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Role of Human Papillomavirus (HPV) in the Development and Progression of Cervical Cancer

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Abstract

Cervical cancer remains a major cause of morbidity and mortality, disproportionately affecting women in low- and middle-income countries despite its high preventability. Persistent infection with high-risk human papillomavirus (hrHPV), particularly genotypes 16 and 18, is a necessary causal factor in cervical carcinogenesis. This review synthesizes current evidence on the role of HPV in the initiation and progression of cervical cancer, spanning viral biology, molecular pathogenesis, host determinants, and clinical implications. We summarize HPV structure, classification, transmission, and natural history, highlighting how the E6 and E7 oncoproteins disrupt p53 and pRb pathways, drive genomic instability, and interact with host epigenetic and DNA damage-response machinery. We also examine host genetic susceptibility, hormonal influences, smoking, HIV-associated immunosuppression, cervicovaginal dysbiosis, micronutrient deficiencies, and immune evasion mechanisms that condition progression from transient infection to high-grade lesions and invasive cancer. Finally, we review advances in HPV-based screening, biomarkers, and prophylactic and therapeutic vaccination, and discuss how HPV status and genotype inform prognosis and treatment response. Understanding these viral–host interactions is essential for optimizing implementation of the WHO 90-70-90 strategy and for designing context-appropriate interventions to reduce persistent global inequities in cervical cancer burden. Special emphasis is placed on challenges and opportunities for scaling prevention and care in high-burden, resource-limited settings.

Keywords: Cervical cancer, High-risk HPV (hrHPV), Molecular pathogenesis, HPV screening and vaccination, Global health disparities

Introduction

1.1. Global Burden and Geographic Disparities

Cervical cancer represents a substantial global health challenge, ranking as the fourth most common cancer among women worldwide. In 2020, an estimated 604,127 new cases and 341,831 deaths occurred globally, with significant regional variation. By 2022, these numbers had increased to approximately 660,000 new cases and 348,000-350,000 deaths. Notably, more than 94% of cervical cancer deaths in 2022 occurred in low- and middle-income countries (LMICs), underscoring profound health inequities. The geographic distribution reveals striking disparities. Sub-Saharan Africa (SSA) bears the highest burden globally, with Eastern Africa exhibiting age-standardized incidence rates (ASIR) of 40.4 per 100,000 women-years and mortality rates reaching 28.6 deaths per 100,000 women-years. In contrast, Western Asia reported the lowest incidence at 4.1 cases per 100,000 women-years, while Western Europe demonstrated mortality rates as low as 2.0 per 100,000 women-years. Regional screening coverage in SSA remains critically low at approximately 10.51%, with substantial wealth-related inequalities contributing to the disproportionate burden. Asia accounts for more than 58% of all global cervical cancer cases, with China and India alone representing 39% of worldwide incidence (18% and 21%, respectively) and 40% of total deaths. In Latin America and the Caribbean, cervical cancer remains the third leading cause of cancer death among women, with age-standardized rates of 14.6 per 100,000 for incidence and 7.1 per 100,000 for mortality in 2018. Countries such as Bolivia and Paraguay exhibit some of the highest incidence rates in the Americas [1-3].

A clear inverse relationship exists between Human Development Index (HDI) and cervical cancer burden. In 2020, low-HDI countries experienced incidence rates three times higher and mortality rates five times higher than very high-HDI countries (27.2 versus approximately 9 cases per 100,000 women-years). This socioeconomic gradient reflects differential access to prevention, screening, and treatment services across resource settings. While overall cervical cancer incidence has declined in many regions over the past three decades—particularly in Latin America, Asia, Western Europe, and North America—concerning trends have emerged. Several Eastern European countries (Latvia, Estonia, Lithuania, Bulgaria) and some sub-Saharan African nations have experienced increases in incidence, attributed largely to absent or ineffective population-based screening programs. Age-specific analyses reveal that incidence peaks around ages 50-59 years

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globally. However, a troubling trend shows increasing incidence among younger women (ages 15-49 years), particularly in high-SDI regions. This may reflect earlier sexual debut, increased HPV exposure, higher screening participation, and greater numbers of sexual partners. In contrast, women aged 20-24 have experienced an 11% annual decline, likely representing the first observable cancer prevention benefits from HPV vaccination. In 2020, the World Health Organization launched a global elimination strategy defining cervical cancer as a public health problem when incidence exceeds 4 per 100,000 women-years. Alarmingly, 173 of 185 countries or territories analyzed in 2020 exceeded this threshold. Achieving elimination requires meeting the "90-70-90" targets by 2030: 90% HPV vaccination coverage in girls by age 15, 70% screening coverage with high-performance tests by ages 35 and 45, and 90% treatment of pre-cancerous and invasive lesions [4-6].

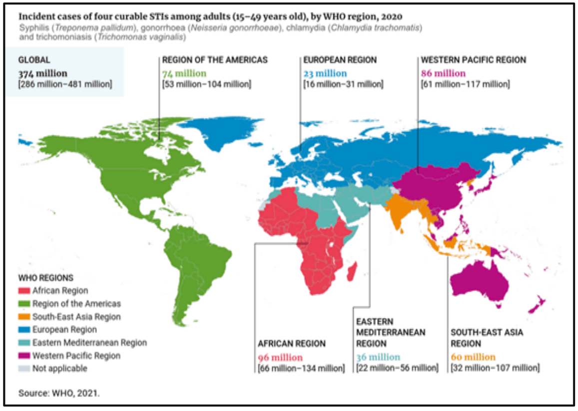

Figure-1: Global Burden of HPV.

1.2. Historical Link Between HPV Infection and Cervical Carcinogenesis

The etiological link between human papillomavirus (HPV) infection and cervical cancer represents a landmark in cancer research, pioneered by Harald zur Hausen between 1977 and 1987. Zur Hausen challenged the prevailing hypothesis that herpes simplex virus type-2 (HSV-2) caused cervical cancer by demonstrating through nucleic acid hybridization that HSV-2 DNA was absent from cervical tumor samples. His systematic investigations led to the identification of HPV-16 in 1983 and HPV-18 in 1984 as the predominant high-risk types in cervical carcinomas. This groundbreaking work, which earned zur Hausen the 2008 Nobel Prize in Physiology or Medicine, established that approximately 70-75% of cervical cancers worldwide are attributable to HPV types 16 and 18. High-risk HPV types drive cervical carcinogenesis through integration of viral DNA into the host genome, resulting in disruption of the viral E2 gene and subsequent overexpression of the E6 and E7 oncoproteins. These oncoproteins orchestrate cellular transformation through multiple complementary mechanisms. E6 Oncoprotein Functions: The E6 protein promotes cellular immortalization and malignant transformation primarily by targeting the tumor suppressor p53 for degradation. E6 recruits the cellular E3 ubiquitin ligase E6AP to form a trimeric complex with p53, marking p53 for proteasome-mediated degradation. This abrogates p53-dependent apoptosis and DNA damage checkpoints, allowing cells harboring genomic abnormalities to survive and proliferate. Additionally, E6 interacts with PDZ-domain proteins, centrosomes, and telomerase, contributing to genomic instability and cellular immortalization. E7 Oncoprotein Functions: The E7 protein binds to and inactivates the retinoblastoma protein (pRb) and related pocket proteins (p107, p130), which normally regulate the G1/S cell cycle transition. E7-mediated disruption of pRb-E2F complexes releases E2F transcription factors, driving expression of S-phase genes and forcing cells into continuous proliferation. Importantly, E7 also promotes proteasome-dependent degradation of pRb, with E7 expression inversely correlating with pRb levels in advanced-stage cervical cancers [7-9].

HPV infection induces extensive epigenetic alterations that facilitate viral persistence and oncogenic progression. E6 and E7 interact with histone acetyltransferases (HATs) and histone deacetylases (HDACs), creating an imbalance that silences tumor suppressor genes while activating oncogenes. Global DNA hypomethylation coupled with promoter hypermethylation of specific tumor suppressors characterizes cervical carcinogenesis. HPV evades immune surveillance through multiple strategies involving viral proteins E1, E2, E5, E6, and E7, which interfere with interferon signaling pathways. This immune evasion enables persistent infection, the critical prerequisite for malignant transformation. While most HPV infections are cleared by the immune system within 1-2 years, persistent infection with high-risk types over decades increases cancer risk substantially. Beyond HPV-16 and -18, five additional high-risk types (HPV-31, -33, -45, -52, -58) contribute significantly to cervical cancer burden. HPV-16 is the most carcinogenic type, associated with more than 50% of high-grade cervical intraepithelial neoplasia (CIN3+) lesions. Viral load studies demonstrate that higher HPV-16 load correlates positively with lesion severity and cancer risk, while HPV-18 shows low loads in precancerous stages but increases dramatically in invasive cancer. Interestingly, HPV-16-related cancers occur at younger ages than other cervical malignancies [10-11].

1.3. Burden of Disease in Relation to Screening and Vaccination Coverage

Organized cervical cancer screening programs have demonstrated remarkable efficacy in reducing disease burden. Population-based studies show that regular Papanicolaou (Pap) cytology screening decreases cervical cancer incidence and mortality by at least 80%. In Iceland, mortality declined by 80% over two decades, while Finland and Sweden achieved reductions of 50% and 34%, respectively. Observational studies report 41-92% mortality reductions among women attending screening, with invitation-based programs yielding 17-79% reductions. However, profound global inequities exist in screening access and coverage. High-income countries achieve screening coverage of approximately 63-84% for lifetime screening among women aged 30-49 years, compared to only 9-19% in LMICs. Within LMICs, coverage ranges from 48% in upper-middle-income countries to merely 4-9% in low-income and lower-middle-income nations. To achieve the WHO target of 70% screening coverage by ages 35-45, 138 of 185 countries would need to substantially increase capacity, with many requiring 7-fold or greater expansion. Recent guidelines increasingly favor HPV primary screening over conventional cytology due to superior sensitivity for detecting high-grade precancerous lesions. The European Commission recommends HPV detection testing for primary screening in women aged 30-50 years, explicitly discouraging cytology-only or co-testing approaches in new programs. In the United States, guidelines now offer three options for women aged 30-65: primary hrHPV testing every 5 years (preferred), cytology alone every 3 years, or co-testing every 5 years. HPV-based screening has proven particularly suitable for resource-limited settings. Novel rapid testing platforms (e.g., careHPV) provide affordable, objective alternatives to cytology, enabling screen-and-treat strategies even in remote areas without cytopathology infrastructure. Only eight lower-middle-income and low-income countries (El Salvador, Guatemala, Haiti, Honduras, Kenya, Myanmar, Rwanda, Uganda) currently recommend HPV screening, highlighting the substantial implementation gap [12-15].

HPV vaccination has demonstrated exceptional real-world effectiveness in preventing cervical cancer. A landmark Swedish study of 1.7 million women found 63% overall reduction in cervical cancer among vaccinated individuals, with 86-88% protection among those vaccinated before age 17 compared to 68% for those vaccinated at ages 17-19. A Scottish cohort study detected zero cases of cervical cancer among women born 1988-1996 who received full vaccination between ages 12-13, representing the first population to achieve complete prevention. HPV vaccines demonstrate near 100% efficacy in preventing persistent infections with vaccine-targeted types and associated precancerous lesions. Despite proven efficacy, global vaccination coverage remains inadequate. As of 2024, HPV vaccine first-dose coverage among the primary target cohort (9-14-year-old girls) reached approximately 57% globally, with completed series coverage at 48%. Critical disparities exist by income level: while high-income countries achieve 68% first-dose coverage, lower-middle-income countries reach only 46%. Regional variation is substantial, with Latin America and the Caribbean achieving 71% coverage compared to just 36% in Central and Southern Asia. In LMICs supported by Gavi, HPV vaccine coverage has increased dramatically from 3% in 2019 to 25% in 2024, with nearly 60 million girls fully immunized by 2024. However, this represents only 25% coverage against the 90% WHO target, underscoring the vast remaining gap. Notably, the transition to single-dose HPV vaccination schedules recommended by WHO's Strategic Advisory Group of Experts (SAGE) in 2022 offers promise for accelerating coverage by reducing logistical and cost barriers [16].

Mathematical modeling studies project transformative benefits if the 90-70-90 targets are achieved. Models predict that girls-only HPV vaccination at 90% coverage would halve cervical cancer incidence in LMICs by 2061, advancing to 2055 with once-lifetime screening and 2048 with twice-lifetime screening. Over the century 2020-2120, achieving 90-70-90 targets would avert approximately 74 million cervical cancer cases and 62 million deaths in LMICs. By 2045, median cervical cancer incidence in low- and lower-middle-income countries would fall by 42%, reaching 97% reduction by 2120. Country-specific modeling for South Korea demonstrates that transitioning from Pap-based to HPV-based screening could accelerate elimination from 2044 to as early as 2038 under current coverage, or 2034 under ideal 90% vaccination and 70% screening scenarios. These projections emphasize that screening strategy effectiveness matters as much as coverage levels, with HPV testing preventing 20-27% more cancers than cytology-based approaches [17].

Multiple structural barriers impede screening and vaccination scale-up in LMICs. These include inadequate healthcare infrastructure, shortage of trained personnel, geographic remoteness, high costs, low awareness, and sociocultural factors. In sub-Saharan Africa, where cervical cancer screening coverage averages only 10.51%, significant wealth-related inequalities concentrate services among affluent populations. Indigenous women in Latin America face particularly acute barriers, exhibiting HPV infection prevalence of 12.6-72% (substantially higher than general populations) yet experiencing reduced access to preventive services. Successful implementation strategies in resource-constrained settings include school-based vaccination delivery (achieving 94% coverage in Rwanda), integration of screening into primary care services, mobile screening units, community health worker programs, and single-visit screen-and-treat approaches. Cost-effectiveness analyses consistently demonstrate that combined vaccination and screening interventions offer exceptional value, with returns of approximately $10 per dollar invested over 30 years.Women living with HIV face six-fold higher risk of developing cervical cancer compared to the general population, with an estimated 5% of all cervical cancers attributable to

HIV infection. This syndemic relationship substantially amplifies disease burden in high HIV-prevalence regions, particularly Eastern and Southern Africa where both conditions converge. Despite elevated risk, screening coverage among women living with HIV in sub-Saharan Africa remains inadequate, highlighting an urgent need for integrated HIV-cervical cancer prevention services. The global and regional epidemiology of cervical cancer reveals profound inequities, with the vast majority of cases and deaths concentrated in LMICs, particularly sub-Saharan Africa, Asia, and Latin America. The historical elucidation of HPV's causal role by Harald zur Hausen provided the scientific foundation for prevention through vaccination and screening. The molecular mechanisms of HPV-mediated carcinogenesis, centered on E6 and E7 oncoprotein disruption of p53 and pRb tumor suppressors, have been comprehensively characterized. Current evidence unequivocally demonstrates that achieving WHO's 90-70-90 targets through scaled-up HPV vaccination, transition to HPV-based screening, and treatment of detected lesions could eliminate cervical cancer as a public health problem. However, substantial gaps in implementation—particularly vaccination coverage of only 25-57% globally and screening coverage below 20% in most LMICs—represent the primary barriers to elimination. Closing these gaps requires sustained political commitment, adequate financing, health system strengthening, and targeted interventions addressing structural, social, and economic determinants of health inequity [18-20].

2. Biology and Classification of Human Papillomaviruses:

2.1. Structure and Genome Organization of HPV

Human papillomaviruses are non-enveloped, icosahedral viruses approximately 50 nm in diameter, composed of 360 copies of the major capsid protein L1 arranged into 72 capsomers—60 hexavalent and 12 pentavalent—forming a $T = 7^d$ icosahedral lattice. Recent high-resolution cryo-electron microscopy (cryo-EM) analysis at 3.1 Ångström resolution has revealed that HPV capsids exhibit dynamic structural properties rather than perfect geometric symmetry. The L1 protein adopts a conserved jellyroll fold with anti-parallel beta-strands (BIDG and CHEF domains) connected by flexible loops that constitute the hypervariable regions and extend outward from the capsomer surface. Critically, the C-terminal arms (residues 402-439) linking adjacent capsomers demonstrate variable conformations despite identical chemical composition, with disulfide bonds forming between Cys428 of the connecting arm and Cys175 of the neighboring capsomer. This structural flexibility, particularly in the solvent-exposed region (His431-Asp439), enables capsid contraction and expansion—a property likely facilitating viral entry and cellular trafficking. The minor capsid protein L2 was previously uncharacterized structurally but recent cryo-EM studies have revealed unambiguous L2 density adjacent to conserved L1 loops. L2 plays essential roles in viral assembly, DNA packaging, and intracellular trafficking, though its complete capsid incorporation mechanisms remain incompletely understood [21].

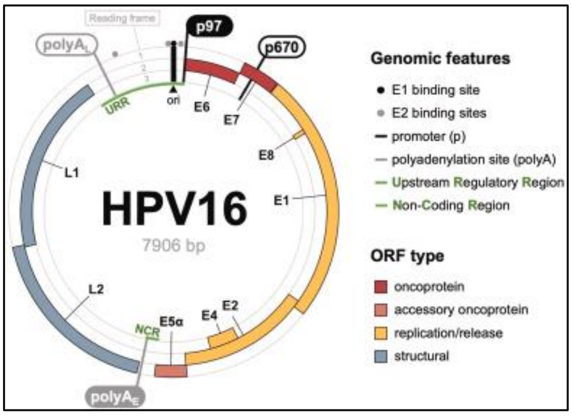

Figure-2: HPV Structure and Genome.

The HPV genome comprises approximately 8,000 base pairs of circulars, double-stranded DNA encoding six early (E1, E2, E4, E5, E6, E7) open reading frames (ORFs), two late (L1, L2) ORFs, and a non-coding long control region (LCR), also designated as the upstream regulatory region (URR) or non-coding control region (NCCR). The early region occupies more than 50% of the genome and encodes regulatory and transforming proteins, while the late region encodes structural capsid proteins. Notably, alternative splicing generates multiple transcripts from a single locus. For example, HPV-16 E6/E7 pre-mRNA transcribed from the P97 promoter undergoes alternative 3′ splice site utilization producing three mRNA species: E6*I*, *E6*II, and E6E7. Crucially, splicing patterns dramatically affect protein levels—unspliced E6E7 mRNA produces low-level E7 translation, whereas spliced transcripts provide more E7 templates and promote enhanced E7 expression. The E1 and E2 proteins function as viral replication factors, with E1 serving as an ATP-dependent helicase recognizing the origin of replication and E2 acting as a transcriptional regulator binding to specific DNA sequences in the LCR. E1 and E2 cooperatively initiate viral DNA replication by recruiting host cell DNA synthesis machinery. The E4 protein, first expressed late in infection, associates with cytokeratin filament collapse and facilitates virion release. Critically, E5, E6, and E7 function as viral oncoproteins mediating cell immortalization and transformation. E6 inactivates the tumor suppressor p53 through proteasome-mediated degradation via interaction with cellular E6-associated protein (E6AP), while E7 primarily disrupts retinoblastoma protein (pRb) function by competing for pRb-binding and promoting its degradation, thereby deregulating E2F-driven S-phase progression. Late gene expression (L1, L2) occurs exclusively in keratinocytes undergoing terminal differentiation in the granular epithelial layer. The late promoter (P670 for HPV-16) is positioned within the E7 ORF and its activation depends upon keratinocyte differentiation signals and proper DNA replication orientation. Recent mechanistic studies demonstrate that viral lagging-strand DNA replication activates the late promoter through interactions with heterogeneous nuclear ribonucleoproteins (hnRNPs) D0B and A/B, which function as transcriptional repressors. Intriguingly, E2 protein at high concentrations induces late gene expression by inhibiting polyadenylation at the early termination signal, permitting read-through transcription into the late region. This molecular switch permits sequential temporal regulation of viral gene expression coupled to epithelial differentiation [22-23].

2.2. Classification into High-Risk and Low-Risk Types

Over 200 human papillomavirus genotypes have been identified and classified into five main genera—Alpha, Beta, Gamma, Mu, and Nu—based on L1 open reading frame sequence homology. Approximately 90% of genotypes fall into either the Alpha genus (infecting mucosae) or Beta/Gamma genera (infecting cutaneous tissues). Within the Alpha genus, genital HPVs are subdivided into phylogenetic species groups, most notably Alpha species 7 (A7) and Alpha species 9 (A9), which group phylogenetically-related types that share similar biological properties. Fifteen mucosal HPV types are classified as definitively high-risk (hr-HPV): HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -68, -73, and -82. Three additional types (HPV-26, -53, -66) are designated probable high-risk. HPV-16 and HPV-18 account for approximately 70-75% of all cervical cancers globally, with HPV-16 being the most carcinogenic type. Current evidence demonstrates a hierarchical pathogenicity among high-risk types: HPV-16 confers the highest oncogenic risk (odds ratio [OR] = 7.96), followed by HPV-58, multiple coinfections, HPV-18, and HPV-35. HPV-16 exhibits approximately 10.85-fold higher risk for cervical carcinoma in women ≥35 years compared to other genotypes, and HPV-16-related cancers characteristically occur at younger ages than other types. Phylogenetically, Alpha species 9 (A9)—comprising HPV-16, -31, -33, -35, -52, and -58—demonstrates greater carcinogenic potential and more aggressive progression to invasive cancer compared to Alpha species 7 (A7; HPV-18, -39, -45, -59, -68, -70, -85). Women infected with A9 types are significantly more likely to develop high-grade cervical intraepithelial neoplasia (CIN) grade 3 compared to A7-infected women. Twelve mucosal HPV types are classified as low-risk (lr-HPV): HPV-6, -11, -40, -42, -43, -44, -54, -61, -70, -72, -81, and -89. These types are primarily associated with benign manifestations including genital warts and condyloma acuminata and rarely progress to malignancy. Beta papillomaviruses comprise over 54 types subdivided into five species (β1-5) that primarily infect cutaneous epithelium, though some β3 types show dual tropism for mucosal tissues. Meta-analysis evidence indicates a specific association between genus Beta HPV seropositivity and cutaneous squamous cell carcinoma (SCC) risk (meta-odds ratio = 1.45), particularly for Beta-2 subtypes, distinct from associations with Alpha or Gamma HPVs. Gamma genus HPVs show only weak associations with SCC risk and appear dependent upon concurrent Beta HPV seropositivity [24-25].

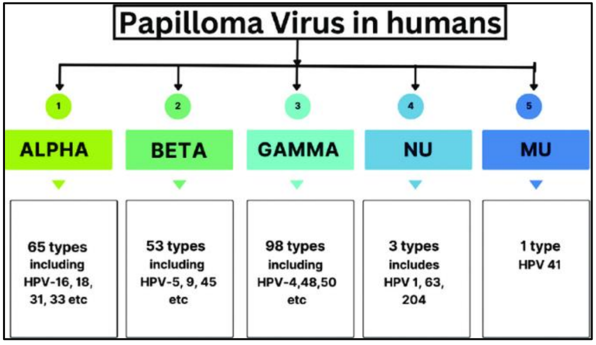

Figure-3: Classification of HPV.

2.3. Transmission Routes and Natural History of Infection

HPV infection occurs following transmission of viral particles to epithelial surfaces through direct skin-to-skin or mucosal contact with an infected individual. Transmission requires epithelial barrier disruption, as an intact epithelial layer provides the predominant protection against viral entry. Microabrasions or microwounds, commonly resulting from sexual intercourse, expose the basement membrane and permit HPV access to basal epithelial cells—the primary target cell population. At specific anatomical sites with naturally accessible basal layers, such as the squamocolumnar junction (SCJ) of the cervix and anal canal transition zones, HPV demonstrates preferential tropism and persistent infection propensity. Emerging evidence suggests an alternative retro-transport mechanism at epithelial transition zones. HPV virions can bind to cellular filopodia and undergo retrograde transport across significant distances, enabling cell-to-cell or cell-to-extracellular matrix (ECM) transfer mechanisms that bypass requirement for direct wounding. This mechanism may explain selective establishment of persistent infections at specific anatomical sites and could reflect differential immune monitoring and microbiome composition at oral versus anogenital mucosae. Primary viral attachment occurs via interaction of the L1 capsid with heparan sulfate proteoglycans (HSPGs) on epithelial cell and basement membrane surfaces. The L1 capsid surface charge influences HSPG binding affinity—HPV types with higher positive charge exhibit stronger heparin inhibition patterns and potentially lower tropism compared to types with reduced charge. Cell surface binding is followed by an unusually slow internalization process occurring over 2-4 hours, markedly slower than most other viruses. HPV internalization proceeds via clathrin- and caveolae-independent endocytic pathways, with acidification of endocytic compartments essential for successful infection [26].

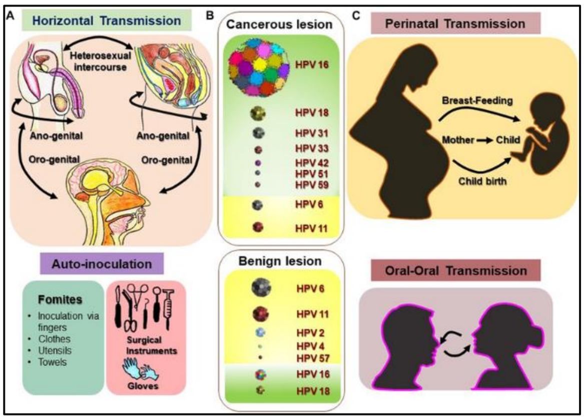

Figure-4: Transmission Routes of HPV.

Following endocytosis, the capsid is transported to the trans-Golgi network where host cyclophilins (CyPs) dissociate the L1 protein from the L2/viral DNA (vDNA) complex. The L2 protein contains conserved nuclear localization signals (nNLS and cNLS) essential for nuclear import and mediates egress of the pseudogenome from endosomes and retrograde transport along microtubules to the nucleus. Critically, HPV nuclear entry requires cell cycle progression into early mitosis—viruses cannot establish productive infection in S-phase-arrested interphase cells due to blocked nuclear import. Upon nuclear envelope breakdown during mitosis, the vDNA-L2 complex associates with host cell chromatin on the metaphase plate and subsequently localizes to promyelocytic leukemia (PML) nuclear bodies (ND10). Following nuclear establishment, HPV maintains its genome as episomal copies—independent circular DNA molecules—in the basal and lower suprabasal layers of stratified epithelium. This episomal persistence represents a non-lytic infection permitting indefinite viral maintenance without cell death. The natural history of HPV infection varies substantially across individuals. Most HPV infections are asymptomatic and transient, with high spontaneous clearance rates: approximately 80-90% of infections become undetectable within 2 years, with more than 50% clearing within 6 months. Average viral clearance times are shorter for men (163 days) compared to women (243 days), and substantially shorter for low-risk types (215 days) compared to high-risk types (284 days). Among high-risk infections specifically, 6-month clearance approaches 73.7%, rising to 86.8% by 24 months. However, this natural history exhibits considerable genotype specificity—HPV-59, -68, -66, -52, and -16 demonstrate the highest persistence rates after 24 months, while HPV-45 exhibits rapid clearance [27].

The stochastic processes underlying HPV clearance remain incompletely understood. Mathematical models incorporating episomal biology reveal that random partitioning of viral episomes during asymmetric cell divisions of infected basal stem cells critically influences infection extinction. In the basal epithelial layer, infected stem cells normally undergo asymmetric divisions producing one daughter stem cell (receiving episomes) and one daughter differentiated cell (losing episomes upon terminal differentiation and surface shedding). However, symmetric cell divisions occasionally occur, generating either two stem cells (favoring viral persistence) or two differentiated cells (eliminating infection). Intriguingly, this model predicts substantial clearance rates—approximately 70% in early infection phases—occurring through purely stochastic mechanisms independent of immune responses. Persistent high-risk HPV infection for ≥1-2 years represents the primary risk factor for cervical precancer and cancer development. However, uncertainty exists regarding whether HPV truly clears completely or establishes latency with potential for reactivation. Recent epidemiological evidence from unvaccinated men demonstrates that infection with HPV-16 increases the 1-year probability of type-specific reinfection by 20.4-fold, with probabilities remaining 13.5-fold elevated even 3 years after initial infection clearance. This elevated reinfection risk in sexually inactive and celibate individuals suggests mechanisms beyond new sexual partner acquisition, including autoinoculation across anatomical sites (supported by HPV DNA detection on fingers and type-concordant infections across sites) or episodic reactivation of latent reservoirs. Studies in HIV-positive women showing increased recurrent infection with higher CD4+ T-cell counts provide additional evidence supporting latent reservoir models, though enhanced susceptibility to autoinoculation remains an alternative explanation [28].

Overall HPV reinfection rates following clearance differ substantially by type: HPV-52 exhibits the highest reinfection incidence (17.96 per 1,000 person-months), while HPV-45 shows minimal conservative reinfection. This substantial reinfection burden indicates that previous natural infection provides incomplete or short-lived type-specific homologous immunity. Clearance of HPV infection fundamentally depends upon adaptive immune responses, particularly T-cell mediated immunity. Cell-mediated immunity through cytotoxic CD8+ T cells expressing granzyme B demonstrates direct correlation with regression of cervical precancerous lesions. HPV has evolved sophisticated immune evasion mechanisms: the intraepithelial, non-lytic life cycle limits systemic immune exposure and viremia. Early HPV gene expression remains limited in initial infection stages, reducing antigenic presentation to the adaptive immune system. The E6 and E7 oncoproteins additionally suppress toll-like receptor 9 (TLR9) expression, impairing dendritic cell recognition and antigen presentation. Despite these immune evasion properties, HPV vaccination generates exceptional protective antibody responses, suggesting that natural infection induces suboptimal humoral immunity while maintaining antigen availability for T-cell priming. The fact that current vaccines are non-therapeutic against established infections underscores the importance of adaptive cellular immunity in clearance, which is not adequately generated through natural infection in all individuals [29].

HPV exhibits striking epithelial tropism—the selective establishment of infection at specific anatomical sites—determined by multiple interrelated mechanisms. Initial viral attachment involves differential HSPG binding affinity based on L1 capsid charge and composition. Additionally, HPV transcription is regulated by epithelial-specific constitutive enhancers within the LCR that respond to tissue-specific transcription factors. For example, the HPV-5 LCR demonstrates twice the transcriptional efficiency in cutaneous keratinocytes compared to HPV-16, while HPV-16 LCR exhibits nearly twice the activity in cervical cells compared to HPV-5. These findings indicate that HPV anatomical tropism is determined at multiple steps in the infection lifecycle—initial attachment, internalization, and differential gene expression regulation—reflecting millions of years of viral-epithelial coevolution. The HPV incubation period exhibits marked variability, ranging from 3-4 weeks to months or even years, likely dependent on initial viral load exposure. Most infected individuals remain asymptomatic throughout transient infections. For those with genital warts caused by low-risk types, symptoms typically develop 6-10 months after initial infection, though some individuals experience much delayed onset. Despite classification into discrete genotypes, substantial genetic heterogeneity exists within individual HPV types. Nucleotide variation within HPV-18 reaches 3.82% with 4.73% amino acid variation, while HPV-45 demonstrates 2.39% nucleotide and 2.87% amino acid variation. This within-type genetic diversity generates distinct lineages and sub-lineages—for example, HPV-16 is classified into four phylogenetic lineages (A, B, C, D) based on evolutionary distance [30-32].

Recent investigations have identified inter-genotype and intra-genotype recombination events in HPV populations, particularly among low-risk types HPV-6 and HPV-11. Analysis of full-length genome sequences identified ten recombination events, with nine being inter-genotype and one intra-genotype, involving exchanges in E1, E2, E7 ORFs and L1/L2 capsid-encoding regions. These recombination events suggest active genetic exchange mechanisms among HPV types and potential mechanisms for generating genetic diversity and novel phenotypes. Contemporary structural, genomic, and epidemiological investigations have dramatically advanced understanding of HPV biology and classification. High-resolution cryo-EM has revealed dynamic capsid architecture enabling cellular trafficking; genomic analysis has delineated complex gene regulation coupled to epithelial differentiation; and longitudinal studies have elucidated the stochastic and immunological processes governing infection clearance versus persistence. Classification of HPV types into distinct risk categories—particularly the identification of Alpha-9 species exhibiting heightened carcinogenic potential—provides essential frameworks for predicting clinical outcomes and prioritizing vaccination and screening strategies. Understanding transmission routes, epithelial tropism determinants, and the natural history of infection remains fundamental for optimizing cervical cancer prevention strategies addressing global health inequities in HPV-related diseaseease burden [33-37].

3. Molecular Pathogenesis of HPV in Cervical Carcinogenesis

3.1. Viral Life Cycle in Cervical Epithelium:

The HPV life cycle initiates following entry of viral particles through microabrasions or microwounds in the stratified cervical epithelium, exposing the basal cell layer. Initial viral attachment involves interaction of the L1 capsid protein with heparan sulfate proteoglycans (HSPGs) on cellular and basement membrane surfaces, followed by transfer to secondary receptors including integrin α6. Upon receptor engagement, HPV undergoes slow internalization over 2-4 hours via clathrin- and caveolae-independent endocytic pathways, with critical requirements for endocytic acidification. Notably, cell cycle progression through mitosis is essential for productive viral infection—G1-synchronized cells remain refractory to infection until M-phase entry permits HPV nuclear entry and episomal establishment. This M-phase requirement reflects the necessity for nuclear envelope breakdown to permit HPV DNA-L2 complex access to chromatin and promyelocytic leukemia (PML) nuclear bodies. Following nuclear entry, the HPV genome establishes itself as extrachromosomal episomal DNA in basal and lower suprabasal epithelial cells, representing a non-lytic, persistent infection state. During the establishment phase (initial infection), E1 and E2 proteins cooperatively initiate viral DNA replication by recognizing and binding to palindromic 12-base pair sequences flanking the viral origin of replication. E2 recruits the ATP-dependent helicase E1 to the replication origin and assembled E1-E2-origin ternary complexes undergo stepwise oligomerization into E1 double-trimers and double-hexameric helicases. E1 helicase activity unwinds viral DNA while recruiting host cell replication machinery components including DNA polymerase epsilon, replication protein A (RPA), DNA polymerase alpha-primase, and topoisomerase I. Critically, E1 physically binds and stimulates DNA polymerase epsilon activity in a manner distinct from other viral systems, conferring processivity by tethering polymerase epsilon to template DNA [38].

During the maintenance phase, viral episomes replicate in synchrony with host cell DNA during S-phase, maintaining relatively constant copy number at approximately 50-100 copies per infected basal cell. This stable maintenance replication depends upon partitioning of episomes to daughter cells, with retention rates approaching 90% per cell division. Notably, E6 and E7 are both required for stable episomal maintenance but not for transient replication of exogenously introduced viral genomes, indicating essential contributions to the productive viral lifecycle beyond their well-established roles in cell cycle deregulation. As infected basal cells divide, daughter cells detach from the basement membrane and initiate terminal differentiation, entering the suprabasal epithelial layers. Within these differentiated, normally non-cycling cells, HPV orchestrates a dramatic switch to high-copy replication amplification. Paradoxically, HPV must reactivate DNA replication machinery in cells that have exited the cell cycle—a challenge overcome through E6 and E7 inactivation of tumor suppressors p53 and pRb. E1 and E2 proteins recruit host cell DNA repair and replication factors, with E2 serving as a critical facilitator of translocation of E1 and associated DNA damage response (DDR) proteins to nuclear foci containing HPV replication complexes. Within these factories, viral DNA undergoes amplification to thousands of copies per cell. Late gene expression (L1, L2 capsid proteins) proceeds through P670 late promoter activation, which critically depends upon epithelial differentiation signals and proper viral DNA replication orientation [39].

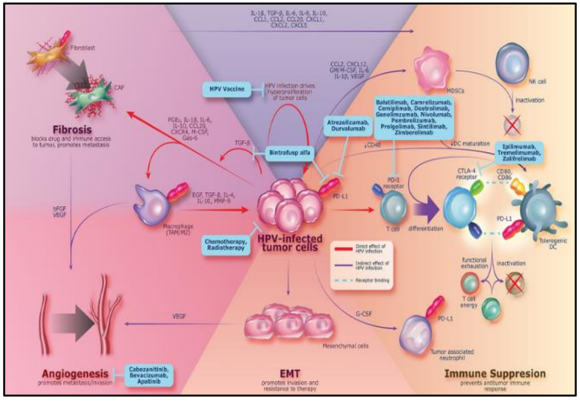

Figure-5: HPV-Cervical Cancer Pathogenesis.

3.2. Oncogenic Roles of E6 and E7 Proteins:

The HPV-16 and HPV-18 E6 oncoproteins inactivate the p53 tumor suppressor through a tripartite mechanism involving direct E6-p53 interaction, recruitment of the cellular E3 ubiquitin ligase E6-associated protein (E6AP), and proteasome-mediated degradation. Structural analysis reveals that E6 recognizes conserved acidic leucine-rich motifs (LxxLL consensus sequences) within E6AP's HECT domain, establishing a functional E6/E6AP heterodimer capable of recognizing p53. Critically, recent mechanistic studies have revealed that E6 itself undergoes ubiquitination by E6AP in a p53-dependent manner, and this E6 ubiquitination is essential for triggering E6AP ligase activity toward p53. Specifically, p53 binding to the E6/E6AP complex induces conformational changes that position E6 for ubiquitination by E6AP, and this ubiquitination step facilitates the transfer of ubiquitin chains from E6AP to p53, marking p53 for 26S proteasome-mediated degradation. The dominance of this mechanism is evidenced by studies demonstrating that dominant-negative p53 mutations (such as R175H) that fail to efficiently bind E6 substantially reduce E6 ubiquitination and block p53 degradation, indicating the complex assembly and sequential ubiquitination model. E6-mediated p53 degradation abrogates multiple critical p53 functions: transcriptional activation of p21 (cyclin-dependent kinase inhibitor), apoptotic response genes, and DNA damage checkpoint genes. Loss of p53 prevents p21-mediated hypophosphorylation of retinoblastoma protein (pRb), eliminating the G1/S checkpoint that normally arrests cells following DNA damage. In differentiated epithelial cells where p53-mediated functions are normally preserved even during differentiation, E6 expression prevents DNA damage-induced G1 arrest, enabling continued proliferation in the face of genomic insults. This is particularly consequential in the suprabasal epithelium where HPV replication generates replication stress, DNA damage, and genomic instability [40].

Additionally, E6 targets multiple PDZ domain-containing proteins for proteasome-mediated degradation, including human discs large (hDlg), human scribble (hScrib), and membrane-associated guanylate kinase (MAGI-1). These PDZ proteins function in cell polarity networks and tight junction organization. E6-mediated degradation of MAGI-1 directly disrupts tight junction integrity through mislocalization of the tight junction protein ZO-1. Par3 protein, a key component of the polarity network, undergoes E6-mediated mislocation without substantial degradation, resulting in impaired tight junction formation. These polarity defects constitute hallmarks of transformation and promote invasion and metastatic potential. The HPV E7 oncoprotein targets all three retinoblastoma family members—pRb, p107, and p130—though with differential efficiency depending on HPV type and E7 variant. High-risk HPV-16 E7 efficiently binds and destabilizes all three pocket proteins, whereas low-risk HPV-6 E7 primarily targets p130. E7 accomplishes this through a conserved LXCXE binding motif within conserved region 2 (CR2) that directly contacts the pocket protein binding groove. This binding interaction disrupts pRb-E2F transcriptional repressor complexes, releasing E2F transcription factors and driving expression of S-phase genes including DNA polymerase, thymidine kinase, and other nucleotide biosynthesis enzymes [41].

Beyond simple competition for E2F binding, high-risk E7 proteins promote proteasome-mediated degradation of pocket proteins through sequences outside the LXCXE motif. Casein kinase II (CKII) phosphorylation of E7 significantly enhances E7's ability to bind and destabilize p130, and in differentiated keratinocytes within the suprabasal layer, E7-mediated p130 destabilization is particularly important for driving S-phase re-entry. The differential expression of pRb family members during the epithelial cell cycle—pRb predominant in proliferating cells, p107 abundant during S-phase, and p130 highly expressed in differentiated cells—indicates that E7's ability to target all three pocket proteins enables viral DNA replication across multiple epithelial compartments. Advanced proteomics investigations reveal that HPV E6 and E7 co-expression dysregulates more than 2,500 cellular proteins in primary keratinocytes. Beyond individual p53 and pRb targeting, E6/E7 expression profoundly disrupts multiple integrated cellular networks: DNA damage response pathways, DNA replication machinery, interferon signaling pathways, proteins associated with cell organization and differentiation, and inflammatory response networks. This genome-wide dysregulation indicates that E6/E7 oncoproteins simultaneously hijack multiple cellular processes to support persistent infection and malignant transformation [42].

3.3. Integration of HPV DNA into Host Genome and Carcinogenic Consequences

Persistent high-risk HPV infection frequently progresses to HPV DNA integration into host chromosomes, representing a critical transition in cervical carcinogenesis. Integration of the viral genome is typically considered a relatively late event in cervical cancer development, with episomal genomes predominating in low-grade lesions (cervical intraepithelial neoplasia [CIN]1 and CIN2), while integration is characteristic of advanced precancerous lesions (CIN3) and invasive carcinoma. However, integration events can vary in frequency by HPV type—all HPV-18-positive samples show integration, whereas only approximately 76% of HPV-16-positive cancer samples demonstrate integrated genomes. HPV integration occurs preferentially at common fragile sites, chromosomal loci susceptible to replication stress due to shortage of replication origins or collision between replication and transcriptional machinery. Approximately 18% of integration breakpoints are associated with FANCD2-marked fragile sites in both cervical and head and neck squamous cell carcinomas. Additionally, HPV integration is significantly enriched at cellular enhancers and super-enhancers, particularly at integration hotspots (defined as five or more integration sites <5 megabases apart). The mechanistic explanation involves HPV E2 protein binding to transcriptionally active chromatin and recruitment to FANCD2-associated fragile sites; consequently, HPV replication factories form adjacent to genomic instability-prone regions, substantially increasing integration probability at these sites. Inflammation constitutes a critical facilitator of HPV integration. Chronic inflammation generates reactive oxygen species and reactive nitrogen species, which induce double-strand breaks (DSBs) in both viral and host DNA, providing substrates for integration through non-homologous end joining and microhomology-mediated end joining mechanisms. This inflammation-mediated integration model is supported by evidence that co-infections with sexually transmitted pathogens causing cervical inflammation act as cofactors in cervical cancer progression [43].

A hallmark consequence of HPV DNA integration is disruption or deletion of the viral E2 open reading frame, occurring in approximately 60-80% of integration events. E2 protein normally functions as a transcriptional repressor of the viral early promoter P97, which drives E6 and E7 expression. Loss or truncation of E2 during integration leads to de-repression and dramatically elevated E6 and E7 expression levels—a critical determinant of oncogenic potential. In cell lines and tumor samples where integrated HPV DNA is present, E6 and E7 expression occurs at constitutively high levels, contrasting sharply with the tightly regulated low-level expression in episomal infections. Notably, E2 disruption is not uniformly required for malignant progression; approximately 24% of HPV-16-positive cancers retain intact E2 genes at integration sites. In these cases, epigenetic or genetic alterations affecting the P97 promoter region result in dysregulated E6 and E7 expression despite intact E2 coding sequence. This indicates that dysregulation of E6 and E7 oncogene expression—regardless of mechanism—represents the essential requirement for oncogenic progression. HPV integration frequently generates fusion transcripts encoding chimeric proteins combining viral sequences with host sequences. Representative fusion proteins include E1-C (E1-cellular), formed through integration events joining viral E1 sequences to downstream host genomic sequences. These fusion proteins typically retain transformative capacity and continue contributing to oncogenic progression. Integration-associated chromosomal rearrangements generate additional mechanisms promoting carcinogenesis. At breakpoint-induced cellular super-enhancers (BP-cSEs) formed adjacent to HPV integration sites, dysregulation of local chromatin and transcriptome occurs. These super-enhancer elements interact with distant chromosomal regions, inducing genomic rearrangements and facilitating oncogene amplification. When flanking or interspersed host DNA containing enhancer elements is co-amplified with viral genomes to 20-40 copies per cell, super-enhancer-like structures drive extraordinarily high E6/E7 expression through "enhancer-hijacking" mechanisms. This exemplifies how physical proximity between viral genomes and transcriptional regulatory elements during integration can generate clonal selection advantages driving tumor progression [44].

HPV integration directly induces chromosomal instability (CIN) and aneuploidy, mechanisms contributing to progressive genomic evolution and intratumoral heterogeneity. HPV-16 E6 expression specifically increases misaligned chromosomes at spindle poles during mitosis—termed "polar chromosomes"—through proteasome-mediated degradation of kinetochore-associated protein CENP-E. Restoration of CENP-E levels substantially reduces polar chromosome formation, indicating direct E6-mediated CENP-E targeting as a mechanistic driver. This specific aneuploidy phenotype—where polar chromosomes frequently rejoin the main nucleus after chromosome segregation—promotes whole chromosome aneuploidy, which significantly predominates in HPV-positive versus HPV-negative squamous cell carcinomas. Both E6 and E7 can independently induce centrosome amplification, leading to multipolar mitotic spindles and increased missegregation. E6-mediated p53 degradation permits continued proliferation of tetraploid cells after cytokinesis failure, which doubles centrosome number. E7 can directly promote centriole overduplication during prolonged S-phase. Lagging chromosomes and chromosome bridges resulting from segregation defects undergo decatenation failure at topoisomerase II, culminating in micronuclei formation—structures strongly associated with structural aneuploidy, genomic catastrophe, and oncogenic evolution. HPV replication—both episomal and following integration—hijacks cellular DNA damage response (DDR) pathways that normally detect and repair DNA lesions. HPV E7 directly impedes double-strand break (DSB) repair by interacting with RNF168, an E3 ubiquitin ligase essential for recruiting 53BP1 and mediating homology-directed recombination. This disruption of DSB repair increases genomic instability and fuels cancer progression [45].

During viral DNA replication, HPV expression induces replication stress through increased origin firing, generating DSBs particularly at common fragile sites prone to replication-associated stress. Rather than triggering apoptosis, HPV modulates ATM and ATR replication stress responses to activate nucleotide biosynthesis and support viral replication while suppressing cellular senescence. E6 and E7 selectively inhibit STAT-1 (which suppresses HPV replication) while activating STAT-5 (which promotes HPV replication) and NF-κB pathways. The FAanconi anemia repair pathway is preferentially activated by E7, which enhances FANCD2 foci and recruits FANCD2 and BRCA2 to chromatin, supporting both viral replication and integration events. HPV E6 and E7 profoundly dysregulate epigenetic marks and chromatin state. HPV-16 E7 increases EZH2 (PRC2 methyltransferase) expression through abrogation of E2F6-mediated repression. While global H3K27 trimethylation may marginally decrease, local epigenetic changes dysregulate specific tumor suppressor loci and activate oncogenic transcriptional programs. HPV E6 downregulates E-cadherin through enhanced DNMT1 DNA methyltransferase activity, contributing to epithelial-to-mesenchymal transition features. Furthermore, HPV E6 and E7 dysregulate multiple other cellular transcription factors essential for epithelial development: Krüppel-like factors, Oct-1, Sp1, and members of the STAT transcription factor family are differentially modulated to suppress apoptotic and differentiation signals while promoting proliferation and viral amplification [46].

The molecular pathogenesis of HPV cervical carcinogenesis involves coordinated, multi-step disruption of cellular homeostasis. During persistent episomal infection, E6 and E7 cooperatively degrade p53 and pRb tumor suppressors, enabling viral replication in differentiated epithelial cells while simultaneously preventing DNA damage-induced apoptosis. These early phases establish persistent infection and dysplastic lesions. Integration of HPV DNA, occurring preferentially at genomic fragile sites and enhancer-rich regions, represents a critical transition to malignancy through E2 disruption, de-repression of E6/E7 oncogenes, virus-host fusion gene generation, and massive chromosomal rearrangements. The integrated state generates chronically elevated E6/E7 expression and chromosomal instability through aneuploidy induction, centrosome amplification, and hijacking of DNA damage responses. These mechanisms collectively transform persistently infected cervical epithelium from dysplastic lesions into invasive carcinoma, representing a paradigm of stepwise viral-mediated carcinogenesis involving both viral and host genetic/epigenetic alterations [47-51].

4. Host Factors and Co-factors Modulating Disease Progression

4.1. Role of Host Genetics in HPV Infection and Cervical Cancer Susceptibility

The p53 tumor suppressor gene harbors a functionally significant polymorphism at codon 72 (rs1042522) that encodes either arginine (Arg) or proline (Pro) residues. The p53 Arg and Pro variants demonstrate distinct susceptibilities to HPV E6-mediated degradation, with mechanistic studies suggesting that the Arg variant may be more rapidly degraded by HPV16 E6. In cervical adenocarcinoma samples, the Arg/Arg homozygous genotype was overrepresented at 71% compared to 47% in controls, with particularly striking enrichment among HPV-positive cancers. Meta-analyses of 28 Asian case-control studies comprising 3,580 cervical cancer patients and 3,827 controls demonstrated that the Pro/Pro genotype conferred increased cervical cancer risk, particularly among Indian populations, though associations were weaker in Chinese, Japanese, and Korean populations. These population-specific differences likely reflect underlying genetic ancestry differences and linkage disequilibrium patterns with other functional variants. Human leukocyte antigen (HLA) polymorphisms profoundly influence HPV persistence and cervical cancer risk through effects on T-cell mediated immune responses. Specific HLA-DRB1 alleles show dramatically different binding affinities for HPV-derived peptide epitopes—HLA-DRB115:03 ("clearance allele") demonstrates stronger peptide binding predictions and is significantly associated with decreased risk of persistent high-risk HPV infection, while HLA-DRB113:02 and HLA-DRB103:01 show weaker peptide binding and increased risk of persistence. *Similarly, HLA-DQB1*05:02 is associated with increased persistent HPV risk. Mechanistically, polymorphisms in HLA alleles generate proteins with lower binding affinity to HPV antigens, reducing recognition by cervical CD8+ T cells and substantially increasing likelihood of persistent infections. Among African women, genome-wide and HLA allele studies identified multiple significant associations: TPTE2, SMAD2, and CDH12 loci associated with persistent hrHPV, with cumulative polygenic risk scores substantially predicting infection outcomes [52-54].

HLA-G, a non-classical HLA molecule, functions as an immunosuppressive checkpoint molecule that can promote immune escape during HPV infection. HLA-G expression is significantly elevated in cervical intraepithelial neoplasia (CIN) and cancer patients with HPV16/18 infection compared to uninfected CIN patients. The HLA-G*01:04:01 homozygous genotype confers significantly decreased HPV infection risk, while HLA-G*01:01:02, HLA-G*01:06, and 3'UTR 14bp insertion alleles associate with progression from preinvasive to invasive cervical cancer. In mother-child studies, the HLA-G*01:01:01/01:04:01 genotype increased risk of high-risk HPV infection in both cord blood and infant oral mucosa, indicating maternal-fetal transmission facilitation. These findings suggest that HLA-G expression shapes the tumor microenvironment to generate immunosuppressive conditions favoring viral persistence and carcinogenesis. Polymorphisms in TLR9, a pattern recognition receptor essential for innate immune responses, associate with differential cervical cancer risk in HPV-positive women. The TLR9 2848 G/A polymorphism in Chinese Han women was significantly associated with increased cervical cancer risk in the presence of HPV16 infection. HPV16 E6 protein actively inhibits TLR9 transcriptional pathways, affecting the immune system's ability to recognize viral pathogens. Dysregulated TLR expression patterns characterize cervical cancer progression—TLR4, TLR7, and TLR9 expression increases with lesion severity, while TLR1 expression decreases in squamous cell carcinoma. Paradoxically, elevated TLR9 without HPV clearance in persistently infected women drives chronic inflammation contributing to malignant transformation, suggesting that HPV manipulates TLR pathways toward oncogenic rather than protective immune responses. Xenobiotic metabolism genes including GSTP (rs1695 GG genotype), DNA repair genes (XRCC1 rs1799782 TT), and apoptosis genes (CASP8 rs3134129 del/del) associate with distinct HPV genotype susceptibility. The XRCC1 TT genotype, conferring reduced DNA repair capacity, particularly associates with HPV58 persistence. Mechanistically, HPV E6 directly binds and displaces DNA polymerase β from the XRCC1-DNA polymerase β complex, hijacking this critical DNA repair pathway to promote uncontrolled proliferation in the differentiation zone where productive infection occurs. Genome-wide association studies have identified additional loci (TPTE2, SMAD2, CDH12) associated with persistent hrHPV infection, with polygenic risk scores substantially improving prediction of infection outcomes [55].

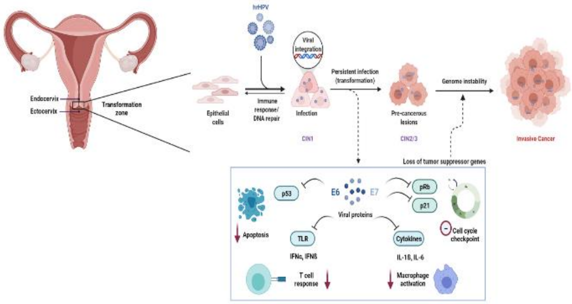

Figure-6: Genomic factors of HPV-cervical Cancer.

4.2. Hormonal Factors and Estrogen Dependence

Compelling experimental evidence from HPV-transgenic mouse models demonstrates that estrogen plays a critical role not only in the genesis of cervical cancer but also in its persistence and continued development. Chronic exposure to physiological estrogen levels sufficient to induce continuous estrus generates substantially larger tumors and more aggressive phenotypes compared to shorter treatment intervals. Critically, withdrawal of exogenous estrogen from tumor-bearing mice results in significantly smaller tumors and partial regression of pre-existing cervical intraepithelial neoplasia lesions, indicating estrogen dependence of established neoplasia. These preclinical findings have profound clinical implications, as they raise the possibility that estrogen dependence characterizing human cervical cancers might render them susceptible to anti-estrogen therapy such as selective estrogen receptor modulators (SERMs) that inhibit estrogen receptor-α (ERα) function in the cervix. Epidemiological studies reveal that long-term use of hormonal contraceptives increases cervical cancer risk in HPV-positive women. Higher doses of ethinyl estradiol (EE) demonstrate stronger associations with HPV-induced lesions—women taking EE doses of 0.03 mg show significantly elevated risk compared to those taking 0.02 mg formulations. The mechanism likely involves estrogen stimulation of cervical ectopy (columnar epithelium eversion into the ectocervix), an anatomical change that exposes the metaplastic transformation zone to HPV acquisition and persistence. The transformation zone contains multipotent stem cells hypothesized to harbor long-term HPV reservoirs and represents the anatomical site of HPV-driven cervical cancer origin in most cases. Multiparity increases cervical cancer risk up to 3.8-fold for seven or more pregnancies, a relationship explained by continuous estrogen elevation during pregnancy. Among HPV-infected women, multiparous women show significantly elevated odds for cervical intraepithelial neoplasia grade 3 (CIN3) progression compared to nulliparous women. This dose-dependent relationship between pregnancy number and cancer risk supports estrogen as a primary driver of HPV-related cervical carcinogenesis [56].

4.3. Impact of Smoking and Immunosuppression

Smoking demonstrates particularly potent synergy with HPV infection in accelerating cervical disease progression. Among HPV-infected women, current smokers show 2.5-fold increased risk for CIN3 compared to nonsmokers, with type-specific analysis revealing even more pronounced effects for HPV16 (2.7-fold increased risk for CIN3). Smoking is associated with 1.33-fold increased relative hazard for incident HPV infection among HIV-positive women and 1.81-fold increased risk specifically for high-risk HPV-16 infection. The mechanistic basis involves smoking-induced immunosuppression affecting both systemic and mucosal immunity, combined with synergistic viral-carcinogen interactions. Importantly, smoking effects are independent of CD4+ cell count, HIV viral load, and antiretroviral therapy use, indicating direct smoking-mediated effects on HPV natural history rather than purely immunosuppression-mediated mechanisms. Women living with HIV face substantially elevated cervical HPV burden and disease progression rates. HIV-positive women are 3.13-fold more likely to acquire incident HPV infection compared to HIV-negative women, with prevalence increasing to 3-fold higher than HIV-negative women at baseline. Critically, persistence is more common when CD4+ T-cell count is reduced, indicating that immunosuppression directly facilitates HPV persistence. Among HIV-positive women, those with lower CD4+ counts show dramatically increased likelihood of multiple HPV type infections simultaneously, generating complex genotypic patterns rarely observed in immunocompetent women. The combination of HIV-related immunosuppression and concurrent smoking substantially amplifies cervical disease risk, suggesting additive and potentially synergistic mechanisms [57].

4.4. Microbiome Alterations and Cervicovaginal Dysbiosis

The cervicovaginal microbiome profoundly influences HPV infection persistence and cervical carcinogenesis through multiple interconnected mechanisms. More than 40% of women with persistent high-risk HPV infection display Community State Type IV (CST IV) cervicovaginal microbiota characterized by marked Lactobacillus depletion and increased diversity featuring anaerobic bacteria including Gardnerella, Megasphaera, Sneathia, and Prevotella spp.. In prospective longitudinal studies, Lactobacillus depletion at time of CIN2 diagnosis associated with significantly lower probability of regression at 12- and 24-month follow-up. Conversely, women with high Lactobacillus crispatus abundance maintain stable microbiota composition across time and exhibit higher clearance rates. The protective mechanisms conferred by Lactobacillus abundance involve production of lactic acid maintaining low vaginal pH, bacteriocin production inhibiting pathogenic colonization, and maintenance of tight epithelial barrier integrity. In dysbiotic states, anaerobic bacteria including Gardnerella vaginalis form biofilms that harbor other pathogenic organisms, generating chronic pro-inflammatory microenvironments. Dysbiosis facilitates HPV persistence through multiple pathways: increased epithelial cell damage and desquamation enhancing viral acquisition, decreased mucus production reducing viral trapping, and chronic production of pro-inflammatory cytokines creating persistent cervical inflammation. Elevated Prevotella and other anaerobic bacteria characterize dysbiotic microbiota associated with HPV persistence and cervical dysplasia progression. The pro-inflammatory state generated by dysbiosis involves elevated vaginal proinflammatory cytokines including TNF-α, IL-6, and IL-8, which can cause chronic cervical inflammation—a critical risk factor for cervical carcinogenesis. Importantly, specific bacterial taxa beyond Lactobacillus depletion predict outcomes—studies reveal that increased vaginal microbiota diversity, particularly higher Prevotella abundance, associates with HPV infection and progression to cervical cancer. However, this relationship appears complex, as Prevotella is also commonly found in bacterial vaginosis and pelvic inflammatory disease without HPV, suggesting microbiota composition effects depend upon overall dysbiotic phenotype rather than individual taxa [58].

4.5. Co-infections with Other Sexually Transmitted Infections

Recent epidemiological evidence demonstrates high prevalence of non-HPV sexually transmitted infections (STIs) in women with cervical intraepithelial neoplasia, with Ureaplasma urealyticum identified as a particularly important cofactor. Multiple STIs contribute to cervical cancer progression by inducing chronic inflammation through microabrasions and microtrauma of cervical epithelium, increasing free radical production, impairing cellular immunity, and promoting angiogenesis. These inflammatory and tissue damage mechanisms create local microenvironments conducive to HPV persistence and oncogenic progression [59].

4.6. HPV Immune Evasion Mechanisms

HPV E6 and E7 oncoproteins have evolved sophisticated mechanisms to antagonize type I interferon (IFN) signaling—the core antiviral innate immune response pathway. E6 directly represses IFN-κ expression through manipulation of host DNA methylation, with this repression reversible by DNA methyltransferase inhibitors. High-risk HPVs decrease K310 acetylation of NF-κB in keratinocytes by enhancing interferon-related developmental regulator 1 (IFRD1) expression, resulting in downregulation of proinflammatory cytokines. HPV18 E6 directly interacts with non-receptor tyrosine kinase 2 (TYK2), reducing IFN-α-induced phosphorylation of both TYK2 and signal transducer and activator of transcription 2 (STAT2) proteins, thereby blocking downstream IFN signaling. HPV16 E7 binds interferon regulatory factor 9 (IRF9), further repressing IFN signaling. Removal of either E6 or E7 substantially increases innate immune gene expression in HPV16-containing cells, indicating E6 and E7 synergistically repress interferon-stimulated genes (ISGs). IFN-β treatment significantly inhibits HPV infection in primary and immortalized keratinocytes, establishing that evasion of IFN signaling represents a critical requirement for HPV persistence. The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway senses cytosolic DNA and initiates antiviral type I interferon responses. HPV exhibits remarkable ability to evade cGAS-STING surveillance through its unique subcellular trafficking mechanism. During infection, HPV L2/viral DNA-containing vesicles remain intact until G1, following nuclear envelope reformation, permitting viral DNA to escape cytoplasmic sensing. In contrast, direct DNA transfection triggers acute and robust IRF3 phosphorylation and downstream interferon responses, while HPV infection elicits minimal cGAS-STING and interferon responses despite equivalent DNA delivery. Perturbation of vesicular membranes during infection renders HPV susceptible to cGAS-STING detection, demonstrating that vesicular trafficking underlies HPV's stealthy properties [60].

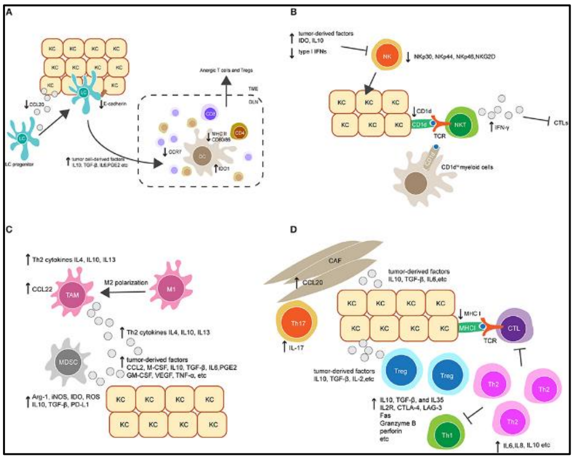

Figure-7: HPV Evasion Strategies.

Beyond initial infection evasion, HPV E1 and E4 proteins directly inhibit cGAS-STING signaling through interactions with STING, TBK1, and IRF3, preventing phosphorylation and nuclear translocation of IRF3. HPV16 E7 specifically interacts with NLRX1, promoting autophagic degradation of STING and blocking cGAS-STING response, while knockdown of E7 or NLRX1 deficiency restores STING signaling and interferon induction. HPV targets multiple pattern recognition receptors (PRRs) to evade innate immunity. HPV E1 protein broadly inhibits antiviral signaling across multiple PRR pathways including RIG-I/MDA5-MAVS and TLR3-TRIF, with E1 reducing mRNA levels of interferon-β, chemokine CXCL10, and interferon-stimulated gene 56 (ISG56). Critically, HPV E1 inhibits phosphorylation and nuclear translocation of IRF3, a process essential for type I interferon production. HPV E5 impairs TLR3-TRIF signaling, while E6 downregulates TLR3 expression, limiting immune detection of viral components. HPV-transformed cells exhibit altered HMGB1-TLR4 signaling, with alterations in TLR expression and activation contributing to the oncogenic potential of cells expressing HPV oncogenes. While global TLR expression patterns change during lesion progression, specific components including SARM1 upregulation and MyD88 downregulation facilitate HPV immune evasion. The TLR4-HMGB1 signaling axis emerges as highly expressed in HPV-positive cervical cancers, potentially explaining how HPV-transformed cells evade immune surveillance. HPV demonstrates remarkable ability to suppress interferon signaling not only in infected epithelial cells but also in surrounding stromal fibroblasts. HPV16 E5-dependent mechanisms suppress interferon-stimulated genes and extracellular matrix remodeling genes in stroma, with transcriptional analysis revealing significant downregulation of STAT1, IFNAR1, IRF3, and IRF7 in stromal fibroblasts. This systemic suppression of antiviral responses in the tumor microenvironment creates conditions permitting unopposed tumor progression [61].

4.7. Micronutrient Deficiencies Modulating Immune Function

Vitamin D deficiency is associated with persistent HPV infection and CIN progression. Across five studies comprising 727 women, oral and vaginal vitamin D supplementation significantly reduced CIN2/3 lesions and improved inflammatory markers. High-dose vaginal vitamin D suppositories (12,500 IU daily) resolved HPV and CIN lesions in most study participants, suggesting potent local anti-inflammatory effects. Mechanistically, vitamin D regulates immune system function through effects on regulatory T cells (Tregs), dendritic cells, and antimicrobial peptide (AMP) production critical for mucosal barrier function. Across four studies of 1,130 women, folate and vitamin B12 supplementation showed protective effects in reducing HPV persistence and CIN progression, with favorable effects on DNA methylation and viral clearance. Folate may slow cervical lesion evolution by controlling DNA methylation and gene expression linked to tumor suppression, while B12 regulates DNA synthesis and repair processes in concert with folate. Zinc supplementation associates with improved HPV clearance and lesion regression, with intravaginal zinc citrate administered twice weekly for three months demonstrating 64.47% HPV clearance versus 25.51% in controls ($p < 0.001$) and substantially reduced risk of persistent HPV (OR 0.079). Selenium supplementation, particularly in Iranian trials, improved oxidative and immune profiles and associated with CIN2 regression. These trace minerals enhance antioxidant capacity and support CD8+ T-cell mediated immune responses essential for HPV clearance [62,63].

HPV-associated cervical carcinogenesis emerges as a multifactorial disease process where viral persistence results from coordinated suppression or evasion of multiple host immune mechanisms. Host genetic polymorphisms in p53 codon 72, HLA alleles, TLR9, and DNA repair genes substantially influence susceptibility to HPV acquisition and persistence, with population-specific variation reflecting genetic ancestry and linkage disequilibrium patterns. Hormonal factors, particularly sustained estrogen exposure from oral contraceptives, pregnancy, and potentially endogenous ovarian production, provide critical cofactors enabling viral-driven carcinogenesis. Smoking and HIV-associated immunosuppression synergize with HPV to dramatically accelerate disease progression through combined immunological and metabolic disruption. Cervicovaginal dysbiosis is characterized by Lactobacillus depletion and proliferation of pro-inflammatory anaerobic bacteria facilitates HPV persistence through epithelial barrier disruption and chronic inflammation. HPV has evolved exceptional sophistication in antagonizing innate immunity through multiple non-redundant mechanisms: evasion of cGAS-STING surveillance via vesicular trafficking, direct suppression of interferon signaling through interactions with STAT, IRF, and NF-κB pathways, hijacking of pattern recognition receptors to promote rather than prevent infection, and systemic suppression of antiviral responses in both infected epithelium and surrounding stroma. Micronutrient deficiencies in vitamin D, folate, B12, zinc, and selenium impair mucosal and cellular immunity, promoting viral persistence. Understanding these interconnected host factors and viral immune evasion mechanisms provides essential frameworks for identifying high-risk individuals, developing adjunctive therapeutic interventions targeting immune dysfunction, and potentially improving cervical cancer prevention strategies beyond vaccination and screening alone [63-64].

5. Diagnostic and Screening Approaches Targeting HPV

5.1. Cytology-Based Screening versus HPV DNA Testing

Landmark prospective studies directly comparing HPV DNA testing with cervical cytology (Papanicolaou smear) demonstrate substantially superior sensitivity for detecting cervical intraepithelial neoplasia grade 2 or higher (CIN2+) and more advanced disease. In a large multicenter study of 30,552 women aged 30-64 years, HPV testing demonstrated 97.9% sensitivity for detecting CIN3+ (95% confidence interval [CI]: 96.1–99.1) compared with cytology sensitivity of 45.4% (95% CI: 40.4–50.5), while HPV testing demonstrated specificity of 94.4% versus cytology specificity of 97.9%. Among 241 women screened concurrently with liquid-based cytology (LBC) and HPV DNA testing, HPV DNA exhibited 95.24% sensitivity versus LBC's 89.68%, though specificity was slightly lower (72.16% versus 79.92%). The area under the receiver operating characteristic curve for HPV DNA (0.79) exceeded that for LBC (0.74), establishing HPV DNA's superior overall diagnostic accuracy. Critically, the lower specificity of HPV DNA compared to cytology reflects HPV's detection of both transient and persistent infections, including those unlikely to progress to cancer. However, HPV's markedly superior sensitivity translates to earlier detection of precancerous lesions before progression to invasive disease. A crucial observation is that HPV testing permits substantially extended screening intervals—five years for HPV testing versus three years for cytology—while maintaining equivalent or superior safety. In resource-limited settings, primary HPV screening every five years achieving 70% coverage predicts 60-67% reduction in cervical cancer mortality, substantially outperforming visual inspection with acetic acid (VIA) or cytology strategies. Notably, polymerase chain reaction (PCR)-based HPV testing demonstrates even higher sensitivity (95.5%) but lower specificity (67.4%) than commercial HPV testing platforms, indicating that

PCR may detect non-pathogenic genotypes and transient infections. This explains why commercial HPV tests, which employ hybrid capture or signal amplification technologies with higher specificity thresholds, demonstrate superior clinical utility for triage decisions [65-67].

5.2. Co-Testing Strategies and Marginal Benefit

Co-testing (simultaneous HPV testing and cytology) was advocated for cervical cancer risk stratification, but emerging evidence demonstrates negligible additional clinical benefit compared with primary HPV testing alone. In an analysis of 10,643 cervical cancer cases, co-testing detected only 2 additional CIN2+ cases compared to HPV screening alone. European Commission guidelines explicitly recommend against co-testing, citing low certainty of evidence for additional benefit, moderate-to-high undesirable effects including unnecessary colposcopy referrals, and substantial cost without clinical benefit. The lack of co-testing benefit reflects the mechanistic reality that HPV testing's superior sensitivity for detecting high-grade lesions is the rate-limiting step in screening performance. Cytology adds minimal incremental risk stratification when HPV positivity is already present. Furthermore, co-testing's requirement for cytopathology expertise reduces program equity and feasibility in resource-limited settings lacking laboratory infrastructure.

5.3. Primary HPV Testing with Triage Strategies

Primary HPV testing effectiveness varies meaningfully across age groups. In analysis of 1,160,981 Chinese women, HPV testing with HPV-16/18 genotyping plus cytology triage increased CIN2+ detection by 36% (rate ratio [RR]: 1.36) for women aged 35-44 years and 34% (RR: 1.34) for women aged 45-54 years compared with cytology alone. However, among women aged 55-64 years, HPV genotyping with cytology triage did not significantly increase CIN2+ detection (RR: 1.09, 95% CI: 0.91–1.30) while increasing colposcopy referral rates by 19%, indicating diminished net benefit in older populations where HPV prevalence substantially decreases. These findings have important programmatic implications: HPV testing with extended genotyping appears optimal for women aged 35-54 years to maximize lesion detection, while cytology triage alone may balance detection and referral efficiency in older cohorts [68].

5.4. Emerging Biomarkers for Enhanced Triage

p16/Ki-67 dual staining represents a paradigm shift in HPV-positive triage, identifying oncogenic transformation through simultaneous expression of two cell-cycle regulatory proteins. p16 is a cyclin-dependent kinase inhibitor expressed exclusively in G0 phase of the cell cycle (normally), while Ki-67 is expressed throughout G1 through S phase but not in G0. Simultaneous expression of both markers in the same cell indicates aberrant cell-cycle dysregulation characteristic of HPV-induced oncogenic transformation. In the PALMS study (Primary ASC-US and LSIL Marker Study) of 27,349 women, p16/Ki-67 dual stain demonstrated 82.8% sensitivity and superior specificity compared to conventional cytology for detecting CIN2+, achieving this performance while requiring fewer colposcopies per case detected (3.81 versus 4.73 for cytology). In the IMPACT trial involving 35,263 women screened by HPV testing and cytology, dual stain triage would have resulted in 49% versus 56% colposcopy referral ($p < 0.001$) compared to HPV genotyping and cytology, achieving higher colposcopy efficiency (4.09 versus 5.35 colposcopies per CIN2+ detected). Critically, negative predictive value for CIN3+ within 1 year exceeded 98%, indicating robust reassurance for women testing negative by dual stain. FDA approval in 2020 for dual stain triage of HPV-positive women has led to incorporation into major management guidelines. Recent systematic reviews demonstrate consistent superiority across geographically diverse settings and clinical populations, with particular utility in reducing unnecessary colposcopy referrals in resource-limited settings where colposcopy capacity constraints limit screening effectiveness [69].

HPV E6/E7 mRNA expression represents a promising marker of active oncogenic transformation, as continuous E6/E7 oncoprotein expression is essential for maintaining the dysplastic phenotype. E6/E7 mRNA detection shows markedly stronger correlation with cervical disease severity than HPV DNA: mRNA positivity increased from 5.0% in CIN1 to 25% in CIN2, 50% in CIN3, and 70.1% in cervical cancer, demonstrating a dose-response relationship with lesion grade. For detecting CIN2+, E6/E7 mRNA demonstrated 65.2% sensitivity (95% CI: 57.5%-72.2%) and 90.0% specificity (95% CI: 84.6%-93.4%), compared with HPV DNA sensitivity of 84.8% and specificity of 74.1%. Meta-analyses demonstrate that E6/E7 mRNA testing exhibits significantly higher specificity than HPV DNA testing (relative specificity 1.66) and higher specificity than E6/E7 oncoprotein testing (relative specificity 1.34), indicating superior ability to distinguish transient from clinically relevant infections. Furthermore, women with persistent hrHPV infection demonstrated 40-fold higher odds of expressing E6 oncoprotein compared to incident infections, and E6 oncoprotein positivity showed 21.2-fold increased odds of subsequent HPV DNA persistence. This suggests mRNA/oncoprotein testing may better identify women requiring closer surveillance or aggressive treatment. HPV E6 and E7 oncoprotein detection has emerged as a complementary approach to mRNA testing, with systematic review revealing superior specificity to both DNA and mRNA testing (relative specificity 1.34 and 1.66, respectively). E6/E7 oncoprotein tests show stronger correlation with cervical lesion severity than HPV DNA positivity alone, supporting their role in risk stratification [70].

5.5. Liquid-Based Cytology Technologies

Liquid-based cytology platforms (SurePath, ThinPrep) show variable performance depending on brand, age, and computer-assisted reading technology employed. In routine Danish screening, SurePath/FocalPoint demonstrated 85% increased detection of CIN3+ in women aged 23-29 years compared to manually read conventional cytology, while ThinPrep showed only an 11% non-significant increase. However, SurePath/FocalPoint doubled the frequency of false-positive tests at all ages, potentially contributing to overtreatment. For women aged 45-59 years, both SurePath and ThinPrep showed either nonsignificant changes or decreases in CIN detection, suggesting that performance improvements are age-dependent. ThinPrep in particular demonstrated increased specificity at older ages, with false-positive test frequencies decreasing by two-thirds compared to conventional cytology. These findings underscore the importance of brand- and age-specific validation when implementing liquid-based cytology platforms [71].

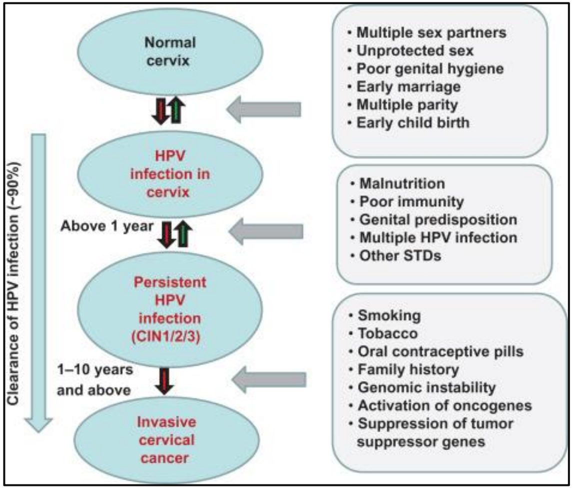

Figure-8: Clinical pattern of HPV infection and Cervical cancer.

6. Prevention and Therapeutic Strategies

6.1. Prophylactic HPV Vaccines: Types, Coverage, and Impact

Three prophylactic HPV vaccines have been licensed globally: bivalent vaccine (Cervarix), quadrivalent vaccine (Gardasil/Gardasil-4), and 9-valent vaccine (Gardasil-9). The bivalent vaccine targets HPV-16 and HPV-18, responsible for approximately 70% of cervical cancers. The quadrivalent vaccine adds low-risk types of HPV-6 and HPV-11, responsible for ~90% of genital warts. The 9-valent vaccine (9vHPV) adds five additional high-risk types (HPV-31, -33, -45, -52, -58), increasing cervical cancer prevention potential from ~70% to ~90%. Cross-protection against non-vaccine types occurs, though with substantially higher magnitude in the bivalent vaccine trials than in quadrivalent trials. For HPV-31 persistent infection, cross-protection was 77.1% with bivalent versus 46.2% with quadrivalent vaccine; for HPV-45 high-grade lesions (CIN2/3), cross-protection reached 100% with bivalent versus −51.9% (suggesting slight increased risk) with quadrivalent [72].

6.2. Single-Dose Vaccine Efficacy

Recent evidence supports WHO's 2022 recommendation for single-dose HPV vaccination schedules, particularly relevant for resource-limited settings. In the KEN SHE study from Kenya, single-dose bivalent and 9-valent vaccine efficacy reached 98% and 99%, respectively, over three years. In Tanzanian girls aged 9-14 years, one-year post-single-dose vaccination, immunoglobulin G seropositivity exceeded 99% for HPV-16 and 93% for HPV-18, with stability maintained over five years. This remarkable single-dose efficacy, if substantiated in additional populations, has transformative implications for global vaccination scale-up, substantially reducing logistical requirements and cost barriers [73].

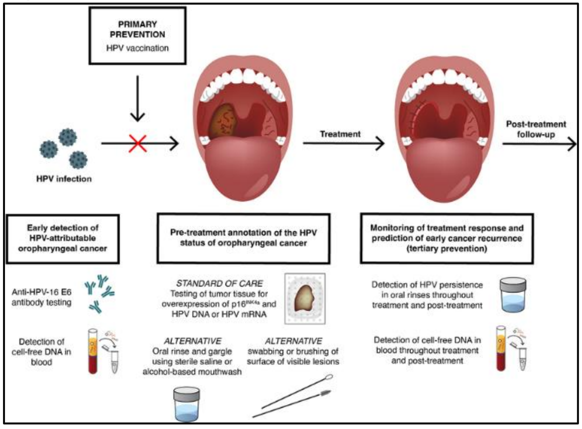

Figure-9: Primary, secondary, and tertiary prevention strategies of HPV.

6.3. Global Coverage and Epidemiological Impact

As of 2024, global HPV vaccine first-dose coverage among girls aged 9-14 years reached 57%, with completed series coverage at 48%. Regional variation is substantial: Latin America and Caribbean achieved 71% coverage, while Central and Southern Asia reached only 36%. In high-income countries, coverage approaches 68%, while lower-middle-income countries achieve only 46%. Critical gaps persist in sub-Saharan Africa, where more than half of cervical cancer cases occur yet vaccination coverage remains below 10%. Despite incomplete global coverage, documented impact on cervical cancer incidence has emerged in pioneering vaccination programs. In England, HPV immunization programs markedly reduced cervical cancer and CIN3 incidence in eligible cohorts (women <30 years), with particularly pronounced reductions in those vaccinated at age 12-13. Mathematical models predict that achieving 90% vaccination coverage at age 9 years could reduce cervical cancer incidence by 99% (range: 89–100%) in resource-limited settings, projecting elimination as a public health problem [74].

6.4. Therapeutic Approaches Under Investigation

Unlike prophylactic vaccines, therapeutic HPV vaccines target E6 and E7 oncoproteins to induce immune responses against established HPV-positive lesions. Multiple vaccines target these transforming proteins: TG4001, VGX-3100, ISA101, and PDS0101 have entered clinical trials. Meta-analysis of 18 phase II-III clinical trials demonstrated that therapeutic vaccines achieved CIN2/3 lesion regression rates averaging 58% (range: 27-90%), with corresponding HPV clearance rates averaging 48% (range: 13-79%). Across systematic reviews, therapeutic vaccines demonstrate superior safety profiles compared to standard treatments, with most adverse events being mild to moderate local reactions. However, efficacy remains modest when used as monotherapy compared to surgical/ablative approaches. The most promising data emerge from combination strategies with immunotherapy (described below). A phase 1/2 clinical trial demonstrated exceptional activity when combining the HPV-16 therapeutic vaccine PDS0101, the tumor-targeting interleukin-12 antibody-drug conjugate PDS01ADC, and the anti-PD-L1/TGF-β bifunctional antibody bintrafusp alfa in advanced HPV-associated cancers. In immune checkpoint blockade (ICB)-naive HPV-16–positive patients, the triplet combination achieved 30.5% response rate compared with 10% for ICB-resistant patients. Critically, patients developing multifunctional HPV-16–specific CD4+ and CD8+ T-cell immune responses showed substantially better clinical responses. This triple combination demonstrated acceptable toxicity with improved overall survival outcomes in both ICB-naive and ICB-resistant patient populations, supporting further development [75].

Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have demonstrated clinical efficacy in cervical cancer, with mechanistic rationale grounded in HPV-associated immune biology. PD-L1 expression correlates with HPV positivity and increases with CIN grade and tumor stage in cervical cancer. Approximately 35% of cervical squamous cell carcinomas express PD-L1, with enrichment at tumor-stroma interfaces. HPV E6 protein directly upregulates PD-L1 expression through miR-143/HIF-1α axis regulation, creating mechanistic linkage between viral oncogenes and immune checkpoint activation. Phase II studies of durvalumab in recurrent/metastatic head-and-neck squamous cell carcinoma revealed that HPV-positive patients achieved higher response rates and improved survival compared to HPV-negative subjects, suggesting HPV-specific immune priming enhances checkpoint inhibitor efficacy. Pembrolizumab and other PD-1 inhibitors are currently under investigation in combination with chemoradiation for locally advanced cervical cancer, with trials demonstrating improved progression-free survival in high-risk patient populations. The rationale for combining PD-1/PD-L1 inhibition with HPV-targeted interventions reflects that persistent HPV infection generates chronic activation of regulatory T cells and myeloid-derived suppressor cells, creating an immunosuppressive tumor microenvironment. PD-1/PD-L1 blockade reverses this suppression, restoring CD8+ T-cell effector function and permitting recognition of HPV-transformed cells [76].

6.5. Role of HPV Status in Guiding Management and Prognosis

Robust meta-analytic evidence demonstrates that HPV-positive cervical cancer status predicts significantly superior overall survival (OS) and disease-free survival (DFS) compared to HPV-negative disease. Pooled analysis of 17 studies including 2,838 cervical cancer patients revealed HPV-positive cervical cancer associated with superior OS (pooled hazard ratio [HR]: 0.610, 95% CI: 0.457–0.814, P = 0.001) and DFS (pooled HR: 0.362, 95% CI: 0.252–0.519, P < 0.001). In one prospective study of 40 women with locally advanced cervical cancer treated with curative radiotherapy, HPV positivity represented the only significant predictor of superior overall survival, disease-free survival, and local progression-free survival (all P < 0.05). HPV-positive tumors additionally demonstrated significantly better clinical complete remission rates (67% versus 33%, P = 0.04). HPV-negative cervical cancers represent a distinct biological entity with substantially worse prognostic features and outcomes. Meta-analysis demonstrated that HPV-negative cervical cancer patients exhibited 1.99-fold increased risk of lymph node metastasis (95% CI: 1.46–2.72, P < 0.0001), 1.42-fold increased likelihood of advanced staging (Ib2 or higher; 95% CI: 1.15–1.77, P = 0.0001), and 2.36-fold increased risk of adenocarcinoma (95% CI: 1.44–3.89, P = 0.005). HPV-negative cervical cancers are typically diagnosed at significantly more advanced stages—median age 72 versus 49 years for HPV-positive patients—and frequently represent adenocarcinoma or non-squamous histology. HPV-negative patients demonstrated dramatically inferior survival: disease-free survival of 59.8 months versus 132.2 months for HPV-positive disease, and overall survival of 77.0 months versus 153.8 months for HPV-positive neoplasms. This survival disparity likely reflects advanced FIGO stage and lymph node metastasis predominating in HPV-negative cohorts rather than independent HPV negativity prognostic effects [77].

Among HPV-positive cervical cancers, specific genotype associations with prognosis emerge. Cervical cancer patients infected with HPV-18 demonstrated significantly worse disease-free survival (HR: 2.66, 95% CI: 1.44–4.94), progression-free survival, and overall survival compared to HPV-16–infected or other HPV type-infected patients. HPV-18 positivity associated with worse PFS compared to HPV-16 (HR: 1.34, 95% CI: 1.06–1.70). Some evidence suggests HPV-58 and HPV-31 infection predict favorable outcomes, while HPV-33 predicts poorer prognosis. Interestingly, HPV-16 monoinfection (versus multiple HPV types) in some studies predicted superior response to radiotherapy, though conflicting results exist regarding HPV-16-

specific prognostic effects when compared against HPV-negative disease. These genotype-specific differences warrant further investigation with larger cohorts to determine if HPV genotyping should guide treatment intensification or de-intensification strategies. Critically, intact HPV E2 gene presence (indicating episomal rather than integrated genomes) showed trends toward better disease-free survival compared to E2-disrupted (integrated) genomes. This molecular marker of persistent episomal infection, reflecting less accumulated genomic instability, may represent an independent favorable prognostic factor warranting investigation as a stratification factor for therapeutic de-escalation trials in favorable-risk cohorts [78].

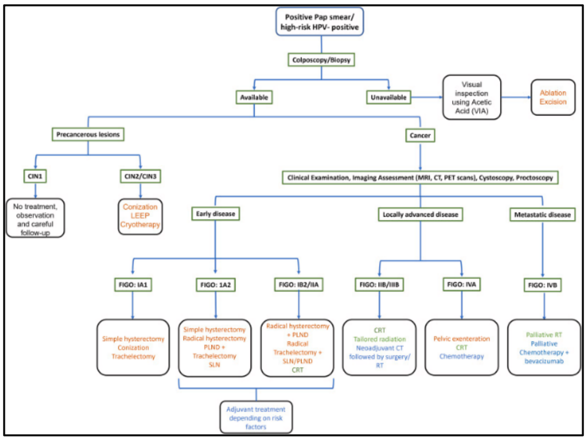

Figure-10: Management of Cervical cancer.

6.6. Treatment Response and HPV Status Interplay

While HPV positivity predicts superior overall prognosis, some evidence suggests variable chemotherapy/radiotherapy response by HPV genotype. One study of 89 squamous cell carcinoma patients found poorer radiotherapy response in HPV-16–positive patients (21% persistent disease after radiotherapy versus 5% in HPV-16–negative patients; P = 0.096), suggesting possible HPV-16–specific biologic differences in treatment sensitivity requiring validation in larger cohorts. These observations have important clinical implications: HPV-positive cervical cancer patients may represent candidates for treatment de-intensification strategies (reduced chemotherapy doses, shortened radiation courses, or alternative modalities) in the quest to improve quality of life while maintaining curative intent. HPV-negative patients, conversely, warrant intensified treatment approaches and potentially augmented systemic therapy. Future HPV genotype-specific therapeutic trials are warranted to determine if HPV-16 infection specifically requires intensified approaches while other types might benefit from de-escalation strategies [79].

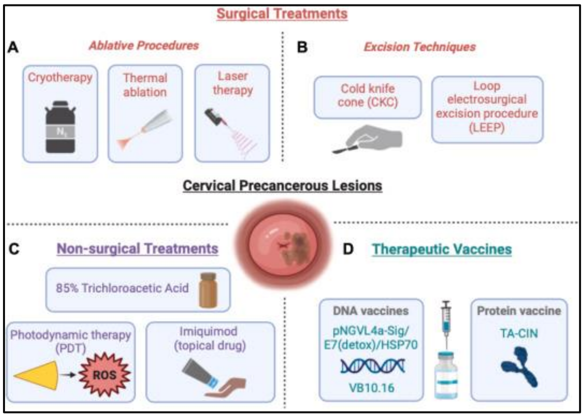

Figure-11: Management of HPV-positive cervical cancer.

Contemporary cervical cancer screening and prevention strategies have undergone paradigm shifts driven by evidence from large prospective studies and real-world implementation. Primary HPV testing demonstrates unequivocally superior sensitivity and cost-effectiveness compared to cytology, permitting substantially extended five-year screening intervals while maintaining equivalent or superior cancer detection safety. Emerging biomarkers—particularly p16/Ki-67 dual stain cytology and HPV E6/E7 mRNA/oncoprotein testing—enable refined risk stratification of HPV-positive women, substantially reducing unnecessary colposcopy referrals while maintaining high negative predictive values. Prophylactic HPV vaccines, particularly the 9-valent formulation, demonstrate remarkable efficacy with emerging evidence supporting single-dose schedules, though global coverage remains inadequate at 48-57%, especially in high-burden regions. Therapeutic vaccines combined with immune checkpoint modulation represent promising strategies for managing established HPV-related lesions and cancers, with phase 1/2 data suggesting durable responses in both immunotherapy-naive and resistant populations. HPV status emerges as a critical prognostic factor and treatment stratification variable: HPV-positive cervical cancers exhibit substantially superior overall and disease-free survival compared to HPV-negative disease, with potential implications for treatment de-intensification; conversely, HPV-negative patients present at advanced stages and warrant intensified therapeutic approaches. HPV genotype-specific prognostic associations (particularly HPV-18 worse prognosis) warrant validation in larger cohorts to guide future genotype-stratified therapeutic trials. Integration of these diagnostic, preventive, and therapeutic advances within organized population-based programs remains critical for reducing global cervical cancer burden, particularly in resource-limited settings where combined screening/vaccination approaches could achieve 90% disease elimination [80].

Conclusion:

Cervical cancer exemplifies a largely preventable malignancy in which persistent infection with high-risk HPV is a necessary but not sufficient cause. The development of cancer reflects a prolonged, multistep interaction between viral factors—particularly E6/E7-mediated disruption of p53 and pRb, genomic instability, epigenetic reprogramming, and immune evasion—and host determinants including genetic susceptibility, hormonal exposure, smoking, HIV-related immunosuppression, cervicovaginal dysbiosis, and micronutrient deficiencies. At the population level, the greatest burden falls on women in low- and middle-income countries, where gaps in HPV vaccination, HPV-based screening, and access to treatment sustain marked geographic and socioeconomic inequities. Evidence from large trials and real-world programs clearly shows that high-coverage prophylactic vaccination, primary HPV testing with appropriate triage, and timely management of pre-invasive disease can avert the vast majority of cervical cancers. HPV status and genotype increasingly inform prognosis and may guide future treatment de-intensification or intensification strategies. Moving from proof of principle to elimination will require sustained political commitment, financing, health-system strengthening, and integration with HIV and sexual-reproductive health services. Future priorities include context-specific implementation research, affordable point-of-care diagnostics and therapeutics, and targeted interventions for high-risk populations, alongside rigorous monitoring of progress toward the WHO 90-70-90 targets to maintain momentum and accountability.

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