

Human Papillomavirus Associated Cervical Squamous Cell Carcinoma Pathogenesis Diagnosis Prevention and Contemporary Management

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ABSTRACT

The most prevalent histological subtype of cervical cancer is cervical squamous cell carcinoma (SCC), which is causally associated with ongoing infection with high-risk HPV genotypes, especially types 16 and 18. The virus is a tiny, non-enveloped, double-stranded DNA virus that causes cervical intraepithelial neoplasia to proceed to invasive carcinoma by inactivating the p53 and retinoblastoma tumor-suppressor pathways through its oncoproteins E6 and E7. Sub-Saharan Africa, Southeast Asia, and Latin America have the greatest rates of cervical cancer, which is still the fourth most frequent cancer in women globally. The structure and molecular biology of HPV, the epidemiology and pathogenesis of cervical carcinogenesis, immune-evasion mechanisms, the histopathological classification of squamous cell carcinoma, and the diagnostic pathway that includes cytology, HPV DNA testing, colposcopy, biopsy, and immunohistochemistry are all summarized in this review. The immunohistochemistry biomarkers p16INK4a and Ki-67, which help differentiate benign mimics from high-grade squamous intraepithelial lesions, receive special attention. The review comes to the conclusion that prevention by HPV vaccination and early detection through organized screening are still essential for lowering the worldwide morbidity and mortality linked to cervical cancer. Particularly in low-resource settings, improved screening infrastructure and laboratory capacity for HPV-related diagnoses are required.

Keywords: Cervical Cancer, Human Papillomavirus, Squamous Cell Carcinoma, P16, Ki-67, Screening, Vaccination.

Received: September 25, 2026;

Accepted: October 02, 2026;

Published: October 09, 2026

Introduction

One significant but mostly avoidable cause of cancer-related morbidity and mortality is cervical cancer. Cervical cancer was the fifth most common cancer diagnosed in women worldwide, with the highest incidence and mortality in low- and middle-income countries, according to the World Health Organization (WHO), which projected 604,000 new cases and 280,000 deaths in 2024 [1]. Previous GLOBOCAN estimates also showed significant geographic disparity, with sub-Saharan Africa, portions of Latin America, Melanesia, and Southeast Asia bearing the brunt of the load [2].

The most common histological type is still squamous cell carcinoma (SCC). It typically

develops in the cervical transformation zone, where the oncogenic human papillomavirus (HPV) can infect metaplastic squamous epithelium. While truly HPV-independent cervical SCC is uncommon and necessitates careful exclusion of false-negative viral testing and misclassified tumors from adjacent sites, persistent carcinogenic HPV infection is the required causal event for nearly all cervical cancers [3,4]. With a focus on implications for pathology and laboratory practice, this review explores HPV-associated cervical SCC from viral pathogenesis to prevention and current clinical therapy.

Review Methods

The method employed was a narrative review. Targeted searches were conducted in

Citation: Bernard Kafor and Juwah Jeffery Chukwudi (2026) Human Papillomavirus Associated Cervical Squamous Cell Carcinoma Pathogenesis Diagnosis Prevention and Contemporary Management. J Gyne Womens Heal Care 2: 1-5.

PubMed/MEDLINE and reputable institutional sources, such as international cervical cancer guidelines, WHO publications, and the WHO Classification of Tumors. "Human papillomavirus," "cervical squamous cell carcinoma," "E6," "E7," "immune evasion," "p16," "Ki-67," "dual stain," "HPV screening," "vaccination," and "cervical cancer treatment" were among the search terms used. Systematic reviews, consensus classifications, international guidelines, key randomized trials, and papers published after 2020 were prioritized; earlier seminal research that created concepts that are still relevant were kept. A thematic synthesis of the evidence was done. There was no rigorous risk-of-bias assessment or meta-analysis because this was a narrative rather than a systematic evaluation.

HPV Structure and Molecular Biology

HPVs belong to the Papillomaviridae family of tiny, non-enveloped viruses. A late region that codes for the structural capsid proteins L1 and L2, an early region that codes for regulatory proteins (E1, E2, E4, E5, E6, and E7), and a non-coding long control region that contains the origin of replication and transcriptional regulatory elements make up their roughly 8-kb circular double-stranded DNA genome. L2 helps with genome packaging, entrance, and intracellular trafficking, while L1 forms the majority of the icosahedral capsid and self-assembles into virus-like particles utilized in preventative vaccinations [5,6].

Over 200 genotypes of HPV have been identified. Carcinogenic potential is used to classify mucosal types. While HPV16, HPV18, HPV31, HPV33, HPV35, HPV45, HPV52, and HPV58 are among the main carcinogenic forms, HPV6 and HPV11 are low-risk varieties mostly linked to anogenital warts. While HPV18 is comparatively more common in adenocarcinoma, HPV16 is responsible with the majority of cervical SCC. Although type attribution varies by region, HPV16 and HPV18 jointly account for about 70% of cervical cancer cases [7,8].

Epidemiology and Cofactors

The majority of sexually active people have HPV, however most infections are temporary. Persistent infection with a carcinogenic type, rather than acquisition alone, is the main predictor of precancer and cancer, with over 90% becoming undetectable within two years [9]. Although it may happen more quickly in those with compromised immunity, progression typically takes many years. According to WHO projections, women living with HIV are almost six times more likely than women without HIV to develop cervical cancer, precancer, and persistent HPV infection [1].

Smoking, immunosuppression, high parity, long-term exposure to hormonal contraceptives, coinfection, or vaginal inflammation are cofactors that promote persistence or advancement. These variables operate within broader structural determinants, such as poverty, low immunization rates, insufficient screening, delayed diagnosis, and limited access to systemic treatment and radiotherapy [8,1].

Pathogenesis of HPV Associated Squamous Carcinogenesis

Through epithelial microtrauma, especially in the transformation zone, HPV enters basal keratinocytes. The viral genome is preserved as an episome in basal cells throughout productive infection, and viral gene expression is associated with epithelial development. Host immunity controls the majority of illnesses. Persistently dysregulated expression of E6 and E7 dissociates normal epithelial differentiation from viral oncogene activity in transforming infection. Although it is not necessary for malignant transformation, viral integration is common in cancer and can increase E6/E7 expression, frequently by interfering with E2-mediated suppression [6,9].

E6 and E7 Oncoproteins

High-risk HPV E6 weakens DNA-damage checkpoints, senescence, and apoptosis by recruiting the E6-associated protein ubiquitin ligase and encouraging p53 degradation. Additionally, E6 interacts with PDZ-domain proteins to activate telomerase and disrupt cell polarity. High-risk HPV E7 causes improper S-phase entrance, releases E2F transcription factors, and binds retinoblastoma-family pocket proteins. Block-positive p16 immunohistochemistry is useful for diagnosis because compensatory p16INK4a overexpression results from functional inactivation of retinoblastoma protein. E7 also interferes with centrosome control and cyclin-dependent kinase inhibitors. When combined, E6 and E7 cause chromosomal instability, replication stress, poor DNA repair, and selection for further host genomic changes [10,6].

Immune Evasion

Throughout its epithelial life cycle, HPV reduces inflammation and obstructs both innate and adaptive immune recognition. Pattern-recognition receptor, interferon, NF- κ B, antigen processing, and major histocompatibility complex pathways are all altered by E5, E6, and E7. Persistence is facilitated by decreased antigen presentation, compromised dendritic-cell activity, modified chemokine production, and an immunosuppressive tumor microenvironment. These pathways offer a biological explanation for immune-checkpoint inhibition in advanced disease and help explain why immunological competence has a significant impact on natural history [11,12].

Natural History and Precancerous Squamous Lesions

Low-grade squamous intraepithelial lesions (LSIL), which are generally associated with cervical intraepithelial neoplasia grade 1 (CIN1), are the result of productive low-grade infection. High-grade squamous intraepithelial lesions (HSIL), which include the physiologically significant precursors typically represented by CIN2 and CIN3, are caused by transforming infection. Because of its heterogeneity, CIN2 should be evaluated using morphology and p16 staining when low-grade lesions or immature metaplasia are included in the differential diagnosis. Atypical proliferation that extends over most or all of the epithelium thickness and a noticeable maturation abnormality are characteristics of CIN3, a high-risk precursor. Invasive SCC is distinguished from HSIL by stromal invasion [3].

Histology and cytology employ similar but distinct terms. While tissue diagnosis uses LSIL/HSIL terminology with

optional CIN qualification, the Bethesda System identifies squamous cytological abnormalities as atypical squamous cells, LSIL, HSIL, or SCC. An evaluation of specimen adequacy, transformation-zone sampling, lesion location, and the potential for an undetected glandular or invasive lesion should be prompted by cytology-histology discordance [13].

Histopathology and Classification

Cervical SCC is primarily divided into HPV-associated and HPV-independent categories according to the fifth edition of the WHO classification. The use of keratinizing, non-keratinizing, basaloid, warty, papillary, and lymphoepithelioma-like designations as distinct main tumor types is superseded by this etiologic classification. These morphologic features may nevertheless be present in SCC linked to HPV. Although there is less evidence for HPV-independent SCC than for HPV-associated illness, it is rare, typically affects older patients, may exhibit aberrant p53 expression, and seems to have less favorable outcomes [4,3].

Grossly, invasive SCC can be endophytic, exophytic, or ulcerative; an endophytic tumor might result in a firm cervix that resembles a barrel. Under a microscope, invasion manifests as irregular nests, ropes, or individual malignant squamous cells penetrating the cervical stroma, frequently accompanied by inflammation or desmoplasia. Non-keratinizing tumors develop sheets or nests of polygonal cells without noticeable pearl production, whereas keratinizing tumors exhibit individual-cell keratinization and keratin pearls. Because these characteristics

influence staging and care, the pathology report should include information on the histological type, tumor size, depth of stromal invasion, lymphovascular-space invasion, margin status, and lymph-node discoveries where appropriate [14].

Diagnostic and Screening Pathway

Screening tests do not prove invasive cancer on its own; instead, they identify those who are at higher risk. When practical, WHO advises using a high-performance HPV test as the main screening technique. Triage and treatment routes based on age, HIV status, genotype, cytology, visual assessment, and program resources are used to manage HPV-positive persons. While a clinician-collected cervical sample may still be necessary for triage, self-collected vaginal samples can increase access when validated tests and protocols are utilized [15,1].

Cytology is still crucial for cotesting or triage programs because it can identify morphologic problems. Colposcopy guides biopsies and detects aberrant epithelium. Precancer or invasion is confirmed by histopathological analysis of punch biopsies, excisional specimens, or endocervical samples. Sufficient tissue is needed for histological categorization and, if necessary, auxiliary tests in cases of suspected invasive malignancy. Pre-analytical identification and sampling, validated molecular assays, cytology screening, histology processing, interpretative concordance, and prompt transmission of crucial results are all necessary components of laboratory quality assurance.

Table 1: Complementary methods used in cervical screening and diagnosis

Method	Primary role	Major strength	Important limitation
High-risk HPV test	Primary screening or risk stratification	High sensitivity for CIN3+; supports extended screening intervals	Lower specificity than cytology; requires triage and validated platforms
Cervical cytology	Screening or triage	Evaluates cellular morphology and may indicate cancer	Sampling- and observer-dependent; lower sensitivity than HPV testing
Colposcopy	Localization and biopsy guidance	Directs tissue sampling to suspicious areas	Performance varies with examiner and transformation-zone visibility
Histopathology	Definitive diagnosis	Confirms grade, invasion, type, margins, and prognostic features	Requires adequate representative tissue and expert interpretation
p16 or p16/Ki-67	Adjunctive classification or triage	Improves risk stratification in defined settings	Must not replace morphology or be used outside validated algorithms

Immunohistochemistry and Biomarkers

p16INK4a

A surrogate for changing high-risk HPV activity is block-positive p16 staining, which is continuous, strong nuclear with or without cytoplasmic staining including the basal layer and extending upward. It aids in the adjudication of some CIN2 diagnoses and supports HSIL when morphology raises a differential diagnosis between HSIL and a benign mimic. Block positive is not the same as patchy or focal staining. Convincing morphology cannot be overridden by a negative stain, therefore p16 should not be employed frequently to upgrade unequivocal CIN1. While indiscriminate use may result in overdiagnosis, appropriate use enhances repeatability [16,3].

Ki-67 and Dual Staining

Cycling nuclei are marked with Ki-67. Staining is mostly limited to basal and parabasal cells in normal squamous mucosa; expansion into upper epithelial layers supports dysregulated proliferation but is not selective on its own. Cells expressing a cell-cycle inhibitor and a proliferation marker at the same time are identified by cytological p16/Ki-67 dual staining, an aberrant combination linked to transforming HPV infection. Dual staining can stratify risk and direct surveillance or colposcopy in specific HPV-positive screening populations. Its application should follow validated assay-specific thresholds and consensus recommendations rather than ad hoc interpretation [17].

Predictive Biomarkers in Advanced Cancer

Systemic therapy is becoming more and more influenced by biomarker testing. In relevant nations, first-line pembrolizumab-containing therapy is chosen based on program death-ligand 1 expression, which is often evaluated using a validated combined positive score assay. Performance status, previous therapy, tumor histology, and local regulatory approval are still crucial factors. In challenging situations, HPV identification confirms etiologic connection; nevertheless, when HPV status is clinically crucial, p16 is not a perfect replacement for direct HPV testing [14,18].

Treatment and Contemporary Management

The extent of the disease, nodal status, fertility choices, comorbidities, pathology, imaging, and accessible expertise all influence management, which necessitates multidisciplinary staging. Depending on the features of the lesion and eligibility for guidelines, HSIL is typically treated with an excisional or ablative method. Fertility-sparing trachelectomy is an option for carefully chosen early invasive malignancies, while conization or straightforward surgery may be used to treat certain stage IA illness. For many early-stage diseases, radical surgery combined with nodal evaluation is still appropriate. Morbidity is decreased when combined radical surgery and postoperative radiation are avoided [14].

Cisplatin-based chemotherapy is used in conjunction with image-guided brachytherapy and definitive external-beam radiation to treat locally advanced cervical cancer. Pembrolizumab was added to chemoradiotherapy to increase progression-free and overall survival in KEYNOTE-A18 for high-risk locally advanced illness, and it has been used in areas where it is authorized and available [19]. Renal function, marrow reserve, HIV care, nutritional health, and the ability to finish radiation therapy without preventable interruption must all be taken into consideration while making treatment selections.

Platinum-taxane chemotherapy with bevacizumab is still a significant choice for persistent, recurring, or metastatic illness that cannot be cured locally. In patients with PD-L1-positive chronic, recurrent, or metastatic cervical cancer, pembrolizumab combined to chemotherapy—with or without bevacizumab—improved survival [18]. Regardless of the trial population's PD-L1 status, cemiplimab increased survival when compared to investigator-choice single-agent chemotherapy following platinum therapy [20]. Following previous systemic therapy,

survival has also been enhanced by tisotumab vedotin, an antibody-drug combo that targets tissue factor [21]. Selection must be guided by patient preferences, regulatory status, toxicity profiles, access, and contraindications.

Prevention and Elimination

L1 virus-like particle-based prophylactic vaccinations do not treat pre-existing infections; instead, they prevent future infections and related precancer induced by vaccine-targeted HPV strains. Prioritizing vaccination of girls between the ages of 9 and 14 prior to sexual exposure, WHO allows immunocompetent individuals in eligible age groups to receive one or two doses, with additional doses for immunocompromised individuals in accordance with policy [22]. Vaccination campaigns should be combined with trustworthy safety messaging, community and school distribution methods, and methods for contacting teenagers who are not enrolled in school.

Because many individuals were not vaccinated prior to exposure and current vaccinations do not cover all carcinogenic types, vaccination does not obviate the necessity for screening. The 90–70–90 targets are used in WHO's eradication strategy: 90% of girls must be fully immunized by the age of 15, 70% of women must be screened with a high-performance test by the ages of 35 and 45, and 90% of women who have precancerous or aggressive cancer must receive the necessary treatment. For women living with HIV, screening should begin earlier and happen more often [23,1].

Implications for Resource Limited Settings

Connecting prevention, diagnosis, and therapy rather than using separate tests will yield the biggest benefits in high-burden settings. Programs require pathology referral networks, digital or paper-based patient tracking, validated HPV platforms, reliable specimen transport, internal and external quality review, and treatment assurance following a positive result. When used with suitable eligibility assessment and quality controls, screen-and-treat or screen-triage-treat routes can lower loss to follow-up [15].

For suspected invasion, inconsistent results, glandular abnormalities, and excisional specimens, histopathology capability is still essential. Thus, trained cytologists, pathologists, colposcopists, medical laboratory scientists, oncology teams, and biomedical engineering assistance should all be included in the investment. Test performance should be tracked with equity metrics such as coverage, turnaround time, loss to follow-up, stage at diagnosis, and treatment completion.

Limitations of the Review

Since this is a narrative synthesis, not all relevant studies may be included. The study selection was not repeated, and the search was focused rather than protocol-registered. Specific practice details may change due to rapid changes in national recommendations, prescription approvals, and screening technology. Therefore, while making clinical judgments, readers should consider local regulatory information as well as current national guidelines.

Conclusion

Persistent carcinogenic HPV infection and ongoing E6/E7 activity, which interfere with p53 and retinoblastoma pathways, hinder immune identification, and encourage genomic instability, are the causes of HPV-associated cervical SCC. Differentiating between screening and diagnosis, using p16 and Ki-67 only in approved situations, and recording the pathological characteristics that dictate stage and treatment are all essential to providing accurate care. Most deaths can be avoided with vaccination, high-performance HPV screening, prompt precancer treatment, and fair access to multimodal cancer care. Reliable linkage from a positive screen to diagnosis and therapy, as well as laboratory quality systems, are just as crucial in settings with limited resources as test selection.

Declarations

Funding: No specific funding was reported for this review.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: Not applicable because this article is a review of published literature and did not involve human participants or animals.

Author Contribution: Kafor Bernard and Juwah Jeffery Chukwudi conceptualized the review, Jeffery synthesized the literature, while Bernard prepared the manuscript,

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