

## REVIEW

Editorial Process: Submission:11/11/2019 Acceptance:04/28/2020

# Association of *IL-12B rs3212227* and *IL-6 rs1800795* Polymorphisms with Susceptibility to Cervical Cancer: A Systematic Review and Meta-Analysis

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### Abstract

**Background:** Primary studies have shown that the *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms are associated with an increased risk of cervical cancer. However, conflicting results warrant a meta-analysis to obtain more precise estimates. **Methods:** A comprehensive literature search on PubMed, Web of Science, Scopus, CNKI, and SciELO was performed to collect all eligible studies up to November 10, 2019. The pooled odds ratios (OR) and 95% confidence intervals (CI) were used to calculate the risk. This meta-analysis was carried out by utilizing CMA software. **Results:** A total of eleven case-control studies including four studies on *IL-12B rs3212227* and seven studies on *IL-6 rs1800795* were selected. Pooled ORs revealed that the *IL-6 rs1800795* polymorphism was significantly associated with an increased risk of cervical cancer (C vs. G: OR = 1.294, 95% CI 1.071-1.564, p=0.007; CC vs. GG: OR = 1.633, 95% CI 1.059-2.520, p=0.027; CC+CG vs. GG: OR = 1.312, 95% CI 1.048-1.643, p=0.018; and CC vs. CG+GG: OR = 1.592, 95% CI 1.268-1.999, p≤0.001), but not *IL-12B rs3212227* polymorphism. Stratified analysis by ethnicity revealed that both *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms were associated with risk of cervical cancer in Asian women. **Conclusions:** Our pooled data revealed that the *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms may be used to identify individuals at high risk of cervical cancer in Asian women.

**Keywords:** Cervical cancer- cervix- interleukin- polymorphism- association- meta-analysis

*Asian Pac J Cancer Prev*, 21 (5), 1197-1206

### Introduction

Cervical cancer is the second most commonly diagnosed malignancy and third leading cause of cancer-related mortality among women in less developed countries (Karimi Zarchi et al., 2010; Mousavi et al., 2008). According to GLOBOCAN, cervical cancer accounts for 528,000 new cases and 266,000 deaths worldwide in 2012 (Parkin et al., 2005). Although, it has been widely accepted for several decades that Human papillomavirus (HPV) is the main risk factor for development of cervical cancer (Behtash et al., 2009; Farbod et al., 2019; Ghaemmaghani et al., 2008), HPV infections have developed to persistent infection in only a very few cases and it is sufficient to induce cervical cancer in an even smaller proportion

(Cheng et al., 2018). Thus, many scientists acknowledge that etiology of cervical cancer is multifactorial and several factors such as sexually transmitted infections, reproductive factors, hormonal influences, genetics and host factors are responsible for development of cervical cancer (Momenimovahed and Salehiniya, 2017; Akhavan et al., 2012). However, studies revealed a preventive role for antiretroviral therapy (ART) on cervical lesion incidence and progression and promotion of regression (de Vries et al., 2018; Jarahzadeh et al., 2014; Jarahzadeh et al., 2011). In the recent years, several number of genome-wide association studies (GWAS) have been performed to evaluate the effects of different cytokines in development of cervical cancer, and many case-control studies have reported the association of *IL-12* and *IL-6*

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with an increased risk of cervical cancer.

*IL-12* is a potent pro-inflammatory cytokine that plays a central role in cellular immunity which is mainly produced by phagocytic cells, such as dendritic cells, monocytes, macrophages, neutrophils, and microglia in response to antigenic stimulation. *IL-12* has a number of proinflammatory biological functions and its pleiotropic functions which drive cellular immunity support its exploration as an antitumor agent. Therefore, in clinical studies it has been evaluated as an experimental agent for treatment of numerous tumours (Van Herpen et al., 2005; Xu et al., 2004). The *IL-12B* gene is mapped to chromosome 5q31-33 and encodes the p40 subunit of interleukin 12 (Randolph et al., 2004). Moreover, *IL-6* is a multipotent cytokine that regulates immune and inflammatory responses (Aflatoonian et al., 2019b; Salimi et al., 2019; Sheikhpour et al., 2017). Moreover, *IL-6* has been considered as a “metabolic hormone” which affects metabolism of glucose, protein and lipids (Gholami et al., 2019). The human *IL-6* gene is localized to chromosome 7p21-24, consists of seven exons and spanning 12.8 kb (Salimi et al., 2019).

Up to now, many related articles have evaluated the association of *IL-12 rs3212227* and *IL-6 rs1800795* polymorphisms with risk of cervical cancer. Some epidemiological studies suggested that *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms are associated with an increased risk of cervical cancer. However, two recent meta-analyses were performed to evaluate *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms with cervical cancer risk and their results indicated that no significant association was found among all ethnicities (Chang et al., 2015; Liu et al., 2017; Pu et al., 2016; Zheng et al., 2017). Therefore, controversy and inconformity still remained about *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms and most of studies recruited a limited sample capacity, which is insufficient to get a firm conclusion about the associations of these polymorphisms with development of cervical cancer. Thus, we systematically reviewed previous publications and a meta-analysis was conducted to evaluate the associations of *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms with risk of cervical cancer.

## Materials and Methods

### Primary Search Strategy

Ethical approval was not necessary for the present meta-analysis. We systematically searched PubMed, EMBASE, Web of Science, Elsevier, Google Scholar, Cochrane Library, SciELO, SID, WanFang, VIP, Chinese Biomedical Database (CBD) and Chinese National Knowledge Infrastructure (CNKI) comprehensively for all publications regarding the association *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms and cervical cancer risk up to November 10, 2019. The combination of following keywords and terms were used: (“Uterine Cervical Neoplasm” OR “Cervix Cancer” OR “Cervical Cancer” OR “Cervical Neoplasm” OR “Cervical Carcinoma”) AND (“Interleukin 12” OR “IL-12” OR “1188A>C” OR “rs3212227”) AND

(“Interleukin 6” OR “-174G>C” OR “rs1800795”) AND (“Polymorphism” OR “Mutation” OR “Genotype” OR “Allele” OR “Variation” OR “Variant”). Meanwhile, hand searching of the references in retrieved reviews and eligible articles were performed as sources to find other relevant publications. Languages were limited to English, Portuguese, Farsi and Chinese.

### Including and Excluding Criteria

We set these inclusive criteria for recruited publications: a) studies with case-control or cohort design; 2) published studies in English, Chinese and Farsi; 3) studies evaluated the association of *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms with risk of cervical cancer; and 4) enough and available data to figure out odds ratios (ORs) and 95% confidence intervals (CIs). In addition, we also restricted these exclusive criteria: 1) studies without control group (case only studies); 2) insufficient data offered to analyze or unavailable data; 3) studies were carried out based on animals and in vitro studies; 4) studies evaluated the association of other polymorphisms at *IL-12* and *IL-6* genes with cervical cancer; 5) case reports, case series, letters, comments, reviews, and previous meta-analyses 6) overlapped data or duplication.

### Data extraction

All recruited studies had to be seriously scanned by two individual researchers separately. If there was a dispute between the two researchers, they would reach a consensus by discussing or a third researcher. We extracted the following information from eligible studies: name of the first author, year of publication, country of origin, ethnicity of participants, genotyping methods, source of controls, total numbers of cases and controls, genotyping method, genotypes frequencies of cases and controls, minor allele frequencies (MAFs) and Hardy-Weinberg equilibrium test in control subjects.

### Statistical Analysis

An ethical approval was not necessary as this study was a meta-analysis based on previous studies. The strength of association of *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms with risk of cervical cancer was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The statistical significance of the pooled OR was determined using the Z-test. Pooled estimates of the OR were obtained by calculating a weighted average of the OR from each study. The pooled ORs was calculated under all five genetic models, i.e., allele (B vs. A), homozygote (BB vs. AA), heterozygote (BA vs. AA), dominant (BB+BA vs. AA) and recessive (BB vs. BA+AA). A  $\chi^2$ -based Q test was calculated for assessing the heterogeneity among recruited investigations and if the P-value of Q test exceeded 0.05 that meant there was no obvious heterogeneity. In addition, I<sup>2</sup>-value was used to quantify the proportion of the between study heterogeneity (range of 0 to 100%: I<sup>2</sup>=0-25%, no heterogeneity; I<sup>2</sup>=25-50%, moderate heterogeneity; I<sup>2</sup>=50-75%, large heterogeneity; I<sup>2</sup>=75-100%, extreme heterogeneity). Random-effect models (DerSimonian-Laird method) would be adopted for analyses if I<sup>2</sup> was >50%. Otherwise, analyses would

be conducted with fixed-effect models (Mantel-Haenszel method). Genotype frequencies of controls for each study using goodness-of-fit test (chi-square) and a p-value less than 0.05 was considered as significant disequilibrium (HWE-violating). Sensitivity analysis was conducted by excluding one study at a time to examine the stability of the pooled results. Begg's funnel plot and Egger's linear regression test were applied to assess potential publication bias, in which  $P < 0.05$  was considered statistically significant. All of the statistical calculations were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Biostat, USA). Two-sided P-values  $< 0.05$  were considered statistically significant.

## Results

### Characteristics of Included Studies

By electronic and manual searches concerning the association of *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms and cervical cancer risk, 297 relevant studies up to November 05, 2019 were identified. After reading titles and abstracts, 139 irrelevant and duplicate articles were excluded. Another 95 articles were subsequently excluded because not reporting useful data for meta-analysis, review, case only study, and not being case-control studies. Finally, a total of eleven case-control studies including four studies on *IL-12B rs3212227* (Chen

et al., 2009; Do Carmo Vasconcelos De Carvalho et al., 2012; Han et al., 2008; Roszak et al., 2012) and seven studies on *IL-6 rs1800795* (Gangwar et al., 2009; Grimm et al., 2011; Nogueira De Souza et al., 2006; Pu et al., 2016; Shi et al., 2013; Zidi et al., 2017) were selected. Characteristics of included studies are shown in Table 1. All eligible studies were published in English and Chinese between April, 2008 and November, 2017. Among them, five studies were based on Asians, three studies based on mixed populations, two studies based on Caucasians, and one study was based on African populations. The selected studies were conducted in Korea, China, Brazil, Poland, India, Austria and Tunisia. Five different genotyping methods including SNaPShot, PCR-RFLP, direct Sequencing, TaqMan and qRT-PCR were used by selected studies. The allele, genotype and minor allele frequency (MAF) distributions in the cases and controls are shown in Table 1. Moreover, the distribution of genotypes in the controls was in agreement with Hardy-Weinberg equilibrium (HWE) for all selected studies, except for two studies on *IL-6 rs1800795* polymorphism (Table 1).

### Quantitative Data Synthesis

#### *IL-12B rs3212227* Polymorphism

The summary of the meta-analysis of the association of between *IL-12B rs3212227* polymorphism and cervical cancer risk are shown in Table 2. Overall, there was

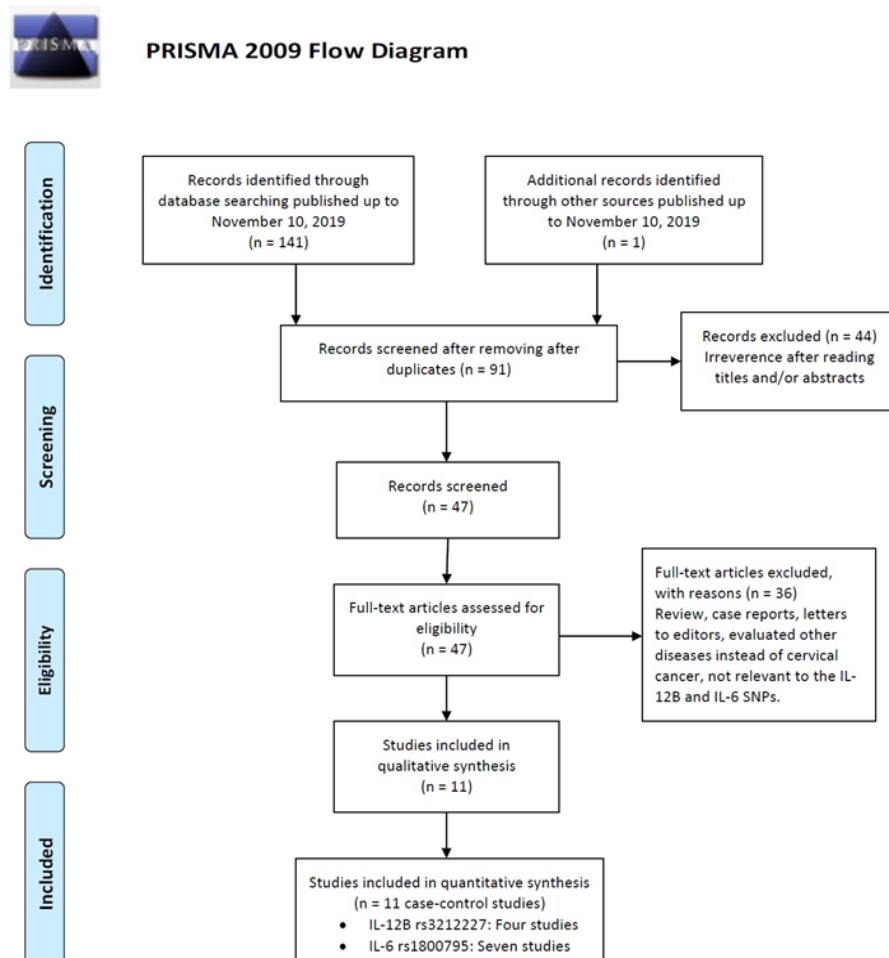


Figure 1. Flow Chart for the Process of Selecting Eligible Studies

no significant association between *IL-12B rs3212227* polymorphism and cervical cancer risk under all five genetic models genetic models, i.e., allele (C vs. A: OR = 1.076, 95% CI 0.783-1.479, p=0.651, Figure 2A), homozygote (CC vs. AA: OR = 1.330, 95% CI 0.988-1.790, p=0.060), heterozygote (CA vs. AA: OR = 1.119, 95% CI 0.696-1.800, p=0.643), dominant (CC+CA vs. AA: OR = 1.125, 95% CI 0.704-1.799, p =0.623, Fig2B), recessive (CC vs. CA+AA: OR = 1.140, 95% CI 0.874-1.487, p =0.333). However, subgroup analysis by ethnicity showed a significant association between *IL-12B rs3212227* polymorphism and an increased risk of cervical cancer in Asian women (CA vs. AA: OR = 1.349, 95% CI 1.032-1.762, p=0.028 and CC+CA vs. AA: OR = 1.340, 95% CI 1.041-1.725, p =0.023, Table 2).

*IL-6 rs1800795 Polymorphism*

The summary of the meta-analysis of the association of between *IL-6 rs1800795* polymorphism and cervical cancer risk are shown in Table 2. Pooled ORs revealed that *IL-6 rs1800795* polymorphism was significantly associated with an increased risk of cervical cancer under four genetic models, i.e., allele (C vs. G: OR = 1.294, 95% CI 1.071-1.564, p= 0.007, Figure 2C), homozygote (CC vs. GG: OR = 1.633, 95% CI 1.059-2.520, p= 0.027), dominant (CC+CG vs. GG: OR = 1.312, 95% CI 1.048-1.643, p= 0.018) and recessive (CC vs. CG+GG: OR = 1.592, 95% CI 1.268-1.999, p<0.001, Figure 2D). Moreover, subgroup analysis by ethnicity revealed an increased risk of cervical cancer in Asian women. When stratified by country of origin, there was a significant association between *IL-6 rs1800795* polymorphism and cervical cancer risk among Chinese women (C vs. G: OR = 1.422, 95% CI 1.025-1.971, p= 0.035; CC vs. GG: OR = 1.851, 95% CI 1.377-2.488, p<0.001; and CC vs. CG+GG: OR = 1.641, 95% CI 1.251-2.151, p<0.001), but not among Brazilian women (Table 2).

*Between-Study Heterogeneity Test*

As shown in Table 2, there was significant between-study heterogeneity under almost genetic models for both *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms in the overall population. To explore the potential sources of heterogeneity, subgroup analyses by ethnicity, country of origin and HWE was performed. The results suggested that ethnicity might be contributed to between-study heterogeneity in the current meta-analysis.

*Sensitivity Analysis*

A sensitivity analysis was used to test the effects of each study on pooled ORs. There were no significant differences observed upon removal of any of the studies, suggesting that our findings were statistically robust and reliable. Moreover, we performed sensitivity analysis by excluding those HWE-violating studies for *IL-6 rs1800795*. However, after excluding those studies the pooled ORs were not changed statically in the overall population, indicating that this meta-analysis result were statistically robust and reliable.

Table 1. Characteristics of All Studies Included in the Current Meta-Analysis

| First Author     | Country (Ethnicity) | Genotyping Methods | SOC | Case/Control | Cases Genotypes |     | Allele |     | Controls Genotypes |     | Allele |    | MAFs | HWE   |       |
|------------------|---------------------|--------------------|-----|--------------|-----------------|-----|--------|-----|--------------------|-----|--------|----|------|-------|-------|
|                  |                     |                    |     |              | AA              | AC  | A      | C   | AA                 | AC  | A      | C  |      |       |       |
| IL-12B rs3212227 |                     |                    |     |              |                 |     |        |     |                    |     |        |    |      |       |       |
| Han 2008         | Korea(Asian)        | SNAPshot           | HB  | 150/179      | 32              | 87  | 31     | 151 | 149                | 52  | 88     | 39 | 192  | 0.464 | 0.877 |
| Chen 2009        | China(Asian)        | PCR-RFLP           | PB  | 404/404      | 127             | 199 | 78     | 453 | 355                | 150 | 185    | 69 | 485  | 0.4   | 0.357 |
| de Carvalho 2012 | Brazil(Mixed)       | PCR-RFLP           | PB  | 162/76       | 100             | 49  | 13     | 249 | 75                 | 31  | 37     | 8  | 99   | 0.349 | 0.531 |
| Rozak 2012       | Poland(Caucasian)   | PCR-RFLP           | PB  | 405/450      | 212             | 174 | 19     | 598 | 212                | 289 | 151    | 10 | 729  | 0.19  | 0.055 |
| IL-6 rs1800795   |                     |                    |     |              |                 |     |        |     |                    |     |        |    |      |       |       |
| de Souza 2006    | Brazil(Mixed)       | PCR-RFLP           | PB  | 56/253       | 24              | 32  | 0      | 80  | 32                 | 148 | 102    | 3  | 398  | 0.213 | 0.001 |
| Gangwar 2009     | India(Asian)        | ARMS-PCR           | HB  | 160/200      | 107             | 36  | 17     | 250 | 70                 | 142 | 51     | 7  | 335  | 0.163 | 0.371 |
| Grimm 2011       | Austria(Caucasian)  | Sequencing         | HB  | 131/208      | 55              | 51  | 25     | 161 | 101                | 85  | 96     | 27 | 266  | 0.361 | 0.989 |
| Junior 2012      | Brazil(Mixed)       | Sequencing         | PB  | 115/115      | 72              | 39  | 4      | 183 | 47                 | 67  | 37     | 11 | 171  | 0.257 | 0.093 |
| Shi 2014         | China(Asian)        | PCR-RFLP           | HB  | 518/518      | 160             | 253 | 105    | 573 | 463                | 181 | 259    | 78 | 621  | 0.401 | 0.348 |
| Pa 2016          | China(Asian)        | TaqMan             | HB  | 360/728      | 185             | 141 | 34     | 511 | 209                | 476 | 220    | 32 | 1172 | 0.195 | 0.309 |
| Zidi 2017        | Tunisia(African)    | qRT-PCR            | HB  | 112/164      | 81              | 25  | 6      | 187 | 37                 | 133 | 25     | 6  | 291  | 0.113 | 0.002 |

PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; ARMS, amplification-refractory mutation system; qRT-PCR, Real-Time qRT-PCR; SOC, source of controls; HB, hospital-based; PB, population-based; MAFs, minor allele frequencies; HWE, Hardy-Weinberg equilibrium

Table 2. Summary Risk Estimates for Association of IL-12B rs3212227 and IL-6 rs1800795 Polymorphisms with Cervical Cancer Risk

| Subgroup                | Genetic Model | Type of Model | Heterogeneity      |                | Odds Ratio |             |                   |                 | Publication Bias  |                    |
|-------------------------|---------------|---------------|--------------------|----------------|------------|-------------|-------------------|-----------------|-------------------|--------------------|
|                         |               |               | I <sup>2</sup> (%) | P <sub>H</sub> | OR         | 95% CI      | Z <sub>test</sub> | P <sub>OR</sub> | P <sub>Begg</sub> | P <sub>Egger</sub> |
| <i>IL-12B rs3212227</i> |               |               |                    |                |            |             |                   |                 |                   |                    |
| Overall Population      | C vs. A       | Random        | 81.69              | 0.001          | 1.076      | 0.783-1.479 | 0.452             | 0.651           | 0.308             | 0.236              |
|                         | CC vs. AA     | Random        | 54.75              | 0.085          | 1.33       | 0.988-1.790 | 1.878             | 0.06            | 0.734             | 0.782              |
|                         | CA vs. AA     | Random        | 82.52              | 0.001          | 1.119      | 0.696-1.800 | 0.463             | 0.643           | 0.308             | 0.356              |
|                         | CC+CA vs. AA  | Random        | 83.68              | ≤0.001         | 1.125      | 0.704-1.799 | 0.492             | 0.623           | 0.308             | 0.317              |
|                         | CC vs. CA+AA  | Random        | 24.76              | 0.263          | 1.14       | 0.874-1.487 | 0.969             | 0.333           | 0.734             | 0.946              |
| Asians                  | C vs. A       | Fixed         | 0                  | 0.87           | 1.166      | 0.988-1.377 | 1.812             | 0.07            | NA                | NA                 |
|                         | CC vs. AA     | Fixed         | 0                  | 0.932          | 1.323      | 0.941-1.860 | 1.61              | 0.107           | NA                | NA                 |
|                         | CA vs. AA     | Fixed         | 0                  | 0.454          | 1.349      | 1.032-1.762 | 2.191             | 0.028           | NA                | NA                 |
|                         | CC+CA vs. AA  | Fixed         | 0                  | 0.594          | 1.34       | 1.041-1.725 | 2.271             | 0.023           | NA                | NA                 |
|                         | CC vs. CA+AA  | Fixed         | 0                  | 0.507          | 1.086      | 0.807-1.461 | 0.542             | 0.588           | NA                | NA                 |
| <i>IL-6 rs1800795</i>   |               |               |                    |                |            |             |                   |                 |                   |                    |
| Overall Population      | C vs. G       | Random        | 60                 | 0.02           | 1.294      | 1.071-1.564 | 2.675             | 0.007           | 0.763             | 0.701              |
|                         | CC vs. GG     | Random        | 54.07              | 0.042          | 1.633      | 1.059-2.520 | 2.217             | 0.027           | 0.763             | 0.587              |
|                         | CG vs. GG     | Random        | 52.47              | 0.049          | 1.232      | 0.971-1.562 | 1.718             | 0.086           | 0.763             | 0.728              |
|                         | CC+CG vs. GG  | Random        | 53.01              | 0.047          | 1.312      | 1.048-1.643 | 2.371             | 0.018           | 1                 | 0.583              |
|                         | CC vs. CG+GG  | Fixed         | 48.97              | 0.068          | 1.592      | 1.268-1.999 | 3.999             | ≤0.001          | 0.548             | 0.646              |
| Asians                  | C vs. G       | Fixed         | 65.97              | 0.053          | 1.395      | 1.230-1.582 | 5.195             | ≤0.001          | 1                 | 0.793              |
|                         | CC vs. GG     | Fixed         | 56.74              | 0.099          | 1.951      | 1.472-2.584 | 4.656             | ≤0.001          | 1                 | 0.375              |
|                         | CG vs. GG     | Fixed         | 66.54              | 0.05           | 1.289      | 1.077-1.543 | 2.769             | 0.006           | 1                 | 0.613              |
|                         | CC+CG vs. GG  | Fixed         | 61                 | 0.077          | 1.429      | 1.207-1.692 | 4.136             | ≤0.001          | 1                 | 0.766              |
|                         | CC vs. CG+GG  | Fixed         | 53.87              | 0.114          | 1.736      | 1.339-2.251 | 4.166             | ≤0.001          | 0.296             | 0.205              |
| By Country              |               |               |                    |                |            |             |                   |                 |                   |                    |
| China                   | C vs. G       | Random        | 82.88              | 0.016          | 1.422      | 1.025-1.971 | 2.111             | 0.035           | NA                | NA                 |
|                         | CC vs. GG     | Fixed         | 70.12              | 0.067          | 1.851      | 1.377-2.488 | 4.083             | ≤0.001          | NA                | NA                 |
|                         | CG vs. GG     | Random        | 75.83              | 0.042          | 1.351      | 0.912-1.999 | 1.502             | 0.133           | NA                | NA                 |
|                         | CC+CG vs. GG  | Random        | 77.92              | 0.033          | 1.466      | 0.994-2.162 | 1.929             | 0.054           | NA                | NA                 |
|                         | CC vs. CG+GG  | Fixed         | 56.13              | 0.131          | 1.641      | 1.251-2.151 | 3.581             | ≤0.001          | NA                | NA                 |
| Brazil                  | C vs. G       | Random        | 77.49              | 0.035          | 1.043      | 0.534-2.307 | 0.123             | 0.902           | NA                | NA                 |
|                         | CC vs. GG     | Fixed         | 0                  | 0.568          | 0.385      | 0.127-1.164 | -1.691            | 0.091           | NA                | NA                 |
|                         | CG vs. GG     | Fixed         | 62.94              | 0.1            | 1.356      | 0.905-2.032 | 1.474             | 0.14            | NA                | NA                 |
|                         | CC+CG vs. GG  | Fixed         | 75.47              | 0.043          | 1.239      | 0.559-2.748 | 0.528             | 0.598           | NA                | NA                 |
|                         | CC vs. CG+GG  | Fixed         | 0                  | 0.704          | 0.37       | 0.124-1.105 | -1.781            | 0.075           | NA                | NA                 |
| HWE*                    | C vs. G       | Random        | 71.99              | 0.006          | 1.239      | 0.979-1.564 | 1.783             | 0.075           | 0.806             | 0.451              |
|                         | CC vs. GG     | Random        | 68.89              | 0.012          | 1.633      | 0.978-2.727 | 1.876             | 0.061           | 0.806             | 0.682              |
|                         | CG vs. GG     | Fixed         | 57.83              | 0.05           | 1.198      | 1.019-1.407 | 2.194             | 0.028           | 0.462             | 0.18               |
|                         | CC+CG vs. GG  | Random        | 63.28              | 0.028          | 1.213      | 0.928-1.587 | 1.412             | 0.158           | 0.22              | 0.163              |
|                         | CC vs. CG+GG  | Random        | 64.82              | 0.023          | 1.588      | 1.004-2.510 | 1.977             | 0.048           | 1                 | 0.827              |

NA, Not Applicable; \*, By excluding HWE-violating studies

### Publication Bias

Begg's funnel plot and Egger's test were inspected to evaluate the possible publication bias in this meta-analysis. The shape of the funnel did not show any obvious asymmetry under all five genetic models for both *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms (Figure 3). Moreover, Egger's test was statistically revealed that there was no a significant bias for *IL-12B rs3212227* polymorphism (C vs. A: P<sub>Begg</sub> = 0.308; P<sub>Egger</sub> = 0.236; CC vs. AA: P<sub>Begg</sub> = 0.734, P<sub>Egger</sub> = 0.782; CA vs. AA: P<sub>Begg</sub> = 0.308, P<sub>Egger</sub> = 0.356; CC+CA vs. AA: P<sub>Begg</sub> = 0.308, P<sub>Egger</sub> = 0.317; and

CC vs. CA+AA: P<sub>Begg</sub> = 0.734, P<sub>Egger</sub> = 0.946) and *IL-6 rs1800795* polymorphism (C vs. G: P<sub>Begg</sub> = 0.763, P<sub>Egger</sub> = 0.701; CC vs. GG: P<sub>Begg</sub> = 0.763, P<sub>Egger</sub> = 0.587; CG vs. GG: P<sub>Begg</sub> = 0.763, P<sub>Egger</sub> = 0.728; CC+CG vs. GG: P<sub>Begg</sub> = 1.000, P<sub>Egger</sub> = 0.583; and CC vs. CG+GG: P<sub>Begg</sub> = 0.548, P<sub>Egger</sub> = 0.646).

### Discussion

Our pooled data showed that *IL-12B rs3212227* polymorphism was not significantly associated with an increased risk of cervical cancer. However, our subgroup

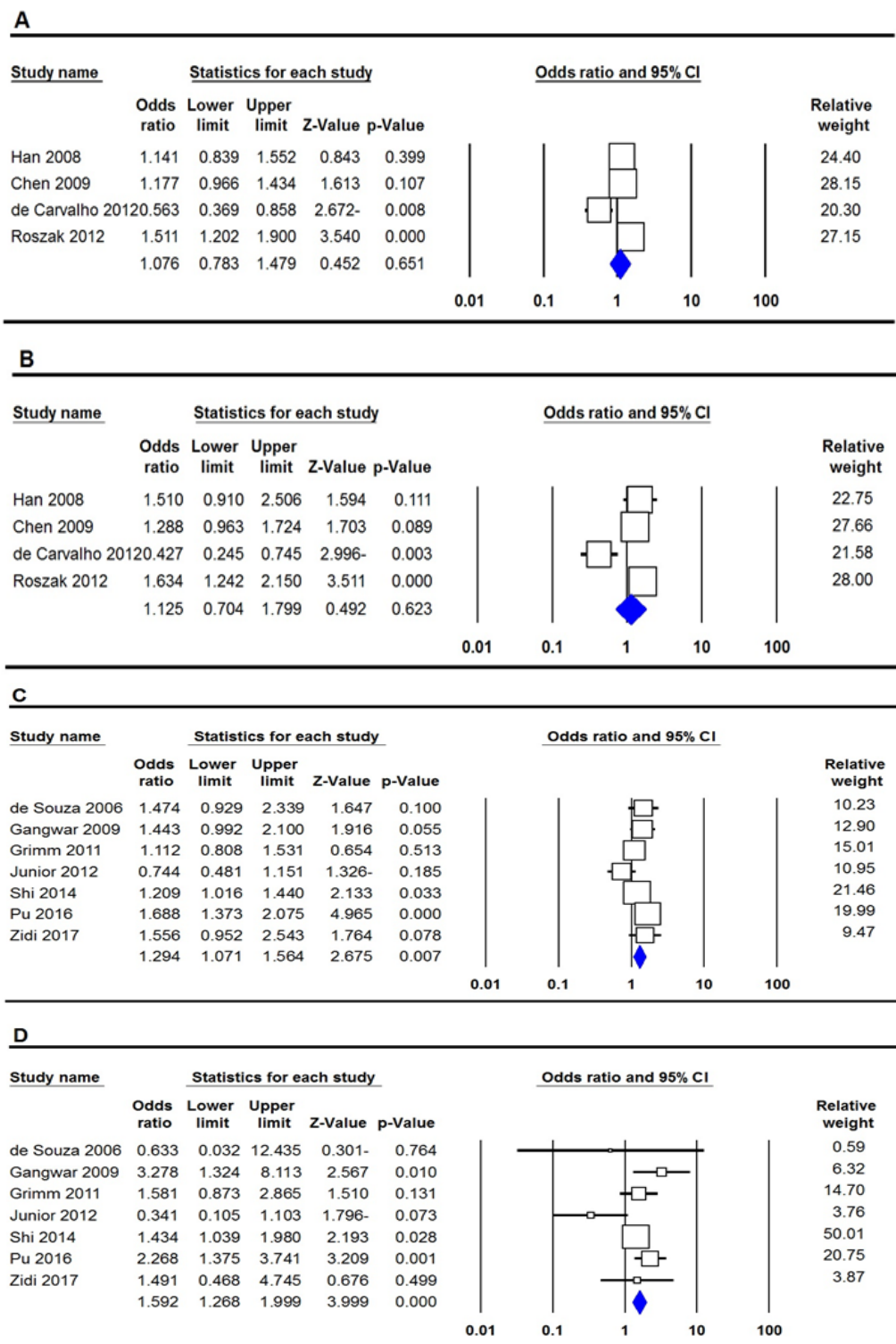


Figure 2. Forest Plot for the Association of *IL-12B rs3212227* and *IL-6 rs1800795* Polymorphisms with Risk of Cervical Cancer in the Overall Population. A, *IL-12B rs3212227* (allele model: C vs. A); B, *IL-12B rs3212227* (dominant model: CC+CA vs. AA); C, *IL-6 rs1800795* (allele model: C vs. G); D, *IL-6 rs1800795* (recessive model: CC vs. CG+GG).

analysis revealed that *IL-12B rs3212227* polymorphism was significantly associated with risk of cervical cancer in Asians. Roszak et al., in a case-control study reported that the *IL-12B rs3212227* might be contributed to an increased risk of cervical cancer in Polish population. However, de Carvalho et al., (2012) reported that *IL-12B rs3212227* polymorphism has a protective effect in development of cervical cancer among Brazil women. Moreover, Han et

al., (2008) in an earlier study identified that there was no relationship between cervical cancer and *IL-12B rs3212227* in Korean population. In 2017, Zheng et al., (2017) in a meta-analysis of 33 studies with 10,587 cancer cases and 12,040 cancer-free controls evaluated association of *IL-12B rs3212227* with cancer risk. Their pooled data showed a significant association between *IL-12B rs3212227* polymorphisms and overall cancer risk,

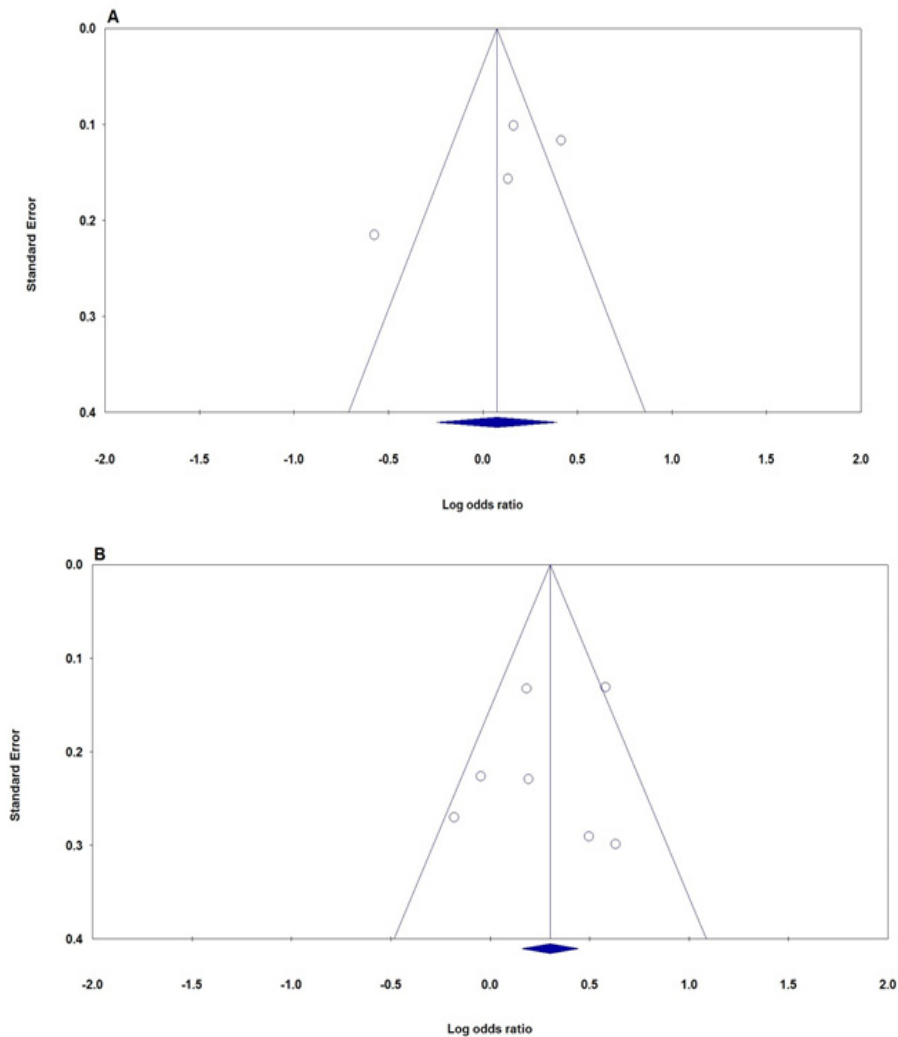


Figure 3. Begg's Funnel Plot for the Association of *IL-12B rs3212227* and *IL-6 rs1800795* Polymorphisms with Risk of Cervical Cancer. A, *IL-12B rs3212227* (allele model: C vs. A); B, *IL-6 rs1800795* (dominant model: CC+CG vs. GG).

especially in hepatocellular carcinoma, nasopharyngeal cancer, and among Asians. However, their stratification analyses demonstrated that *IL-12B rs3212227* was not associated with cervical cancer. In 2015, Chang et al., (2015) in a meta-analysis of five case-control studies with 2,552 cases and 2,232 controls were evaluated association of *IL-12B rs3212227* with cervical cancer. Their results revealed that *rs3212227* polymorphism in *IL-12* gene may not be the risk factor to cervical cancer.

In 2006, Nogueira De Souza et al., (2006) for first time in a case-control study with 56 cases and 253 controls evaluated the association of *IL-6 rs1800795* polymorphism with cervical cancer in a Brazilian population. Since a few studies evaluated the association in different population. Our pooled data revealed that *IL-6 rs1800795* polymorphism was associated with an increased risk of cervical cancer in the overall population. Similarly, Duan et al., (2018) in a meta-analysis of seven publications found that *IL-6 rs1800795* polymorphism was associated with cervical cancer risk. In 2017, Zidi et al., (2017) in a case-control study evaluated the effects of *IL-6 rs2069845*, *rs2069840*, *rs1474348*, *rs1800795*, *rs1800797*, and *rs2069827* polymorphisms with risk of cervical cancer among Tunisian women. Their results

revealed high linkage disequilibrium (LD) between *rs2069845*, *rs2069840*, *rs1474348*, and *rs1800795* polymorphism. Moreover, their 6-locus haplotype analysis have identified that GACCCA haplotype to be positively associated with an increased risk of cervical cancer, while GAGGGG haplotype was negatively associated with occurrence of cervical cancer, thus suggesting a protective role for this haplotype in development of this disease. They have reported that *IL-6 rs1800795* polymorphism might be has a protective role in development of cervical cancer. In 2016, Pu et al., (2016) in a case-control study of 360 cervical cancer cases and 728 controls evaluated the relationship between *rs1800795* and *rs2069837* polymorphisms at *IL-6* and cervical cancer among Chinese women. Their results revealed that mutant alleles of *rs1800795* and *rs2069837* polymorphisms were associated with an increased risk cervical cancer. de Lima et al., (2016) revealed that there was no significant association between the *IL-6 rs1800795* polymorphism and HPV infected women or uninfected controls. Moreover, they have not found any significant association between *TGF-β1 +869T>C* and *+915G>C* polymorphisms and the risk of HPV infection in the patients. Thus, they have hypothesized that the *IL-6 rs1800795* polymorphism did

not play a role in the risk of HPV infection in the Brazilian population.

Between-study Heterogeneity in a meta-analysis refers to the variation in study outcomes between studies (Bahrami et al., 2019; Yazdi et al., 2017). Moreover, the extent to which effect sizes vary within a meta-analysis is called heterogeneity. Heterogeneity is to be expected in a meta-analysis and assessment of heterogeneity. Thus, the proportion of between-study heterogeneity is one of the major concerns in meta-analysis because nonhomogeneous study has high possibility to mislead results (Gohari et al., 2019). Therefore, the assessment of heterogeneity is necessary, as high heterogeneity could be caused by the fact that there are actually two or more subgroups of studies present in the data, which have a different true effect. According to our previous meta-analyses, we suggested that heterogeneity might be due to differences in study design, sample size, genotyping methods, disease heterogeneity, and to the different roles played by gene-gene and gene-environment interactions (Aflatoonian et al., 2019a; Mirjalili et al., 2018; Moghimi et al., 2019, 2018). Moreover, after subgroup analysis, heterogeneity was obviously decreased in Asians; however, the corresponding pooled ORs were not materially altered after deleting these studies, indicating that our results were statistically robust. Publication bias is another key factor that might affect the quality of a meta-analysis (Niktabar et al., 2019; Veisian et al., 2019). Both Begg's and Egger's test were used to assess publication bias in this study. No significant publication bias was observed when all studies were included.

Several limitations should be acknowledged for interpretation of our pooled ORs. First, in the current meta-analysis we have selected only eligible published articles, so some relevant unpublished studies might be missed, generating certain publication bias, though not detected even with funnel plot or Egger test. Second, the sample size for both *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms was relatively small, with limited statistical power to explore the associations. Third, included studies are still so limited that we cannot perform subgroup analysis by ethnicity, genotyping methods and source of controls. Accordingly, it is required that a more precise analysis could be performed if sufficient individual study in globally populations were available. Fourth, there was heterogeneity between studies for both *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms which could distort our pooled data. Fifth, due to lack of original data in the selected studies restricted us to continue investigating some potential interactions, such as age, HPV infection, reproductive factors, hormonal influences, family history, environmental factors, and lifestyle. Hence, our pooled ORs might have some bias to a certain degree. Finally, cervical cancer is a complex disease with etiological factors that can be subdivided into extrinsic and intrinsic factors, whereas, in the current meta-analysis, the effects of these factors were not performed due to the insufficient data. Furthermore, plausible effects of gene-gene and gene-environment interactions on development of cervical cancer risk were not taken into account because of limited data as well.

In summary, our pooled data revealed that *IL-12B rs3212227* and *IL-6 rs1800795* polymorphisms could be used to identify individuals at high risk of cervical cancer in Asian women. In view of the above mentioned restrictions, high-quality researches with larger sample sizes are needed to assess the effect among different ethnicities and to validate our results.

## Acknowledgments

We thank the anonymous reviewers for reviewing this manuscript.

### Ethics Declarations

This meta-analysis was based on previously published studies, the ethical approval and the patient consent was not required.

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### Competing of Interest

The authors do not have any conflict of interest to declare.

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