

Genetic predisposition of interleukin-6 (rs1800797) polymorphism in cervical cancer: A Meta-analysis

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ABSTRACT

Background: Cervical cancer is a significant health burden, especially in less developed countries with limited access to HPV vaccines and screening. Dysregulation of immune cells, interleukin-6 (IL-6), and proinflammatory mediators have been implicated in cancer progression. SNPs in the IL-6 gene are thought to influence cervical cancer. A meta-analysis investigated the relationship between the IL-6 rs1800797 polymorphism and cervical cancer risk. **Methods:** We conducted data mining on the PubMed database to identify relevant studies meeting specific criteria, including genotype data for IL-6 rs1800797, publication between 2015 and 2023, and reporting covariate risk factors. The meta-analysis comprised six publications focusing on the polymorphism at rs1800797 in IL-6 associated with cervical cancer. **Results:** None of the five genetic models studied proved a significant link between the IL-6 rs1800797 polymorphism and cervical cancer risk. Because it included data from many ethnic groups, some racial groups may not experience the same consequences as others, based on this meta-analysis. The research revealed substantial heterogeneity. Egger's test and sensitivity analysis showed no evidence of publication bias. **Conclusion:** Based on this comprehensive meta-analysis, we find no evidence that the IL-6 rs1800797 polymorphism contributes substantially to cervical cancer risk. However, further study is needed to investigate possible connections with additional IL-6 polymorphisms and the interplay between genetic and environmental variables in the development of cervical cancer. Identifying reliable tumor markers for cancer therapy remains an important area of investigation.

Key words: Cervical cancer, Meta-analysis, Polymorphism, SNP, genetics

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INTRODUCTION

Women worldwide have cervical cancer at a rate three times greater than that of breast and colorectal cancers, with 569,000 new cases annually. It occurs in the cells of the cervix and is predominantly caused by an infection with the Human Papillomavirus (HPV), with a higher incidence rate in less developed countries, likely due to the high cost of HPV vaccines and less accessible screening¹. It has been reported that low- and middle-income countries have an 18-fold increase in deaths compared to high-income countries². The adherence of rural women to cervical cancer screening highly depends on their knowledge of the condition and the screening process. Limited awareness about the disease or misconceptions about preventative measures may hinder screening uptake³. The study examined the factors affecting rural women's commitment to cervical cancer screening in South Chennai⁴. All women need to be informed about cervical cancer and its prevention. A recent study recommends that awareness among women regarding cervical cancer and ways to prevent it should be heightened⁵. Cancer progression is often associ-

ated with the dysregulation of various immune cells; moreover, cytokines and chemokines can induce inflammation, including Interleukin-6, an essential cytokine whose dysfunction can lead to chronic inflammation, autoimmunity, and cancers⁶.

Interleukin-6 (IL-6) is a bioactive peptide located on chromosome 7 (7p21-14), with a length of 5 kb, consisting of four introns and five exons⁷. It modulates several cellular mechanisms such as cell proliferation, differentiation, immune response, invasion, metastasis, and tumorigenesis⁸. Factors such as Single Nucleotide Polymorphism (SNP) may also influence gene expressions; hence, polymorphisms in specific genotypes of IL-6 have a higher chance of developing cervical cancer⁹. The SNP is possibly due to differences in the production of cytokines in the regulatory regions, and genetic polymorphisms result from modifications in the function of proteins¹⁰. The polymorphism at the 5' flanking regions affects expressions based on the IL-6 promoter (rs1800795, rs1800796, and rs1800797)¹¹. Although several hereditary predispositions to cervical cancer have been reported, the results have been inconsistent due to varying sample

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sizes, genders, and ethnicities. Hence, a meta-analysis is conducted to determine the connection between the rs1800797 variant and cervical cancer.

METHODS

Literature Search

After data mining the PubMed database, we identified several relevant studies on cervical cancer/cervical carcinoma and genetic variations (polymorphisms/single nucleotide polymorphisms, SNP/SNV/Mutation). To be included in the meta-analysis, studies had to meet certain conditions. These included reporting covariate risk factors such as HPV status, smoking status, oral contraceptive use, age at menarche, age at menopause, age at first pregnancy, and parity. They also had to provide case-control genotype data for the polymorphic variant, complete research articles, and be published between 2015 and 2023. Only polymorphisms referred to in two or more papers were considered.

Data Extraction and Quality Assessment

Six papers were chosen for further meta-analysis, including data on various factors. When citing a study, it is essential to include critical details such as the first author's name, year of publication, median age (including standard deviation), gender distribution, smoking and HPV statuses, ages at menarche and menopause, ages at marriage and first pregnancies, number of children, use of oral contraceptives, genetic variations, and specific data on case-control groups. The selected papers specifically focused on one gene and one genetic polymorphism. The Newcastle-Ottawa Scale was created to evaluate the quality of case-control studies that are deemed acceptable¹². This scale comprises three domains: selection, exposure, and comparison, each assessed based on five parameters, including the Hardy-Weinberg equilibrium (HWE) index, the number of cases and controls, the method of association assessment, and the genotyping method. A maximum score of 8 indicates high quality in the evaluation process.

Statistical Analysis

Individual analyses were conducted for gene polymorphisms with at least two available studies, estimating Odds Ratios (OR) and their corresponding confidence intervals (CI). These were derived from the primary data obtained during the review. We estimated odds ratios (ORs) for each genetic polymorphism and conducted heterogeneity tests using Cochran's Q to assess variations within and between studies. The null

hypothesis for these tests suggests that any observed variability is due to chance alone, indicating no significant differences in associations among studies. The alternative hypothesis proposes the presence of heterogeneity in the associations between studies. To quantify the level of heterogeneity, we calculated I^2 based on Cochran's Q. The I^2 value indicates the degree of heterogeneity, with low heterogeneity (I^2 : 25-50%), moderate heterogeneity (I^2 : 50-75%), and high heterogeneity ($I^2 > 75%$)^{13,14}. If I^2 is less than 50%, we used a fixed-effects model; if I^2 is more than 50%, random effects were chosen to interpret the results. Heterogeneity indicates notable variations among the studies included in the meta-analysis. Delving deeper into the origins of this heterogeneity could offer valuable insights. Potential sources of heterogeneity may stem from differences in study design, characteristics of the study populations, or methods of measurement. Exploring these factors could elucidate why certain studies diverge in their findings and enhance the understanding of the overall results.

The Cochran's Q test was employed to determine whether to use the random or fixed-effects models for pooled odds ratio estimation for each polymorphism. The random-effects model was utilized if the two measures showed significance with a significance level (α) of 0.05 (corresponding to at least moderate I^2). If both tests were not statistically significant (equivalent to low I^2), fixed-effects models were employed. We performed sensitivity analyses on polymorphisms with more than four studies. To ensure consistency of results, this was done by removing studies iteratively and recalculating the pooled odds ratio (OR) each time. Additionally, the Egger Test was used to assess publication bias for polymorphisms with more than five studies, regardless of whether a significant association was observed^{15,16}.

The significance level for all analyses was set at 0.05, a commonly used value in the field's original studies. This choice was made to address the limitation of statistical power in the meta-analysis and minimize the risk of Type II errors. Despite this, all reported p-values are provided for transparency, allowing readers to interpret the results critically, regardless of whether the associations were significant^{17,18}.

RESULTS

Study Characteristics

The study selection and assessment process were thoroughly illustrated in a PRISMA flow diagram (Figure 1); this refers to the rigorous criteria for inclusion and exclusion. Initially, overall, 541 publications

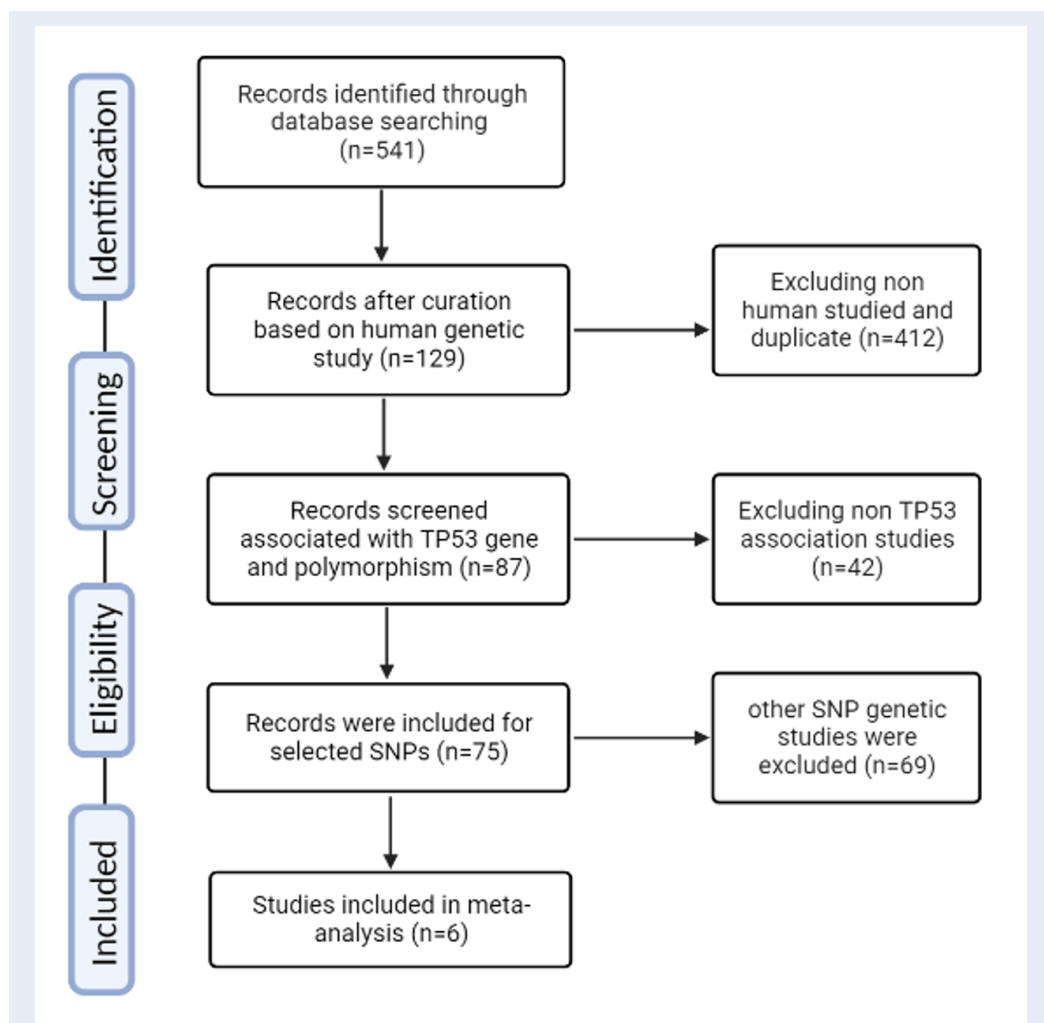


Figure 1: Flow chart of meta-analysis (PRISMA flow diagram).

Table 1: Characteristics of the study included in a meta-analysis

Study Name	Year	Country	Source of DNA	No of Cases	No of Control	NOS Score	Genotyping Method
Agne <i>et al.</i>	2021	Lithuania	Blood	89	84	6	Real-time PCR
Kushwah <i>et al.</i>	2020	India	Venous Blood	246	246	6	PCR-RFLP
Maneesh <i>et al.</i>	2015	India	Peripheral Blood	100	100	7	PCR-RFLP
Monishita <i>et al.</i>	2023	Bangladesh	Venous Blood	126	120	8	PCR-RFLP
Sabrina <i>et al.</i>	2016	Tunisia	Blood	112	164	8	Real-time PCR
Sayma <i>et al.</i>	2020	Bangladesh	Blood	252	228	7	ARMS-PCR

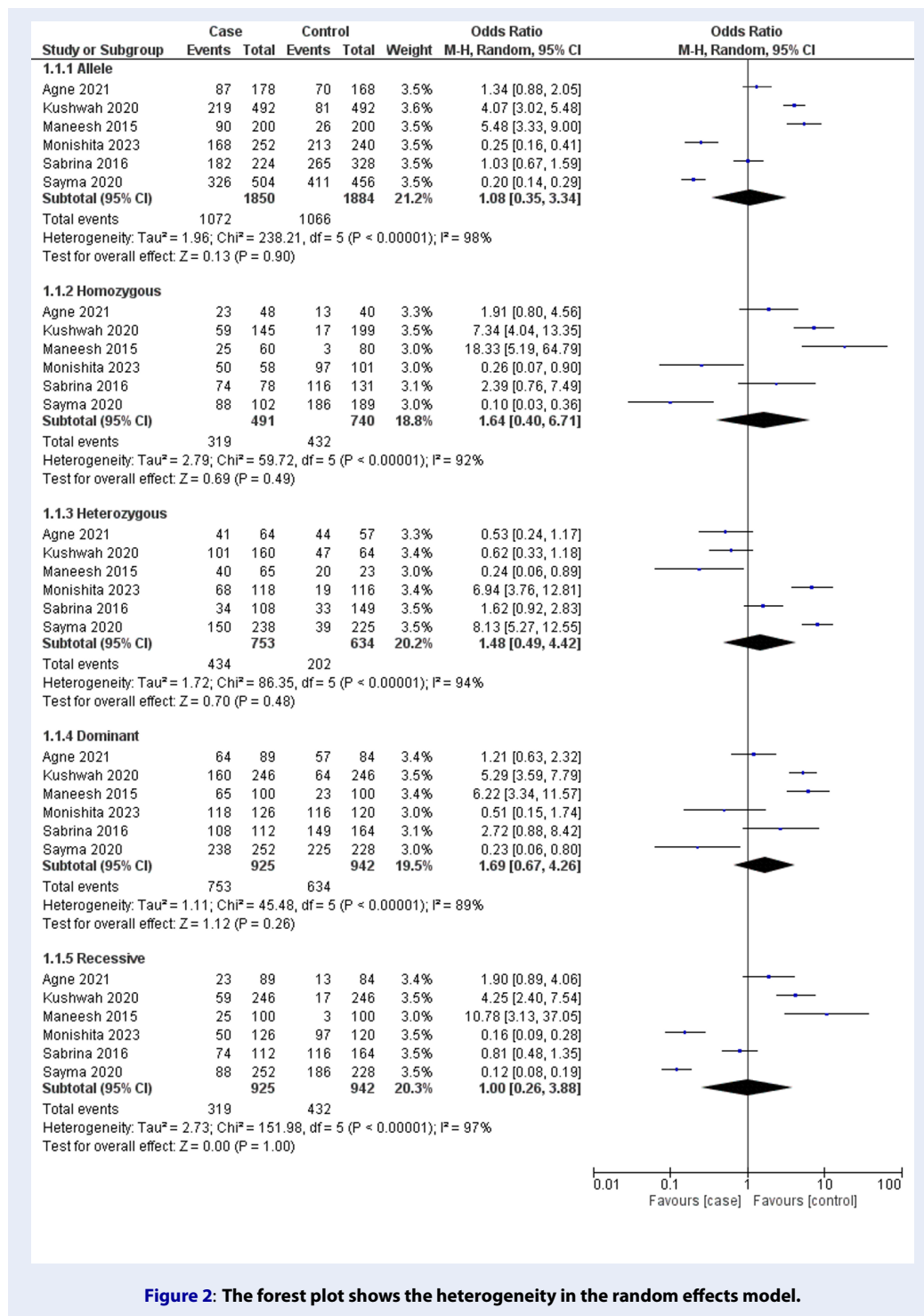


Figure 2: The forest plot shows the heterogeneity in the random effects model.

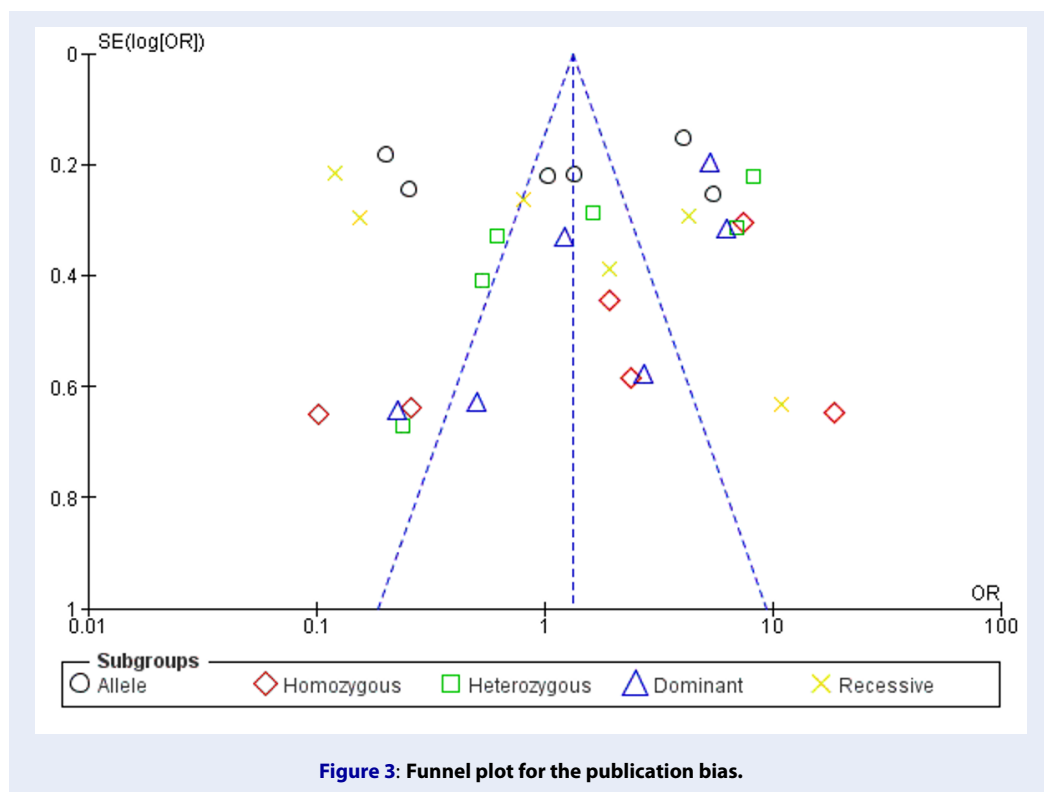


Table 2: Genotyping and allele frequency of IL-6 (rs1800797) gene polymorphism

Author	Genotype						Allele				X2	HWE
	Case			Control			Case		Control			
	GG	GA	AA	GG	GA	AA	G	A	G	A		
Agne <i>et al.</i>	25	41	23	27	44	13	98	70		238	0.5	0.47
Kushwah <i>et al.</i>	86	101	59	182	47	17	411	81	445	573	22.9	0.000002
Maneesh <i>et al.</i>	35	40	25	77	20	3	174	26	180	226	1.34	0.24
Monishita <i>et al.</i>	8	68	50	4	19	97	27	213	221	453	5.14	0.02
Sabrina <i>et al.</i>	4	34	74	15	33	116	63	265	295	593	20.2	0.000007
Sayma <i>et al.</i>	14	150	88	3	39	186	45	411	417	867	0.33	0.56

were gathered and evaluated for eligibility. Afterward, the selected studies underwent thorough evaluation using the HWE and NOS scales¹⁹, which led to the inclusion of nine studies in this meta-analysis. The characteristics of each study, including their NOS scores, were presented in **Table 1**. Detailed information on the genotype distribution, allelic frequency, and HWE/Chi-square values of the selected polymorphisms was also provided in **Table 2**.

Association between IL-6 Variant and Cervical Cancer Risk

None of the five genetic models showed any significant associations. Random effects were implemented due to high heterogeneity, indicated by I^2 values greater than 50%. In the allelic model, I^2 was 98%, OR = 1.08, 95% CI [0.35-3.34], $p = 0.90$; in the homozygous model, I^2 was 92%, OR = 1.64, 95% CI [0.40-6.71], $p = 0.49$; in the heterozygous model, I^2 was 94%, OR = 1.48, 95% CI [0.49-4.42], $p = 0.48$; in the dominant model, I^2 was 89%, OR = 1.69, 95% CI [0.61-4.26], $p = 0.26$; in the recessive model, I^2 was 97%, OR = 1.00, 95% CI [0.26-3.88], $p = 1.00$. Forest plots were used to display all the results obtained. A thorough analysis was conducted to determine the sensitivity of interleukin-6 (rs1800797) polymorphisms, which included the execution of Begg's funnel plot and Egger's test. The results showed no publication bias for all five genetic models, as illustrated in **Figure 2** and **Figure 3**.

DISCUSSION

Our study examined a possible relationship between cervical cancer risk and specific IL-6 rs1800797 gene variants. Our results indicate there is insufficient evidence to connect the IL-6 rs1800797 polymorphism to an elevated risk of cervical cancer. Zidi's research on the Tunisian population, however, yielded opposite results. There was no discernible variation in the genotype distribution of IL-6 SNPs, including IL-6 rs1800797, between the cervical cancer cases and the control groups. The researchers concluded that more study is required to establish if these genetic variations are indeed related to cervical cancer²⁰. Contrary to our results, Shi's analysis showed that the IL-6 rs1800797 polymorphism is associated with a greater prevalence of cervical cancer in the Chinese population²¹.

According to Gupta *et al.*, individuals who have the IL-6-597A/G 597 G allele had up to a 6.2 times increased chance of developing cervical cancer ($p <$

0.001)²². However, the quality of the data and our capacity to evaluate the relationships between these genetic changes and cervical cancer susceptibility may be constrained by the paucity of studies and the small sample sizes. The existence of ethnically diverse groups may factor into the variations in findings across research. Our research found no statistically significant link between the IL-6 rs1800797 polymorphism and vulnerability to cervical cancer, in contrast to the results of Gupta *et al.* and Shi *et al.*

There is no evidence that the genotype and allele frequencies of the IL-6 rs1800797 gene polymorphism influence tumor growth in patients with cervical cancer. However, confirming any links has proven difficult in further studies. Results from Peng's research indicate that rs1800797 is more closely related to cancer risk in Caucasians than in Asians. Furthermore, IL-6 promoter polymorphisms are closely linked to cancer prognosis. These encouraging results imply that IL-6 promoters, particularly rs1800795 and rs1800797, might be beneficial as tumor indicators in cancer treatment²³.

In the past, studies analyzing individual cases (as opposed to large groups) found no significant connection between the IL-6 rs1800797 polymorphism and the likelihood of developing cancer²⁴. However, a recent study showed a meaningful relationship—not just a correlation—between this genetic variation and an increased risk of cervical cancer. Furthermore, there is a strong connection between the rs1800797 polymorphism and a higher cancer risk among African ethnic groups. The results of a previous meta-analysis examined each subgroup analysis finding by ethnicity²⁵. Using meta-analyses is a great way to gain a more thorough and reliable understanding of how a genetic variant (rs1800797) relates to disease. With the small sample sizes in this study, these analyses can uncover potential genetic predispositions or correlations that may not have been noticeable otherwise. However, it's essential to confirm these discoveries and conduct additional research to explore the molecular pathways involved in this relationship. Our investigation did not examine how hereditary and environmental variables combine to cause cervical cancer.

Limitations of the study include the relatively small sample size and the lack of ethnic diversity among the included studies, which potentially limits the generalizability of the findings beyond the populations studied. Despite efforts to assess publication bias and heterogeneity, these factors could still influence the reliability of the pooled estimates. Additionally, variations in the quality of included studies, potential confounding variables not accounted for, and incomplete

reporting of crucial data could introduce biases and affect the robustness of the results. Future research should aim for larger, more diverse samples, prioritize high-quality studies with comprehensive reporting, and consider potential confounders to strengthen the evidence base and provide more reliable insights into the relationship between the IL-6 rs1800797 variant and cervical cancer risk.

CONCLUSIONS

The research investigated the relationship between the IL-6 rs1800797 variant and the risk of developing cervical cancer. According to the findings, the IL-6 rs1800797 variant may not play a significant role in the risk of cervical cancer. However, larger sample sizes and participants from diverse ethnic origins are needed to corroborate these findings. Furthermore, studying the combination of genetic and environmental variables in the development of cervical cancer might reveal more information about the disease's underlying processes.

In addition to exploring genetic factors like the IL-6 rs1800797 variant, future research on cervical cancer development should also investigate potential environmental factors that may interact with genetic predispositions. Environmental factors such as lifestyle choices, exposure to certain chemicals or toxins, socioeconomic status, and access to healthcare services could play a significant role in cervical cancer risk, especially in conjunction with genetic variations. For instance, studies could examine how factors like smoking, diet, reproductive history, and HPV infection interact with genetic polymorphisms like IL-6 rs1800797 to influence cervical cancer susceptibility. Understanding these interactions could provide valuable insights into the underlying mechanisms of cervical cancer development and help identify high-risk populations for targeted interventions and preventive strategies. Moreover, investigating gene-environment interactions in cervical cancer could lead to the development of personalized prevention and treatment approaches. By identifying individuals who are genetically predisposed to cervical cancer and understanding how their genetic makeup interacts with environmental factors, healthcare providers can offer tailored screening protocols, lifestyle interventions, and therapeutic strategies to reduce cancer risk and improve outcomes. In conclusion, while the current study found no significant association between the IL-6 rs1800797 variant and cervical cancer risk, further research into the interplay between genetic and environmental factors is warranted. By elucidating these complex interactions, we can enhance our

understanding of cervical cancer etiology and pave the way for more effective prevention and treatment strategies in the future.

ABBREVIATIONS

CI: Confidence Interval, **HPV:** *Human Papillomavirus*, **HWE:** Hardy-Weinberg Equilibrium, **IL-6:** Interleukin-6, **NOS:** Newcastle-Ottawa Scale, **OR:** Odds Ratio, **PRISMA:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses, **SNP:** Single Nucleotide Polymorphism, **SNV:** Single Nucleotide Variation

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AUTHOR'S CONTRIBUTIONS

AGP, IBK and RV has collected the data and written the contents of this manuscript IBK edited the figures and tables of this manuscript RV designed the study, corrected and approved the manuscript for submission. All authors read and approved the final manuscript.

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Not Applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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