrial carcinoma, and that the 399Gln allele in XRCC1 gene may be a risk factor for endometrial carcinoma in women, especially in the Caucasian women. The study population of hOGG1 Ser326Cys polymorphism was Caucasians, which was also associated with endometrial carcinoma susceptibility. Therefore, the 326Cys allele in Caucasians may increase the risk of endometrial carcinoma.

In the subgroup analysis based on race, the heterogeneity was lower than that of the general population, indicating that the overall heterogeneity was mainly derived from race differences. In the sensitivity analysis excluding the included literatures one by one, the results of meta-analysis have no significant change.

Although it was found that DNA repair gene XRCC1 Arg399Gln and hOGG1 Ser326Cys polymorphisms were associated with EC incidence. However, it should be acknowledged that there are many bias and confounders in these studies. Firstly, all the included articles published only in language of English and Chinese, so that potential language bias may exist in this meta-analysis. Secondly, most of the studies are reported in the Caucasian population, the sample in the Asian was small which could led to insufficient statistic power to detect slight associations. Thirdly, several risk factors such as age, gender, genetic variants and exposure opportunity to environment factors and their interaction each other have impacts on onset of endometrial carcinoma. However, only gene polymorphisms were considered in this study. The occurrence and development of EC
involves gene-gene and gene-environment interaction, so we need more high-quality studies to verify the results of this meta-analysis.

Conclusions

The present meta-analysis provided evidence that the Arg399Gln polymorphism of DNA repair gene XRCC1 may lead to an increased risk of endometrial carcinoma, especially in the Caucasian. Moreover, Ser326Cys polymorphism of hOGG1 increased endometrial carcinoma risk in the Caucasian.

Declarations

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Authors’ contributions

WH drafted the manuscript. WH and XSZ contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. WH and YL developed the search strategy. WH and ZHW provided statistical expertise. All authors read, provided feedback and approved the final manuscript.

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Availability of data and materials

Raw data can be accessed from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethics approval and consent to participate is not needed because this is a study of published data.

Consent for publication

Not applicable.
**Competing interests**

The authors declare that they have no conflict of interest.

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Tables

Table 1. Characteristics of inclusive literature and distribution of XRCC1, HOGG1 genotypes on case and control groups.
| Author [ref.] | Year | Country | Ethnicity | NOS scores | Sample size |
|--------------|------|---------|-----------|------------|-------------|
| Cincin [12]  | 2012 | Turkey  | Caucasian | 7          | 104-158     |
| Chen [13]    | 2016 | China   | Asian     | 6          | 108-110     |
| Hosono [14]  | 2013 | Japan   | Asian     | 6          | 91-261      |
| Makowska [15]| 2011 | Poland  | Caucasian | 7          | 150-150     |
| Samulak [16] | 2011 | Poland  | Caucasian | 7          | 456-300     |
| Sobczuk [17] | 2012 | Poland  | Caucasian | 7          | 94-114      |
| Smolarz [18] | 2018 | Poland  | Caucasian | 7          | 610-610     |

| Author [ref.] | Year | Country | Ethnicity | NOS scores | Sample size |
|--------------|------|---------|-----------|------------|-------------|
| Cincin [12]  | 2012 | Turkey  | Caucasian | 7          | 104-158     |
| Makowska [15]| 2011 | Poland  | Caucasian | 7          | 150-150     |
| Renata [19]  | 2011 | Poland  | Caucasian | 7          | 30-30       |
| Sobczuk [17] | 2012 | Poland  | Caucasian | 7          | 94-114      |
| Smolarz [18] | 2018 | Poland  | Caucasian | 7          | 610-610     |

Table 2. Summary of meta-analysis on DNA repair gene XRCC1, HOGG1 variants and endometrial carcinoma susceptibility.

| Population | Genetic model | Genetic model | No. of studies | OR    | 95% CI | Test of assoc |
|------------|---------------|---------------|----------------|-------|--------|---------------|
| XRCC1-Arg399Gln | G vs. A | Allelic | 7 | 1.36 | 1.23–1.5 | F |
|               | GG+AG vs. AA | Dominant | 7 | 1.36 | 1.13–1.5 | F |
|               | GG vs. AA+AG | Recessive | 7 | 1.53 | 1.31–1.7 | F |
|               | G vs. A | Allelic | 2 | 0.96 | 0.72–1.2 | F |
|               | GG+AG vs. AA | Dominant | 2 | 1.04 | 0.52–2.0 | F |
|               | GG vs. AA+AG | Recessive | 2 | 0.93 | 0.65–1.3 | F |
| Asian       | G vs. A | Allelic | 5 | 1.44 | 1.29–1.6 | F |
| Caucasian   | GG+AG vs. AA | Dominant | 5 | 1.36 | 1.14–1.6 | F |
|               | GG vs. AA+AG | Recessive | 5 | 1.72 | 1.45–2.0 | F |
| HOGG1-Ser326Cys | C vs. S | Allelic | 5 | 1.54 | 1.34–1.7 | F |
| Caucasian   | CC+CS vs. SS | Dominant | 5 | 1.38 | 1.14–1.6 | F |
|               | CC vs. CS+SS | Recessive | 5 | 2.03 | 1.63–2.5 | F |

Table 2. Summary of meta-analysis on DNA repair gene XRCC1, HOGG1 variants and endometrial carcinoma susceptibility.

F, fixed effects model; R, random effects model
Selection of studies on the association between DNA repair gene XRCC1, hOGG1 with susceptibility to endometrial carcinoma.
**Figure 2**

Forest plots for pooled ORs for the associations between XRCC1 Arg399Gln and endometrial carcinoma risk in the overall population.
Figure 3

Forest plots for pooled ORs for the associations between hOGG1 Ser326Cys and endometrial carcinoma risk in the Caucasian population.
Figure 4

Sensitive analysis for the associations between hOGG1 Ser326Cys and endometrial carcinoma risk in the Caucasian population.

Figure 5

Begg’s funnel plots for association between XRCC1 Arg399Gln (Figure A) and hOGG1 Ser326Cys (Figure B) and endometrial carcinoma risk in the overall population.
