Volume 3, Issue 5, May 2025 ISSN (E): 2938-3765

# DIAGNOSIS AND TREATMENT OF CERVICAL DISEASES ASSOCIATED WITH HPV IN WOMEN OF REPRODUCTIVE AGE

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**Abstract**
This article is dedicated to the study of early detection and effective treatment methods for cervical diseases associated with human papillomavirus (HPV), a common and serious health threat among women of reproductive age. The research thoroughly analyzes the etiology of HPV infection, its transmission routes, and its association with cervical dysplasia and cancer. Additionally, the advantages of screening, colposcopy, cytological, and molecular diagnostic methods are reviewed. The study also highlights the importance of modern treatment approaches such as cryotherapy, LEEP, immunotherapy, and vaccination. Based on the results of the research, advanced strategies are proposed to preserve the health of women of reproductive age, with particular emphasis on preventive measures.

**Keywords**: Human papillomavirus (HPV), cervical dysplasia, cancer, screening, colposcopy, LEEP, vaccine.

## Introduction

Cervical cancer is one of the most dangerous oncological diseases among women. According to data from the World Health Organization (WHO), more than 600,000 new cases are registered worldwide each year, with HPV being the primary etiological factor. HPV is a sexually transmitted virus, and many of its types affect the genital organs and cervix. Types 16 and 18 are particularly oncogenic and can lead to the development of cervical cancer.

Among women of reproductive age, HPV infection is widespread and often asymptomatic, with the immune system eliminating the virus on its own. However, in some cases, the infection persists and leads to serious changes, including cervical dysplasia and eventually cancer. If these diseases are detected and treated early, they are not life-threatening. Therefore, early diagnosis and treatment of HPV-associated cervical diseases are of critical importance in healthcare.

The goal of this article is to explore the diagnostic and treatment methods for HPV infection. This includes HPV screening, colposcopy, cytological and molecular diagnostic techniques, as well as modern treatment approaches such as LEEP (Loop Electrosurgical Excision Procedure),



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cryotherapy, immunotherapy, and the importance of HPV vaccination. The research findings suggest effective strategies for preserving the health of women of reproductive age, with an emphasis on prevention. Papillomaviruses are small, double-stranded DNA viruses that specifically infect squamous epithelia or cells capable of squamous maturation. These viruses are strictly species-specific, meaning that human papillomaviruses (HPVs) exclusively infect humans. They exhibit remarkable tissue tropism, completing their infectious cycle only in fully differentiated squamous epithelium. Over the past 25 years, one of the most significant breakthroughs in cancer research has been the identification of persistent infection with certain HPV genotypes as the cause of cervical cancer. Comprehensive virological, molecular, clinical, and epidemiological studies have provided definitive evidence that cervical cancer results from prolonged, unresolved infection by specific HPV genotypes. Consequently, it is now understood that cervical cancer is the outcome of a viral infection. This recognition highlights vaccination as a vital strategy for the primary prevention of cancers and other diseases associated with HPV. Considering the findings of the research conducted in recent years, HPV infection may be a contributing factor in the development of many other types of cancer. The aim of this paper is to discuss the current state of knowledge about the HPV virus, present the latest discoveries in this field, and explore potential future possibilities infection, HPV related cancers, cervical cancer screening, cervical cancer treatment, advanced cervical cancer, and HPV E6 E7.

HPV-Related Cancers: Pathogenesis and Epidemiology

The most significant role in the pathogenesis of neoplastic changes resulting from HPV infections is played by the proteins E5, E6, and E7. The E5 protein, present in all types of HRHPV, except for Betapapillomaviruses, promotes cancer progression by binding to platelet growth factor receptors (PDGFR) and epidermal growth factor receptors (EGFR). The E6 protein plays a key role in inhibiting the regulation of the cell cycle, as it inactivates the p53 protein. By stimulating the Wnt/β-catenin and Notch pathways, it disrupts normal cell signaling. It also promotes cell immortality by activating telomerase. The E7 protein inhibits the action of pRb, p107, p130. As a result, the E2F factor is activated, which promotes the transition from G1 to S phase (Figure 2) . Moreover, in oncogenic HPV types, it binds to the non-receptor protein tyrosine phosphatase PTPN14, leading to its degradation, which results in inhibition of keratinocyte differentiation and their immortality. Both proteins may activate the PI3K/AKT/mTOR and JAK/STAT signaling pathways, which play a role in the pathogenesis of cancer. In particular, JAK/STAT plays an important role in the development of cervical cancer . These proteins also participate in the inhibition of the immune response. The E5 protein suppresses interferon (IFN) signaling pathway and retains MHC-I molecules in the ER and Golgi Apparatus. The E6 protein has the ability to reduce antigen presentation through a transporter associated with antigen processing complex (TAP) interference. In turn, E7 increases the population of Treg lymphocytes, thereby reducing cytotoxic T, and inhibits pyroptosis. Moreover, both proteins cause up-regulation of immune checkpoint molecules such as PD-L1.



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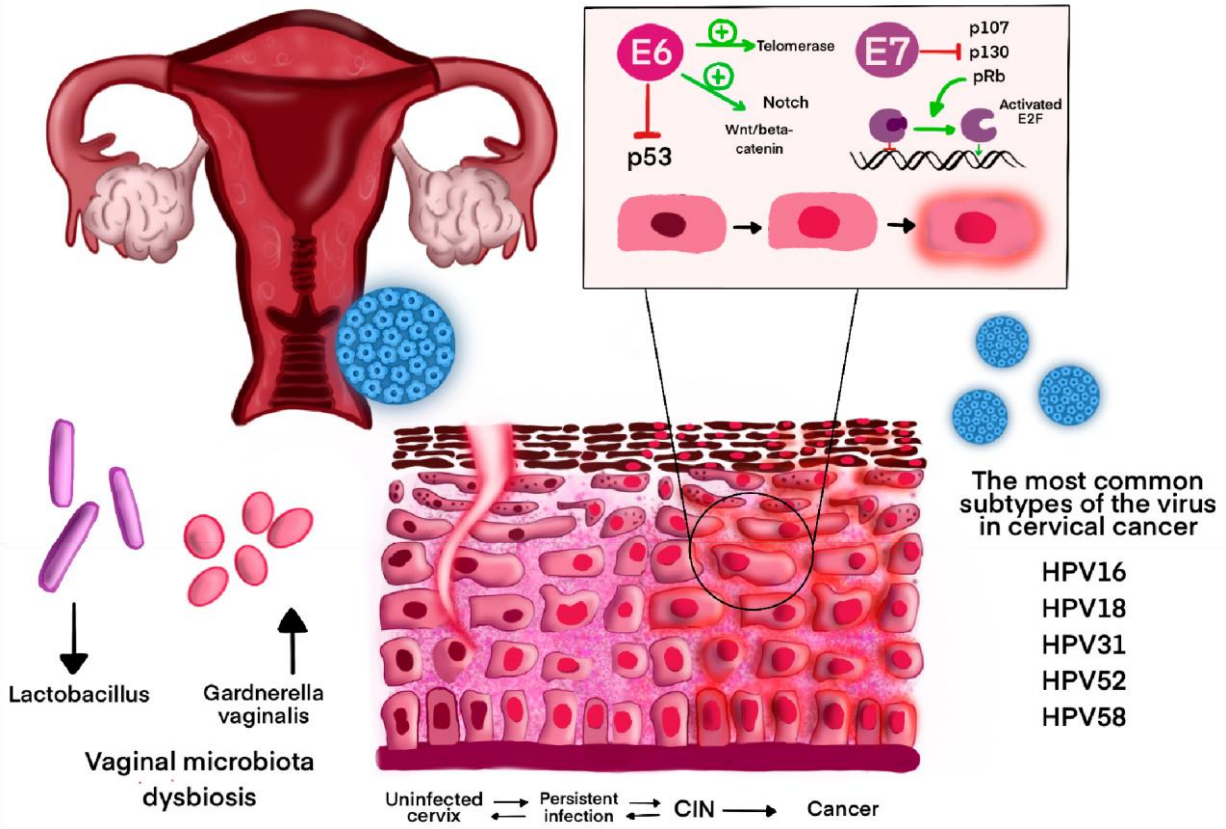


**Figure 1.** Pathogenesis of HPV-related cervical cancer. Abbreviations: CIN–cervical intraepithelial neoplasia. The graphic shows the mechanism leading from human papillomavirus (HPV) infection to the progression to cervical cancer. After infection of the epithelium, the virus can persist as a chronic infection, leading to pre-cancerous changes (CIN—cervical intraepithelial neoplasia) and then cervical cancer. The oncogenic mechanism of HPV proteins E6 and E7 is shown in the upper right corner. The E6 protein inhibits the action of the tumor suppressor p53 and activates telomerase, supporting uncontrolled cell proliferation. Additionally, it stimulates the Wnt/beta-catenin pathway and the Notch pathway, disrupting cell signaling. On the other hand, E7 deactivates proteins regulating the cell cycle (pRB, p107, p130). Deactivation of pRB protein leads to continuous activation of E2F, dysregulation of the cell cycle promoting the transition from G1 to S phase, and uncontrolled division of epithelial cells. Moreover, the graphic shows the impact of vaginal microbiota dysbiosis on HPV infection. A reduction in the number of protective *Lactobacillus* spp. and an increase in the population of *Gardnerella vaginalis* may promote chronic HPV infection and the progression to cancer. The graphic also shows the most common oncogenic HPV types associated with cervical cancer: HPV16, HPV18, HPV31, HPV52, and HPV58.

The HPV is associated with 4.5% of all cancers, 8.6% of cancers in women, and 0.8% in men. According to GLOBOCAN data, in 2022, cervical cancer (CC) occurred at a rate of 19.3 per 100,000 women and was the fourth most common cancer in both incidence and mortality in women, with an estimated 660,000 new cases and 350,000 deaths worldwide. The risk of acquiring cervical cancer is 75.4 times higher for women with chronic HR-HPV infections than for women who are HPV-negative, according to a 16-year follow-up study . HPV16 is the most common subtype of the virus in CC globally. The next positions are occupied by HPV18, HPV52, HPV31,



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and HPV58 . Chronic HR-HPV infection causes cervical illness, which in turn causes cervical cancer. Cervical lesions originate in the transformation zone (TZ), which is situated at the junction between the ectocervix and the endocervix. Low-grade squamous intraepithelial lesions (LSIL) are represented by CIN 1 and high-grade squamous intraepithelial lesions (HSIL) are represented by CIN 2 and CIN 3. The replication activity decreases as the grade of lesion increases.

Cervical cancer is not the only cancer associated with HPV infection. Vulvar cancer and vaginal cancer are associated with HPV in 70% and 75%, respectively. Moreover, HPV viruses cause about 26–30% of head and neck cancers, where the incidence of HPVrelated oropharyngeal squamous cell carcinoma (OSCCC) is about 30% (data from 2020) and is constantly increasing, especially in developed countries. In the last two decades in some European countries, the incidence has increased significantly. Women have a higher incidence of anal cancer and precancerous anal lesions than men, and 90% of these lesions are related to HPV16, 18, and 33. The incidence is particularly high in men who have sex with men (MSM), especially those with HIV. Penile cancer is related to HPV in 60% of cases. Moreover, this virus can be detected in 79.8% of cases of penile intraepithelial neoplasia (PeIN) and 90% of genital warts cases. The most frequently documented subtype was HPV16. It has been demonstrated that HR-HPV found in benign prostatic tissues immortalizes prostate cells, which could be connected to the gradual transformation of the prostate gland from a benign neoplasm to prostate cancer.

Cervical cancer is one of the most threatening oncological diseases among women. WHO reports approximately 600,000 new cases annually, with a large portion affecting women of reproductive age. Human papillomavirus (HPV) is the leading cause, especially oncogenic strains 16 and 18, which play a crucial role in the development of cervical cancer.

Pathogenesis of HPV infection: HPV is transmitted mainly through sexual contact. The virus penetrates the epithelial cells of the cervix, integrates with the DNA structure, and disrupts the normal process of cell division. This leads to dysplasia, intraepithelial neoplasia, and eventually invasive cancer. In most individuals, HPV is asymptomatic and cleared by the immune system within 1–2 years. Persistent infection, however, increases the risk of disease progression.

**Epidemiological indicators:** In Uzbekistan, recent years have seen a rise in cervical conditions such as dysplasia and cancer, particularly due to insufficient early screening, lack of preventive measures, and limited implementation of HPV vaccination. Women aged 25–45 are especially at risk.

**Diagnostic methods:** Several effective techniques are used for early detection of cervical diseases:

1. Papanicolaou (PAP) test – cytological analysis of cervical cells to detect dysplasia and precancerous changes.
2. HPV genotyping – determines the presence of the virus and identifies high-risk strains.
3. Colposcopy – magnified visual examination of the cervix to identify affected areas.
4. Biopsy – sampling of suspicious tissue areas for histological analysis.

Treatment methods: Treatment depends on the stage of disease, age, and reproductive plans of the woman. Main methods include:



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a. Cryotherapy – destruction of abnormal cells by freezing.
b. LEEP – removal of affected tissue using an electric loop.
c. Conization – excision of a cone-shaped portion of the cervix.
d. Immunotherapy – boosting the immune system to combat the virus.
e. Local treatment with antiviral and antiseptic medications.

In advanced cases, radiotherapy and chemotherapy are applied. All treatments are chosen based on individual circumstances.

Prevention and Immunization: Preventive measures are crucial in reducing HPV infection. The most effective strategy is HPV vaccination. Currently, vaccines such as Gardasil and Cervarix are recommended for girls and women aged 9 to 26. These vaccines provide immunity against the oncogenic types 16 and 18. Vaccination before the onset of sexual activity offers the best protection.

## Conclusion

Cervical diseases associated with HPV pose a serious threat to the health of women of reproductive age. However, early diagnosis, effective treatment, and broad implementation of preventive measures can prevent these conditions. Regular gynecological checkups, expanded screening programs, and the nationwide introduction of HPV vaccination are essential in safeguarding women's health.

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