




Review Article

Association of the *Interleukin-10-592C/A* Polymorphism and Cervical Cancer Risk: A Meta-Analysis

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A literature review showed some discrepancies regarding the association of *-592C/A* with the risk of cervical cancer. To allow more precise analysis of the data by increasing the number of cases studied and more acceptable generalization by considering results from different sources, the present meta-analysis was performed on available published studies that explored the relationship between SNP-*592C/A* of the *IL-10* gene and the risk of cervical cancer. Eleven available studies, including 4187 cases and 3311 controls, were included in this study investigating the relationship between the *-592C/A* polymorphism of *IL-10* and cervical cancer risk. Fixed-effects or random-effects models were performed with pooled odds ratios (ORs). Heterogeneity and bias tests were performed by the inconsistency test and funnel plot, respectively. The overall analysis showed an increased susceptibility to cervical cancer with the *-592C/A* polymorphism of the *IL-10* gene for the recessive model (OR = 1.30, 95% CI = 1.14–1.49), dominant model (OR = 1.36, 95% CI = 1.09–1.70), and additive model (OR = 1.25, 95% CI = 1.09–1.44). Regarding ethnicity, a significant association of the *-592C/A* polymorphism of the *IL-10* gene was linked to an elevated risk of cervical cancer for all genetic models (recessive, dominant, and additive) in the Asian populations and for the recessive and additive models in Caucasians with $P < 0.05$. The *-592C/A* polymorphism of the *IL-10* gene may be considered a risk factor for cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer in the world, accounting for 6.5% of all cancers, after breast, colorectal, and lung cancer. It is also the fourth highest cause of

cancer death in women in both high-income and low-middle-income countries, with an estimated mortality rate of 7.7% worldwide (GLOBOCAN 2020) [1]. Exposure to high-risk human papillomavirus (HPV) is required but is not a sufficient cause of cervical cancer [2, 3]. Oncogenic HPV DNA is present

in nearly 100% of invasive cervical cancers. A limited immune response to HPV linked to the host's genetic make-up may increase the risk of cervical cancer [4]. Many authors have been interested in the research of risk factors related to cervical cancer throughout the last few decades [5]. It appears from their investigations that genetic factors seem to exert a significant influence on the carcinogenesis of the cervix. Notably, the reported results are conflicting. However, mutations in genes involved in cytokine synthesis, such as interleukin 10 (IL-10), appear to be strong predictors of cervical cancer risk [6–8]. Physiologically, IL-10 is an essential cytokine for inflammatory modulation. Several cell types are involved in the production of this cytokine, including Th1, Th2, Th17 lymphocytes, B lymphocytes, mast cells, eosinophils, monocytes, macrophages, and dendritic cells [9, 10]. The *IL-10* gene, which contains five exons, has been found on the long arm of chromosome 1q31-32 in humans [11, 12]. The significance of the *IL-10* gene in the control of immune-mediated illness responses has resulted in the discovery of numerous polymorphisms in different portions of the gene, including the promoter region [4, 11]. The majority of identified genetic polymorphisms are single nucleotide polymorphisms (SNPs). The SNP-592C/A of the *IL-10* gene promoter is located near a number of transcription factor binding sites. This SNP has been implicated in the pathogenesis of cutaneous malignant melanoma and prostate, breast, gastric, and cervical cancer [6, 13–18]. Association studies carried out in different populations have shown that this SNP increases the risk of developing cervical cancer [6, 17, 19]. However, other studies have reported conflicting results [7, 20, 21]. Furthermore, the expression of the *IL-10* gene and/or the production of IL-10 has been demonstrated in various types of tumors, suggesting that IL-10 could, by promoting escape from the immune system, constitute a step in tumorigenesis [22–24]. Given the contradictory results of numerous studies on the role of SNP-592C/A of the *IL-10* gene in the pathogenesis of cervical cancer, we conducted a meta-analysis to assess the association between SNP-592C/A in the *IL-10* gene and the risk of cervical cancer.

2. Materials and Methods

2.1. Literature Search Strategy. The identification of initial manuscripts or published articles, available in English, was performed using the online databases PubMed, the Harvard University Library, Web of Science, and Genetics Medical Literature Database. Additional articles were identified from references cited in relevant reports and journals. The key search words “Interleukin-10” or “IL-10,” “-592C/A” or “-592C > A” or “rs1800872,” “polymorphism” or “variant” or “mutation” or “gene” or “cervical tumor” or “cervical cancer” were used to locate and select the articles.

2.2. Inclusion Criteria. The eligibility criteria were as follows: (1) case-control study design evaluating the association of the -592C/A polymorphisms of the *IL-10* gene with the risk of cervical cancer, (2) availability of the full scientific manuscript, (3) distribution of polymorphisms in the controls in agreement with Hardy-Weinberg equilibrium

(HWE), (4) availability of proportions of the different genotypes (CC, CA, AA for -592C/A of the *IL-10* gene) in both cases and controls, and (5) no significant change in the value of the odds ratio (OR).

2.3. Data Extraction. Three authors independently carried out the literature search to optimize the convergence of the retrieved data, including principal author, year of publication, study design, study population, racial and ethnic groups, sample size, genotypic and allelic proportions in cases and controls, HWE calculation, and genetic models tested.

2.4. Statistical Analysis. The statistical analyses were conducted using Review Manager v5.3 and MedCalc v14.8.1. The distribution of the -592C/A polymorphism of the *IL-10* gene in agreement with HWE in the controls was evaluated by a chi-square test, with $P < 0.05$. A pooled OR test with a 95% confidence interval (CI) was used to assess the strength of the association between the -592C/A polymorphism in the *IL-10* gene and the risk of cervical cancer, including the recessive model (AA vs. CC + CA), the dominant model (AA + CA vs. CC), and the additive model (A vs. C). To avoid type I error, the level of significance was corrected using Bonferroni's adjustment during multiple comparisons. An inconsistency (I^2) statistical test was used to determine heterogeneity [25, 26]. If there was no heterogeneity ($I^2 < 50\%$), a fixed-effect model (FEM) was retained for interpretation of a global OR. In the case of heterogeneity, the OR was interpreted using a random-effect model (REM). A funnel plot was used to determine bias [27]. The trial sequential analysis (TSA) software was used to estimate the sample size required for each arm to assess the robustness of the meta-analysis findings with 90% statistical power [28].

3. Results

3.1. Characteristics of Eligible Studies. Four Caucasian studies with 2221 cases and 1240 controls [17, 21, 29, 30] and seven Asian studies with 1966 cases and 2071 controls [6, 7, 20, 31–34] were eligible to conduct the current meta-analysis out of thirteen studies (Figure 1) (Table 1). Only one study on Africans was found, and it was discarded due to Hardy-Weinberg's imbalance [8]. Another study that had a major impact on the overall OR was also excluded [19].

3.2. Quantitative Analysis. Table 2 denotes the association between cervical cancer and SNP-592C/A of IL-10 for the genetic models. Overall, a significant association was found between the risk of cervical cancer and the three genetic models, including the recessive (OR (FEM) = 1.30, 95% CI = 1.14–1.49, $P = 0.0001$), dominant (OR (REM) = 1.36, 95% CI = 1.09–1.70, $P = 0.006$), and additive models (OR (REM) = 1.25, 95% CI = 1.09–1.44, $P = 0.001$) (Figure 2).

Based on analysis by race/ethnicity (Table 2), the -592C/A polymorphism of the *IL-10* gene was significantly associated with an increased risk of cervical cancer in Caucasians for the recessive model (OR (FEM) = 1.50, 95%

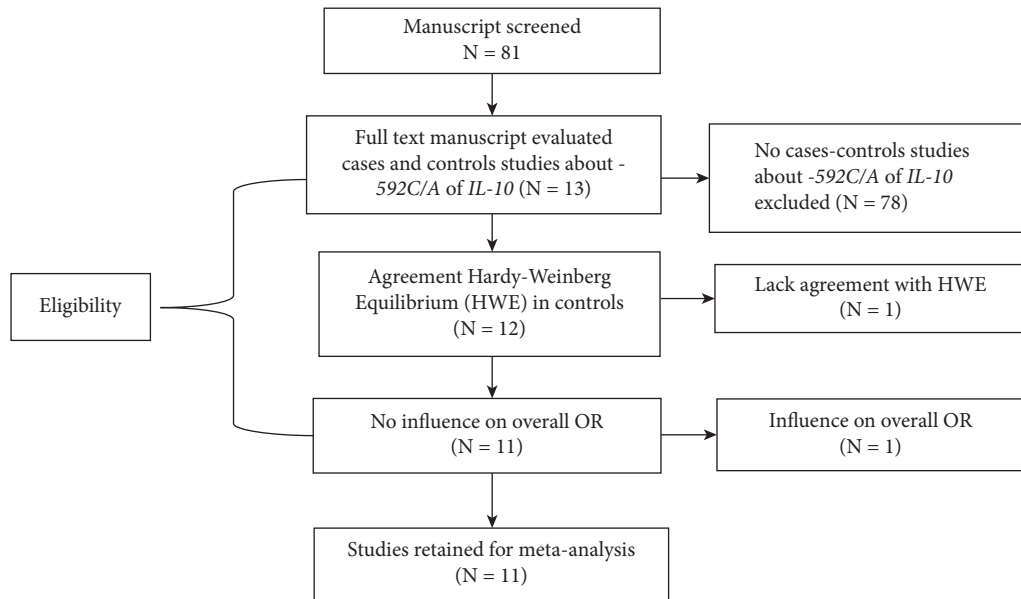


FIGURE 1: Flow diagram of eligible studies included.

TABLE 1: Genotypic distribution of the *IL-10-592C/A* polymorphism in eligible studies.

Author/year	Race/ethnicity	N	Cases			N	Controls			HWE
			CC	CA	AA		CC	CA	AA	
[20]	Asian	165	20	82	63	165	15	80	70	0.24
[6]	Asian	240	49	133	58	204	65	111	28	0.07
[7]	Asian	1044	380	522	142	1100	458	520	122	0.15
[29]	Caucasian	1282	736	464	82	288	162	112	14	0.33
[21]	Caucasian	85	24	50	11	146	68	62	16	0.74
[31]	Asian	144	11	56	77	179	15	77	87	0.72
[32]	Asian	200	16	96	88	200	17	102	81	0.05
[17]	Caucasian	200	44	98	58	200	85	85	30	0.25
[33]	Asian	70	12	23	35	108	13	44	51	0.46
[34]	Asian	103	7	37	59	115	19	44	52	0.07
[30]	Caucasian	654	393	231	30	606	405	175	26	0.20

N: number.

TABLE 2: Genetic models and *SNP-592C/A* in the *IL-10* gene in cervical cancer.

Study	N	Cases/control	Models	Effect estimate/statistical		Bonferroni		Heterogeneity	
				OR (95% CI)	P value	α	Sig	I^2 (%)	P'
All studies	11	4187/3311	Recessive	1.30 (1.14–1.49)*	0.0001	0.016	Yes	28	0.18
			Dominant	1.36 (1.09–1.70)**	0.006	0.016	Yes	66	<0.05
			Additive	1.25 (1.09–1.44)**	0.001	0.025	Yes	66	<0.05
Caucasian	4	2221/1240	Recessive	1.50 (1.12–2.00)*	0.006	0.016	Yes	39	0.18
			Dominant	1.57 (1.03–2.40)**	0.04	0.016	No	84	<0.05
			Additive	1.15 (1.15–1.46)**	<0.0001	0.025	Yes	81	<0.05
Asian	7	1966/2071	Recessive	1.25 (1.07–1.46)*	0.004	0.016	Yes	24	0.25
			Dominant	1.26 (1.09–1.46)*	0.002	0.016	Yes	42	0.11
			Additive	1.19 (1.08–1.30)*	0.0002	0.035	Yes	50	0.06

N: number; P: P value OR; P' : P value of heterogeneity; I^2 : inconsistency; recessive model: AA vs. CC + CA; dominant model: AA + CA vs. CC; additive model: A vs. C; * = fixed-effect model, ** = random-effect model; N = number; α = Bonferroni correction; Sig = Bonferroni significance.

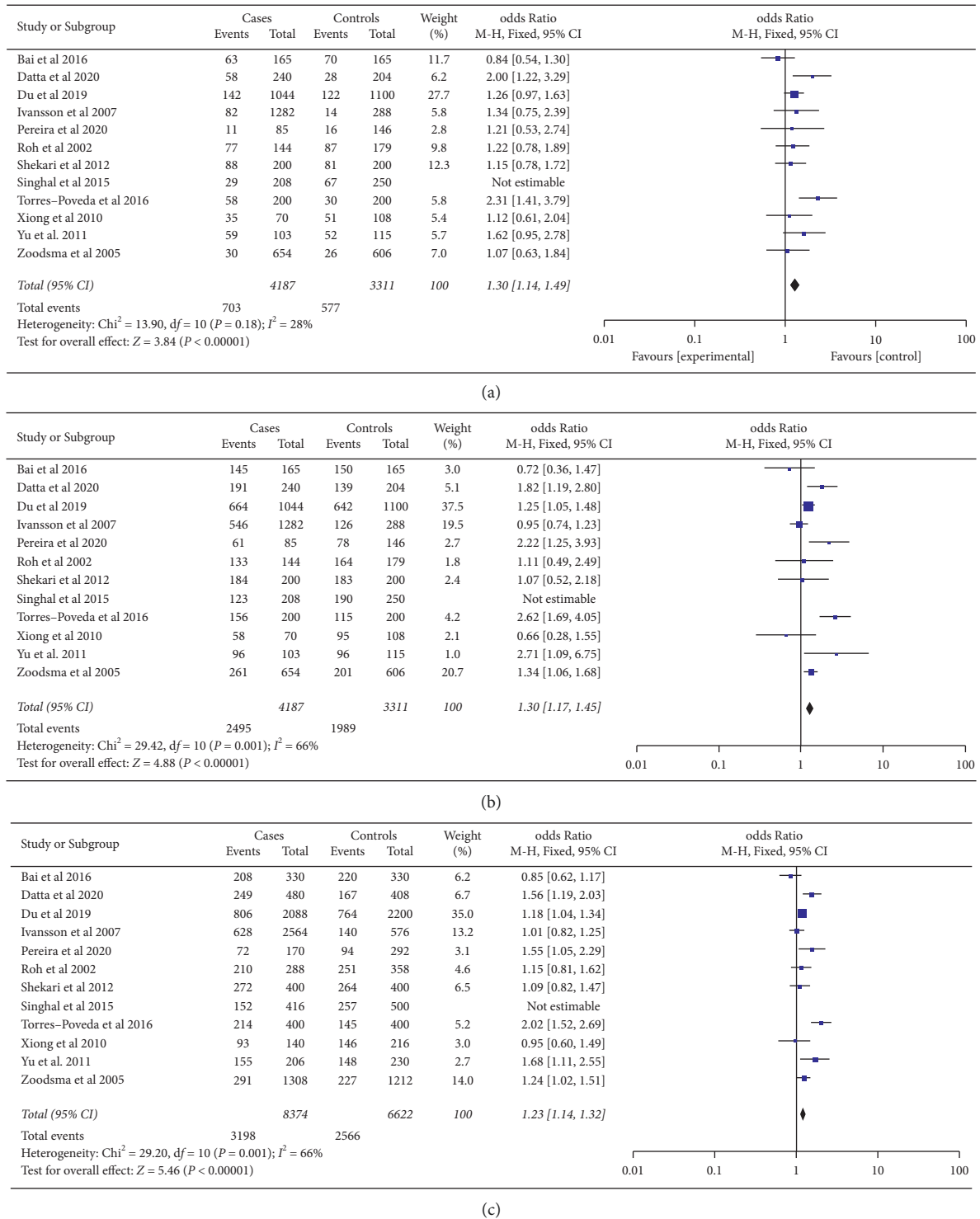


FIGURE 2: Forest plots of the association between the -592C/A polymorphism of the *IL-10* gene and cervical cancer for the (a) recessive model, (b) dominant model, and (c) additive model. The pooled OR is represented by a black diamond, the OR in each study is represented by blue squares with square sizes inversely proportionate to the standard error of the OR, and the horizontal lines represent the 95% CI.

CI = 1.12–2.00, $p = 0.006$), dominant model (OR (REM) = 1.57, 95% CI = 1.03–2.40, $P = 0.04$), and additive model (OR (FEM) = 1.15, 95% CI = 1.15–1.46, $P < 0.0001$) (Figure 3). Furthermore, an association of this polymorphism with

cervical cancer was observed in the Asian populations for the recessive (OR (FEM) = 1.25, 95% CI = 1.07–1.46, $P = 0.004$), dominant (OR (FEM) = 1.26, 95% CI = 1.09–1.46, $P = 0.002$), and additive (OR (FEM) = 1.19, 95%

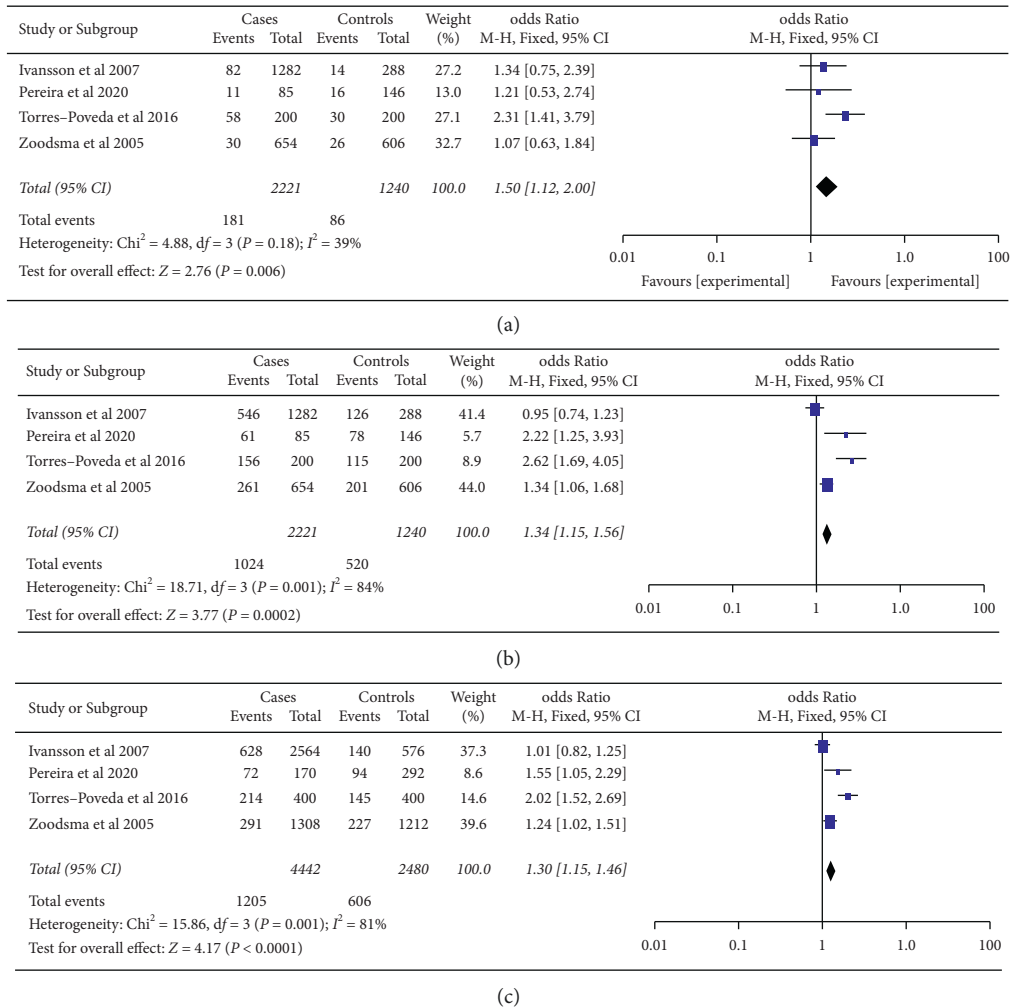


FIGURE 3: Forest plots of the association between SNP-592C/A in the *IL-10* gene and cervical cancer for the (a) recessive model, (b) dominant model, and (c) additive model in the Caucasian population. The pooled OR is represented by a black diamond, the OR in each study is represented by blue squares with square sizes inversely proportionate to the standard error of the OR, and the horizontal lines represent the 95% CI.

CI = 1.08–1.30, $P = 0.0002$) models (Figure 4). After Bonferroni correction adjusts P value, a nonsignificant association was found between *IL-10* -592C/A polymorphism and cancer for the dominant model in Caucasians.

3.3. *Sensitivity Analysis.* The stability of the meta-analysis was maintained by removing studies that significantly changed the overall OR and P value after excluding those that deviated from HWE [8]. In this regard, only the article by Singhal et al. has been omitted [19].

3.4. *Heterogeneity Source.* We found heterogeneity for the dominant and additive models with $I^2 > 50$ and $I^2 = 66$ percent, respectively, when we excluded studies that deviated from HWE and the ones that significantly affected the cumulative OR value (Figures 2(b) and 2(c)). The genetic models showed no heterogeneity in the race/ethnicity study, except for the dominating pattern in Caucasians ($I^2 = 84$ percent, $P = 0.0003$) (Figure 3(b)).

3.5. *Publication Bias.* The evaluation of publication bias was conducted by performing funnel plots. An absence of publication bias was observed for the recessive, dominant, and additive models after removing studies, not in agreement with the HWE and the study modifying the value of the pooled OR (Figure 5).

4. Results of TSA

The TSA’s outcome is depicted in Figure 6. The conclusions of the present meta-analysis are strong because the required sample size is 3669 and the cumulative z -curve reached the requested sample size by crossing the upper limit of sequential trial monitoring.

5. Discussion

HPV infection is one of the leading causes of cervical cancer, yet it is not sufficient to trigger cervical carcinogenesis. Smoking, HIV, fetal exposure to diethylstilbestrol, and oral

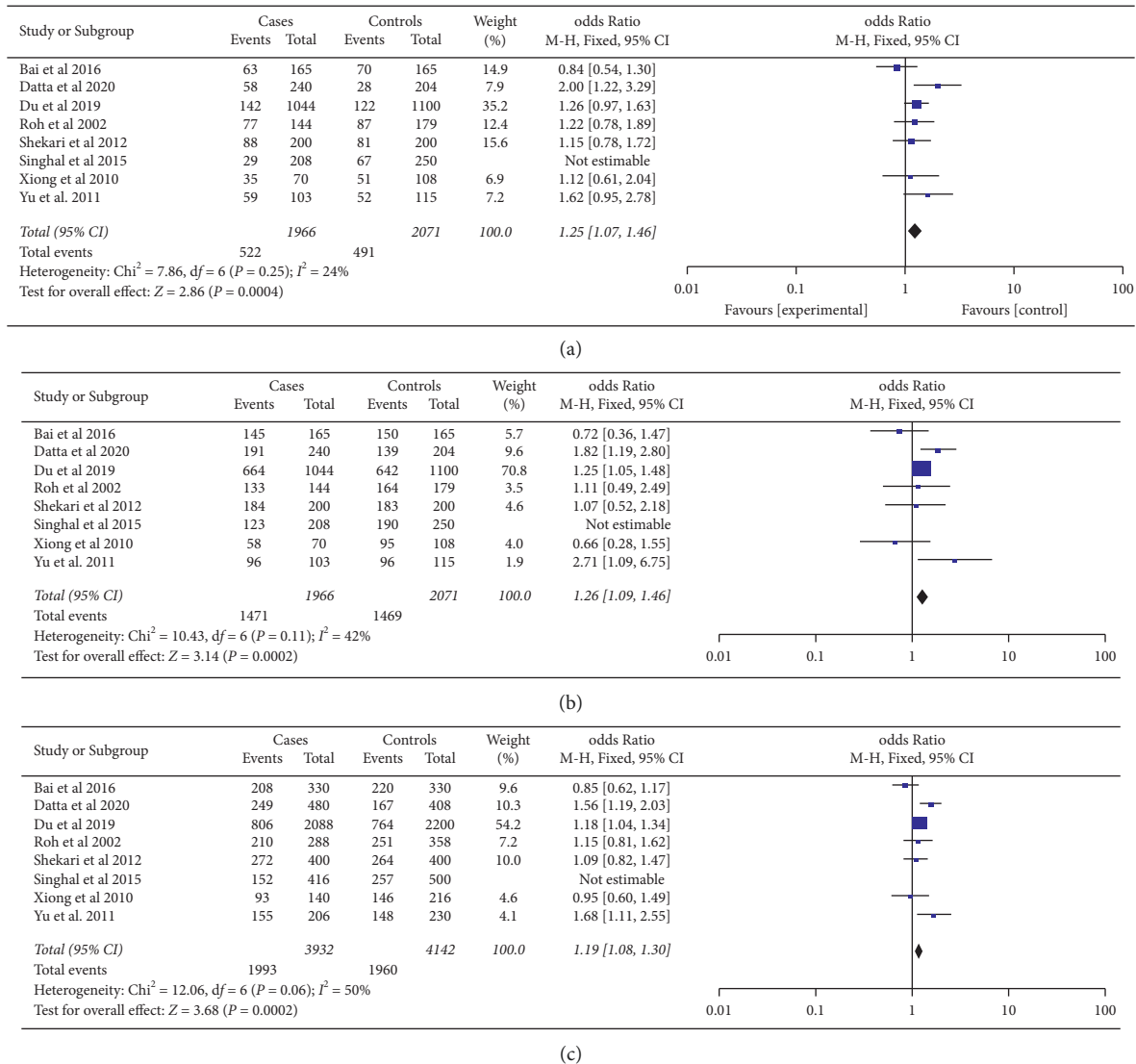


FIGURE 4: Forest plots of the association between the $-592C/A$ polymorphism of the *IL-10* gene and cervical cancer for the (a) recessive model, (b) dominant model, and (c) additive model in the Asian population. The black diamond represents the pooled OR, the blue squares show the OR in each study with square sizes inversely proportional to the standard error of the OR, and the horizontal lines denote the 95% CI.

contraceptives have all been identified as additional risk factors. Although genetic variables have been linked to carcinogenesis, the mechanism by which the *IL-10* gene polymorphism causes cervical cancer is unknown. In vitro, *IL-10* has been shown to have powerful immunosuppressive and antiinflammatory activities [35–37].

This cytokine is produced by a variety of cell types, such as CD4 T cells and monocytes/macrophages [38, 39]. Macrophages' ability to present antigens to T cells, as well as their ability to provide a costimulatory signal to T cells, is reduced by *IL-10*. It performs this function by inhibiting the activation of class II MHC-11 molecules and specific accessory molecules on their surfaces, including the B7.1 molecule [40]. By blocking cell-mediated immune responses

and inflammatory reactions, *IL-10* can promote carcinogenesis by limiting the development of an adequate anti-tumor response against tumor cells [40, 41].

It is worth noting that, in addition to its inhibitory characteristics, *IL-10* stimulates antibody production, as well as the differentiation and proliferation of B lymphocytes, which in turn produce *IL-10* [42–44]. Furthermore, the expression of the *IL-10* gene has been confirmed in various tumors, suggesting that *IL-10* could play a nonnegligible role in carcinogenesis by allowing the immune system to escape [4]. In promoter regions, functional polymorphisms of the *IL-10* gene such as $-592C/A$ can lead to changes in the affinity of transcriptional factors, thereby altering levels of mRNA expression (dose-

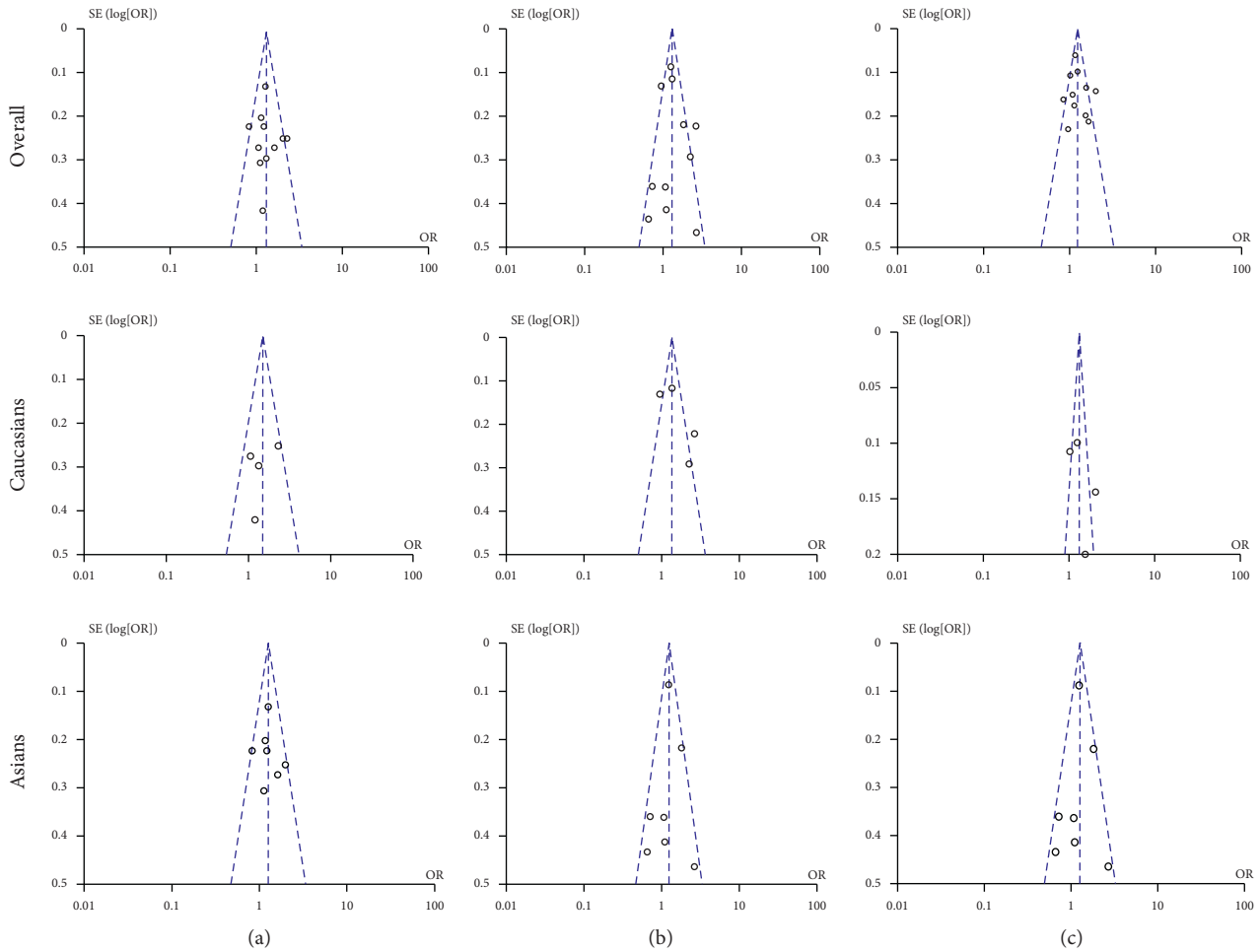


FIGURE 5: Funnel plots of the (a) recessive model, (b) dominant model, and (c) additive model precision by OR.

dependent effect) of inflammatory cytokines associated with the occurrence of cancer [22, 45].

In the present study, including 4187 cases and 3311 controls, we noted that the $-592C/A$ polymorphism of the *IL-10* gene was correlated with the overall risk of cervical cancer for the recessive, dominant, and additive models. This finding is in line with a previous meta-analysis that identified a significant association between the $-592C/A$ polymorphism and an increased risk of cervical cancer in 2396 cases and 1388 controls [46]. Contrary to our results, Guo et al. reported in a meta-analysis of 3,149 cases and 2,237 controls that the $-592C/A$ polymorphism was not globally correlated with cervical cancer for the three genetic models [14]. A recent meta-analysis with 1,393 cases and 1,307 controls also found conflicting results [47]. In Caucasians and Asians, our meta-analysis adjusted for race and ethnicity found an association between the $-592C/A$ polymorphism and cervical cancer in all models. Some meta-analyses supported our conclusions in some respects. This was the case in the meta-analysis by Guo et al. on the Caucasian population, which found that only the recessive model was associated with an increased risk of cervical cancer [14], and another meta-analysis from the Asian population, which found that the

additive model was associated with the risk of cervical cancer [46]. However, Wang et al. found that the $-592C/A$ polymorphism had no effect on the risk of cervical cancer in Caucasian and Asian populations across all genetic models tested [47].

Furthermore, Torres-Poveda et al. and Pereira et al. found a correlation between the $-592C/A$ polymorphism and cervical cancer in the Mexican and Brazilian populations for all three models, respectively [17, 21]. Zoodma et al., Du et al., and Datta et al. reported that the risk of cervical cancer was correlated with the $-592C/A$ SNP in the *IL-10* gene for the dominant and additive models in Netherlander, Chinese, and Bangladeshi populations, respectively [6, 7, 30]. These discrepancies between studies can be explained by a few factors, including (1) sample size differences between studies, (2) inclusion of studies with allele frequencies that deviate from the HWE, (3) inclusion of studies that change the pooled OR value, (4) population genetic background, and (5) inclusion of studies based on noncancerous cervical lesions [8, 19, 48].

The present study shows certain limitations as follows: the limited number of case and control studies carried out on the association of SNP-592C/A in the *IL-10* gene with the

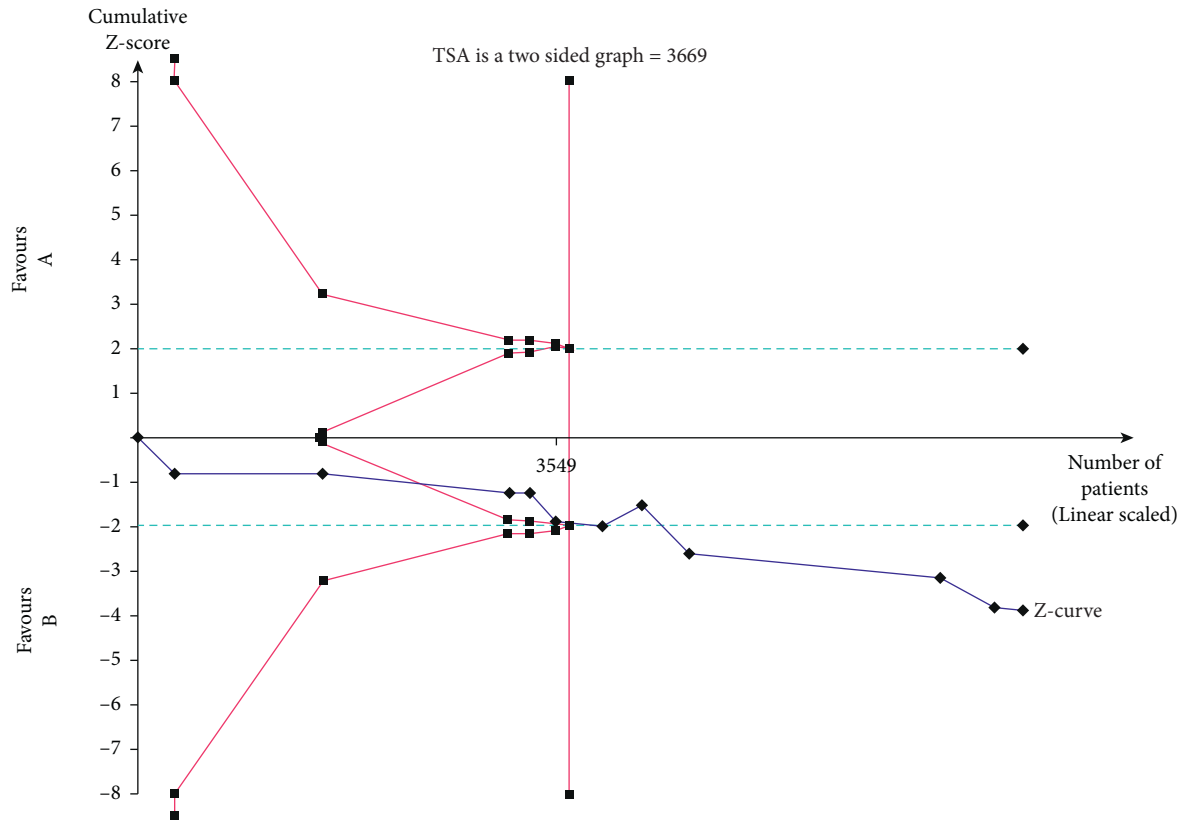


FIGURE 6: Trial sequential analysis for *IL10-592C/A* polymorphism under the genotype contrast model. The x-axis shows the number of participants (cases and controls) of the meta-analysis in each branch. The y-axis z-score shows the z-score. The red line represents the required sample size. The green line represents the conventional test boundary ($P = 0.05$).

risk of cervical cancer, particularly in the Caucasian and African populations (almost absent), and the sample size. Although the sample size requirement showed statistical power of 90%, a more representative sample size from different populations worldwide could confirm or refute a robust conclusion.

6. Conclusions

Based on an analysis of a large sample with precise inclusion criteria, this study reveals that women with the *-529C/A* polymorphism of the *IL-10* gene promoter have a high risk of cervical cancer for genetic models and provides evidence of an association of the *IL-10* gene promoter in the pathogenesis of cervical cancer.

7. Disclosure

This manuscript was presented as a preprint in “Association of *Interleukin-10 -529C/A* Polymorphism and Cervical Cancer Risk: A Meta-Analysis” (Preprint) [49]

Abbreviations

AA vs. CC + CA: Recessive model
 AA + CA vs. CC: Dominant model
 A vs. C: Additive model
 CI: Confidence interval

FE: Fixed effect
 Fig: Figure
 HWE: Hardy–Weinberg equilibrium
 I^2 : Inconsistency
 IL-10: Interleukin-10
 N: Number
 OR: Odds ratio
 RE: Random effect
 vs: Versus.

Data Availability

The supplementary material represents all the data analyzed in this meta-analysis.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

The final manuscript has been read and approved by all authors. Study conceptualization and design were done by BD, YK, MM, and LH. View, collection, analysis, and interpretation of the meta-analysis data were performed by BD, YK, MM, GD, OK, JLH, and LH. BD drafted of the

manuscript with assistance from YK, MM, GD, OK, JM, IMB, BT, CBT, BK, AC, SB, SN, RLM, JLH, and LH. Critical review of the manuscript for significant intellectual content was done by YK, MM, GD, OK, JM, IMB, BT, CBT, BK, AC, SN, RLM, JLH, and LH. JLH, LH, and RLM supervised the work.

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Supplementary Materials

PubMed accession numbers and Google scholar link of all data and references are given for meta-analysis. (*Supplementary Materials*)

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