



Serum IL-10 and TGF- β Levels in HPV Infection and HPV-Associated Cervical Cancer: A Case–Control Study

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Abstract

Cervical cancer remains a major global health burden, with persistent infection by high-risk human papillomavirus (HPV) being the principal etiological factor in cervical carcinogenesis. Immune evasion plays a critical role in HPV persistence and disease progression, particularly through the dysregulation of immunoregulatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β). This case–control study aimed to evaluate serum IL-10 and TGF- β levels in HPV-infected women and patients with HPV-associated cervical cancer compared with healthy controls.

A total of 120 women aged 20–60 years were enrolled and divided into three age-matched groups: healthy controls (n = 40), HPV-infected women without cervical cancer (n = 40), and patients with HPV-associated cervical cancer (n = 40). Serum concentrations of IL-10 and TGF- β were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using SPSS version 25, and differences among groups were assessed using one-way analysis of variance followed by post-hoc comparisons, with statistical significance set at $p < 0.05$.

Serum IL-10 levels showed a significant progressive increase across the study groups, rising from 3.00 ± 0.18 pg/mL in healthy controls to 9.10 ± 0.31 pg/mL in HPV-infected women and 24.70 ± 0.75 pg/mL in cervical cancer patients. Similarly, serum TGF- β levels were significantly elevated in HPV-infected women compared with controls and reached the highest levels in cervical cancer patients, with mean concentrations of 31.36 ± 8.50 , 58.66 ± 12.52 , and 103.35 ± 18.33 pg/mL, respectively. These findings indicate a stepwise shift toward an immunosuppressive cytokine profile during HPV infection and malignant transformation.

In conclusion, elevated serum IL-10 and TGF- β levels may reflect immune dysregulation associated with HPV persistence and cervical cancer progression. These cytokines may serve as supportive immunological indicators for understanding HPV-associated immune evasion and cervical carcinogenesis; however, further studies incorporating HPV genotyping, viral load assessment, tumor staging, and tissue-based immune profiling are recommended to confirm their predictive and mechanistic significance.

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Keywords: HPV, cervical cancer, IL-10, TGF- β , immune evasion, cytokines, immunoregulation

Introduction

Cervical cancer remains a major global public health challenge and is one of the leading causes of cancer-related morbidity and mortality among women worldwide. According to recent global cancer statistics, cervical cancer ranks as the fourth most frequently diagnosed cancer and the fourth leading cause of cancer-related deaths among women, particularly in low- and middle-income countries where access to screening and vaccination programs remains limited ^[1, 2].

Human Papillomavirus (HPV) is recognized as the primary etiological agent of cervical cancer and represents one of the most prevalent sexually transmitted viral infections worldwide. Although the majority of HPV infections are transient and are effectively cleared by the host immune system within one to two years, approximately 10% of infected individuals develop persistent infections that may progress to cervical intraepithelial neoplasia and ultimately invasive cervical cancer [3]. Persistent infection with high-risk HPV genotypes is considered a prerequisite for cervical carcinogenesis, highlighting the importance of understanding the mechanisms that enable the virus to evade host immune surveillance.

The oncogenic potential of HPV is primarily attributed to the viral proteins E6 and E7. These proteins interfere with key cellular regulatory pathways by promoting degradation of the tumor suppressor protein p53 and inactivating the retinoblastoma protein (pRb), respectively. Consequently, infected cells acquire enhanced proliferative capacity, genomic instability, and increased susceptibility to malignant transformation [4]. Beyond their oncogenic functions, E6 and E7 proteins also contribute significantly to the establishment of an immunosuppressive microenvironment that facilitates viral persistence and disease progression.

Successful clearance of HPV infection relies predominantly on an effective cell-mediated immune response involving T-helper type 1 (Th1) lymphocytes, cytotoxic CD8+ T cells, and natural killer (NK) cells. However, HPV has evolved multiple immune evasion mechanisms that suppress antiviral immunity and promote long-term survival of infected cells. Among these mechanisms, dysregulation of immunoregulatory cytokines, particularly Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF- β), plays a central role in establishing local immune tolerance and facilitating viral persistence [5].

Under physiological conditions, IL-10 and TGF- β are essential anti-inflammatory cytokines that maintain immune homeostasis and prevent excessive inflammatory responses. Nevertheless, HPV exploits these regulatory pathways to create an immunosuppressive tumor microenvironment favorable for viral survival. Previous studies have demonstrated that HPV oncogenic proteins can enhance the transcription and secretion of IL-10 and TGF- β within infected cervical tissues, resulting in progressive suppression of antiviral immune responses and promotion of persistent infection [3].

Transforming Growth Factor-beta (TGF- β) exerts profound immunosuppressive effects through inhibition of T-cell proliferation, suppression of NK-cell cytotoxicity, and promotion of regulatory T-cell (Treg) differentiation. Elevated TGF- β levels have also been implicated in epithelial-mesenchymal transition (EMT), a crucial process associated with tumor invasion, metastasis, and progression from precancerous lesions to invasive cervical carcinoma [6, 7]. Furthermore, TGF- β -mediated expansion of Tregs reinforces local immune suppression through continuous production of additional immunoregulatory cytokines, thereby sustaining a permissive environment for HPV persistence and tumor progression [8].

Similarly, IL-10 plays a pivotal role in suppressing antiviral immunity by inhibiting macrophage activation, reducing pro-inflammatory cytokine production, and impairing Th1-

mediated immune responses. Activation of the IL-10/STAT3 signaling pathway suppresses IL-12 production and limits differentiation of protective antiviral T-cell responses [9]. In addition, IL-10 reduces the concentration of major histocompatibility complex class I (MHC-I) molecules, impairing antigen presentation and facilitating immune escape from cytotoxic T lymphocytes [10]. Elevated IL-10 levels have consistently been associated with HPV persistence and progression toward cervical malignancy [11]. Accumulating evidence indicates that IL-10 and TGF- β may act synergistically to suppress both innate and adaptive immune responses. Elevated levels of these cytokines have been associated with reduced expression of activating receptors such as NKG2D on NK cells, diminished cytotoxic activity, impaired antiviral responses, and enhanced viral persistence [12]. This cytokine imbalance reflects dysregulated immunomodulatory pathways that normally maintain immune homeostasis but, when exploited by persistent viral infections, may promote immune suppression, chronic inflammation, and disease progression. Therefore, the balance between pro-inflammatory and immunosuppressive cytokines may provide useful insight into HPV-associated cervical carcinogenesis and may serve as a supportive immunological indicator for monitoring disease progression [13, 14].

Despite significant advances in understanding HPV-induced immune dysregulation, data regarding the immunological contribution of IL-10 and TGF- β among Iraqi women with HPV infection and cervical cancer remain limited. Moreover, the association between circulating levels of these cytokines and disease progression has not been adequately characterized in local populations. Therefore, evaluating these biomarkers may provide valuable insights into the mechanisms underlying HPV persistence and cervical carcinogenesis.

This study aimed to assess serum IL-10 and TGF- β levels in women with high-risk HPV infection and HPV-associated cervical cancer compared with healthy controls, and to evaluate their potential association with HPV-related immune dysregulation and cervical carcinogenesis.

Materials and Methods

Study Design

This case-control study was conducted at Al-Sadr Teaching Medical City, Najaf, Iraq. The study was designed to evaluate serum levels of the immunoregulatory cytokines Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF- β) among women with Human Papillomavirus (HPV) infection and HPV-associated cervical cancer compared with healthy controls. Participants were classified into three age-matched groups: healthy controls, HPV-infected women without cervical cancer, and patients with HPV-associated cervical cancer.

Study Population

A total of 120 women aged 20–60 years were enrolled in this study. Samples were collected between January 2024 and September 2025. Participants were categorized into three age-matched groups: healthy controls (n = 40), HPV-infected women without cervical cancer (n = 40), and women diagnosed with HPV-associated cervical cancer (n = 40). The control group consisted of apparently healthy women with no

clinical or laboratory evidence of HPV infection, inflammatory diseases, autoimmune disorders, chronic systemic illnesses, or malignancy. Age matching was performed across the three groups to minimize the potential confounding effect of age on serum cytokine levels.

Diagnosis of HPV Infection and Cervical Cancer

Molecular detection of high-risk HPV DNA was performed on cervical swab specimens using conventional polymerase chain reaction (PCR). The assay targeted HPV-16, HPV-18, and other oncogenic high-risk HPV genotypes according to the manufacturer's genotyping panel. Samples showing HPV-specific amplification bands were considered positive for high-risk HPV infection.

Inclusion and Exclusion Criteria

Eligible participants were women aged 20–60 years who provided written informed consent and fulfilled the diagnostic criteria for their assigned study group. HPV-infected women were included if they had confirmed HPV infection without cervical cancer, while cervical cancer patients were included if their diagnosis was histopathologically confirmed and associated with HPV infection.

Participants were excluded if they had evidence of active co-infections, including viral, bacterial, or parasitic infections other than HPV, chronic inflammatory diseases, autoimmune disorders, endocrine disorders, or systemic diseases known to affect immune responses. Women receiving immunosuppressive, corticosteroid, or anti-inflammatory medications were also excluded. Pregnant women and patients with other malignancies, except cervical cancer in the cancer group, were excluded from the study.

Measurement of Immunological Biomarkers

Serum concentrations of Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF- β) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits obtained from Elabscience Biotechnology Inc. (Wuhan, China), following the manufacturer's instructions. All serum samples were analyzed in duplicate to ensure analytical accuracy and reproducibility. Absorbance

was measured using a calibrated microplate reader, and cytokine concentrations were calculated from standard calibration curves generated for each analyte. Internal quality-control procedures were implemented throughout the assay process to maintain analytical precision and reliability. The assay characteristics, including catalog numbers, detection ranges, analytical sensitivities, and intra-assay/inter-assay coefficients of variation, were provided by the manufacturer and complied with the quality specifications recommended for research applications.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of the University of Al-Furat Al-Awsat Technical University. All research procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and its later revisions. Written informed consent was obtained from all participants before their inclusion in the study and prior to the collection of biological specimens.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0. Continuous variables were expressed as mean \pm standard deviation (SD), while categorical variables were presented as frequencies and percentages. The normality of data distribution was assessed using the Shapiro–Wilk test. Differences in serum IL-10 and TGF- β levels among the three-study groups were evaluated using one-way analysis of variance (ANOVA).

Results

The study included 120 women who were divided into three groups according to disease status: healthy controls (n = 40), HPV-infected women without cervical cancer (n = 40), and patients with HPV-associated cervical cancer (n = 40). The age distribution was comparable among the three groups. The highest proportion of participants was observed in the 36–45-year age group, followed by the 20–35-year age group, whereas the lowest proportion was recorded among women aged 46–60 years.

Table 1: Distribution of participants according to age group among the control, HPV-infected, and cervical cancer groups.

Age group	Control group (n=40)	HPV-infected group (n = 40)	Cervical cancer group (n = 40)	Total n=120
20–35 years	13 (32.5%)	12 (30.0%)	13 (32.5%)	38 (31.7%)
36–45 years	19 (47.5%)	17 (42.5%)	18 (45.0%)	54 (45.0%)
46–60 years	8 (20.0%)	11 (27.5%)	9 (22.5%)	28 (23.3%)
Total	40 (100%)	40 (100%)	40 (100%)	120 (100%)

Table 2 shows a significant increase in serum IL-10 and TGF- β levels among the study groups. Both biomarkers were lowest in the control group, increased in HPV-infected women, and reached their highest levels in patients with HPV-associated cervical cancer. One-way ANOVA revealed highly significant differences among the three groups for IL-10 and TGF- β ($p < 0.001$). Tukey's post-hoc test confirmed

significant differences between all pairwise comparisons. These findings suggest that elevated IL-10 and TGF- β levels may be associated with HPV infection and cervical cancer progression, possibly reflecting an immunosuppressive microenvironment that facilitates viral persistence and tumor development.

Table 2: Comparison of serum IL-10 and TGF- β levels among the study groups

Biomarker	Control group (n = 40)	HPV-infected group (n = 40)	Cervical cancer group (n = 40)	p-value
IL-10 (pg/mL)	3.00 \pm 0.18	9.10 \pm 0.31	24.70 \pm 0.75	< 0.001
TGF- β (pg/mL)	31.36 \pm 8.50	58.66 \pm 12.52	103.35 \pm 18.33	< 0.001

Note: Data are presented as mean \pm standard deviation. Comparisons among the three groups were performed using one-way analysis of variance (ANOVA), A p-value < 0.05 was considered statistically significant.

Serum IL-10 Levels

Serum IL-10 levels differed significantly among the three study groups. The lowest mean IL-10 concentration was observed in the healthy control group, while higher levels were detected in HPV-infected women, and the highest levels were recorded among patients with HPV-associated cervical cancer. The mean serum IL-10 level was 3.00 \pm 0.18 pg/mL in controls, 9.10 \pm 0.31 pg/mL in HPV-infected women, and 24.70 \pm 0.75 pg/mL in cervical cancer patients. One-way

ANOVA demonstrated a highly significant difference among the groups, $P < 0.001$, post-hoc analysis confirmed significant pairwise differences among all groups between all pairwise comparisons: controls versus HPV-infected women, controls versus cervical cancer patients, and HPV-infected women versus cervical cancer patients. These findings indicate a progressive increase in serum IL-10 levels with HPV infection and cervical cancer progression.

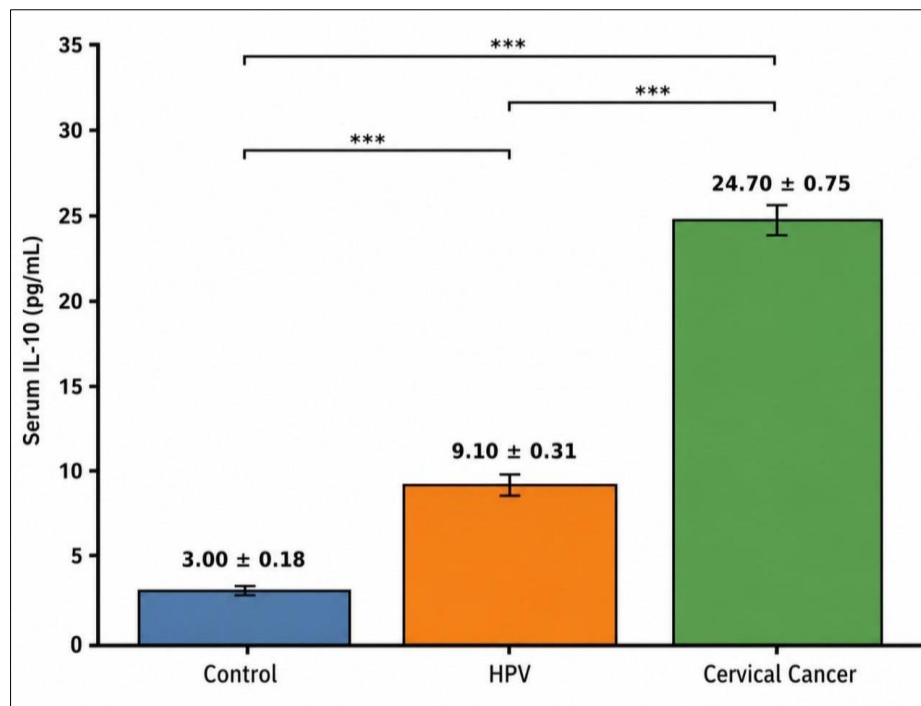


Fig 1: Comparison of serum IL-10 levels among healthy controls, HPV-infected women, and patients with HPV-associated cervical cancer. Data are presented as mean \pm SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test, *** $p < 0.001$.

Serum TGF- β Levels

Serum TGF- β levels also showed a significant progressive increase across the study groups. The mean serum TGF- β level was 31.36 \pm 8.50 pg/mL in the control group, 58.66 \pm 12.52 pg/mL in the HPV-infected group, and 103.35 \pm 18.33 pg/mL in the cervical cancer group. One-way ANOVA revealed a highly significant difference among the groups,

analysis showed that TGF- β levels were significantly higher in HPV-infected women than in controls, significantly higher in cervical cancer patients than in controls, and significantly higher in cervical cancer patients than in HPV-infected women. These results suggest that increased serum TGF- β levels are associated with HPV persistence and malignant transformation.

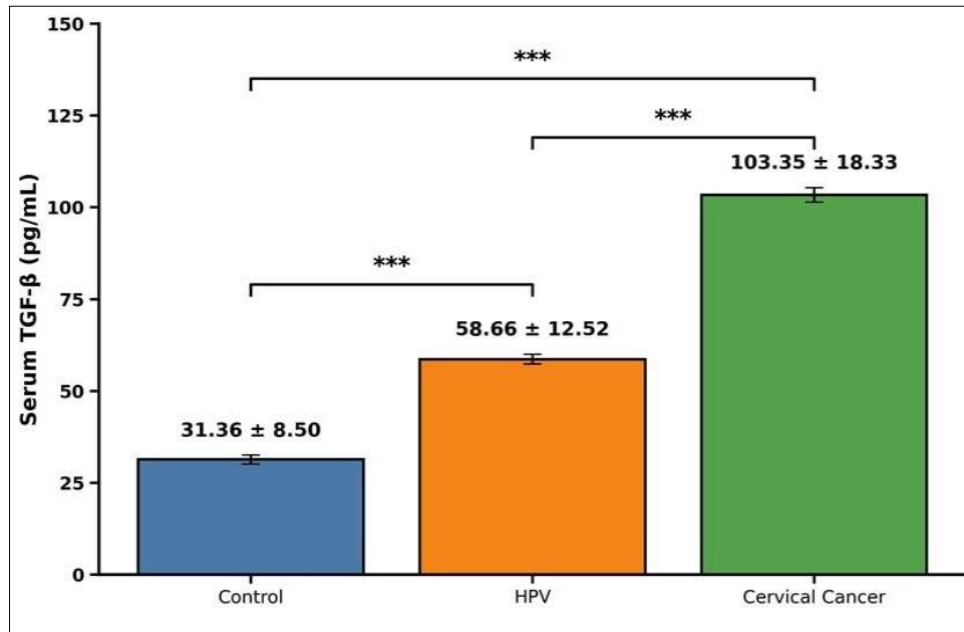


Fig 2: Comparison of serum TGF- β levels among healthy controls, HPV-infected women, and patients with HPV-associated cervical cancer. Data are presented as mean \pm SD. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test; *** $p < 0.001$

Discussion

The present study demonstrated a significant progressive increase in serum IL-10 and TGF- β levels across the study groups, with the lowest concentrations observed in healthy controls, intermediate levels in HPV-infected women, and the highest levels in patients with HPV-associated cervical cancer. This stepwise elevation suggests that HPV infection and cervical malignant transformation are associated with a shift toward an immunosuppressive cytokine profile. The comparable age distribution among the groups supports the interpretation that the observed differences in cytokine levels are more likely related to disease status rather than age-related variation in immune response.

The marked increase in serum IL-10 among HPV-infected women and its further elevation in cervical cancer patients may reflect suppression of antiviral and antitumor immune responses. IL-10 is a key immunoregulatory cytokine that can inhibit Th1-mediated immunity, reduce pro-inflammatory cytokine production, impair dendritic cell maturation, and weaken antigen presentation. These effects may decrease the efficiency of cytotoxic T-cell responses against HPV-infected epithelial cells and contribute to viral persistence. The present findings are consistent with previous studies reporting increased IL-10 levels in high-risk HPV infection and cervical lesion progression, supporting the role of IL-10 as an important mediator of immune regulation in HPV-associated cervical disease [14, 15].

A possible explanation for the progressive increase in IL-10 is the interaction between high-risk HPV oncogenic proteins and host immune-regulatory pathways. HPV E6 and E7 proteins are well known for their roles in disrupting p53 and pRb signaling; however, they may also influence immune escape by modulating cytokine production, antigen-processing mechanisms, and local inflammatory responses. In this context, elevated IL-10 may contribute to the creation of a permissive immune microenvironment in which HPV-infected cells become less effectively recognized and eliminated by host immune surveillance [16, 17].

Similarly, serum TGF- β levels were significantly higher in

HPV-infected women and reached their maximum levels in patients with cervical cancer. TGF- β has a complex role in carcinogenesis. In normal epithelial cells, it may act as a growth-inhibitory cytokine, whereas in advanced tumor settings, cancer cells may exploit TGF- β signaling to promote immune tolerance, tumor progression, angiogenesis, invasion, and epithelial-mesenchymal transition. Therefore, the elevated TGF- β levels observed in the cervical cancer group may reflect not only immune suppression but also tumor microenvironment remodeling and increased malignant potential [18, 19].

The immunological relevance of TGF- β is further supported by its ability to promote regulatory T-cell differentiation and suppress the cytotoxic activity of natural killer cells and CD8+ T lymphocytes. In cervical cancer, increased TGF- β activity may reduce antitumor immune surveillance by enhancing regulatory immune pathways and limiting effective cellular immune responses. This mechanism may partly explain the association between higher TGF- β levels and progression from HPV infection to cervical malignancy [20, 21].

The combined elevation of IL-10 and TGF- β suggests that these cytokines may act in a coordinated manner during HPV-associated cervical carcinogenesis. IL-10 primarily suppresses antigen presentation and Th1-mediated antiviral immunity, whereas TGF- β promotes immune tolerance, regulatory T-cell activity, NK-cell inhibition, and tumor-promoting stromal changes. Together, these effects may contribute to a gradual transition from protective cellular immunity toward a more immunosuppressive immune profile that favors HPV persistence and cervical cancer progression [15, 20, 22].

From a clinical perspective, the present findings suggest that serum IL-10 and TGF- β may serve as supportive immunological indicators of immune dysregulation in HPV-associated cervical disease. However, these cytokines should not be interpreted as standalone diagnostic biomarkers. Their clinical value would be stronger if assessed together with HPV genotyping, viral load, cytological findings,

histopathological grading, tumor staging, and additional immune markers such as IFN- γ , IL-6, IL-17, PD-1/PD-L1, and regulatory T-cell markers. Such combined immune profiling may improve the understanding of HPV persistence and the progression of cervical lesions [14, 21, 23].

Although the present study focuses on HPV-associated cervical disease, immune dysregulation caused by persistent viral infection is a broader biological phenomenon. Other chronic viral infections, including HIV, also illustrate how long-term viral activity can disturb host immune regulation and weaken antiviral immune responses; however, the mechanisms, target cells, and clinical consequences differ substantially from those observed in HPV-associated cervical carcinogenesis [24, 25].

Despite the significant differences observed among the study groups, the findings should be interpreted with caution. The case-control design allows the identification of associations but does not establish a causal relationship between cytokine elevation and disease progression. In addition, serum cytokine levels may not fully reflect local immune activity within cervical tissues. Future studies with larger sample sizes, longitudinal follow-up, HPV genotyping, viral load assessment, tumor staging, and tissue-based immune profiling are recommended to clarify the predictive and mechanistic significance of IL-10 and TGF- β in HPV persistence and cervical cancer progression.

Conclusion

The progressive elevation of IL-10 and TGF- β from healthy controls to HPV-infected women and cervical cancer patients supports their potential involvement in HPV-associated immune evasion and cervical carcinogenesis. IL-10 appears to contribute mainly to the suppression of antiviral cellular immunity, while TGF- β may promote both immune tolerance and tumor progression. Together, these cytokines may represent important components of the immunosuppressive network that facilitates HPV persistence and progression toward cervical malignancy.

Limitations

Although the present study provides important evidence regarding the association of IL-10 and TGF- β with HPV-associated immune evasion and cervical carcinogenesis, some limitations should be acknowledged. First, the case-control design allows identification of significant associations but does not confirm a causal relationship between cytokine elevation and disease progression. Second, the study measured serum cytokine levels while local cytokine concentration in cervical tissues may provide more direct insight into the tumor microenvironment. Third, HPV genotypes, viral load, histopathological grade, and tumor stage were not fully analyzed in relation to IL-10 and TGF- β levels. Therefore, future longitudinal studies with larger sample sizes, cervical tissue analysis, and detailed HPV genotyping are recommended to better clarify the predictive and mechanistic roles of these cytokines in HPV persistence and cervical cancer progression.

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