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ORIGINAL ARTICLE

Polymorphisms in *XPC* Gene and Risk of Uterine Leiomyoma in Reproductive Women

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Abstract

XPC gene belongs to DNA repair pathway, which is involved in the development of uterine leiomyoma. However, its relationships with leiomyoma risk were never reported. We here hypothesized that *XPC* gene was associated with the risk of uterine leiomyoma. In this case–control study with a total of 391 leiomyoma cases and 493 tumor-free controls in a reproductive women population in South China, two missense polymorphisms rs2228001 A > C (Lys939Gln) and rs2228000 C > T (Ala499Val) were genotyped by quantitative polymerase chain reaction (qPCR). Then, the associations between these two polymorphisms and leiomyoma risk were investigated. It was revealed that the rs2228000 CT/TT variant genotypes had a decreased leiomyoma risk (adjusted odds ratio = 0.73, 95% confidence interval = 0.54–0.94) compared with rs2228000 CC genotype. Further stratified analysis also revealed that the protective effect of rs2228000 CT/TT on the risk of uterine leiomyoma was more evident among subjects who were younger than 35 years old compared with those with larger tumors (diameter of tumor >5 cm), and those with fewer number of myomas (only one). However, no significant association was observed for leiomyoma risk for rs2228001 A > C. This study indicated that genetic variations in *XPC* gene are associated with leiomyoma susceptibility in a reproductive women population. It warrants further confirmation in larger prospective studies with different populations.

Keywords Uterine leiomyoma · *XPC* · Polymorphism · Genetic susceptibility

Introduction

Uterine leiomyoma is the most common benign neoplasm in women, which is estimated to be present in 30–70% of clinically reproductive women, and may cause a variety of symptoms, such as infertility, menometrorrhagia, and dysmenorrhoea [1]. Leiomyoma has been reported to be derived from growth and proliferation of a single smooth muscle cell [2], therefore unsuccessful DNA repair may be a driving force in myoma development [3]. For example, single nucleotide polymorphisms (SNPs) of DNA repair genes, such as *XRCC1* [4], *XRCC3* [5], and *XRCC4* [6], were associated with leiomyoma risk.

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The *XPC* gene is a key gene in the nucleotide excision repair (NER) pathway, a major DNA repair mechanism [7]. The human *XPC* gene is located at chromosome 3p25, contains 15 introns and 16 exons, and encodes a 940-amino acid protein -xeroderma pigmentosum complementation Group C (XPC). This molecule interacts with another protein, that is RAD23 homolog B (RAD23B). In addition, the XPC-HR23B complex involves in the recognition of DNA-distorting lesions, stimulates the activity of 8-oxoguanine DNA glycosylase (also known as OGG1), and limits the rate of NER [8]. *XPC* gene is highly polymorphic, and around 2600 variants of this gene have been identified in the Short Genetic Variations database (dbSNP, http://www.ncbi.nlm.nih.gov/projects/SNP). However, their relationships with leiomyoma risk were never reported. We here hypothesized that genetic variants of *XPC* gene may alter the carriers' susceptibility to uterine leiomyoma.

Several major symptoms in leiomyoma, such as infertility and dysmenorrhoea, occur in reproductive women [1]. Therefore, this study was conducted in a reproductive women population in South China, in order to understand the associations between two missense polymorphisms rs2228001 A >

C (Lys939Gln) and rs2228000 C > T (Ala499Val) of *XPC* gene and the risk of uterine leiomyoma.

Materials and Methods

Study Population

Smoking [9] and drinking [10] associate with DNA lesions and tumorigenesis. However, there are extremely limited females with a history of smoking or drinking in South China. Therefore, we conducted the current case–control study in a non-smoking and non-drinking Chinese population.

Leiomyoma patients were enrolled between January 2015 and February 2018 from Baoan Maternal and Child Health Hospital, Jinan University, Shenzhen, China. Herein, 403 newly diagnosed cases with histologically confirmation were recruited, with a 98.8% respond rate. We excluded 7 postmenopausal cases and 5 cases with a history of smoking or drinking. After the written informed consents of remaining 391 tumor cases were obtained, their information was abstracted from the medical records, including age, the number, location, and size of tumors, etc.

Simultaneously, more than 1000 healthy women admitted to our hospital for annual medical examinations, including physical examination, blood testing, and ultrasound examination. Among them, 733 controls without uterine tumor and other diseases were randomly selected, in which the respond rate of controls was 85.9%. After we ruled out 217 postmenopausal women and 23 subjects with a history of either smoking or drinking, there were 493 tumor-free controls who were included in this study. The subjects were interviewed face-to-face by specially trained professional interviewers, and signed written informed consent forms as well.

After that, 2 ml blood samples were donated from the cases and controls. All the research subjects were unrelated ethnic Han Chinese population from South China.

This study was approved by the Ethics Committee of the Baoan Maternal and Child Health Hospital, Jinan University (No. of Institutional Review Board: LLSC2018-02-01).

SNPs Selection and Genotyping

We applied the following three criteria to select the potentially functional SNPs by using the dbSNP database [11, 12]: 1) the minor allele frequencies reported in HapMap database (the Haplotype Map of the Human Genome, http://hapmap.ncbi.nlm.nih.gov/) were more than 5% for Chinese Han subjects; 2) missense SNPs; and 3) SNPs in low linkage disequilibrium with each other ($R^2 < 0.8$). Based on these criteria, two missense SNPs rs2228001 A > C (Lys939Gln) and rs2228000 C > T (Ala499Val) were selected in the present study.

Genomic DNA was extracted from blood samples using the Qiagen Blood DNA Mini Kit (Qiagen Inc., Valencia, CA, USA) according to the manufacturer's instructions. As described previously, we performed genotyping of above-mentioned SNPs by the quantitative polymerase chain reaction (qPCR) using a 7900 Sequence Detection System (Thermo Fisher Scientific, Waltham, MA, USA) [13–15]. Genotyping was repeated on a random 10% of the samples, and the results were 100% concordant.

Statistical Analysis

Chi-square test and Student's *t* test were used to compare the differences between cases and controls regarding demographic characteristics. The Chi-Square goodness of fit test was applied to indicate whether the genotype frequency distribution of each polymorphism in controls was in Hardy–Weinberg equilibrium. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the associations between each SNP and leiomyoma risk using univariate and multivariate logistic regression models. Further stratification analyses by age, and the number, location, and size of tumors were performed as well. All statistical analyses were carried out by using SPSS 18.0 software (IBM, Armonk, NY, USA). A two-sided statistical significance level of 0.05 was chosen as well.

Results

Population Characteristics

The clinical and demographic characteristics of the study population, consisting of 391 cases and 493 healthy controls, are summarized in Table 1. The average age of cases was not significantly different from controls (36.1 ± 7.4 years vs. 36.9 ± 9.8 years, $P = 0.090$). Among leiomyoma patients, 38.1% (149 cases) had 2 or more myomas. For the largest myomas of these cases, their mean diameter was (6.1 ± 2.5) cm, and they more likely located in intramural (66.2%) and subserous myomas (21.2%).

Associations between *XPC* Gene Polymorphisms and Leiomyoma Risk

The genotype distributions of the selected *XPC* gene polymorphisms in cases and controls and their associations with uterine leiomyoma risk are summarized in Table 2. Distributions of these genotype frequencies of both SNPs in the control subjects were in agreement with Hardy–Weinberg equilibrium ($P = 0.769$ for rs2228001; and $P = 0.931$ for rs2228000). The

Table 1 Clinical and demographic characteristics of uterine fibroid patients and fibroid-free controls

Variables	Cases, n (%)	Controls, n (%)	P [b]
All subjects	391 (100.0)	493 (100.0)	
Age, years			
Mean	36.1 ± 7.4	36.9 ± 9.8	0.090
≤ 35	234 (59.8)	289 (58.6)	0.713
> 35	157 (40.5)	204 (41.4)	
No. of myoma			
1	242 (61.9)	–	
2	67 (17.1)	–	
≥3	82 (21.0)	–	
Site of myomas [a]			
Intramural	259 (66.2)	–	
Subserous	83 (21.2)	–	
Intraligamentary	11 (2.8)	–	
Submucous	34 (8.7)	–	
Cervical	4 (1.0)	–	
Diameter, cm [a]			
Mean	6.1 ± 2.5	–	
≤ 5.0	161 (40.5)	–	
> 5.0	230 (59.5)	–	

[a] The characteristics of the biggest myoma

[b] Chi-square test or student t test

variable "age" was adjusted in the subsequent multivariate logistic regression analyses. The results showed that compared with the rs2228000 CC genotype, the CT genotype had a significantly decreased leiomyoma risk (adjusted OR = 0.71, 95% CI = 0.51–0.95, P = 0.031), however, the TT genotype was not associated with tumor risk (adjusted OR = 0.73, 95% CI = 0.49–1.09, P = 0.120). We further found that rs2228000 was significantly associated with tumor risk under a dominant genetic model with adjustment for age. When CC genotype served as a reference, the rs2228000 CT/TT variant genotypes had a decreased leiomyoma risk (adjusted OR = 0.73, 95% CI = 0.54–0.94, P = 0.029).

However, the polymorphism rs2228001 A > C was not notably associated with tumor risk under either of dominant, co-dominant, and recessive genetic models. Because only rs2228000 of two studied SNPs was significantly associated with leiomyoma risk in this population, a haplotype or combined genotype analysis was not carried out for the variants of *XPC*.

Stratification Analysis

Further investigation was undertaken on the potential association between *XPC* rs2228000 C > T polymorphism and the leiomyoma risk in the stratified study by age, the number, location, and size of tumors. The results of stratified analysis are presented in Table 3. The rs2228000 CT/TT genotypes were found to be associated with a significantly decreased risk of uterine leiomyoma among individuals who were younger than 35 years (adjusted OR = 0.57, 95% CI =0.40–0.82, P = 0.006), when CC genotype served as a reference. Similarly, compared with CC genotype, carriers of rs2228000 variant genotypes CT/TT showed a significantly decreased risk of leiomyoma among patients with just one myoma (adjusted OR = 0.69, 95% CI = 0.50–0.95, P = 0.019), and those with larger myomas (diameter of the largest myoma >5.0 cm, adjusted OR = 0.71, 95% CI = 0.52–0.97, P = 0.035).

In addition, stratification analysis showed different roles of *XPC* rs2228000 C > T polymorphism in different types of myoma; decreased tumor risk was found in subserous

Table 2 Association between *XPC* gene polymorphisms and uterine fibroid risk

Genotypes	Cases n (%)	Controls n (%)	OR (95% CI) [a]	P	Adjusted OR (95% CI) [b]	P [b]
rs2228001 A > C						
AA	163 (41.7)	210 (42.7)	1.00		1.00	
AC	165 (42.2)	217 (44.1)	0.98 (0.81–1.18)	0.831	0.96 (0.72–1.29)	0.791
CC	63 (16.1)	65 (13.2)	1.25 (0.80–1.95)	0.328	1.28 (0.81–2.04)	0.356
Dominant	228(58.3)	282 (57.3)	1.04 (0.73–1.48)	0.819	1.05 (0.70–1.57)	0.893
Recessive	328(83.9)	427 (86.8)	1.26 (0.84–1.90)	0.263	1.29 (0.85–2.02)	0.289
rs2228000 C > T						
CC	178 (45.5)	183 (37.1)	1.00		1.00	
CT	159 (40.7)	232 (47.0)	*0.70 (0.53–0.93)*	*0.014*	*0.71 (0.51–0.95)*	*0.031*
TT	54 (13.8)	78 (15.8)	0.71 (0.49–1.05)	0.079	0.73 (0.49–1.09)	0.120
Dominant	213 (54.5)	310 (62.9)	*0.71 (0.54–0.92)*	*0.010*	*0.73 (0.54–0.94)*	*0.029*
Recessive	337 (86.2)	415 (84.2)	0.85 (0.61–1.19)	0.354	0.86 (0.59–1.26)	0.462

[a] odds ratio (OR), 95% CI = confidence interval at 95%

[b] Adjusted for age as a continuously variable. The italic showed a significant association between rs2228000 C > T and fibroid risk

Table 3 Stratification analysis for association between *XPC* rs873601 G > A genotypes and uterine fibroid risk

Genotypes	rs2228000 C > T (cases/controls)		OR (95% CI) [b]	*P*	Adjusted OR (95% CI) [c]	*P*[c]
	CC	CT + TT				
Age, years						
≤ 35	114/102	120/187	*0.57 (0.41–0.81)*	*0.001*	*0.57 (0.40–0.82)*	*0.006*
> 35	64/81	93/123	0.96 (0.73–1.26)	0.756	0.99 (0.66–1.45)	0.943
No. of myomas						
1	112/183	130/310	*0.69 (0.51–0.93)*	*0.014*	*0.70 (0.50–0.95)*	*0.019*
2	32/183	35/310	0.65 (0.40–1.04)	0.070	0.65 (0.39–1.08)	0.099
≥3	34/183	48/310	0.83 (0.55–1.25)	0.382	0.84 (0.52–1.31)	0.401
Site of myoma [a]						
Intramural	116/183	143/310	*0.73 (0.54–0.98)*	*0.034*	0.75 (0.54–1.08)	0.091
Subserous	44/183	39/310	*0.52 (0.34–0.82)*	*0.004*	*0.53 (0.32–0.82)*	*0.006*
Other types	18/183	31/310	1.02 (0.74–1.40)	0.919	1.02 (0.55–1.57)	0.945
Diameter, cm [a]						
≤ 5.0	73/183	88/310	0.71 (0.51–1.01)	0.052	0.70 (0.49–1.13)	0.224
> 5.0	105/183	125/310	*0.70 (0.52–0.95)*	*0.024*	*0.71 (0.52–0.97)*	*0.035*

[a] The characteristics of the biggest myoma

[b] odds ratio (OR), 95% CI = confidence interval at 95%

[c] Adjusted for age as a continuously variable. The italic showed significant associations in stratified analyses

myomas (adjusted OR = 0.53, 95% CI = 0.32–0.82, *P* = 0.006), rather than in other types (all *P* values >0.05).

Discussion

In the present study, we found that *XPC* polymorphism rs2228000 C > T was associated with a decreased leiomyoma risk, and this protective role was more evident among younger subjects, and those with lager tumors.

Although a limited number of studies have investigated the role of *XPC* polymorphisms in various tumors, the reported results were largely inconsistent. A number of researches showed increased risks of rs2228000 variant genotypes TT and/or CT in breast cancer [16], gastric cancer [13, 17], lung cancer [11], and bladder cancer [18]. Moreover, it was reported that this SNP was associated with chemotherapy induced severe toxicities [19] and survival [20, 21] in cancer. However, another study demonstrated null associations between *XPC* rs2228000 and tumor risk (e.g., gastric cancer) [22]. In contrary, a Poland population study showed a decreased risk of melanoma in carries with rs2228000 CT/TT genotypes [23]. In addition, Chinese scholars reported a weak protective role for this SNP in gastric cancer, which was more evident among subjects who were older than 58 years [15]. Zhao et al. [24] revealed that *XPC* rs2228000 was significantly associated with a reduced risk of ovarian cancer under dominant genetic model in Chinese population. With merging the results of our study with these two reports conducted in China, *XPC* rs2228000 might be a candidate genetic marker for tumor risk in China. The discrepancies among these studies might be partly due to tumor specificity, ethnic and demographic differences. For instance, the frequency of rs2228000 T allele was 0.31 in Chinese (CHB), 0.28 in Caucasian (CEU), while that was only 0.04 in Africans (YRI), according to HapMap database. In this study, the frequency of rs2228000 T allele in the controls was 0.39, that is close to that in CHB population in HapMap database, and in controls of the two reports performed in China [15, 24].

Given the critical role of the *XPC* gene in the NER pathway, thus, functional *XPC* variants may alter the DNA repair capacity of NER, thereby modifying the risk of leiomyoma. Additionally, *XPC* rs2228000 C > T is a missense SNP (Ala499Val), and can alter gene expression in Asian individuals [25]. Consequently, our results on the association of leiomyoma risk and *XPC* rs2228000 C > T polymorphism are biologically plausible.

In the stratification analysis, our data suggested that the risk of *XPC* rs2228000 CT/TT genotypes remained significant in subgroups of those cases with the age of less than 35 years. Similar to our results, Paszkowska-Szczur et al. also reported that *XPC* rs2228000 had more evident protective role in colorectal cancer in young subjects [26]. This phenomenon can be explained by those young individuals who have higher

competence of DNA repair than elders [27, 28], leading to less tumor risk. We also found that the association between decreased tumor risk and this SNP was more evident in cases with larger tumors. The expression levels of DNA damage response proteins are negatively associated with tumor size [29–31]. Because *XPC* rs2228000 C > T can alter the gene expression [25], the association between this SNP and a decreased risk in lager tumors can be logically explained. It seems contradicted that the association between decreased tumor risk and this SNP was found in cases with just one tumor. However, young patients typically have a small number of myomas than elders. For instance, Bray et al. reported that patients who aged at the range of 43–47 years have 3.37-fold chance to have multiple tumors compared with those aged 18–36 years in 2302 American women with fibroids [32]. The association of this SNP with few tumor numbers might be related to younger age. In addition, incident submucous or cervical tumors were often observed in patients with a limited number of tumors, which were prone to have infertility and menometrorrhagia in reproductive women [1]. In the present study, 13.6% (33/242) of submucous or cervical leiomyoma were found in cases with only one tumor, while only 3.6% (5/149) of the cases had two or more myomas ($P < 0.001$). This phenomenon can be explained by those symptoms of the fibroids in "harmful" location (submucous or cervical) are more obvious and easier to diagnoses when there is only one tumor. However, whether *XPC* rs2228000 C > T plays a protective role in more "harmful" location of fibroids (submucous or cervical) should be further verified by different and lager populations.

It also has been reported that patients who were under age of 35 years could have faster-growing tumors than those who were over 45 years [33]. Larger fibroids can result in bulk symptoms, that are responsible for increased daytime urinary frequency and urinary incontinence [34]. Occurrence of infertility and recurrent miscarriage depends on size and location of tumors, especially for submucous and intramural myomas [35]. Furthermore, the choice of treatment is guided by patient's age, and the number, size, and location of the fibroids [36]. Furthermore, age, and number and size of tumors were reported as risk factors for tumor recurrence [37]. This study implied a prospect for the prevention and treatment of fibroids.

This study had some limitations which are presented as follows: First, it was a hospital-based case–control study. As a result, selection bias was inevitable. Second, several confounders influencing leiomyoma susceptibility, such as gene–environment interaction, were not taken into consideration. Third, the subjects in this study were from South China, which may not well represent other Chinese populations in different regions.

In conclusion, it was revealed that the *XPC* rs2228000 C > T polymorphism was associated with a decreased leiomyoma risk in reproductive women. Well designed, prospective studies with a larger sample size, involving different ethnicities, are warranted to clarify the effects of polymorphisms in *XPC* gene on uterine leiomyoma in the future.

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Author's Contributions Conceived and designed the experiments: BL. Performed the experiments: ZL and ML. Collected samples: ML. Analyzed data: ZL and BL. Contributed to the writing of manuscript: ZL and BL. All authors approved the final manuscript.

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Data Availability Data will not be shared, because it is part of a clinical database.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethics Approval All the study participants gave a written informed consent. A formal consent was also issued by the Ethics Committee of the Baoan Maternal and Child Health Hospital, Jinan University (No. of Institutional Review Board: LLSC2018-02-01).

Consent for Publication Not applicable, the manuscript doesn't contain any individual person's data.

Conflict of Interest Authors declare no conflict of interest.

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