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The Correlation Between TNF-α Promoter Gene Polymorphism and Genetic Susceptibility to Cervical Cancer

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Abstract

To investigate the association between the susceptibility to cervical cancer and the single nucleotide polymorphisms of 5 tumor necrosis factor-α promoter genes (rs361525, rs1800629, rs1800750, rs1799964, and rs673) in Chinese women. A total of 946 peripheral blood samples were collected from women of Han Ethnicity in Shandong province. Of them, 452 were diagnosed with cervical squamous cell carcinomas. The study also included a control group of 494 healthy women. The targeted single nucleotide polymorphisms were analyzed by TaqMan probe method. (1) The rate of high-risk subtype human papillomavirus infection in exfoliated cervical epithelial cells was significantly higher in patients with cervical cancer than the control group (91.4% vs 10.3%, $P < .01$). The rate of human papillomavirus infection was lower in patients with carcinoma in situ than those with invasive carcinoma (77.9% vs 95.4%, $P < .01$). (2) There was a significant difference for rs361525 genotype (CC/CT/TT) between the control, carcinoma in situ, and invasive carcinoma groups ($P < .001$). Both rs1800629 and rs1799964 genotypes (both GG/GA/AA) were also different between these groups ($P < .001$ and $P < .001$). (3) The allele frequencies of rs361525, rs1800629, and rs1799964 were significantly correlated with the diagnosis of cervical cancer. The frequency of T allele in rs361525 was significantly higher for cervical cancer group (10.8%) than control group (3.8%; odds ratio = 3.04, 95% confidence interval = 1.76-5.25, $P < .01$). The frequency of A allele in rs1800629 was significantly higher for cervical cancer (29.9%) than control group (14.2%; odds ratio = 2.58, 95% confidence interval = 1.87-3.56, $P < .01$). The frequency of A allele in rs1799964 was also higher for cervical cancer group (38.3%) than control group (16.4%; odds ratio = 1.43, 95% confidence interval = 1.07-1.91, $P < .05$). The rs361525, rs1800629, and rs17999645 were significantly correlated with the diagnosis of cervical cancer.

Keywords

gene polymorphism, TNF-α, rs361525, rs1800629, rs1800750, rs1799964, and rs673, cervical cancer, genetic susceptibility

Abbreviations

CI, confidence interval; CIN, cervical intraepithelial neoplasia; CIS, carcinoma in situ; HPV, human papillomavirus; IC, invasive carcinoma; OR, odds ratio; SNP, single nucleotide polymorphisms; TNF-α, tumor necrosis factor-α

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Introduction

China's National Health and Family Planning Commission estimates that in China every year approximately 132 000 new cases of cervical cancer are diagnosed, and 30 000 deaths are due to cervical cancer.[1] Worldwide, cervical cancer is also the fourth most common type of malignancy in women and the second most common type of cancer in developing countries.[2] Studies have proved that human papillomavirus (HPV)

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infection and cervical cancer are closely related, with more than 95% of patients with cervical cancer being positive on high-risk HPV subtype infection.[3-6] While the pathogenesis of cervical cancer has not yet been fully elucidated, its occurrence involves a multifactorial, multistep complex process.[7-9] Although nearly 30% of sexually active women were infected with HPV shortly after their first sexual intercourse, most of them were able to clear HPV infection through autonomous cellular immunity when they were young.[10] Only a small number of patients with persistent infection develop cervical cancer. Studies have shown that gene-based genetic polymorphisms of individual immune response were closely related to the risk of cervical cancer.[11-13] Tumor necrosis factor-α (TNF-α) is a multifunctional cytokine produced by monocytes and macrophages and plays an important role in promoting inflammatory response, cell proliferation, and inducing apoptosis. Tumor necrosis factor-α is a polypeptide that directly kills or inhibits tumor cells and plays an important role in the development and progression of tumors and is the most important proinflammatory cytokine.[14,15]

Single nucleotide polymorphisms (SNPs) refer to DNA sequence polymorphisms at the genomic level due to the presence of a single nucleotide switch (or transversion).[16] By comparing the genotype frequency of the SNP locus and allele frequency between the normal control and the patients, the association between a locus gene and the risk of a disease can be explored.[17] In studies of SNPs of TNF-α gene promoter, rs361525 (−238) and rs1800629 (−308) were most frequently investigated. Polymorphism of rs1800629 (−308) has been shown to be a risk factor for a variety of cancers, such as breast cancer, gastric cancer, and liver cancer.[18-20] The rs361525 (−238) locus is located on a 25-base pair repressor gene,[21] and its SNP has been shown to be associated with the protection against cancer.[22,23] In addition, the relationship between SNP of rs1800629 (−308) and cervical cancer has been studied in various racial populations, including Spanish, Mexican, and Indian, and A allele was associated with an increased risk of cervical cancer[24-27] as confirmed by a meta-analysis.[23] Although a large number of epidemiological studies of TNF-α gene SNPs have been conducted to investigate their relationship with the patients' susceptibility to cervical cancer, the results are inconsistent, and significant racial differences may also exist. Furthermore, there are also conflicting results on the association between rs361525 (−238) polymorphism and cervical cancer risk.[28,29]

Our team has previously (2015) reported the findings of detecting the SNP of the TNF-α gene −857 locus (rs1799724) using TaqMan SNP Genotyping assay. The results showed that SNP of this locus was significantly correlated with cervical cancer. The frequency of T allele at the TNF-α gene −857 was markedly higher in cervical cancer group than that in control group. The TT+AT genotype was associated with the risk of cervical cancer, while CC genotype was not.[30] Studies have shown that the polymorphism of TNF-α promoter region on chromosome 6 is also closely related to the susceptibility to cervical cancer.[31,32] In many studies of SNPs of TNF-α promoter gene, the data from the Asian population are relatively scarce, especially in the Chinese women.

Based on the findings of previous study, 5 SNP loci from the candidate genes for TNF-α promoter that may be associated with genetic susceptibility to cervical cancer rs361525 (−238), rs1800629 (−308), rs1800750 (−376), rs1799964 (−1031), and rs673 (−244) were selected to study their genotype and allele frequency distribution. The correlation between these 5 SNP loci and cervical cancer in Chinese women has not been reported.

Materials and Methods

A total of 946 female participants were enrolled, and their peripheral blood samples were collected. All of them were of Han ethnicity and lived in Shandong province in China. The cases were consecutively enrolled from a single large medical center.

Study Population

Cervical cancer group. The inclusion criteria were patients with pathologically confirmed cervical squamous cell carcinoma; no other history of malignancy did not undergo radiation and/or chemotherapy. A total of 452 cases (including 104 cases of carcinoma in situ and 348 cases of invasive cervical carcinoma) were enrolled from January 2011 to October 2015. All of them were married, aged from 27.7 to 67.0 years (mean 47.0 ± 14.5 years). The survey questionnaire was adopted from the United States Seattle Hospital Cervical Cancer Epidemiologic study.[33] Investigators conducted the interview after obtaining informed consent. Epidemiological survey included demographics, occupational exposure history, family history of cancer, smoking history, sexual behavior, pregnancy and delivery history, and so on.

Healthy control group. Control participants were healthy and married women randomly selected from the same area during the study period. They were matched with the cases by age and geographic location. A total of 494 control participants were enrolled, aged from 26.0 to 69.0 years, with an average age of 47.0 ± 15.5 years. This study was approved by the Institutional Ethics Committee prior to initiation (No. 2013ZX05).

Genetic Polymorphism Testing

For specific SNP loci, real-time quantitative polymerase chain reaction (PCR) using TaqMan probe method was performed for the detection and analysis of polymorphism.

DNA extraction from peripheral blood lymphocytes. Peripheral venous blood (4-5 mL) was collected from each participant using EDTA anticoagulated tube and stored at −70°C. DNA extraction kit (Beijing Tiangen Biotechnology Company, Bejing, China) was used to extract DNA from peripheral blood lymphocytes according to the manufacture instruction.

Experimental materials and equipment. TaqMan SNP genotyping probes for SNP loci rs361525, rs1800629, rs1800750,

Table 1. TaqMan Probes and Sequences.

SNP Site	Items	Sequence
rs361525	Forward primer	CTCGGTTTCTTCTCCATCGC
	Reverse primer	CAGCCTCCAGGGTCCTACAC
	Wild probe	TET-TCCCCATCCTCCCTGCTCtG ATT-BHQ
	Mutation probe	FAM-CCCATCCTCCCTGCTCcG ATT-BHQ
rs1800629	Forward primer	TTAGAAGGAAACAGACCACAG ACCT
	Reverse primer	GTAGGACCCTGGAGGCTGAAC
	Wild probe	TET-TAGGTTTTGAGGGGCATGa GGACG-BHQ
	Mutation probe	FAM-TAGGTTTTGAGGGGCATGg GGAC-BHQ
rs1800750	Forward primer	CTTTCTGAAGCCCCTCCCA
	Reverse primer	TGCCCCTCAAAACCTATTGC
	Wild probe	TET-CCTGCATCCTGTC TGGAAaTTAGAAGGA-BHQ
	Mutation probe	FAM-CCTGCATCCTGTC TGGAAgTTAGAAGG-BHQ
rs1799964	Forward primer	CATTCCTCAGAGCCGCTACAT
	Reverse primer	GGGATATGTGATGGACTCACCAG
	Wild probe	TET-CTCCAGACCCTG ACTTTTCCTTCgTC-BHQ
	Mutation probe	FAM-CCTCCAGACCCTGA CTTTTCCTTCaTC-BHQ
rs673	forward primer	GGGTCCTACACACAAATCAGTC AGT
	Reverse primer	CCCTCACACTCCCCATCCT
	Wild probe	TET-AAGACCCCCCTCgGA-MGB
	Mutation probe	FAM-AAGACCCCCCTCaGA-MGB

Abbreviation: SNP, single nucleotide polymorphisms.

rs1799964, and rs673 were provided by Shanghai Keikang Biotechnology Co, Ltd (Table 1). Master MIX and Applied Biosystems 7900HT Fast Real-Time PCR System were manufactured by ABI Genes (Applied Biosystems, USA). The 384-well PCR plate was purchased from Roche, Germany.

Experimental methods. Dilution of real-time PCR primers and probes such as TaqMan Universal Master Mix, TaqMan probe, and 10 ng of extracted DNA were mixed for each reaction. Polymerase chain reaction was performed according to the manufacture instruction. Each cycle included 95°C 3-minute degeneration, 95°C 15-second degeneration, followed by −60°C annealing for 1 minute. After a total of 40 cycles, the genotyping was performed. The examiner was blinded from the grouping of the specimens.

Statistical Analysis

Hardy-Weinberg equilibrium test was performed using Haploview 4.2. The relationship of gene polymorphism and disease susceptibility was analyzed using multiple logistic regression, and the odds ratios (ORs) were estimated. The allele frequency and genotype–phenotype were compared between the cervical cancer group and the control group and between the subgroup of patients with carcinoma in situ (CIS) and those with invasive carcinoma (IC). The analysis was performed using SPSS version 17.0 and $P < .05$ was determined to be statistically significant.

Result

Comparison Between Cervical Cancer Group and the Control Group

There was statistical significance in Hardy-Weinberg balance test of cervical squamous cell carcinoma in the study of rs1800629 and rs1799964 loci ($P < .05$), the remaining 3 loci (rs361525, rs1800750, and rs673) compound Hardy-Weinberg balance test ($P > .05$), indicating that the samples were representative of the population and that the 5 loci were independent of each other, and there is no genetic linkage (linkage disequilibrium: $r^2 < 0.8$). Statistical analysis also showed that the 2 groups were similar in the general demographics, occupational history, history of pregnancy, and sexual behavior ($\chi^2 = 1.623$, $P = .203$; $\chi^2 = 0.976$, $P = .323$). However, the rate of high-risk HPV subtype infection in exfoliated cervical epithelial cells of patients with cervical cancer was significantly higher than that in the control group (91.4% vs 10.3%, $P < .01$). The rate of HPV infection in patients with CIS was lower than those with IC (77.9% vs 95.4%, $P < .01$; Table 2).

Tumor Necrosis Factor-α Promoter Gene SNP Genotyping Test Results by Group

There was a significant difference in the rs361525 genotype (CC/CT/TT) between the control, CIS, and IC groups ($\chi^2 = 20.71$, $P < .001$, Table 3). The same was true for rs1800629 and rs1799964 (GG/GA/AA; $\chi^2 = 34.92$, $P < .001$ and $\chi^2 = 57.40$, $P < .001$, respectively). There was no significant difference between the groups on rs1800750 and rs673 (all GG/GA/AA) genotypes ($\chi^2 = 2.54$, $P = .28$ and $\chi^2 = 0.21$, $P = .90 > .05$).

Single Nucleotide Polymorphism Allele Frequency of TNF-α Promoter in Cervical Cancer and Control Group

Allele frequencies of 5 SNPs (rs361525, rs1800629, rs1800750, rs1799964, and rs673) by study groups were summarized in Table 4. Univariate logistic regression showed that the missense SNPs (rs361525, rs1800629, and rs1799964) were significantly correlated with cervical cancer. The C allele frequencies of rs361525 in cervical cancer group and control group were 89.2% and 96.2%, respectively (OR = 0.33, 95% confidence interval [CI] = 0.19-0.57, $P < .01$). The frequency of T allele in cervical cancer group (10.8%) was also significantly higher than that in the control group (3.8%; OR = 3.04, 95% CI = 1.76-5.25, $P < .01$). rs1800629 had significant correlation with cervical cancer: the G allele frequencies at rs1800629 locus in cervical cancer and control group were 70.1% and 85.8%, respectively (OR = 0.39, 95% CI = 0.28-0.54, $P < .01$). The A allele frequency was also

Table 2. Comparison of Demographics and HPV Infection Between Cervical Cancer Group, CIS Group, and Control Group.

Group	N	Age	Age at First Marriage	Pregnancy (N)	Delivery (N)	Employed % (n)	χ^2/P^a	Smoking % (n)	χ^2/P^a	HPV Infection % (n)	χ^2/P^a
Cervical cancer	452	47.0 ± 14.5	24.5 ± 2.0	4.2 ± 2.0	2.4 ± 1.1	42.0% (190)		19.9% (90)		91.4% (413)	
CIS	104	42.5 ± 8.5	25.0 ± 2.3	4.7 ± 1.7	2.2 ± 0.7	76.9% (80)	$\chi^2 = 1\ 62/P = .20$	32.7% (34)	$\chi^2 = 0.98/P = .32$	77.9% (81)	$\chi^2 = 620.4/P < .001$
IC	348	49.7 ± 16.5	22.1 ± 3.7	4.3 ± 1.5	2.9 ± 1.6	28.6% (110)		16.1% (56)		95.4% (332)	
Control	494	47.0 ± 15.5	24.8 ± 3.1	5.1 ± 2.8	2.3 ± 1.7	46.2% (228)		17.4% (86)		10.3% (51)	

Abbreviations: CIS, carcinoma in situ; IC, invasive carcinoma; HPV, human papillomavirus.
[a]Used χ^2 test.

Table 3. Results of TNF-α Promoter Gene SNP Genotype by Group.[a]

		rs361525 (N)				rs1800629 (N)				rs1800750 (N)				rs1799964 (N)				rs673 (N)			
Group	N	CC	CT	TT	χ^2/P^b	GG	AG	AA	χ^2/P^b	GG	AG	AA	χ^2/P^b	GG	AG	AA	χ^2/P^b	GG	AG	AA	χ^2/P^b
Control	494	475	19	0		424	70	0		492	2	0		410	81	3		483	11	0	
Cervical squamous cell carcinoma	452	403	49	0	$\chi^2 = 20.707$	317	135	0	$\chi^2 = 34.916$	450	2	0	$\chi^2 = 2.539$	275	173	4	$\chi^2 = 57.396$	440	12	0	$\chi^2 = 0.212$
Carcinoma In situ	104	97	7	0	$P < .001$	76	28	0	$P < .001$	104	0	0	$P = .281$	67	37	1	$P < .001$	101	3	0	$P = .899$
Invasive carcinoma	348	306	42	0		241	107	0		344	4	0		212	136	3		339	9	0	

Abbreviations: TNF-α, tumor necrosis factor-α; SNP, single nucleotide polymorphisms.
[a]C-cytosine; T-thymidine; A-adenine, and G-guanine. The base pair of rs361525 gene is C and T, where CC and TT being homozygous and CT being heterozygous; the base pair for other 4 SNP sites were all G, A, GG, and AA being homozygous, and AG being heterozygous.
[b]Used the Cochran-Mantel-Haenszel (CMH) test.

Table 4. Allele Frequencies of the 5 SNPs of TNF-α Promoter Gene by Groups.[a]

	Allele frequency								
	Control group (N = 494)		Cervical Cancer group (N = 452)			OR (95% CI)		P	
SNPs	Homozygous	Heterozygous	Homozygous	Heterozygous	χ^2/P^b	G/(C*)	A/(T*)	G/(C*)	A/(T*)
rs361525	0.962 (475)	0.038 (19)	0.892 (403)	0.108 (49)	$\chi^2 = 17.3/P < .001$	0.33 (0.19-0.57)	3.04 (1.76-5.25)	<.01	<.01
rs1800629	0.858 (424)	0.142 (70)	0.701 (317)	0.299 (135)	$\chi^2 = 34.3/P < .001$	0.39 (0.28-0.54)	2.58 (1.87-3.56)	<.01	<.01
rs1800750	0.996 (492)	0.004 (2)	0.996 (450)	0.004 (2)	$\chi^2 = 0.008/P = 0.929$	1.09 (0.15-7.79)	0.92 (0.13-6.52)	.929	.929
rs1799964	0.836 (413)	0.164 (81)	0.617 (279)	0.383 (173)	$\chi^2 = 57.52/P < .001$	0.32 (0.23-0.43)	3.16 (2.33-4.28)	<.01	<.01
rs673	0.978 (483)	0.022 (11)	0.973 (440)	0.027 (12)	$\chi^2 = 0.182/P = 0.669$	0.84 (0.37-1.91)	1.20 (0.52-2.74)	0.6697	0.6697

Abbreviations: OR, odds ratio; SNP, single nucleotide polymorphisms; TNF-α, tumor necrosis factor-α.
[a]OR using the recessive genetic model (OR = 1, indicating that the factor does not influence the occurrence of the disease; OR > 1, indicating that the factor is a risk factor; OR < 1, indicating that the factor is protective factors). The allele base of the rs361525 allele is C, T, CC, and TT being homozygous, CT being heterozygous; the other 4 sites are G, A, GG, and AA being homozygous, and AG being heterozygous.
[b]Used χ^2 test.

Table 5. Comparison of Genotype and Allele Frequency of 5 Loci Between Patients With CIS and IC.

			Genotype Frequency (%)				Allele Frequency (%)		
SNP Locus	Group	N	CC/GG	CT/GA	TT/AA	χ^2/P^a	C/G	T/A	χ^2/P^b
rs361525	Carcinoma in situ	104	97 (93.3)	7 (6.7)	0 (0.0)	$\chi^2 = 2.356/P = .1248$	201 (96.6)	7 (3.4)	$\chi^2 = 2.225/P = .1358$
	Invasive cancer	348	306 (87.9)	42 (12.1)	0 (0.0)		654 (94.0)	42 (6.0)	
rs1800629	Carcinoma in situ	104	76 (73.1)	28 (26.9)	0 (0.0)	$\chi^2 = 0.558/P = .4552$	180 (86.5)	28 (13.5)	$\chi^2 = 9.474/P = .002$
	Invasive cancer	348	241 (69.3)	107 (30.7)	0 (0.0)		589 (93.3)	42 (6.7)	
rs1800750	Carcinoma in situ	104	104 (100.0)	0 (0.0)	0 (0.0)	$\chi^2 = 1.203/P = .2726$	208 (100.0)	0 (0.0)	$P = .5790$[c]
	Invasive cancer	348	344 (98.9)	4 (1.1)	0 (0.0)		692 (99.4)	4 (0.6)	
rs1799964	Carcinoma in situ	104	66 (64.3)	37 (35.6)	1 (0.01)	$\chi^2 = 0.414/P = .8117$	171 (81.4)	39 (18.6)	$\chi = 0.279/P = .5971$
	Invasive cancer	348	209 (60.0)	136 (39.1)	3 (0.9)		692 (83.0)	142 (17.0)	
rs673	Carcinoma in situ	104	101 (97.1)	3 (2.9)	0 (0.0)	$\chi^2 = 028/P = .8682$	205 (98.6)	3 (1.4)	$\chi^2 = 0.000/P = 1.000$[d]
	Invasive cancer	348	339 (98.9)	9 (1.1)	0 (0.0)		692 (98.7)	9 (1.3)	

Abbreviations: CIS, carcinoma in situ; IC, invasive carcinoma; SNP, single nucleotide polymorphisms.
[a]Using Cochran-Mantel-Haenszel (CMH) test.
[b]Using χ^2 test.
[c]Using Fisher test.
[d]Use continuity correction card.

higher in cervical cancer group (29.9%) than that in the control group (14.2%; OR = 2.58, 95% CI = 1.87-3.56, $P < .01$).

rs1799964 SNP had a significant association with cervical cancer: G allele frequency at rs1799964 in cervical cancer group and control group were 61.7% and 83.6%, respectively (OR = 0.70, 95% CI = 0.52-0.94, $P = .016$). A allele frequency was also higher for the cervical cancer group (38.3%) than for the control group (16.4%; OR = 3.16, 95% CI = 2.33-4.28, $P = .016$). This indicates that the high-risk allele of rs361525 was TT + TC, and the nonrisk allele was CC; for rs1800629 and rs1799964, the high-risk allele was AG + AA, and the nonrisk allele was GG.

Comparison of Genotype and Allele Frequencies of 2 Loci in Patients With Cervical Carcinoma In Situ and Patients With Invasive Cervical Cancer

Among patients with cervical cancer, the comparison of the genotype (TT/TC/CC or GG/AG/AA) frequency and allele frequency (T/C or G/A) of the 5 loci between those with CIS and those with IC only showed significant difference at rs1800629 ($\chi^2 = 9.474$, $P = .002$), and there was no difference at other 4 loci ($P \geq .05$, Table 5).

Discussion

Based on the information from HapMap database, this is the first study that investigated the association between genotype and allele frequency at 5 SNP loci of TNF-α promoter (rs361525, rs1800629, rs1800750, rs1799964, and rs673) and the risk of cervical cancer in Shandong province, China.

The study found that the rate of high-risk HPV subtype infection in exfoliated cervical epithelial cells was significantly higher for patients with cervical cancer than the control group; the rate of HPV infection in patients with CIS was also significantly lower than that in the patients with IC. The genotype of rs191525 (CC/CT/TT) was significantly different between control, CIS, and IC groups. So were rs1800629 and rs1799964

(GG/GA/AA), and there was no significant difference between these groups at rs1800750 and rs673 loci (GG/GA/AA). Compared to the control group, the SNPs of rs361525, rs1800629, and rs1799964, which were missense mutation and can cause amino acid change, were significantly correlated with cervical cancer risk. The frequency of C allele at rs361525 was lower in cervical cancer group than in the control group, but the frequency of T allele was higher in cervical cancer group.

rs1800629 genotype was shown to be associated with cervical cancer: The frequency of G allele at this locus was lower in cervical cancer group than control group, while the frequency of A allele was significantly higher in patients with cancer than the control group (OR = 2.58, 95% CI = 1.87-3.56). rs1799964 genotype was also shown to be associated with the cervical cancer risk. G allele frequency at rs1799964 locus was lower, but the frequency of A allele was significantly higher in patients with cervical cancer than those in the control group. The risk allele at rs361525 locus was TT + TC, and the nonrisk allele was CC. The risk allele for rs1800629 and rs1799964 was AG + AA, and the nonrisk allele was GG.

The possible explanation for the rs361525, rs1800629, and rs1799964 SNP mutation and increased susceptibility to cervical cancer is that, the alteration in the frequencies of the genotype and allele at these 3 loci may change the level of TNF-α expression and affect the body's immune system, which leads to the increased risk of persistent HPV infection, the main risk factor of cervical cancer, and thus becomes carcinogenic. This has been confirmed in other cancer researches.

Johnson *et al* reported that the risk of cervical cancer is associated with genetic polymorphisms in chromosome 5 cytokine clusters.[34] De Oliveira and colleagues studied the 10 SNP loci, including TNF-α (rs1799724), in 669 cases of digestive tract malignancies, found that genotype G/A of TNF-α was not associated with the risk of gastrointestinal malignancy, whereas C/T genotype was (TNF-a-857 C/T, $P = .022$), suggesting that the interaction between the inflammatory process and the SNP is a potential contributor to the occurrence of gastrointestinal cancer.[31] However, Danforth and others reported that abnormal SNPs (rs1799724) at the TNF site and long-term inflammatory stimuli were not associated with the increased risk of prostate cancer.[35] In this study, the infection by high-risk HPV subtype in cervical exfoliated epithelial cells was prevalent (91.4%). Cervical inflammatory lesions and cervical intraepithelial neoplasia (CIN) due to the HPV infection,[5,6] in combination with abnormalities of genotype and allele frequency at rs361525, rs1800629, and rs1799964 loci, may be one of major contributing factors for the occurrence of cervical cancer.

In other researches of rs361525 polymorphisms and cervical cancer, the results were controversial.[28,29] In certain ethnic groups, rs1800629 polymorphism was shown to be associated with an increased risk of cervical cancer,[24-27] but in the study of different ethnicity, this relationship was not identified.[36] In Mexican, a study found that rs1800750 polymorphism was protective for intraepithelial neoplasia, and rs1799964 and rs673 were neutral.[25]

In summary, rs361525, rs1800629, and rs1799964 were all shown in this study to be associated with increased risk of cervical cancer in Chinese women of Han ethnicity. Patients with these SNP loci abnormalities and infected by HPV represent a high-risk population for cervical cancer and should be given more attention for prevention and early detection. Finally, it should be noted that the patients with cervical cancer enrolled in this study were limited to squamous cell carcinoma. Future study should be considered to confirm this study findings in patients with adenocarcinoma and CIN.

Declaration of Conflicting Interests

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