Molecular Pathogenesis and Preventive Advances in HPV-Associated Cervical Carcinogenesis

Qila Sa
West China School of Public Health and West China Fourth Hospital, Sichuan University, Chengdu, Sichuan, China

Keywords: Human Papillomavirus (HPV), Cervical Cancer, Prophylactic Vaccines.

Abstract: Cervical cancer poses a significant threat to women's health worldwide, with its pathogenesis being strongly associated with persistent infection by high-risk human papillomavirus (hrHPV). As the predominant oncogenic subtypes, HPV16 and HPV18 encode E6 and E7 proteins that disrupt cell cycle control through p53 degradation and pRb inactivation, drive genomic instability, and establish an immunosuppressive microenvironment to evade host immune surveillance. Prophylactic HPV vaccines (bivalent, quadrivalent, and nonavalent), utilizing virus-like particle (VLP) technology, effectively prevent targeted HPV infections and significantly reduce the incidence of premalignant lesions and invasive carcinomas. However, existing vaccines demonstrate limited efficacy in already infected individuals and against non-vaccine-targeted HPV types, while global disparities in vaccine accessibility and suboptimal vaccination coverage in males further compromise their preventive impact. Future directions should prioritize the development of pan-HPV spectrum vaccines, optimization of immunization protocols for high-risk populations, and breakthroughs in therapeutic vaccine design. Concerted efforts to ensure equitable vaccine allocation, implement male vaccination programs, and establish integrated prevention-screening-treatment frameworks will be crucial for accelerating the global elimination of cervical cancer. This review explores the evolving landscape of HPV vaccines, highlighting current challenges and emerging opportunities, aiming to inform evidence-based strategies for preventing and managing cervical cancer.

1 INTRODUCTION

Cervical cancer remains a leading cause of global female cancer burden, with the World Health Organization (WHO) estimating 604,000 incident cases and 342,000 attributable deaths in 2020 alone. Notably, this malignancy disproportionately affects resource-limited settings, where over 85% of both incident cases and mortality clusters in low- and middle-income countries (LMICs) (Sung et al., 2021). Epidemiological evidence establishes cervical cancer incidence as inversely associated with regional socioeconomic development gradients, where structural determinants including healthcare access inequities, screening program deficiencies, and HPV vaccine implementation gaps synergistically contribute to disproportionate disease burden distribution (Bruni et al., 2016). Cervical cancer is primarily classified histologically as squamous cell carcinoma (75%-90%), with adenocarcinoma and adenosquamous carcinoma occurring less frequently (Wang et al., 2020). Despite marked improvements in clinical outcomes through early screening and surgical interventions, survival rates among patients with advanced-stage or recurrent cervical cancer remain suboptimal, underscoring the critical imperative for elucidating pathogenic mechanisms and refining prevention strategies.

Persistent infection with high-risk human papillomavirus (hrHPV) is a critical factor in cervical carcinogenesis. More than 99% of cervical cancer cases are associated with hrHPV infection, with HPV16 and HPV18 accounting for 70% and 12% of cases respectively, constituting the predominant oncogenic subtypes (Singh et al., 2023). hrHPV disrupts host cell cycle regulation through the encoding of early proteins E6 and E7: E6 induces ubiquitin-mediated degradation of p53 to suppress apoptosis, while E7 binds to and inactivates the retinoblastoma protein (pRb), thereby promoting aberrant cell proliferation (Moody and Laimins, 2010). The HPV-induced immunosuppressive microenvironment (PIM) facilitates viral immune evasion and tumorigenesis by impairing dendritic cell functionality, recruiting regulatory immune cells, and

Sa, Q.
Molecular Pathogenesis and Preventive Advances in HPV-Associated Cervical Carcinogenesis.
DOI: 10.5220/0014494700004933

In *Proceedings of the 1st International Conference on Biomedical Engineering and Food Science (BEFS 2025)*, pages 430-434
ISBN: 978-989-758-789-4

inducing metabolic reprogramming (Zhou et al., 2019).

The implementation of HPV vaccination has revolutionized primary prevention strategies for cervical cancer. Current prophylactic vaccines—bivalent, quadrivalent, and nonavalent formulations—are designed using virus-like particles (VLPs) to elicit neutralizing antibodies, demonstrating >90% protective efficacy against targeted HPV types (Joura et al., 2015). Large-scale clinical studies have demonstrated that prophylactic HPV vaccination significantly reduces the incidence of HPV infections, genital warts, and high-grade cervical lesions (Garland et al., 2016). However, existing prophylactic vaccines demonstrate limited efficacy in individuals with established HPV infections and against immune escape phenomena mediated by non-vaccine-targeted HPV types (Malagón et al., 2012). Thus, the development of second-generation vaccines covering a broader spectrum of HPV types and therapeutic vaccines targeting E6/E7 proteins has become a current research priority (Hancock, Hellner and Dorrell, 2018). By analyzing epidemiological data, pathogenic mechanisms, and prevention strategies of HPV-positive cervical cancer, this review aims to provide theoretical support for future prevention and control efforts, while offering a solid foundation for formulating public health policies.

2 ASSOCIATION OF HPV WITH CERVICAL CARCINOGENESIS

2.1 Virological Characteristics of HPV

Human papillomavirus (HPV) is a circular double-stranded DNA virus with more than 200 identified subtypes. Categorized by oncogenic risk, HPV strains are stratified into low-risk and high-risk types. Low-risk HPV (e.g., HPV type 6, HPV type 11) primarily induces benign proliferative lesions such as genital warts, whereas high-risk HPV (e.g., HPV type 16, HPV type 18) is strongly associated with cervical carcinoma and other anogenital/oropharyngeal malignancies (Singh et al., 2023). HPV is primarily transmitted through sexual contact and can also establish infection via direct skin-to-skin or mucosal contact. The virus gains entry into cervical basal epithelial cells through microtraumas, where it exerts its oncogenic effects. Following cellular entry, HPV early genes (e.g., E6 and E7) are transcribed, initiating abnormal cellular proliferation that progresses to precancerous lesions. Late genes (L1 and L2) mediate viral capsid protein assembly, facilitating virion production and subsequent transmission (Moody and Laimins, 2010).

2.2 Association of HPV Infection with Cervical Carcinogenesis

Epidemiological evidence establishes persistent high-risk human papillomavirus (hrHPV) infection as a necessary causal factor for cervical carcinogenesis. Globally, 99% of cervical cancer cases demonstrate hrHPV association, with HPV16 and HPV18 accounting for 70% and 12% of cases respectively, constituting the predominant oncogenic subtypes (Singh et al., 2023). These genotypes demonstrate strong etiological associations not only with cervical squamous cell carcinoma (SCC) but also with adenocarcinoma (ADC) pathogenesis (Wang et al., 2020). Notably, although approximately 90% of HPV infections are cleared by the immune system, persistent infections (>2 years) may lead to the progression of cervical intraepithelial neoplasia (CIN) to invasive carcinoma (Sung et al., 2021). Chronic HPV persistence drives the accumulation of oncogenic mutations in host cells, culminating in malignant transformation.

2.3 Pathogenesis

The oncogenic potential of hrHPV is primarily mediated by its early oncoproteins E6 and E7. The E6 protein induces ubiquitin-mediated proteasomal degradation of the tumor suppressor p53, thereby suppressing apoptosis and fostering cellular survival with accumulated genomic alterations. Meanwhile, the E7 protein binds to and inactivates retinoblastoma protein (pRb), derepressing cyclin E to drive cell cycle progression, ultimately resulting in genomic instability and neoplastic transformation (Moody and Laimins, 2010). Furthermore, HPV infection facilitates the establishment of a protumorigenic immunosuppressive microenvironment (PIM). Mechanistically, viral-mediated downregulation of major histocompatibility complex (MHC) class I expression facilitates immune evasion, while concurrent recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) suppresses effector T-cell-mediated antitumor immunity (Zhou et al., 2019). Emerging evidence has elucidated that HPV infection induces metabolic reprogramming in host cells, exemplified by upregulated glycolytic flux (Warburg effect), which fosters tumor microenvironment evolution through

metabolic crosstalk, ultimately providing bioenergetic and biosynthetic support for neoplastic proliferation (WHO, 2020).

3 HPV VACCINATION IN CERVICAL CANCER PREVENTION

3.1 Classification and Mechanistic Basis of Prophylactic HPV Vaccines

Currently approved HPV vaccines encompass bivalent, quadrivalent, and nonavalent formulations, all employing virus-like particle (VLP) technology. These vaccines utilize self-assembling L1 capsid proteins to generate structurally authentic viral mimics, effectively eliciting high-titer neutralizing antibodies. The bivalent vaccine Cervarix specifically targets HPV16/18 - the two predominant oncogenic types. Incorporating the AS04 adjuvant system (monophosphoryl lipid A + aluminum hydroxide) to potentiate immunogenicity, pivotal clinical trials (NCT00128661; PATRICIA) have demonstrated 93% efficacy in preventing HPV16/18-associated cervical intraepithelial neoplasia grade 2+ (CIN2+) lesions (Joura et al., 2015). The quadrivalent vaccine Gardasil targets HPV types 6, 11, 16, and 18, providing dual protection against both oncogenic (HPV16/18) and benign pathological manifestations (HPV6/11-induced genital warts). Population-based studies demonstrate its implementation has significantly reduced the incidence of HPV-associated malignancies (cervical/vaginal/vulvar cancers) and precursor lesions across vaccinated cohorts (Garland et al., 2016). The nonavalent vaccine Gardasil 9 expands coverage to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58, collectively accounting for approximately 90% of global cervical cancer-associated HPV genotypes. This formulation elicits robust cross-neutralizing immunity against targeted types, with phase III trials (NCT00543543) demonstrating 97% efficacy in reducing high-grade squamous intraepithelial lesions (HSIL) attributable to these genotypes (Huh et al., 2017).

3.2 Clinical Efficacy and Safety Profile of Prophylactic HPV Vaccines

Large-scale clinical trials have demonstrated that prophylactic HPV vaccination significantly reduces the incidence of HPV infections and cervical intraepithelial neoplasia. In a phase III randomized controlled trial (FUTURE II) enrolling 14,215 women, the nonavalent vaccine demonstrated 96.7% efficacy (95% CI: 94.2-98.2) against high-grade squamous intraepithelial lesions (HSIL) associated with HPV31/33/45/52/58 genotypes (Huh et al., 2017). Furthermore, long-term follow-up data indicate that the vaccine's protective efficacy persists for more than a decade, with no serious adverse events observed (Phillips et al., 2018). Common vaccine-associated adverse reactions comprise injection-site pain (84%) and pyrexia (13%), with the majority of these reactions being self-limited and resolving spontaneously within 48-72 hours post-vaccination (Garland et al., 2016).

3.3 Global HPV Vaccine Voverage Landscape and Population Health Implications

As of 2022, 110 countries/territories have integrated HPV vaccination into their national immunization schedules under WHO's Expanded Program on Immunization (EPI) framework, however, vaccination coverage rates remain under 15% in low-income countries (WHO, 2020). High-income countries have demonstrated remarkable success through national school-based vaccination programs. A prime example is Australia, where implementation of the quadrivalent vaccine in 2007 has led to a 92% reduction in HPV prevalence rates among vaccine-eligible cohorts (Brotherton Julia M L., 2019). Nevertheless, persisting challenges such as inequitable global vaccine allocation, suboptimal vaccination coverage in males, and the emergence of non-vaccine-targeted HPV genotypes remain critical barriers to achieving global cervical cancer elimination targets.

4 HALLENGES IN PROPHYLACTIC HPV VACCINE DEVELOPMENT

4.1 Inherent Limitations of Prophylactic HPV Vaccines

Although current prophylactic HPV vaccines demonstrate high efficacy in preventing de novo infections, their inherent limitations warrant critical attention. Foremost, these vaccines provide limited therapeutic benefit for individuals with pre-existing HPV infections, as they neither clear established viral

reservoirs nor reverse HPV-induced cervical intraepithelial neoplasia (CIN) or invasive carcinomas (Malagón et al., 2012). Second, a principal limitation lies in the predominant mechanism of current vaccines, which primarily elicit neutralizing antibodies to prevent de novo viral entry but fail to modulate the expression of HPV oncogenic drivers (e.g., E6/E7) integrated into host genomic DNA, resulting in minimal therapeutic efficacy against established precursor or invasive malignancies (Hancock, Hellner and Dorrell, 2018). Furthermore, prophylactic HPV vaccines lack the capacity to remodel established protumor genic immunosuppressive microenvironments (PIM), thereby compromising their clinical utility in patients with advanced-stage malignancies (Zhou et al., 2019).

4.2 Narrow Spectrum Coverage of Current HPV Vaccines

While the nonavalent HPV vaccine provides coverage against approximately 90% of cervical cancer-associated HPV genotypes globally (including HPV16/18/31/33), the remaining 10% of cases are attributable to non-vaccine-targeted high-risk genotypes such as HPV35/39/51, as evidenced by global HPV genotyping surveillance data (Huh et al., 2017). Emerging epidemiological surveillance data reveal an increasing prevalence of non-vaccine-targeted HPV genotypes in specific geographic regions, a trend potentially amplified through vaccine-mediated selective pressure driving type replacement dynamics (Singh et al., 2023). Consequently, the development of next-generation pan-genotypic HPV vaccines and the engineering of multivalent vaccine platforms capable of inducing cross-neutralizing immunity represent an imperative trajectory for advancing prophylactic HPV vaccination strategies (Hancock, Hellner and Dorrell, 2018).

4.3 Impact of Host Immunogenetic Heterogeneity on Vaccine-Induced Adaptive Immunity

The immunogenicity of prophylactic HPV vaccines exhibits marked interindividual variation attributable to host immunogenetic determinants. Immunocompromised populations, particularly individuals with HIV/AIDS (PLWH), demonstrate significantly attenuated neutralizing antibody seroconversion rates (Phillips et al., 2018). scents exhibiting significantly higher geometric mean titers (GMTs) of neutralizing antibodies and prolonged serological protection following immunization. In contrast, adult females demonstrate age-dependent waning of humoral immunity, necessitating supplemental booster immunization or regimen modifications to ensure sustained vaccine effectiveness (Brotherton Julia M L., 2019). These immunobiological disparities underscore the imperative for developing demographically tailored vaccination protocols aligned with WHO's age-stratified immunization guidelines.

4.4 Male HPV Vaccination: An Underrecognized Pillar of Herd Immunity

Current global HPV vaccination strategies predominantly prioritize female immunization, while male vaccination coverage remains suboptimal (Bruni et al., 2016). Notably, vaccinating males—who serve as principal HPV transmission vectors—provides dual preventive benefits: reducing their susceptibility to HPV-associated malignancies (penile, oropharyngeal, and anal carcinomas) and establishing population-level herd immunity effects that significantly reduce heterosexual transmission to female populations (WHO, 2020). Evidence from Australia and other countries demonstrates that enhancing male HPV vaccination coverage accelerates the reduction in HPV transmission rates. However, this progress necessitates targeted public health education to rectify the prevalent misconception that HPV exclusively affects females (Brotherton Julia M L., 2019).

4.5 Therapeutic HPV Vaccine Development Challenges

Therapeutic HPV vaccine development for infected individuals remains in experimental stages. Candidate platforms—including E6/E7-targeting DNA vaccines, viral-vectored vaccines, and dendritic cell-based vaccines—are designed to prime antigen-specific cellular immunity against infected cells, yet demonstrate suboptimal clinical outcomes in phase II/III trials (Hancock, Hellner and Dorrell, 2018). Key challenges stem from HPV oncoproteins' immunoevasive properties and the multifaceted complexity of tumor microenvironments, exemplified by the suboptimal immunogenicity of E6/E7 antigens coupled with regulatory T cell (Treg)-mediated immunosuppression (Zhou et al., 2019). Therapeutic vaccine efficacy enhancement requires combinatorial immunotherapy approaches targeting

multiple antigens alongside synergistic integration with immune checkpoint inhibitors.

5 CONCLUSION

The broad implementation of HPV vaccination has precipitated a marked decline in cervical cancer incidence globally, representing a landmark achievement in oncology prevention. Nevertheless, critical barriers persist—including restricted therapeutic efficacy in established infections, non-pan-genotypic coverage, interindividual heterogeneity in immunogenicity, and inadequate male immunization rates—which collectively constitute multifactorial obstacles to achieving full cervical cancer eradication (WHO, 2020). Future research priorities should center on three strategic axes: (1) developing pan-genotypic HPV vaccines with extended valency to broaden protective coverage, while harnessing cross-neutralizing immunity to address type replacement dynamics; (2) optimizing vaccine delivery platforms and immunization regimens to enhance immunogenicity in immune-vulnerable populations; (3) accelerating translational pipelines for therapeutic vaccines, synergizing them with existing screening protocols and surgical interventions to establish integrated prevention frameworks (Hancock, Hellner and Dorrell, 2018). Policymaking necessitates multinational collaborations to implement tiered pricing mechanisms and equitable allocation frameworks, prioritizing vaccination coverage expansion in low-resource settings (Bruni et al., 2016). Concurrently, scaling up health literacy initiatives is critical to counteract vaccine hesitancy rooted in misinformation, while codifying gender-inclusive vaccination policies. The synergistic integration of tripartite prevention-screening-treatment paradigms, augmented by technological innovation and coordinated public health action, provides a viable pathway toward achieving WHO's cervical cancer elimination threshold (WHO, 2020).

REFERENCES

Brotherton Julia M L. 2019. Impact of HPV vaccination: Achievements and future challenges. *Papillomavirus Res* 7:138-140.

Bruni, Laia, et al. 2016. Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis. *Lancet Glob Health* 4(7): e453-63.

Garland, Suzanne M., et al. 2016. Impact and effectiveness of the quadrivalent human papillomavirus vaccine. *Clin Infect Dis* 15;63(4):519-27.

Hancock, Gemma, Hellner, Karin, and Lucy Dorrell. 2018. Therapeutic HPV vaccines. *Best Pract Res Clin Obstet Gynaecol* 47:59-72.

Huh, Warner K., et al. 2017. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. *Lancet Infect Dis* 11;390(10108):2143-2159.

Joura, Elmar A., et al. 2015. A 9-Valent HPV Vaccine against Infection and Intraepithelial Neoplasia in Women. *N Engl J Med* 19;372(8):711-23.

Malagón, Talía, et al. 2012. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *Lancet Infect Dis* 12(10):781-9.

Moody, C. A., & Laimins, L. A. 2010. Human papillomavirus oncoproteins: pathways to transformation. *Nat Rev Cancer* 10(8):550-60.

Phillips, Anastasia, et al. 2018. Safety of Human Papillomavirus Vaccines: An Updated Review. *Drug Saf* 41(4):329-346.

Singh, Deependra, et al. 2023. Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *Lancet Glob Health* 11(2): e197-e206.

Sung, Hyuna, et al. 2021. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.*71(3):209-249. 40(6):1499.

Wang, Renjie, et al. 2020. Human papillomavirus vaccine against cervical cancer: Opportunity and challenge. *Cancer Lett* 28:471:88-102.

WHO. 2020. Global strategy to accelerate the elimination of cervical cancer as a public health problem. CC BY-NC-SA 3.0 IGO.

Zhou, Chenhao, et al. 2019. Papillomavirus immune evasion strategies target the infected cell and the local immune system. *Front Oncol* 2:9:682.