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Association of HPV viral load, estrogen receptor α signaling, and inflammatory serum biomarkers with cervical cancer progression

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The persistence of HPV is a high-risk factor of cervical cancer development, although the development of the disease is highly dependent on estrogen receptor signaling and HPV-associated serum biomarkers that have a synergistic effect in promoting the development of malignancy. The aim of the study is examine the relationship between HPV viral load, estrogen receptor expression, and the presence of serum biomarkers and their interactive effects in the development of cervical cancer. The case control study was carried out in one of the tertiary teaching hospitals in Iraq in the period between January 2024 and January 2025 involving 100 women diagnosed with cervical cancer via histopathology and 50 age-matched healthy women as controls. ELISA and immunohistochemistry methods were used to measure serum estradiol, CA-125, IL-6, TNF-α and CRP, and high-risk HPV viral load was measured using the qPCR, after obtaining ethical approval. The findings showed that there is similarity in the age distribution of the cervical cancer patients and the control with body mass index and parity being significantly higher in the former. There were significant differences in the HPV viral load and ER of high-grade cases as compared to low-grade. Patients especially with high viral load had high levels of serum estradiol, CA-125, IL-6, TNF-α, and CRP. Correlation analysis showed that there were strong positive links between the HPV load, hormonal activity, the presence of inflammatory biomarkers, and the aggressiveness of the tumors, demonstrating the combined effect of all the factors in cervical cancer development. The interplay between increased HPV viral load and estrogen receptor signaling and general systemic inflammation leads to the cervical cancer progression. High hormonal and inflammatory biomarkers probably encourage tumor growth and aggressiveness through the effects of supporting viral persistence, dysregulation of the immune system, and oncogenic pathways that depend on estrogen.

Keywords: cervical cancer; human papillomavirus; estrogen receptor alpha; estradiol; inflammatory cytokines; CA-125.

Introduction

Cervical cancer is a significant worldwide health issue, especially in the low and middle-income nations, where it is one of the most prevalent causes of morbid and deadly cancer-related diseases in women (Reza et al., 2024). Although there is progress in screening tests and vaccination policies, an impressive percentage of cases are diagnosed at late stages and thus there is a need to gain a better insight on the molecular and hormonal events that fuel the development of the disease (Singh et al., 2023). There is convincing evidence that persistent infection of high-risk human papillomavirus (HPV) genotypes is the key etiological variable in cervical carcinogenesis; nevertheless, it has not been found that HPV infection is the sole determinant of the broad variation in disease manifestation in women who are infected. This inconsistency has indicated that there exist other host related factors that are important in the control of viral persistence, oncogenic transformation and tumor progression (Huang et al., 2022).

The parameter of HPV viral load has become a significant parameter that is used to reflect the biological activity of the virus and its interaction with the host cells (Mir et al., 2023). A number of studies have proven that increased HPV viral loads are linked to increased risk of high-grade cervical intraepithelial neoplasia and invasive cervical cancer. High viral load might augment the viral oncoproteins, including E6 and E7, disruptive to vital tumor suppressor pathways, including p53 and retinoblastoma, and so stimulate genomic instability and unregulated cell growth. However, the prognostic importance of HPV viral load is debatable because its effect is potentially affected by the host immune response, hormonal environment, and molecular features of the cervical mucous membrane (Zhou et al., 2023; Wolf et al., 2024).

Among host related factors, estrogen signaling has been attracting with increased attention in cervical cancer studies. It is already known that estrogen and its receptors, specifically estrogen receptor alpha (ER-α) are fundamental components of cell growth, differentiation, and reproductive tissue homeostasis regulation. There is experimental and clinical evidence to support the cooperation of estrogen signaling with HPV-mediated oncogenesis, which leads to the promotion of malignant transformation and disease progression. Estrogen has been indicated to support transcriptional activity of HPV oncogenes and increase a pro-tumorigenic microenvironment in cervical tissue. In addition, it has been reported that ER-alpha is expressed more frequently in cervical cancer lesions than in normal cervical epithelium and thus it serves as a potential culprit in aggressiveness and progression of tumors (Kothari, 2024).

Systematic inflammatory and tumor-related serum biomarkers have been increasingly recognized as helpful markers of disease activity and progression in cervical cancer in parallel with viral and hormonal factors. The biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and cancer antigen 125 (CA-125), indicate the presence of inflammatory reactions, immune malfunction, and presence of cancer (Georgievska et al., 2022). Chronic inflammation has been an established characteristic of cancer and it has a central role in facilitating angiogenesis, immune evasion and metastatic potential. Within the framework of HPV-related cervical cancer, the inflammatory cytokines can contribute to viral persistence, activate the oncogenic signaling pathways, and interact with the estrogen-mediated pathways, boosting the progression of the disease (Mishra et al., 2024; Farahani et al., 2025).

Although there is an increasing body of evidence showing the individual contributions of HPV viral load, estrogen receptor expression

and serum biomarkers in cervical cancer, the interaction between the two variables is not fully comprehended (Swase et al., 2025). The past studies have mostly examined these variables individually and restrict the possibility to study the complex biological interactions that regulate the development and progression of cervical cancer. An all-inclusive methodology incorporating viral, hormonal and systemic biomarkers is thus important to get better understanding of disease pathologies and identify potential predictive markers or treatment targets (Martinelli et al., 2023; Pavone et al., 2024).

The interdependence between HPV viral load and estrogen receptor signaling information is also of significance because it can be the key to the differences in tumor behavior and treatment response in patients. Additionally, an association of these parameters with circulating serum biomarkers would provide a minimal invasive method of disease surveillance and risk identification. This method can prove particularly useful in environments with limited resources, where the resources for sophisticated diagnostic tools are often limited (Laesche et al., 2022; Qi et al., 2024).

This study aims to make an addition to a more comprehensive understanding of disease development by explaining the relationships between these factors and their connection with the extent of disease. The results can provide clinically relevant information on the biological basis of HPV-mediated cervical cancer development and can be used to inform the creation of better diagnostic, prognostic, and treatment interventions.

Materials and methods

The human ethics committee was gave consent to the protocol of the study. The participants were thoroughly briefed on the aims and methods of the study and gave informed consent obtained in writing before the research commenced. The confidentiality of the participants and their data privacy were respected throughout the research according to the principles of ethical research and the Declaration of Helsinki.

The study was a case-control study performed in the period between January 2024 and January 2025 within the Oncology and Gynecology Unit of a tertiary care teaching hospital in Iraq. One hundred and fifty women were recruited, 100 patients were in the group with established histopathologically cervical cancer and 50 age-matched healthy women were controls. Patients were recruited consecutively via confirmed diagnosis and in regards to clinical staging based on the FIGO classification system. Patients identified as having newly diagnosed untreated cervical cancer and positive high-risk HPV infection aged 30 to 65 years were included in the study, and those who were pregnant, had previously received chemotherapy or radiotherapy, autoimmune disorders, chronic inflammatory diseases, hormonal therapy in the past six months, and those with malignancies were excluded. Healthy controls were sampled among women who were taking regular gynecological check-ups, whose cervical cytology was normal, and who had no history of malignancy or chronic systemic illness. 5 mL of peripheral venous blood of each sample of the participants given after informed consent was received under aseptic conditions, clotting, and centrifugation at 3000 rpm for 10 minutes to obtain serum, which was aliquoted and frozen at –80 °C until analysis. Quantified serum biomarkers, such as estradiol, CA-125, IL-6, TNF-α, and C-reactive protein (CRP) were enzyme-linked immunosorbent assay (ELISA) kits in accordance with the instructions provided by the manufacturers. Cervical tissue biopsies were carried out to confirm by histopathology and to determine the expression of estrogen receptor alpha (ER-α) in patients through immunohistochemistry. The results were reported in terms of H-scores. HPV DNA was isolated in cervical samples and the viral load was determined by real-time polymerase chain reaction (qPCR) of high-risk HPV genotypes. Every laboratory test was performed in duplicate to achieve accuracy and reproducibility.

The SPSS version 26 was used to analyze quantitative data. The variables were represented as mean plus standard deviation in the case of continuous variables and frequencies and percentages in the case of categorical variables. The analysis was done after evaluation of data normality. Normally distributed variables were analyzed using independent and paired two tails t-tests, and non normality variables and categorical variables were analyzed using Mthe ann Whitney U test, Wilcoxon signed-rank test and Chi-square test respectively. The statistically significant P-value was taken to be less than 0.05.

Results

The Table 1, shows the demographic and clinical characteristics of cervical cancer patients compared to the healthy control group. No statistically significant difference was found in mean age between the two groups (P = 0.214), indicating homogeneity in age groups. Conversely, the body mass index (BMI) in cervical cancer patients was considerably greater than those of healthy people (P = 0.041), and this fact could be taken as the evidence of the potential impact of the metabolic factors in the development of the disease. There was also a greatly superior rate of multiple births (≥3) among patients versus the control group (P = 0.018), which indicates the established relationship between multiple births and high risk of developing cervical cancer. There was no statistically significant difference of premenopausal status or postmenopausal status, or smoking status between the two groups (P > 0.05). With respect to clinical distribution, most of the patients were at an early FIGO stages (I–II) with a smaller proportion of the sample being at advanced stages (III–IV), indicating the difference in disease severity in the sample of the study.

Table 1
Demographic variables, reproductive factors and clinical staging compared between study groups (mean ± SD)

Variable	Cervical cancer patients (n = 100)	Healthy controls (n = 50)	P-value
Age, years	49.6 ± 8.7	47.9 ± 7.9	0.214
BMI, kg/m²	28.3 ± 4.6	26.9 ± 3.8	0.041
Premenopausal, n (%)	42 (42%)	24 (48%)	0.512
Postmenopausal, n (%)	58 (58%)	26 (52%)	–
Parity (≥3), n (%)	63 (63%)	21 (42%)	0.018
Smoking status, n (%)	29 (29%)	9 (18%)	0.173
FIGO stage (I–II / III–IV)	61 / 39	–	–

The Table 2, indicates that there are major statistically significant variations in the low grade and high-grade cases of cervical cancer as regards the viral load and expression of estrogen receptor in association with human papillomavirus (HPV). The viral load was significantly higher in high-grade cancers than in low-grade cancers (P < 0.001), thus showing that there was a direct relationship between high viral load and disease development. ERA estrogen receptor was also dramatically more expressed in high-grade cancers with high-percentage of estrogen receptor-positive samples than the low-grade cancers (H-score P = 0.001). These results indicate that there may be a synergistic effect between high viral load and hormonal activation in the progression of cervical cancer and the aggressiveness of the tumor.

Table 2
Association of viral burden and ERα expression with tumor grade in cervical cancer patients (mean ± SD)

Parameter	Low-grade CC (n = 48)	High-grade CC (n = 52)	P-value
HPV viral load, copies/mL	$(3.2 \pm 1.1) \times 10^5$	$(9.6 \pm 2.4) \times 10^5$	<0.001
Estrogen receptor (ERα) expression (H-score)	146.2 ± 32.5	214.7 ± 41.3	<0.001
ER-positive cases, n (%)	31 (64.6%)	45 (86.5%)	0.009

The Table 3, indicates a significant difference in the level of serum biomarkers of cervical cancer patients and the healthy control group. The levels of estradiol were also notably high in the patients (P < 0.001), indicating the potentiality of hormonal regulation in the development of the disease. The CA-125 tumor marker also expressed a significant increase in the levels between the patients and the healthy individuals (P < 0.001), which demonstrates the presence of increased tumor activity. In addition, the patients had significant changes in the levels of inflammatory cytokines IL-6 and TNF-α and C-reactive protein (CRP) (P < 0.001), which reflects the systemic in-

flammatory response related to progression of cervical cancer. The above results highlight the functional interplay between hormonal, inflammatory, and tumor markers factors in disease progression mechanisms.

Table 3
Differences in hormonal, tumor, and inflammatory biomarkers between study groups (mean ± SD)

Biomarker	Patients (n = 100)	Controls (n = 50)	P-value
Estradiol, pg/mL	78.4 ± 21.6	52.9 ± 15.3	<0.001
CA-125, U/mL	41.7 ± 18.9	17.6 ± 6.8	<0.001
IL-6, pg/mL	12.3 ± 4.8	4.1 ± 1.9	<0.001
TNF-α, pg/mL	9.8 ± 3.6	3.7 ± 1.5	<0.001
CRP, mg/L	8.9 ± 3.1	2.4 ± 1.2	<0.001

The Table 4, demonstrates statistically significant differences in the level of serum biomarkers in cervical cancer patients with low and high viral load of human papillomavirus (HPV). Estradiol levels were much more increased in the high viral load group than in the low viral load group ($P < 0.001$) and there was probably a response of the hormonal activity to the high viral load. The high level of CA-125 tumor marker ($P = 0.002$), found in the high viral load group, was an indicator of increased tumor activity with increasing viral load. In addition, the levels of the inflammatory cytokines IL-6 and TNF-α were significantly higher in the high viral load group ($P < 0.001$), which means that the inflammatory response is enhanced with the rise in viral load. These results highlight the complementary nature of high viral load, hormonal and inflammatory factors in enhancing the cervical cancer progression and the severity of the illness.

Table 4
Comparison of hormonal, tumor, and inflammatory biomarkers according to HPV viral load (mean ± SD)

Biomarker	Low HPV load (n = 46)	High HPV load (n = 54)	P-value
Estradiol, pg/mL	65.3 ± 17.4	89.2 ± 22.7	<0.001
CA-125, U/mL	34.8 ± 14.6	47.9 ± 19.3	0.002
IL-6, pg/mL	9.6 ± 3.2	14.6 ± 4.9	<0.001
TNF-α, pg/mL	7.1 ± 2.5	12.1 ± 3.8	<0.001

Correlation analysis showed that there were statistically significant positive correlations of human papillomavirus (HPV) viral load and the expression of the estrogen receptor and the biomarkers investigated. The viral load and the ER-alpha estrogen receptor expression correlated strongly ($r = 0.68$, $P < 0.001$) showing a definite interaction of the viral activity and hormonal control in cervical cancer progression. Viral load and estradiol levels were also found to be strongly positively correlated ($r = 0.61$, $P < 0.001$), which supports the contribution of the hormonal environment to the development of the viral load. Moreover, there was a strong positive correlation between ER-α expression and the tumor marker CA-125 and inflammatory cytokine IL-6, which represented the association with tumor activity and inflammatory reaction. Another positive correlation of importance was also found between viral load and CRP levels ($r = 0.46$, $P < 0.001$), which showed the contribution of systemic inflammation with the high-viral load. These findings substantiate integrated and intricate interaction of viral, hormonal and inflammatory factors in the progression mechanisms of cervical cancer.

Table 5
Pearson correlation coefficients illustrating the relationships among viral, hormonal, and inflammatory markers (mean ± SD)

Variables	Correlation coefficient (r)	P-value
HPV viral load vs ERα expression	0.68	<0.001
HPV viral load vs Estradiol	0.61	<0.001
ERα expression vs CA-125	0.54	<0.001
ERα expression vs IL-6	0.49	<0.001
HPV viral load vs CRP	0.46	<0.001

Discussion

The main aim of the current project was to clarify the interactions between HPV viral load, estrogen receptor alpha (ER-α) expression, and the selected serum biomarkers in the development of cervical cancer and to establish the interactions between these variables in displaying the severity of the disease. This paper offers a multidimensional perspective of cervical carcinogenesis, not just single-factor perspective, by combining virological, hormonal and inflammatory parameters.

The sociodemographic and clinical data provided showed that patients with cervical cancer had increased parity and body mass index (BMI) compared to the healthy controls and this is congruent to other epidemiological studies that found multiparity and obesity were associated with elevated risk of cervical cancer (Li et al., 2024). Increased BMI can have an indirect effect on tumor progression by affecting estrogen metabolism and inflammation of the body. But there was no significant difference in age distribution and menopausal status in both groups, which reduced the possibility of confounding factors and enhanced validity in further comparisons of biomarkers (Guo et al., 2023; Ghazi et al., 2025).

The most significant observation of this study was that there were high levels of HPV viral load in patients having advanced or high-grade cervical cancer, as opposed to low-grade cancer. This confirms the hypothesis that the viral load is critical in the development of the disease. The elevated HPV viral load is linked to the elevated expression of viral oncogenes, E6 and E7, inactivation of tumor suppressor proteins, p53 and Rb, and genomic instability and malignant transformation (Fobian et al., 2024). This has been documented in similar studies by Zhou et al. (2023) and Li et al. (2025), who showed that continuous high HPV viral load is associated with the severity of cervical lesion and cervical cancer risk. Conversely, there are also studies that have found weak or inconsistent associations between the viral load and the stage of the disease, which could be because of variances in the HPV genotypes, sample type, or viral integration status, which could influence the viral copy number notwithstanding the oncogenic potential (Bahadoran et al., 2025).

The other focus observation was that the expression of ER-α was significantly elevated in cervical cancer tissues particularly in patients with high HPV viral load. This result is consistent with experimental and clinical results that estrogen signaling is synergistic with HPV-induced oncogenesis (Laesche et al., 2022). It has been demonstrated that estrogen boosts the transcription of HPV oncogenes and the protumorigenic cervical microenvironment (Zhang et al., 2025). Research papers by Rani et al. (2025), showed that estrogen receptor signaling is critical to the development of cervical cancer in mouse models that are HPV transgenic. On the other hand, few studies have indicated decreased or diverged ER-α expression in cervical cancer (Hakim et al., 2025), which could be as a result of heterogeneity of tumors, discrepancies in detection procedures or the stage of the disease.

The use of serum biomarker analysis also helped to support the study purpose by showing that estradiol, CA-125, IL-6, TNF-α and CRP levels were significantly higher in cervical cancer patients than in healthy controls. These data indicate the role of systemic inflammation and hormonal imbalance in the development of the disease. High estradiol also has the potential to stimulate estrogen receptor signaling in the cervical tissues and promote HPV-driven oncogenic signaling (Ramadan et al., 2022). A CA-125 level increase despite its conventional link to ovarian cancer has been observed in progressive cervical malignancy and is an indication of tumor burden and inflammatory reactions (Ahmed et al., 2025; Kliber-Gałuszka et al., 2025).

There was a significant increase in the pro-inflammatory cytokines IL-6 and TNF-α in patients and especially those with high viral load of HPV. Chronic inflammation is known to be a typical characteristic of cancer and to stimulate angiogenesis, immune evasion, and metastatic capacity (Xiao et al., 2025). It was also demonstrated that IL-6 can activate STAT3 signaling that promotes cell survival and proliferation in tumor cells and that TNF-α can induce DNA damage and favor tumor-promoting inflammation (Borowczak et al., 2022). The findings agree with the research conducted by Borowczak et al. (2022), who found a high level of inflammatory cytokines in cervical cancer patients and their role in leading to poor outcome (Zhou et al., 2022). Nonetheless, there are some contradictory reports of small or insignificant increases in cytokines (Harsanyi et al., 2022), which may

be due to different patient groups, disease phases, or assays levels. Correlation analysis indicated that there were strong positive correlations between HPV viral load, ER-alpha expression, and inflammatory biomarkers with inflammatory pathways in cervical cancer being interrelated. These associations indicate that HPV persistence could not only contribute to the oncogene's expression, but also regulate the host hormonal and inflammatory responses to form a vicious cycle promoting the development of the disease. This composite view is useful in supporting the previous molecular studies that indicate that the evolution of cervical cancer is a complicated assembly of viral oncogenesis, endocrine signals and persistent inflammation (Porter & Marra, 2022; Pavone et al., 2024).

Conclusion

In conclusion, the study provides a solid argument that the level of HPV virus, increased ER, and tumor-associated biomarkers in serum are conjugated well among themselves, and as such, result in the development of cervical cancer. These findings highlight the potential clinical value of integrated viral, hormonal and inflammatory profiling for new risk stratification, prognosis and as well as therapeutic targeting. The opportunity to better realize the causality and improve the possibility to cure cervical cancer using the HPV-estrogen-inflammation axis justify the longitudinal and mechanistic study of the relationship between HPV and serum biomarkers in the future.

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