RESEARCH ARTICLE

Association of Rs11615 (C>T) in the Excision Repair Cross-complementing Group 1 Gene with Ovarian but not Gynecological Cancer Susceptibility: a Meta-analysis

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Abstract

Background: Evidence suggests that the rs11615 (C>T) polymorphism in the ERCC1 gene may be a risk factor for gynecological tumors. However, results have not been consistent. Therefore we performed this meta-analysis. Methods: Eligible studies were identified by search of PubMed, MEDLINE and Chinese National Knowledge Infrastructure (CNKI). Odds ratios (ORs) and 95% confidence intervals (CIs) were applied to assess associations between rs11615 (C>T) and gynecological tumor risk. Heterogeneity among studies was tested and sensitivity analysis was applied. Results: A total of 6 studies were identified, with 1,766 cases and 2,073 controls. No significant association was found overall between rs11615 (C>T) polymorphism and gynecological tumors susceptibility in any genetic model. In further analysis stratified by cancer type, significantly elevated ovarian cancer risk was observed in the homozygote and recessive model comparison (TT vs. CC: OR=1.69, 95% CI=1.03–2.77, heterogeneity=0.876; TT vs. CT/CC: OR=1.72, 95% CI=1.07–2.77, heterogeneity=0.995). Conclusion: The results of the present meta-analysis suggest that there is no significant association between the rs11615 (C>T) polymorphism and gynecological tumor risk, but it had a increased risk in ovarian cancer.

Keywords: ERCC1 - polymorphism - gynecological tumor - ovarian cancer - meta-analysis

Introduction

Gynecological tumor is a one of the public health problem around the world. Some studies identified that genetics play a vital role in determining cancer risk and various genetic variations have been identified to increase cancer risk (Goode et al., 2002; He et al., 2008). Excision repair cross-complementing group 1 (ERCC1) is one of the key genes in nucleotide excision repair (NER). The polymorphisms in ERCC1 may alter protein function and an individual's capacity to repair damaged DNA; deficits in repair capacity may lead to genetic instability and carcinogenesis. Some studies have investigated the association between ERCC1 polymorphisms and gynecological tumor risk, but results are inconclusive and inconsistent. Therefore, we conducted this meta-analysis to synthesize the results of these studies and to establish a more durable conclusion.

Materials and Methods

Search strategy

PubMed, MEDLINE and Chinese National Knowledge Infrastructure (CNKI) were comprehensively searched using combinations of the terms "ERCC1", "polymorphism or variant" and "gynecological tumor or ovarian cancer or cervical cancer or endometrial cancer" (the last search update on September 15, 2012) without any restriction on language or publication year. And additional studies were sought from its citations, references.

Inclusion and exclusion criteria

Studies were eligible if they met the following criteria: 1) case-control studies, 2) the association between polymorphism (rs11615C>T) and endometrial cancer risk was explored, 3) sufficient genotype data was provided. Major reasons for exclusion of studies were: 1) overlapping study populations, 2) control subjects in these studies were departed from Hardy-Weinberg equilibrium (HWE). If multiple studies had overlapping populations, only those with complete data or largest populations were included.

Data extraction

Two investigators (Ma and Feng) independently extracted the data from eligible studies selected according to the inclusion and exclusion criteria listed above. The following information was gathered from each study: the first author's name, year of publication, country of origin, ethnicity, source of controls, genotyping method,

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cancer type, sample size, distribution of genotypes in case and control groups. Ovarian cancer, cervical cancer and endometrial cancer were included in gynecological tumor.

Statistical analysis

To test the distribution of Hardy-Weinberg equilibrium (HWE) in controls, chi-square test for goodness of fit was conducted and a *p*<0.05 indicated disequilibrium of HWE (Guo and Thompson, 1992). Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association between the rs11615 polymorphism and gynecological tumor risk. Pooled ORs were performed for homozygote comparison (TT vs. CC), heterozygote comparison (CT vs. CC), dominant model (TT/CT vs. CC), and recessive model (TT vs. CT/CC), respectively. Subgroup analyses were performed by cancer type, ethnicity and source of controls. The heterogeneity among different studies was checked by the Q-test (Lau et al., 1997). If the P value is <0.10, a random effect model was used to pool the results. Otherwise, a fixed-effect model was then used (Mantel and Haenszel, 1959; DerSimonian and Kacker, 2007). To assess the stability of the results, a sensitivity analysis was performed.

Begg's funnel plot and the Egger' linear regression test were conducted to detect publication bias, and a P<0.05 was considered significant (Begg and Mazumdar, 1994; Egger et al., 1997). All analyses were done using STATA software, version 11.0 (STATA Corp., College Station, TX, USA) and all tests were two-sided.

Results

Characteristics of studies

The preliminary literature search yielded 6 articles that explored the association of rs11615 (C>T) polymorphism

with the susceptibility to gynecological tumor. Totally, 1766 cases and 2073 controls were included in the meta-analysis (Figure 1). The study characteristics are displayed in Table 1. There were 4 studies of Asian and 2 studies of USA. 3 studies discussed the risk of endometrial cancer, 2 studies discussed the risk of ovarian cancer, and 2 studies discussed the risk of cervical cancer. All studies showed that the distribution of genotypes in the control group was in agreement with the Hardy-Weinberg equilibrium (HWE).

Quantitative synthesis

Table 2 showed the main results of this meta-analysis. We found no significant association of the rs11615 (C>T) polymorphism with overall cancer risk in any of four models. In the sub-group analyses by cancer types, significant increased risks were found in the homozygote and recessive model comparison for ovarian cancer (TT vs. CC: OR=1.69, 95% CI=1.03–
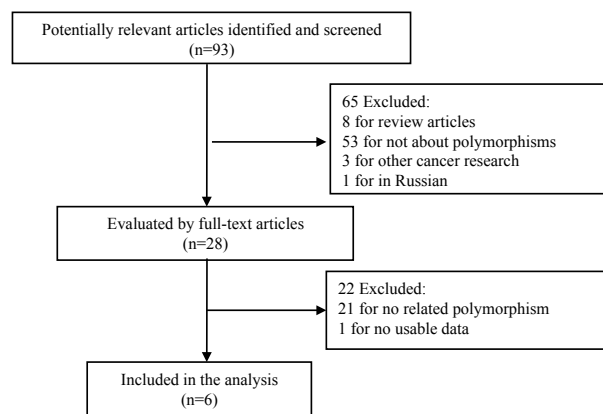

Figure 1. The Detailed Process of Identifying Eligible Studies

Table 1. Main Characteristics of Included Studies

First author/year	Country	Ethnicity	Control source	Genotyping method	Cancer types	Cases			Controls			χ^2 for HWE in controls[†]
						CC	CT	TT	CC	CT	TT	
He et al (2012)	China	Asian	HB	RFLP	Ovarian	70	61	24	152	130	30	0.774
Han et al (2012)	Korea	Asian	HB	Taqman	Cervical	131	85	13	115	78	11	0.635
Doherty et al (2011)	USA	USA	PB	Taqman	Endometrial	103	338	283	92	337	275	0.478
Xiong et al (2010)	China	Asian	HB	RFLP	Cervical	23	26	8	66	32	5	0.663
Jo et al (2007)	Korea	Asian	HB	RFLP	Ovarian	56	29	9	189	121	19	0.950
					Endometrial	61	39	2	189	121	19	0.950
Weiss et al (2005)	USA	USA	PB	RFLP	Endometrial	134	188	49	170	196	54	0.831

HB, Hospital based; PH, Population based; RFLP, Restriction fragment length polymorphism; [†]χ^2, for testing Hady-Weinberg equilibrium

Table 2. Results from Meta-Analysis of rs11615 (C>T) and Gynecological Tumor Risk

Variables	N	Case/ Control	TT vs CC		CT vs CC		TT/CT vs CC		TT vs CT/CC	
			OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Total	6	1776/2073	1.12 (0.90, 1.39)	0.115	1.05 (0.90, 1.22)	0.178	1.08 (0.93, 1.24)	0.074	1.08 (0.91, 1.28)	0.264
Cancer type										
Ovarian	2	249/642	1.69 (1.03, 2.77)*	0.876	0.93 (0.67, 1.28)	0.488	1.05 (0.78, 1.41)	0.456	1.72 (1.07, 2.77)*	0.995
Cervical	2	320/307	2.04 (0.48, 8.72)	0.048	1.42 (0.60, 3.39)	0.03	1.54 (0.58, 4.10)	0.01	1.52 (0.78, 2.97)	0.129
Endometrial	3	1197/1453	0.95 (0.67, 1.34)	0.254	1.04 (0.89, 1.27)	0.385	1.07 (0.93, 1.23)	0.35	0.98 (0.81, 1.18)	0.327
Ethnicity										
Asian	4	671/949	1.46 (0.99, 2.15)	0.131	1.04 (0.84, 1.29)	0.124	1.10 (0.90, 1.35)	0.042	1.43 (0.98, 2.09)	0.292
USA	2	1095/1124	0.99 (0.76, 1.29)	0.426	1.05 (0.85, 1.31)	0.172	1.05 (0.85, 1.29)	0.184	1.01 (0.83, 1.22)	0.9

N, number of studies included; OR, odds ratio; P_h, P value for heterogeneity; *OR with statistical significance; A fixed-effects model was used when the *P*-value for heterogeneity test was <0.10; otherwise, a random-effects model was used; In the subgroup analyses by source of controls was in consent with analyses by ethnicity (Hospital based subgroup = Asian subgroup; Population based subgroup = USA subgroup)

2.77, heterogeneity=0.876; TT vs. CT/CC: OR=1.72, 95% CI=1.07–2.77, heterogeneity=0.995). And no association was found in heterozygote and dominant model. It's worth noting that a trend of increased risk could be drawn in the homozygote and recessive model comparison in Asians (TT vs. CC: OR=1.46, 95% CI=0.99–2.15, heterogeneity=0.131; TT vs. CT/CC: OR=1.43, 95%CI=0.98–2.09, heterogeneity=0.292).

Publication bias and sensitivity analysis

Publication bias were evaluated by Egger's test and Begg's test, and we found any evidence of publication bias (TT vs. CC: Begg's test *p*=0.009, Egger's test *p*=0.003; CT vs. CC: Begg's test *p*=0.009, Egger's test *p*<0.001; TT/CT vs. CC: Begg's test *p*=0.009, Egger's test *p*=0.001; TT vs. CT/CC: Begg's test *p*=0.009, Egger's test *p*<0.001). Sensitivity analysis was performed to estimate individual study's influence on the pooled ORs by deleting one single study each time from pooled analysis, and the results indicated that no single study influenced the pooled ORs qualitatively, suggesting that the results of our meta-analyses are stable.

Discussion

DNA damage is known to play a causative role in the development of several human cancers. The NER pathway plays important roles in the repair of bulky lesions in the maintenance of genomic stability and it can protects against mutations caused indirectly by environmental carcinogens (Friedberg, 2001; Hoeijmakers, 2001; Sancar et al., 2004; Hiyama et al., 2007). It has been reported that a number of single nucleotide polymorphisms (SNPs) of nucleotide excision repair (NER) genes can alter the function of the respective genes, contributing to inter-individual variations of DNA repair capacity and a reduced DNA repair capacity may predispose an individual to cancer (Dunlop et al., 1997; Cheng et al., 1998; Park et al., 2002; Marin et al., 2004; Chen et al., 2007). The human ERCC1 protein is essential for a functional NER system and genetic variation in ERCC1 may contribute to impaired DNA repair capacity and increased cancer risk. Shin et al. evaluated genotype-phenotype relationship between DNA repair gene genetic polymorphisms (ATM-5144A>T, IVS21+1049T>C, IVS33-55T>C, IVS34+60G>A, and 3393T>G, XRCC2 31479G/A, XRCC4 921G/T, XRCC6 1796G/T, LIG4 1977T/C, RAD51 135G/C, 172G/T, RAD52 2259C/T, LIG1 583A/C, ERCC1 8092A/C, 354C/T, hMLH1 5' region -93G/A, 655A/G) and DNA repair capacity. DNA repair capacity was measured by a host cell reactivation assay of repair of ultraviolet damage. Their results suggest that DNA repair capacity might be influenced by genetic polymorphisms (Shin et al., 2008). The rs11615 (C>T) is a common polymorphism of ERCC1 gene and significantly associated with the risk of several types of cancers (Chen et al., 2000; Sturgis et al., 2002; Mort et al., 2003; Matullo et al., 2005; Zhou et al., 2005). Luo et al. conducted a case-control study to assess the role of potential SNPs of DNA repair genes on the risk of glioma and meningioma. However, they did not find rs11615 (C>T) polymorphism

was associated with a higher risk when compared with the wild-type genotype, partially because of the relatively small sample size the study (Luo et al., 2013). Li et al. evaluated ERCC1 association with response to platinum-based chemotherapy in ovarian cancer and found that negative ERCC1 expression had a better response to platinum-based chemotherapy. Their results proved that genetic variation in ERCC1 might contribute to impaired DNA repair capacity (Li et al., 2013).

In the present study, a total of 6 eligible studies, including 1766 cases and 2073 controls were identified and analyzed in this meta-analysis. For the rs11615 (C>T) polymorphism, we did not find it was associated with a statistical increased risk of gynecological tumor susceptibility in four models comparison. In the subgroup analysis according to ethnicity, a significant association was detected in ovarian cancer in homozygote and recessive models in our study. In terms of stratified analysis by ethnicity, we found this polymorphism had a trend of increased risk in Asian populations in homozygote and recessive models comparison.

To some extent, limitations of this meta-analysis should be addressed. Firstly, detailed individual data was not available, and a more precise analysis should be conducted on other covariates such as age, sex, and environmental factors. Secondly, the sample sizes of six included studies were rather small and not adequate enough to detect the possible risk for ERCC1 polymorphisms. Thirdly, only published studies were included in our studies, many unpublished data have been ignored in this analysis. Fourthly, publication bias existed in some comparisons, which may potentially influence the results of our meta-analysis.

In summary, this meta-analysis suggests that the rs11615 (C>T) polymorphism of the ERCC1 do not contribute to gynecological tumor risk, while it seemed to be associated with an increased ovarian tumor risk. Future large-scale studies are still needed to confirm these findings.

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