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Age-Specific Trends and Clinical Management of Cervical Cancer: A Comprehensive Review of Epidemiology, Risk Factors, and Treatment Approaches

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Abstract: Cervical cancer is a significant public health concern, ranking as the second most common cancer among women. The incidence rate is particularly high in rural areas, with higher mortality rates compared to the global average. Although screening is common for these cases, the time taken for screening can vary depending on age of patient and the frequencies produced through each screening can interrupt actual results. Even though the most common cases are found in the age group between 35 and 44, recent cases show that around 21% are diagnosed in women aged between 20-29. Since the last decade, around 78% cases were found in women aged 30-39. This lets us pave an opportunity to discover on how the HPV virus affects different age groups of women and how phytochemicals can reduce the risk of spreading by marking the proteins with biomarkers that can be easily found by upcoming technologies that target specific cell lines or proteins in a case.

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I. INTRODUCTION

Cervical cancer, although largely preventable, is the most common site of gynecologic malignancy in women under the age of 35-44. Worldwide cervical cancer is listed as the second most affective cancers in women, where the first being Breast cancer. Cervical cancer is predominantly caused by persistent infection with high-risk human papillomavirus (HPV) types, notably HPV16 and HPV18. These viruses integrate their DNA into the host genome, leading to the expression of viral oncoproteins E6 and E7, which disrupt normal cell cycle regulation and promote malignant transformation. E6 binds to p53 which promotes degradation of tumor suppressor protein inhibiting apoptosis and E7 interacts with retinoblastoma protein (pRb), which

releases E2f transcription factors and leads to uncontrolled cell proliferation. There is another protein – E5 that enhances mitogenic signalling by interacting with epidermal growth factor receptor (EGFR) and modulates in immune evasion. The inactivation of TP53 by E6 leads to DNA damage response and apoptosis. CDKN2A inhibits cyclin dependent kinases and the overexpression of CDKN2A serves as a biomarker for HPV associated cases. FANCF which involves in DNA repair leads to gene silencing and genomic instability.

Oestrogen signalling, particularly through oestrogen receptor alpha (ERα), plays a role in cervical carcinogenesis. ERα activation supports the proliferation of HPV-infected cells and may cooperate with viral oncoproteins. HPV oncoproteins downregulate major histocompatibility complex (MHC) class I and II molecules, impairing antigen presentation and facilitating immune escape. Analyzing cervical cancer based on different age groups is important because it helps researchers, scientists and clinicians to understand how biological factors, socio-economic factors, and behavioural factors vary across life stages and influence risks, progression and the final stage of disease development.

II. EPIDEMIOLOGICAL SIGNIFICANCE

What is important to note is that this type of cancer doesn't affect all the age groups neither similarly or equally. It typically rises in the starting phase of adulthood. Recent cases have shown us that Adolescents and young women in between the age of 15-25 years have high rates of HPV infection due to early onset of sexual activity. This is mainly cause during these peak time periods of a woman's life, the

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amount of oestrogen produced can induce the cervical cells that are still maturing and are more susceptible to viral changes. These cases are often under-screened due to lack of awareness. The highest rate of cervical cancer is seen in the middle ages between 30 to 49 years in which cervical intraepithelial neoplasia can lead to tumor progression if not treated before hand. This is considered as the ideal age for routine screening for Pap smear or HPV test and other preventive measures. For further cases that include women from postmenopausal category, that is above 50 years of age; they may have shown persistent HPV infections from earlier decades but wasn't wary of the disease. The most important thing that clinicians miss in this age group is that the symptoms may be misinterpreted or missed due to assumptions like risks of getting cervical cancer decreases after menopause. Hormonal differences, immune responses, and genetic susceptibility can vary with age which plays an important role in influence of the human papilloma virus.

- *Implication for Screening and Diagnosis:*

Global cervical cancer screening recommendations rely heavily on age. The current protocols, including cytology-based (Pap smear), HPV DNA testing, and co-testing approaches, are defined based on age groups due to differing risk profiles (Saslow et al., 2012, CA: A Cancer Journal for Clinicians). For women under 21 years, routine screening is not recommended, as HPV infections are usually transient and self-limiting (ACOG, 2016, Obstetrics & Gynecology). For those aged 21–29 years, Pap smear every 3 years is advised, with HPV testing reserved for abnormal cytology findings (US Preventive Services Task Force, 2018, JAMA). In women aged 30–65 years, co-testing (Pap + HPV) every 5 years or cytology every 3 years is the standard due to the increased risk of persistent infections (Perkins et al., 2020, Journal of Lower Genital Tract Disease). Above 65 years, screening may be discontinued if adequate prior screening has occurred and results have been consistently negative (Saslow et al., 2012, CA: A Cancer Journal for Clinicians). These age-specific screening guidelines reflect the natural history of HPV infection and its progression to cervical cancer. In younger women (under 21), the high rate of spontaneous HPV clearance renders routine screening unnecessary, helping to avoid overdiagnosis and overtreatment of transient lesions (Gravitt, 2012, The Lancet Oncology). For women aged 21–29, cytology-based screening remains the mainstay, as HPV prevalence is still relatively high, but the risk of persistent infection is lower (Wright et al., 2015, Gynecologic Oncology). The addition of HPV testing in this age group is only recommended when cytological abnormalities are present, to avoid unnecessary follow-up for transient infections (USPSTF, 2018, JAMA). In the 30–65 age group, the risk of persistent HPV infection and progression to high-grade lesions increases, justifying the use of co-testing as a more sensitive method for early detection (Perkins et al., 2020, Journal of Lower Genital Tract Disease). Co-testing not only increases diagnostic accuracy but also allows for longer screening intervals, reducing healthcare burden without compromising patient safety (Saslow et al., 2012, CA: A Cancer Journal for Clinicians). For women above 65, continued screening is generally unnecessary if prior screenings were consistent and negative; however, exceptions are made for those with inadequate screening history, immunocompromised status, or history of cervical precancer (ACOG, 2016, Obstetrics & Gynecology). Tailoring screening methods based on age optimizes resource allocation, minimizes harm, and enhances early detection of high-risk cases. Additionally, understanding the age-specific performance of these tools is essential for designing population-wide screening programs, especially in low-resource settings where cost-effectiveness is crucial (Sankaranarayanan et al., 2013, New England Journal of Medicine).

- *HPV Oncoplayers:*

The E6 and E7 oncoproteins of high-risk human papillomavirus (HPV), particularly types 16 and 18, are key drivers of cervical carcinogenesis and are referred to as "oncoplayers" due to their pivotal role in promoting malignant transformation (Doorbar, 2006, Journal of Pathology). E6 primarily targets the tumor suppressor protein p53, binding to it and promoting its ubiquitin-mediated degradation via the E6-AP ubiquitin ligase complex (Scheffner et al., 1993, Cell). This inactivation prevents apoptosis, allows accumulation of DNA damage, and enables the infected cell to bypass genomic surveillance (Münger et al., 2004, Oncogene). Meanwhile, E7 binds to and inactivates the retinoblastoma protein (pRb), which normally regulates the cell cycle by inhibiting E2F transcription factors (Dyson et al., 1989, Science). When pRb is inactivated, E2F is released, leading to unregulated progression from the G1 to the S phase of the cell cycle and uncontrolled cellular proliferation (McLaughlin-Drubin & Münger, 2009, Journal of Virology). The persistent expression of E6 and E7 disrupts normal cell cycle checkpoints, inhibits DNA repair mechanisms, and promotes chromosomal instability—hallmarks of cancer development (Moody & Laimins, 2010, Annual Review of Microbiology). Together, these oncoproteins override critical tumor suppressor pathways, making them central to HPV-induced oncogenesis and valuable targets for therapeutic intervention and diagnostic biomarker development (Yim & Park, 2006, Cancer Letters).

III. EXPRESSION IN DIFFERENT AGE GROUPS

The expression levels and oncogenic impact of HPV E6 and E7 oncoproteins can vary across different age groups due to hormonal, immunological, and epigenetic differences. In younger women, particularly those under 30, transient HPV infections often result in lower and short-lived expression of E6 and E7, with a high rate of immune-mediated viral clearance (Doorbar, 2006, Journal of Pathology). However, in women aged 30–45, persistent infections are more likely, and studies have shown sustained overexpression of E6 and E7 due to integration of the viral genome into host DNA (Hopman et al., 2004, Journal of Pathology). This persistence correlates with higher rates of cervical intraepithelial neoplasia and malignant transformation. Additionally, hormonal fluctuations such as elevated estrogen levels during the reproductive years may amplify E6/E7 transcription by interacting with the viral long control region (Chung et al., 2010, Cancer Research). In postmenopausal women, immune senescence and decreased estrogen levels contribute to

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altered viral gene regulation and may either suppress or unpredictably enhance E6/E7 activity, especially in cases of latent reactivation (Gravitt, 2012, The Lancet Oncology). Furthermore, older women tend to show greater genomic instability around E6/E7 integration sites, which worsens prognosis (Wentzensen et al., 2009, International Journal of Cancer). These age-related differences in viral oncoprotein expression underline the importance of age-specific diagnostic strategies and therapeutic targeting.

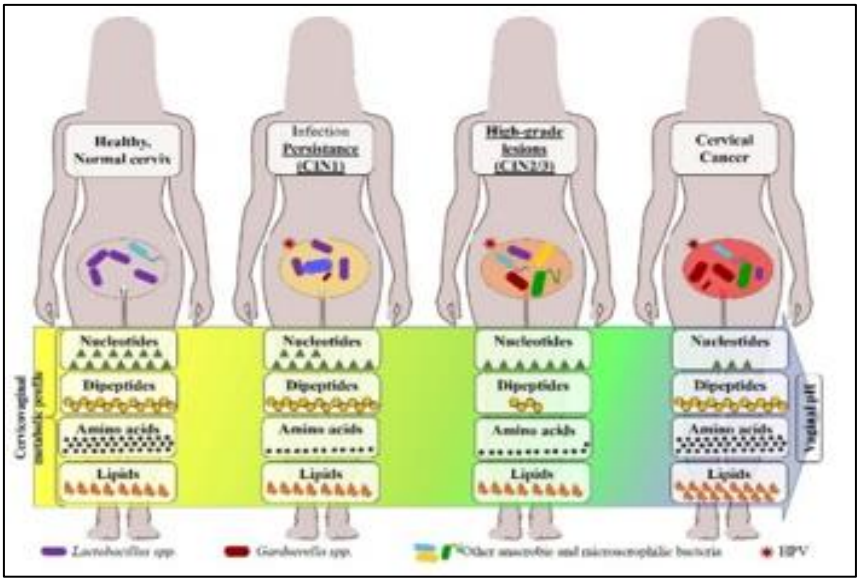

Fig. 1. The Above Figure Illustrates the Interplay Between Microbial Composition, Metabolism and HPV Infection Risk Relevant for Understanding Age-Specific Epidemiology and for Optimizing Cervical Cancer Management.

➢ *E6/E7 as Therapeutic Targets*

Given their central role in HPV-mediated carcinogenesis, E6 and E7 oncoproteins have emerged as attractive therapeutic targets for cervical cancer. Because these viral proteins are consistently expressed in HPV-positive tumor cells but absent in normal tissues, they offer high tumor specificity with minimal off-target effects (Yim & Park, 2006, Cancer Letters). Therapeutic vaccines aiming to stimulate cytotoxic T lymphocyte responses against E6 and E7, such as VGX-3100 and ADXS11-001, have shown promising immunogenicity and lesion regression in clinical trials (Trimble et al., 2015, The Lancet). Additionally, RNA interference (RNAi) strategies targeting E6 and E7 mRNA have been successful in inducing apoptosis and restoring p53 and pRb functions in vitro (Jin et al., 2011, International Journal of Oncology). Small molecules and peptides designed to inhibit E6–E6AP and E7–pRb interactions are also under investigation, although challenges remain in ensuring efficient cellular delivery and stability (Ramakrishna et al., 2015, Oncotarget). Furthermore, the integration of E6/E7 targeting with immune checkpoint blockade is being explored to enhance antitumor immune responses. These therapeutic innovations represent a significant step forward in the personalized treatment of HPV-associated cervical cancers, especially for patients with persistent high-grade lesions or treatment-resistant disease.

➢ *Disruption of Tumor Suppressor Pathways*

One of the hallmarks of cervical carcinogenesis driven by high-risk human papillomavirus (HR-HPV) infection is the disruption of host tumor suppressor pathways. The E6 and E7 oncoproteins from HPV types 16 and 18 are central to this process, as they directly inactivate key tumor suppressors p53 and retinoblastoma protein (pRb), respectively. E6 forms a complex with the E6-associated protein (E6AP), an E3 ubiquitin ligase, leading to the ubiquitination and proteasomal degradation of p53. The loss of functional p53 compromises the cell's ability to initiate apoptosis and respond to DNA damage, resulting in unchecked survival of genetically unstable cells. Simultaneously, E7 binds to pRb and displaces E2F transcription factors, which in turn drives the transcription of genes required for S-phase entry and DNA replication. This unchecked progression through the cell cycle promotes hyperproliferation and loss of cell cycle control. Additionally, the viral oncoproteins influence other regulators such as CDKN2A (p16^INK4a), which becomes overexpressed in an attempt to compensate for pRb loss. Although p16 overexpression is a diagnostic marker of HPV-related transformation, its presence also signals the failure of intrinsic growth suppression mechanisms. Long-term expression of E6 and E7 also affects the DNA damage response by interfering with other checkpoint proteins like ATM and CHK1, contributing to genomic instability. Furthermore, HPV-mediated epigenetic modifications, such as promoter methylation of tumor suppressor genes (e.g., RASSF1A, DAPK), lead to their transcriptional silencing, enhancing oncogenic potential. The persistent evasion of tumor suppressor pathways not only facilitates malignant transformation but also limits the effectiveness of immune surveillance, as damaged cells continue to proliferate unchecked. This multilevel disruption underscores the critical importance of targeting these viral-host interactions in both diagnostics and therapeutic interventions for cervical cancer.

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IV. RESISTING CELL PROLIFERATION:

A crucial step in the development of cervical cancer is the infected cell's ability to resist programmed cell death or apoptosis. Normally, apoptosis serves as a safeguard mechanism to eliminate damaged or infected cells, preventing malignant transformation. However, high-risk human papillomavirus (HR-HPV), particularly types 16 and 18, undermines this defense by manipulating key apoptotic regulators through the actions of its E6 and E7 oncoproteins. E6 promotes the degradation of the tumor suppressor protein p53, a master regulator of apoptosis that normally activates pro-apoptotic genes like BAX, PUMA, and NOXA in response to DNA damage (Scheffner et al., 1990; Munger et al., 2001). Without functional p53, cells evade apoptosis even when they accumulate harmful mutations. E7 further contributes to apoptosis resistance by inactivating the retinoblastoma protein (pRb), indirectly promoting the overexpression of anti-apoptotic proteins such as Bcl-2 (Dyson et al., 1989; Moody & Laimins, 2010). Additionally, E6 has been shown to interact with and inhibit several caspases, including caspase-8 and caspase-9, which are crucial executioners in both intrinsic and extrinsic apoptotic pathways (Thomas & Banks, 1998; Filippova et al., 2002). This inhibition stalls the apoptotic cascade, enabling prolonged survival of cells that would otherwise be eliminated. HPV also modulates the expression of host microRNAs involved in apoptosis regulation, shifting the balance toward cell survival. For instance, HPV-related dysregulation of miR-21 and miR-34a is associated with increased resistance to apoptotic signals (Wang et al., 2009; Martinez et al., 2008). Furthermore, hypoxic regions within the tumor microenvironment—common in cervical neoplasms—trigger a cellular stress response where HPV oncoproteins help cells adapt rather than die. By suppressing mitochondrial apoptotic signaling and activating survival pathways like PI3K/Akt, infected cells not only avoid cell death but also gain a growth advantage (Spangle & Münger, 2010; Zheng et al., 2013). This ability to resist apoptosis ensures the persistence of virally transformed cells and contributes to tumor progression, therapeutic resistance, and poor clinical outcomes in cervical cancer.

- *Sustained Proliferative Signalling in HPV-Induced Cancer*

Human papillomavirus (HPV), particularly high-risk types like HPV-16 and HPV-18, promotes sustained proliferative signalling one of the hallmarks of cancer by hijacking cellular pathways that regulate the cell cycle. This is primarily mediated by the viral oncoproteins E6 and E7, which target tumor suppressors to remove growth constraints. E7 binds and inactivates the retinoblastoma protein (pRb), leading to the release of E2F transcription factors that drive the transcription of genes involved in DNA replication and cell cycle progression (Dyson et al., 1989, Science). This uncontrolled E2F activity propels the host cell into S-phase even in the absence of growth factors. In parallel, E6 degrades the tumor suppressor p53 via the ubiquitin–proteasome pathway, disrupting the DNA damage checkpoint and allowing the cell to continue dividing despite genomic instability (Scheffner et al., 1990, Cell). Moreover, HPV oncoproteins have been shown to activate pro-survival and mitogenic signalling cascades, including the PI3K/Akt/mTOR and MAPK pathways, which further enhance cellular proliferation and inhibit senescence (Spangle & Münger, 2010, J. Virology). This mimics the effect of continuous growth factor stimulation, despite the absence of such stimuli from the microenvironment. Additionally, HPV E5, another early gene product, contributes to proliferative signalling by modulating growth factor receptor trafficking. E5 stabilizes epidermal growth factor receptor (EGFR) at the cell membrane, sensitizing the cell to mitogenic cues (Straight et al., 1995, PNAS). This aberrant receptor recycling intensifies downstream proliferative signals, compounding the effects of E6 and E7. Collectively, these mechanisms override normal growth restrictions, granting HPV-transformed cells a proliferative advantage essential for tumor development.

- *Replicative Immortality in HPV-Driven Cervical Carcinogenesis*

Replicative immortality, the capacity of cells to bypass normal senescence and divide indefinitely, is a defining trait of cancer. In HPV-associated cervical cancer, this is primarily mediated by the viral E6 oncoprotein, which activates the expression of human telomerase reverse transcriptase (hTERT)—the catalytic subunit of telomerase. Normally, somatic cells experience progressive telomere shortening, leading to growth arrest or apoptosis. However, HPV E6 circumvents this barrier by binding to cellular transcription factors such as c-Myc and Sp1, enhancing hTERT promoter activity and restoring telomerase function (Klingelhutz et al., 1996, Genes & Development; Gewin & Galloway, 2001, J Virology). This reactivation of telomerase allows infected cells to maintain telomere length, thereby escaping replicative senescence and enabling prolonged cell proliferation. Moreover, E6-mediated degradation of p53 removes an essential checkpoint for telomere damage response, further facilitating cellular immortality (Scheffner et al., 1990, Cell). Additionally, studies show that telomerase upregulation is an early and consistent event in HPV-mediated transformation, suggesting its critical role in the early stages of cervical neoplasia (Kyo et al., 1999, International Journal of Cancer). Importantly, hTERT is not only essential for immortalization but also contributes to chromosomal instability and malignant progression, making it a promising biomarker and therapeutic target in HPV-induced cancers (Chung et al., 2000, Cancer Research).

- *Angiogenesis and Metastasis in HPV-Associated Cervical Cancer*

Angiogenesis and metastasis are two hallmarks of cancer progression that are critically involved in the development and advancement of cervical cancer, particularly those driven by high-risk human papillomavirus (HPV) infections. Persistent infection with high-risk HPV types, especially HPV 16 and 18, leads to the sustained expression of viral oncoproteins E6 and E7, which play central roles in disrupting normal cellular regulation and facilitating tumorigenesis. These oncoproteins not only interfere with cell cycle control but also indirectly promote angiogenesis and metastasis, thereby contributing to the invasive and aggressive phenotype of cervical cancer (Moody

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& Laimins, 2010, Nature Reviews Cancer). Angiogenesis which is the formation of new blood vessels from existing vasculature, is essential for tumor survival, as it provides a growing tumor with adequate oxygen and nutrients. In cervical carcinogenesis, HPV E6 and E7 proteins contribute to a hypoxic tumor microenvironment by interfering with normal cell cycle and apoptosis mechanisms. E6, by promoting the ubiquitin-mediated degradation of p53, downregulates anti-angiogenic factors such as thrombospondin-1 and allows stabilization of pro-angiogenic proteins like hypoxia-inducible factor-1 alpha (HIF-1α) (Lopez-Beltran et al., 2021, Pathology – Research and Practice). Under normal physiological conditions, p53 regulates HIF-1α levels by promoting its degradation, thus maintaining a balance between pro- and anti-angiogenic factors. However, in the HPV-infected cell, the degradation of p53 leads to the accumulation of HIF-1α, which in turn activates the transcription of vascular endothelial growth factor (VEGF)—a potent inducer of angiogenesis (Ravi et al., 2015, Journal of Clinical Oncology). Elevated VEGF expression has been observed in cervical intraepithelial neoplasia (CIN) and invasive cervical cancer, and it is often associated with poor prognosis due to increased tumor vascularization (Chen et al., 2014, Molecular Medicine Reports). Moreover, the E7 protein indirectly contributes to angiogenesis by disrupting the retinoblastoma (pRb) protein pathway, leading to the release of E2F transcription factors. These factors activate genes that promote cell cycle progression and also upregulate HIF-1α, further contributing to VEGF expression and angiogenesis (Zhou et al., 2011, Cancer Research). Studies have shown that cervical cancer tissues with integrated HPV DNA display significantly higher microvessel density compared to normal tissues or low-grade lesions, reinforcing the link between persistent HPV infection and tumor vascularization (Shin et al., 2010, International Journal of Gynecological Cancer). Inhibiting the VEGF pathway has shown promise in improving outcomes for patients with recurrent or metastatic cervical cancer, underscoring its therapeutic relevance (Tewari et al., 2014, New England Journal of Medicine). While angiogenesis supports primary tumor growth, metastasis is the process that allows cancer cells to spread from their site of origin to distant organs, which is the leading cause of cancer-related mortality. The metastatic potential of cervical cancer is significantly enhanced by the molecular actions of HPV oncoproteins, which disrupt cell-cell adhesion, increase cellular motility, and degrade extracellular matrices. E7 promotes epithelial-to-mesenchymal transition (EMT), a cellular program that reduces epithelial characteristics such as E-cadherin expression and promotes mesenchymal traits, including the expression of vimentin and fibronectin (Shanmugasundaram et al., 2017, Cancer Letters). EMT not only aids in local invasion but also contributes to chemoresistance and stemness in cervical cancer cells. Further, E6 and E7 upregulate the expression and activity of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, which are enzymes capable of degrading basement membrane and extracellular matrix components. This facilitates the invasion of cancer cells through surrounding tissues and into the vasculature or lymphatic system (Park et al., 2010, Gynecologic Oncology). Elevated levels of MMPs have been found in the cervical secretions of women with high-grade cervical lesions and are considered markers of metastatic potential. Additionally, inflammatory cytokines such as IL-6 and TNF-α, which are often elevated in HPV-infected tissues, further enhance MMP activity and EMT through NF-κB and STAT3 signaling pathways (Yang et al., 2013, PLOS One). Postmenopausal hormonal changes and immune senescence also contribute to metastasis in older women by weakening immune surveillance and altering the tumor microenvironment in favor of cancer progression. Reduced estrogen levels may diminish protective immune responses while promoting inflammatory cascades that facilitate cancer cell invasion and survival (Gravitt, 2012, The Lancet Oncology). Furthermore, aging-related decline in natural killer cell activity and cytotoxic T-cell response allows HPV-infected and transformed cells to evade immune-mediated destruction, increasing the likelihood of distant metastases (Wentzensen et al., 2009, International Journal of Cancer). Taken together, angiogenesis and metastasis in HPV-associated cervical cancer are driven by complex interactions between viral oncoproteins and host cellular pathways. These processes not only support tumor survival and expansion but also pose major challenges to treatment and prognosis. Targeting angiogenic factors such as VEGF, as well as molecules involved in EMT and MMP activation, holds significant therapeutic potential. Agents like bevacizumab (a VEGF inhibitor) have already demonstrated clinical efficacy and extended survival in patients with advanced cervical cancer (Tewari et al., 2014). Continued research into the molecular pathways regulating angiogenesis and metastasis will be critical for developing precision medicine approaches in HPV-related malignancies.

- *Therapeutic Vaccines Targeting HPV and E6/E7 Oncoproteins*

Therapeutic vaccines targeting human papillomavirus (HPV), especially the E6 and E7 oncoproteins, have gained significant attention in recent years due to their potential to treat established infections and HPV-associated malignancies. Unlike prophylactic vaccines like Gardasil and Cervarix, which are effective at preventing new HPV infections but offer no benefit for individuals already infected, therapeutic vaccines aim to generate a cell-mediated immune response against the infected or transformed cells (Trimble & Frazer, 2009, *Gynecologic Oncology*). The E6 and E7 proteins of high-risk HPV types, such as HPV16 and HPV18, are constitutively expressed in infected cells and are essential for the maintenance of the malignant phenotype. E6 degrades p53, while E7 disrupts the pRb pathway, promoting uncontrolled proliferation and survival (Moody & Laimins, 2010, *Nature Reviews Cancer*). Their consistent expression and immunogenic nature make them ideal targets for immunotherapy. Several types of therapeutic vaccines have been developed to target these proteins. DNA-based vaccines, which use plasmids encoding E6 and E7 genes, are one of the most promising approaches. For instance, VGX-3100, a DNA vaccine targeting HPV16/18 E6 and E7, has demonstrated regression of cervical intraepithelial neoplasia (CIN 2/3) and viral clearance in Phase II trials (Trimble et al., 2015, *The Lancet*). Protein- and peptide-based vaccines have also been explored, such as TA-CIN, which combines E6/E7 with the

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L2 capsid protein to enhance immune recognition (de Jong et al., 2002, *Clinical Cancer Research*). Although safe, these often require potent adjuvants to elicit strong cytotoxic T lymphocyte (CTL) responses. Another strategy involves viral vector vaccines, such as TG4001, which uses a modified vaccinia virus to deliver E6 and E7 antigens, successfully stimulating cellular immunity in early studies (Kaufman et al., 2007, *Human Gene Therapy*).

Recent advances have brought mRNA-based vaccines into the spotlight. BNT113, an mRNA vaccine developed by BioNTech, encodes HPV16 E6 and E7 and is undergoing trials for HPV-positive head and neck cancers (Sahin et al., 2021, *Nature*). These vaccines offer safety, rapid scalability, and strong T-cell activation. Furthermore, combining therapeutic vaccines with immune checkpoint inhibitors like anti-PD-1 antibodies can enhance efficacy by reversing local immune suppression in the tumor microenvironment (Sabbatini et al., 2015, *Clinical Cancer Research*). Despite these advances, therapeutic vaccines face challenges, including variability in patient immune responses and immunosuppressive tumor niches. However, ongoing improvements in delivery systems, adjuvants, and combination therapies continue to boost their clinical potential. Ultimately, targeting E6 and E7 through therapeutic vaccination offers a promising path for treating persistent HPV infections and HPV-driven cancers, especially when integrated with broader immunotherapeutic strategies.

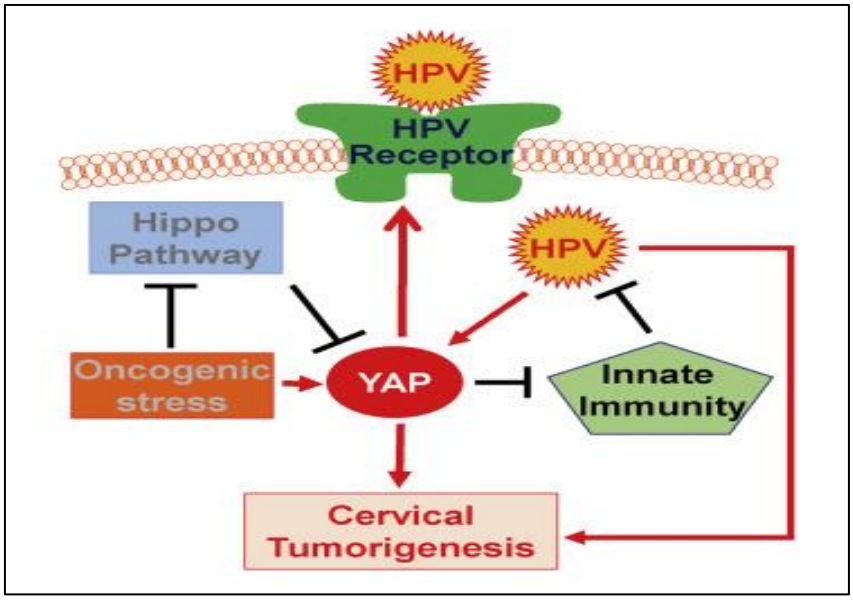

Fig. 2. YAP Signaling in Cervical Tumorigenesis: Integration of Immune Response, Oncogenic Stress, and Hippo Pathway

➢ *Gene Editing tools:*

Gene editing technologies have emerged as promising therapeutic tools to directly target the oncogenic drivers of HPV-associated cancers, particularly the E6 and E7 oncoproteins of high-risk strains like HPV16 and HPV18. Among these tools, CRISPR-Cas systems have gained the most traction due to their precision, versatility, and relative ease of design. CRISPR-Cas9 can be programmed to introduce double-stranded breaks at specific sequences within the HPV genome, leading to frameshift mutations or functional knockout of E6 and E7 genes (Kennedy et al., 2014, Journal of Virology). In vitro and in vivo studies have demonstrated that targeting E6 restores p53 function, while editing E7 allows reactivation of pRb-mediated cell cycle control, collectively inducing apoptosis and halting tumor progression (Hu et al., 2015, Oncotarget). For instance, a dual-targeting CRISPR-Cas9 approach against both E6 and E7 in HPV-positive cervical cancer cells led to significant tumor regression in mouse models (Kang et al., 2017, Molecular Therapy). Beyond CRISPR-Cas9, other tools like TALENs (Transcription Activator-Like Effector Nucleases) and ZFNs (Zinc Finger Nucleases) have been utilized to disrupt E6 and E7 expression. TALENs targeting HPV16 E7 have shown the ability to arrest cell proliferation and induce senescence in HPV-transformed cells (Zhen et al., 2014, PLoS One). Although TALENs and ZFNs preceded CRISPR, their complex design and higher off-target potential have limited their widespread adoption compared to CRISPR-based methods. However, newer modifications, such as base editors and CRISPR interference (CRISPRi), offer an even more refined approach. Base editors can induce single nucleotide changes without double-stranded DNA breaks, reducing genotoxicity and improving specificity (Komor et al., 2016, Nature). CRISPRi, which uses a catalytically dead Cas9 (dCas9) fused to transcriptional repressors, can silence E6/E7 expression without permanent DNA alterations, which may be advantageous in certain therapeutic settings (Thakore et al., 2015, Cell). Delivery remains one of the biggest challenges in clinical translation. Viral vectors such as adeno-associated virus (AAV) and lentivirus are commonly used to deliver CRISPR components but concerns regarding immunogenicity and insertional mutagenesis persist. Non-viral delivery systems, including lipid nanoparticles and polymer-based vectors, are actively being developed to safely deliver gene editing tools to HPV-infected epithelial cells (Wang et al., 2018, Advanced Drug Delivery Reviews). Moreover, combining gene editing with immunotherapy or therapeutic vaccines could yield synergistic effects by both eliminating viral oncogenes and stimulating immune clearance of residual transformed cells.

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➢ *Phytotherapy Targeting E6&E7:*

Phytotherapy, the use of plant-derived compounds for therapeutic purposes, has garnered increasing attention for its potential in combating HPV-induced cervical carcinogenesis by targeting viral oncoproteins E6 and E7. Numerous phytochemicals demonstrate antiviral, pro-apoptotic, and anti-proliferative effects against HPV-infected cells, primarily through modulation of E6/E7 expression or reactivation of host tumor suppressor pathways. One of the most studied compounds is curcumin, a polyphenol from Curcuma longa, which has been shown to suppress E6 and E7 mRNA expression, thereby restoring p53 and pRb activity and inducing apoptosis in HPV16/18-positive cervical cancer cell lines (Maher et al., 2011, Molecular Carcinogenesis). Curcumin also modulates NF-κB and AP-1 transcription factors, which are crucial for HPV gene transcription, further diminishing viral oncoprotein levels. Another potent phytochemical is epigallocatechin-3-gallate (EGCG), the major catechin found in green tea, which exerts inhibitory effects on E7-mediated degradation of pRb, leading to cell cycle arrest at the G1 phase (Yang et al., 2013, Cancer Letters). EGCG also promotes p53 accumulation in E6-expressing cells and can sensitize HPV-positive cells to chemotherapeutic agents. Additionally, resveratrol, a stilbene compound found in grapes and berries, has demonstrated ability to downregulate E6/E7 expression, reduce telomerase activity, and promote caspase-mediated apoptosis (Kumar et al., 2014, Journal of Pharmacy and Pharmacology).

These mechanisms not only target viral persistence but also reverse the oncogenic phenotype of HPV-transformed cells. Several lesser-known but promising phytochemicals include withaferin A from Withania somnifera, which inhibits E6/E7 expression and induces oxidative stress–mediated apoptosis, and berberine, an isoquinoline alkaloid from Berberis species, which interferes with HPV16 promoter activity and modulates the Wnt/β-catenin pathway involved in E6/E7-driven tumorigenesis (Nair et al., 2015, Phytomedicine). Luteolin, a flavonoid found in celery and green peppers, has also been reported to inhibit the PI3K/Akt pathway, leading to reduced E6/E7 protein levels and restored tumor suppressor function (Kang et al., 2017, Journal of Ethnopharmacology). Collectively, these phytochemicals act at various levels epigenetic regulation, transcriptional silencing, post-translational degradation to mitigate the oncogenic effects of HPV.

Importantly, phytotherapeutic agents often possess multi-targeted effects and low toxicity, making them attractive as adjuncts or alternatives to conventional therapies, particularly in low-resource settings where access to vaccines or advanced treatments may be limited. However, despite promising preclinical data, clinical translation remains limited due to issues such as poor bioavailability, lack of standardized dosing, and insufficient human trials. Strategies such as nano formulation, synergistic combinations, and improved delivery systems are currently being explored to overcome these barriers and enhance therapeutic efficacy (Wang et al., 2020, Frontiers in Pharmacology).

Table.1. Phytocompounds Targeting HPV E6/E7 Oncoproteins: Plant Sources, Mechanisms, and Potential for Cervical Cancer Therapy"

Phytocompound		Plant Source	Mechanism of Action	Target (E6/E7)	Reference
1.	Curcumin	Curcuma longa (Turmeric)	Downregulates E6/E7 mRNA; restores p53 and pRb; inhibits NF-κB and AP-1 transcription	E6 and E7	Maher et al., 2011, Mol Carcinog
2.	Resveratrol	Grapes, Berries	Downregulates E6/E7; reduces telomerase activity; promotes caspase-mediated apoptosis	E6 and E7	Kumar et al., 2014, J Pharm Pharmacol
3.	Withaferin A	Withania somnifera (Ashwagandha)	Suppresses E6/E7 expression; induces ROS-mediated apoptosis	E6 and E7	Nair et al., 2015, Phytomedicine
4.	Berberine	Berberis species	Inhibits HPV promoter activity; modulates Wnt/β-catenin signaling	E6 and E7	Nair et al., 2015, Phytomedicine
5.	Luteolin	Celery, Green Peppers	Inhibits PI3K/Akt pathway; downregulates E6/E7; restores tumor suppressors	E6 and E7	Kang et al., 2017, J Ethnopharmacol

V. CONCLUSION

Human papillomavirus (HPV), particularly high-risk types such as HPV-16 and HPV-18, plays a pivotal role in cervical carcinogenesis through the persistent expression of its E6 and E7 oncoproteins. These viral factors disrupt critical tumor suppressor pathways by targeting p53 and pRb, respectively, thereby promoting uncontrolled proliferation, genomic instability, and resistance to apoptosis. The integration of HPV DNA into the host genome further exacerbates malignant progression by stabilizing E6/E7 expression and enhancing their oncogenic effects. Age-dependent differences in immune response, hormonal influence, and epigenetic modulation underscore the need for tailored screening and treatment strategies across age groups.

In response to this molecular insight, diverse therapeutic approaches are being developed to specifically target E6 and E7 oncoproteins. Prophylactic vaccines have significantly reduced HPV infection rates, while therapeutic vaccines and gene-editing platforms such as CRISPR/Cas systems show promise in directly disrupting viral oncogene expression. Additionally, phytocompounds like curcumin, EGCG, and withaferin A demonstrate potent anti-HPV activity, offering a

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natural and accessible avenue for intervention, particularly in resource-limited settings. Continued research into the molecular mechanisms of HPV-induced oncogenesis, combined with the development of precise, multi-modal therapies, holds great potential for effective cervical cancer prevention and treatment. The integration of molecular diagnostics, personalized medicine, and innovative biotechnological tools will be essential in eliminating HPV-driven cancers and improving global health outcomes.

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