

The Correlation between the Risk of Cervical Cancer and the STK11 Genes rs12977689, rs60755851, and rs9282860

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Abstract: Objective Exploring the correlation between single nucleotide polymorphisms (SNPs) of the STK11 gene rs12977689, rs60755851, and rs9282860 and the risk of cervical cancer. **Methods** 350 patients with cervical cancer were selected as the cervical cancer group, and 351 normal women who underwent physical examinations during the same period were selected as the control group. Adopting imLDR™ Multiple SNP typing technology was used to genotype the rs12977689, rs60755851, and rs9282860 loci in two groups of people, and analyze the correlation between these three SNP loci and the risk of cervical cancer. **Results** The genotype AA, allele A, and recessive model CA+CC of rs12977689 increase the risk of cervical cancer (OR=2.20, OR=1.35, OR=2.06); The rs9282860 allele T and dominant model CT+TT reduce the risk of cervical cancer (OR=0.72 and OR=0.70); However, there was no correlation between rs60755851 and cervical cancer ($P>0.05$). The above three SNPs were not associated with clinical pathological parameters of cervical cancer ($P>0.05$). The haplotypes A-A-C constructed at three loci have an increased risk of cervical cancer (OR=1.32), while haplotypes C-A-C and C-A-T have a reduced risk of cervical cancer (OR=0.75 and OR=0.72). **Conclusion** The STK11 gene rs12977689 may increase the risk of cervical cancer, while rs9282860 may reduce the risk of cervical cancer.

Keywords: STK11; SNP; Cervical Cancer; Disease Risk.

1. Introduction

Cervical cancer is the most common gynecological malignancy among women worldwide, with the highest incidence rate of gynecological malignancies. It is one of the most common cancers leading to cancer-related deaths in women, and its incidence and mortality rates have not significantly declined[1]. The occurrence of cervical cancer is associated with persistent infection by high-risk human papillomavirus (HPV), but it is also closely related to genetic mutations and abnormal expression[2]. Serine-Threonine Kinase 11 (STK11), also known as Liver Kinase B1 (LKB1), is located at the short arm of human chromosome 19 at position 13.3. It consists of 9 coding exons and 1 non-coding exon and is a tumor suppressor gene that plays a key role in the occurrence and development of cancer mainly by participating in the regulation of gene expression and signal pathways[3]. Genetic mutations of this gene may be associated with the occurrence of cervical cancer [4]. Currently, no studies have found a correlation between STK11 gene SNPs and cervical cancer. This study analyzes the correlation between STK11 gene SNPs and the risk of cervical cancer by detecting the genotypes of STK11 gene rs12977689, rs60755851, and rs9282860 loci in the cervical cancer group and the normal control group

2. Materials and Methods

2.1. Research Object

A total of 350 cases of cervical cancer patients diagnosed at the Affiliated Hospital of Youjiang Medical University for Nationalities or the Affiliated Tumor Hospital of Guangxi Medical University from 2018 to 2020 were randomly

selected, with complete clinical data. None of the patients had received drug treatment or radiotherapy before surgery, and there were no malignant tumors in other sites, serving as the case group. A total of 351 age-matched healthy women from health check-ups were selected as the control group. The age difference between the two groups was not statistically significant ($P=0.052$). This study was approved by the ethics committee.

2.2. Methods

2.2.1. Specimen Collection and Preservation

In the early morning, collect 5ml of venous blood from the above research subjects on an empty stomach and place it in a heparin anticoagulant tube, gently shaking to mix. Then, place the collected fresh whole blood specimen into two 1.5ml EP tubes, label the sample information, and store it in a -80°C freezer for preservation.

2.2.2. Extraction of Sample DNA

Use the DNA extraction kit (centrifuge column type) produced by Shenzhen Yanan Biotechnology Co., Ltd. to extract DNA from the blood samples of the research subjects, and store it in a -80°C freezer for future use.

2.2.3. Selection of SNP Loci

Obtain 362 candidate genes related to cervical cancer (correlation coefficient $r > 0.6$) from the Targetvalidation database (<https://www.targetvalidation.org/>) and intersect them with 9525 candidate genes obtained from the Blood eQTL database (<https://genenetwork.nl/bloodeqtlbrowser/>) to identify 202 candidate genes related to cervical cancer that can be expressed in blood, along with their corresponding SNP sites (sites with P values less than or equal to $E-5$). Then, select the key gene STK11 related to cervical cancer through literature review. Finally, filter the

associated sites with a mutation frequency greater than 10% in the Asian population from the 1000 Genomes Project database, ultimately selecting rs12977689, rs60755851, and rs9282860 for this study.

2.2.4. Genotyping

Using the imLDR™ multiplex SNP genotyping technology to genotype rs12977689, rs60755851, and rs9282860. First, perform multiplex PCR on the study sample DNA using HotStar Taq (Qiagen). The total volume of the PCR reaction system is 20µl: 1 µl sample DNA, 0.3mM dNTP, 1 µl multiplex PCR primers, 1U HotStarTaq polymerase (Qiagen Inc.), 2U 3.0 mM Mg²⁺, 1x HotStarTaq buffer, and the remaining volume is made up to 20µl with ultrapure water. PCR reaction conditions: 95°C pre-denaturation for 2 minutes, 94°C denaturation for 20 seconds, 65°C annealing for 40 seconds, 72°C extension for 1.5 minutes, a total of 11 cycles, each cycle conducted at -0.5°C, followed by 94°C denaturation for 20 seconds, 59°C annealing for 30 seconds, 72°C extension for 1.5 minutes, 24 cycles, and a final extension at 72°C for 2 minutes, then stored at 4°C. Then, purify the multiplex PCR products, detect the ligation products using the ABI3730XL sequencer, and analyze the collected raw data using GeneMapper 4.1 (Applied Biosystems, USA), and verify using direct sequencing method.

2.3. Statistical Methods

The genotype and allele frequency distribution (%) of three loci in the control group and cervical cancer group were calculated using the direct counting method. Logistic regression was used to calculate the differences in genotypes and alleles between the two groups, and the odds ratio (OR) and 95% confidence interval (95% CI) were calculated after age adjustment. The correlation between the three loci SNPs and the clinical pathological features of cervical cancer was analyzed using the χ^2 test or Fisher's exact test. The differences in haplotype distribution constructed from the three loci were analyzed using the SHEsis online software. Statistical analysis was performed using SPSS Statistics 24 software, with a significance level of $\alpha=0.05$, and $P<0.05$ was considered statistically significant.

3. Result

3.1. The Correlation Between the Genotypes and Alleles of Three Loci and the Risk of Cervical Cancer

This study used logistic regression analysis to compare the differences in genotype and allele distribution frequencies of the STK11 gene polymorphic sites rs12977689, rs60755851, and rs9282860 between the control group and the cervical cancer group, and further analyzed the correlation of the above three SNPs with the risk of cervical cancer.

The rs12977689 site is located on chromosome 19 and is an intronic variant. As shown in Table 1, the distribution frequencies of genotypes CC, CA, and AA at the rs12977689 site in the control group were 51.00%, 42.17%, and 6.83%, respectively, while in the cervical cancer group, they were 44.57%, 42.29%, and 13.14%, respectively; the difference in the distribution frequency of genotype CA between the control group and the cervical cancer group was not statistically significant ($P > 0.05$), while the difference in the distribution frequency of genotype AA was statistically

significant ($P = 0.004$), and the AA genotype at the rs12977689 site significantly increased the genetic risk of cervical cancer, with patients carrying rs12977689 AA having a 2.20 times higher risk of developing cervical cancer compared to those carrying rs12977689 CC (AA vs CC: OR = 2.20, 95% CI = 1.28-3.77). The distribution frequencies of alleles C and A at rs12977689 in the control group were 72.08% and 27.92%, respectively, while in the cervical cancer group, they were 65.71% and 34.29%, respectively; the difference in the distribution frequency of allele C between the two groups was not statistically significant ($P > 0.05$), while the difference in the distribution frequency of allele A was statistically significant ($P = 0.010$), and allele A at rs12977689 significantly increased the risk of cervical cancer, with patients carrying allele A having a 1.35 times higher risk of developing cervical cancer compared to those carrying allele C (A vs C: OR = 1.35, 95% CI = 1.07-1.69). Meanwhile, the recessive model CA + CC significantly increased the risk of cervical cancer, with patients carrying rs12977689 CA + CC having a 2.06 times higher risk of developing cervical cancer compared to those carrying rs12977689 AA (AA vs CA + CC: OR = 2.06, 95% CI = 1.23-3.46, $P = 0.006$), while the dominant model CA + AA was not statistically significant ($P > 0.05$).

The rs9282860 site is located on chromosome 19 and is an intronic variant. As shown in Table 3, the distribution frequencies of genotypes CC, CT, and TT at the rs9282860 site in the control group were 70.94%, 27.35%, and 1.71%, respectively, while in the cervical cancer group, they were 77.71%, 21.43%, and 0.86%, respectively; the distribution frequency differences of homozygous TT and heterozygous CT genotypes between the two groups were not statistically significant ($P > 0.05$). The distribution frequencies of alleles C and T at rs9282860 in the control group were 84.62% and 15.38%, respectively, while in the cervical cancer group, they were 88.43% and 11.57%, respectively; the difference in the distribution frequency of allele C between the two groups was not statistically significant ($P > 0.05$), while the difference in the distribution frequency of allele T was statistically significant ($P = 0.037$), and allele T at rs9282860 reduced the risk of cervical cancer, with patients carrying allele T having a 0.72 times lower risk of developing cervical cancer compared to those carrying allele C (T vs C: OR = 0.72, 95% CI (0.53-0.98)). Meanwhile, the dominant model CT + TT reduced the risk of cervical cancer, with patients carrying rs9282860 CT + TT having a 0.70 times lower risk of developing cervical cancer compared to those carrying rs9282860 CC (CT + TT vs CC: OR = 0.70, 95% CI = 0.50-0.99, $P = 0.041$), while the recessive model CT + TT was not statistically significant ($P > 0.05$).

The rs60755851 site is located on chromosome 19 and is a promoter. As shown in Table 2, the distribution frequencies of genotypes AA, CA, and CC at the rs60755851 site in the control group were 37.32%, 50.14%, and 12.54%, respectively, while in the cervical cancer group, they were 34.00%, 52.57%, and 13.43%, respectively; the distribution frequencies of alleles A and C in the control group were 62.39% and 37.61%, respectively, while in the cervical cancer group, they were 60.29% and 39.71%, respectively. The differences in the distribution frequencies of genotypes, alleles, dominant models, and recessive models at the rs60755851 site between the control group and the cervical cancer group were not statistically significant ($P > 0.05$).

Table 1. Rs12977689 SNPs Frequency distribution in control group and cervical cancer group [n (%)]

	Control group (n=351)	Cervical cancer group (n=350)	OR(95%CI)	P	OR (95%CI) ^a	P ^a
rs12977689 Genotype						
CC	179(51.00)	156(44.57)				
CA	148(42.17)	148(42.29)	1.14(0.84-1.57)	0.389	1.14(0.83-1.56)	0.389
AA	24(6.83)	46(13.14)	2.20(1.28-3.77)	0.004	2.26(1.32-3.88)	0.003
Dominant model						
CA+AA/CC			1.29(0.96-1.74)	0.089	1.30(0.97-1.75)	0.084
Recessive model						
AA/CA+CC			2.06(1.23-3.46)	0.006	2.12(1.26-3.57)	0.005
Allele						
C	506(72.08)	460(65.71)				
A	196(27.92)	240(34.29)	1.35(1.07-1.69)	0.010	1.36(1.08-1.71)	0.008

Table 2. Rs60755851 SNPs Frequency distribution in control group and cervical cancer group [n (%)]

	Control group (n=351)	Cervical cancer group (n=350)	OR(95%CI)	P	OR (95%CI) ^a	P ^a
Rs60755851 Genotype						
AA	131(37.32)	119(34.00)				
CA	176(50.14)	184(52.57)	1.15(0.83-1.59)	0.394	1.15(0.83-1.59)	0.403
CC	44(12.54)	47(13.43)	1.18(0.73-1.90)	0.508	1.21(0.75-1.97)	0.431
Dominant model						
CA+CC/AA			1.16(0.85-1.58)	0.359	1.16(0.85-1.58)	0.345
Recessive model						
CC/CA+AA			1.08(0.70-1.68)	0.725	1.12(0.72-1.74)	0.618
Allele						
A	438(62.39)	422(60.29)				
C	264(37.61)	278(39.71)	1.09(0.88-1.36)	0.418	1.10(0.89-1.37)	0.369

Table 3. Rs9282860 SNPs Frequency distribution in control group and cervical cancer group [n (%)]

	Control group (n=351)	Cervical cancer group (n=350)	OR (95%CI)	P	OR (95%CI) ^a	P ^a
Rs9282860 Genotype						
CC	249(70.94)	272(77.71)				
CT	96(27.35)	75(21.43)	0.72(0.51-1.01)	0.059	0.70(0.49-0.99)	0.044
TT	6 (1.71)	3(0.86)	0.46(0.11-1.85)	0.273	0.46(0.11-1.85)	0.272
Dominant model						
CT+TT/CC			0.70(0.50-0.99)	0.041	0.68(0.49-0.96)	0.030
Recessive model						
TT/CT+CC			0.50(0.12-2.00)	0.326	0.50(0.12-2.01)	0.329
Allele						
C	594 (84.62)	619 (88.43)				
T	108 (15.38)	81 (11.57)	0.72(0.53-0.98)	0.037	0.71(0.52-0.96)	0.029

Note: P: P value; OR: Odd Ratio; 95% CI: 95% confidence interval, ^a: Value adjusted by age

3.2. The Correlation between Single Nucleotide Polymorphisms of the STK11 Gene and Clinical Pathological Features of Cervical Cancer

Table 4. Correlation of the rs12977689 SNPs and Clinical Characteristics of Cervical Cancer [n (%)]

rs12977689	n	Genotype			χ^2	P	Allele		χ^2	P
		CC	CA	AA			C	A		
Cancer types										
Squamous carcinoma	272	122(44.9)	111(42.6)	34(12.5)			360(66.2)	184(33.8)		
Non-squamous carcinoma	78	34(43.6)	32(41.0)	12(15.4)	0.351	0.839	100(64.1)	56(35.9)	2.097	0.148
Tumor staging										
I+ II	225	96(42.7)	95(42.2)	34(15.1)			287(63.8)	163(36.2)		
III+ IV	125	60(48.0)	53(42.4)	12(9.6)	0.351	0.839	173(69.2)	77(30.8)	2.097	0.148
Lymph node metastasis										
No	265	116(43.8)	113(42.6)	36(13.6)			345(65.1)	185(34.9)		
Yes	85	40(47.1)	35(41.2)	10(11.7)	0.229	0.892	115(67.6)	55(32.4)	0.372	0.542
Distant metastasis										
No	326	144(44.2)	139(42.6)	43(13.2)			427(65.5)	225(34.5)		
Yes	24	12(50.0)	9(37.5)	3(12.5)	0.318	0.853	33(68.8)	15(31.2)	0.211	0.646

Table 5. Correlation of the rs60755851 SNPs and Clinical Characteristics of Cervical Cancer [n (%)]

Rs60755851	n	Genotype			χ^2	P	Allele		χ^2	P
		AA	CA	CC			A	C		
Cancer types										
Squamous	272	88(32.4)	145(53.3)	39(14.3)			321(59.0)	223(41.0)		
Non-squamous	78	31(39.7)	39(50.0)	8(10.3)	2.298	0.317	101(64.7)	55(35.3)	2.032	0.154
Tumor staging										
I+ II	225	82(36.4)	115(51.1)	28(12.4)			279(62.0)	171(38.0)		
III+ IV	125	37(29.6)	69(55.2)	19(15.2)	2.736	0.416	222(88.8)	28(11.2)	0.052	0.819
Lymph node metastasis										
No	265	203(76.6)	59(22.3)	3(1.1)			465(87.8)	65(12.2)		
Yes	85	69(81.2)	16(18.8)	0(0.0)	1.817	0.403	143(57.2)	107(42.8)	1.547	0.214
Distant metastasis										
No	326	115(35.3)	168(51.5)	43(13.2)			398(61.0)	254(39.0)	326	
Yes	24	4(16.7)	16(66.7)	4(16.6)	3.452	0.178	24(50.0)	24(50.0)	2.277	0.131

Table 6. Correlation of the rrs9282860 SNPs and Clinical Characteristics of Cervical Cancer [n (%)]

Rs9282860	n	Genotype			χ^2	P	Allele		χ^2	P
		CC	CT	TT			C	T		
Cancer types										
Squamous	272	80(29.4)	135(49.6)	57(21.0)			295(54.2)	249(45.8)		
Non-squamous	78	21(26.9)	43(55.1)	14(18.0)	0.155	0.925	85(54.5)	71(45.5)	0.375	0.540
Tumor staging										
I+ II	225	71(31.6)	108(48.0)	46(20.4)			250(55.6)	200(44.4)		
III+ IV	125	30(24.0)	70(56.0)	25(20.0)	2.609	0.271	130(52.0)	120(48.0)	0.819	0.366
Lymph node metastasis										
No	265	74(27.9)	136(51.3)	55(20.8)			284(53.6)	246(46.4)	265	
Yes	85	27(31.8)	42(49.4)	16(18.8)	0.493	0.781	96(56.5)	74(43.5)	0.432	0.511
Distant metastasis										
No	326	96(29.4)	164(50.3)	66(20.3)			356(54.6)	296(45.4)	326	
Yes	24	5(20.8)	14(58.4)	5(20.8)	0.908	0.635	24(50.0)	24(50.0)	0.381	0.537

In order to further analyze the correlation between STK11 gene single nucleotide polymorphisms and clinical pathological features of cervical cancer (tumor type, clinical stage, lymph node metastasis, and distant metastasis), this study conducted an in-depth analysis of 350 cases of cervical cancer tissues. The results of the in-depth analysis are shown in Tables 4, 5, and 6. The genotype and allele frequency distribution of STK11 gene loci rs12977689, rs60755851, and rs9282860 showed no statistically significant differences in relation to tumor type, clinical stage, lymphatic metastasis, and distant metastasis of cervical cancer ($P > 0.05$).

3.3. Comparison of STK11 SNPs Haplotypes

By comparing the distribution frequencies of STK11 SNPs loci rs12977689, rs60755851, and rs9282860 haplotypes between cervical cancer patients and healthy control populations, the results are shown in Table 7. There are seven haplotype genotypes present in both the cervical cancer group

and the normal group, with the most predominant haplotype being C-C-C, which accounts for 39.0% and 37.2% in the cervical cancer group and the normal group, respectively. The distribution frequency of haplotype C-C-C between the two groups is not statistically significant, but there is a trend towards an increased risk of cervical cancer ($P=0.466$, $OR=1.08$). The distribution frequencies of haplotype A-A-C between the two groups are 33.3% and 27.5%, respectively, with a statistically significant difference ($P=0.016$), and it shows a trend towards an increased risk of cervical cancer ($OR=1.32$). The distribution frequencies of haplotypes C-A-C and C-A-T in the cervical cancer group are 15.4% and 11.3%, respectively, while in the healthy control group, they are 19.5% and 15.1%, with both differences being statistically significant ($P=0.046$ and $P=0.039$), and both show a trend towards a decreased risk of cervical cancer ($OR=0.75$ and $OR=0.72$).

Table 7. Correlation of the STK11 SNPs and Clinical Characteristics of Cervical Cancer [n (%)]

Haplotype	Cervical cancer	Normal group	χ^2	P	OR (95%CI)
A-A-C	233(33.3)	193(27.5)	5.768	0.016	1.32(1.05~1.66)
C-A-C	108(15.4)	137(19.5)	3.986	0.046	0.75(0.57~1.00)
C-A-T	79(11.3)	106(15.1)	4.258	0.039	0.72 (0.53~0.99)
C-C-C	273(39.0)	261(37.2)	0.533	0.466	1.08(0.87-1.35)
A-A-T	2(0.20)	2(0.30)	-	-	-
A-C-C	5(0.80)	3(0.40)	-	-	-
C-C-T	0(0.00)	0(0.00)	-	-	-

4. Discussion

STK11 is a tumor suppressor that controls 5' AMP-activated protein kinase (AMPK) signaling in various cellular functions. Mutated STK11 has been identified as a novel driver gene that promotes cancer progression, playing a significant role in various cancers, including cervical cancer [5]. Frequent genomic mutations of the STK11 gene have been observed in. Additionally, the expression of STK11 inhibits the proliferation of cervical cancer HeLa cells and activates AMPK (AMP-activated protein kinase), with STK11 gene expression loss found in over 50% of cervical cancers. [7]. Recent studies have also found that mutations in the STK11 gene are a contributing factor to the progression and poor prognosis of cervical cancer [8]. The above studies indicate that STK11 mutations are associated with cervical cancer.

In recent years, SNPs have become extremely important in population genetics and medical research, and gene polymorphisms have different effects on disease susceptibility, serving as etiological and risk factors for certain diseases, as well as genetic markers for related diseases. Lee SJ et al [9] found that the GG genotype at the rs741765 locus was identified as an independent prognostic factor for disease progression in colorectal cancer patients in their study on the polymorphism of the STK11 gene and colorectal cancer. The most common single nucleotide variations in the comprehensive genome of patients with recurrent or advanced cervical cancer include STK11 [10]. This study found that the AA genotype of rs12977689, allele A, and the recessive model CA+CC increase the risk of cervical cancer, indicating that mutations at this locus play a protective role for cervical cancer patients; while the allele T of rs9282860 and the dominant model CT+TT reduce the risk

of cervical cancer. Haplotype analysis constructed from the three loci showed that haplotype A-A-C may increase the risk of cervical cancer, while haplotypes C-A-C and C-A-T may reduce the risk of cervical cancer. MA X et al [11] found that allele A of rs12977689 significantly increases the risk of coronary heart disease in Han Chinese patients with type 2 diabetes compared to homozygous CC genotype. STK11 rs9282860 is a risk factor for the occurrence of secondary progressive sclerosis in African Americans and can affect early (onset) and later events [12]. slam MJ et al [13] found that various SNPs of the STK11 gene may be related to cancer susceptibility, although the exact mechanisms remain to be further elucidated. However, some studies have shown that cervical adenocarcinoma has more STK11 alterations associated with immune therapy resistance than squamous cell carcinoma [14]. In this study, the three SNP loci were found to be unrelated to clinical pathological parameters of cervical cancer (including cancer type), indicating the possibility of ethnic differences.

In summary, this study found that the SNP loci rs12977689 and rs9282860 of the STK11 gene are associated with the risk of cervical cancer, while rs60755851 is not associated with the risk of cervical cancer. This provides new target indicators for the prevention, early diagnosis, and treatment of cervical cancer, and offers a theoretical basis for future research on the correlation between STK11 gene polymorphisms and disease susceptibility in different ethnic populations. The Guangxi region is an area where ethnic minorities are concentrated, possessing rich resources in ethnic genetics and disease genes. The results of this study are of significant importance for future research on the association between the STK11 gene and diseases.

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