RESEARCH COMMUNICATION

Predictive Value of Excision Repair Cross-complementing Rodent Repair Deficiency Complementation Group 1 and Ovarian Cancer Risk

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Abstract

Objective: We aimed to analyze the association between excision repair cross-complementing rodent repair deficiency complementation group 1 (XRCC1) and ovarian cancer risk. Methods: We performed a hospital-based case-control study with 155 cases and 313 controls in China. All Chinese cases with newly diagnosed primary ovarian cancer between May 2005 to May 2010 in our hospital were invited to participate within 2 months of diagnosis. Controls were randomly selected from people who requested general health examinations in the same hospital during the same period. SNPs in EXCC1, ERCC1 C8092A and ERCC1 T19007C, were analyzed by PCR-RFLP method. Results: We observed a non-significantly increased risk of ovarian cancer among individuals with ERCC1 8092TT compared with those with the 8092CC genotype (adjusted OR=1.55, 95% CI%=0.74-2.97). Moreover, 19007TT genotype carriers also showed a non-significant increased risk of ovarian cancer over those with the 19007CC genotype (adjusted OR=1.78, 95% CI%=0.91-3.64). Conclusion: Our firstly investigation of links between polymorphisms in the ERCC1 gene and the risk of ovarian cancer in Chinese population demonstrated no significant association. Further large sample studies in Chinese populations are needed.

Keywords: Ovarian cancer - ERCC1 – polymorphism - Chinese population

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Introduction

Ovarian cancer has the highest mortality rate of all female cancers; more than 50% of the 21,650 women diagnosed with ovarian cancer die annually from this disease (Ries et al., 2007). China has a relatively low incidence of 3-5/105 females, which is about one-fourth of the incidence in northern European countries (Jin et al., 1993). We would hypothesis the genetic and environmental factors play a role in the carcinogenesis of ovary. Currently, the etiology of ovarian cancer has not been completely understood. Most of the known risk factors are related to parity and family history of ovarian cancer.

DNA damage is considered to be an important mechanism in the development of cancer. The DNA damage, included oxidative DNA damage, single- and double-strand breaks in DNA chains, and DNA–DNA or DNA–protein cross-links. Such damages, if not repaired, may cause errors during DNA synthesis leading tomutations that increase cancer risk (Liu et al., 2009; Rajaraman et al., 2010). Thus, polymorphisms of DNA repair genes are plausible candidates that can modify the risk of human cancers. Previous epidemiology and experimental studies have also reported that a number of single nucleotide polymorphisms (SNPs) in DNA repair genes may modify ovarian cancer (Li et al., 2001; Reed et al., 2003; Avraam et al., 2011).

The excision repair cross-complementing rodent repair deficiency complementation group 1 (ERCC1) gene is an essential subunit of the nucleotide excision repair (NER) system, which can recognize DNA damage, form heterodimers with xeroderma pigmentosum group F (XPF), and then perform DNA strand incision (Van et al., 1986; Bessho et al., 1997; Wilson et al., 2001). C8092A (rs3212986) and T19007C (rs11615) are two common polymorphisms of ERCC1 gene and their associations with altered risk of several types of cancers, including lung, bladder, colorectal cancers, etc., have been previously examined (Matullo et al., 2005; Zhou et al., 2005; Moreno et al., 2006; Zienolddingy et al., 2006). Associations between polymorphisms in ERCC1 gene and ovarian cancer risk have also been examined in Western countries but the results remained inconsistent (Li et al., 2001; Avraam et al., 2011). In contrast, evidences from Chinese populations are still lacking. Therefore, we

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conducted a hospital-based case-control study in China to evaluate the association between polymorphisms in ERCC1 gene and the risk of ovarian cancer.

Materials and Methods

This case-control study was conducted in the largest teaching hospital in the First Affiliated Hospital of Sun Yat-Sen University of China. All Chinese cases with newly diagnosed primary ovarian cancer between May 2005 to May 2010 in this hospital were invited to participate within 2 months after diagnosis. All cases recruited in this study were histological confirmed. Among a total of 160 eligible cases, 155 were successfully interviewed and donated blood samples with a participation rate of 96.8%. Controls were randomly selected from people who requested general health examinations in the same hospital during the same period. Controls were required to be without any history of any type of cancer and frequency matched by 5-year age groups. Among a total of 349 eligible controls, 313 were successfully interviewed and donated blood samples with a participation rate of 89.7%. Informed consent was obtained before each interview and blood taking. Trained interviewers conducted face-to-face interviews using a structured questionnaire to collect information on sociodemographic characteristics, tobacco smoking, alcohol use, radiation exposure, number of delivery, menopausal status, oral contraceptive use, family history of cancer, and other potential confounders. Proxies were interviewed if the participants were unable to participate because of cognitive disability. Among participants, 78% of cases and 97% of controls were direct respondents and the remainder was proxy respondents. Most proxy respondents were either spouses (64%) or other first-degree relatives (37%). All interviews were completed within 2 weeks after their diagnosis and each interview took around 10–15 min. All interviews and blood samples collection were conducted after obtaining signed informed consent from participants.

Genotyping

Genomic DNA was extracted from whole-blood samples using a commercially Blood Kit (Qiagen, Valencia, CA, USA). Genotyping was conducted by TaqMan Gene Expression assays using the ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems, Poster City, CA). Primer, probes, and reaction conditions were available upon request. Genotyping was done by laboratory personnel blinded to case-control status. We also performed the genotyping of internal positive control samples, use of no template controls, and use of replicates for 10% samples for quality control.

Statistical analysis

All the statistical analyses were performed with the software Stata version 9 (Stata, College Station, TX). Differences in the distributions of demographic characteristics, selected variables, and frequencies of genotypes of the ERCC1 polymorphism between the cases and controls were evaluated by using the Student's t-test (for continuous variables) or chi-square test (for categorical variables). Deviation of genotype frequency distribution in controls from those expected under Hardy-Weinberg Equilibrium (HWE) was assessed using chi square tests. Unconditional logistic regression was used to estimate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for each polymorphism. The associations between each polymorphism and ovarian cancer were further examined after adjusting for potential confounders using multivariate logistic regression models. Inclusion of potential confounders was based on biological and statistical considerations. Variables entered into the final model included: age, tobacco smoking, alcohol use, radiation exposure, number of delivery, menopausal status, oral contraceptive use and family history of cancer.

Results

The distribution basic characteristics among cases and controls are shown in Table 1. The mean age was 47.4±6.2 years among cases and 46.6±5.9 years among controls. There were no significant differences between cases and controls in age, drinking status, menopausal status and oral contraceptive use. Compared with controls, patients with ovarian cancer tended to have a higher ionizing radiation history and consumption of tobacco cigarettes. Cancer patients tended to have less number of delivery, and also had apparent family susceptibility. The distributions of the genotype frequencies were in agreement with those expected from the HWE model at the 0.05 level for controls (p=0.11 for ERCC1 C8092A and p=0.14 for ERCC1 T19007C).

Table 2 showed the genotype frequencies of the ERCC1 C8092A and ERCC1 T19007C polymorphisms

Table 1. Characteristics of Included Cases and Controls in Our Studies

Variables	Cases(%) N=155	Controls(%) N=313	P value
Age (mean±SD, years)	47.4±6.2	46.6±5.9	0.08
Smoking status			
Smokers	11(7.4)	7(2.3)	<0.05
Nonsmokers	144(92.6)	306(97.7)	
Drinking status			
Drinkers	29(18.5)	51(16.2)	0.52
Nondrinkers	126(81.5)	262(83.8)	
Number of delivery			<0.05
0	18(11.3)	12(3.8)	
1	78(50.6)	141(45.1)	
2	50(32.5)	118(37.8)	
≥3	9(5.6)	42(13.3)	
Menopausal status			
Yes	76(49.3)	163(52.1)	0.53
No	79(50.7)	150(47.9)	
Oral contraceptive use			
Yes	37(23.7)	92(29.3)	0.21
No	118(76.3)	221(70.7)	
Ionizing radiation history			
Yes	11(6.9)	5(1.6)	<0.05
No	144(93.1)	308(98.4)	
Family history of cancer			
Yes	27(17.4)	39(12.5)	0.15
No	128(82.6)	274(87.5)	

Table 2. Associations Between ERCC1 Gene Polymorphisms and Ovarian Cancer Risk

Genotype	Cases(%) N=155	Controls(%) N=313	Crude OR	Adjusted OR[1]
ERCC1 C8092A				
CC	73(47.3)	164(52.4)	1.0(Reference)	1.0(Reference)
CT	57(36.7)	109(34.7)	1.17(0.75-1.98)	1.20(0.71-2.23)
TT	25(16.0)	40(12.9)	1.41(0.76-2.57)	1.55(0.74-2.97)
ERCC1 T19007C				
CC	70(45.2)	152(48.7)	1.0(Reference)	1.0(Reference)
CT	61(38.0)	130(41.6)	1.02(0.66-1.58)	1.15(0.68-1.73)
TT	24(15.6)	30(9.7)	1.73(0.89-3.32)	1.78(0.91-3.64)
Combined C8092A and T19007C				
8092CC and 19007CC	41(26.5)	96(30.7)	1.0(Reference)	1.0(Reference)
8092CC and 19007T allele	32(20.6)	68(21.7)	1.10(0.61-2.0)	1.14(0.59-2.13)
8092T allele and 19007CC	29(18.7)	56(17.9)	1.21(0.65-2.25)	1.23(0.67-2.44)
8092T allele and 19007T allele	53(34.2)	92(29.4)	1.34(0.80-2.30)	1.52(0.84-2.53)

[1]Adjusted for age, smoking, drinking, number of delivery, menopausal status, oral contraceptive use and ionizing radiation history

in cases and controls and the corresponding ORs and adjusted ORs as well as their CIs. Polymorphisms in the ERCC1 C8092A and ERCC1 T19007C did not showed significant difference between the ovarian cancer cases and controls. We observed the a non-significantly increased risk of ovarian cancer among individuals with ERCC1 8092TT compared with those with the 8092CC genotype (adjusted OR=1.55, 90% CI%=0.74-2.97). Moreover, and 19007TT genotype carriers showed a moderate increased risk of ovarian cancer than those with 19007CC genotype (adjusted OR=1.78, 90% CI%=0.91-3.64). Individuals with both 8092T allele and 19007T allele genotypes showed an non-significant increased risk of ovarian cancer (adjusted OR=1.52, 90% CI%=0.84-2.53). We also performed subgroup analysis regarding tumor types (Invasive or borderline types) and smoking status (Smokers and Non-smokers), but the results did not substantially change.

Discussion

This study is the first time to evaluated the associations between polymorphisms in ERCC1 gene and the risk of ovarian cancer in Chinese population. However, we did not found an significant association between the two polymorphisms in ERCC1 gene, C8092A and T19007C, and the risk of ovarian cancer in a Chinese population. Our finding is different with previous study regarding the ERCC1 gene and ovarian cancer risk (Krivak et al., 2008; Weberpals et al., 2009; Avraam et al., 2011). One previous study was from American population showed the ERCC1 C8092A gene polymorphism is associated with the increased risk of ovarian cancer and clinic outcome. Another two previous studies with a significant association between ERCC1 polymorphism and the risk of ovarian cancer risk were from Greece and Canada with a relatively large sample sizes (Weberpals et al., 2009; Avraam et al., 2011). Another study conducted in Chinese population regarding the prognosis of ovarian cancer and ERCC1 gene polymorphisms also showed a significant association (Lin et al., 2010). The inconsistency of the studies' results may be explained by the differences in the susceptibility of genes, variations of different ethnicities, source of control subjects, sample size, different environment factors or by chance. Therefore, further large sample study regarding the association between them is still warranted.

Strengths of our study include its collection of control group. All the controls were selected from those who came to hospital for routine health examination, probably making the controls more representation of the general population. However, the selection of control was not a randomized method, therefore, they also could not better represent the general population, there was still as certain risk of selection bias if people seeking routine health examination had any difference in terms of the studies exposures. Secondly, all cases in this study were histologically confirmed, which minimized misclassification. Thirdly, due to the low incidence of ovarian cancer, we only had a relative small sample size of cases in our study, and we increased the number of controls to case-control ratio of 1:2 or more can, at least to some extent, increase the study power. Moreover, some limitations should be considered. The DNA repair is a complex collection of processes that involves many genes and factors. In our study, we only analyze the ERCC1 gene polymorphisms in the risk of ovarian cancer, and further studies on the modification of the other polymorphisms and environment factors in the ERCC1 and other DNA repair genes are warranted.

In conclusion, our study firstly investigated the association between the association between polymorphisms in ERCC1 gene and the risk of ovarian cancer in Chinese population, and our study did not found a significant increased risk of ovarian cancer among ERCC1 8092TT and 8092TT carriers. Therefore, further large sample studies are needed.

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