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# THE ROLE OF ONCOGENIC TYPES OF THE HUMAN PAPILLOMAVIRUS IN THE DEVELOPMENT OF PRECANCEROUS CONDITIONS AND CERVICAL CANCER

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**Abstract.** Persistent infection with oncogenic, high-risk human papillomavirus is the necessary etiologic driver of virtually all cervical cancers, yet only a small fraction of infections progress to clinically significant precancer or invasive malignancy. This review synthesizes current evidence on how carcinogenic HPV genotypes, especially HPV16 and HPV18 and several additional high-risk types, contribute to the natural history of cervical intraepithelial neoplasia and adenocarcinoma in situ, and ultimately to invasive cervical cancer. We discuss genotype-specific differences in carcinogenic potential, viral and host mechanisms that promote persistence and malignant transformation, and the stepwise biological continuum from transient infection to high-grade precancer. The central molecular events include expression of E6 and E7 oncoproteins that disrupt p53 and retinoblastoma tumor suppressor pathways, remodeling of the cellular epigenetic landscape, immune evasion, and, in many cancers, viral DNA integration with sustained oncoprotein expression.

**Keywords:** human papillomavirus; high-risk HPV; HPV16; HPV18; cervical intraepithelial neoplasia; CIN2+; adenocarcinoma in situ.

## INTRODUCTION

Cervical cancer remains one of the most preventable malignancies because its cause is well-defined, its precursor lesions are detectable, and effective interventions exist at multiple steps of the disease pathway. The pivotal etiologic discovery is that long-lasting infection with high-risk types of human papillomavirus is responsible for virtually all cervical cancers. Unlike many cancers with complex multifactorial etiologies, cervical carcinogenesis has a necessary causal agent, which enables rational population-level prevention through primary prophylaxis with HPV vaccination and secondary prevention through screening and treatment of precancer [1].

HPV infection is extremely common among sexually active people, and most infections clear spontaneously within one to two years. Therefore, the key biological and public-health challenge is not infection per se, but persistence of oncogenic HPV and the sequence of molecular and histopathologic changes that arise when viral oncogene expression is maintained over time. Persistent high-risk HPV can induce precancerous lesions, classically described as cervical intraepithelial neoplasia grades 2 and 3, and adenocarcinoma in situ for glandular

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disease. Without detection and effective management, a subset of these high-grade precancers progresses to invasive cancer.

A second central insight is that not all high-risk HPV genotypes confer equal risk. HPV16 and HPV18 account for the largest proportion of cervical cancers worldwide, while additional oncogenic genotypes contribute a substantial minority of cases with geographic variation. Genotype-specific differences influence persistence, the likelihood of progression to high-grade lesions, and the distribution of histologic cancer subtypes such as squamous cell carcinoma and adenocarcinoma. Understanding these differences is essential for modern HPV-based screening algorithms, risk-based management, and post-vaccination surveillance.

## MATERIALS AND METHODS

More than 100 HPV types have been identified, and roughly half infect the genital tract. Only a subset are classified as high-risk or carcinogenic because they are consistently found in high-grade precancer and cervical cancers. Classic high-risk types include HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, and HPV68, among others described in major epidemiologic and carcinogenicity syntheses.

Global attribution studies converge on a clear hierarchy: HPV16 is the single most oncogenic type and is responsible for roughly half of cervical cancers, while HPV16 and HPV18 together account for around two-thirds of cases. Broader analyses show that HPV16 and HPV18 together may account for approximately three-quarters of cases in some datasets, reflecting methodological differences in sampling, geography, and inclusion criteria. Beyond 16 and 18, five additional high-risk types—HPV31, HPV33, HPV45, HPV52, and HPV58—contribute another 15–20% of cervical cancer cases worldwide. The remaining causal genotypes account for a relatively small fraction overall, though regional patterns matter: for example, HPV35 contributes a higher proportion in parts of Africa than in other regions [2].

These genotype distributions have major implications. First, vaccines targeting HPV16 and HPV18 should prevent most cervical cancers; second, the added types included in the nonavalent vaccine cover a large additional fraction of cancers and high-grade precancers; third, screening strategies must remain robust in vaccinated populations because non-vaccine oncogenic types, though less common, still pose risk.

## RESULTS AND DISCUSSION

Cervical carcinogenesis is best understood as a continuum. The initiating event is infection of the cervical epithelium, usually at the transformation zone where squamous and glandular epithelia meet. Infection requires microabrasions that allow access to the basal layer, where HPV can establish its genome in epithelial stem or progenitor cells. In most individuals, immune responses control infection, and viral DNA becomes undetectable within 1–2 years.

In a minority of individuals, infection persists. Persistence is the strongest predictor of progression to high-grade lesions and is a prerequisite for cancer development. Persistent infection can lead to premalignant cellular changes. Low-grade lesions often reflect productive viral infection and frequently regress, while high-grade lesions reflect transforming infection with deregulated oncoprotein expression and a higher probability of progression if untreated.

Histopathologically, squamous precancer is commonly classified as CIN1, CIN2, and CIN3, which correspond to increasing degrees of dysplasia and increasing association with persistent oncogenic HPV. CIN2 is biologically heterogeneous: some lesions behave like transient infection and regress, while others are true precancers closer to CIN3. This

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heterogeneity is one reason why modern clinical management increasingly incorporates HPV genotype, cytology, and risk-based algorithms rather than relying solely on histologic grade.

Glandular precancer, adenocarcinoma in situ, is often strongly linked to HPV18 and HPV45 and may be harder to detect by cytology alone, emphasizing the value of HPV testing and careful colposcopic evaluation in high-risk scenarios.

High-risk HPV is necessary but not sufficient for cervical cancer. Progression depends on persistence and additional viral, host, and environmental cofactors. Key cofactors supported across major cancer prevention sources include immunosuppression, especially HIV infection; smoking; long-term inflammation; co-infections; and reproductive and hormonal factors that may influence cervical epithelium vulnerability and immune response. These factors do not replace HPV as the causal agent; rather, they alter the probability that infection persists and that transforming events occur [3].

Persistence itself is influenced by genotype. HPV16 tends to persist more readily and progress more frequently than other types, which is consistent with its disproportionately high contribution to both CIN3 and invasive cancer. In practice, HPV16 (and often HPV18) positivity is treated as a higher-risk marker in triage and management pathways because it implies a greater short- and medium-term risk of CIN3+.

Host immune surveillance is crucial. Many infections clear because innate and adaptive responses eliminate infected cells or suppress viral replication. HPV's evolutionary success partly derives from immune evasion strategies: limited viremia, infection confined to epithelium, low levels of inflammation in productive infection, and modulation of antigen presentation pathways. When immune control is impaired, persistence becomes more likely, and the risk of precancer rises.

Oncogenic HPV types share a conserved transforming strategy centered on continuous expression of two early proteins: E6 and E7. These oncoproteins promote cell-cycle entry and survival of infected keratinocytes, creating a permissive environment for viral genome maintenance and replication. In transforming infections and cancers, the same activities drive neoplastic progression [4].

E6 promotes degradation and functional inactivation of p53, weakening DNA damage responses, apoptosis, and cell-cycle arrest. E7 binds and inactivates retinoblastoma family proteins, releasing E2F transcription factors and pushing cells into S-phase. The combined effect is sustained proliferation, impaired genomic integrity checkpoints, and selection for additional host genetic and epigenetic alterations. Over time, these changes facilitate accumulation of chromosomal instability, copy-number alterations, and mutations that cooperate with viral oncogene expression to produce malignant phenotypes.

A major biological turning point is viral genome integration, which is frequent in cancers, particularly those associated with HPV16 and HPV18. Integration can disrupt the viral E2 regulatory gene, leading to deregulated high-level expression of E6 and E7. Even without integration, episomal HPV can drive cancer if E6/E7 expression becomes persistently high; therefore, integration is common but not strictly required. The defining feature is sustained oncogene expression and the cellular selection it imposes.

These molecular mechanisms explain important clinical correlates. For example, overexpression of p16 is a cellular response to Rb pathway disruption by E7, making p16 a useful biomarker in histopathologic evaluation and triage of ambiguous lesions. Similarly, the

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genotype-specific carcinogenic potential relates to differences in oncoprotein affinity for host targets, immune escape capacity, and probability of persistence.

HPV16 is the dominant type in cervical squamous cell carcinoma and is also strongly linked to other HPV-associated cancers. HPV18, while less prevalent than HPV16 in squamous cancer, is disproportionately represented in cervical adenocarcinoma and adenocarcinoma in situ, contributing to the clinical observation that HPV18-positive infections may warrant special attention even when cytology is not severely abnormal.

The next tier of oncogenic types—HPV31, HPV33, HPV45, HPV52, HPV58—collectively accounts for a meaningful fraction of cervical cancers worldwide. Their presence matters especially in partially vaccinated populations or in regions where these types are relatively common. From a prevention standpoint, their inclusion in the 9-valent vaccine is a major advance, because it expands protection beyond HPV16/18 and captures much of the remaining preventable burden through vaccination [5].

Other carcinogenic types contribute a smaller fraction but are not negligible. In addition, some types may be more associated with certain geographic regions, which underscores the need for local surveillance and for screening programs that do not assume elimination of risk after vaccination.

Cervical cancer prevention increasingly relies on HPV testing because it is more sensitive than cytology for detecting high-grade precancer and because it aligns directly with etiology. Modern screening recommendations in many settings include primary high-risk HPV testing as an option for individuals aged 30–65, alongside cytology-based or co-testing strategies.

However, because HPV infection is common and often transient, HPV testing must be coupled with triage to avoid overtreatment. Genotype information is a powerful triage tool. HPV16 and HPV18 confer higher immediate and future risk of CIN3+ than other high-risk types, so many algorithms treat HPV16/18 positivity as an indication for closer evaluation even when cytology is normal. Risk-based management approaches integrate current test results with prior screening history to estimate an individual's risk of CIN3+ and determine the appropriate next step. The ASCCP 2019 risk-based management guidelines are a landmark in this regard, recommending management based on risk thresholds rather than rigid result categories.

In practical terms, low-grade abnormalities with low estimated risk may be managed with repeat testing at one year, while higher-risk patterns prompt colposcopy, biopsy, or in selected circumstances expedited treatment. This risk-based paradigm is compatible with ongoing technological change, including new biomarkers and improved HPV assays.

After treatment for high-grade precancer, HPV testing is also central to follow-up because persistent HPV indicates elevated risk of recurrence. Evidence-based follow-up intervals and testing schedules aim to ensure that treated individuals return to routine screening only after sufficiently low-risk results are achieved.

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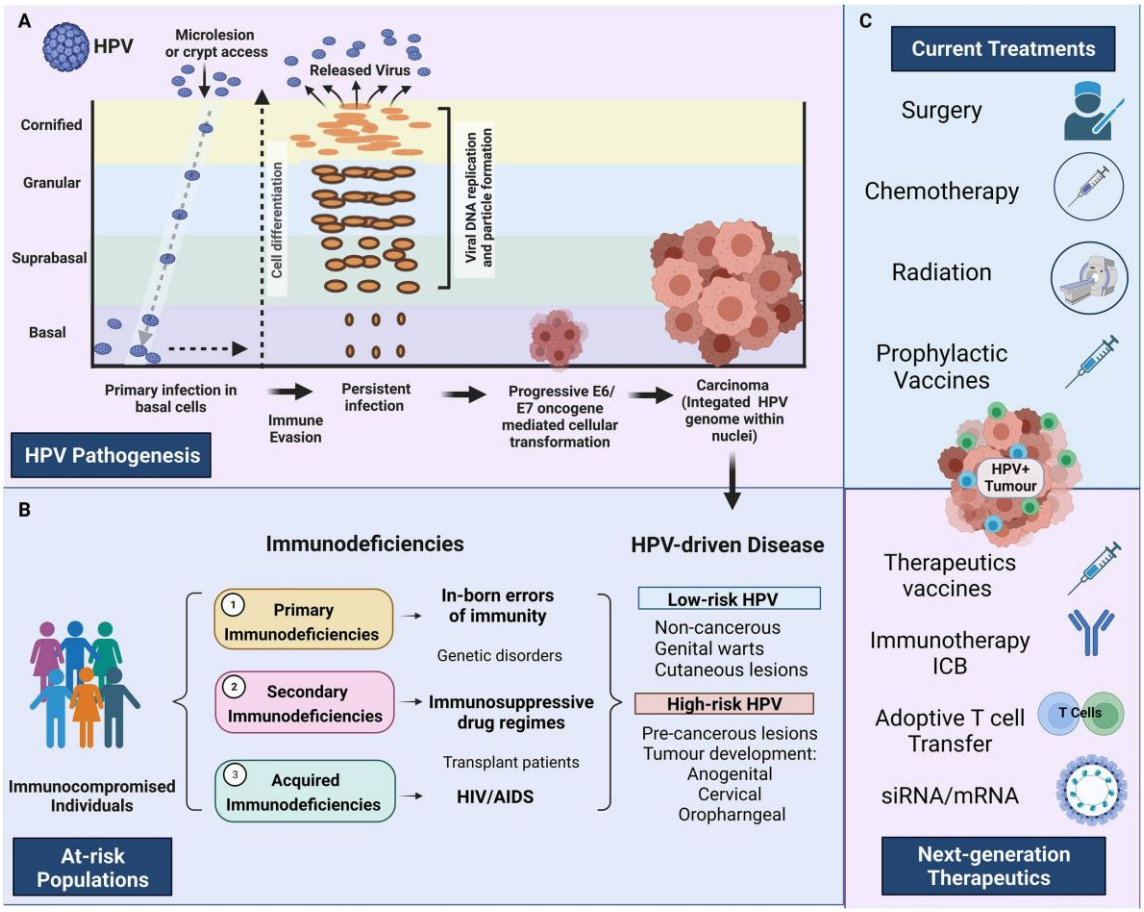


*Fig.1*

HPV vaccination is primary prevention, targeting infection before it occurs. As of 2025, multiple licensed HPV vaccines exist globally, and WHO notes that all available vaccines protect against HPV16 and HPV18, which account for the majority of cervical cancers. The 9-valent vaccine extends protection to five additional high-risk types—31, 33, 45, 52, 58—alongside low-risk types 6 and 11 responsible for most anogenital warts.

Population studies in settings with established vaccination programs show marked reductions in vaccine-type infections and high-grade cervical lesions among vaccinated cohorts, along with evidence of herd effects in some communities. The biological logic is straightforward: if infection with the most carcinogenic types is prevented, the pipeline feeding CIN3 and invasive cancer is disrupted, and over time cancer incidence falls.

Importantly, vaccination does not eliminate the need for screening, especially for cohorts vaccinated later, for those not fully vaccinated, and because a residual burden from non-vaccine oncogenic types persists. Nevertheless, vaccination changes the genotype landscape, making HPV16/18 less frequent and potentially increasing the relative proportion of lesions associated with other high-risk types, even if absolute numbers decline. Screening programs must adapt to this transition, potentially shifting to HPV-based screening with appropriate triage rather than cytology-centric methods that were optimized for pre-vaccine epidemiology.

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prognosis and treatment design.

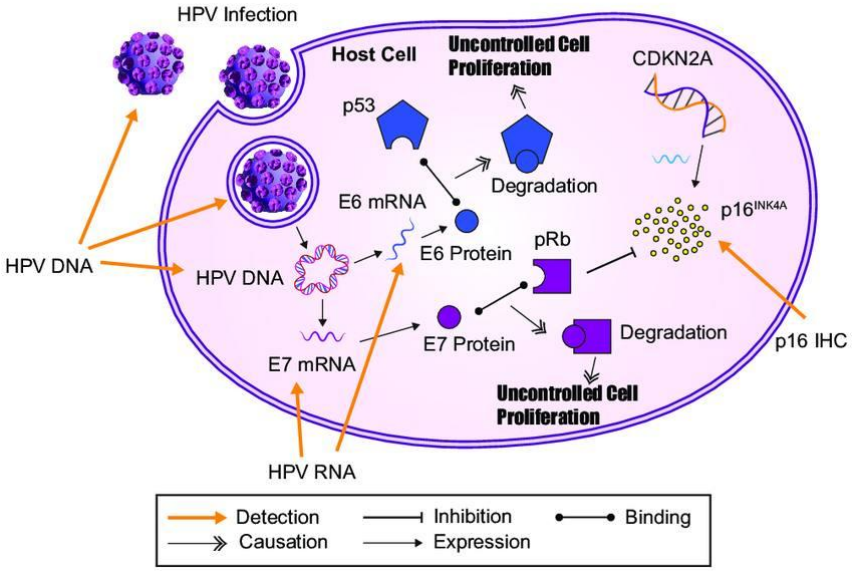


*Fig.2*

Finally, advances in molecular triage—such as dual staining, methylation markers, and improved risk modeling—are gradually refining the precision of identifying which HPV-positive individuals are most likely to harbor or develop CIN3+. While these tools continue to evolve, the foundational principle remains constant: persistent high-risk HPV, particularly HPV16 and HPV18, drives the majority of disease, and prevention is most effective when interventions target the infection–precancer–cancer continuum early and systematically [6].

**CONCLUSION**

Oncogenic high-risk HPV types are the necessary cause of virtually all cervical cancers, but infection alone is not destiny. Most HPV infections clear spontaneously, whereas persistent infection with carcinogenic genotypes—especially HPV16 and HPV18—creates the biological conditions for precancer and eventual invasive cancer. The stepwise pathway from infection to CIN2/3 or adenocarcinoma in situ and then to cancer is driven by sustained E6/E7 oncoprotein activity, disruption of p53 and Rb tumor suppressor pathways, immune evasion, and the gradual accumulation of host genomic and epigenomic alterations. Genotype matters because carcinogenic potential is unevenly distributed: HPV16 and HPV18 account for most cases globally, while HPV31, 33, 45, 52, and 58 add a substantial fraction and shape regional patterns.

Clinically, these biological realities justify HPV-based screening, genotype-informed triage, and risk-based management frameworks such as the ASCCP consensus guidelines. At the population level, vaccination that includes HPV16/18—and, in nonavalent vaccines, five additional oncogenic types—offers the most powerful route to reducing future precancer and cervical cancer burden. The most effective control strategy is integrated: prevent infection where possible, detect persistent oncogenic HPV early, manage high-grade precancer promptly, and continuously adapt screening policies to post-vaccination epidemiology. With sustained implementation, the combination of vaccination, high-performance screening, and appropriate treatment makes cervical cancer elimination a realistic public-health goal.

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