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Review Article

Epigenetic Modification and Host Gene Silencing Profile Induced by High-Risk HPV Strains in Cervical Cancer

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Abstract: Persistent infection with high-risk human papillomavirus (HR-HPV) is the primary driver of cervical cancer; however, viral presence alone is insufficient to induce malignancy. The progression from initial infection to invasive carcinoma requires a coordinated series of alterations in both the viral genome and the host cell's regulatory machinery. This review focuses on three principal mechanisms by which HR-HPV bypasses host regulatory controls: epigenetic modifications, immune evasion, and endocrine signaling. Specifically, we describe how the viral oncoproteins E6 and E7 recruit host DNA methyltransferases—particularly DNMT1, DNMT3A, and DNMT3B—to silence tumor suppressor genes such as *CCNA*, *hTERT*, and *E-cadherin* via promoter hypermethylation. Beyond DNA methylation, HPV disrupts histone acetylation and methylation patterns through interactions with p300/CBP, the NuRD complex, and Polycomb group proteins, while simultaneously dysregulating non-coding RNAs and specific microRNAs to reinforce this transcriptionally silenced state. The review further details how HPV escapes immune clearance by driving a Th1-to-Th2 cytokine shift, downregulating MHC class I expression, and recruiting myeloid-derived suppressor cells and regulatory T cells to the cervical microenvironment. Additionally, we discuss the role of cofactors, focusing on the synergistic interaction between estradiol and HPV oncogenes; this interaction promotes local immunosuppression via estrogen receptor alpha signaling on stromal fibroblasts and infiltrating immune cells. We also examine the contribution of high parity as a key epidemiological risk factor. A comparative analysis of patient data across three distinct studies is presented to illustrate how demographic and reproductive variables correlate with cervical lesion severity in different populations. Ultimately, cervical carcinogenesis stems from multi-pathway interactions where viral oncogenes, epigenetic changes, immune escape, and hormonal factors act in unison rather than in isolation, highlighting the critical need for integrated diagnostic approaches that capture this biological complexity.

Keywords: HPV, HR-HPV, LCR, ORF, CIN, Neoplasia, Cervical cancer, Estrogen, Parity.

INTRODUCTION

Persistent infection with high-risk HPV types is well established as principal etiological agent of cervical carcinogenesis yet viral presence alone is insufficient for malignant transformation. Progression to invasive disease additionally requires the accumulation of host gene and epigenetic modulation [1]. Viral etiologies underlie approximately 15-20% of human malignancies, underscoring the substantial oncogenic contribution of diverse viral agent to carcinogenesis [2]. Among these, Human Papillomavirus is a key cause of cancer and has a major impact on cancer rates. HPV belongs to the family Papillomaviridae and infects squamous epithelial cells found in the skin and mucous membranes [3, 4]. More than 200 types of HPV have been identified and are divided into two groups depending on their ability to cause cancer: low-risk HPV (LR-HPV)[5], and high-risk HPV (HR-HPV). Cancers linked to HPV account for about 5 % of all cancers each year, with HPV16 and HPV18 being the most common types[6]. HPV infects the basal cells of the stratified squamous epithelium, often entering the body through small cuts or wounds on the skin [7]. It is associated with cancers of the genital area, such as cervical cancer, penile cancer, anal cancer, vulvar cancer, and vaginal cancer, as well as head and

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neck squamous cell carcinomas [1]. The life cycle of HPV is closely related to the development of epithelial or mucosal tissues and ends with the release of new virus particles [8]. Most HPV infections do not cause noticeable symptoms or only result in small growths like warts on the hands or feet. During high-risk HPV infections, various changes in the genetic material of both the virus and the host cells have been observed. These changes include reduced methylation of viral DNA and increased methylation of genes that normally prevent cancer in host cells [9]. Also, changes in the structure of proteins involved in controlling gene expression have been noted. For example, the E6 and E7 proteins of the virus interact with or alter cellular proteins that regulate these processes, which increases the activity of enzymes that change the way DNA is packaged inside cells. This leads to significant changes in how genes are expressed in the host. Additionally, the E2 gene of HPV contains regions that are easily affected by methylation. These epigenetic changes together lead to long-term infections, transformation of cells, and the development of invasive cancers by disrupting the normal function of genes that suppress tumors and promote cancer [9].

Features of HPV

HPV is a non-enveloped virus with double-stranded DNA of approximately 8000 bp enclosed in an icosahedral protein capsid, inside which is a circular viral DNA associated with histone of 7906 bp [10]. The HPV capsid is composed of 2 key proteins: the major and minor structural proteins L1 and L2(Figure 1). The L1 subunit forms 72 pentameric capsomers whose C-terminal interaction stabilizes the shell, and the mature particle gains additional rigidity via disulfide bonds. L2 is present in small variable amounts, with some exposed areas on the surface of the mature virions, while a significant portion remains internally [11, 12]. Papillomaviridae family, classified into three primary regions which are early regions that encode for early proteins (E1-E7) (Figure 1). E6 promotes p53 degradation through the ubiquitin-dependent proteolytic pathway by interacting with E6-associated protein (E6AP), which is an E3 ubiquitin ligase, causing uncontrolled cellular proliferation. The other one is late regions that encode for two proteins (L1 and L2) as well as an LCR (long control region). The early proteins are involved in the process of replication and transcription of HPV DNA, while the late proteins are major capsid proteins (L1) and the minor protein (L2) that form a capsid at the end of a productive viral cycle in fully differentiated outermost layers of epithelial or mucous cells. The genome classified within the Papillomaviridae family is organized into three functionally distinct regions. These regions are demarcated by two polyadenylation(pA) sites -The early pA (AE) site and the late pAL (AL) site, which conduct transcription and stability [13, 14]. Moreover, two viral promoters categorized as early (p97 for HPV16 and 31, p105for HPV18) and late (p742 for HPV31, p670 for HPV16, phase of the viral life cyclep811 for HPV18) oversee the regulation of viral gene expression and exhibit activity during distinct phases of the viral life cycle [15]. The early promoter located at E6 ORF (Open Reading Frames) consists of a TATA box 35 nucleotides upstream of its transcription start site, directing the transcription of the viral early protein. Whereas the late promoter lacks the TATA box and is responsible for the transcription of late genes[16]. The HPV genome exhibits polycistronic characteristics, employing various forms of alternative splicing to produce the resulting HPV mRNA transcripts. The early (E) region comprises over 50% of the viral genome and encodes six ORFs, such as E1, E2, E6, E7, E4, and E5. On the other hand, the late region, denoted as (L), comprises 40% of the viral genome, consisting of L1 and L2. The latter encodes for structural proteins and major and minor proteins, respectively. The LCR, a non-coding region spanning approximately up-to 10% of the viral genome, is situated between the termination point of ORF L1 and the initiation codon E6. The LCR harbors the origin of replication and binding sites for both host and viral transcription factors [14]. Human papillomavirus type 16 (HPV16) utilizes three reading frames to encode its proteins: frame 1 directs synthesis of E7, E1, E5, and L2; frame 2 encodes E6, E2, and L1; and frame 3 is dedicated exclusively to E4 [15]. E1 is a highly conserved protein of approximately 68 kDa that is essential for viral genome replication [17]. Although E1 alone binds only weakly to the LCR origin, its affinity is markedly increased upon complex formation with E2. The principal role of E2 is to recruit E1 to the replication origin; together, E1 and E2 attract host replication factors to initiate DNA synthesis at that site [17]. E1 also possesses intrinsic ATPase and 3′→5′ helicase activities, which are necessary for origin unwinding and replication-fork progression. E2, a ~50 kDa protein, is required for both replication and transcriptional regulation. It is organized into three regions: an N-terminal conserved transactivation domain (TAD), a hinge region, and a C-terminal DNA-binding domain (DBD) [18]. The TAD mediates interactions with viral and cellular proteins, including E1, to initiate replication, and it can bind E7, thereby inhibiting E7's transforming activity. In high-risk HPV, the E2 TAD can indirectly promote apoptosis through interactions with APC activators Cdh1 and Cdc20, and it associates with bromodomain-containing protein 4 (Brd4), facilitating tethering of the viral genome to segregating mitotic chromosomes. The DBD has been reported to interact with p53, suggesting a role for E2 in directly inducing apoptosis [18]. Via its DBD, E2 can function as either an activator or a repressor of oncogene (E6 and E7) transcription, with its regulatory outcome dependent on E2 abundance, isoform composition (produced by alternative splicing), and the repertoire of host proteins with which it interacts[18].

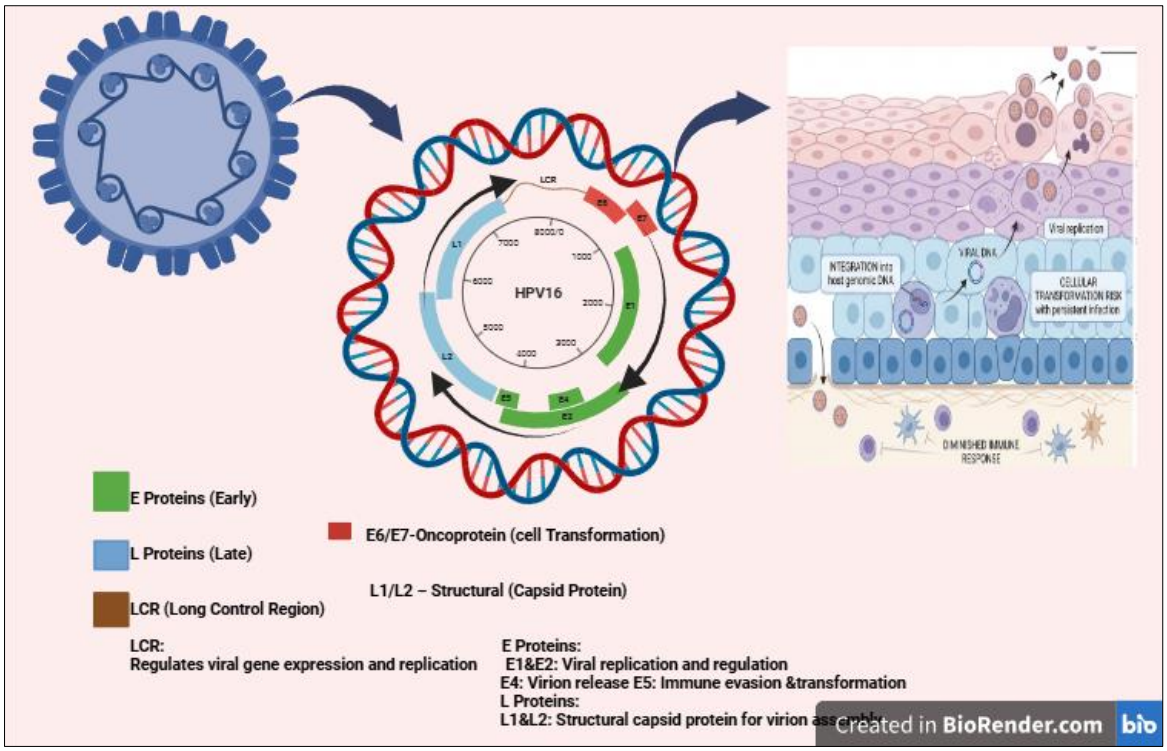

Figure 1: Structure of HPV DNA highlighting the important structural proteins, oncoproteins, and capsid protein. Besides there is a brief representation of HPV persistent infection and evasion from basal epithelial layer to integration into host cell. Created in https://BioRender.com

Persistant Viral Infection and HPV Genome Integration

High-risk HPV can establish a persistent infection instead of executing a typical productive cycle. This sustained infection drives a step-by-step pathological progression where low-grade abnormalities, i.e., low-grade squamous intraepithelial lesions (CIN-1), gradually evolve into severe high-grade squamous intraepithelial neoplasias (CIN2-3), which is termed as high-grade squamous intraepithelial lesion (HSIL), occasionally culminating in invasive cervical carcinoma(Figure 2). Cervical epithelial lesion and carcinogenesis are significantly influenced by persistent human papilloma virus (HPV) infection. According to statistical analysis, a women's lifetime risk of contracting HPV is as high as 80%; however, the majority of these infections are temporary with the immune system eliminating 90%of cases only 2-3% of HPV infection transform into cervical carcinogenesis.

An identical diagnostic classification is applied to other lower anogenital tracts, specifically using the terms vulvar [19], and anal [20], intraepithelial neoplasia [21, 22]. Notably, spontaneous tissue regression back to a completely healthy state is frequently observed across these different stages. A major driver of malignant transformation is the physical integration of the viral DNA into the host genome, which disrupts the productive viral life cycle and renders large fragments of its genetic material functionally inert. This structural insertion typically fractures the ORF of the viral E2 gene, and the ORFs for E1,E4, or E5 can also be compromised [23, 24]. Because the functional E2 protein operates as a natural transcriptional repressor of viral oncogenes, its elimination permanently disrupts the negative feedback loop [25]. This results in the continuous biosynthesis of the primary viral protein, E6 and E7, a fundamental prerequisite for cellular transformation. This integration process manifests in two primary structural configurations: Type 1, featuring a solitary integrated viral copy, and Type 2, characterized by multiple full-length viral copies integrated in head-to-tail concatemers [26].These viral–host genetic hybrids are generated through a combination of virus-directed DNA replication and cellular recombination. In Type 2 integration, the host cell activates an epigenetic defence mechanism that hypermethylates the viral long control region (LCR), silencing oncogenic expression in every integrated copy except for the single copy positioned at the 3' boundary of the concatemer [27]. This localized transcriptional silencing may mitigate total E6/E7 levels, functioning as a protective buffer against highly destructive host genomic instability [28]. Furthermore, transcripts derived from integrated viral fragments display significantly greater molecular stability than those generated from unintegrated, episomal viral bodies, granting a distinct selective growth advantage to HPV-dependent cells [20]. Integrated HPV sequences cause severe host genomic damage, including gene amplifications, large deletions, inversions, and chromosomal translocations[23]. Alternatively, carcinogenesis can entirely bypass integration. In this pathway, direct chemical methylation of *E2* promoter binding motifs prevents the E2 protein from repressing

viral oncogenes. This allows unintegrated, episomal viral genomes to maintain high E6 and E7 expression, driving a distinct subset of cervical cancers [29]. Behavioural variations exist between major high-risk strains: HPV16 frequently remains completely episomal throughout transformation, whereas HPV18 almost universally integrates into the host chromosome [30]. Overall, viral integration frequency directly reflects the specific malignant potential of different high-risk HPV genotypes [19].

Chromosomal instability resulting from persistent infection promotes viral genome integration into host DNA [31]. Insertion typically occurs at common fragile sites (CFSs) through microhomology-mediated repair, causing insertional mutagenesis by either mutating tumor suppressors or activating oncogenes [32]. This integration clusters within common fragile sites (CFSs) and hot spots via a micro-homology-mediated repair mechanism [32]. Notably, these integrations frequently upregulate host *hTERT* expression and alter genomic loci near *c-Myc*, directly supporting malignant transformation [33, 34]. Viral persistence and integration trigger a vast array of downstream epigenetic alterations, including altered viral and host DNA methylation landscapes, chromatin remodelling via histone modifications, and the dysregulation of host microRNAs. This epigenetic manipulation complements the non-epigenetic protein interactions of E6 and E7. Together, these dual pathways accelerate cell proliferation, evade the host immune response, and block natural cell death pathways.

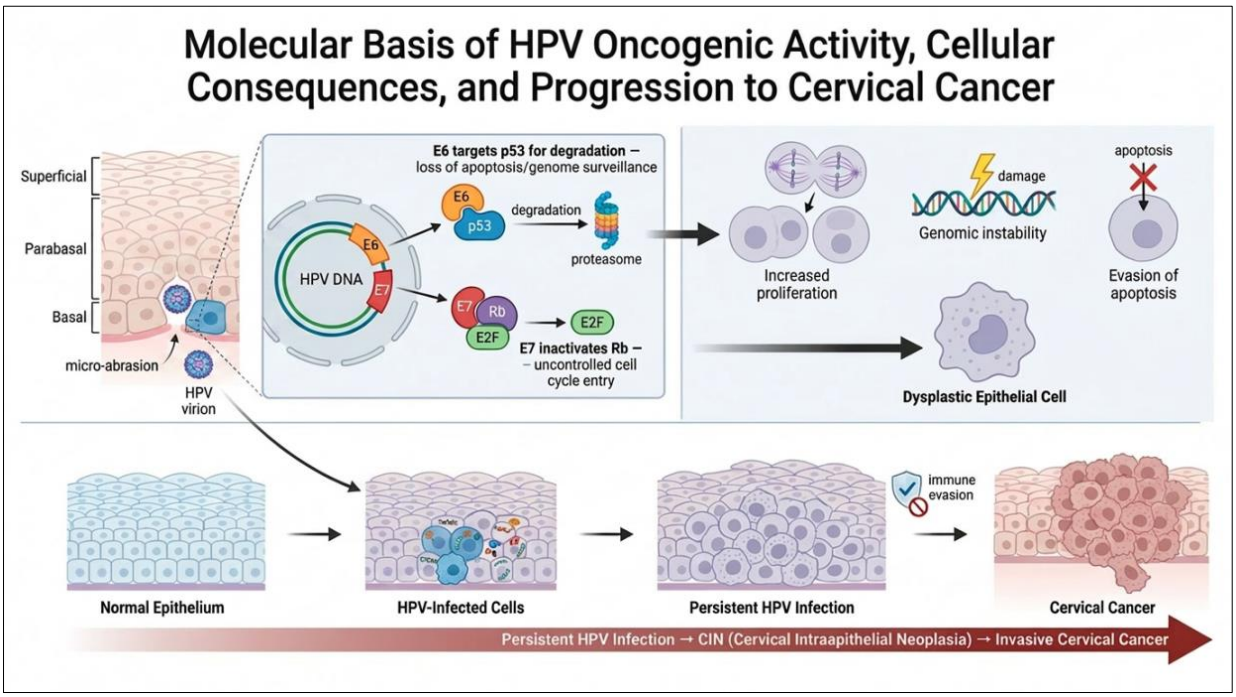

Figure 2: Molecular representation of vital oncoprotein E6 & E7 in degrading p35 and leading to loss of apoptosis by E6 and inactivating Rb by E7 and induce uncontrolled cell cycle, which is a systemic progression from normal epithelium to occurrence of cervical cancer

Epigenetic Modulation and DNA Methylation

Instead, progression relies heavily on heritable changes in gene expression that leave the primary DNA sequence intact [35]. These epigenetic shifts disrupt intrinsic defences networks and activate oncogenic pathways, facilitating malignant conversion [36]. Within the context of high-risk Human Papilloma Virus (HR-HPV) infection this process of epigenetic rewriting becomes particularly pronounced. It operated through three functionally interconnected molecular pathway: molecular alteration in DNA methylation histone modification and dysregulation of non-coding RNA species.

DNA Methylation

DNA methylation involves the covalent addition of a methyl group to the cytosine residue within CpG dinucleotides, catalysed by the DNMT enzyme family [35]. Among the various epigenetic alterations studied in HPV- associated cervical neoplasia, aberrant DNA methylation has generated the most extensive scientific attention [36]. Under physiological conditions, the DNA methyltransferase enzyme, principally DNMT1, DNMT3A, and DNMT3B, establishes and perpetuates specific methylation patterns by appending a methyl group to the cytosine residue situated within CpG dinucleotide sequences [35]. These clusters are characteristically concentrated in the regulatory region proximal to gene promoters and exert a transcriptional silencing function when methylated, and participate in genomic imprinting and chromosome inactivation [35]. Conversely, global hypomethylation at repetitive elements promotes chromosomal instability in cancer. HPV16E7 activates DNMT1 by two distinct routes:

direct physical binding via its zinc-finger CR3 domain, and transcriptional induction through the pRb/E2F pathway [37]. E6 independently upregulates DNMT1 by suppressing p35, while high-risk E7 also elevates DNMT3A and DNMT3B protein levels, collectively producing sustained pathological hypermethylation of critical TSG promoters [37]. Documented targets include CCNA1(cyclin A 1, hypermethylation rising from 0% in healthy controls to 93%in cervical carcinomas), hTERT (whose promoter methylation paradoxically blocks repressive sequences and elevates telomerase) [38]. E-cadherin (silenced by both E6and E7 via DNMT activity inhibition with consequent recovery of Langerhans cell-mediated immune surveillance)[37]. Multi-gene methylation panels encompassing CDH1,DAPK1, and HIC1 show a significant and progressive increase in promoter methylation across successive stages of cervical neoplasia, underscoring the stage-dependent nature of epigenetic silencing and the potential of such panels as diagnostic biomarkers [39].

Histone Modification and Chromatin Remodeling

HPV oncoprotein engages a remarkably broad array of histone-modifying and chromatin remodelling enzymes. Regarding histone acetyltransferases (HATs) E6 inhibits p300/CBP mediated acetylation of p53,repressing p53targets gene independently of p53 degradation, while E7 forms a ternary complex with p300/CBP and pRb, promoting pRb, acetylation and its subsequent degradation [4]. E7 also binds PCAF(KAT2B),reducing its HAT activity toward histones H3/H4 and cooperating with E6 to suppress the IL-8 promoter, thereby dampening neutrophil and T-lymphocyte chemotaxis and facilitating immune evasion [4]. Regarding HDACs:E7 is associated with HDAC1/HDAC2 indirectly through Mi2β, a component of the NuRD complex; this interaction represses IFN-β transcription (suppressing antiviral immunity) while paradoxically activating E2F2 transcription in differentiated cells to facilitate viral genome replication. Beyond HAT and HDAC interactions, E7 engages additional chromatin regulatory systems. It associates with BRG1/SMARCA4 of the SWI/SNF remodelling complex, altering c-fos transcriptional control, and induces the demethylases KDM6A and KDM6B, which globally erase the repressive H3K27me3 mark [40]. A notable consequence is p16INK4A overexpression—normally a senescence trigger, but because E7 concurrently targets pRb for proteasomal degradation, the CDK4/6-pRb checkpoint through which p16 would arrest proliferation is non-functional, allowing cell cycle progression to continue unchecked. E7 also associates with polycomb group proteins (BMI1, PCGF2, CBX4, RING1, MGA, L3MBTL2) and the repressor E2F6, dismantling polycomb-mediated silencing of cell cycle genes, and induces EZH2 in a manner that promotes PRC4 rather than canonical PRC2 activity, resulting in H1K26 modification [40].

On the E6 side, inhibition of the arginine methyltransferases CARM1 and PRMT1 reduces histone methylation at p53-responsive promoters, suppressing p53 occupancy at those sites through a mechanism independent of p53 protein degradation [41]. E6 additionally blocks SET7, which ordinarily stabilizes p53 by monomethylating it at K372; loss of this modification accelerates E6-mediated p53 turnover. E6 further destabilizes TIP60/NuA4 through the ubiquitin ligase EDD/UBR5—removing the H4 acetylation that normally recruits the BRD4 repressor to the HPV early promoterthereby de-repressing the promoter and sustaining oncoprotein expression. Finally, studies of W12 clones harbouring integrated HPV16 genomes reveal that oncogene output per viral template is governed by epigenetic chromatin accessibility, with occupancy of BRG1/INI1, MLL1, SETD1A, and histone acetyltransferases at the long control region being key determinants—confirming that the epigenetic status of integrated viral chromatin directly shapes neoplastic progression [41].

Non-Coding RNA Dysregulation

Non-coding RNAs constitute a third regulatory axis subverted by HPV. The IncRNA HOTAIR normally scaffolds polycomb repressive complexes to target loci, maintaining transcriptional silencing; direct interaction between HOTAIR and HPV16 E7 disrupts this scaffolding function, permitting aberrant gene expression at otherwise silenced genomic regions[42]. More broadly, HPV positive cells exhibit widespread dysregulation of additional IncRNAs and microRNAs that collectively promote tumor cell proliferation, augment invasive and migratory capacity, and suppress apoptosis and cell-adhesion pathways. Rather than acting in isolation, these altered non-coding RNAs reinforce existing DNA methylation and histone modifications, creating a feed-forward loop that stabilizes the transformed cell state [42, 41].

HPV Mediated Immune Evasion in Cervical Cancer

The cervical epithelium constitutes the principal interface where HPV encounters and subverts the host immune system. Keratinocytes, despite being non-professional antigen-presenting cells, serve as the initial defenders against HPV because the virus replicates within these cells without inducing cytolysis, leaving infected cells structurally intact and capable of displaying viral peptides on MHC class I molecules for immune inspection [43]. Cytokines such as interferon-gamma can additionally trigger MHC class II expression on keratinocytes, further boosting their ability to stimulate cell-mediated immunity [43]. At the molecular level, Toll-like receptor 9 on keratinocytes detects double-stranded HPV DNA and sets off an innate signalling cascade that produces type I interferons, tumour necrosis factor-alpha, interleukin-18, and chemokines including CCL2, CCL20, and CXCL9, which collectively recruit natural killer cells, natural killer T cells, macrophages, and dendritic cells to the site

of infection. These professional antigen-presenting cells engulf HPV-derived material and channel it toward T cell activation, thereby linking innate detection to adaptive effector responses, including CD4+ helper T cell polarisation, CD8+ cytotoxic T lymphocyte priming, and B cell antibody production [43]. However, HPV counters this coordinated defence at the adaptive level with particular effectiveness [44]. The Th1 arm of CD4+ T helper cells, which orchestrates the cell-mediated response responsible for viral elimination, is actively undermined by HPV oncoproteins E5, E6, and E7, which drive a polarisation shift from a Th1 toward a Th2 phenotype [45]. This reprogramming blunts the cytotoxic immune machinery needed for viral clearance and is a key contributor to both HPV persistence and the progression of cervical intraepithelial neoplasia [45]. Concurrently, the CD8+ cytotoxic T lymphocyte arm, which normally destroys infected cells through direct recognition, is crippled because E5 and E7 diminish the expression of MHC class I molecules on the cell surface, rendering infected cells functionally invisible to cytotoxic T lymphocytes and producing the characteristically weak or absent HPV-specific CTL responses observed during chronic infection [44]. Clinical evidence supports this model: in patients with regressing genital warts or early cervical intraepithelial neoplasia, detectable HPV-specific CD8+ T cell populations track with lesion regression and viral clearance, whereas in individuals with persistent infection, these cytotoxic populations are markedly reduced or undetectable, reflecting the cumulative impact of HPV's multi-pronged immune evasion strategy on both innate recognition and adaptive effector function [43].

FACTORS DRIVING TO CERVICAL CARCINIGENESIS

Although high-risk HPV infection initiates cervical dysplastic changes, viral exposure alone rarely causes overt malignancy. Progression from initial infection to invasive carcinoma occurs over years through cumulative interactions with genetic, lifestyle, and environmental cofactors. While persistent infection with high-risk HPV strain especially HPV16 and HPV18 is the dominant cause found in over 95% of cases,infection alone rarely leads to cancer [46]. Most infected women clear the virus naturally through immune defence mechanisms, other biological factors must drive progression toward malignancy [46].Among these cofactors sex steroid hormones,particularly estrogen and progesterone have emerged as significant modulator of cervical carcinogenesis. Estrogen is known to stimulate cervical cell proliferation and enhance viral persistence, whileprogesterone exert both protective and promoting effects depending on the biological context [47].High-risk HPV evades host immunity by downregulating antigen-processing machinery and interferon signalling, while estrogenic compounds this immunosuppression by recruiting regulatory T cells and myeloid-derived suppressor cells to the cervical microenvironment. Epidemiological evidence links prolonged use of oral contraceptives and high parity with an elevated risk of cervical cancer underscoring the importance of hormonal exposure in disease progression [46].

Estrogen Signalling in Cervical Carcinogenesis

Estrogen, particularly estradiol (E2), is a critical cofactor in HPV-driven cervical carcinogenesis. While HPV infection is the primary etiological agent, estrogen acts synergistically with HPV oncogenes E6 and E7 to promote tumor initiation, persistence, and progression [48, 49]. Estrogen promotes cervical cancer through multiple molecular pathways. It stimulates cell proliferation in cervical epithelial cells via estrogen receptor alpha (ER-α) signalling[48], and during the early stages of HPV infection, estrogen increases viral load, exacerbates viral persistence, and worsens the severity of cervical lesions [50].

Estradiol (E2), the predominant circulating estrogen, exerts its biological effects through both genomic and non-genomic signaling pathways. In the classical genomic pathway, E2 binds to the nuclear estrogen receptors Era and ERb, or to the membrane-bound G protein-coupled estrogen receptor 1 (GPER1/GPR30). The resulting hormone-receptor complexes translocate to the nucleus, where receptor dimers bind to estrogen-responsive elements [22], on target gene promoters, thereby regulating transcription of genes involved in cell proliferation, survival, and epigenetic modification. This genomic signaling effectively positions the estrogen receptor as a transcription factor that governs the proliferative capacity of cervical epithelial cells [51]. In addition to this classical mechanism, estradiol can activate non-genomic signalling independently of ERs, through transactivation of growth factor receptors including the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR), and fibroblast growth factor receptor (FGFR) [52]. These pathways trigger rapid cytoplasmic signalling cascades, enabling estradiol to influence cellular responses without direct nuclear involvement.

Critically, the biological impact of estrogen signalling extends beyond the transformed keratinocytes themselves. Estradiol modulates the tumor microenvironment through paracrine effects on infiltrating immune cells, stromal cells, and cancer-associated fibroblasts (CAFs), all of which contribute to the immunosuppressive milieu that facilitates HPV persistence and cervical cancer progression.

Estrogen Mediated HPV Oncogene Activation in Cervix

Estrogen reaches the cervical tumor via two distinct routes, and the local route is arguably the more significant one for cancer progression. Systemically,

estradiol(E20) travels through the bloodstream from the ovaries under normal physiological regulation. However, what makes cervical carcinoma particularly dangerous is that the tumor itself becomes a site of autonomous estrogen production. The enzyme aromatase, encoded by the CYP19A1 gene, is upregulated within cervical tumor tissue, where it converts circulating androstenedione and testosterone directly into estradiol [48-53]. Researchers have documented that while circulating plasma estrogen levels remain within normal ranges, the concentration of estradiol measured inside the tumor microenvironment is substantially elevated, confirming that the local biosynthetic machinery is the primary source of the hormone driving malignancy [48-53]. This pattern of local synthesis is further supported by the observation that aromatase distribution within the tissue mirrors the distribution of estradiol itself, both being found within the cytoplasm of transformed keratinocytes, the infiltrating immune cells, and the stromal compartment. Beyond the aromatase pathway, cervical tissue also possesses an alternative route for local estradiol production, the enzyme estrone sulfatase converts into estrone, which is then further reduced to estradiol by 17beta-hydroxysteroid dehydrogenase type 1 [48-54]. This dual-capacity for local estrogen synthesis essentially gives the tumor an internal hormonal fuel supply that operates independently of systemic endocrine regulation.

One of the most counterintuitive aspects of estrogen's role in cervical cancer is that its effect on tumor cells is entirely dose-dependent, producing opposite outcomes at different concentrations. At physiological levels typical of the menstrual cycle, estradiol promotes the proliferation of HPV-positive cervical cells and simultaneously suppresses the apoptotic pathways that would otherwise eliminate damaged or transformed cells [48-56]. This creates a permissive environment where early malignant cells can expand unchecked. However, when estradiol concentrations rise above this physiological threshold, the hormone begins to interfere with ribosomal protein translation machinery, triggering a cascade that ultimately kills cancer cells[48, 56]. This high-dose killing effect operates through activation of phosphodiesterase 3A, which in turn activates the Schlafen family member 12 protein, a negative regulator of cell proliferation. The downstream effect is mitochondrial shutdown and the blockade of anti-apoptotic proteins Bcl2 and Mcl1, tipping the balance toward programmed cell death[56].What adds another layer of complexity is that the estrogen receptor alpha, or ERα, is the critical molecular mediator of these effects, and its expression pattern changes dramatically during cervical carcinogenesis. Transgenic mouse models engineered to express HPV16 or HPV18 E6/E7 oncogenes demonstrate that tumor development requires both the presence of estrogen and functional ERα signalling. Remarkably, as cervical cells progress through the stages of intraepithelial neoplasia toward invasive carcinoma, they progressively lose ERα expression, with mature tumor cells showing no detectable ERα at all [51]. This apparent paradox, where the tumor depends on estrogen yet loses the receptor for it, is resolved by two mechanisms: first, the tumor cells can still receive estrogen signals through non-genomic, non-classical pathways that do not require ERα, and second, the surrounding stromal cells retain strong ERα expression and relay estrogen's growth-promoting signals back to the tumor through paracrine communication [57].

The Tumor Stroma Uses Estrogen to Feed the Cancer

While malignant cervical cancer cells lose ERα expression during progression, the surrounding stromal tissue retains it, creating a paracrine signalling loop where stromal cells act as intermediaries for estrogen's pro-tumorigenic effects [58]. Between 30% and over 50%of stromal cells surrounding precancerous and invasive lesions express ERα, concentrated in cancer-associated fibroblasts, myeloid-derived suppressor cells, and lymphocytes, while the tumor cells themselves express none [59, 60]. Transgenic mouse models with selective stromal ERα deletion confirmed that estrogen signals received by stromal fibroblasts are relayed to cancer cells through secreted soluble factors. Among these, cancer-associated fibroblasts exposed to estradiol produce molecules that collectively promote tumor cell proliferation, migration, angiogenesis, and epithelial-to-mesenchymal transition [59]. Treatment of these fibroblasts with selective estrogen receptor modulators or disruptors suppressed the expression of cell cycle and metabolism-related genes, attenuating both tumorigenesis and the tumor's blood supply [59]. This makes the stromal estrogen signalling axis a viable therapeutic target that attacks the tumor's support infrastructure rather than the cancer cells themselves, which have already escaped direct hormonal control.

Although high-risk HPV infection initiates cervical dysplastic changes, viral exposure alone rarely causes overt malignancy. Progression from initial infection to invasive carcinoma occurs over years through cumulative interactions with genetic, lifestyle, and environmental cofactors [59, 58].

Estrogen Suppresses the Immune System

Estrogen reshapes the immune microenvironment of cervical tumors through five interconnected mechanisms that collectively shield the malignancy from immune destruction [48].

MDSC Mobilization from Bone Marrow to Tumor

Estradiol stimulates myeloid haematopoiesis in the bone marrow, expanding the myeloid-derived suppressor cell population and enhancing their migratory capacity toward the tumor and draining lymph nodes [61].In pregnant women, elevated estradiol levels were sufficient to accelerate this process, driving MDSC mobilization from bone marrow to the spleen and local

tumors, with granulocytic myeloid-derived suppressor cell ERα signalling potentiating intratumoral immunosuppression and promoting progression of ERα -negative cervical carcinoma cells [62]. The estrogen receptor antagonist fulvestrant neutralized this suppressive activity in both vivo and orthotopic animal models [61].

Treg Expansion via the FOXP3 Pathway

Estradiol expands the regulatory T cell pool by inducing the FOXP3 gene promoter, which contains eight estrogen-responsive elements through which the ERα -estradiol complex binds directly to the FOXP3 locus.Intratumoral Tregs show the highest intracellular estradiol levels compared to any other immune cell type in the tumor or draining lymph nodes[60].This ERα -mediated cascade also drives the release of immunosuppressive cytokines TGF-beta and IL-10 via cell contact with Tregs.Beyond cytokine-mediated suppression, estrogen equips Tregs with cytolytic through non-genomic signalling via GPER1, which activates PD1 signalling and upregulates perforin expression [48]. Perforin forms pores in target cell membranes, allowing granzyme B to enter and trigger caspase-dependent apoptosis, with CD8-positive cytotoxic T cells and NK cells as primary targets.This creates a paradox where granzyme B serves both a pro-tumorigenic role by destroying immune effectors and an anti-tumorigenic role by degrading extracellular matrix collagen to permit immune infiltration.

Estrogen-HPV E7 Cooperation in Immune Evasion

The HPV16 E7 oncoprotein collaborates with estradiol to downregulate granzyme B expression in infected keratinocytes through two pathwaysincreased expression of proteinase inhibitor 9 in immune cells, which suppresses granzyme B both intracellularly and extracellularly, and direct transcriptional downregulation of the granzyme gene family via E7-estrogen interaction[63].Preserving collagen in the extracellular matrix by reducing granzyme B prevents cytotoxic T lymphocyte infiltration, while simultaneously shielding transformed keratinocytes from granzyme-mediated apoptosis [63].

ROLE OF PROGESTERONE

Progesterone plays a more complex and paradoxical role in cervical carcinogenesis compared to estrogen. The progesterone receptor typically inhibits the growth of cervical epithelial cells in a ligand-dependent manner, acting as a tumor suppressor [49]. In HPV-transgenic mice, genetic ablation of PR promotes cervical carcinogenesis without exogenous estrogen [64], and medroxyprogesterone acetate (a PR-activating drug) has been shown to regress cervical cancer. However, progesterone also has pro-tumorigenic effects. Progesterone (P4) binds to PR, enhancing the expression of c-myc and COX-2, which promotes cellular proliferation [65]. It also inhibits tumor suppressor proteins including p53, RB, LRIG1, and p16, thereby suppressing apoptosis. The membrane-associated progesterone receptor PGRMC1 stimulates epithelial-mesenchymal transition (EMT) markers, promoting invasive behavior.

During pregnancy, the hormonal environment shifts dramatically. Progesterone levels rise throughout gestation, reaching their peak during the third trimester, during which the HPV genome is particularly responsive to hormonal stimulation [66]. This hormonal surge, combined with increased squamous metaplasia of the transformation zone, creates a permissive environment for HPV replication. In multiparous women, the transformation zone remains on the ectocervix for longer periods, increasing direct exposure to HPV. A study of HR-HPV-infected women found that significantly elevated progesterone levels were associated with cervical cancer in premenopausal women, and the estradiol-to-progesterone ratio was significantly decreased in cancer cases.

MULTIPARITY AND DELIVERY-RELATED FACTORS

Among the recognized epidemiological cofactors of cervical carcinogenesis, parity has emerged as one of the most consistently reproducible, particularly in women who already carry a high risk of HPV infection. The landmark IARC multicentric case control study establishes that women with four or more terms pregnancies face more than double the risk of squamous cell cervical cancer compared with nulliparous or low parity women, and critically this effect held even after adjusting for age at first intercourse and other markers of sextual behaviour, indicating that parity acts as a genuine cofactor rather than a confound proxy for sextual exposure [67]. Subsequently longitudinal follow-up work has reinforced this pattern showing that parity specially accelerate progression from persistent HPV infection to high grade cervical diseases, rather than simply increasing the odds of acquiring the virus in the first place [68]. Several overlapping biological explanations have been proposed to account for this relationship. Pregnancy exposes the cervix to sustained, supraphysiological levels of estrogen and progesterone, and because the HPV LCR carries hormone responsive elements, this hormonal surge is thought to enhance E6/E7 oncogene transcription each time a woman carries a pregnancy to term [46].

Repeated pregnancies also cause the cervical transformation zone to evert outward (ectropion), leaving the more HPV vulnerable metaplastic epithelium chronically exposed rather than tucked safely within the endocervical canal. Finally, pregnancy is an immunologically distinct state, the same tolerogenic shift thatprotects the fetus from maternal immune attack appears to blunt the mother's ability to clear HPV, so each pregnancy effectively gives the virus another window to persist rather than resolve [46]. The mode of

delivery adds a further, somewhat counterintuitive layer to this picture. Mechanical trauma during vaginal birth was long assumed to be more damaging exposure, given the repetitive cervical stretching and microtrauma involved across repeated vaginal birth is in fact one of the mechanisms proposed to explain why multiparity elevates long term cancer risk [67]. Yet within a single pregnancy, the opposite pattern is seen for existing precancerous lesions postpartum regression of cervical intraepithelial neoplasia is substantially more common after vaginal delivery [69]. The leading explanation is that the physical debridement of dysplastic tissue during vaginal passage, combined with a burst of local immune activation triggered by the trauma of labour, can mechanically and immunologically clear abnormal cells that might otherwise persist [69]. Caesarean delivery, by sparing the cervix this trauma, appear to leave existing lesions comparatively undisrupted [69]. The relationship between parity and lesion behaviour depends heavily on time scale. Repeated vaginal births increase long-term risk through cumulative tissue trauma and prolonged exposure to elevated gestational hormones [67]. Conversely, a single vaginal delivery can promote short-term regression of CIN 3 lesions, likely due to acute mechanical clearance and localized labor-induced inflammation.

Secondary Risk Factors for Cervical Cancer

Beyond persistent HPV infection, several well-established risk factors independently raise the likelihood of cervical cancer. High parity is among the most robust reproductive risk factors: an IARC multicentric study showed that women carrying seven or more pregnancies had nearly four times the odds of squamous cell carcinoma compared with those who had never delivered, owing to prolonged exposure of the cervical transformation zone to hormonal fluctuations and repeated mechanical trauma that facilitates HPV entry and impairs local immune clearance [67-70]. Age exerts a bimodal influence, with an initial HPV prevalence peak in young women aged 17 to 24 years linked to sexual debut and immune immaturity, and a second rise around ages 40 to 45 driven by declining oestrogen, reduced immune surveillance, and diminished capacity to clear the virus [71]. Education operates primarily through its effect on health behaviour rather than viral exposure: Franceschi *et al*., found that although HPV prevalence did not differ across education strata, women with no formal schooling carried a 1.5-fold greater risk of cervical cancer, a relationship largely explained by earlier age at first intercourse, earlier childbearing, and higher cumulative parity [5]. Lower education is likewise associated with poorer awareness of risk factors and reduced uptake of screening, which delays diagnosis and allows progression to advanced disease [72]. Collectively, these factors form a reinforcing pattern in which socioeconomic disadvantage amplifies reproductive exposures and diminishes access to preventive healthcare, thereby compounding cervical cancer risk.

Comparative Studies on Patient Survey who are Infected by HPV and Shows Low Grade - High Grade Cervical Intraepithelial Lesion Has Been Statistically Analysed Below:

Age Distribution [Reference]

Age Distribution	[73]	[74]	[75]
≤20 years	2 (2.44%)	-	-
21-30 years	26 (31.71%)	72 (45.0%)	6 (6.3%)
31-40 years	34 (41.46%)	88 (55.0%)	89 (93.7%)
41-50 years	12 (14.63%)	-	-
51-60 years	7 (8.54%)	-	-
>60 years	1 (1.22%)	-	-

Education level

Education	[73]	[74]	[75]
Low	17 (20.73%)	-	32 (33.7%)
Primary/Junior	36 (43.90%)	-	52 (54.7%)
Senior High	18 (21.95%)	95 (59.4%)	-
Higher	11 (13.41%)	65 (40.6%)	11 (11.6%)

Reproductive factors: Parity Distribution

Parity Status	[73]	[76]	[75]
Nullipara (0)	-	-	3 (3.2%)
Primipara (1)	11 (13.42%)	27 (16.9%)	13 (13.7%)
Multipara (2-3)	41 (50.00%)	113 (70.6%)	65 (68.4%)
Multipara (>3)	30 (36.59%)	20 (12.5%)	14 (14.7%)

Across the overall analysis of this studies it can be observed that women aged from 31-40 consistently showed highest burden of HPV related cervical lesion reflecting the well-known window when early HPV exposer and post immunosenescence both raise risk. Lower education levels were common across most cohorts, generally linked to reduced literacy and awareness, later presentation and limited access to screening programmes. Multiparity emerged as the clearest and most consistent findings among the majority of patients across all the studies had two or more deliveries, reinforcing multiparity as established role as causing cervical carcinogenesis, likely through repeated cervical trauma, prolonged ectropion and weakened local immune surveillance.

DISCUSSION

Cervical carcinogenesis relies on coordinated crosstalk between viral gene expression, epigenetic modifications, local immune suppression, and steroid hormone activity. Translating these molecular findings into targeted therapies will require multi-modal treatment strategies. Given the central role of E6 and E7 in driving both epigenetic silencing of tumor suppressors [9], and immune evasion through MHC downregulation [44], therapeutic vaccine strategies that restore T cell recognition of these oncoproteins represent a promising avenue worthy of further clinical investigation, particularly in combination with immune checkpoint inhibitors that could overcome the PD-1-mediated exhaustion of HPV-specific cytotoxic T lymphocytes. The demonstration that estrogen acts as a critical cofactor in cervical carcinogenesis through both direct genomic signalling [51], and paracrine stromal communication suggests that selective estrogen receptor modulators and aromatase inhibitors [53-59], already approved for breast cancer treatment, should be evaluated in well-designed clinical trials for their capacity to disrupt the hormonal support network that sustains HPV-driven tumors, especially in postmenopausal women where local estrogen synthesis in the cervical microenvironment remains active despite declining systemic levels [48-53]. Similarly, the emerging evidence that epigenetic marks imposed by HPV oncoproteins are potentially reversible through pharmacological inhibition of DNA methyltransferases and histone deacetylases warrants systematic preclinical evaluation using patient-derived organoid models and careful dose-finding studies to determine whether epigenetic therapy can reactivate silenced tumor suppressors without inducing widespread genomic instability. The role of the cervical and gut microbiomes in shaping local and systemic anti-tumor immunity [51], offers an additional therapeutic dimension that has barely been explored in the context of HPV-associated malignancies, and future studies examining how microbial composition influences immune checkpoint inhibitor efficacy and HPV clearance could open entirely new strategies for disease prevention and management. Furthermore, advances in liquid biopsy technologies measuring circulating HPV DNA and methylated host gene promoters in peripheral blood hold considerable promise for non-invasive monitoring of treatment response and early detection of recurrence, and their validation against tissue-based biomarkers in prospective clinical cohorts should be prioritized. The interaction between pregnancy-associated hormonal surges and the cervical immune microenvironment [46-66], which may explain the well-documented association between high parity and cervical cancer risk [67], requires dedicated investigation through longitudinal studies that track hormonal levels, immune cell populations, and viral persistence markers across successive pregnancies and the postpartum period. Ultimately, the development of combination therapeutic strategies that simultaneously target the viral, epigenetic, hormonal, and immune dimensions of cervical carcinogenesis, guided by single-cell and spatial transcriptomic profiling of individual patient tumors to identify which pathways are most active in a given disease stage, offers the most realistic path toward more effective and personalized treatment of this malignancy.

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