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HUMAN PAPILLOMAVIRUS (HPV): CURRENT STRATEGIES FOR THE PREVENTION AND TREATMENT OF PRECANCEROUS LESIONS

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ABSTRACT

Background: Human papillomavirus (HPV) infection is the primary etiology of cervical cancer and its immediate precursors, collectively known as cervical intraepithelial neoplasia (CIN). Although primary prevention via prophylactic vaccination and secondary screening have significantly reduced incidence, cervical cancer remains a major global health burden, particularly in low- and middle-income countries. This comprehensive review evaluates the current landscape of HPV virology, pathogenesis, advanced diagnostic risk-stratification biomarkers, and evolving management paradigms.
Methods: This review synthesizes current literature regarding high-risk HPV types (predominantly HPV16 and 18), viral oncogene mechanisms (E6 and E7), multi-modal screening protocols, and therapeutic interventions ranging from standard surgical excisions to novel non-invasive modalities.
Results: While large loop excision of the transformation zone (LLETZ) remains the gold standard for high-grade CIN, its associated obstetric complications necessitate fertility-sparing alternatives. Recent advances highlight the efficacy of non-invasive modalities—including thermal ablation, photodynamic therapy (PDT), and topical immunomodulators such as imiquimod—which achieve high rates of lesion regression and viral clearance while preserving cervical structural integrity. Furthermore, diagnostic precision has been markedly improved through the integration of molecular markers (p16/Ki-67, DNA methylation signatures, and circulating microRNAs) and emerging microbiome-targeted adjunctive therapies.
Conclusions: The management of HPV-associated precancerous lesions is shifting from standardized surgical excision to a personalized, molecularly guided, and fertility-preserving paradigm. Future clinical efforts must focus on expanding global vaccine access while implementing multi-modal, minimally invasive therapeutic strategies.

KEYWORDS

Cervical Intraepithelial Neoplasia, Human Papillomavirus, Photodynamic Therapy, Cancer Preventon

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1. Introduction

Human papillomavirus (HPV) infection represents the most common sexually transmitted infection globally, with persistent infection by high-risk HPV types being a necessary cause of cervical cancer and other HPV-related malignancies (Pruski et al., 2025). Cervical cancer remains a significant global health burden, ranking as the fourth most common cancer among women with an estimated 605,000 new cases annually, yet approximately 95% of these deaths occur in low- and middle-income countries (Islam et al., 2023). The development of cervical cancer is invariably preceded by cervical intraepithelial neoplasia (CIN), a precancerous condition classified into grades 1, 2, and 3, with high-grade squamous intraepithelial lesions (HSILs) representing the immediate precursor to invasive disease (Gupta et al., 2023). Among the numerous HPV genotypes, HPV types 16 and 18 are responsible for approximately 70% of cervical cancers, while additional types including HPV31, 33, 45, 52, and 58 contribute to significant disease burden (De La Cour et al., 2019).

2. Human Papillomavirus: Virology and Pathogenesis

The central mechanism of HPV-induced neoplastic transformation involves the viral E6 and E7 oncoproteins, which interfere with critical cell cycle regulatory proteins, particularly the suppressive tumor protein p53 (p53) and the retinoblastoma protein (pRB), fundamentally disrupting cellular proliferation control (Haręża et al., 2022). These E6 and E7 proteins of high-risk HPV bind to cell cycle regulatory proteins and interfere with both G1/S and G2/M cell cycle checkpoints much more effectively than low-risk HPV types, enabling the loss of multiple cell cycle checkpoints that are crucial for host genome fidelity and potentially resulting in the accumulation of genetic abnormalities (Brenna & Syrjänen, 2003). Additionally, the E5 protein may play a significant role in tumorigenesis, contributing further to the oncogenic potential of HPV (Haręża et al., 2022). HPV infection clearly precedes the development of malignancy and is regularly associated with cervical cancer precursor lesions of all grades of squamous intraepithelial lesions (Brenna & Syrjänen, 2003).

3. HPV-Associated Precancerous Lesions

3.1 Molecular Mechanisms of Carcinogenesis

The transformation from normal cervical epithelium to precancerous lesions involves sophisticated molecular disruption (Li & Hua, 2023). HPV integrates its DNA into basal cells located at the transformation zone—the region where the epithelium transitions from columnar endocervical cells to stratified squamous epithelial cells of the ectocervix. This integration triggers production of viral oncoproteins E6 and E7, which cause dysplasia through interference with cell cycle regulation and apoptosis control (Septikasari, 2025).

The E6 and E7 proteins interfere directly with cell cycle regulation and apoptosis, consequently causing dysplasia and increasing progression to malignancy. These oncoproteins are critical for maintaining the transformed state: HPV-16 E7 demonstrates the highest potency among papillomaviral oncogenes in cervical disease development, and experimental suppression of E7 expression in HPV-positive cervical cancer cell lines inhibits their proliferative capacity. Animal model studies confirm that repressing E7 expression causes regression of high-grade cervical dysplasia and established cervical tumors, indicating persistent dependence on continuous E7 expression (Jabbar et al., 2009).

3.2 Progression from Low-Grade to High-Grade Lesions

HPV-associated precancerous lesions follow a progressive classification system (Septikasari, 2025). Cervical cancer develops through stepwise progression from low-grade lesions (LSIL/CIN 1 - cervical intraepithelial neoplasia grade 1) to high-grade lesions (HSIL/CIN 2 and 3 - cervical intraepithelial neoplasia grade 2 and 3). The two most common types of HPV-related cervical disease are squamous cell carcinoma (SCC) and cervical adenocarcinoma (AD), each with a prolonged preinvasive stage designated as high-grade squamous intraepithelial lesion (HSIL) or adenocarcinoma in situ (AIS), respectively. However, not all HPV infections follow identical progression patterns. Interestingly, some individuals with HPV infections develop HSIL while others develop AIS, suggesting differential pathogenic mechanisms. Understanding these distinctions at the cellular level remains an active area of investigation, with emerging single-cell transcriptomics approaches revealing distinct immune and epithelial cell characteristics between different preinvasive lesion types (Li & Hua, 2023).

3.3 Environmental and Immunological Factors in Disease Development

Environmental and immunological conditions profoundly affect precancerous lesion development (Oliferuk & Berbets, 2025). Chronic stress, sleep disturbances, and exposure to airborne pollutants can compromise immune function, thereby creating favorable conditions for cervical carcinogenesis. Beyond viral factors, co-infections and characteristics of the cervicovaginal microbiota significantly impact infection persistence and disease progression, indicating that local immune and microbial ecology influence lesion development and evolution (Kamzayeva et al., 2025).

3.4 Timeline of Disease Progression

The natural history timeline provides critical insight into disease management windows The interval between onset of precancerous cervical lesions (CIN) and development of invasive carcinoma spans 10–20 years, providing a substantial opportunity for intervention before malignant transformation. This prolonged precancerous phase underscores the importance of understanding the biological mechanisms driving progression during this extended window (Oliferuk & Berbets, 2025).

4. Current Strategies for Primary Prevention

Primary prevention of human papillomavirus-related cervical cancer relies on prophylactic HPV vaccination, achieving near-complete protection (99% efficacy) when administered to HPV-naive individuals before sexual debut (Plotzker et al., 2023)(Sehnal et al., 2022). The World Health Organization recommends vaccination of 90% of girls by age 15 years, with school-based programs in high-income countries demonstrating substantial reductions in HPV prevalence and precancerous lesions (Hall et al., 2025). The nonavalent vaccine (Gardasil 9) is now preferred, providing protection against nine HPV types, while simplified one- and two-dose schedules improve global accessibility (Miazga et al., 2025)(Murillo & Reyes, 2019). Expanding vaccination to boys through gender-neutral programs enhances herd immunity and prevents HPV-related malignancies in males (Lipsky et al., 2025). Addressing vaccine hesitancy through mobile health technologies, community-based engagement, and culturally adapted educational campaigns has proven effective in improving uptake, particularly in underserved populations, with mHealth interventions and structured clinical workflows significantly increasing vaccination completion rates (Opaleye & Esan, 2026)(Rodriguez et al., 2025).

5. Secondary Prevention

Secondary prevention of HPV-related cervical cancer focuses on early detection and treatment of precancerous lesions before they progress to invasive disease (Pache et al., 2022). Key screening approaches include visual inspection with acetic acid (VIA), cervical cytology (Pap smear), and HPV DNA testing (Ngoma & Autier, 2019). Once precancerous lesions are detected through screening—such as cervical intraepithelial neoplasia (CIN)—they can be treated through minimally invasive procedures including loop electrosurgical excision procedures (LEEP) and surgical conization to prevent progression to invasive cancer (Michalczyk et al., 2022). However, recurrence of high-grade lesions occurs in approximately 6.6% of treated patients, highlighting the need for careful follow-up and emerging adjuvant approaches (Plotzker et al., 2023). These integrated screening and treatment approaches, combined with HPV vaccination programs, represent a comprehensive strategy to reduce cervical cancer burden, particularly in resource-limited settings where cost-effective VIA-based screening followed by treatment has proven feasible and effective.

6. Diagnosis and Risk Stratification of Precancerous Lesions

The diagnosis and risk stratification of HPV-associated precancerous lesions constitute critical components of effective cervical cancer prevention programs, requiring an integrated approach combining molecular testing, cytological evaluation, and colposcopic assessment. High-risk HPV (HR-HPV) testing has emerged as the cornerstone of modern cervical screening, demonstrating superior sensitivity compared to traditional cytology for detecting cervical intraepithelial neoplasia and cervical cancer (Wang et al., 2024). HPV genotyping, particularly the identification of HPV type 16 and 18, provides essential risk stratification information, as these genotypes carry substantially higher odds ratios for advanced cervical lesions compared to other high-risk types (Özbilgeç et al., 2025). When HR-HPV testing is combined with liquid-based cytology and colposcopic examination, the diagnostic accuracy improves markedly, with combined approaches achieving area under the curve values significantly higher than any single modality alone (Wang et al., 2024). The triage of HPV-positive women represents a key challenge in contemporary screening algorithms, as HPV positivity alone has limited specificity; therefore, cytological assessment plays a crucial complementary role in identifying which HPV-positive individuals require colposcopic evaluation (Indarti et al., 2025). Immunohistochemical markers, including p16 and Ki-67 biomarkers, have demonstrated substantial utility in distinguishing reactive cervical changes from dysplastic processes and in improving the accuracy of histopathological diagnosis by reducing interobserver variability (Oliferuk & Berbets, 2025). DNA methylation biomarkers, particularly FAM19A4 and miR124-2, have shown promising diagnostic and prognostic potential in detecting high-grade cervical intraepithelial neoplasia and stratifying women at increased risk for progression (S. & D.a., 2025). Circulating microRNA signatures represent an emerging minimally invasive approach to risk stratification, with specific miRNA panels (such as miR-21, miR-205, and miR-218) demonstrating improved detection of high-grade lesions compared to individual biomarkers (Tamenang et al., 2026). HPV persistence status, particularly persistence of HPV16/18 types, serves as a powerful independent predictor of recurrent or progressive cervical disease following treatment and is more reliable than cytological findings alone in identifying high-risk patients requiring intensive surveillance (Dimitrov et al., 2013). Advanced diagnostic methodologies, including E6/E7 oncoprotein detection and optical coherence tomography (OCT), have shown enhanced diagnostic value for triage of HPV-positive women, with OCT demonstrating higher specificity than traditional cytology and HPV testing for detecting high-grade lesions (Cui et al., 2024). Self-sampling methodologies using HPV testing have emerged as viable alternatives to clinician-collected specimens, offering comparable sensitivity and negative predictive value while potentially improving screening accessibility and participation in underserved populations (Waly et al., 2025). The integration of HPV viral load quantification alongside genotyping provides additional risk stratification capacity, as higher HPV16 viral loads independently predict increased risk for cervical intraepithelial neoplasia grade 2 or worse lesions (Asaturova et al., 2025). Demographic and clinical factors, including age, smoking status, and comorbid conditions such as hypertension and hypercholesterolemia, interact with HPV status to influence progression risk and should be incorporated into comprehensive risk assessment strategies (Zhang et al., 2025). Finally, HPV vaccination status following diagnosis has been shown to influence disease regression, suggesting that post-diagnosis vaccination combined with conventional diagnostic strategies may enhance the precision of risk stratification and clinical outcomes (Erkmen & Arkan, 2026).

7. Current Treatment of HPV-Related Precancerous Lesions

7.1. Surgical Excisional and Ablative Treatment Modalities

7.1.1 Large Loop Excision of the Transformation Zone (LLETZ)

Large loop excision of the transformation zone (LLETZ) is the primary surgical treatment for high-grade cervical intraepithelial neoplasia in developed countries (Gupta & Kalwaniya, 2024). It provides both diagnosis and treatment, with success rates exceeding 95% (Hendriks et al., 2022). However, LLETZ has notable limitations, including bleeding, infection, and cervical stenosis, as well as an increased risk of preterm birth in subsequent pregnancies (Koeneman et al., 2016), which is particularly concerning for women of childbearing age.

7.1.2 Thermal Ablation and Cryotherapy

Thermal ablation (TA) offers an advantageous alternative to LLETZ across diverse healthcare settings (Armstrong & Ragupathy, 2022). Eight-year follow-up data show TA achieves significantly lower high-grade CIN recurrence and higher double-negative test-of-cure rates compared to LLETZ (Armstrong & Ragupathy, 2022).

Liquid nitrogen cryotherapy is optimal for resource-limited settings due to low cost, portability, and minimal complications (Gupta & Kalwaniya, 2024). Consequently, WHO recommends a "screen-and-treat" protocol—visual inspection with acetic acid (VIA) followed by immediate cryotherapy—to ensure compliance and arrest high-grade CIN progression (Gupta & Kalwaniya, 2024). Modern handheld noncontact nitrous oxide cryodevices yield a 74.6% clinical remission rate within four months, exhibiting high tolerability and minimal adverse events (Ruymbeke et al., 2026).

7.1.3 Laser Therapy and CO2 Laser Treatment

CO2 laser ablation serves as an effective alternative to LLETZ in selected patients, offering similar therapeutic efficacy with reduced postoperative recovery time, shorter vaginal discharge duration, and lower adverse event rates—14.29% compared to 28.74% for LEEP (Huang et al., 2025). However, modality selection requires individualization based on lesion characteristics, transformation zone type, and fertility preservation preferences.

7.2. Topical Pharmacological Treatments

7.2.1 Imiquimod as an Immune Response Modifier

Imiquimod, a topical toll-like receptor 7 (TLR7) agonist and immunomodulator, serves as a non-invasive alternative to surgical excision for high-grade CIN (Hendriks et al., 2022). While achieving lower regression rates (~60%) than LLETZ (~95%) (Hendriks et al., 2022), a meta-analysis of 398 CIN 2/3 patients confirmed a pooled regression rate of 61% (95% CI: 0.46–0.75) alongside ~60% HPV clearance (Hamar et al., 2024). Mechanistically, it induces local cell-mediated immunity, yielding over a five-fold increase in cervical tissue-resident CD4+ and CD8+ memory T-cells (Sheth et al., 2024). Despite inferior efficacy compared to conization, its non-invasive nature avoids initial surgical intervention in >40% of cases, making it favorable for fertility preservation (Hendriks et al., 2022). Adverse events are predominantly mild-to-moderate, including headache, fatigue, myalgia, and localized vaginal symptoms (Hendriks et al., 2019).

7.2.2 Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) offers a targeted, non-invasive alternative to surgical excision for CIN. Two main protocols have been studied: 5-aminolevulinic acid (ALA)-PDT and systemic talaporfin sodium PDT.

ALA-PDT yields complete remission and HPV clearance rates comparable to LEEP while preserving cervical structural integrity (Liu et al., 2024). A 30-pair retrospective study found no significant differences between ALA-PDT and LEEP in overall complete remission (73.33% vs. 84.00%) or HPV remission (59.26% vs. 53.85%) (Liu et al., 2024). However, in high-grade lesions (HSIL), ALA-PDT achieved superior lesion remission (83.3% vs. 64.7%, $p<0.05$) and HPV clearance (78.6% vs. 60.3%, $p<0.05$) over LEEP, with minimal adverse pregnancy outcomes (Li et al., 2025).

Systemic talaporfin sodium PDT with diode laser demonstrated high efficacy in Phase I/II trials, showing complete response rates of 95% at 3 months and 98% at 6 months, alongside 95% 12-month HPV clearance (Sakamoto et al., 2026). Post-treatment reproductive outcomes were favorable: 74% conception rate, 79% live birth rate, and a 3.7% preterm birth rate—substantially lower than post-conization historical controls (Sakamoto et al., 2026). Overall, PDT achieves robust oncological control while avoiding tissue excision and maximizing fertility preservation (Sakamoto et al., 2026).

7.2.3 Other Topical Agents

Topical therapies offer important non-invasive alternatives in selected populations and resource-limited settings, despite lower overall potency compared to surgical excision. 5-Fluorouracil (5-FU): Demonstrates remission rates exceeding 80% in CIN, though evidence is restricted to small studies (Mutombo et al., 2019). Trichloroacetic Acid (TCA 85%): Achieves response rates of 52–54% in CIN 2/3, with a randomized trial showing no significant clinical benefit from a second application over single dosing (Ayatollahi et al., 2022). Cidofovir: As an antiviral nucleotide analog, it shows potential against HPV-driven lesions, though efficacy data remain inconsistent. Given their variable efficacy, judicious patient selection is required when considering topical pharmacotherapy over standard ablative or excisive procedures.

8. Emerging and Investigational Therapies

Therapeutic vaccines emerge as a leading investigational strategy for treating HPV infection and cervical intraepithelial neoplasia (CIN) (Barra et al., 2020). These vaccines aim to generate immune responses against HPV-infected cells, with several clinical trials demonstrating promise in achieving complete regression in select cases (Ikeda et al., 2021).

Natural products are being investigated as adjunctive therapies. Curcumin, applied topically intravaginally, shows potential for increasing HPV clearance rates—with previous studies documenting clearance in up to 80% of subjects (Wang et al., 2020). Similarly, phytotherapy combining herbal extracts has demonstrated decreased viral load and improved outcomes when combined with local anti-inflammatory therapy in young women (Beniuk et al., 2025).

Microbiome-targeted interventions are emerging as novel approaches. Lactobacillus species and elevated acetic acid levels correlate with successful HPV clearance post-LEEP, suggesting potential for probiotics or microbiome modulation as adjunctive therapies (Pu et al., 2025). Gut microbiota also influences systemic immune responses critical for HPV clearance and immunotherapy efficacy (Li et al., 2026).

CO_2 laser combined with PDT shows even higher efficacy, with cure rates of 72.5% and HPV clearance rates of 75.0%, particularly for high-grade vaginal intraepithelial lesions (Sun et al., 2025).

9. Conclusions

The management of HPV-associated precancerous lesions is rapidly evolving from standardized surgical excision toward a highly personalized, molecularly guided paradigm. While prophylactic vaccination and high-risk HPV (HR-HPV) screening remain the fundamental cornerstones of primary and secondary prevention, the integration of advanced molecular biomarkers—including DNA methylation signatures, microRNAs, and immunohistochemical markers (p16/Ki-67)—has substantially enhanced diagnostic accuracy and risk stratification.

Therapeutically, although excisional procedures such as LLETZ continue to be the gold standard for high-grade cervical intraepithelial neoplasia (CIN), their associated obstetric morbidities necessitate tissue-sparing alternatives for women of childbearing age. Consequently, non-invasive, fertility-preserving modalities are gaining clinical prominence. Photodynamic therapy (PDT) and topical immunomodulators, particularly imiquimod, have demonstrated robust oncological efficacy and viral clearance rates comparable to traditional surgery, while preserving cervical structural integrity.

Looking forward, the clinical landscape is being further expanded by emerging investigational strategies, including therapeutic vaccines, targeted microbiome modulation, and combined ablative-photodynamic protocols. Ultimately, the future of cervical cancer prevention relies on mitigating global disparities in vaccine access while transitioning clinical practice toward precision diagnostics and minimally invasive, immunologically targeted therapeutic interventions.

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