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Relationship of IL-18 genetic polymorphism to cervical cancer risk: A meta-analysis.

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Abstract

Published studies about the association between Interleukin-18 (*IL-18*) gene polymorphisms and cervical cancer susceptibility were inconsistent. A meta-analysis for the association between IL-18-607C/A (rs1946518) and risk of cervical cancer was carried out to collectively analyse existing comparative studies. PubMed, Embase, Science Citation Index (SCI), CNKI and Wanfang were researched on the associations between Interleukin-18 and cervical cancer risk. Five studies with 775 cervical cancer patients and 1004 controls met the criteria and included into this study. By meta-analysis analyses, we found that IL-18 rs1946518 CA and AA genotypes were not significantly associated with an increased risk of cervical cancer. The heterogeneities existed in the association between the IL-18 rs1946518 AA genotype and risk of cervical cancer in comparison to the CC genotype (P for heterogeneity<0.001, I^2=87.2%). We found that the AA genotype of IL-18-607C/A rs1946518 was associated with a decreased risk of cervical cancer in studies with population-based design, when compared with the CC genotype (OR=0.19, 95% CI=0.04-0.98). In summary, our meta-analysis suggests that IL-18 polymorphism may not contribute to the development of cervical cancer, but the IL-18-607 AA genotype is associated with cervical cancer risk in studies with population-based design. Further studies with well study design and large sample size are greatly needed to confirm the association between IL-18-607C/A rs1946518 and cervical cancer risk.

Keywords: IL-18-607C/A, rs1946518, Polymorphism, Cervical cancer.

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Introduction

Cervical cancer is the second most common form of cancer diagnosed in women and the third leading cause of death from cancer, accounting for about 8% of total cancer cases and cancer deaths in women [1]. It is estimated that there were an estimated 528,000 new cases and 266,000 deaths in 2012 worldwide in 2012 [2]. Cervical cancer affects the cervix and includes squamous cell carcinomas (90%), adenocarcinoma (10%), and other subtypes [3,4]. The etiology of cervical cancer has been largely attributed to infection of Human Papilloma Virus (HPV) [5-7]. However, HPV infection does not necessarily lead to cervical cancers, only a few of these infected cases would develop cervical cancer during their lifetime [8].

Chronic systemic inflammation has emerged as an important factor in the pathogenesis of chronic diseases, including cervical cancer [9,10]. Inflammatory cytokines may be important factors in the pathogenesis of cervical cancer [10,11]. IL-18, pro-inflammatory cytokine, induces the production of Tumor Necrosis Factor-alpha (TNF-α), and it promotes IL-6 synthesis and regulates C-reactive protein synthesis in the liver [12-14]. IL-18-607C/A (rs1946518) is located in the up-stream of *IL-18* gene, and previous studies have reported their association between IL-18-607C/A (rs1946518) polymorphisms and risk of cervical cancer, but they are controversial. The discrepancy may be attributed to the relatively small sample size of previous studies and the genetic heterogeneity of polymorphisms in cervical cancer among different populations. Therefore, further reconcile these conflicting findings to obtain a more definitive conclusion using multiple statistical analysis, a meta-analysis for the association between IL-18-607C/A (rs1946518) and risk of cervical cancer was carried out to collectively analyse existing comparative studies.

Materials and Methods

Literature search

A comprehensive literature search was independently performed by two of the authors until June 1, 2017 without restriction on the geographic region or language of publication

on the following online databases: PubMed, Embase, Science Citation Index (SCI), CNKI and Wanfang. References appearing in relevant reports and recent reviews were all screened to identify potential articles of interest. The following keywords and subject terms “Interleukin-18”, “polymorphism” and “cervical cancer” were used in databases. All references in these studies were examined to identify additional research not indexed by the databases. We selected only published articles written in English or in Chinese.

Inclusion criteria

Studies included in the current meta-analysis had to meet the following criteria: 1) the study design had to be a case-control study (including retrospective or prospective studies); 2) the focus had to be on IL-18 promoter polymorphisms (-607C/A; rs1946518); 3) the case group had to include women with cervical cancer and control group women without cervical cancer; 4) the reports had to include sufficient information on the frequency distribution of different genotypes to calculate the Odds Ratios (ORs) and 95% Confidence Intervals (CIs); 5) in the case of duplicate studies, we included the most recent or those with the largest samples.

Data extraction and quality evaluation

Two investigators independently extracted the following information from all the included studies: first author, year of publication, study country or region where the study was performed, ethnicity (Asian, Caucasian or African), source of the controls, sample sizes for patients and controls, data on the frequency distribution of different genotypes, Hardy-Weinberg equilibrium (HWE) for controls, and the genotyping method.

Statistical analysis

ORs with 95% CIs were calculated to assess the strength of the association between IL-18 polymorphisms and cervical cancer susceptibility. For the IL-18-607C/A rs1946518 polymorphism, the following three genetic models were used: co-dominant, dominant and recessive models. The Hardy-Weinberg equilibrium (HWE) in the control group was assessed, and a $P<0.05$ was considered as significant disequilibrium. Subgroup analysis was performed according to ethnicity difference, control design, and genotyping method. Heterogeneity between studies was determined by means of Cochran’s Q-test and I^2 statistic. The fixed-effect model (the Mantel-Haenszel method) was used when the P-value was more than 0.10 and I^2 was less than 40%, while a random-effects model (DerSimonian and Laird method) was used. Sensitivity analyses were also conducted to evaluate the robustness of our results. Egger's linear regression and Begg’s funnel plots were used to examine potential publication bias All statistical calculations were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA). A two-sided P value<0.05 was considered significant.

Results

Study characteristics

Initially, a total of forty one articles were identified in the initial search. The title and duplicate screening step excluded 15 studies. Of the remaining 26 studies, 21 studies were excluded due to not on the research polymorphism locus. Finally, five studies involving 775 cervical cancer patients and 1004 controls met the criteria and included into this study [15-19]. Among these studies, four studies were in Asian population, and one study in Brazil population (Figure 1).

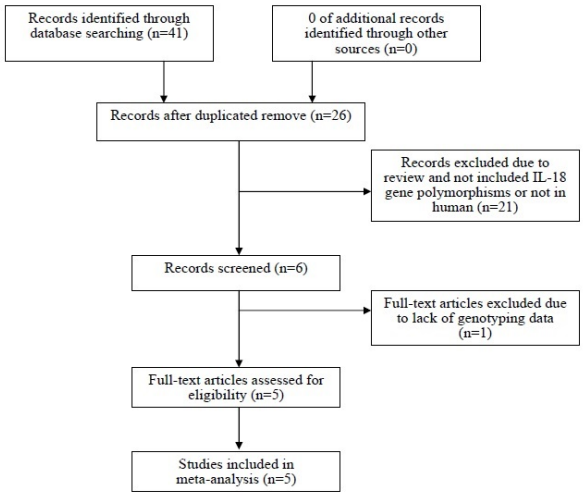

Figure 1. *Flow diagram of study selection.*

Two studies deviated from HWE existed in IL-18 rs1946518 polymorphisms loci [15,20]. All characteristics of included studies are summarized in Tables 1 and 2.

Association between IL-18 rs1946518 polymorphism and cervical cancer risk

By meta-analysis analyses, we found that IL-18 rs1946518 CA genotype was not significantly associated with an increased risk of cervical cancer in fix-effect model, when compared with the CC genotype (OR=0.90, 95% CI=0.71-1.14, P=0.37, Figure 2). The AA genotype was not related to an elevated risk of cervical cancer in random-effect model, when compared with the CC genotype (OR=1.02, 95% CI=0.38-2.76, P=0.97, Figure 3). We found that the heterogeneities existed in the association between the IL-18 rs1946518 AA genotype and risk of cervical cancer in comparison to the CC genotype (P for heterogeneity<0.001, I^2=87.2%, Table 2).

Subgroup analysis

We performed subgroup analyses based on the HWE status, the control design and genotyping method (Table 3). We did not find significant association between IL-18-607C/A rs1946518 polymorphism and risk of cervical cancer by stratified analysis on HWE status, ethnicity and genotype method. However, we found that the AA genotype of IL-18-607C/A rs1946518 was

associated with an decreased risk of cervical cancer in studies with population-based design, when compared with the CC genotype (OR=0.19, 95% CI=0.04-0.98) (Table 3).

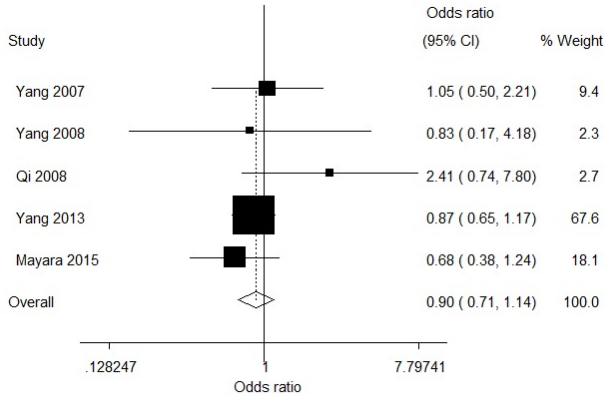

Figure 2. *Forest plot for the comparison of the CA genotype of IL-18-607C/A rs1946518 with the CC genotype in the risk of cervical cancer.*

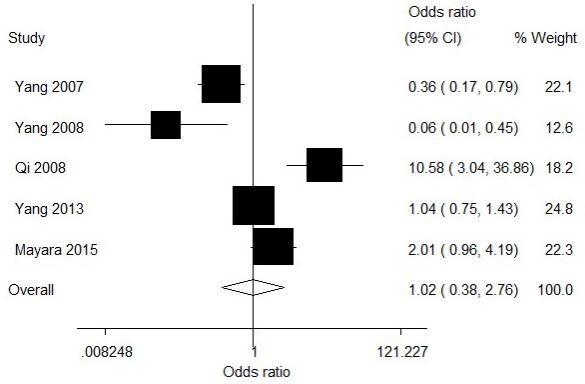

Figure 3. *Forest plot for the comparison of the AA genotype of IL-18-607C/A rs1946518 with the CC genotype in the risk of cervical cancer.*

Sensitivity analysis and publication bias

By using a stepwise process, meta-analysis was performed repeatedly when each particular study was sequentially excluded. We found that the removal of any study one by one did not alter the statistical results. Egger's test was performed to assess publication bias of the literature. The shape of the funnel plot was symmetrical and the statistical results did not show any publication bias (Egger's test: P=0.36 for IL-18-607CA *vs.* CC, Figure 4; Egger's test: P=0.96 for IL-18-607AA *vs.* CC, Figure 5).

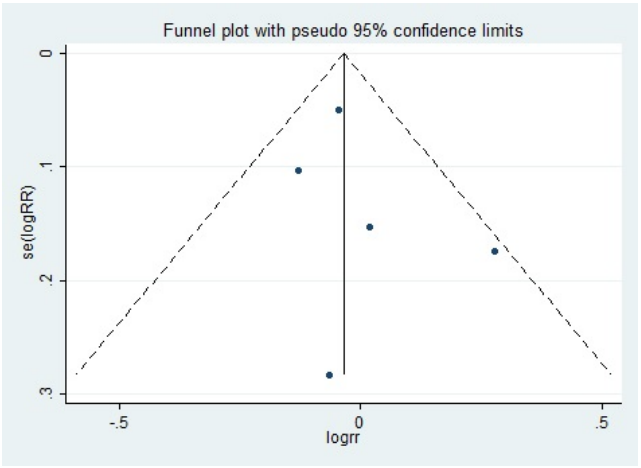

Figure 4. *Begg's funnel plot of publication bias for the comparison of the CA genotype of IL-18-607C/A rs1946518 with the CC genotype in the risk of cervical cancer.*

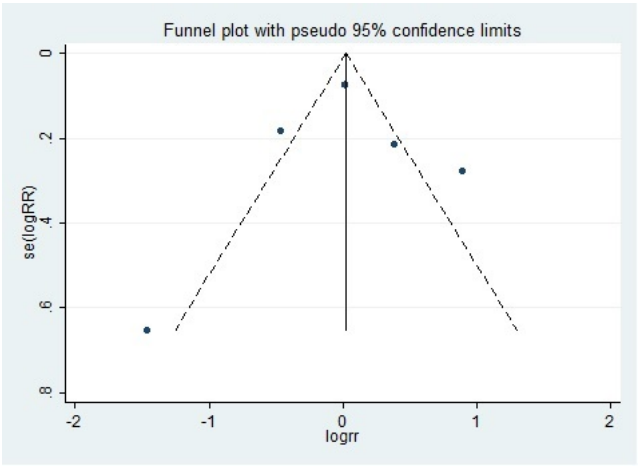

Figure 5. *Begg's funnel plot of publication bias for the comparison of the AA genotype of IL-18-607C/A rs1946518 with the CC genotype in the risk of cervical cancer.*

Table 1. *Characteristics of studies on the association between IL-18-607C/A rs1946518 and cervical cancer risk.*

First author	Country	Source of controls	Age of patients	Age of controls	Patients	Controls	Genotyping
Yang [15]	China (Mainland)	Population-based	45.9 ± 15.2	NA	107	80	Pyrosequencing
Yang [17]	China (Mainland)	Population-based	46.0 ± 15	NA	26	20	Pyrosequencing
Qi [16]	China (Mainland)	Hospital-based	45 ± 10	NA	50	50	Pyrosequencing
Yang [18]	China (Taiwan)	Hospital-based	53.2 ± 13.1	52.4 ± 12.1	470	722	TaqMan

Mayara [19]	Brazil	Hospital-based	32.9 ± 10.8	37.7 ± 10	122	132	SSP-PCR

Table 2. *Genotype distributions of studies on IL-18-607C/A rs1946518 polymorphism and association with risk of cervical cancer.*

Studies	Patients			Controls			HWE in controls		CA *vs.* CC		AA *vs.* CC	
	CC	CA	AA	CC	CA	AA	χ2	P value	OR (95% CI)	P value	OR (95% CI)	P value
Yang [15]	33	50	24	18	26	36	7.96	0.005	1.05 (0.46-2.35)	0.9	0.36 (0.16-0.84)	0.01
Yang [17]	9	15	2	3	6	11	1.63	0.2	1.70 (0.20-12.20)	0.54	0.06 (0.004-0.58)	0.003
Qi [16]	5	17	28	17	24	9	0.01	0.92	2.41 (0.67-9.88)	0.14	10.58 (2.64-45.75)	<0.001
Yang [18]	116	215	139	169	358	195	0.04	0.85	0.68 (0.36-1.30)	0.21	1.04 (0.74-1.45)	0.82
Mayara [19]	32	53	37	33	80	19	6.74	0.01	0.68 (0.36-1.30)	0.21	2.01 (0.90-4.49)	0.06
Pooled results	162	300	206	222	468	234			0.89 (0.70-1.13)	0.31	1.21 (0.91-1.61)	0.18
P value for heterogeneity									0.45		<0.001	
I^2									0%		87%	

Table 3. *Subgroup analysis for the association between IL-18-607C/A rs1946518 polymorphism and risk of cervical cancer.*

Subgroup	CA *vs.* CC		AA *vs.* CC	
	OR (95% CI)	P value	OR (95% CI)	P value
HWE status				
HWE yes	1.40 (0.64-3.03)	0.39	1.89 (0.07-51.90)	0.71
HWE no	0.83 (0.64-1.08)	0.17	0.80 (0.27-2.35)	0.69
Ethnicity				
Asian	0.94 (0.72-1.22)	0.64	0.81 (0.22-3.06)	0.76
South American	0.68 (0.38-1.24)	0.21	2.01 (0.96-4.19)	0.06
Design				
Population-based	1.01 (0.51-1.98)	0.98	0.19 (0.04-0.98)	0.04
Hospital-based	0.91 (0.59-1.42)	0.69	2.41 (0.81-7.14)	0.11
Genotype method				
Pyrosequencing	1.25 (0.70-2.25)	0.45	0.66 (0.05-9.45)	0.76
TaqMan	0.87 (0.65-1.17)	0.37	1.04 (0.75-1.43)	0.82
SSP-PCR	0.68 (0.38-1.24)	0.21	2.01 (0.96-4.19)	0.06

Discussion

Development of cervical cancer is involved in both oncogenic HPV infection and host immunity. HPV plays an important role in directly subverting the immunity through interfering with the interferon pathway, modulating the antigen presentation and suppressing the IL-18 activity [21,22]. IL-18, T-helper 1-type cytokines, could contribute to the cell-mediated immunity. Previous study reported that both E6 and E7 oncoproteins of HPV could inhibit IL-18 induced IFN-γ production in human peripheral blood mononuclear and NK cells through inhibition of IL-18 binding to its alpha-chain receptor [23]. They also reported that IL-18 expression was downregulated in HPV-positive cervical cancer cells by combining E6 oncoprotein with IL-18 [24]. Therefore, IL-18 plays an important role in protective cell-mediated immunity against HPV infections [24], and thus influences the pathogenesis of cervical cancer.

Since 2006, a large number of molecular epidemiological case-control studies have been conducted to explore the association between IL-18-607C/A rs1946518 polymorphism in a Chinese population, and the AA genotype was associated with a reduced risk of cervical cancer when compared with the CC genotype (OR=0.36, 95% CI=0.16-0.84) [15]. Another study in China also reported a significant association between IL-18-607C/A rs1946518 AA genotype and risk of cervical cancer (OR=0.06, 95% CI=0.004-0.58) [17]. However, two recent studies in China reported inconsistent results. Qi et al. found that IL-18-607C/A rs1946518 AA was significant associated with an increased risk of cervical cancer in comparison to the CC genotype [16]. Yang et al. did not report a significant association between IL-18-607C/A polymorphism and cervical cancer risk [18]. In a Brazil population, Mayara et al. did not find a significant association between IL-18-607C/A polymorphism and cervical cancer risk [19]. There is still controversy about the relationship between these two polymorphisms and cervical cancer susceptibility. In this study, we firstly performed a meta-analysis on the association between IL-18-607C/A polymorphism and cervical cancer risk. We found no significant association was found between IL-18-607C/A polymorphism and cervical cancer risk, but we observed that the AA genotype of IL-18-607C/A rs1946518 was associated with a decreased risk of cervical cancer in studies with population-based design. Therefore, further studies with well study design and large sample size are greatly needed to confirm the association between IL-18-607C/A rs1946518 and cervical cancer risk.

Limitations

Some limitations of this study that should be addressed. First, only five publications were included in our meta-analysis, and the limited number and sample size for the polymorphic locus may reduce the reliability of the results and affect the assessment of associations between IL-18-607C/A polymorphism and cervical cancer risk. Second, additional risk factors, such as smoking, drinking, and HPV infection, were not considered. The interactions of genetic and environmental factors on cancer development could not be evaluated in our analysis. Fourth, the heterogeneity that exists in studies on comparison of IL-18-607AA *vs.* CC genotype could influence the current results and distort the conclusions. In this regard, the meta-regression analysis could not find the source of the heterogeneity, although it could be reduced in the subgroup analysis.

As far as we know, this is the first meta-analysis to examine the association between IL-18-607C/A polymorphism and cervical cancer risk. However, our meta-analysis suggests that the IL-18-607C/A could not influence the cervical cancer susceptibility, but the IL-18-607 AA genotype is associated with cervical cancer risk in studies with population-based design.

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