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Original Research

The association between murine double minute 2 (MDM2) rs2279744 and endometrial cancer risk in a Chinese Han population

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Abstract: Some studies investigated the association between the murine double minute 2 (MDM2) rs2279744 polymorphism and endometrial cancer susceptibility, but provided controversial or inconclusive results. Thus, we decided to perform this case-control study to determine the association between MDM2 rs2279744 polymorphism and endometrial cancer in a Chinese Han population. A total of 215 endometrial cancer patients and 212 cancer-free controls were included in this case-control study. We genotyped the MDM2 rs2279744 polymorphism by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). GG genotype showed a statistically significantly increased risk of developing endometrial cancer (OR=1.72, 95%CI 1.08-2.76, *P*=0.02). Statistically significant difference was observed when the patients and controls were compared according to G versus I (OR=1.40, 95%CI 1.07-1.84, *P*=0.01). A significantly higher frequency of G allele was observed in patients with stage III+IV, compared to stage I+II (OR=2.24, 95%CI 1.49-3.38, *P*=0.001). In conclusion, the study found that MDM2 rs2279744 polymorphism was significantly associated with endometrial cancer risk in a Chinese Han population.

Key words: Endometrial cancer; Murine double minute 2; Polymorphism; Association.

Introduction

Endometrial cancer is the most frequent gynecological tumor in developed countries, and its incidence is increasing (1). It is also the most common malignancy within the female reproductive system, representing 37.7% of all disorders (1). Several factors, such as obesity, early menarche, menstrual disorders, and polycystic ovary syndrome, could increase the risk of endometrial cancer (2). Recently, genetic factors were also recognized as risk factors.

Murine double minute 2 (MDM2) was first found from the double mimute in transformation mice. MDM2 is an oncoprotein with ubiquitin E3 ligase activity. MDM2 could bind to p53 and negatively modulates the functions of p53 tumor suppressor by promoting p53's ubiquitination (3). The polymorphism SNP309T>G (rs2279744) has been found to locate in the MDM2 intronic promoter. This polymorphism could enhance Sp1 transcription factor binding, thereby leading to increased MDM2 expression (4). Some studies investigated the association between the MDM2 rs2279744 polymorphism and endometrial cancer susceptibility, but provided controversial or inconclusive results (5, 6). Thus, we decided to perform this case-control study to determine the association between MDM2 rs2279744 polymorphism and endometrial cancer in a Chinese Han population.

Materials and Methods

Study subjects

A case-control study was performed in 215 endometrial cancer patients and 212 cancer-free controls between 2013 and 2016. All subjects were ethnically Chinese Han population. Tumor types and stages were determined according to the World Health Organization classification. The controls were randomly selected from healthy individuals who underwent routine physical examination in the same area during the same time period as the cases. Information on individuals was gathered from both cases and controls. The study protocol was approved by the Institutional Review Boards.

Genotyping method

The blood samples were collected from each enrolled subjects. The genomic DNA was extracted from peripheral venous blood using the Axygen DNA isolation kit (Axygen, USA). DNA fragments containing the polymorphism were amplified with the forward primer 5'-CGCGGGAGTTCAGGGTAAAG-3' and 5'-AGCTGGAGACAAGTCAGGACTTAAC-3'. The PCR reaction was carried out in a 20 ml reaction mixture containing 1× Phusion High-Fidelity PCR Master Mix (Thermo Scientific, Finland) and 0.25 mM of each primer. The PCR cycle consisted of an initial denaturation step at 98 °C for 30 s, followed by 35 cycles of denaturation (98 °C for 5 s), annealing (65 °C for 5 s) and extension (72 °C for 5 s), and a final extension at 72 °C

Table 1. Characteristics of the included subjects.

Characteristics	Case (%)	Control (%)	*P* value
Age (years)			
≤60	107 (49.8%)	114 (53.7%)	0.21
>60	108 (50.2%)	98 (46.2%)	
Menopausal status			
Yes	114 (53.0%)	115 (54.2%)	0.75
No	101 (47.0%)	97 (45.8%)	
Histology			
Endometrioid adenocarcinoma	181 (84.2%)		
Non-endometrioid adenocarcinoma	34 (15.8%)		
FIGO stage			
I+II	71 (33.0%)		
III+IV	144 (67.0%)		

for 5 min. The 237 bp amplified product was digested overnight with 1 U of MspA1I (BioLaps, New England) at 37°C. The wild-type allele T was identified by the presence of 237 bp band, while the mutant allele G was represented by 189 and 48 bp bands.

Statistical analysis

All statistical analyses were performed by the Statistical Package for Social Sciences for Windows software (Windows version release 19.0; SPSS, Inc., Chicago, IL, USA). The frequencies of allele and genotype in cases and controls were calculated by gene counting method. Differences between cases and controls in demographic characteristics and frequencies of genotypes were evaluated by using chi-square ($\chi 2$) test. Hardy–Weinberg equilibrium (HWE) was also tested by a chi-square ($\chi 2$) test. Differences were considered significant when $P<0.05$.

Results

A total of 215 endometrial cancer patients and 212 cancer-free controls were included in this case-control study. Age and menopausal status were balanced between case and control. Between case and control, the age, gender, and smoking habits were well balanced. The distribution of MDM2 rs2279744 polymorphism was in HWE ($P=0.114$). In endometrial cancer patients, endometrioid adenocarcinoma represented 84.2%, and non-endometrioid adenocarcinoma represented 15.8%.

The genotype and allele frequencies of MDM2 rs2279744 polymorphism were shown in Table 2. The frequencies of TT, TG and GG genotypes in the patients were 20.5%, 54.5%, and 26.0% and were 28.3%, 54.7%, and 17.0% in the controls, respectively. GG genotype showed a statistically significantly increased risk of developing endometrial cancer (OR=1.72, 95%CI 1.08-2.76, $P=0.02$). Statistically significant difference was observed when the patients and controls were compared according to G versus I (OR=1.40, 95%CI 1.07-1.84, $P=0.01$).

We did subgroup analyses according to histology and FIGO stage. There was a significantly higher frequency of G allele observed in patients with stage III+IV, compared to stage I+II (OR=2.24, 95%CI 1.49-3.38, $P=0.001$). There was no statistically significant association of MDM2 rs2279744 polymorphism with histology (OR=1.34, 95%CI 0.79-2.26, $P=0.28$).

Discussion

In this study, we determined MDM2 rs2279744 polymorphism for endometrial cancer risk in a Chinese Han population. Results from this study indicated that

Table 2. Genotype and allele frequencies in cases and controls.

Genotype/allele	Case (%)	Control (%)	OR (95%CI)	*P* value
TT	44 (20.5%)	60 (28.3%)	1 (Reference)	
TG	115 (54.5%)	116 (54.7%)	0.95 (0.65-1.39)	0.80
GG	56 (26.0%)	36 (17.0%)	1.72 (1.08-2.76)	0.02
T	203 (47.2%)	236 (55.7%)	1 (Reference)	
G	227 (52.8%)	188 (44.3%)	1.40 (1.07-1.84)	0.01

Table 3. Association of *MDM2* rs2279744 with clinicopathological characteristics.

Characteristics	Case (%)	G (%)	T (%)	OR (95%CI)	*P* value
Histology					
Endometrioid adenocarcinoma	181 (84.2%)	187 (82.4%)	175 (86.2%)	1 (Reference)	
Non-endometrioid adenocarcinoma	34 (15.8%)	40 (17.6%)	28 (13.8%)	1.34 (0.79-2.26)	0.28
FIGO stage					
I+II	71 (33.0%)	56 (24.7%)	86 (42.4%)	1 (Reference)	
III+IV	144 (67.0%)	171 (75.3%)	117 (57.6%)	2.24 (1.49-3.38)	0.0001

MDM2 rs2279744 polymorphism was significantly associated with the risk of endometrial cancer. This result suggested that MDM2 rs2279744 polymorphism might be involved in development of endometrial cancer. We showed that GG genotype and G allele were associated with an increased risk of endometrial cancer. Besides, we also showed that MDM2 rs2279744 polymorphism was significantly associated with higher stage of endometrial cancer risk.

Previous studies showed that MDM2 rs2279744 polymorphism was significantly associated with other cancer risk. Ding et al. found an association between MDM2 SNP309 and urinary cancer risk (7). Zhou et al. found that MDM2 SNP309 may be a low-penetrant risk factor for head and neck carcinoma, and G allele may confer nasopharyngeal cancer susceptibility (8). He *et al.* showed that the MDM2 T309G variation might be associated with an increased risk of leukemia (9). Kong *et al.* showed that the MDM2 T309G polymorphism may contribute to individual differences in non-small cell lung cancer susceptibility and prognosis (10).

We should acknowledge that this study had some limitations. First, this was a case–control study, thus selection bias cannot be excluded. Second, this present study only analyzed one polymorphism in. Third, further influence factors are not investigated, e.g. common effects of further MDM2 SNPs and exogeneous risk factors. Finally, we did not do functional study since this was a meta-analysis study.

In conclusion, the study found that MDM2 rs2279744 polymorphism was significantly associated with endometrial cancer risk in a Chinese Han population. More studies are required to validate the results of this study.

Conflicts of interest

None

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