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The association between *XRCC1* genetic polymorphisms and the risk of endometrial carcinoma in Chinese

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ABSTRACT

Accumulated evidences report that X-ray repair cross-complementing group 1 gene (*XRCC1*) genetic polymorphisms play an important role in the development of endometrial carcinoma (EC). This study aims to evaluate the association of *XRCC1* c.1161G>A and c.1804C>A genetic polymorphisms with the risk of EC. A total of 218 EC patients and 243 cancer-free controls were included in this study. The genotypes of *XRCC1* genetic polymorphisms were determined by the created restriction site-polymerase chain reaction (CRS-PCR) and PCR-restriction fragment length polymorphism (PCR-RFLP) methods. We found that these two genetic polymorphisms were statistically associated with the risk of EC. As for c.1161G>A, in comparison with GG wild genotype, the AA genotype was significantly associated with the increased risk of EC (OR = 2.36, 95% CI 1.28–4.37, $\chi^2 = 7.71$, P = 0.005). As for c.1804C>A, the CC genotype significantly increased the risk of EC in comparison with CC wild genotype (OR = 2.77, 95% CI 1.38–5.58, $\chi^2 = 8.54$, P = 0.003). Our data indicate that the A allele of c.1161G>A and c.1804C>A genetic polymorphisms could contribute to increase the risk of EC (for c.1161G>A: A versus (vs.) G, OR = 1.34, 95% CI 1.02–1.76, $\chi^2 = 4.56$, P = 0.033; for c.1804C>A: A vs. C, OR = 1.34, 95% CI 1.01–1.77, $\chi^2 = 4.03$, P = 0.045). Our results indicate that the *XRCC1* c.1161G>A and c.1804C>A genetic polymorphisms significantly influenced the risk of EC in Chinese populations, and might be used as molecular markers for evaluating EC risk.

1. Introduction

Endometrial carcinoma (EC) is one of the most common and complex gynecological malignancies in the world (Prat et al., 2007; Meyer et al., 2008; Sorosky, 2008; Jemal et al., 2011; Spurdle et al., 2011; Hosono et al., 2013). It has been proposed that the possible risk factors for EC include genetic factors, environmental factors, and other risk factors, such as age, menarche age, body mass index, regular exercise, diabetes mellitus, hypertension, smoking status, alcohol consumption, oral contraceptive consumption, uterine bleeding, use of hormone replacement therapy (HRT), and family history of EC (Pieretti et al., 2001; Kaaks et al., 2002; Weiss et al., 2005; Prat et al., 2007; Meyer et al., 2008; Sorosky, 2008; Fader et al., 2009; Krupa et al., 2011; Romanowicz-Makowska et al., 2011; Cincin et al., 2012; Sobczuk et al., 2012; Hosono et al., 2013). However, EC is still a major unsolved health problem in female, and the exact mechanism basis of EC remains poorly understood. Currently, accumulated evidences report that X-ray repair cross-complementing group 1 gene (*XRCC1*) genetic polymorphisms play an important role in the development of EC. The *XRCC1* gene has been regarded as one of the most important candidate genes in influencing the risk of EC (De Ruyck et al., 2005; Romanowicz-Makowska et al., 2011; Cincin et al., 2012; Sobczuk et al., 2012; Hosono et al., 2013). The *XRCC1* gene locates at chromosome 19q13.2–13.3, comprised 17 exons, and expresses a 70-kDa protein, and encodes an enzyme which plays key roles in base excision repair (BER) pathway (Wood et al., 2001; Tudek, 2007; Mutamba et al., 2011; Zhang et al., 2012). *XRCC1* is a polygenetic gene, and the single nucleotide polymorphisms (SNPs) of *XRCC1* gene might affect the expression and function of *XRCC1* protein, which are potentially associated with the risk of EC. Recently, several studies have observed the potential association of *XRCC1* SNPs (such as arginine (Arg) 194 tryptophan (Trp), Arg399 glutanine (Gln)), with the risk of EC (Romanowicz-Makowska et al., 2011; Cincin et al., 2012; Sobczuk et al., 2012; Hosono et al., 2013). These *XRCC1* genetic polymorphisms resulted into non-synonymous amino acid replacement, which might play a genetic influence on the altered function of *XRCC1* protein and the risk of EC in different populations. However, up to now, there are no similar

Abbreviations: *XRCC1*, X-ray repair cross-complementing group 1 gene; EC, endometrial carcinoma; SNPs, single nucleotide polymorphisms; HWE, Hardy–Weinberg equilibrium; CRS-PCR, created restriction site-polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; HRT, hormone replacement therapy; FIGO, International Federation of Gynaecology and Obstetrics; ORs, odds ratios; CIs, confidence intervals; SD, standard deviation.

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studies on the potential association of *XRCC1* c.1161G>A and c.1804C>A genetic polymorphisms with the risk of EC. Considering the important role of *XRCC1* gene in the development of EC, this study aims to indentify *XRCC1* c.1161G>A and c.1804C>A genetic polymorphisms, and to evaluate the effects of *XRCC1* c.1161G>A and c.1804C>A genetic polymorphisms on the risk of EC.

2. Materials and methods

2.1. Subjects

218 patients with a histologically proven diagnosis of EC and 243 cancer-free controls were enrolled in this case–control study. All subjects were unrelated genetically Chinese with Han ethnicity and included consecutively from March 2009 to June 2014 in Sun Yat-Sen Memorial Hospital (Sun Yat-Sen University, Guangzhou, China). The controls were age frequencies-matched with EC patients. Those with a history of EC cancer and other medical diseases were excluded. The criteria of the International Federation of Gynaecology and Obstetrics (FIGO) were utilized to identify the tumors' FIGO Grade and FIGO Stage. All subjects had agreed to complete a risk factor questionnaire. The general characteristics of the endometrial EC patients and controls are summarized in Table 1, including age, menarche age, body mass index, regular exercise, diabetes mellitus, hypertension, smoking status, alcohol consumption, oral contraceptive consumption, uterine bleeding, use of hormone replacement therapy (HRT), family history of EC, histology, FIGO Grade, and FIGO Stage. The protocol of this study was approved by the local ethics committee of Sun Yat-Sen Memorial Hospital (Sun Yat-Sen University, Guangzhou, China), and informed written consents were collected from all subjects.

2.2. Genomic DNA extraction and genotyping analyses

A 5 mL peripheral blood sample was collected from each subject. Genomic DNA was extracted using the Qiagen Blood Kit (Qiagen, Chatsworth, CA). According to the human *XRCC1* gene DNA sequences (GenBank ID: NC_000019.9) and mRNA sequences (GenBank ID: NM_006297.2), the specific polymerase chain reaction (PCR) primers for analyzing *XRCC1* genetic polymorphisms were designed by the Primer Premier 5.0 software (Premier Biosoft International, Palo Alto, CA). Table 2 shows the detailed information of primer sequences, annealing temperature, amplification fragment size and region. The 20 μL PCR mixture contained about 50 ng template DNA, 1× buffer (100 mmol Tris–HCl, pH 8.3; 500 mmol KCl), 0.25 μmol primers, 2.0 mmol $MgCl_2$, 0.25 mmol dNTPs, and 0.5U Taq DNA polymerase (Promega, Madison, WI, USA). The PCR reaction was conducted at an initial denaturation at 94 °C for 5 min, followed by 35 cycles of 94 °C for 30 s, annealing at

Table 1
The general characteristics of the endometrial carcinoma (EC) cases and controls.

Characteristics	Cases (n)	%	Controls (n)	%	χ^2-Value	P-value
Number	218	47.29	243	52.71		
Mean age, years ± SD	56.35 ± 9.42		59.27 ± 8.75			0.0865
Menarche age, years ± SD	13.16 ± 1.88		13.37 ± 1.59			0.0722
Body mass index (n)					2.3989	0.1214
<25 kg/m^2	152	69.72	185	76.13		
≥25 kg/m^2	66	30.28	58	23.87		
Regular exercise					3.2432	0.0717
Yes	139	63.76	174	71.60		
No	79	36.24	69	28.40		
Diabetes mellitus (n)					3.4523	0.0632
Yes	90	41.28	80	32.92		
No	128	58.72	163	67.08		
Hypertension (n)					3.4607	0.0628
Yes	65	29.82	54	22.22		
No	153	70.18	189	77.78		
Smoking status					3.5411	0.0599
Yes	47	21.56	36	14.81		
No	171	78.44	207	85.19		
Alcohol consumption					0.2116	0.6455
Yes	63	28.90	75	30.86		
No	155	71.10	168	69.14		
Oral contraceptive consumption					3.4980	0.0614
Yes	50	22.94	39	16.05		
No	168	77.06	204	83.95		
Uterine bleeding					3.4993	0.0614
Yes	115	52.75	107	44.03		
No	103	47.25	136	55.97		
Use of hormone replacement therapy (HRT)					0.1969	0.6572
Yes	43	19.72	52	21.40		
No	175	80.28	191	78.60		
Family history of endometrial carcinoma (n)					3.4691	0.0625
Yes	53	24.31	42	17.28		
No	165	75.69	201	82.72		
Histology						
Endometrioid	165	75.69	–			
Others	53	24.31	–			
FIGO Grade						
G1	89	40.83	–			
G2	98	44.95	–			
G3	31	14.22	–			
FIGO Stage						
I	185	84.86	–			
II	10	4.59	–			
III	17	7.80	–			
IV	6	2.75	–			

P-values calculated by chi-square (χ^2) test. SD, standard deviation.