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ORIGINAL RESEARCH

The Association of *TNF-α* Promoter Polymorphisms with Genetic Susceptibility to Cervical Cancer in a Chinese Han Population

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Background: The tumour necrosis factor-α (*TNF-α*) gene plays an important role in the host immune response, which will influence the development and clearance of cancer. Polymorphism of the *TNF-α* promoter region is considered to influence its transcription and be a risk factor for tumorigenesis. In the current study, we evaluated the role of *TNF-α* promoter region polymorphisms in susceptibility to cervical intraepithelial neoplasia (CIN) and cervical cancer (CC).

Methods: A total of 2732 subjects, including 1173 healthy controls, 579 patients with CIN and 980 patients with CC in a Chinese Han population, were selected for the current study. Five SNPs in the *TNF-α* promoter, rs1799964 (−1031 C>T), rs1800630 (−863 A>C), rs1799724 (−857 C>T), rs1800629 (−308 A>G) and rs361525 (−238 A>G), were selected and genotyped using TaqMan Assays. The association of these SNPs with CIN and cervical cancer was evaluated among healthy controls, CIN and CC patients.

Results: The frequency distribution of rs1800629 and rs361525 alleles was significantly different between the CC group and the control group (P=0.009 and P=0.002). The rs1800629 A allele was found to be a protective factor for CC (OR=0.72; 95% CI=0.56–0.92). The rs361525 A allele was found to be a risk factor for CC (OR=1.69; 95% CI=1.21–2.38). After pathological subtyping of CC, the allele distribution of rs1800629 and rs361525 were both significantly different between the cervical squamous cell carcinoma and control groups (P=0.002 and P<0.001). The rs1800629 A allele was protective factor for cervical squamous cell carcinoma (OR=0.66; 95% CI=0.50–0.86). The rs361525 A allele was a risk factor for cervical squamous cell carcinoma (OR=1.87; 95% CI=1.32–2.65). Moreover, the genotypic frequency of rs361525 was significantly different between cervical cancer stage I and stage II (P=0.003).

Conclusion: The rs1800629 and rs361525 in the TNF-α promoter are associated with susceptibility to CC in the Chinese Han population.

Keywords: cervical intraepithelial neoplasia, CIN, cervical cancer, CC, promoter, single-nucleotide polymorphism, SNP, tumour necrosis factor-α, TNF-α

Introduction

Cervical cancer is the fourth most common cancer among women worldwide and the second leading cause of cancer death in developing countries.[1] Persistent infection with high-risk human papilloma virus is considered to be the main cause of cervical cancer. Epidemiological studies have shown that most cases of HPV infection can be cleared by the host immune system, with only a small portion of chronically infected patients and further developing cervical intraepithelial neoplasia (CIN) and progressing to cervical cancer.[2]

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The host immune system plays an important role in the clearance and development of cancers. As one of immune system proinflammatory cytokine, tumour necrosis factor (TNF), which includes tumour necrosis factor-α (TNF-α) and tumour necrosis factor-β (TNF-β), participates in multiple biological activities. TNF-α, which is mainly produced by monocytes or macrophages, is a pro-inflammatory cytokine that plays an important role in homeostasis of the immune system and host defense.[3,4] TNF-α is highly expressed in a variety of tumours and participates in cell transformation.[5] Overall, TNF-α promotes tumour cell proliferation, invasion and metastasis by regulating tumour angiogenesis.

The human TNF-α gene is 2.76 kb long and located on chromosome 6; it contains 3 introns and 4 exons and is closely related to the major histocompatibility complex region. TNF-α polymorphisms are mainly concentrated in the promoter region and closely related to the risk of cervical cancer. Nevertheless, the results of associations between TNF-α polymorphisms and cervical cancer are still controversial in different populations, even the same population.[6–15] For example, in 2001, Jang et al reported that the rs361525 A allele is a protective factor for cervical cancer in a Korean population.[13] In 2018, Li et al reported that the rs361525 A allele is a risk factor for cervical squamous cell carcinoma in a Chinese population from Shandong Province, Northern China.[14] For another example, Du et al also found the rs1800629 A allele to be associated with an increased risk of cervical cancer in a Chinese population from Sichuan Province, Southwest of China.[7] However, in 2012, Wang et al reported that rs1800629 was not significantly associated with cancer in a Chinese population from Liaoning Province, Northeast of China.[10] Thus, more populations from different regions should be investigated.

In the current study, five single-nucleotide polymorphisms (SNPs) located in the *TNF-α* promoter, rs1799964 (−1031 C>T), rs1800630 (−863 A>C), rs1799724 (−857 C>T), rs1800629 (−308 A>G) and rs361525 (−238 A>G), were selected to investigate allele distribution and genotypes in CIN, cervical cancer and healthy controls in a Chinese Han population to clarify the role of these SNPs in the occurrence and development of cervical cancer.

Materials and Methods

Ethics Declarations

The current study obtained approval from the Institutional Review Board of the No. 3 Affiliated Hospital of Kunming Medical University. The protocol employed in this investigation was in accordance with the principles expressed in the Helsinki Declaration of 1975, as revised in 2008.

Subjects

A total of 2732 subjects, including 1173 healthy controls, 579 patients with CIN, and 980 patients with cervical cancer (CC), were recruited to participate in the present study. The CIN and cervical cancer patients were all diagnosed at the Third Affiliated Hospital of Kunming Medical University from October 2013 to May 2018. Inclusion criteria for the patients were as follows: (1) CIN or cervical cancer diagnosed according to the World Health Organization Comprehensive Cervical Cancer Control: A Guide to Essential Practice[16] and the International Federation of Gynaecology and Obstetrics, 2009; (2) no other malignancy; and (3) no preoperative neoadjuvant therapy (including chemotherapy and radiotherapy). The exclusion criteria for the patients were as follows: (1) presented with a history of primary cancer other than cervical cancer; (2) malignant tumours other than cervical cancer; and (3) receiving radiotherapy or chemotherapy with unclear pathological diagnosis. Over the same period, 1173 women from a healthy screening at the same hospital served as healthy controls in the present study. The inclusion criteria for control individuals were as follows: (1) absence of any malignancy history; (2) absence of any cervical lesion; (3) tested negative for HPV; and (4) no chronic diseases. All subjects were Han Chinese from Yunnan Province (Southwest of China) and signed informed consent. The geographic origin and pedigree (unrelated through at least three generations) of each individual were ascertained.

DNA Extraction

A total of 5 mL of fasting venous blood was collected from the subjects. Genomic DNA from peripheral blood was extracted using a whole-blood genomic DNA mini kit to extract DNA (QIAamp DNA Blood Mini Kit). An ultramicro UV-visible spectrophotometer (ND-2000, Thermo Scientific, USA) was used to detect the concentration and purity of the DNA.

SNP Genotyping

The probes and primers used for genotyping these five SNPs were all purchased from ABI (http://www.appliedbiosystems.com). Primers and probes for the genotyping were commercially available. The array ID were

C___7514871_10(rs1799964), C__11918223_10(rs179972), C___7514879_10(rs1800629), C___2215707_10(rs361525). For rs1800630, the primers and probes for the genotyping were not commercially available. Thus, the primers and probe were designed by ABI. The primer sequence is: forward 5′-GGGCTATGGAAGTCGAGTATGG-3′, reverse 5′-CCCTCTACATGGCCCTGTCT-3′; VIC probe sequence is ACCCCCACTTAACG, FAM probe sequence is ACCCCCCCTTAACG. The five SNPs were genotyped using the TaqMan fluorescent quantitative PCR method with a QuantStudio™ Real-Time PCR instrument. The TaqMan Genotyping Master Mix used in the typing test was purchased from ABI. The PCR volume was 5 μL, and the reaction conditions were 95°C predenaturation for 10 minutes, 40 cycles of 95°C denaturation for 15 seconds and 60°C annealing for 1 minute, and 60°C extension for 5 minutes. Deionized water was used to replace the template DNA as a negative control. The PCR experiment data were analysed using TaqMan Genotyper Software (Version 1.3.1). To identify the accuracy of SNP genotyping using the TaqMan assay, samples of each genotype of the five SNPs were sequenced. Then, each genotype samples were used as positive sample in TaqMan assay

Statistical Analysis

Hardy–Weinberg equilibrium (HWE) was calculated using Plink software. Differences in age among the CIN group, cancer group and control group were analysed using one-way ANOVA (Analysis of Variance) with GraphPad Prism 7 software. The associations between the five SNP alleles and genotypes and the CIN, CC groups were analysed using the SHEsis program.[17,18] The association of the genotypes of these SNPs with CIN and CC was evaluated using inheritance model analysis with SNPstats software.[19] The analysed inheritance models included the codominant model, dominant model, recessive model, overdominant model and log-additive model. The Akaike information criterion (AIC) and the Bayesian information criterion (BIC) were applied to determine the best fit model for each SNP.[19] The inheritance model corresponding to the smallest AIC and BIC was the best fit model. Bonferroni correction was applied in multiple comparisons. A difference was considered statistically significant at $P<0.01$ (0.05/5).

Results

Subject Characteristics

Table 1 shows the clinical data for the subjects in this study. The cervical cancer group contained 980 patients, including 794 cases of squamous cell carcinoma (SCC), 162 cases of adenocarcinoma (AC), and 24 cases of other types of cancer. According to cervical cancer staging, 679 patients were in stage I, 265 in stage II, and 36 in stage III+IV. The CIN group contained 579 cases, of which 120 were in CIN stage I, 104 in CIN stage II, and 355 in CIN stage III. Comparing the ages among the control, CIN and CC groups, no statistically significant difference among the three groups was observed ($F=2.082$, $P=0.125$).

Association Analysis of Five SNPs in the *TNF-α* Promoter with CIN and Cervical Cancer

The alleles and genotype frequencies of the five SNPs in the *TNF-α* promoter among the control, CIN and

Table 1 Characteristics of the Subjects Enrolled in the Current Study

		Cervical Cancer	CIN	Control	*F*	P-value
N		980	579	1173		
Age (years)		45.91±9.85	45.53±9.83	46.49±9.72	2.082	0.125
Pathologic types	SCC (n)	794				
	AC(n)	162				
	Others (n)	24				
Stages of CC	I	679				
	II	265				
	III and IV	36				
Stages of CIN	I		120			
	II		104			
	III		355			

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma.

Table 2 The Allelic and Genotypic Distribution of Five SNPs in *TNF-α* Gene Among Control, CIN and Cervical Cancer Groups

SNPs	Alleles	Control (n, %)	CIN (n, %)	CC (n, %)	CIN vs Control		CC vs Control	
					P-value	OR (95% CI)	P-value	OR (95% CI)
rs1799964	C	543(23.1)	252(21.8)	428(21.8)	0.357	0.92 [0.80–1.09]	0.306	0.93 [0.80–1.07]
	T	1803(76.9)	906(78.2)	1532(78.2)				
	C/C	57(4.9)	37(6.4)	52(5.3)	0.035		0.231	
	C/T	429(36.6)	178(30.7)	324(33.1)				
	T/T	687(58.6)	364(62.9)	604(61.6)				
rs1800630	A	543(23.1)	240(20.7)	391(19.9)	0.106	0.87[0.73–1.03	0.011	0.83[0.72–0.96]
	C	1803(76.9)	918(79.3)	1569(80.1)				
	A/A	103(8.8)	50(8.6)	78(8.0)	0.117		0.023	
	A/C	337(28.7)	140(24.2)	225(24.0)				
	C/C	733(62.5)	389(67.2)	667(62.5)				
rs1799724	C	2092(89.2)	1046(90.3)	1742(88.9)	0.293	1.13 [0.90–1.43]	0.757	0.97 [0.80–1.18]
	T	254(10.8)	112(9.7)	218(11.1)				
	C/C	925(78.9)	467(80.7)	771(78.7)	0.179		0.526	
	T/C	242(20.6)	112(0.19.3)	200(20.4)				
	T/T	6(0.5)	0(0.00)	9(0.9)				
rs1800629	A	177(7.5)	63(5.4)	109(5.6)	0.020	0.71[0.52–0.95]	0.009	0.72 [0.56–0.92]
	G	2169(92.5)	1095(94.6)	1851(94.4)				
	A/A	5(0.4)	2(0.3)	4(0.4)	0.056		0.023	
	A/G	167(14.2)	59(10.2)	101(10.3)				
	G/G	1001(85.3)	518(89.5)	875(89.3)				
rs361525	A	59(2.5)	32(3)	82(4.2)	0.664	1.10 [0.71–1.70]	0.002	1.693[1.21–2.38]
	G	2287(97.5)	1126(97)	1878(95.8)				
	A/A	2(0.2)	0(0.00)	3(0.3)	0.460		0.009	
	A/G	55(4.7)	32(5.5)	76(7.8)				
	G/G	1116(95.1)	547(94.5)	901(91.9)				

Abbreviations: CC, cervical cancer; CIN, cervical intraepithelial neoplasia.

cervical cancer groups are shown in Table 2. The results of HWE showed that rs361525, rs1799964 and rs1800629 were in HWE except for the rs1799724 and rs1800630 in the control group (P<0.05). For the control and CC groups, the allele frequencies of rs1800629 were significantly different between these two groups after Bonferroni correction (*P*=0.009), which indicates that the A allele is a protective factor against cervical cancer (OR=0.72; 95% CI=0.56–0.92). For rs361525, the allele and genotype frequencies were significantly different between these two groups after Bonferroni correction (*P*=0.002 and *P*=0.009, respectively), and the A allele might be a risk factor for cervical cancer (OR=1.69; 95% CI=1.21–2.38). For the control and CIN groups, no difference of alleles and genotypes was observed between these two groups after Bonferroni correction (P>0.01).

Inheritance Model Analysis of Five SNPs in the *TNF-α* Promoter in CIN and Cervical Cancer

The results of inheritance model analysis of five SNPs in the *TNF-α* promoter among the control, CIN and cervical cancer groups are shown in Table 3. Comparison between the cervical cancer and control groups showed that the dominant inheritance model was the best fit model for rs1800630. In this model, the A/C-A/A genotype was related to a reduced risk of cervical cancer (*P*=0.006, OR=0.77; 95% CI=0.64–0.93). For rs1800629, the overdominant inheritance model was the best fit. In this model, the A/G genotype was related to a reduced risk of cervical cancer (*P*=0.008, OR=0.70; 95% CI=0.53–0.91). For rs361525, the dominant inheritance model was the best fit, in which the A/G-A/A genotype was related to an increased risk of cervical cancer (*P*=0.008, OR=1.63; 95% CI=1.14–2.35). Comparison between the

Table 3 Inheritance Model Analysis of Five SNPs in *TNF-α* Gene Among Control, CIN and Cervical Cancer Groups

SNPs	Model	Genotype	Control	CIN	CC	CIN vs Control				CC vs Control			
						P-value	OR (95% CI)	AIC	BIC	P-value	OR (95% CI)	AIC	BIC
rs1799964	Dominant	T/T	687 (58.6%)	364 (62.9%)	604 (61.6%)	0.036	1.00	1978.0	1994.4	0.098	1.00	2851.0	2868.0
		C/T-C/C	486 (41.4%)	215 (37.1%)	376 (38.4%)		0.79 (0.63–0.99)				0.86 (0.72–1.03)		
	Recessive	T/T-C/T	1116 (95.1%)	542 (93.6%)	928 (94.7%)	0.380	1.00	1981.6	1998.0	0.680	1.00	2853.6	2870.6
		C/C	57 (4.9%)	37 (6.4%)	52 (5.3%)		1.23 (0.78–1.96)				1.09 (0.73–1.62)		
	Overdominant	T/T-C/C	744 (63.4%)	401 (69.3%)	656 (66.9%)	0.010	1.00	1975.7	1992.1	0.059	1.00	2850.2	2867.2
		C/T	429 (36.6%)	178 (30.7%)	324 (33.1%)		0.74 (0.59–0.93)				0.84 (0.70–1.01)		
	Log-additive	—	—	—	—	0.170	0.88 (0.73–1.06)	1980.5	1996.9	0.220	0.91 (0.79–1.06)	2852.3	2869.3
rs1800630	Dominant	C/C	733 (62.5%)	389 (67.2%)	667 (68.1%)	0.027	1.00	1977.6	1994.0	0.006	1.00	2846.1	2863.1
		A/C-A/A	440 (37.5%)	190 (32.8%)	313 (31.9%)		0.78 (0.62–0.97)				0.77 (0.64–0.93)		
	Recessive	C/C-A/C	1070 (91.2%)	529 (91.4%)	902 (92%)	0.630	1.00	1982.2	1998.6	0.430	1.00	2853.1	2870.1
		A/A	103 (8.8%)	50 (8.6%)	78 (8%)		0.91 (0.62–1.33)				0.88 (0.64–1.21)		
	Overdominant	C/C-A/A	836 (71.3%)	439 (75.8%)	745 (76%)	0.037	1.00	1978.1	1994.5	0.013	1.00	2847.5	2864.6
		A/C	337 (28.7%)	140 (24.2%)	235 (24%)		0.77 (0.60–0.99)				0.78 (0.64–0.95)		
	Log-additive	—	—	—	—	0.067	0.86 (0.72–1.01)	1979.1	1995.5	0.017	0.85 (0.74–0.97)	2848.0	2865.0
rs1799724	Dominant	C/C	925 (78.9%)	467 (80.7%)	771 (78.7%)	0.150	1.00	1980.4	1996.8	0.770	1.00	2853.7	2870.7
		C/T-T/T	248 (21.1%)	112 (19.3%)	209 (21.3%)		0.82 (0.63–1.08)				0.97 (0.78–1.20)		
	Recessive	C/C-C/T	1167 (99.5%)	579 (100%)	971 (99.1%)	0.030	1.00	1977.7	1994.1	0.360	1.00	2852.9	2869.9
		T/T	6 (0.5%)	0 (0%)	9 (0.9%)		—				1.65 (0.56–4.82)		
	Overdominant	C/C-T/T	931 (79.4%)	467 (80.7%)	780 (79.6%)	0.230	1.00	1980.9	1997.4	0.630	1.00	2853.5	2870.5
		C/T	242 (20.6%)	112 (19.3%)	200 (20.4%)		0.85 (0.65–1.11)				0.95 (0.76–1.18)		
	Log-additive	—	—	—	—	0.110	0.81 (0.62–1.05)	1979.8	1996.2	0.920	0.99 (0.81–1.21)	2853.7	2870.8
rs1800629	Dominant	G/G	1001 (85.3%)	518 (89.5%)	875 (89.3%)	0.021	1.00	1977.1	1993.5	0.010	1.00	2847.1	2864.1
		A/G-A/A	172 (14.7%)	61 (10.5%)	105 (10.7%)		0.68 (0.49–0.95)				0.71 (0.54–0.92)		
	Recessive	G/G-A/G	1168 (99.6%)	577 (99.7%)	976 (99.6%)	0.750	1.00	1982.3	1998.7	0.840	1.00	2853.7	2870.7
		A/A	5 (0.4%)	2 (0.4%)	4 (0.4%)		0.75 (0.13–4.31)				1.15 (0.30–4.42)		
	Overdominant	G/G-A/A	1006 (85.8%)	520 (89.8%)	879 (89.7%)	0.023	1.00	1977.3	1993.7	0.008	1.00	2846.7	2863.7
		A/G	167 (14.2%)	59 (10.2%)	101 (10.3%)		0.68 (0.49–0.95)				0.70 (0.53–0.91)		
	Log-additive	—	—	—	—	0.024	0.70 (0.51–0.96)	1977.3	1993.7	0.016	0.73 (0.57–0.95)	2847.9	2864.9
rs361525	Dominant	G/G	1116 (95.1%)	547 (94.5%)	901 (91.9%)	0.860	1.00	1982.4	1998.8	0.008	1.00	2846.6	2863.6
		A/G-A/A	57 (4.9%)	32 (5.5%)	79 (8.1%)		1.04 (0.65–1.69)				1.63 (1.14–2.35)		
	Recessive	G/G-A/G	1171 (99.8%)	579 (100%)	977 (99.7%)	0.320	1.00	1981.4	1997.8	0.500	1.00	2853.3	2870.3
		A/A	2 (0.2%)	0 (0%)	3 (0.3%)		—				1.85 (0.30–11.41)		
	Overdominant	G/G-A/A	1118 (95.3%)	547 (94.5%)	904 (92.2%)	0.780	1.00	1982.3	1998.7	0.010	1.00	2847.1	2864.1
		A/G	55 (4.7%)	32 (5.5%)	76 (7.8%)		1.07 (0.66–1.74)				1.62 (1.12–2.34)		
	Log-additive	—	—	—	—	0.950	1.02 (0.64–1.62)	1982.4	1998.8	0.008	1.59 (1.13–2.24)	2846.7	2863.7

Abbreviations: CC, cervical cancer; CIN, cervical intraepithelial neoplasia.

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CIN and control groups showed that no significant differences between the control group and the CIN group in the inheritance models ($P>0.01$).

Association Analysis of Five SNPs in the *TNF-α* Promoter with Different Pathological Types of Cervical Cancer

Comparison between patients with different pathological types of cervical cancer and healthy controls is shown in Table 4. The allelic frequency and genotype frequency of rs1800629 were significantly different between the SCC group and the control group ($P=0.002$ and $P=0.006$, respectively), which indicates that the A allele of this SNP is a protective factor for SCC (OR=0.66; 95% CI=0.50–0.86). The frequency of rs361525 was also significantly different between the SCC group and the control group ($P<0.001$ and $P=0.002$ respectively), and the A allele was a risk factor for SCC (OR=1.87; 95% CI=1.32–2.65). In addition, the frequencies of the five SNPs showed no significant differences between the AC group and the control group ($P>0.01$).

Inheritance Model Analysis of Five SNPs in the *TNF-α* Promoter with Different Pathological Types of Cervical Cancer

The results of analysis of different pathological types of cervical cancer under different inheritance models are shown in Table 5. For rs1800629, comparison between the SCC group and the control group showed that the overdominant model was the best fit. In this model, the A/G genotype was related to a reduced risk of SCC ($P=0.002$, OR=0.63; 95% CI=0.47–0.84). For rs361525, the dominant and log-additive inheritance models were best fitting models. The A/G-A/A genotype was related to an increased risk of SCC in the dominant

Table 4 The Allelic and Genotypic Distribution of Five SNPs in TNF-α Gene Among Control, Cervical Squamous Cell Carcinoma and Adenocarcinoma

SNPs	Alleles	Control (n, %)	SCC (n, %)	AC (n, %)	SCC vs Control		AC vs Control	
					P-value	OR (95% CI)	P-value	OR (95% CI)
rs1799964	C	543(23.1)	360(22.7)	58(17.9)	0.728	0.97 [0.83–1.13]	0.034	0.72 [0.54–0.98]
	T	1803(76.9)	1228(77.3)	266(82.1)				
	C/C	57(4.9)	46(5.8)	5(3.1)	0.344		0.095	
	C/T	429(36.6)	268(33.8)	48(29.6)				
	T/T	687(58.6)	480(60.5)	109(67.3)				
rs1800630	A	543(23.1)	322(20.3)	60(18.5)	0.033	0.85[0.72–0.99]	0.062	0.76[0.56–1.02]
	C	1803(76.9)	1266(79.7)	264(81.5)				
	A/A	103(8.8)	66(8.3)	10(6.2)	0.044		0.228	
	A/C	337(28.7)	190(23.9)	40(24.7)				
	C/C	733(62.5)	538(67.8)	112(69.1)				
rs1799724	C	2092(89.2)	1401(88.2)	297(91.7)	0.355	0.91[0.74–1.11]	0.170	1.34[0.88–2.02]
	T	254(10.8)	187(11.8)	27(8.3)				
	C/C	925(78.9)	616(77.6)	135(83.3)	0.273		0.317	
	T/C	242(20.6)	169(21.3)	27(16.7)				
	T/T	6(0.5)	9(1.1)	0(0.00)				
rs1800629	A	177(7.5)	81(5.1)	23(7.1)	0.002	0.66 [0.50–0.86]	0.775	0.94[0.60–1.47]
	G	2169(92.5)	1507(94.9)	301(92.9)				
	A/A	5(0.4)	3(0.4)	1(0.6)	0.006		0.861	
	A/G	167(14.2)	75(9.4)	21(13.0)				
	G/G	1001(85.3)	716(90.2)	140(86.4)				
rs361525	A	59(2.5)	73(4.6)	7(2.2)	<0.001	1.87[1.32–2.65]	0.700	0.86[0.39–1.89]
	G	2287(97.5)	1515(95.4)	317(97.8)				
	A/A	2(0.2)	3(0.4)	0(0.00)	0.002		0.851	
	A/G	55(4.7)	67(8.4)	7(4.3)				
	G/G	1116(95.1)	724(91.2)	155(95.7)				

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma.

Table 5 Inheritance Model Analysis of Five SNPs in TNF-α Gene Among Control, Cervical Squamous Cell Carcinoma and Adenocarcinoma

SNPs	Model	Genotype	Control	SCC	AC	SCC vs Control				AC vs Control			
						OR (95% CI)	P-value	AIC	BIC	OR (95% CI)	P-value	AIC	BIC
rs1799964	Dominant	T/T	687 (58.6%)	480 (60.5%)	109 (67.3%)	1.00	0.300	2560.4	2577.1	1.00	0.024	951.6	967.2
		C/T-C/C	486 (41.4%)	314 (39.5%)	53 (32.7%)	0.91 (0.75–1.09)				0.67 (0.47–0.95)			
	Recessive	T/T-C/T	1116 (95.1%)	748 (94.2%)	157 (96.9%)	1.00	0.390	2560.7	2577.5	1.00	0.200	955.1	970.7
		C/C	57 (4.9%)	46 (5.8%)	5 (3.1%)	1.20 (0.79–1.81)				0.56 (0.22–1.44)			
	Overdominant	T/T-C/C	744 (63.4%)	526 (66.2%)	114 (70.4%)	1.00	0.140	2559.3	2576.1	1.00	0.078	953.6	969.2
		C/T	429 (36.6%)	268 (33.8%)	48 (29.6%)	0.87 (0.71–1.05)				0.73 (0.50–1.04)			
	Log-additive	—	—	—	—	0.96 (0.82–1.12)	0.590	2561.2	2577.9	0.70 (0.51–0.95)	0.018	951.1	966.7
rs1800630	Dominant	C/C	733 (62.5%)	538 (67.8%)	112 (69.1%)	1.00	0.016	2555.6	2572.3	1.00	0.077	953.6	969.2
		A/C-A/A	440 (37.5%)	256 (32.2%)	50 (30.9%)	0.79 (0.65–0.96)				0.73 (0.51–1.04)			
	Recessive	C/C-A/C	1070 (91.2%)	728 (91.7%)	152 (93.8%)	1.00	0.670	2561.3	2578.0	1.00	0.160	954.8	970.4
		A/A	103 (8.8%)	66 (8.3%)	10 (6.2%)	0.93 (0.67–1.29)				0.63 (0.32–1.25)			
	Overdominant	C/C-A/A	836 (71.3%)	604 (76.1%)	122 (75.3%)	1.00	0.019	2556.0	2572.7	1.00	0.300	955.6	971.2
		A/C	337 (28.7%)	190 (23.9%)	40 (24.7%)	0.78 (0.63–0.96)				0.82 (0.56–1.20)			
	Log-additive	—	—	—	—	0.86 (0.75–1.00)	0.048	2557.5	2574.3	0.77 (0.58–1.01)	0.055	953.0	968.6
rs1799724	Dominant	C/C	925 (78.9%)	616 (77.6%)	135 (83.3%)	1.00	0.740	2561.3	2578.1	1.00	0.081	953.7	969.3
		C/T-T/T	248 (21.1%)	178 (22.4%)	27 (16.7%)	1.04 (0.83–1.30)				0.68 (0.44–1.06)			
	Recessive	C/C-C/T	1167 (99.5%)	785 (98.9%)	162 (100%)	1.00	0.190	2559.7	2576.5	1.00	0.210	955.1	970.7
		T/T	6 (0.5%)	9 (1.1%)	0 (0%)	2.04 (0.70–5.94)				—			
	Overdominant	C/C-T/T	931 (79.4%)	625 (78.7%)	135 (83.3%)	1.00	0.960	2561.4	2578.2	1.00	0.110	954.2	969.7
		C/T	242 (20.6%)	169 (21.3%)	27 (16.7%)	1.01 (0.80–1.26)				0.70 (0.45–1.10)			
	Log-additive	—	—	—	—	1.06 (0.86–1.31)	0.570	2561.1	2577.9	0.67 (0.44–1.04)	0.065	953.3	968.9
rs1800629	Dominant	G/G	1001 (85.3%)	716 (90.2%)	140 (86.4%)	1.00	0.002	2551.8	2568.5	1.00	0.790	956.6	972.2
		A/G-A/A	172 (14.7%)	78 (9.8%)	22 (13.6%)	0.64 (0.48–0.85)				0.94 (0.58–1.52)			
	Recessive	G/G-A/G	1168 (99.6%)	791 (99.6%)	161 (99.4%)	1.00	0.990	2561.4	2578.2	1.00	0.630	956.5	972.1
		A/A	5 (0.4%)	3 (0.4%)	1 (0.6%)	1.01 (0.23–4.37)				1.75 (0.20–15.45)			
	Overdominant	G/G-A/A	1006 (85.8%)	719 (90.5%)	141 (87%)	1.00	0.002	2551.5	2568.2	1.00	0.720	956.6	972.2
		A/G	167 (14.2%)	75 (9.4%)	21 (13%)	0.63 (0.47–0.84)				0.91 (0.56–1.50)			
	Log-additive	—	—	—	—	0.66 (0.50–0.87)	0.003	2552.6	2569.4	0.96 (0.61–1.53)	0.870	956.7	972.3
rs361525	Dominant	G/G	1116 (95.1%)	724 (91.2%)	155 (95.7%)	1.00	0.002	2551.8	2568.6	1.00	0.630	956.5	972.1
		A/G-A/A	57 (4.9%)	70 (8.8%)	7 (4.3%)	1.80 (1.24–2.61)				0.82 (0.36–1.85)			
	Recessive	G/G-A/G	1171 (99.8%)	791 (99.6%)	162 (100%)	1.00	0.370	2560.6	2577.4	1.00	0.520	956.3	971.9
		A/A	2 (0.2%)	3 (0.4%)	0 (0%)	2.27 (0.37–13.97)				—			
	Overdominant	G/G-A/A	1118 (95.3%)	727 (91.6%)	155 (95.7%)	1.00	0.003	2552.6	2569.4	1.00	0.680	956.5	972.1
		A/G	55 (4.7%)	67 (8.4%)	7 (4.3%)	1.77 (1.21–2.59)				0.84 (0.37–1.91)			
	Log-additive	—	—	—	—	1.74 (1.22–2.48)	0.002	2551.8	2568.6	0.80 (0.36–1.79)	0.580	956.4	972.0

Abbreviations: SCC, squamous cell carcinoma; AC, adenocarcinoma.

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model (*P*=0.002, OR=1.80; 95% CI=1.24–2.61) and 2A/A-A/G genotype was related to an increased risk of SCC in the log-additive inheritance model (*P*=0.002, OR=1.74; 95% CI=1.22–2.48). No significant differences between the AC and control group were found for the frequencies of the five SNPs in the inheritance model (*P*>0.01).

Association Analysis of Five SNPs in the *TNF-α* Promoter with Different Stages of Cervical Cancer

As only 36 patients were stage III+IV of cervical cancer, we just analysed the association of five SNPs in the *TNF-α* promoter with stage I and stage II of cervical cancer. Comparison between stage I (n=679) and stage II (n=265) of cervical cancer is shown in Table 6. The genotypic frequency of rs361525 was significantly different between stage I and stage II (*P*=0.003). The allelic frequency showed no significantly difference. In addition, the frequencies of the other four SNPs showed no significant differences between stage I and stage II (*P*>0.01).

Inheritance Model Analysis of Five SNPs in the *TNF-α* Promoter with Different Stages of Cervical Cancer

The results of analysis of different stage I and stage II of cervical cancer under different inheritance models are shown in Table 7. For rs361525, the frequency of A/A genotype was 0% and 1.1% in stage I and stage II, respectively. The recessive inheritance models were best fitting models and the A/A genotype was related to an increased risk of stage in recessive inheritance model (P=0.004). No significant differences between stage I and stage II were found for the frequencies of the other four SNPs in the inheritance model (P>0.01).

Discussion

Cervical cancer is a gynaecological malignancy with a high incidence worldwide that seriously influences

Table 6 The Allelic and Genotypic Distribution of SNPs in TNF-α Gene Promoter Between Stage I and Stage II of Cervical Cancer

SNPs	Alleles	Stage I (n, %)	Stage II (n, %)	Stage I vs Stage II	
				P-value	OR (95% CI)
rs1799964	C	1062(78.2)	418(78.9)	0.753	1.04 (0.81–1.33)
	T	296(21.8)	112(21.1)		
	C/C	35(5.2)	13(4.9)	0.952	
	C/T	226(33.3)	86(32.5)		
	T/T	418(61.6)	166(62.6)		
rs1800630	A	1093(80.5)	422(79.6)	0.672	0.95 (0.74–1.22)
	C	265(19.5)	108(20.4)		
	A/A	51(7.5)	24(9.1)	0.696	
	A/C	163(24.0)	60(22.6)		
	C/C	465(68.5)	181(68.3)		
rs1799724	C	1205(88.7)	473(89.2)	0.751	1.05 (0.76–1.45)
	T	153(11.3)	57(10.8)		
	C/C	530(78.1)	211(79.6)	0.542	
	T/C	145(21.4)	51(19.2)		
	T/T	4(0.6)	3(1.1)		
rs1800629	A	1281(94.3)	503(94.9)	0.622	1.12 (0.71–1.76)
	G	77(5.7)	27(5.1)		
	A/A	2(0.3)	2(0.8)	0.404	
	A/G	73(10.8)	23(8.7)		
	G/G	604(89.0)	240(90.6)		
rs361525	A	60(4.4)	19(3.6)	0.416	1.24 (0.74–2.10)
	G	1298(95.6)	511(96.4)		
	A/A	0(0)	3(1.1)	0.003	
	A/G	60(8.8)	13(4.9)		
	G/G	619(91.2)	249(94.0)		

Table 7 Inheritance Model Analysis of SNPs in TNF-α Gene Promoter Between Stage I and Stage II of Cervical Cancer

SNPs	Model	Genotype	Stage I	Stage II	Stage I vs Stage II			
					P-value	OR (95% CI)	AIC	BIC
rs1799964	Dominant	T/T	418 (61.6%)	166 (62.6%)	0.700	1	1114.5	1129.1
		C/T-C/C	261 (38.4%)	99 (37.4%)		0.94 (0.70–1.27)		
	Recessive	T/T-C/T	644 (94.8%)	252 (95.1%)	0.780	1	1114.6	1129.1
		C/C	35 (5.2%)	13 (4.9%)		0.91 (0.47–1.76)		
	Overdominant	T/T-C/C	453 (66.7%)	179 (67.5%)	0.790	1	1114.6	1129.1
		C/T	226 (33.3%)	86 (32.5%)		0.96 (0.71–1.30)		
	Log-additive	—	—	—	0.670	0.95 (0.74–1.21)	1114.5	1129
rs1800630	Dominant	C/C	465 (68.5%)	181 (68.3%)	0.970	1	1114.7	1129.2
		A/C-A/A	214 (31.5%)	84 (31.7%)		0.99 (0.73–1.35)		
	Recessive	C/C-A/C	628 (92.5%)	241 (90.9%)	0.540	1	1114.3	1128.8
		A/A	51 (7.5%)	24 (9.1%)		1.18 (0.71–1.96)		
	Overdominant	C/C-A/A	516 (76%)	205 (77.4%)	0.660	1	1114.5	1129
		A/C	163 (24%)	60 (22.6%)		0.93 (0.66–1.30)		
	Log-additive	—	—	—	0.810	1.03 (0.82–1.29)	1114.6	1129.2
rs1799724	Dominant	C/C	530 (78.1%)	211 (79.6%)	0.590	1	1114.4	1128.9
		C/T-T/T	149 (21.9%)	54 (20.4%)		0.91 (0.64–1.29)		
	Recessive	C/C-C/T	675 (99.4%)	262 (98.9%)	0.340	1	1113.7	1128.3
		T/T	4 (0.6%)	3 (1.1%)		2.15 (0.47–9.86)		
	Overdominant	C/C-T/T	534 (78.7%)	214 (80.8%)	0.450	1	1114.1	1128.7
		C/T	145 (21.4%)	51 (19.2%)		0.87 (0.61–1.25)		
	Log-additive	—	—	—	0.760	0.95 (0.68–1.32)	1114.6	1129.1
rs1800629	Dominant	G/G	604 (89%)	240 (90.6%)	0.420	1	1114	1128.6
		A/G-A/A	75 (11.1%)	25 (9.4%)		0.82 (0.51–1.33)		
	Recessive	G/G-A/G	677 (99.7%)	263 (99.2%)	0.310	1	1113.6	1128.2
		A/A	2 (0.3%)	2 (0.8%)		2.86 (0.39–21.13)		
	Overdominant	G/G-A/A	606 (89.2%)	242 (91.3%)	0.290	1	1113.6	1128.1
		A/G	73 (10.8%)	23 (8.7%)		0.77 (0.47–1.26)		
	Log-additive	—	—	—	0.580	0.88 (0.56–1.38)	1114.4	1128.9
rs361525	Dominant	G/G	619 (91.2%)	249 (94%)	0.140	1	1112.5	1127
		A/G-A/A	60 (8.8%)	16 (6%)		0.66 (0.37–1.16)		
	Recessive	G/G-A/G	679 (100%)	262 (98.9%)	0.004	1	1106.2	1120.8
		A/A	0 (0%)	3 (1.1%)		-		
	Overdominant	G/G-A/A	619 (91.2%)	252 (95.1%)	0.029	1	1109.9	1124.5
		A/G	60 (8.8%)	13 (4.9%)		0.52 (0.28–0.97)		
	Log-additive	—	—	—	0.420	0.81 (0.48–1.36)	1114	1128.6

women's lives. Many studies have shown that host genetic variation, especially immune genes variations, has a certain association with susceptibility to cervical cancer.[20–23] In the current study, we found that rs1800629 and rs361525 in the TNF-α gene promoter are related to susceptibility to cervical cancer in a Chinese Han population.

Recently, a Meta-Analysis found that rs1800629 (−308 A>G) was associated with the cervical cancer in different inheritance models in the general population.[24] In 2005, Duarte et al reported that the rs1800629 A allele is associated with an increased risk of invasive cervical cancer in the Portuguese population.[6] Then, Singh et al and Du et al also found the rs1800629 A allele to be associated with an increased risk of cervical cancer in an Indian population and a Chinese population from Sichuan Province, Southwest of China, respectively.[7,8] However, we found that the rs1800629 A allele is a protective factor for cervical cancer, and the A/G genotype was related to a reduced risk of cervical cancer in the current study. Our findings are similar to those of Zidi et al, which also found that A/G genotype is a protective factor for cervical cancer in Tunisia.[11] The discrepancy between Du and Singh et al study and our study could be due to the

relatively small sample sizes and population genetic background. For example, the sample sizes in Du et al and Singh et al involved 522 and 150 cervical cancer patients, 550 and 162 healthy individuals, whereas 1173 healthy controls, 579 patients with CIN, and 980 patients with cervical cancer were enrolled in the current study. In 1997, Kroeger et al demonstrated that rs1800629 affected the affinity of factor binding and resulted in a factor binding to A allele but not G allele.[25] Their results showed that the level of transcription of rs1800629 A allele has increased twofold greater level by comparing to that of the G allele. In 2019, Du et al found the PBMCs carrying the rs1800629 AA genotype showed significantly higher rates of T-cell proliferation which play a major role in the surveillance of cancer cells. Thus, the rs1800629 AA genotype positively regulate T-cell activation, and might confer reduced susceptibility to cervical cancer.[7] Thus, the rs1800629 A allele and AA genotype could increase the TNF-α level and T-cell activation to protect from cervical cancer.

Recently, Wang et al reported that rs361525 was associated with the cervical cancer in Asians using meta-analysis.[24] In 2019, Du et al showed that rs361525 A allele and AA genotype is a protective factor against cervical cancer in Sichuan Province, Southwest of China.[7] In 2018, Li et al reported that the rs361525 A allele is a risk factor for SCC in a Chinese population from Shandong Province, North of China.[14] In the current study, we also found the rs361525 A allele and A/G-A/A genotype to be a risk factor for cervical cancer in a Chinese population, which was similar to the meta-analysis results of de Moura et al, which showed that rs361525 A/A genotype in codominant model and recessive model with increased risk for cervical cancer.[26] In the de Moura study, they also identified two transcription factors, MZF1 and ZNF263, which binds to rs1800629 and rs361525 in the TNF-α promote by using bioinformatic method. The binding could affect the affinity between promoter and transcription factors and influence the expression of TNF-α transcriptional levels, which is associated with cervical cancer.[26] In addition, in subgroup analysis, the A allele was a risk factor for SCC but not AC. Our results are similar to those of Li et al, in which the rs361525 A allele was a risk factor for cervical cancer, especially SCC. One of the reasons for the discrepancy between the studies of Du et al and ours might be the different pathological types of cervical cancer included. We found that the A allele of rs361525 is a risk factor for SCC, which indicates that the A allele has different roles in pathological types of cervical cancer. SCC is the most common pathological type of cervical cancer, accounting for approximately 75% to 80%, followed by AC, which accounts for approximately 10.0% to 25%.[27] Therefore, it is necessary to study the role of rs361525 in the different pathological types of cervical cancer in the future.

In the current study, we found that rs1800629 and rs361525 in the TNF-α promoter gene are associated with cervical cancer and SCC in a Chinese Han population. The A allele of rs1800629 is a protective factor for cervical cancer and SCC, whereas the A allele of rs361525 is a risk factor for cervical cancer and SCC. Nevertheless, association results vary among different populations in different studies. As a result, multicentre and more samples from different regions should be evaluated to study the association between TNF-α gene polymorphisms and cervical cancer. Moreover, the function of polymorphisms should be investigated in the future.

Abbreviations

TNF-α, tumour necrosis factor-α; TNF-β, tumour necrosis factor-β; CIN, cervical intraepithelial neoplasia; CC, cervical cancer SNPs, single nucleotide polymorphisms; ANOVA, analysis of variance; HWE, Hardy–Weinberg equilibrium; ORs, odds ratios; CIs, confidence intervals: AIC, Akaike information criterion; BIC, Bayesian information criterion; SCC, squamous cell carcinoma; AC, adenocarcinoma.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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