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ORIGINAL ARTICLE

Estrogen Receptor 1 (ESR1) genetic variations in cancer risk: A systematic review and meta-analysis

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Summary
Background: Emerging published data on the association between single nucleotide polymorphisms (SNPs) in the estrogen receptor 1 (*ESR1*) gene and cancer susceptibility are inconsistent. This review and meta-analysis is performed to derive a more precise evaluation of this relationship.
Methods: The literature search of PubMed, Embase, Web of Science and CNKI databases was conducted from their inception through June 2014. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the association.
Results: Twenty-two literatures were enrolled in this meta-analysis. The results indicated that ESR1 rs1801132 (C > G) was associated with cancer risk in Caucasian populations. However, the results of stratified analysis by cancer type and source of controls indicated that no significant association was found. Furthermore, rs2077647 (A > G) was only associated with an increased risk of hepatocellular carcinoma, but was an adverse effect on cancer risk in Caucasian populations.
Conclusions: This present meta-analysis indicated that rs1801132 (C > G) and rs2077647 (A > G) may be protective factors in Caucasian populations. Meanwhile, rs2077647 (A > G) may be closely related with hepatocellular carcinoma.

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Introduction

Malignant tumor is one of the most common diseases threatening public health, and is becoming more prevalent worldwide, due to late diagnosis, limited treatment and deprived prognosis. New cases about 12.7 million were diagnosed and 7.6 million patients died from malignant tumor in 2008 [1]. Generally, cancer has been shown to be a multifactorial disease induced by complex interactions between genetic and environment factors [2]. Hormonal factors also play an essential role in the carcinogenesis and progression of cancer through estrogen synthesis, metabolism and signal transduction pathways [3,4]. In recent years, evidence from epidemiological and genetic investigations provides more closely focus on the inherited susceptibility to cancer, such as variations in hormonal gene, considered as the key players in various cancers development [5,6]. Currently, several hormonal genes have been identified to be associated with cancer risk, such as *CYP17/19*, *AR*, *ESR1/2*, etc [7—9].

Estrogen receptor 1 (ESR1), spanning approximately 300 kb in length, is located on chromosome 6, locus 6p25.1, which includes eight exons and seven introns [10]. Epigenetic and genetic changes in *ESR1* gene may lead to differences in estrogen metabolism, such as ESR1 functions as a ligand-activated transcription factor contained of several domains important for hormone binding, DNA binding, as well as activation of transcriptions; it can also interact with estrogens receptors to stimulate to alter the expression of downstream genes and proliferation of mammary epithelial tissue [11]. Therefore, these possibly explain inter-individual differences in cancer risk. Recently, a number of investigations have been conducted to study the potential associations between ESR1 genetic variations and cancer risk, such as rs1801132 (C > G) located on exon 4 and rs2077647 (A > G) which is a silent polymorphism located in exon 1 (S10S). Some studies support the mechanism in which ESR1 genetic variations promote the development and progression of various cancers by altering estrogen metabolism. However, there are also some studies showing no association between *ESR1* gene mutations and their effects on cancer susceptibility. The inconsistent conclusions between *ESR1* gene mutations and cancer risk may be due to the limitations in sample size of the corresponding studies or the inadequate statistical power in genetic studies of complex characteristics, like age, gender, race, differentiation on tumor stage and research methodology. Therefore, we performed a search of the relevant literatures and carried out a meta-analysis to achieve a more accurate evaluation of the association between ESR1 genetic variations and cancer risk.

Material and methods

Publication selection

Papers were determined by an electronic search of PubMed, Embase, Web of Science and CNKI using the following terms: ''estrogen receptor 1'', ''estrogen receptor α'', ''ESR1'', ''ESRα'', ''polymorphism'', ''cancer'', ''tumor'' or ''carcinomas''. Meanwhile, we also manually searched the references of these publications in order to retrieve additional studies. Only those published as full-text articles were included as candidates. The search updated on June 2014.

Inclusion and exclusion criteria

Studies assessing the association between ESR1 genetic variations and cancer risk had to meet all of the following criteria:

- they were original epidemiological studies on the association between ESR1 genetic variations and cancer susceptibility;
- case-control studies;
- effective information provided to estimate odds ratios (ORs) with 95% confidence intervals (CIs).

However, case-only studies, case reports, duplicated studies, unpublished data, letters, comments and reviews must be excluded.

Data extraction

For every eligible study, two investigators (WBS and JJH) using a standardized and uniform method of data extraction collected carefully information regarding the first author's last name, country of origin, year of publication, race of the study population, cancer type, the source of control, genotyping method, polymorphism site and the numbers of cases and controls. All disagreements about eligibility were resolved by discussion after data collection and got consensus following with another reviewer.

Statistical methods

Hardy-Weinberg equilibrium (HWE) was used to evaluate every eligible study by using the goodness-of-fit χ^2 test as previous study described [12]. ORs with the corresponding 95% CIs were used to estimate the strength of association between ESR1 rs1801132 (C > G), rs2077647 (A > G) and cancer risk. The pooled ORs were also assessed for rs1801132 (C > G) by homozygous, heterozygous, recessive and dominant models as well as allele comparison and so were rs2077647 (A > G). Subsequently, stratified analyses were also performed by cancer type, race and source of control (if one of cancer type contained less than two individual studies, it would have been combined into the ''others'' group).

The random-effects model (the DerSimonian and Laird method) was chose if $P_{\text{heterogeneity}}$ (P_h) < 0.05 for the Q test [13]. Otherwise, a fixed-effects model (Mantel-Haenszel method) was selected [14]. Chi^2-based Q-test was used to assess the heterogeneity across the studies [15]. Additionally, the stability for results was used to be estimated by excluding each study individually and recalculating the ORs with the corresponding 95% CIs for the remaining ones in the sensitivity analysis. The publication bias was conducted by Funnel plots and Egger's linear regression test [16]. All the *P* values were two-sided and $P < 0.05$ was considered as