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Human papillomavirus infection associated with cervical cancer and other malignancies

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Abstract

Human papillomavirus (HPV) consists in a great clinical importance worldwide, being involved in the most frequent sexually transmitted viral infection, genital warts, with high incidence in both men and women. Furthermore, HPV can also develop a broad spectrum of cancers, the most common is cervical cancer, being one of the main causes of morbidity and mortality in women worldwide, especially in low-and middle-income countries (LMICs). Here we discuss the importance of cervical cancer prevention and others related cancers caused by HPV, information about HPV vaccines, evaluation of single-dose use, low vaccination coverage, as well as other topics regarding viral transmission, biology, and epidemiology, aiming for the reduction of cervical carcinoma cases and others HPV associated diseases, reducing infections and death in the world as regarding to HPV, through the wide people immunization.

Keywords: Human papillomavirus; HPV; Cervical cancer; Prophylaxis; Vaccine; Immunization

1. Introduction

The development of cervical cancer is strongly associated with persistent infection with high-risk human papillomavirus (HR-HPV). The association of HPV infection and the development of cervical cancer were proposed by Dr. Harald zur Hausen in the 1980s, when he found that viral DNA is commonly integrated into the genome of infected cells [1]. This identification was fundamental for the development of vaccines against HPV to control HPV16 and HPV18 infections, as also contributed to novel techniques for cervical cancer prevention. The involvement of HPV in almost all cervical cancer cases and other types of anogenital (vulvar, vaginal, penile, and anal), head and neck cancers were also confirmed [2].

Currently, HPV infections has a great clinical relevance, being considered the most common pathogen in sexually transmitted disease, with an estimated of 60% transmission between partners [3] and about 80% of sexually active individuals can be infected at any stage of their lives [4].

Chronic infections with some HPV types are associated with the development of precancerous lesions on the cervix known as cervical intraepithelial neoplasia (CIN). These lesions have a wide spectrum of intraepithelial changes and depending on the severity they are classified histopathologically in different grades as CIN1: low-grade lesions or mild dysplasia, CIN2: high-grade or moderate dysplasia, CIN3: high grade or severe epithelial dysplasia. According to Bethesda classification system, the CIN1 lesions correspond to LSIL designation and CIN2 and CIN3 lesions are equivalent to high-grade squamous intraepithelial lesions [5, 6].

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Majority of HPV infections are transient with approximately 70% of cases regressing spontaneously within 1 year and 90% of cases resolve in 2 years, due to an immunological response [3], however the infection can persist in some cases, increasing the risk of cervical cancer development [7, 8]. Persistent infection and HPV genotype has been shown to be a risk factor for progression to severe high CIN and cancer [9]. Examples add impact to studies which have demonstrated the clinical utility of HPV genotyping in cervical cancer screening. A recent systematic review concluded that the evidence supports a clinical utility for HPV genotyping in risk discrimination during cervical cancer screening [10]. After high-risk HPV infection, the risk of progression to severe high-grade NIC and cancer is strongly associated with HPV genotype and genotype-specific persistence. Each HPV genotype has a specific associated risk for cervical cancer precursors and for cervical cancer [10].

The persistent infection can be defined as the continuous presence of viral DNA of the same HR-HPV type on a minimum of two occasions for at least 6 months in the anogenital tract [11], allowing the development of high-grade lesions (CIN 2 or 3). CIN 3 pathology is generally associated with the integration of viral DNA into the host genome [1], if not treated can increase the probability of progression to invasive cancer after 20-30 years [12].

Furthermore, there are more risk factors that may contribute to persistence and cancer progression such as: sexual behavior, smoking, multiparity, immunosuppressed individuals, genetic predisposition, long-term use of oral contraceptives and coinfection with other sexually transmitted diseases, such as *Chlamydia trachomatis* bacteria, *Herpes simplex* virus and human immunodeficiency virus (HIV) [3, 4].

High-risk HPV infection can be associated with other anogenital malignancies, being responsible for more than 90% anal cancer, about 70% vaginal and vulvar carcinomas and more than 60% penile cancers [4].

The incidence of anal cancer cases is increasing worldwide in both sexes, particularly in men who have sex with men, HIV-positive groups, women with HPV-related disease, and immunosuppressed individuals [3, 12, 13]. These cases are more frequent in women (90%), than in men (75%). The highest incidence rate occurs in women over 50 years, but in men, anal cancer is diagnosed between 20-49 years old [14]. HPV16 is the most common cause of anal carcinoma cases, followed by HPV18, 31, 33, and 45 [12, 15].

Vulvar, vaginal, and penile cancers are all rare [3], however, the incidence of penile cancer is higher in certain regions of Africa, South America, and Asia, accounting for more than 10% of cancers among men [16]. Vulvar cancer is responsible for 4% of gynecological cancers worldwide and approximately 65% of cases occur in higher income regions [17].

Among the head and neck cancers, the sites associated with HPV include the oral cavity, oropharynx and larynx [18]. The incidence of oropharyngeal cancer has declined due to the reduction of tobacco smoking and alcohol use, however, the incidence associated with HPV is rapidly increasing during the last two decades [18, 19]. HPV is responsible for approximately 30% of oropharyngeal cancer cases (29,000 cases/year), mainly in the tonsils and base of the tongue [18]. Oropharyngeal cases are found in young men in groups aged < 60 years in a part of high-income countries [20].

2. Human papillomavirus (HPV)

Papillomaviruses (PVs) can infect humans (*Human papillomavirus* - HPV) and various animal species such as fishes, reptiles, birds, and mammals [5, 21].

The HPVs belong to the *Papillomaviridae* family and classified in five genera: Alpha, Beta, Gamma, Mu, and Nupapillomavirus [22, 23]. HPVs can infect the cutaneous epithelia (beta, gamma, mu, and nu genus) or both cutaneous epithelia and mucosa (alpha genus) [24, 25]. Currently, more than two hundred genotypes of HPV have been identified and approximately sixty genotypes infect the genital mucosa [26- 28].

Human papillomavirus types are phylogenetically classified based on the homology of their L1 genes. A novel viral type has been continuously found and requires more than 10% nucleotide variation in relation to the other types, 2-4% for subtype and less than 2% for variants [23, 29].

The cutaneous types are associated with the development of benign lesions and their infections are asymptomatic, being observed in HPV types 1 and 2, responsible for common skin warts. The HPV5 and 8 (beta genus) are asymptomatic in healthy individuals, however, have been associated with non-melanoma skin cancer (NMSC) in patients with the rare hereditary disease epidermodysplasia verruciformis (EV) and immunocompromised individuals, such as solid organ transplant recipients and HIV-infected patients [30, 31].

Mucosal HPV types (alpha genus) are classified as low-risk (LR-HPV) and high-risk, (HR-HPV), according to their association with benign and malignant lesions. LR-HPV types 6 and 11 are the most prevalent; causing approximately 90% of anogenital warts (*Condyloma acuminatum*), considered the most common sexually transmitted viral disease [32]. Additionally, both types HPV6 and HPV11 account for most cases of recurrent respiratory papillomatosis (RRP) and a proportion of low grade cervical intraepithelial neoplasia (CIN1), vulval (NIV1), vaginal (NIVA1) and anal (AIN1) [14].

According to oncogenic potential thirteen high-risk HPV types are classified, such as HPVs 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, considered carcinogenic and sixty-eight as probably carcinogenic. The HPV types 26, 30, 34, 53, 66, 67, 69, 70, 73, 82 e 85 are considered possibly carcinogenic [27].

Among the HR-HPV types, HPV16 is the most prevalent and responsible for 50-60% of cervical cancer cases. HPV18 accounts for around 20% of cases [27], while HPV 31 and 45 are responsible for more than 10% of cases worldwide [7].

Infection with multiple types of HPV is common, but not associated with an increased risk of progression. HPV18 and HPV45 are the most frequently detected in adenocarcinoma, which can be more aggressive lesions.

The incidence of HPV infection is highest in young people, soon after initiation of sexual activity and the risk of infection increases with the number of sexual partners. The prevalence declines with age and around 50-55 years occurs a new peak of infection observed in various countries, which could be associated with reactivation of viral latency or incidence of new infection [3, 13].

The main HPV transmission occurs through sexual activity and oral/genital contact can lead to oral or oropharyngeal HPV infection [33]. Cutaneous warts are spread through direct contact or indirectly by contaminated objects or surfaces [3, 34]. The HPV can be incubated for a period of 3- 4 weeks, months, or years, and the duration of the latency period may be related to the dose viral received [13].

Other forms of infection can also occur, such as vertical transmission from mother to newborn during pregnancy or natural birth [3, 35]. Despite the rare incidence, it can occur in children, with the development of recurrent respiratory papillomatosis (RRP), characterized by the presence of warts in the larynx, and requires surgical intervention to prevent airway obstruction [36].

Studies on alternative routes of HPV infection have shown the interaction of human papillomavirus 16 L1L2 VLP with human peripheral blood leukocytes and precursors of hematopoietic stem cell line of human amniotic fluid [37, 38].

3. Epidemiology

Approximately 15 to 20% of global carcinomas are attributed to viral infection [39]. It is estimated that HPV participates in approximately 5% of all cancer cases worldwide [4, 27]. According to World Health Organization (WHO) cervical cancer is the fourth most common type of cancer in women worldwide [40], with 604,127 cervical cancer cases diagnosed, causing 341,831 deaths in 2020 [41]. In Brazil, the cervical cancer is the third most common among women, after breast and colorectal cancer and it is estimated 17,010 new cases of cervical cancer for 2023, representing an estimated rate of 13,25 cases per 100,000 women [42].

Currently, this disease corresponds to a major challenge to global public health, particularly in low-and middle-income countries, where about 90% of cervical cancer cases and deaths occur [41]. In these countries, cervical cancer cases are detected in very advanced stages due to various difficulties such as excessive cost of vaccines to the implementation of screening programs and treatment of pre-cancerous lesions, constituting the main cause of death of women worldwide.

More than 99% of cervical cancer cases contain HPV DNA, although the proportion associated with certain high-risk HPV types varies in different countries and shows a difference between demographic, ethnic, and socio-economic [3].

Based on meta-analysis involving more than one million women have shown a global HPV prevalence of 11.7% in asymptomatic women. The highest HPV prevalence rates were found in sub-Saharan Africa (24%), Latin America and Caribbean (16.1%), Eastern Europe (14%) and South- East Asia (14%) [43-45].

Age HPV prevalence of participants shows a first peak in younger individuals below 25 years, but in Central America and South America a significant second peak occurs in women with more than 45 years and more than 55 years in

Western Africa. Worldwide, five oncogenic HPV types most prevalent among women were HPV16 (3.2%), HPV 18 (1.4%), HPV52 (0.9%), HPV31 (0.8%) and HPV58 (0.7%) [43].

4. Viral genome and proteins of human papillomavirus

Papillomaviruses are non-enveloped viruses with icosahedral capsid of 50-60 nm in diameter [48]. The virus genome is composed of a double-stranded circular DNA with about 8,000 pb associated with histones [46, 47] and constituted by three regions: a long control region (LCR), early (E) region and late (L) region [46, 48].

The long control region (LCR), upstream regulatory region (URR) or non-coding region (NCR) is located between the L1 and E6 open reading frames (ORFs), containing the regulatory elements necessary for viral DNA replication and transcription.

The early (E) region with approximately two thirds of the viral genome [49] holds ORFs that encode six early proteins non-structural (E1, E2, E4, E5, E6 and E7). The first proteins expressed are E1 and E2, which are needed for cell replication and transcription. The E4 is an intermediate protein expressed during viral DNA replication and it engages in the reorganization of the cytoskeleton. The viral protein E5 interacts with growth factor receptors, stimulating cellular proliferation.

The E6 and E7 proteins are essential in cellular transformation and viral malignancy by inhibition of tumor suppressor p53 and pRB, respectively, resulting in dysregulation of the cellular cycle, genomic instability, and uncontrolled cell proliferation [50].

The late (L) region, of approximately one-third of the genome, has two genes (L1 and L2), which encode the L1 and L2 structural capsid proteins [49].

The L1 protein is the major structural protein that forms the icosahedral capsid viral, which consists of 72 L1 pentamers or capsomeres, containing 360 monomers of L1. The L1 protein has a molecular mass of approximately 55 kDa, with the intrinsic ability to self-assemble into virus-like particles or VLPs [51]. These particles are non-infectious and non-oncogenic, being morphologically and antigenically like authentic viruses. In addition, due to its ability of self-assembly, also has been used to generate pseudoviruses (PsVs) for analysis of papillomavirus neutralization and studies of HPV infection [52].

Interactions between capsomeres occur in the carboxi-(C)-terminal of L1 protein, connecting with neighboring capsomeres by disulfide bonds. Studies with HPV16 showed that the disulfide bond between capsomeres involves two cysteines (Cys175 and Cys 428) in C-terminal of L1 protein, both cysteines are conserved in all known types of papillomaviruses [48, 53]. The presence of disulfide bonds inter-capsomeres is crucial for the stability of the virion.

Studies have suggested that the surface of capsomeres are constituted of the loops (BC, DE, FG, and HI), containing surface-specific epitopes. Most monoclonal antibodies can neutralize the infectivity of certain species of papillomavirus, interacting with specific epitopes of loops surfaces. The location and conformation of epitopes are important for the induction of neutralizing antibodies [54]. As an example, the monoclonal antibody (mAb) H16.V5 interacts more intensely with the conformational epitopes in the loop FG (amino acids 262-291, L1) in comparison with loop HI (aa 348-360) of HPV16. [55]. However, the loops BC, DE and HI are important for the neutralization of HPV 6 and 11 [54].

L2 is a minor structural capsid protein, contains less than 500 amino acids and it is an estimated molecular mass of approximately 55 kDa [56]. However, other analysis of SDS-PAGE showed that the L2 protein migrates with a molecular mass of 64-78 kDa [56, 57]. The location and number of L2 molecules in the viral capsid are not fully defined. It has been estimated that there is a variable number of L2 monomers in between 12-72 per viral capsid, which are in the axial lumen of the capsomeres [53].

The amino-terminal region of L2 protein has two highly conserved cysteine residues (C22 and C28), that are present in all types of papillomaviruses.

The amino terminal of protein L2 has highly conserved sequences among divergent HPV types [53], which are found at amino acids 17-36, considered the greatest cross-neutralization epitope that elicits low level, but cross-serotype neutralizing antibody responses.

5. Viral cycle

HPV is exclusively an intraepithelial pathogen, and the viral life cycle depends entirely on the differentiation of keratinocytes. HPV is extremely efficient, capable of evasion of the host immune system, inducing chronic infections without systemic sequel, producing no viremia or cell death. [58].

The virus infects the basal keratinocytes of the cutaneous and mucosal epithelia by micro abrasion. The expression of viral genes with production of viral proteins and virus assembly occurs only in the more differentiated cell layers of the epithelium, with the papillomavirus virions released to the environment through a desquamation process.

The process of virus entry is extremely slow compared to other viral types [59]. The cellular receptor for entry of the virus has not yet been found, however a receptor on keratinocytes such as alpha 6-integrin and growth factor receptors has been considered as candidates in this process [60, 61].

Experimental models of the mechanism of HPV infection have suggested that occur through the binding of protein L1 to heparan sulfate proteoglycans (HSPG) and possibly laminin [62] present on basement membranes exposed after wounding.

Conformational change occurs on the viral capsid after cleavage by a cellular protease (furin), causing exposure of the specific N-terminal region of L2 protein [63]. After cleavage, the virus interacts with a secondary receptor, still unknown, to the basal keratinocyte. After that, viral internalization occurs in the basal cells and delivers the viral genome to the nucleus [1].

After infection, the viral genome is maintained in low-copy number in basal cells. The infected cells migrate to the proliferative compartment of the epithelium and the viral copy is kept constant, and expression of the viral gene is minimal. In this phase of oncogenic viruses, the expression of the potent oncogenes E6 and E7 is very tight and expressed at exceptionally low levels. After that, the infected keratinocyte enters differentiating compartment, occurring an upregulation of viral gene expression and viral DNA replication, with amplification of viral genomes to thousands copies per cell, abundant expression of early genes E6 and E7 and expression of late genes L1 and L2. In the upper layers of epithelium thousands of viral genomes are encapsidated and released as infections virus particles with desquamation of cells [49, 58].

E6 has a significant participation in lesion establishment, maintaining the basal cell reservoir during productive papillomavirus infection. The mechanism that causes chronic infections is shared by other papillomavirus types. A therapeutic target potential probably will be obtained if this interaction blockaded [64].

6. Preventive measures against HPV infection

Cervical cancer is an infectious disease with slow evolution and early detection, which can be a preventable disease. The main strategies to reduce the incidence and mortality of this disease are preventive immunization against HPV, combined with conventional cytological (PAP) screening tests and/or molecular proofs [8].

Molecular testing can significantly improve the screening coverage to detect cervical precancerous, due to their high sensibility to avoid false-positive diagnoses. Furthermore, allowing extended screening intervals and requiring less trained personnel to obtain and analyze the samples, however, they are expensive for implementation in low-income countries [66, 67]. In Brazil, the main screening strategy for cervical cancer, recommended by the Ministry of Health is the Papanicolaou (Pap) test for screening of precancerous lesions in women aged 25-64 years [8, 44].

Since the introduction of cytological (Pap) screening over the last 50 years, considerably decreasing incidence and mortality due to cervical cancer in high-income countries have been observed. The screening coverage of cervical cancer is more than 60% in high-income countries in comparison with approximately 20% in low-income-and lower-middle-income countries [67].

According to the WHO, the main strategies to control cervical cancer include access to primary prevention that is related to the vaccination of girls aged 9-14years. Secondary prevention involves screening and treatment of pre-cancerous lesions in women from 30 years of age and tertiary prevention, which consists of diagnosis and treatment of invasive cervical cancer including surgery, chemotherapy, and radiotherapy for all women and access to palliative care [43].

The discovery that the major capsid protein L1 of HPV could self-assemble into virus-like particles (VLP), which showed to be highly immunogenic and induce protective antibodies were essential for development of HPV vaccine. Experiments in animal models have shown that immunization with VLP can confer protection against viral challenge in rabbits (cottontail rabbit papillomavirus - CRPV), cow (bovine papillomavirus - BPV) and dogs (canine oral papillomavirus - COPV) [68].

Lots approaches have been used for the development of prophylactic vaccines against HPV, based on recombinant proteins expressed in distinct cellular systems, such as mammalian, insect, yeast, and bacterial cells [69-73].

The World Health Organization (WHO) recognizes the relevance of cervical cancer as a global public health problem and recommended the inclusion of HPV vaccines in their national immunization program. To date, a total of 125 countries (64%) in the world had introduced HPV vaccines in their national immunization programs for girls and 47 countries (24%) have expanded the vaccination to boys [74]. In Brazil, the National Immunization Program of the Ministry of Health introduced HPV vaccine in 2014, for girl ages 9 to 13 years. Since 2017, the vaccination has been extended for girls and boys ages 9- 14 years receiving two doses (6 months apart) [8, 44, 75].

HPV vaccine coverage rates are higher (32%) in women aged 10-20 years in high-income countries, while vaccination coverage is most low (around 1%) for adolescent girls in most low-and middle-income countries [15].

In recent years, a social anti-vaccine movement has increased in many cities of the United States, due to concerns of parents about vaccine safety and efficacy based on religious or philosophical beliefs, decreasing adherence to vaccination and contributing to the increase in vaccine preventable diseases [76, 77].

In 2003, the WHO established a surveillance system to ensure the safety of vaccines applied in the National Immunization Programs (NIP). Surveillance of adverse events following vaccination (AEFV) has been used for decades in developing countries, available in the electronic immunization registry (EIR) by the NIP. The EIR is an important instrument for the promotion of vaccination coverage and ensure the secure of vaccines. In Brazil, the AEFV has been evaluated since 1984 in the state of São Paulo and became national in 1998 with the implementation of the AEFV system by the National Immunization Program [78].

The introduction of HPV vaccine in the immunization program represents a huge challenge in many countries related to excessive costs of vaccines, logistical barriers, social and cultural issues [79]. Furthermore, some barriers of acceptance of HPV vaccination due to a lack of knowledge about vaccine safety have decreased the vaccination in some countries such as Ireland, Colombia, Romania. Recent report in Denmark have also shown decline of HPV vaccination, associated with negative media coverage involving the vaccine safety and effectiveness, and the vaccination was recovered after the HPV information campaign [80]. Furthermore, educational actions are important strategies for information about HPV infection and can also improve the adherence to HPV vaccination.

In 2020, WHO announced the global strategy to accelerate the elimination of cervical cancer as a global public health problem, contributing to reduce the incidence of cervical cancer below 4 cases/100,000 women per year. Furthermore, proposed three (90-70-90) goals by 2030, which should reach 90% of girls vaccinated by 15 years of age, 70% of women screened with high performance test at 35 and 45 years of age and 90% of women receive treatment for precancerous or invasive cancer. The implementation of the strategy could prevent 60 million cervical cancer cases and 45 million deaths over the next 100 years [74].

Nowadays three prophylactic HPV vaccines are used worldwide. They are Gardasil (quadrivalent and nonavalent - Merck & Co) and Cervarix (bivalent - GlaxoSmithKline Biologicals). These vaccines are licensed by the U.S. Food and Drugs Administration (FDA) and recognized by the World Health Organization (WHO). In addition, another bivalent Cecolin vaccine has been licensed by the Chinese Food and Drug Administration in December 2019, and has received prequalification by the World Health Organization (WHO) in October 2021 [81-83].

Quadrivalent vaccine Gardasil was the first vaccine against HPV licensed by the U.S. FDA in 2006 [15]. This vaccine contains VLPs against HPV types 16, 18, 6 and 11. Together, HPV16 and HPV18 are responsible for 70% of cervical cancers cases worldwide [7], and 80-90% of HPV-related cancers in other sites [32].

The bivalent (Cervarix) vaccine was licensed in 2009 by U.S. FDA, and produced in insect cells (Trichoplusia ni Hi-5), containing VLPs of HPV types 16 and 18. This vaccine contains an adjuvant ASO4 system, composed of aluminum hydroxide plus MPL-A (3-O-desacyl-4'-monophosphoryl lipid A), which activates innate immunity through toll like

receptor 4 (TLR4) agonist, which induce increase antibody response. The bivalent vaccine prevents against cervical, vulvar, vaginal, and anal premalignant lesions and cervical and anal cancers associated with HPV types 16 and 18.

In 2014, FDA licensed the second generation of HPV vaccine, the nonavalent vaccine (Gardasil-9). Both quadrivalent and nonavalent vaccine are produced in yeast (*Saccharomyces cerevisiae*) and formulated with adjuvant amorphous aluminum hydroxy phosphate sulfate. The nonavalent vaccine contains VLPs of five additional HPV types 31, 33, 45, 52 and 58 in relation to quadrivalent vaccine. The addition of five types of high-risk HPV can improve protection for 90% of cervical cancers cases.

Both vaccines are recommended for the prevention of anogenital warts and premalignant lesions in adults, and cancers of the cervix, vulva, vagina, and anus caused by specific high-risk HPV [84].

The bivalent vaccine Cecolin was developed by Xiamen Innovax Biotech Co., Ltd. The vaccine is produced in *Escherichia coli* containing VLPs of HPV16 and HPV18 and aluminum hydroxide as an adjuvant. This vaccine provide efficacy against high-grade genital lesions associated with HPV16 and HPV18.

Comparison of the prophylactic HPV vaccines, such as: expression system, antigen composition and adjuvants are summarized in Table 1.

Table 1 Prophylactic vaccines against human papillomavirus

Vaccine / manufacturer	L1 VLP type/dose	Expression system	Adjuvant
Cervarix - Bivalent GlaxoSmithKline-GSK	High-risk HPV 16(20μg), 18(20 μg)	Trichoplusia ni (insect cells)	500 μg aluminum hydroxide; -50 μg MPLA (3-O-desacyl 4' monophosphoryl lipid A)
Gardasil - Quadrivalent Merck & Co	Low-risk HPV 6 (20μg), 11 (40μg) High-risk HPV 16(40μg), 18 (20μg)	Saccharomyces cerevisae (Yeast cells)	225 μg aluminum hydroxyphosphate sulphate
Gardasil 9 - Nonavalent Merck & Co	Low-risk HPV 6(30μg), 11(40μg) High-risk HPV 16(60μg), 18(40μg) 31(20μg), 33(20μg) 45(20μg), 52(20μg) 58 (20μg)	Saccharomyces cerevisae (Yeast cells)	500 μg aluminum hydroxyphosphate sulphate
Cecolin - Bivalent Xiamen Innovax Biotech	High-risk HPV 16 (40μg),18 (20μg)	Escherichia coli	208 μg aluminum hydroxyde

Prophylactic vaccines based on virus-like particles (VLPs) are capable to induce high antibody responses with a mean titer 100-fold higher than that found by natural infection [85]. The neutralizing antibody level induced by natural infection is too low in serum and cervical mucosa, which may be insufficient for new infection protection [86, 87].

Clinical trials of current VLP vaccines have indicated that they are safe, well tolerated, and highly immunogenic [88-89].

The bivalent vaccine (Cervarix) and quadrivalent (Gardasil) demonstrated partial cross-protection against other types phylogenetically related to HPV 16 or 18. Cervarix vaccine appears to induce higher cross-protection against HPV 31 (around 45%) and 45 (81%) than Gardasil, probably due to the presence of adjuvant system (ASO_4) containing MPLA [48].

Prophylactic HPV vaccines were originally licensed using a 3-dose schedule (0, 1-2, 6 months) for individuals at age 15 years [91]. However, the WHO revised in 2014 the vaccination with 2-doses schedule for girls aged 9-14 years, based

on studies of immunogenicity that showed non-inferior antibody responses, when compared with three doses in young adult aged 16-26 years [92]. Comparative studies of immunogenicity of two doses of bivalent Cervarix vs two or three doses of quadrivalente Gardasil vaccine demonstrated that the Cervarix vaccine induced higher antibody titer compared with 2 or 3 doses of quadrivalent Gardasil vaccine in girls aged 9-14 years [93].

Currently, the HPV vaccines duration of protection remains unknown, but studies of bivalent (Cervarix) and quadrivalent (Gardasil) vaccine with three-dose schedules have shown neutralizing antibodies for HPV 16/18, sustained over 12 years after vaccination [94]. Nonavalent (Gardasil-9) vaccine has showed protection against HPV-type related disease for at least 6 years after vaccination [95].

Clinical trial in Costa Rica has demonstrated the first evidence that one dose of bivalent (Cervarix) vaccine may protects against HPV infection and precancerous lesions, although, single dose induces a low levels of HPV 16/18 neutralizing antibodies, compared with two or three doses of vaccine in women aged 18-25 years old. Furthermore, single dose of bivalent vaccine Cervarix demonstrated efficacy, inducing neutralizing antibody HPV16/18 levels sustained over 10 years and cross-protection against other types of HPV31, 33 and 45 [96, 97].

Studies evaluating the effectiveness of one dose of quadrivalent (Gardasil) vaccine in India [98], Mongolia [99] and Australia [100] demonstrated similar efficacy to prevent persistent HPV 16/18 infection and cervical neoplasia than two or three doses in young women [101].

The administration of a single-dose HPV vaccination has certain advantages of cost reduction and logistical barriers, which could contribute to the implementation of vaccination [97] and reduce the incidence of HPV infection and others related diseases [102] [103]

Current vaccines against HPV available prevent HPV infections, but they do not treat pre-existent infections. There are not therapeutic vaccines commercially available for the treatment of individual with persistent high-risk HPV infection. For treatments of patients with high-grade squamous intraepithelial lesions, the precursors of cervical cancer are necessary surgical intervention or other interventions to remove the lesions [104]

Therapeutic vaccine for HPV is a promissory alternative treatment against infected cells with HR-HPV and associated malignancies. Several therapeutic vaccines strategies have been developed such as DNA, RNA, peptide, proteins, viral-vector, bacterial- vector and cell- based vaccines [105]. These vaccines stimulate the cell-mediated immune responses, mostly cytotoxic CD8 T cells to eliminate tumor cells. Among the HPV proteins E6 and/or E7 are ideal targets being expressed in both premalignant and invasive lesions [104-106]. To date, unfortunately therapeutic vaccines has shown no efficacy results in randomized clinical trials phase 3. Several studies have shown strategies combining therapeutic HPV vaccines with checkpoint inhibitors such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1), which may prevent excessive and uncontrolled immune responses. Furthermore, other strategies include therapeutic vaccines with chemotherapy as carboplatin and paclitaxel with or without bevacizumab and other therapies combined with therapeutic vaccines [107, 108].

7. Conclusion

Currently, the development of serious human malignancies involving HPV is increasing worldwide, standing for a great epidemiological relevance. The most important disease is cervical cancer causing more than 340,000 deaths annually, and significant efforts have been realized in various countries to reduce the incidence of this disease in the world, through screening precancerous lesions and vaccinations. The current vaccines do not protect from all oncogenic HPV types, being recommended continuous screening to detect other high-risk HPV types such as HPV33, not present in the vaccine's formulation. To date, the introduction of HPV vaccines has been still slow and global efforts have been realized to improve global immunization coverage. The one-dose of vaccination strategy may improve vaccination rates and provide protection for women especially in low-middle countries, aiming greatly to reduce of incidence and mortality of cervical cancer and the other types of cancers in the world.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interests.

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