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Chapter

Recent Advances in Human Papillomavirus Infection and Management

Shailendra K. Saxena, Swatantra Kumar, Madhu Mati Goel, Apjit Kaur and Madan LB Bhatt

Abstract

Human papillomavirus (HPV) accounts for approximately 4.5% of all cancers which differs at the level of economic development and geographical regions. The life cycle of the HPV is completely dependent on the epithelium differentiation without the involvement of cell death and systemic viremia. Carcinogenesis is the consequence of viral gene expression, dysregulated cell proliferation, and genomic instability. Keratinocytes are the target cell for HPV which act as the physical and immunological barrier. In cervical carcinogenesis, the enhanced level of Th17 infiltration has been observed which increases with the disease progression and is coupled with CCL20 expression in the stromal mesenchymal compartment. IL-6 and M-CSF are known as "switch factors" which are imperative for pro-tumorigenic response in monocytes. Screening of cervical cancer includes three major procedures: cytology, nucleic acid test, and co-testing. For evaluating anal lesions, high-resolution anoscopy is performed which is similar to colposcopy. Prophylactic vaccination is the primary preventive measure to control the HrHPV infection and reduce the burden of HPV-related cancer. The precancerous stage of HPV infection includes excision, ablation, and immunotherapy. Radiotherapy is the acceptable primary treatment for the early stage of anogenital cancer, whereas for the advanced-stage metastatic cancer, palliative therapy is the only option.

Keywords: HPV, infection, management, prevention

1. Introduction

Human papillomavirus (HPV) attributes to approximately 4.5% of all cancers which differs at the level of economic development and geographical regions [1]. *Papillomaviridae* family comprises of more than 200 types of HPV which are classified into five genera: *Alphapapillomavirus*, *Betapapillomavirus*, *Gammapapillomavirus*, *Mupapillomavirus*, and *Nupapillomavirus* [2]. All the genera are responsible for the various types of HPV-associated cancers. Furthermore, on the basis of oncogenicity, the mucosal type (alpha) is grouped into two subtypes which are low risk (LR), HPV 6 and HPV 11, which are known to cause benign genital warts and high-risk (HR) cervical cancer [3]. HPV 6 and HPV 11 are also known to cause respiratory papillomatosis predominantly in children [4]. According to IARC classification, high-risk HPV (HrHPV) is of 14 types: HPV 16, HPV 18, HPV 31, HPV 33,

HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59, HPV 66, and HPV 68 [5]. High-risk papillomavirus is responsible for causing cancer related to the cervix, vulva, vagina, anus, penis, and oropharynx [6]. HPV 16 and HPV 18 represent approximately 60% for adenocarcinoma of the endocervix (ADC-CX), and both are equally associated with 15% of adenosquamous carcinoma (ASC) of the endocervix [7]. Among the HrHPV, HPV 16 is the most efficient in evading the host immune response and responsible for persistent infection in the oropharynx, an imperative step in development of malignant lesion [8]. The mucosal HPV is transmitted by sexual contacts, and the transformation zone in females is characterized as the area adjacent to the border of the ecto- and endocervix which are the preferential sites of primary infection [9]. Approximately 80% of the sexually active women get HPV infection where most of them are asymptomatic with the immune system-mediated clearance of infection within 6–12 months [10]. With the impairment of immune function, the infection becomes symptomatic in a small number of individuals. Persistent infection of HPV and the development of cervical intraepithelial neoplasia (CIN) after the period of latency may lead to the regression or progression toward the development of invasive carcinoma [11]. The prevalence of HPV infection is higher in immunocompromised individuals such as HIV [12] and organ transplant recipients (OTRs) [13] suggesting the role of T cell in the clearance of HPV. Other factors including smoking, parity, sexual habits, genetic factors, oral-contraceptives have shown to increase the risk of progression of HPV-driven diseases [14].

Beta genus of HPV principally accounts for progression of nonmelanoma skin cancer (NMSC). The association of beta HPV types with skin cancer can be explained as the prevalence of epidermodysplasia verruciformis (EV). Patients diagnosed with EV are highly susceptible for HPV beta-type infection which results in flat warts and pityriasis versicolor-like lesions [15]. With the advancement detection methods, beta HPV types have been shown to be abundantly present in the skin of the asymptomatic HPV-infected individuals. So far, 43 HPV of beta genus have been isolated. Furthermore, beta HPV types have been speculated as HPV facilitates the accumulation of ultraviolet-mediated DNA damage [16]. In order to prevent the disease, the neutralizing antibody (nAb) has been shown to provide protection. However, immunization with attenuated or killed pathogen is imperative.

2. Global HPV epidemiology

The global burden of HPV-driven cervical cancer accounts for approximately 630,000 cases annually [1] where five other HPV-associated sites of cancer are responsible for further 113,400 cases [17]. In spite of the availability of several preventive strategies, HPV subtypes cause worldwide morbidity and mortality particularly in the less developed countries (**Figure 1**) [18]. Asia contributes to the immense majority of cervical cancer cases of 285,000 with 144,000 deaths followed by Africa where 99,000 cases with 60,000 deaths and America with 83,000 newer cases with 36,000 deaths. Asia, China, and India contribute to 62,000 and 123,000 cases along with 30,000 and 67,000 deaths, respectively [19]. Data from the meta-analysis and systemic reviews are suggesting that the vast majority of the infection is asymptomatic and transient. The incidence of HPV infection particularly cervical cancer is higher in sub-Saharan Africa (SSA) [20]. The worldwide distribution of age-specific HPV infection also varies with the predominance in young women of age less than 25 years in Europe and America [21]. However, in Africa and Asia no significant decline with the age has been observed. 3.2% of HPV 16 infected women shows normal cytology [22]. Cervical precancerous lesion is an imperative factor for HPV prevalence where HPV is detected in 52.5%

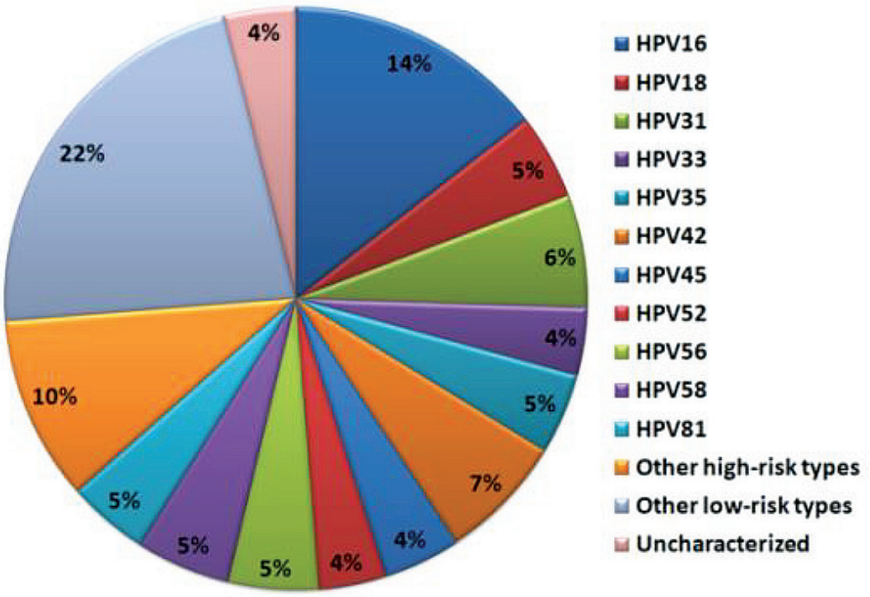

Figure 1.
Worldwide prevalence of HPV (n = 1938) [adapted from ref. 18].

of ascus lesion, 74.8% of low-grade cervical lesions, and 88.9% of high-grade cervical lesions. HPV 16 has been detected in 19.3% of low- and 45.1% of high-grade cervical lesions [23]. Furthermore, anal HPV infection is the most frequent HPV infection of other anogenital areas. The global burden of anogenital cancers caused by HPV is very high where 88% of anal and <50% of cases attribute to the lower genital tract [24]. About 30,000 cases are reported in men with the 56.56% attributed to the anus and 43.33% to penile origin. In the case of women, 38,500 cases are reported with 46.75% cases attributed to the anus, 22% to the vulva, and 31.16% from the vaginal origin [1]. Furthermore, the predominance of anal HPV infection that has been observed in the men sex with men (MSM) is 58.8% or HIV-infected individuals. The oral HPV infection significantly differs by gender and with higher incidence in men [19]. The worldwide prevalence of HPV-associated head and neck cancer is 8.15%, that is, 37,200 cases, where 77.95% of cases belong to the oropharynx, 11.82% of cases correspond to the oral cavity, and 10.21% of cases correspond to the larynx [1].

3. HPV genome and replication

Human papillomavirus is a histone-bound double-stranded DNA virus of ~8 kb with either eight or nine open reading frames (ORFs) on the same DNA strand. HPV genome can be subdivided into three regions: coding region comprises of early genes such as E1, E2, E4, E5, E6, and E7; region encoding major (L1) and minor (L2) capsid proteins; and a noncoding region present between ORFs L1 and E6 known as long control region (LCR), involving in viral DNA replication and transcriptional regulation [25]. HPV genome is highly conserved; however, exclusive features are represented by different genera. As compared with the mucosal HPV types, beta HPV genome is relatively shorter due to reduced size of LCR (400 bp) which ranges from 7.4–7.7 kb, whereas the E2 ORF is relatively larger in beta HPV types (**Figure 2**) [26]. Apart from this, most of the beta HPV types lack E5 gene with the exception of HPV 14 [27]. An additional early protein, E8Ê2C, is expressed exclusively by some of the HrHPV types as HPV 16, HPV 18, and HPV 31 that repress the expression of viral oncoproteins E6 and E7 following proliferation [28].

Recently, three gamma HPV types (101, 103, and 108) have been isolated from the cervical specimens which lack the E6 ORF [29].

Epithelial abrasion is the typical site of HPV infection where the squamocolumnar junction (SCJ) of the cervix is susceptible to HPV transformation [9]. The life cycle of the HPV is completely dependent on the epithelium differentiation without the involvement of cell death and systemic viremia. Heparan sulfate proteoglycans (HPSGs) are exposed by the epithelial abrasion which is the binding site for L1 and defined as the extracellular event of HPV replication [30]. Upon binding the conformational changes in the capsid expose the N terminus of L2 which gets cleaved by extracellular furin, a prerequisite for the virus internalization [31]. Virus uptake is mediated by L1 and endosomal vesicles, following transport of endosomal virus to the nucleus along with the retromer. L1 is degraded, whereas L2 forms the complex with viral genome following the escape from endosome to the trans-Golgi networks [32]. L2 entry into the nucleus is dependent on the cell cycle progression and transpired upon transient nuclear membrane breakdown [33]. The L2 genome complex interacts with ND-10, a promyelocytic leukemia nuclear bodies following initiation of early viral transcripts [34]. The host DNA replication machinery system is utilized by the viral early proteins E1 and E2 to establish 50–100 episomal copies per cells [35]. Dependence on host DNA replication system is the reason for the slow rate of virus evolution due to proofreading mechanism. The productive phase of HPV life cycle exhibits a unique spatial and temporal regulation and differentiation of keratinocyte in squamous epithelium. Upon leaving the basal membrane, HPV enters into the productive phase of life cycle which can be characterized as high copy number (1000 copies per cell) of HPV genome along with

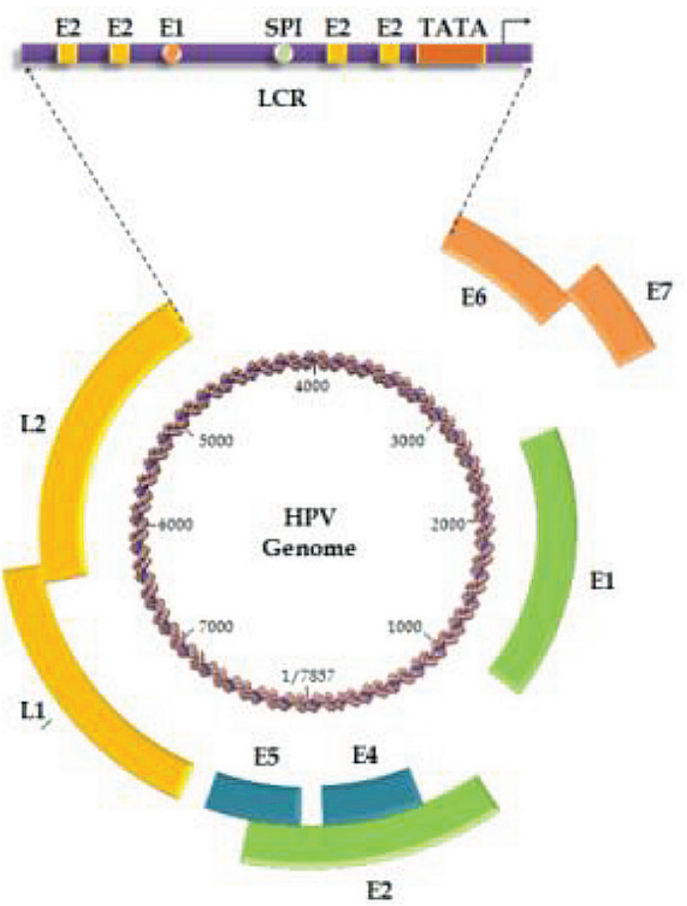

Figure 2.
HPV genome.

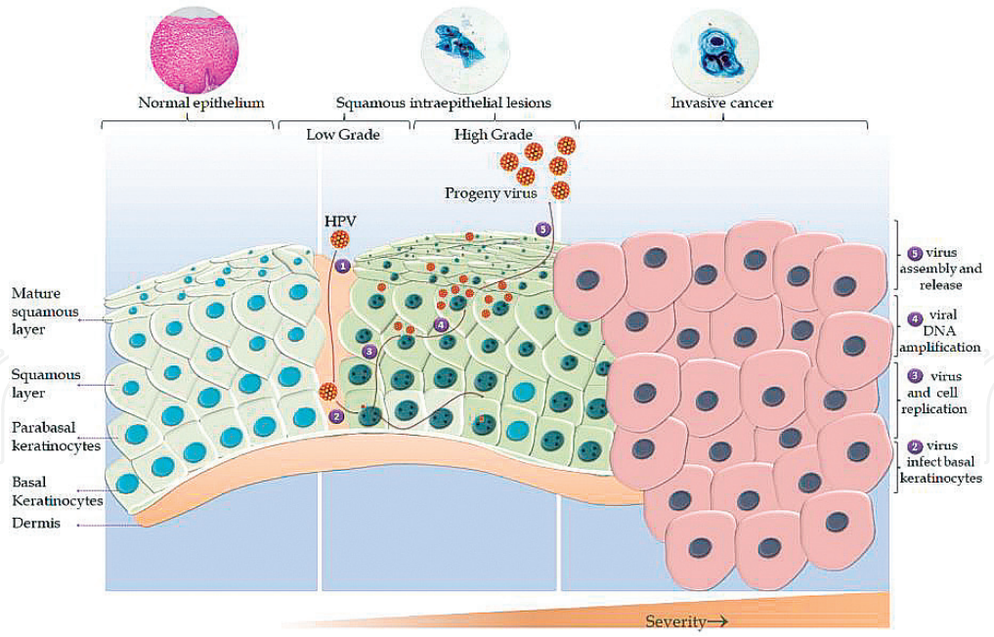

Figure 3.
HPV life cycle.

the late viral capsid expression for assembly transpired only in the upper terminally differentiated epithelial layer (**Figure 3**) [36].

Several of the host factors also play an imperative role in HPV replication where HPV drives the keratinocytes into S phase of the cell cycle mediated by E5, E6, and E7 viral oncoproteins [37]. E5 increases the expression of epidermal growth factor receptor (EGFR) which promotes the progression toward G1 phase [38]. E6 mediates proteasomal degradation upon binding with p53, a PDZ protein to promote de-differentiation of cells and other pro-apoptotic factors to promote the cell survival [39]. Moreover, MYC expression and telomerase get activated by E6 protein [40]. E7 protein is known to bind with multiple targets specifically RB to overcome the restriction points [41]. Primary keratinocytes get immortalized due to ectopic expression of E6 and E7 which also induces the genomic instability [42]. Carcinogenesis is the consequence of viral gene expression, dysregulated cell proliferation, and genomic instability; however, the progression of cancer is not beneficial to the virus.

4. Immunopathogenesis during HPV infection

The skin and mucosal surfaces act as the first line of defense during infection; however, cutaneous and mucosal HPV are known to diminish the recognition process mediated by TLR9 [43]. Mucosal HPV is known to inhibit the IFN signaling and expression which is mediated by both E6 and E7. HPV E6 protein interacts with IFN regulatory factor 3 (IRF3) [44], whereas E7 interferes with pro-apoptotic factor IRF1 and antiviral [45]. Keratinocytes are the target cell for HPV which act as the physical and immunological barrier. The activation of inflammasome in keratinocytes by other DNA viruses results in acute inflammatory responses; however, diminished inflammatory response has been observed in mucosal HPV infection. Mucosal HPV oncoproteins are responsible for abrogated posttranslational modification and secretion of IL-1β via targeting p300/CBP-associated factors/NF-κB pathway [46]. Upon infection the epithelial cells release chemotactic factors for recruiting, differentiation, and activation of Langerhans cells which are the professional antigen-presenting cells (APCs). HPV infection interferes with homeostasis of Langerhans cells in the

epidermal compartment. Low levels of chemokines (CCL20 and CCL2) are mediated by HPV oncoproteins which result in the reduced level of APC recruitment toward the epithelium [47]. HPV infection during the progression of an invasive form of cancer results in expansion of epithelial stem cell compartments.

The increased level of stromal infiltration with the immune cells is associated with the increasing dysplasia. Secretion of chemoattractants is upregulated by HPV-transformed cells, specifically the CCL2 production by monocytes which attracts myelomonocytic cells following maintenance of inflammatory microenvironment via CCR-2 dependent pathway. Remarkably, CCL-2 secretion results in higher production of MMP-9 via intracellular $Ca2^{+}$ signaling by monocytes [48]. MMP-9 has been shown to be involved in the progression toward malignancy where monocytes become infiltrating into high-grade cervical lesions. In cervical carcinogenesis, the enhanced level of Th17 infiltration has been observed which increases with the disease progression and is coupled with CCL20 expression in the stromal mesenchymal compartment [49]. Most importantly, IL-6 and monocyte colony-stimulating factors (M-CSF) are known as "switch factors" which are imperative for pro-tumorigenic response in monocytes and are highly upregulated during the late stage of human cervical cancer which results in activation of JAK/STAT3 signaling pathway in monocytes [46]. In cervical cancer, inhibition of NF-κB in CD83+ dendritic cells is the consequence of the diminished CCR7 expression that leads to interrupted dendritic cell migration to the lymph node-homing chemokine. Antigen transport to the secondary lymphoid tissue by stromal dendritic cells gets impaired due to diminished CCR7 expression. Cervical cancer cell-derived IL-6 immobilizes the dendritic cells in the tumor stroma via suppression of CCR7 resulting in local MMP-9 production [50]. Furthermore, the low level of IFN-γ production by M2-polarized macrophages causes a reduced level of T-cell proliferation in cervical cancer stroma [51]. The programmed cell death ligand-1 (PD-1) is expressed by most of the CD8+ T cells in cervical cancer, and the suppressed cytotoxic cell response is probably due to M2-macrophages [52].

5. Diagnosis for HPV

Screening of cervical cancer includes three major procedures: cytology (microscopic evaluations of sample acquired from cervical regions), nucleic acid test (detection of HrHPV DNA or RNA), and co-testing (combination of microscopy and nucleic acid test) [53]. In the clinical settings, some of the routine tests for HPV detection are biopsy, DNA-based test, Pap smear, colposcopy, and acetic acid test. Colposcopy is the clinical examination of the cervix, vagina, and vulva upon application of acetic acid solution which is known as visual inspection with acetic acid (VIA) and is mostly coupled with biopsy of regions suspected of neoplasia [54]. Colposcopy findings are evaluated and represented on the basis of acetowhite lesion, mosaic pattern, punctuation, and surface contour [55]. Due to the higher chance of false-positive results, colposcopy screening is recommended for various conditions such as HIV-infected individuals, dyskaryosis, borderline nuclear change in endocervical cells, and cervical cytology positive for malignant [56].

For evaluating anal lesions, high-resolution anoscopy is performed which is similar to colposcopy. However, anoscopy is more complex since it requires manipulation to visualize the entire SCJ along with lower accuracy. High-resolution anoscopy is performed as a first-line test for HPV surveillance in MSM population to follow up anal cytological findings [57]. Histopathological evaluations are considered as the reference standards for deciding the treatment in precancerous or cancerous stages of HPV [58]. CIN3 is considered as the precancerous stage of the HPV infection and can be treated, whereas CIN1 is the morphological representation of HPV infection

and cannot be treated [59]. The CIN2 lesions are considered as severe appearing HPV infection rather than a precancerous one. Several of the biomarkers have been developed to screen CIN2 form of HPV infection. p16 staining can be used to discriminate among the p16-positive CIN2 with CIN3 and p16-negative with CIN1 [60]. DNA-based test utilizes the principle of direct probe hybridization such as dot blot and Southern blot which are associated with disadvantages as low sensitivity and requirement of large amount of DNA sample. Currently, hybrid capture HPV DNA test 2 (HC2) and PCR-based test have been approved by the FDA [61]. HC2 test can be used to detect as low as 1 pg. of HPV DNA/ml and its sensitivity is comparable with PCR. HC2 can detect both low-risk (6, 11, 42, 43, 44) and high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) HPV. PCR-based diagnosis of HPV is more accurate and robust as compared to the Pap smear test which is a screening test for HPV detection.

6. Prevention and treatment

Prophylactic vaccination is the primary preventive measure to control the HrHPV infection and reduce the burden of HPV-related cancer [62]. Currently available vaccine for HPV comprises viruslike particles (VLPs) which is the major HPV coat protein L1. VLPs are noninfectious in nature which lacks DNA and have similar geometry to the native virus [63]. Currently, three prophylactic VLP vaccines have been licensed, namely, as the bivalent Cervarix, the nonavalent Gardasil, and the quadrivalent Gardasil [64]. Cervarix is based on the HPV 16 and HPV 18 antigens and proprietary adjuvants for enhancement of immunogenicity [65]. While Gardasil provides protection against wide range of HPV such as HPV 6, HPV 11, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52, and HPV 52 [66]. All the vaccines are intended to provide complete protection against HPV if administered before the exposure and have been shown to be highly efficacious without any adverse effects. More than 64 countries have introduced the HPV vaccination program primarily targeting girls of age 9–13 and boys of higher age group [67]. In both males and females, systemic immunization with HPV vaccine results in higher amount of antibody generation as 1–1000 times higher than the natural infection.

The management of HPV infection depends on the type and severity of the HPV infection. For the precancerous stage of HPV infection, it includes treatment strategies as excision, ablation, and immunotherapy. The gold standard for the management of HPV treatment is various excisional procedures of the transformation zone where the extent of excision depends on the lesion size [68]. Ablation procedures are less invasive and include cold coagulation, laser therapy, and cryotherapy with the disadvantage of procurement of tissue sample for confirmatory diagnosis. The immunotherapy has shown to be effective but is still present in the clinical trial stages [69]. Anogenital cancers are treated by radical local excision and by regional lymphadenectomy during the spread of infection to the lymphatic system [70]. During cervical cancer radical hysterectomy which is the removal of the whole uterus including the upper vagina and supporting ligaments along with excision of paracervical soft tissue is performed. Surgical intervention not only defines the involvement of lymph nodes but also suggests the treatment alternatives as radiotherapy and chemoradiotherapy.

Radiotherapy is the acceptable primary treatment for the early stage of anogenital cancer, whereas for the advanced-stage metastatic cancer, palliative therapy is the only option. In the recurrent cervical cancer, the antiangiogenic treatment such as bevacizumab along with cisplatin and paclitaxel can prolong the survival [71]. In case of invasive form of cervical cancer, treatment is based on surgery, brachytherapy, external beam radiation, and

cisplatin-based chemotherapy [72]. In case of oropharyngeal squamous cell cancer, cisplatin-based chemotherapy has been the primary therapeutic approach [73]. Radiotherapy or surgical intervention is the choice of treatment during the primary early stage of oropharyngeal cancer.

7. Conclusions

Globally, over 4.6% of all the cancer cases are attributed to HPV each year where vast majority of the cases are of cervical cancer. HPV 16 and HPV 18 are predominantly responsible for progression toward cancer development. The greatest burden of HPV infection comes in the form of cervical cancer and can be prevented. The burden of cervical cancer in the form of high toll number can be reduced via vaccination, screening programs, and implementation of the early treatment along with palliation. Vaccination is the ultimate preventive strategy for all the forms of HPV-associated cancers, and the evidences are suggesting the safety of the strategy.

8. Future perspectives

From the last 36 years, the research in the area of HPV focuses on the prevention strategies and led to the development of vaccine and screening programs. However, new treatment for HPV infection and HPV-related cancer is still under investigation. Immunotherapy for the systemic treatment of HPV infection is the most promising area research worldwide, but none of them have been FDA approved. In order to reduce the burden of HPV-associated cancer, global implementation of vaccination and risk-based screening programs must be followed. The use of HPV-FASTER should be compelled to exemplify the current need of vaccination and screening among the higher prevalence of HPV in young generation. Currently, preventive vaccines are being developed targeting a wide range of HPV subtypes which might reduce and eventually eliminate the need of cervical cancer screening.

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