GMR

Role of *IL17A* rs2275913 and rs3748067 polymorphisms in the risk cervical cancer

A.Q. Niu, Y.H. Cao, H. Wang, X. Zhang, B. Zhu and Z.H. Li

Department of Gynecology, The First People's Hospital of Shangqiu, Shangqiu, China

Corresponding author: A.Q. Niu
E-mail: niuaiqinni@163.com

Genet. Mol. Res. 16 (3): gmr16038826
Received December 2, 2016
Accepted May 19, 2017
Published August 31, 2017
DOI http://dx.doi.org/10.4238/gmr16038826

ABSTRACT. Cervical cancer is a serious public health problem and is associated with high cancer-related mortality in females worldwide. The expression of *IL17A* can increase the migration and invasiveness of cervical cancer cells by activating the NF-κB signal pathway. Single-nucleotide polymorphisms (SNPs) can alter gene function and protein expression. We examined the association between two *IL17A* SNPs (rs2275913 and rs3748067) and the risk of cervical cancer. We also investigated the interaction between IL17A -174G/C and -572C/G mutations and environmental factors. Our 1:2 matched case-control study included 185 cervical cancer patients and 370 healthy controls. The *IL17A* rs2275913 and rs3748067 SNPs were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Using logistic regression analysis, we found that individuals harboring the TT genotype of *IL17A* rs3748067 had an increased risk of cervical cancer compared with those carrying the CC genotype, and the adjusted OR (95%CI) was 6.29 (2.30-19.81). Moreover, individuals carrying the T allele of *IL17A* rs3748067 were more susceptible to cervical cancer than those with the C allele, and the adjusted OR (95%CI) was 2.31 (1.53-3.50). No significant interaction was observed between the *IL17A*

rs2275913 polymorphism and cervical cancer risk. In conclusion, our study suggests that the *IL17A* rs3748067 polymorphism is independently associated with the risk of cervical cancer, and has a relationship with human papillomavirus infection with regard to the risk of cervical cancer.

Key words: *IL-17A*; rs2275913; rs3748067; Polymorphism; Cervical cancer

INTRODUCTION

Cervical cancer is a serious public health problem and is associated with high cancer-related mortality in females worldwide, including China (IARC, 2012). Cervical cancer is the seventh leading cause of cancer-related deaths in women in China, and there were approximately 62,000 new cervical cancer cases and 30,000 deaths in 2012 (IARC, 2012). It is well known that the etiology of cervical cancer involves multiple factors such as persistent infection with oncogenic human papillomavirus (HPV) and chronic inflammation, and long-term use of oral contraceptives, as well as multiple sexual partners (Rajeevan et al., 2005; Villa, 2006; Ribeiro, 2008; Jemal et al., 2011; Bedoya et al., 2013). It is believed that such factors enhance carcinogenesis and promote immunosuppression, which in turn increases the inflammation associated with cervical cancer. Recently, many studies have indicated that tumor angiogenesis in cervical cancer is influenced by many growth factors and various cytokines such as vascular endothelial growth factor, chemokines, tumor necrosis factor-α, and various interleukins (IL6, IL2, IL4, IL10, IL17, and IL27) (Saijo et al., 2015; Yin et al., 2015; Akhavan et al., 2016; Sun et al., 2016; Wang et al., 2016).

IL17A is a pro-inflammatory cytokine; its role is crucial in the inhibition of apoptosis, the stimulation of cellular proliferation and angiogenesis, and the promotion of invasive cancers with metastatic potential (Ji and Zhang, 2010; Ngiow et al., 2010). The authors of previous studies have reported that the expression of IL17A can increase the migration and invasiveness of cervical cancer cells by activating the p38/NF-κB signal pathway (Feng et al., 2014). It has also been reported that IL17A can promote the growth of tumors by stimulating angiogenesis and invasiveness, and by inhibiting apoptosis (Benchetrit et al., 2002). Previous studies have indicated that high expression of IL17A is correlated with the development and progression of tumors, and the *IL17A* gene is regulated at the transcriptional level (Chen et al., 2016; Mohammadi et al., 2016; Parajuli et al., 2016). Moreover, single nucleotide polymorphisms (SNPs) can alter gene function and protein expression. To date, four research groups have investigated the association between *IL17A* gene polymorphisms and the risk of cervical cancer, but the results are conflicting (Cong et al., 2015; Li et al., 2015a; Lv et al., 2015; Sun et al., 2015). Moreover, the authors of previous studies did not investigate the interaction between *IL17A* polymorphisms and environmental factors with regard to the risk of cervical cancer. In the present study, we examined the association between two *IL17A* SNPs (rs2275913 and rs3748067) and the risk of cervical cancer. We also investigated the interaction between IL17A -174G/C and -572C/G mutations and environmental factors.

MATERIAL AND METHODS

Subjects

We conducted a 1:2 matched case-control study that included 185 cervical cancer

patients and 370 healthy controls. These patients were recruited from the Department of Gynecology of the First People's Hospital of Shangqiu between March 2013 and March 2015. All the cervical cancer patients underwent surgery in our hospital and all cases were confirmed by histopathologic examination. Patients with cervical cancer were excluded from the study if they had received chemotherapy or radiotherapy treatment before participation. Patients with a history of secondary or recurrent malignant tumors, end-stage renal or liver disease, or malnutrition were also excluded.

During the period mentioned above, a total of 370 individuals were recruited from the outpatients clinics and physical examination centers of the First People's Hospital of Shangqiu. All the controls were pronounced free of malignant tumors, gynecological diseases, end-stage renal or liver disease, or malnutrition.

Details of potential cervical cancer risk factors were obtained using an *ad hoc* questionnaire or from medical records; they included age, number of sexual partners, menopausal status, oral contraceptive use, family history of cancer, HPV status, International Federation of Gynecology and Obstetrics (FIGO) stage, and histology.

Genotyping of *IL17A* rs2275913 and rs3748067

Peripheral blood samples were collected from all subjects in 0.129 M ethylenediaminetetraacetic acid-containing tubes, and were subjected to genomic DNA extraction using a DNA extraction kit (TaKaRa Bio, Dalian, China) according to manufacturer instructions. The genotyping of the *IL17A* rs2275913 and rs3748067 SNPs was carried out by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) using a PCR Thermocycle Instrument (MJ Research Inc., St. Bruno, Canada). The primers were provided by ABI Applied Biosystems (Waltham, MA, USA). The forward and reverse primers for *IL17A* rs2275913 were 5'-ACTTCGTGCATGACTTCAGC-3' and 5'-CTGATTGGAAACCTTATTAAG-3', respectively. The forward and reverse primers for *IL17A* rs3748067 were 5'-GGAGACGCCTTGAAGTAACTGC-3' and 5'-GAGTTTCCTCTGACTCCATCGCAG-3', respectively. The PCR for genotyping *IL17A* rs2275913 and rs3748067 was carried out in a 50-μL reaction mixture comprising 20 pmol each primer, 4 ng (2 μL) DNA, 1.25 μmol dNTP mix (4 μL), 2.0 mM $MgCl_2$ (25 mM), 1.25 U Taq polymerase (0.25 μL), and 5 μL 10X PCR Buffer Tango and ddH_2O (ABI Applied Biosystems Inc.). The PCR regimen for *IL17A* rs2275913 was as follows: initiation at 94°C for 5 min; 35 cycles of 94°C for 30 s, 57°C for 60 s, and 72°C for 60 s; and a final cycle of 72°C for 10 min. The PCR regimen for *IL17A* rs3748067 was as follows: 95°C for 5 min; 35 cycles of 94°C for 30 s, 60°C for 60 s, and 72°C for 60 s; and a final cycle of 72°C for 6 min. The conditions for restriction digestion included 2 μL 10X buffer R, 10 μL PCR products, 1 μL restriction enzyme, and 18 μL ddH_2O. The restriction enzymes (10 U/μL) for *IL17A* rs2275913 and rs3748067 were *Xmn*I and *Apo*I, respectively. The PCR amplification and enzyme digestion products of *IL17A* rs2275913 and rs3748067 were observed on 1.5% agarose gel and presented in ultraviolet light.

Statistical analysis

The differences in potential cervical cancer risk factors between patients with cervical cancer and controls were compared using the Pearson chi-square (χ^2) test or the Student *t*-test. Deviation of the genotype frequencies of *IL17A* rs2275913 and rs3748067 from the Hardy-

Weinberg equilibrium was analyzed using the Pearson chi-square test. The role of *IL17A* rs2275913 and rs3748067 SNPs in cervical cancer risk was evaluated using logistic regression analysis; odds ratios (ORs) and 95% confidence intervals (95%CIs) were taken to estimate the relationship. All P values were two-sided, and P values less than 0.05 were considered statistically significant. All data analyses were performed using SPSS Statistics for Windows, Version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The restriction products of *IL17A* rs2275913 and rs3748067 were 246 and 230 bp in size, respectively. For the *IL17A* rs2275913 SNP, the restriction fragment lengths were 246 and 122 bp for the GG genotype, 368, 246, and 122 bp for the GA genotype, and 368 bp for the AA genotype. For the *IL17A* rs3748067 SNP, the fragment lengths were 230 and 128 bp for the TT genotype, 358, 230, and 128 bp for the CT genotype, and 358 bp for the CC genotype.

General information about the cervical cancer patients and the controls is presented in Table 1. The Pearson chi-square test revealed that cervical cancer patients had more sexual partners (χ^2 = 16.31, P < 0.001), were more likely to have a family history of cancer (χ^2 = 11.79, P = 0.001), and were more likely to have HPV infection (χ^2 = 336.10, P < 0.001) compared with the controls. However, no significant differences were found between cervical cancer patients and controls with respect to age (χ^2 = 10.82, P = 0.37), menopausal status (χ^2 = 1.41, P = 0.23), or oral contraceptive use (χ^2 = 3.45, P = 0.06). Of the 185 cervical cancer patients, 122 (65.95%) were at stage I-II and 63 (34.05%) were at stage III-IV. The histological composition of the patients was as follows: 151 (81.62%) had squamous cell carcinoma, 30 (16.22%) had adenocarcinoma, and 4 (2.16%) had sarcoma.

Table 1. General information about the cervical cancer patients and the controls.

Variables	Patients (N = 185)	%	Controls (N = 370)	%	χ^2 value	P value
Age						
<50	79	42.70	173	46.76		
≥50	106	57.30	197	53.24	0.82	0.37
Sexual partners						
0	2	1.08	13	3.51		
1-3	99	53.51	250	67.57		
≥3	84	45.41	107	28.92	16.31	<0.001
Menopausal						
Pre-menopausal	60	32.43	139	37.57		
Post-menopausal	125	67.57	231	62.43	1.41	0.23
Oral contraceptive users						
No	23	12.43	69	18.65		
Yes	162	87.57	301	81.35	3.45	0.06
Family history of cancer						
No	154	83.24	343	92.70		
Yes	31	16.76	27	7.30	11.79	0.001
HPV infection						
No	0	0.00	304	82.16		
Yes	185	100.00	66	17.84	336.10	<0.001
FIGO stage						
I-II	122	65.95				
III-IV	63	34.05				
Histology						
Squamous cell carcinoma	151	81.62				
Adenocarcinoma	30	16.22				
Sarcoma	4	2.16				

FIGO = International Federation of Gynecology and Obstetrics.

The distribution frequencies of *IL17A* rs2275913 and rs3748067 are shown in Table 2. The *IL17A* rs2275913 and rs3748067 minor allele frequencies in the controls were 0.2959 and 0.0730, respectively [similar to those available on the National Center of Biotechnology Information database (https://www.ncbi.nlm.nih.gov/snp/)]. There were significant differences in the genotype frequencies of *IL17A* rs3748067 between the cervical cancer patients and the controls ($\chi^2 = 18.26$, $P < 0.001$), whereas there were no such differences between the genotype frequencies of *IL17A* rs2275913 ($\chi^2 = 0.77$, $P = 0.68$). The chi-square test revealed that the genotype distributions of *IL17A* rs2275913 ($\chi^2 = 21.52$, $P < 0.001$) and rs3748067 ($\chi^2 = 9.59$, $P = 0.002$) did not agree with the Hardy-Weinberg equilibrium in the controls.

Table 2. Distribution of *IL17A* rs2275913 and rs3748067 polymorphisms in the patients with cervical cancer and in the controls.

IL17A	Patients (N = 185)	%	Controls (N = 370)	%	MA	MAF in controls	χ^2 value	P value	χ^2 for HWE	P for HWE
rs2275913										
GG	95	51.35	202	54.59						
GA	60	32.43	117	31.62						
AA	30	16.22	51	13.78	A	0.2959	0.77	0.68	21.52	<0.001
rs3748067										
CC	145	78.38	322	87.03						
CT	23	12.43	42	11.35						
TT	17	9.19	6	1.62	T	0.0730	18.26	<0.001	9.59	0.002

MA = Minor allele; MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium.

Using logistic regression analysis, we found that individuals harboring the TT genotype of *IL17A* rs3748067 had an increased risk of cervical cancer compared with those with the CC genotype, and the adjusted OR (95%CI) was 6.29 (2.30-19.81) (Table 3). Moreover, individuals carrying the T allele of *IL17A* rs3748067 had a higher risk of developing cervical cancer compared with those with the C allele, and the adjusted OR (95%CI) was 2.31 (1.53-3.50). However, no significant relationship was detected between the *IL17A* rs2275913 SNP and cervical cancer risk.

Table 3. Association between *IL17A* rs2275913 and rs3748067 polymorphisms and risk of cervical cancer.

IL17A	Patients (N = 185)	%	Controls (N = 370)	%	OR (95%CI)	P value
rs2275913						
GG	95	51.35	202	54.59	Reference	-
GA	60	32.43	117	31.62	1.09 (0.72-1.65)	0.67
AA	30	16.22	51	13.78	1.25 (0.72-2.15)	0.39
Allele						
G	250	67.57	521	70.41	Reference	-
A	120	32.43	219	29.59	1.14 (0.86-1.51)	0.33
rs3748067						
CC	145	78.38	322	87.03	Reference	-
CT	23	12.43	42	11.35	1.22 (0.67-2.16)	0.48
TT	17	9.19	6	1.62	6.29 (2.30-19.81)	<0.001
Allele						
C	313	84.59	686	92.71	Reference	-
T	57	15.41	54	7.29	2.31 (1.53-3.50)	<0.001

We investigated the interaction between the *IL17A* rs3748067 polymorphism and environmental factors using Spearman correlation analysis and found that the *IL17A* rs3748067 SNP had a relationship with HPV infection (Spearman correlation coefficient = 0.142, P = 0.005) (Table 4). However, we did not find any relationship between the *IL17A* polymorphism

and age, number of sexual partners, or family history of cancer with regard to the risk of cervical cancer ($P > 0.05$).

Table 4. Interaction between the *IL17A* rs3748067 polymorphism and environmental factors with regard to the risk of cervical cancer.

Variables	rs3748067	
	Spearman correlation coefficient	P value
Age	0.034	0.47
Sexual partner	0.025	0.66
Family history of cancer	0.047	0.31
HPV infection	0.142	0.005

DISCUSSION

Inflammation-related cytokines are involved in altering epithelial tissues in many types of cancer (Sun et al., 2015; Wang et al., 2015; Yang et al., 2016). The inflammatory status of the human body can affect the acceleration of tumor progression, the reconstruction of tumor tissue, the promotion of angiogenesis, and the inhibition of the natural antitumor immune response (Chechlinska et al., 2010). In the current study, we found that the *IL17A* rs3748067 SNP was independently associated with the risk of cervical cancer, and a significant relationship was detected between the *IL17A* rs3748067 SNP and HPV infection with regard to the risk of cervical cancer (Sun et al., 2015; Wang et al., 2015; Yang et al., 2016).

IL17A is a special cytokine that is secreted by helper T cells; it recruits neutrophils that release inflammatory factors, and promotes cell proliferation, angiogenesis, and metastasis, resulting in the onset of chronic inflammation and tumors (Yang et al., 2014). Previous studies have indicated that high expression of IL17A is correlated with the development and progression of tumors, and *IL17A* is regulated at the transcriptional level (Chen et al., 2016; Mohammadi et al., 2016; Parajuli et al., 2016). Polymorphisms in cytokine factors can influence their function and expression, or cause abnormal cell proliferation, thereby triggering cell transformation and maintaining the autonomous proliferation of the transformed cells (Jia et al., 2015; Omrane et al., 2015). Therefore, polymorphisms in *IL17A* could influence the expression of the IL17A protein, and thus influence an individual's susceptibility to tumors.

The authors of previous studies have reported a relationship between *IL17A* polymorphisms and the risk of several kinds of cancer such as hepatocellular carcinoma, gastric cancer, acute myeloid leukemia, colorectal cancer, and papillary thyroid cancer (ELBassuoni et al., 2015; Hou and Yang, 2015; Lee et al., 2015; Ma et al., 2015; Omrane et al., 2015; Zhu et al., 2015). ELBassuoni et al. (2015) carried out a study on 35 hepatocellular carcinoma patients and 20 healthy subjects, which indicated that the GG genotype of *IL17A* was associated with an increased risk of hepatocellular carcinoma in an Egyptian population. Hou and Yang (2015) carried out a study on 326 gastric cancer patients and 326 controls, which revealed a significant association between the *IL17A* rs2275913G>A polymorphism and elevated gastric cancer risk. However, another study on 62 acute myeloid leukemia patients and 125 healthy controls indicated that *IL17A* genetic polymorphisms were not associated with the risk of this cancer (Zhu et al., 2015). Omrane et al. (2015) reported that *IL17A* and *IL17F* genes may be predictive factors for colorectal cancer therapy. Lee et al. (2015) reported that IL17A was not significantly associated with the risk of papillary thyroid cancer in a Korean population. Ma et al. (2015) indicated that *IL17A*-73G/A polymorphism contributes to the pathogenesis of non-small cell lung cancer.

The authors of five previous studies have reported an association between *IL17A* polymorphisms and cervical cancer (Quan et al., 2012; Cong et al., 2015; Li et al., 2015a; Lv et al., 2015; Sun et al., 2015). All the studies indicated that the *IL17A* rs2275913 polymorphism was associated with the risk of cervical cancer. Three studies revealed an association between the *IL17A* rs3748067 polymorphism and the risk of cervical cancer, but the correlation was not significant (Cong et al., 2015; Li et al., 2015a; Lv et al., 2015). However, they did not investigate the interaction between the *IL17A* polymorphism and environmental factors. We initially observed that the *IL17A* rs2275913 polymorphism was positively associated with HPV infection. Previous studies have shown that upregulation of IL17A expression is associated with HPV 16 infection with regard to the risk of cancers (Chang et al., 2010; Li et al., 2015b; Vidal et al., 2015). Further studies are needed to confirm our study.

One important limitation of our study should be considered. The cervical cancer patients and controls were recruited from only one hospital, which may have caused selection bias in our study. In conclusion, our study suggests that the *IL17A* rs3748067 polymorphism is independently associated with the risk of cervical cancer, and has a relationship with HPV infection with regard to the risk of cervical cancer.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank for the great help from staffs in the First People's Hospital of Shangqiu, and they help us to collect the blood sample for us.

REFERENCES

Akhavan S, Safari A, Azizmohammadi S, Azizmohammadi S, et al. (2016). Evaluation of mRNA expression levels of IL-17A and IL-10 cytokines in cervical cancer. *Tumour Biol.*

Bedoya AM, Jaramillo R, Baena A, Castaño J, et al. (2013). Location and density of immune cells in precursor lesions and cervical cancer. *Cancer Microenviron.* 6: 69-77. http://dx.doi.org/10.1007/s12307-012-0097-8

Benchetrit F, Ciree A, Vives V, Warnier G, et al. (2002). Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. *Blood* 99: 2114-2121. http://dx.doi.org/10.1182/blood.V99.6.2114

Chang YH, Yu CW, Lai LC, Tsao CH, et al. (2010). Up-regulation of interleukin-17 expression by human papillomavirus type 16 E6 in nonsmall cell lung cancer. *Cancer* 116: 4800-4809. http://dx.doi.org/10.1002/cncr.25224

Chechlinska M, Kowalewska M and Nowak R (2010). Systemic inflammation as a confounding factor in cancer biomarker discovery and validation. *Nat. Rev. Cancer* 10: 2-3. http://dx.doi.org/10.1038/nrc2782

Chen X, Wang J, Wang R, Su Q, et al. (2016). Th1-, Th2-, and Th17-associated cytokine expression in hypopharyngeal carcinoma and clinical significance. *Eur. Arch. Otorhinolaryngol.* 273: 431-438. http://dx.doi.org/10.1007/s00405-015-3779-2

Cong J, Liu R, Wang X, Sheng L, et al. (2015). Association between interluekin-17 gene polymorphisms and the risk of cervical cancer in a Chinese population. *Int. J. Clin. Exp. Pathol.* 8: 9567-9573.

ELBassuoni MA, Abd El Fatah G, Zaghla H and Zaghla H (2015). IL17A gene polymorphism, serum IL17 and total IgE in Egyptian population with chronic HCV and hepatocellular carcinoma. *Immunol. Lett.* 168: 240-245. http://dx.doi.org/10.1016/j.imlet.2015.09.004

Feng M, Wang Y, Chen K, Bian Z, et al. (2014). IL-17A promotes the migration and invasiveness of cervical cancer cells by coordinately activating MMPs expression via the p38/NF-kB signal pathway. *PLoS One* 9: e108502. http://dx.doi.org/10.1371/journal.pone.0108502

Hou C and Yang F (2015). Interleukin-17A gene polymorphism is associated with susceptibility to gastric cancer. *Int. J. Clin. Exp. Pathol.* 8: 7378-7384.

International Agency for Research on Cancer (IARC) (2012). Cervical Cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx. Accessed August 10, 2016.

Jemal A, Bray F, Center MM, Ferlay J, et al. (2011). Global cancer statistics. *CA Cancer J. Clin.* 61: 69-90. http://dx.doi.org/10.3322/caac.20107

Ji Y and Zhang W (2010). Th17 cells: positive or negative role in tumor? *Cancer Immunol. Immunother.* 59: 979-987. http://dx.doi.org/10.1007/s00262-010-0849-6

Jia W, Fei GH, Hu JG and Hu XW (2015). A study on the effect of IL-6 gene polymorphism on the prognosis of non-small-cell lung cancer. *Onco Targets Ther.* 8: 2699-2704.

Lee YC, Chung JH, Kim SK, Rhee SY, et al. (2015). Association between interleukin 17/interleukin 17 receptor gene polymorphisms and papillary thyroid cancer in Korean population. *Cytokine* 71: 283-288. http://dx.doi.org/10.1016/j.cyto.2014.11.011

Li L, Tian YL, Lv XM, Yu HF, et al. (2015a). Association analysis of IL-17A and IL-17F polymorphisms in Chinese women with cervical cancer. *Genet. Mol. Res.* 14: 12178-12183. http://dx.doi.org/10.4238/2015.October.9.6

Li YX, Zhang L, Simayi D, Zhang N, et al. (2015b). Human papillomavirus infection correlates with inflammatory Stat3 signaling activity and IL-17 level in patients with colorectal cancer. *PLoS One* 10: e0118391. http://dx.doi.org/10.1371/journal.pone.0118391

Lv Q, Zhu D, Zhang J, Yi Y, et al. (2015). Association between six genetic variants of IL-17A and IL-17F and cervical cancer risk: a case-control study. *Tumour Biol.* 36: 3979-3984. http://dx.doi.org/10.1007/s13277-015-3041-y

Ma QY, Chen J, Wang SH, Wu N, et al. (2015). Interleukin 17A genetic variations and susceptibility to non-small cell lung cancer. *APMIS* 123: 194-198. http://dx.doi.org/10.1111/apm.12341

Mohammadi M, Kaghazian M, Rahmani O, Ahmadi K, et al. (2016). Overexpression of interleukins IL-17 and IL-8 with poor prognosis in colorectal cancer induces metastasis. *Tumour Biol.* 37: 7501-7505. http://dx.doi.org/10.1007/s13277-015-4628-z

Ngiow SF, Smyth MJ and Teng MW (2010). Does IL-17 suppress tumor growth? *Blood* 115: 2554-2555, author reply 2556-2557. http://dx.doi.org/10.1182/blood-2009-11-254607

Omrane I, Medimegh I, Baroudi O, Ayari H, et al. (2015). Involvement of IL17A, IL17F and IL23R Polymorphisms in Colorectal Cancer Therapy. *PLoS One* 10: e0128911. http://dx.doi.org/10.1371/journal.pone.0128911

Parajuli P, Anand R, Mandalaparty C, Suryadevara R, et al. (2016). Preferential expression of functional IL-17R in glioma stem cells: potential role in self-renewal. *Oncotarget* 7: 6121-6135.

Quan Y, Zhou B, Wang Y, Duan R, et al. (2012). Association between IL17 polymorphisms and risk of cervical cancer in Chinese women. *Clin. Dev. Immunol.* 2012: 258293. http://dx.doi.org/10.1155/2012/258293

Rajeevan MS, Swan DC, Nisenbaum R, Lee DR, et al. (2005). Epidemiologic and viral factors associated with cervical neoplasia in HPV-16-positive women. *Int. J. Cancer* 115: 114-120. http://dx.doi.org/10.1002/ijc.20894

Ribeiro KCB (2008). Câncer do colo do útero: epidemiologia do câncer do colo do útero-fatores demográficos e fatores de risco. *Tecmedd.* 2008: 18-23.

Saijo Y, Furumoto H, Yoshida K, Nishimura M, et al. (2015). Clinical significance of vascular endothelial growth factor expression and microvessel density in invasive cervical cancer. *J. Med. Invest.* 62: 154-160. http://dx.doi.org/10.2152/jmi.62.154

Sun L, Xia WY, Zhao SH, Liu N, et al. (2016). An asymmetrically dimethylarginated nuclear 90 kDa protein (p90aDMA) induced by interleukin (IL)-2, IL-4 or IL-6 in the tumor microenvironment is selectively degraded by autophagy. *Int. J. Oncol.* 48: 2461-2471.

Sun LX, Wang XB and Huang XJ (2015). Association analysis of rs2275913G>A and rs763780T>C interleukin 17 polymorphisms in Chinese women with cervical cancer. *Genet. Mol. Res.* 14: 13612-13617.

Vidal AC, Skaar D, Maguire R, Dodor S, et al. (2015). IL-10, IL-15, IL-17, and GMCSF levels in cervical cancer tissue of Tanzanian women infected with HPV16/18 vs. non-HPV16/18 genotypes. *Infect. Agent. Cancer* 10: 10. http://dx.doi.org/10.1186/s13027-015-0005-1

Villa LL (2006). Biology of genital human papillomaviruses. *Int. J. Gynaecol. Obstet.* 94: S3-S7. http://dx.doi.org/10.1016/S0020-7292(07)60003-4

Wang GQ, Zhao WH, Zhao XX, Zhang J, et al. (2016). Association between IL-27 2905T/G genotypes and the risk and survival of cervical cancer: a case-control study. *Biomarkers* 21: 272-275. http://dx.doi.org/10.3109/1354750X.2015.1134665

Wang H, Zhang Y, Liu Z, Zhang Y, et al. (2015). The IL-17A G-197A and IL-17F 7488T/C polymorphisms are associated with increased risk of cancer in Asians: a meta-analysis. *Drug Des. Devel. Ther.* 9: 5159-5168.

Yang B, Kang H, Fung A, Zhao H, et al. (2014). The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. *Mediators Inflamm.* 2014: 623759. http://dx.doi.org/10.1155/2014/623759

Yang LJ, Gao W, Bai JY, Zhang XK, et al. (2016). Correlation between Interleukin-17 gene polymorphism and gastric cancer susceptibility in Han Chinese population. *Eur. Rev. Med. Pharmacol. Sci.* 20: 1271-1282.

Yin G, Zhu T, Li J, Wu A, et al. (2015). CXCL12 rs266085 and TNF-a rs1799724 polymorphisms and susceptibility to cervical cancer in a Chinese population. *Int. J. Clin. Exp. Pathol.* 8: 5768-5774.

Zhu B, Zhang J, Wang X, Chen J, et al. (2015). Correlation between acute myeloid leukemia and IL-17A, IL-17F, and IL-23R gene polymorphism. *Int. J. Clin. Exp. Pathol.* 8: 5739-5743.