REVIEW

Editorial Process: Submission:10/22/2023 Acceptance:04/17/2024

A Comprehensive Integration of Data Regarding the Correlation of TNF-α rs1800629 Polymorphism with Susceptibility to Cervical Cancer

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Abstract

Background: Cervical cancer, globally, ranks as the runner-up among the most prevalent forms of cancer affecting women. The role of the tumor necrosis factor alpha (TNF-α) polymorphism in the susceptibility to cervical cancer has been a subject of interest. However, the current evidence regarding this association remains inconclusive. **Methods:** To address this uncertainty, eligible studies were systematically searched and retrieved from various databases including Cochrane Library, EMBASE, PubMed, Web of Science, CNKI, and Wanfang database. The search was conducted until September 01, 2023. The collected literature was then subjected to independent analysis by two authors. The pooled odds ratio along with the corresponding 95% confidence interval was calculated using different genetic models. Additionally, sensitivity and cumulative analyses were performed to assess the stability of the obtained results. **Results:** A total of 29 case-control studies involving 8850 cases and 9286 controls were included in the present analysis. The findings revealed that the TNF-α rs1800629 polymorphism increased the risk of cervical cancer under the allele genetic model (A vs. G: OR = 1.277, 95% CI = 1.104-1.477, P = 0.001) in the general population. Subgroup analysis based on ethnicity demonstrated that this polymorphism was associated with an increased risk of cervical cancer in Caucasian and African women, but not in Asians. Furthermore, subgroup analysis based on country of origin indicated a significant correlation between the TNF-α rs1800629 polymorphism and an increased risk of cervical cancer in American and Chinese women, but not in Iranian women. **Conclusions:** The findings from this meta-analysis suggest that the TNF-α rs1800629 polymorphism is a risk factor for cervical cancer in the general population, particularly in Caucasian and African women. However, further well-designed studies are warranted to validate these findings.

Keywords: Cervical cancer- TNF-α- polymorphism- meta-analysis

Asian Pac J Cancer Prev, **25 (4)**, 1155-1167

Introduction

Cervical cancer is a form of cancer that arises in the cells of the cervix, the inferior portion of the uterus that connects to the vagina [1, 2]. Cervical cancer persists as a significant public health concern, ranking as the fourth most prevalent cause of cancer occurrence and fatality in women across the globe [3], with a projected 604,000 fresh instances in 2020. Among the estimated 342,000 fatalities resulting from cervical cancer in 2020 [4, 5], 85% of the occurrences and 87% of the mortalities arise in countries with lower and middle incomes [6, 7]. The

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primary risk factor for cervical cancer is the contraction of human papillomavirus (HPV) [8]. It is the foremost cancer associated with HPV to be identified and holds great potential for eradication [9, 10]. Cervical screening utilizing the Pap smear method has been implemented in numerous nations through either opportunistic or organized screening initiatives, resulting in a substantial reduction in the incidence and mortality rate of cervical cancer, particularly in countries with an organized screening program [11, 12]. The etiology of cervical cancer has been associated with host genetic and environmental determinants, notably the exposure to specific chemicals and viruses [13, 14]. Among the environmental factors, some of which are smoking, human papillomavirus (HPV) infection, dietary habits, and sexually transmitted infections, have been identified. However, the exact manner in which host genes and environmental factors influence the occurrence or vulnerability to cervical cancer remains unclear [15, 16].

Persistent infection of high-risk HPV is a prerequisite that is inadequate alone for the manifestation of cervical cancer [17]. HPV infection is sufficient, albeit not obligatory, for the manifestation of cervical cancer. HPV, a double-stranded closed-circle DNA virus, has a propensity to infiltrate the basal layer cells of squamous epithelium as well as the cells in the transformation zone. HPV can be classified into two types: high-risk and low-risk [18, 19]. High-risk HPV is inclined to infect the basal cells in the cervical tissue and the proliferative cells in the transformation zone, ultimately leading to carcinogenesis. Among these types, HPV-16 and HPV-18 demonstrate the most potent infectivity and the closest correlation with cervical lesions [19]. Approximately 80% of women have experienced HPV infection at some point in their lives; however, the majority of these infections are transient, as around 90% of infected individuals are capable of spontaneously clearing the virus within 1 to 2 years. Relevant research findings indicate that about 55% to 60% of cervical cancer cases are associated with HPV-16, while 10% to 15% are linked to HPV-18 [20, 21]. Upon infection with the HPV virus, the virus collaborates with risk factors to undermine the body's defense mechanism, heighten susceptibility to HPV, and induce persistent infection. Concurrently, the combination of HPV with host cell genes can trigger gene recombination (including deletions, translocations, and proto-oncogene activation) in the host cells, thereby initiating and advancing the development of cervical lesions [22]. Consequently, screening for high-risk HPV is advantageous in facilitating early detection, early diagnosis, and early treatment of cervical cancer [19].

The identification of the factors that contribute to HPV infection and the vigilant monitoring or meticulous screening of the population at high risk can mitigate the incidence and progression of cervical cancer [23]. With the advancement of research, numerous risk factors pertaining to the occurrence of cervical cancer have been uncovered, particularly the pathogenic role played by HPV. Several developed nations have implemented initiatives encompassing HPV vaccination and screening, yielding noteworthy outcomes [24, 25]. The risk prediction model has the capacity to amalgamate multiple risk factors in order to prognosticate the likelihood of an individual developing cervical cancer and precancerous lesions. Prompt identification of high-risk cohorts can more effectively steer the screening process, thus bearing significant importance in the realm of cervical cancer prevention and control [26, 24]. In recent times, multiple cervical cancer risk prediction models have been globally established, based on factors like HPV infection and demographic characteristics. Nonetheless, there exists a dearth of studies that have systematically collated and evaluated the quality of these models, thereby impeding the models' ability to genuinely aid individual decision-making [27].

The gene known as tumor necrosis factor-alpha (TNF-α; OMIM 191160) is situated on the shorter arm of chromosome 6 (6p21.33), spanning a length of 2,762 base pairs. This gene consists of 3 introns and 4 exons and is closely associated with the major histocompatibility complex region [28-30]. More specifically, a single nucleotide polymorphism (SNP) located in the promoter region at position G-308A has been linked to an increased synthesis of TNF-α [31-33]. Various SNPs in the promoter region of the TNF-α gene have been documented, with particular attention given to two common SNPs: -308G>A (rs1800629) and -238G>A (rs361525) polymorphisms. These polymorphisms have been extensively studied in relation to susceptibility to different types of cancer [34, 35]. The TNF-α rs1800629 polymorphism in the promoter region of the gene has been shown to have a close association with the risk of various cancers, while the impact of others remains uncertain. Polymorphisms in TNF-α are primarily concentrated in the promoter region and are closely linked to the risk of cervical cancer. However, the relationship between the TNF-α rs1800629 polymorphism and cervical cancer has yielded conflicting results in different populations. This discrepancy may be attributed to factors such as ethnicity, source of control, genotyping method, and sample size [36, 37]. Despite previous meta-analyses that have been carried out, a number of relevant studies have not been included in these analyses [38-40]. Hence, we have conducted a meta-analysis in order to obtain a more precise evaluation of the correlation between the TNF-α rs1800629 polymorphism and susceptibility to cervical cancer, incorporating all available studies.

Materials and Methods

Search Strategy

We conducted a thorough search across various databases, including PubMed, Google Scholar, EBSCO, EMBASE, Web of Science, Wanfang, Ovid, Weipu, China National Knowledge Infrastructure (CNKI), Islamic World Science Citation Center (ISC), Scientific Information Database (SID), and Cochrane library, to identify all relevant articles discussing the relationship between the TNF-α rs1800629 polymorphism and cervical cancer. The search terms used were "Cervical Cancer" OR "Cervical Carcinoma" OR "Cervical tumor" OR "Uterine Cervix Cancer" and "Tumor Necrosis Factor" OR "TNF-α" OR

"Cachexin" OR "Cachectin" and "-308G>A" OR "-308G/A" OR "rs1800629" AND "Gene" OR "Single-Nucleotide Polymorphism" OR "SNP" OR "Polymorphism" OR "Genotype" OR "Allele" OR "Variation" OR "Mutation". The retrieval dates were not restricted, and the most recent retrieval was conducted on September 01, 2023. Furthermore, we manually examined the reference lists of eligible studies, reviews, and previous meta-analyses to identify any additional relevant studies that may have been missed. Language restrictions were not imposed during the search process. Two authors independently reviewed and assessed the identified articles. Given that this study is a systematic review and meta-analysis, ethical approval was not required.

Eligibility Criteria

In brief, the inclusion criteria for the studies encompassed the following aspects: (1) an examination of the correlation between TNF-α rs1800629 polymorphism and susceptibility to cervical cancer, (2) a case-control or cross-sectional design, (3) availability of adequate data to compute the odds ratio (OR) with a 95% confidence interval (CI), (4) conformity of the control group to the Hardy-Weinberg equilibrium (HWE) law, (5) provision of original data, either directly or indirectly, pertaining to the allele or genotype frequency of NF-α rs1800629 polymorphism in both the case and control groups, and (6) consideration of two independent sample sets within a single publication as distinct studies. Conversely, the primary exclusion criteria consisted of: (1) studies solely comprising cases without a control group, (2) randomized controlled experimental, animal experimental, or cell research, (3) incomplete or insufficiently published information, or invalid original data, (4) family-based and/or linkage studies, (5) case reports, reviews, abstracts, letters to editors, or posters, and (6) duplications of previous studies.

Data Extraction

Two reviewers independently and meticulously extracted the data from eligible studies utilizing a standardized protocol in accordance with the inclusion criteria. In the event of any disagreement regarding the included studies and data, the authors engaged in thorough discussion to resolve the matter. However, if a conflicting evaluation still persisted, the authors sought the expertise of another author to arbitrate the dispute. In order to ensure comprehensive analysis, an extensive range of data was collected for each of the eligible case-control studies. This included information such as the first authors, year of publication, country, and ethnicity (Caucasian, Asian, African, and Mixed). Furthermore, details regarding the source of healthy controls (hospital-based studies and population-based studies), as well as the number of cases and controls, were also gathered. The numbers of cases and controls for each genotype, along with the assessment of Hardy-Weinberg equilibrium (HWE) in controls and the minor allele frequency (MAF), were additionally recorded.

Statistical Analyses

All analyses were performed with the Comprehensive Meta-Analysis (CMA) 2.0 software (Biostat, USA). Two-sided P-values < 0.05 were considered statistically significant. The allele frequencies of the polymorphism from each study were calculated from genotype distributions or from the minor allele frequencies (MAF) provided in the studies. The correlation between the TNF-α rs1800629 polymorphism in cervical cancer susceptibility was assessed from the odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) for each study in five genetic models i.e., allele (A vs. G), homozygote (AA vs. GG), heterozygote (AG vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG). The Ztest was used to assess the significance of the pooled OR, in which P<0.05 was considered as statistically significant. Between-study heterogeneity was analyzed by a chi-squared-based Q-statistic test, in which the P-value <0.05 was considered significant. In addition, we used the Higgins (I^2) test to assess the degree of between-study heterogeneity, in which the I^2 values of 25%, 50%, and 75% were nominally considered low, moderate, and high estimates, respectively [41, 42]. Accordingly, the pooled ORs were calculated using a fixed-effects (Mantel-Haenszel method) (if P>0.05 or I^2<50%); otherwise, random-effects model (DerSimonian-Laird method) was chosen (if P<0.05 or I^2>50%) based on the level of heterogeneity. For each study, departure of the TNF-α -308G>A polymorphism frequencies in control groups from the Hardy-Weinberg equilibrium (HWE) was tested using the goodness-of-fit test (i. chi-square test), and deviation was considered when P<0.05. We performed subgroup according to ethnicity, source of controls, genotyping methods, and HWE. Begg's funnel plot and the Egger's test were used to determine the publication bias with $p < 0.05$ being statistically significant. the robustness of results was tested by using sensitivity analysis and excluding those studies departure from HWE. We also performed subgroup analyses and a sensitivity analysis to explore sources of heterogeneity. Subgroup analyses stratified studies by ethnicity, ethnicity (African, Asian, Caucasian, and mixed), country of origin (with more than tree studies), sample size ($<100, >100$), the publication year ($\leq 2010, >2010$), detection method and source of control (HB, PB, mixed, nested).

Results

The PRISMA diagram in Figure 1 provides an overview of the study selection and exclusion process. Meanwhile, the main characteristics of the eligible studies can be found in Table 1. Initially, a total of 917 articles were retrieved from various resources such as PubMed, Scopus, Google Scholar, and others. However, 588 of these articles were excluded during the review of titles and abstracts due to not meeting the defined eligibility criteria. This left us with 329 articles for full text evaluation. Upon careful analysis of the full texts, an additional 300 studies were excluded, resulting in a total of 29 studies being included in this study (Table 1 and Figure 1). These 29 studies encompassed 8850 cases

Table 1. Characteristics of the Case-Control Studies Included in the Meta-Analyses

First Author/Year	Country Ethnicity	SOC	Genotyping Method	Case/Control	Cases					Controls					MAFs	HWE
					Genotype			Allele		Genotype			Allele			
					GG	AG	AA	G	A	GG	AG	AA	G	A		
Jang 2001	Korea(Asian)	PB	PCR-RFLP	51/92	46	3	2	95	7	85	7	0	177	7	0.038	0.704
Calhoun 2002	USA(Caucasian)	HB	Sequencing	127/107	91	27	9	209	45	73	30	4	176	38	0.177	0.678
Stanczuk 2003	Zimbabwe(African)	PB	ARMS-PCR	103/101	74	28	1	176	30	81	18	2	180	22	0.108	0.41
Gostout 2003	USA(Caucasian)	HB	Sequencing	127/175	91	27	9	209	45	117	53	5	287	63	0.18	0.731
Duarte 2005	Portugal(Caucasian)	PB	PCR-RFLP	195/244	138	50	7	326	64	200	40	4	440	48	0.098	0.236
Deshpande 2005	USA(Caucasian)	HB	Sequencing	258/411	188	54	16	430	86	297	100	14	694	128	0.155	0.13
Govan 2006	South Africa(African)	HB	ARMS-PCR	244/228	174	62	8	410	78	172	46	10	390	66	0.144	0.005
Kohaar 2007	India(Asian)	HB	PCR-RFLP	120/165	94	22	4	210	30	150	15	0	315	15	0.045	0.54
Wang 2009	China(Asian)	PB	TaqMan	456/800	386	67	3	839	73	666	126	8	1458	142	0.088	0.457
Singh 2009	India(Asian)	HB	PCR-RFLP	150/162	122	17	11	261	39	147	11	4	305	19	0.058	≤0.001
Ivansson 2010	Sweden(Caucasian)	PB	TaqMan	1263/552	891	340	32	2122	404	396	138	18	930	174	0.157	0.169
Zu 2010	China(Asian)	HB	PCR	83/91	30	50	3	110	56	66	16	9	148	34	0.186	≤0.001
Wang 2011	China(Asian)	PB	PCR	186/200	149	30	7	328	44	144	46	10	334	66	0.165	0.019
Zuo 2011	China(Asian)	HB	PCR-RFLP	239/110	158	81	0	397	81	83	25	2	191	29	0.131	0.941
Rotar 2014	Romania(Caucasian)	HB	PCR-RFLP	123/107	85	38	0	208	38	83	23	1	189	25	0.117	0.666
Wang 2012	China(Asian)	HB	PCR-RFLP	285/318	247	30	8	524	46	274	35	9	583	53	0.083	≤0.001
Barbisan 2012	Argentina(Caucasian)	HB	PCR-RFLP	122/176	87	32	3	206	38	126	46	4	298	54	0.153	0.483
Badano 2012	Argentina(Caucasian)	HB	Sequencing	56/113	44	10	2	98	14	101	12	0	214	12	0.053	0.551
Sousa 2014	Portugal(Caucasian)	PB	TaqMan	223/205	152	65	6	369	77	164	39	2	367	43	0.104	0.849
Zidi 2014	Tunisia(African)	HB	ARMS-PCR	130/260	55	33	43	143	119	141	35	84	317	203	0.39	≤0.001
Roszak 2015	Poland(Caucasian)	HB	HMR	362/399	217	123	22	557	167	263	125	11	651	147	0.184	0.397
Chinchai 2016	Thailand(Asian)	HB	Sequencing	121/130	108	11	2	227	15	113	15	2	241	19	0.073	0.09
Li 2018	China(Asian)	HB	PCR-RFLP	142/150	114	24	4	252	32	125	22	3	272	28	0.093	0.102
Babapour 2018	Iran(Asian)	HB	TaqMan	91/161	28	50	13	106	76	94	61	6	249	73	0.227	0.306
Du 2019	China(Asian)	HB	Sequencing	1044/1100	780	168	96	1728	360	862	182	56	1906	294	0.134	≤0.001
Duvlis 2020	Macedonia(Caucasian)	HB	M-PCR	113/134	109	4	0	222	4	127	6	1	260	8	0.03	0.008
Yan 2021	China(Asian)	HB	TaqMan	980/1173	875	101	4	1851	109	1001	167	5	2169	177	0.075	0.492
Behbodi 2021	Iran(Asian)	HB	TaqMan	265/153	157	102	6	416	114	43	88	22	174	132	0.431	0.032
Khorrami 2022	Iran(Asian)	HB	TaqMan	146/169	84	39	23	207	85	81	77	11	239	99	0.293	0.193

Abbreviations: SOC, Source Of Controls; HB, Hospital Based; PB, Population Based; RFLP, Restriction Fragment Length Polymorphism; ARMS, Amplification-Refractory Mutation System; HMR, High Resolution Melting; MAF, Minor Allele Frequency; HWE, Hardy-Weinberg Equilibrium.

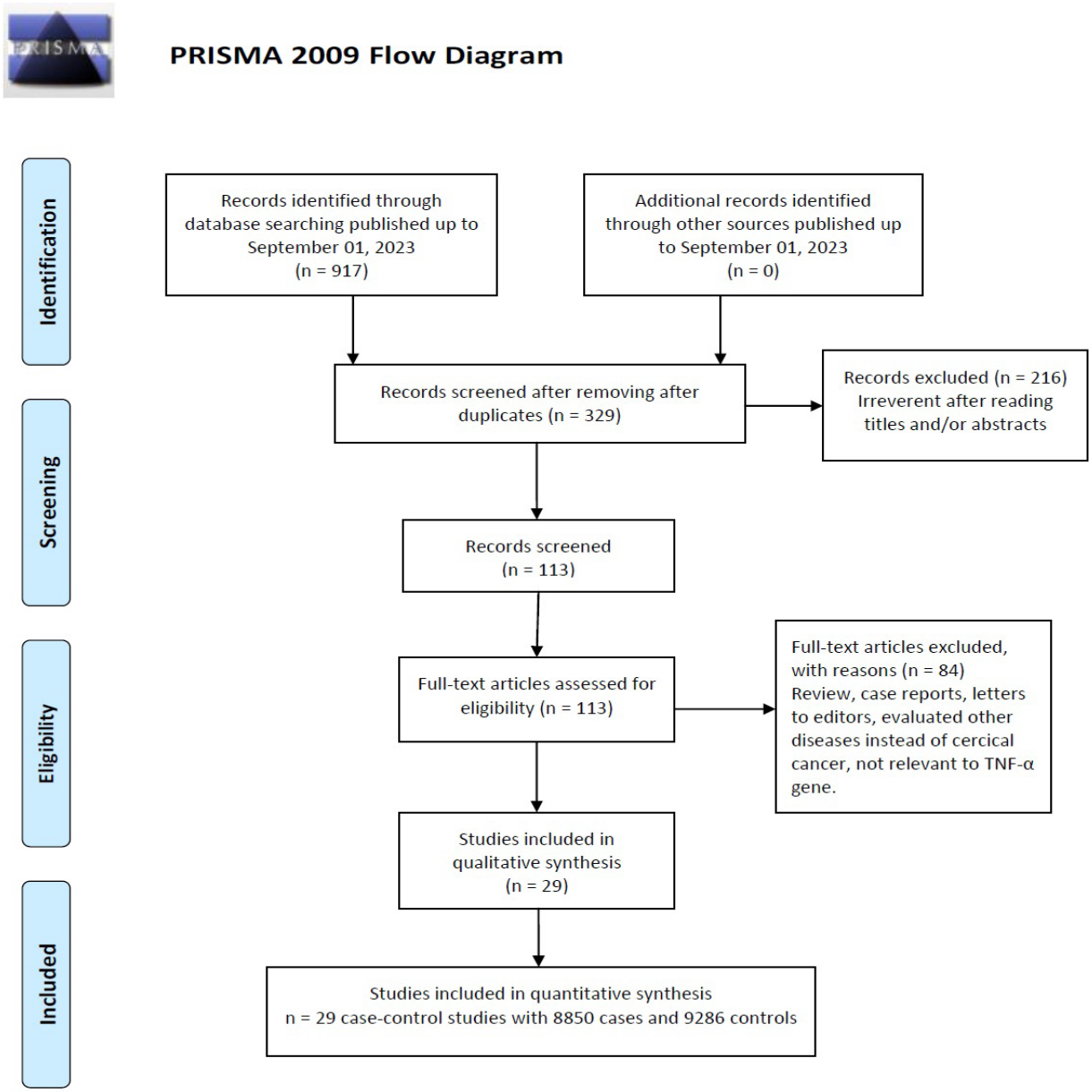

Figure 1. Flow Diagram of Selecting Eligible Studies for the Meta-Analysis.

and 9286 controls for cervical cancer [43-71]. The details of the TNF-α rs1800629 polymorphism in each study, including the frequency in cervical cancer, the results of the HWE test in control groups, and the MAFs, can be found in Table 1. Among these studies, 10 were conducted on Asian populations and 14 on Caucasian populations. In terms of genotyping methods, 8 studies used PCR, 11 used TaqMan, 4 used PCR-RFLP, and one used MALDI-TOF. The distribution of genotypes in all studies was consistent with HWE, with the exception of six studies on cervical cancer (Table 1).

Quantitative Synthesis

Overall Analysis

Table 2 presented the primary findings of the meta-analysis conducted on the TNF-α rs1800629 polymorphism's impact on cervical cancer susceptibility. Our comprehensive analysis, which included 29 studies and involved 8850 cases and 9286 controls, demonstrated a noteworthy association between the TNF-α rs1800629 polymorphism and cervical cancer susceptibility under the allele genetic model (A vs. G: OR = 1.277, 95% CI = 1.104-1.477, P = 0.001) among females.

Subgroup Analysis

In the subgroup analysis that considered ethnicity, a noteworthy increase in the risk of cervical cancer was observed among Caucasian women (Table 2). This increase was observed under four different models, namely allele (A vs. G), homozygote (AA vs. GG), dominant (AA+AG vs. GG), and recessive (AA vs. AG+GG). The corresponding odds ratios (OR) and their respective 95% confidence intervals (CI) were 1.233 (1.043-1.450, P = 0.011), 1.540 (1.117-2.122, P = 0.008), 1.206 (1.002-1.453, P = 0.048), and 1.522 (1.107-2.094, P = 0.010). Similarly, African women showed an increased risk of cervical cancer under three models, namely allele, homozygote, and dominant. The

Table 2. Results of Meta-Analysis for Association of TNF-α rs1800629 Polymorphism with Cervical Cancer and in Different Subgroups.

Polymorphism	Genetic Model	Type of Model	Heterogeneity		Odds Ratio				Publication Bias	
			I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	A vs. G	Random	79.99	≤0.001	1.2	1.024-1.406	2.25	0.024	0.222	0.276
	AA vs. GG	Random	63.61	≤0.001	1.318	0.937-1.855	1.585	0.113	0.778	0.656
	AG vs. GG	Random	78.99	≤0.001	1.161	0.957-1.409	1.515	0.13	0.17	0.151
	AA+AG vs. GG	Random	79.75	≤0.001	1.199	0.997-1.441	1.932	0.053	0.156	0.213
	AA vs. AG+GG	Random	58.6	≤0.001	1.28	0.933-1.756	1.526	0.126	0.807	0.651
Ethnicity										
Asian	A vs. G	Random	88.08	≤0.001	1.178	0.887-1.566	1.13	0.258	0.234	0.463
	AA vs. GG	Fixed	77.64	≤0.001	1.193	0.642-2.217	0.559	0.576	1	0.537
	AG vs. GG	Random	85.61	≤0.001	1.098	0.791-1.523	0.557	0.577	0.137	0.238
	AA+AG vs. GG	Random	87.42	≤0.001	1.162	0.840-1.608	0.906	0.365	0.092	0.354
	AA vs. AG+GG	Random	72.62	≤0.001	1.124	0.678-1.864	0.454	0.65	0.964	0.491
Caucasian	A vs. G	Random	45.73	0.048	1.233	1.043-1.450	2.53	0.011	1	0.462
	AA vs. GG	Fixed	16.47	0.287	1.54	1.117-2.122	2.637	0.008	0.876	0.55
	AG vs. GG	Random	48.49	0.035	1.144	0.937-1.397	1.324	0.186	0.64	0.907
	AA+AG vs. GG	Random	46.11	0.046	1.206	1.002-1.453	1.977	0.048	1	0.661
	AA vs. AG+GG	Fixed	16.88	0.283	1.522	1.107-2.094	2.585	0.01	0.755	0.586
African	A vs. G	Fixed	0	0.764	1.245	1.005-1.542	2.008	0.045	1	0.802
	AA vs. GG	Fixed	0	0.537	1.156	0.757-1.766	0.672	0.502	1	0.289
	AG vs. GG	Fixed	24.82	0.264	1.67	1.228-2.270	3.268	0.001	1	0.564
	AA+AG vs. GG	Fixed	0	0.615	1.443	1.103-1.888	2.679	0.007	1	0.766
	AA vs. AG+GG	Fixed	0	0.714	0.947	0.635-1.411	-0.269	0.788	1	0.185
Country										
China	A vs. G	Random	78.92	≤0.001	1.073	0.829-1.389	0.539	0.59	0.386	0.872
	AA vs. GG	Fixed	35.43	0.146	1.419	1.072-1.877	2.45	0.014	0.386	0.002
	AG vs. GG	Random	83.91	≤0.001	1.157	0.811-1.649	0.805	0.421	0.063	0.166
	AA+AG vs. GG	Random	82.7	≤0.001	1.139	0.827-1.569	0.796	0.426	0.265	0.463
	AA vs. AG+GG	Random	49.73	0.053	1.382	1.046-1.825	2.28	0.023	0.265	0.003
Iran	A vs. G	Random	96.56	≤0.001	0.951	0.323-2.800	-0.09	0.928	0.296	0.069
	AA vs. GG	Random	95.5	≤0.001	1.028	0.082-12.86	0.022	0.983	1	0.967
	AG vs. GG	Random	94.52	≤0.001	0.745	0.219-2.538	-0.47	0.638	0.296	0.155
	AA+AG vs. GG	Random	95.87	≤0.001	0.825	0.217-3.141	-0.282	0.778	0.296	0.178
	AA vs. AG+GG	Random	93.64	≤0.001	1.17	0.152-9.010	0.151	0.88	1	0.858
USA	A vs. G	Fixed	0	0.915	1.038	0.835-1.289	0.335	0.738	1	0.233
	AA vs. GG	Fixed	0	0.932	1.916	1.104-3.26	2.311	0.021	1	0.658
	AG vs. GG	Fixed	0	0.714	0.769	0.584-1.013	-1.87	0.062	1	0.334
	AA+AG vs. GG	Fixed	0	0.802	0.897	0.695-1.157	-0.838	0.402	1	0.309
	AA vs. AG+GG	Fixed	0	0.891	2.046	1.183-3.537	2.563	0.01	1	0.57

corresponding odds ratios (OR) and their respective 95% confidence intervals (CI) were 1.245 (1.005-1.542, P = 0.045), 1.670 (1.228-2.270, P = 0.001), and 1.443 (1.103-1.888, P = 0.007). However, no significant association was found between cervical cancer risk and ethnicity in Asian women. Additionally, the correlation between the TNF-α rs1800629 polymorphism and cervical cancer risk was investigated among Chinese women and USA-American women, stratified by country of origin. It was found that the homozygote model and the d recessive model showed a significant correlation with cervical cancer risk in Chinese women, with odds ratios (OR) and 95% confidence intervals (CI) of 1.419 (1.072-1.877, P = 0.014) and 1.382 (1.046-1.825, P = 0.023) respectively. Similarly, in USA-American women, the homozygote model showed a significant correlation with cervical cancer risk, with odds ratios (OR) and 95% confidence intervals (CI) of 1.419 (1.072-1.877, P = 0.014). However, no significant correlation was observed in Iranian women.

Heterogeneity Test and Sensitivity Analyses

We found a significant between study heterogeneity

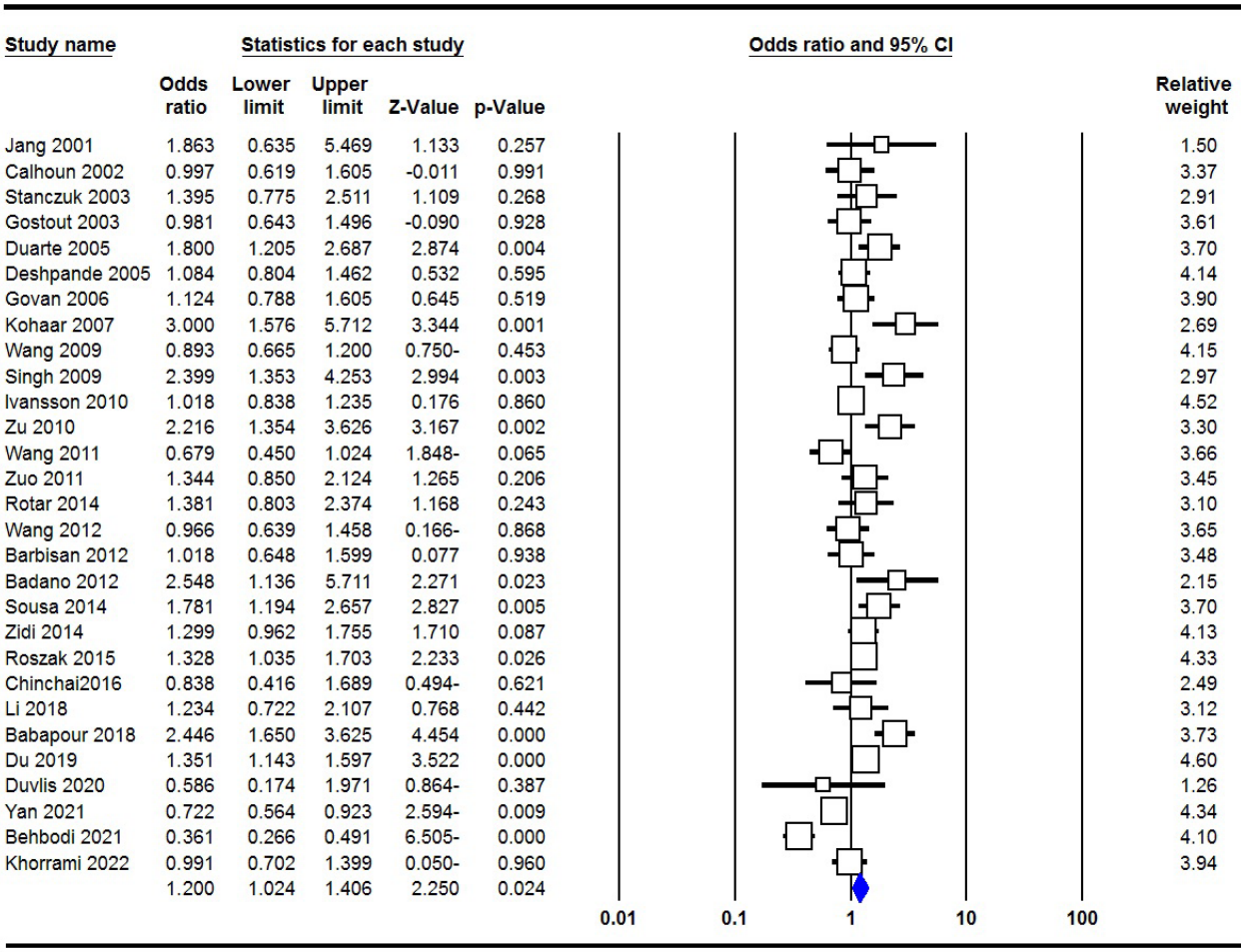

Figure 2. Forest Plot of TNF-α rs1800629 Polymorphism with Cervical Cancer under the Allele Genetic Model (A vs. G).

for TNF-α rs1800629 polymorphism in cervical cancer susceptibility under all five genetic models in general population. Thus subgroup analysis was performed to explore the source of heterogeneity (Figure 2). However, the result indicated that ethnicity, source of controls, and publication year were not the main factor responsible for the heterogeneity in this meta-analysis. In order to evaluate the stability of the pooled data for the TNF-α rs1800629 polymorphism in cervical cancer susceptibility, we conducted a sensitivity analysis by removing each individual research from the analysis at a time. However, sensitivity analysis showed that the initial results were not considerably adjusted by omitting any individual study. Nine studies had PHWE < 0.05. Thus, we compared the pooled data before and after excluding those studies and there were slight changes in the results. It showed that the changes of each genetic contrast model results were not obvious, suggesting that the results of meta-analysis were stable and reliable (Figure 3).

Publication Bias

Begg's funnel plot and Egger's test were utilized to evaluate the publication bias of the literature. Neither Begg's funnel nor Egger's test showed publication bias under all five genetic models. The shape of the funnel plots and Egger's test (allele: P = 0.108, dominant: P = 0.177, recessive: P = 0.240, homozygous: P = 0.132, heterozygous: P = 0.177) showed no publication bias. An absence of publication bias was observed after removing studies, not in agreement with the HWE and the study modifying the value of the pooled OR and by subgroup analyses.

Discussion

In recent times, there has been a significant level of interest in the anti-tumor impact of TNF-α. This particular cytokine, which is not specific to any species, possesses a diverse range of biological activities and serves to combat tumors, viruses, as well as boost the immune system. Certain genes associated with tumors have the ability to regulate the process of transcription and translation through natural genetic variation, thereby influencing an individual's susceptibility to tumors. The susceptibility of certain tumors is linked to functional single nucleotide polymorphisms of the TNF gene. Research studies have indicated that the A allele of TNF-α rs1800629 can influence the binding of a transcriptional repressor known as activator protein 2 (AP-2), leading to an increase in TNF-α expression. Individuals who carry the mutant allele of the TNF-α rs1800629 polymorphism face an elevated risk of developing cervical cancer, breast cancer, and

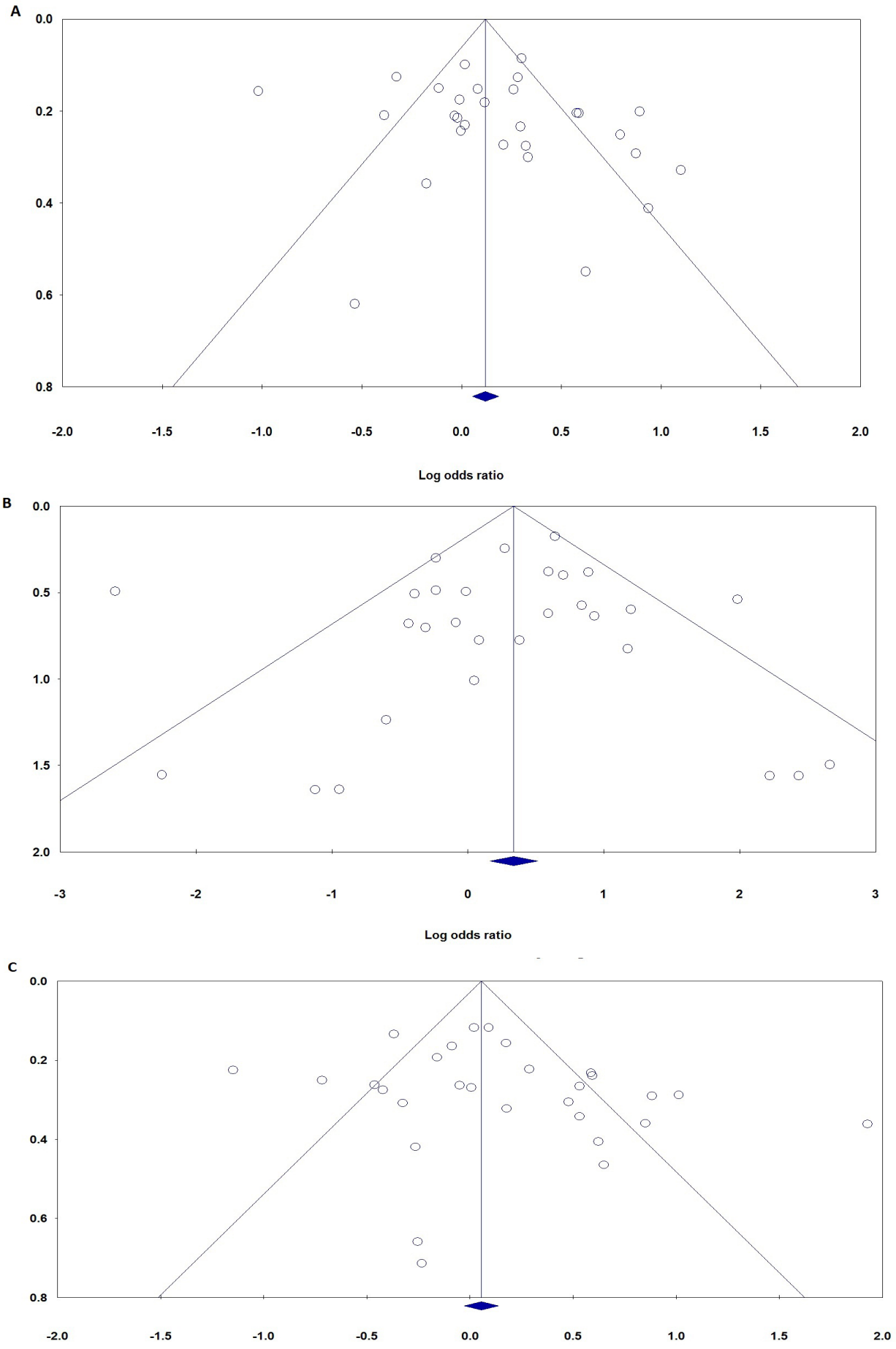

Figure 3. Funnel Plot for Publication bias in the Meta-Analysis of TNF-α rs1800629 Polymorphism with Cervical Cancer. A: allele (A vs. G), B: homozygote (AA vs. GG), C: heterozygote (AG vs. GG)

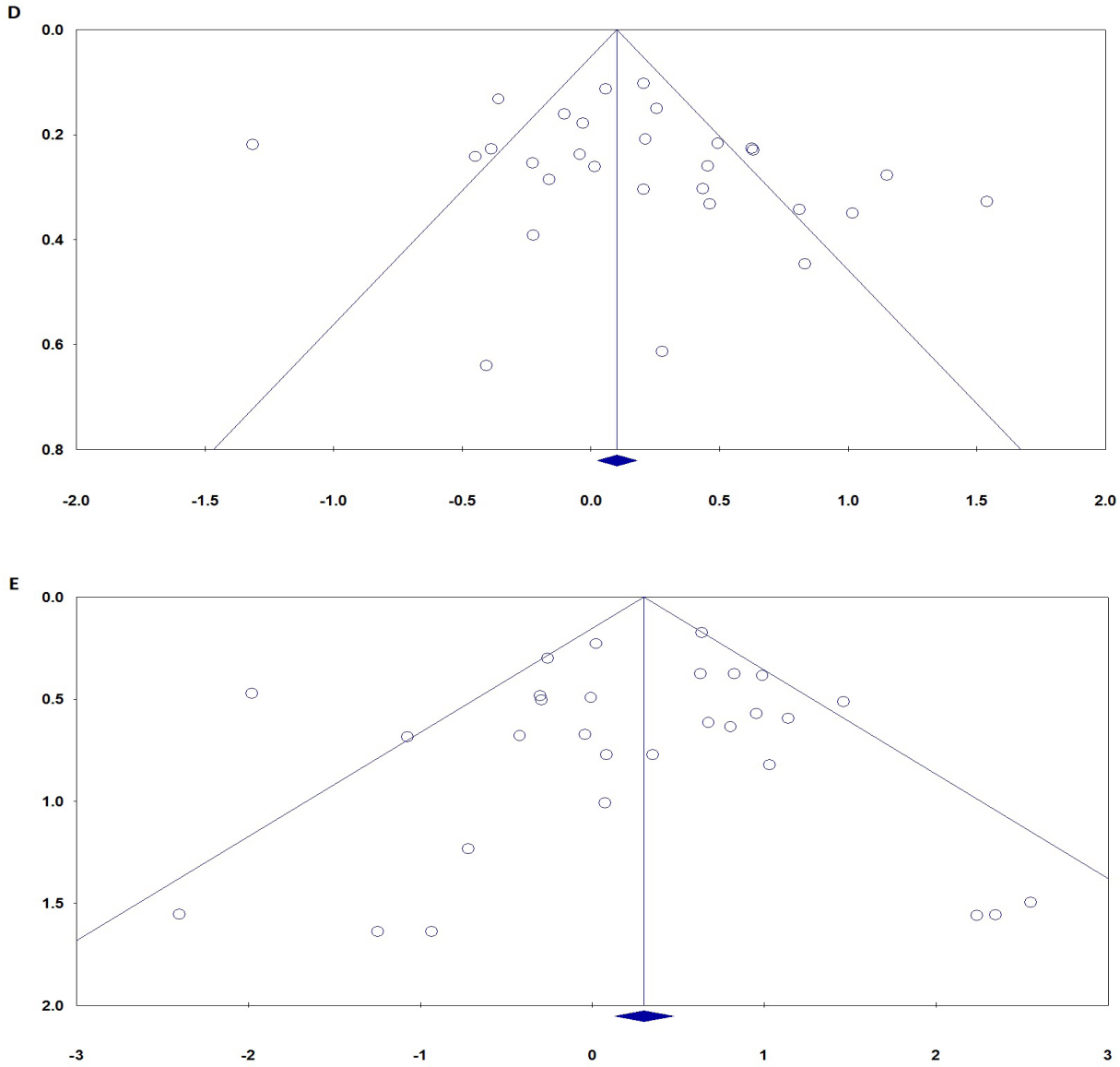

Figure 3. Funnel Plot for Publication bias in the Meta-Analysis of TNF-α rs1800629 Polymorphism with Cervical Cancer. D: dominant (AA+AG vs. GG) and E: recessive (AA vs. AG+GG).

gastric cancer, while being less prone to developing oral squamous cell carcinoma, bladder cancer, and multiple myeloma. Govan et al., assert that TNF-α rs1800629 does not play a role in the occurrence of cervical cancer. The inconsistency in research findings may be attributed to the fact that tumor development is the outcome of the combined action of multiple cytokines and other factors. Furthermore, the expression of TNF-α is not solely influenced by the rs1800629 polymorphism, as other sites also have an impact on the expression of this gene.

A systematic review was conducted in this study to investigate the correlation between the TNF-α rs1800629 polymorphism and the risk of cervical cancer based on 29 studies encompassed 8850 cases and 9286 controls. The findings indicated that the TNF-α rs1800629 polymorphism displayed an association with the risk of cervical cancer under the allele genetic model (A vs. G: OR = 1.277, 95% CI = 1.104-1.477, P = 0.001) within the overall population. In the subgroup analysis conducted on the basis of ethnicity, a noteworthy elevation in the jeopardy of cervical cancer was detected in the Caucasian and African female population. However, no such correlation was observed in Asian women. Additionally, after categorizing the subjects according to their country of origin, a substantial association between the TNF-α rs1800629 polymorphism and the risk of cervical cancer was found in Chinese and USA-American women. Conversely, no such link was noted among Iranian women. It is worth emphasizing that the aforementioned association between the TNF-α rs1800629 polymorphism and cervical cancer susceptibility has been established through a meticulous examination of a considerable number of studies, ensuring the reliability and validity of the findings. This comprehensive analysis serves as a significant contribution to the existing body of literature on the subject matter and offers valuable insights into the genetic factors that play a role in the development of cervical cancer among females. Furthermore, the

substantial sample size utilized in this study enhances the generalizability of the results and strengthens the argument for the existence of a noteworthy association between the TNF-α rs1800629 polymorphism and the susceptibility of cervical cancer. In 2020, Wang et al. conducted a pooled study comprising 19 studies, which demonstrated that the TNF-α rs1800629 polymorphism was linked to cervical cancer under the dominant model (p = 0.0004, OR 0.71, 95% CI 0.58-0.86), recessive model (p = 0.0002, OR 1.46, 95% CI 1.19-1.79), heterozygote model (p = 0.002, OR 1.37, 95% CI 1.12-1.68), and allele model (p < 0.0001, OR 0.72, 95% CI 0.62-0.83) within the overall population. Additionally, their subgroup analysis revealed that the -308 G/A polymorphism was associated with the risk of cervical cancer in both Asian and Caucasian women [72]. In 2019, Farbod et al. conducted a meta-analysis based on 20 studies involving 4,780 cases and 4,620 controls, which showed that this polymorphism was significantly linked to an increased risk of cervical cancer (A vs. G: OR 1.277; 95% CI 1.104-1.477; P = 0.001; AA vs. GG: OR 1.333; 95% CI 1.062-1.674; P = 0.013; AG vs. GG: OR 1.307; 95% CI 1.064-1.605; P = 0.011; and AA + AG vs. GG: OR 1.324; 95% CI 1.104-1.587; P = 0.002) within the overall population [60]. Cai et al., in their meta-analysis of 19 studies, discovered a significant association between the TNF-α rs1800629 polymorphism and the risk of cervical cancer [73]. Furthermore, in another meta-analysis, Jin et al. found that TNF-α rs1800629 may confer susceptibility to cervical cancer in an ethnicity-specific manner [74]. However, their meta-analyses erroneously did not include all eligible and published studies.

The present meta-analysis was conducted using comprehensive and more stringent search criteria and newly published studies on the polymorphism rs1800629 of TNF-α in relation to the risk of cervical cancer, resulting in more dependable and precise findings. Nevertheless, there were certain limitations associated with this meta-analysis that need to be addressed in future studies. Firstly, we only included eligible articles that had been previously published, which implies that some unpublished studies may have been overlooked, leading to an inevitable publication bias. Secondly, since we only retrieved studies from popular English and Chinese bio-databases, studies published in other languages might have been missed, potentially prejudicing the results of the meta-analysis. Thirdly, in the stratified analyses based on ethnicity, we were unable to obtain the number of included studies for mixed populations, which limited the statistical power to determine a true correlation between the polymorphism rs1800629 of TNF-α and the risk of cervical cancer in different populations. Therefore, in order to conduct a more precise analysis of this polymorphism in relation to cervical cancer, additional studies from diverse ethnicities, especially mixed populations, are necessary. Fourthly, in this meta-analysis, we did not assess the stratified analyses based on other confounding factors such as age, HPV, and lifestyle due to insufficient relevant information in the primary literature. Finally, cervical cancer is caused by interactions between genes and between genes and the environment. However, the possible effects of these interactions on the risk of cervical cancer were not taken into account due to a lack of sufficient information in the primary studies. Therefore, it is imperative to conduct further large-scale studies in different populations, with more detailed data and different environmental backgrounds, in order to validate the interactions between genes and between genes and the environment in relation to the polymorphism -308G>A of TNF-α and susceptibility to cervical cancer.

In brief, we have performed a comprehensive and systematic review of the correlation between the TNF-α rs1800629 polymorphism and the risk of developing cervical cancer. The amalgamation of these data sets has revealed a significant association between the TNF-α rs1800629 polymorphism and the risk of cervical cancer in the overall population. Moreover, this correlation has also been observed in both Caucasian and African women, thereby suggesting that these specific polymorphisms could potentially serve as predictive biomarkers for assessing the susceptibility to cervical cancer. Furthermore, subgroup analysis based on country of origin indicated a significant correlation between the TNF-α rs1800629 polymorphism and an increased risk of cervical cancer in American and Chinese women, but not in Iranian women. These compelling findings contribute to the ever-growing body of knowledge in the realm of genetic susceptibility to cervical cancer and hold immense importance for prospective research endeavors and clinical applications. However, it is essential to underscore that further investigations in the form of well-designed, large-scale studies are indispensable in order to validate and further elucidate the results obtained from our comprehensive analysis.

Author Contribution Statement

Conceptualization: Zahra Marzbanrad, Mojgan Karimi-Zarchi; Data curation: Somayeyeh Noei-Teymoordash, Maryam Motamedinasab; Formal analysis: Shahla Noori-Ardebili, Maedeh Barahman; Investigation: Maryam Motamedinasab, Sepideh Azizi, Maedeh Barahman; Methodology: Mojgan Karimi-Zarchi, Maedeh Barahman; Supervision: Mojgan Karimi-Zarchi, Zahra Marzbanrad, Kazem Aghili; Validation: Somayeyeh Noei-Teymoordash, Maryam Aghasipour; Writing – original draft: Maryam Yeganegi, Ali Masoudi; Writing – review & editing: Maryam Motamedinasab, Kamran Alijanpour, Hossein Neamatzadeh.

Acknowledgements

Ethics approval

This article does not contain any studies with human participants or animals performed by any of the authors. An ethical approval was not necessary as this study was a meta-analysis based on previous studies.

Consent to participate

Not applicable for this manuscript.

Data availability

The dataset used and/or analyzed during this study is

available from the corresponding author on a reasonable request.

Conflicts of interest

The authors declare that they have no conflict of interest.

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