Chapter

Human Papillomavirus and Cervical Cancer

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Abstract

Cervical cancer is one of the leading female cancers especially in developing countries and a common cause of death among middle-aged women. The main role of Human Papillomavirus (HPV) in both cervical cancer and pre-invasive lesions of the cervix has been proven in studies. Reducing the incidence of the disease can be achieved by the regular cervical screening of women and vaccination of appropriate age groups. The disease can be better controlled by better elucidating the details of HPV carcinogenesis, the interaction between the host and the virus, and determinants of the systemic and cellular immune response to the viral infection. HPV causes oropharyngeal and anogenital diseases in both men and women and is usually sexually transmitted. Most infections are transient and could be cleared spontaneously by the host immune system. After the first encounter with HPV infection, it takes years to progress to cervical cancer, which gives clinicians a long period to follow these patients in terms of precancerous lesions and to investigate the pathogenesis of the disease. HPV plays a major role in the development of cervical cancer, but histological types have different relationships with HPV genotypes. HPV can remain latent for a long time and the most important thing determining the persistence is the type of HPV. HPV vaccination provides a direct benefit to both men and women by providing safe protection against cancers that may result from persistent HPV infection.

Keywords: cervical cancer, human papillomavirus, casualty, etiology, screening, vaccine

1. Introduction

Worldwide, cervical cancer is the fourth most common cancer among females and the third most common female genital tract cancer. 570,000 cases of invasive cervical carcinoma were diagnosed and 311,000 cervical cancer deaths occurred in 2018 [1, 2]. In low-income countries that do not have access to cervical cancer screening and prevention programs, cervical cancer continues to be a major cause of cancer diseases and deaths. The prevalence of cervical cancer and precancerous lesions depends on how effectively cancer screening programs and HPV vaccines are used in populations. The causal relationship between HPV and cervical cancer has been well documented [3–6] and HPV can be detected in 99.7 percent of cervical cancers [7]. Studies have consistently shown strong geographical correlations between HPV-DNA prevalence and cervical cancer incidence [6]. The worldwide spot prevalence of HPV is about 10 percent detected in a meta-analysis of studies involving more than 150,000 images with normal cervical cytology [8].

Africa is the most prevalent place of HPV infection in the world, where HPV is detected in 22% of African women. The most common types worldwide are HPV types 16 and 18, however, there appears to be geographic variation in the distribution of HPV genotypes.

HPV causes oropharyngeal and anogenital diseases in both men and women and is usually sexually transmitted. HPV infections are considered the most common sexually transmitted disease in sexually active individuals. It is estimated that at least 80% of sexually active individuals have been exposed to HPV once in their lifetime [9].

The most common histological type of cervical cancer is squamous cell carcinoma (SCC) (70%). Although the incidence of invasive cervical adenocarcinoma and its variants has gradually increased in the last few years; this type of neoplasia accounts for approximately 25% of all invasive cervical cancers diagnosed today. Other rare variants also constitute 3–5% of cervical cancer. HPV plays a major role in the development of cervical cancer, but histological types have different relationships with HPV genotypes. Available data state that HPV 18 accounts for 15% of SCCs and about 50% of adenocarcinomas [10]. The highest prevalence of HPV infection typically occurs within the first decade after sexual intercourse, typically between the ages of 15 and 25 in most western countries. Many sexually active young women have sequential infections with different types of oncogenic HPV. These infections are usually detected temporarily, but often reversible cytological changes occur. HPV spreads from the skin to the skin surface, and cutaneous HPV infections are common in the general population. Person-to-person transitions are typically asymptomatic [11]. Therefore, unprotected penetrative sexual intercourse (both vaginal and anal) or close physical contact from skin to skin is the most important factor for HPV infection [12]. Other risk factors are the number of partners [13, 14], new sexual partners [14], high-risk sexual partner, previous sexually transmitted disease, young age, not being married, non-Hispanic black, being the highest school graduate, poverty, low-income, first coitus at younger than 18 years old [8], primary or secondary immunodeficiency conditions. Spread from other HPV-infected genital organs, such as post-toilet wiping from front to back, may also play a role in the transmission of other types of contact [14, 15]. Penetrating vaginal and anal intercourse is not required for passage, but the prevalence of infection is much lower in virgins. Female-to-male transmission may occur at a higher rate than male-to-female transmission [16]. Regular condom use reduces the risk of HPV infection [17]. However, condoms do not completely prevent the transmission of HPV because the virus is spread through skin-to-skin contact.

HPV usually makes its first peak at an early age in unvaccinated sexually active women. Humoral and cellular immunity is provided with natural immunity partially [18, 19]. The presence of anti-HPV antibodies in patients with previous HPV type 16 infection has been associated with a lower risk of infection later, and it is thought that protective immunity is formed [18, 20–22]. However, it is not known how long and how much this protection lasts. It has been documented that some individuals with HPV infection did not develop antibodies [22, 23]. The second peak is in the postmenopausal period [24, 25]. This may be due to weakened cellular immunity or persistence or reactivation of a previously acquired infection. Reactivation may be the main source of newly detected HPV infection in HIV-positive women [26]. The oncogenic activity of HPV increases in the postmenopausal period. New HPV infection in older women does not usually progress to preinvasive disease or cancer.

HPV can remain latent for a long time and the most important thing determining the persistence is the type of HPV. HPV infection is best documented by molecular tests. PCR and in situ hybridization are mostly used in HPV typing.

With cytological examinations, only 30% of the patients represent the presence of a cytological disorder caused by HPV. A high-risk HPV type is responsible for 95% of pre-invasive lesions of the cervix and cervical cancer.

HPV has more than 200 types and can be divided into subgroups as mucous or cutaneous types according to their tissue tropism. Typing depends on DNA sequence and homology. Each type was separately identified as having less than 90% DNA base pair homology with another HPV strain. In addition to HPV genotypes, HPV intratypic variants also have epidemiological and oncogenic value in cervical cancer [27]. Different HPV types tend to infect different parts of the human body and are therefore associated with different diseases. The most common types of HPV associated with certain lesions vary according to the geography and demography of the population studied, but generally HPV types 6 and 11 cause condyloma acuminata, while type 16,18,31,52 cause intraepithelial neoplasms of the cervix [26, 28]. Over 40 HPV types showing tropism to the anogenital epithelium enter the epithelium of the penis, scrotum, perineum, anal canal, perianal area, vaginal introitus, vulva, and cervix. Approximately 15 HPV types are known as high risk, carcinogenic, or cancer-related [8]. High risk HPV types; 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 low-risk HPV types; 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73, and 8. Among these, the most common HPV type in cervical cancer is type 16, and the intraepithelial neoplasia it causes is the type most likely to progress to cancer [3]. The reason of low-risk HPV types not causing cancer is that they cannot integrate into the host cell's chromosome. The E6 and E7 genes of such HPV viruses bind weakly to p53 and pRb. The presence of a cervical transformation site is not necessary for oncogenic HPV to infect the female genital tract. Because HPV can also cause cancer in the vulva, vagina, and anal region, the epithelium of which is mentioned before, squamous keratinized epithelium. HPV 18 causes disease more frequently in younger women and recurrence is more than that of HPV 16. In cervical cancer, the specificity of HPV 18 is higher than that of HPV 16. HPV 16 and 18 involve the cervix more than other HPV types with low oncogenic potential.

2. Basic virology

The link between genital HPV infections and cervical cancer was first demonstrated in the early1980s by Harold Zur Hausen, since then, the biology of HPV viruses has been extensively studied and has proven well connected with neoplasia.

HPV is an epithelotrophic virus from the Papillomaviridae family, small, non-enveloped, encapsulated, 55 nm in diameter, containing double helix 8 kilobase circular DNA. Human papillomaviruses are a big family with the systematic classification of five genera (α, β, γ, μ, and ν), 48 species, and 206 types [27]. The genetic map of HPV-16 is illustrated in **Figure 1** [29]. It is coated with 72-surface icosahedral protein capsid which contains at least two capsid proteins, L1 and L2. HPV genome contains 7900 base pairs. It encodes 8 genes that can encode early and late proteins and URR, which control the transcription of late genes without coding [30]. Early proteins are associated with viral gene regulation and cell transformation, while late proteins form the coat of the virus [31, 32]. Specific gene products are duplicated at each differentiation level of squamous keratinocyte [33]. At the most superficial level, the L1, L2, and E4 genes are duplicated for assembly of the viral capsid in which the HPV genome is packaged. After the short-lived superficial cells desquamate, infectious HPV virions are released for the next round of infection. E1,2,5,6 and 7 are expressed in the early period of differentiation of HPV in the epithelium, L1 and L2 are expressed in the late period, and E4 is expressed during differentiation. E4 is the gene most associated with viral release. E1 and E2 play

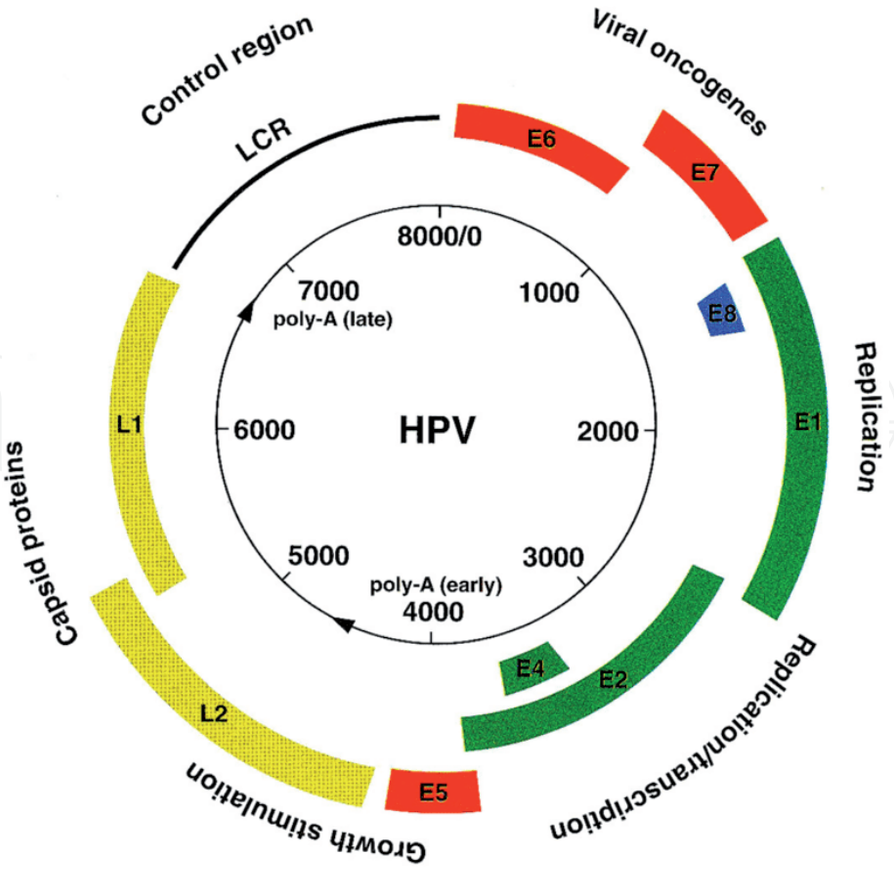

Figure 1.
Genome organization of human papillomavirus. The genetic map of HPV-16.

a critical role in participating in the structure of host DNA. E1 enables the regulation of DNA replication and keeping the virus in episomal form. E2 cooperates with E1, ensures viral DNA replication, downregulates E6 and E7 expression [34]. The HPV genome remains a stable viral episome in the nucleus of the cell, independent of the host cell nucleus. When it causes cervical cancer or pre-invasive diseases of the cervix, the HPV genome in the host nucleus integrates into the host cell's DNA. Viral integration into cellular DNA was proposed as a marker of progression to cervical cancer. Integration is rarely seen in the pre-invasive disease. Whether integration in HSIL stages progresses to cervical cancer is unknown [6]. When E2 is added to the DNA structure, it degrades and as a result, E6 and E7 expression is increased [35]. In other words, the production of E6 and E7 is mainly under the control of E2. E6 and E7 are the major HPV oncoproteins and they work together to immortalize epithelial cells [36]. Both E6 and E7 proteins are consistently expressed in cancerous tissues. E6 can lead to persistent infections and invasive cancer development with its telomerase activity. E6 activates c-myc and increases telomerase activity of the catalytic subunit gene (by increasing hTERT transcription) [37]. It has also been shown that E6 and E7 antagonize the inhibition of hTERT via BRCA [38].

E6 and E7 proteins of HPV 16 bind more tightly to their targets than other HPV types, so HPV 16 becomes more persistent. E6 binds and suppresses p53, which blocks the G1 → S step in the cell cycle [39]. Following E6 binding of p53, p53 is disrupted in the presence of E6-associated protein [40]. If p53 does not participate, DNA damage cannot be repaired. The result is that the global cycle cannot be controlled, there is no apoptosis, and chromosomal mutations accumulate because there is no DNA repair [41, 42]. E7 binds to the retinoblastoma that regulates apoptosis and forces the cell to enter the synthesis step [33]. Retinablostome inactivates the E2F transcription factor that controls DNA synthesis, cyclin function

and promotes the S phase of the cell cycle. When E7 binds to the Rb protein, E2F is released, allowing cyclin A to promote cell turnover [43]. Thus, a cell with unstable chromosomes and high-risk HPV can turn into a malignant cell. E6 and E7 are essential proteins in immortality transformation. But these two genes are not the only ones responsible for cancer development [44]. Progression to neoplasia possibly involves a genetic change in the pathways that control intracellular or intercellular signaling [45].

E5, on the other hand, disrupts the antigen presentation of MHC-I and MHC-II. E5 also activates the EGF pathway [34]. The L1 protein self-assembles in the absence of the viral genome to form a virus-like particle (VLP). L1 VLP is the immunogen used in HPV vaccines. L2 is the minor capsid protein that mediates HPV infection with L1 [46, 47].

3. HPV infection causality in cervical cancer

The role of the HPV virus in cervical cancer development is proven by the demonstration of HPV DNA and viral oncogenes E6 and E7 in cancerous tissues, that E6 and E7 gene products have host cell transforming properties, and HPV has been shown as a major factor in cervical cancer development in epidemiological studies. There are four main steps in the development of cervical cancer [48];

1. One or more oncogenic types of HPV infection of the metaplastic epithelium at the cervical transformation zone,

2. Persistence of the HPV infection rather than clearance,

3. Progression of a clone of epithelial cells from persistent viral infection to precancer (CIN3)

4. Carcinoma invasion through the basement membrane

Initial infection of the basal cell of cervical epithelium occurs as a result of microscopic breaks in the epithelium [33]. HPV targets and binds to the heparin sulfate proteoglycan receptor located in the basement membrane [49] indicating that HPV infection starts from the basement membrane. The replication cycle of the virus depends on the maturation of the keratinocyte. Since HPV does not enter the bloodstream, it does not cause viremia and inflammation. Therefore, the antigen is not formed against HPV and HPV cannot be detected by blood tests. There are also no FDA-approved serological or blood tests to detect HPV infection.

Although HPV infection is common in the population, cervical cancer develops in a minority of these infected patients. Because most HPV infections are temporary and additional factors are required for cancer development. The period from the first infection with HPV to the development of cancer is approximately 15 years. Different subtypes of HPV are detected at different rates in histological types of cervical cancer. In squamous cell carcinoma, HPV 16,18,58,33and 45 is found in 59%, 13%, 5%,5% and 4% of cases,respectively. In adenocarcinoma, HPV 16,18,45,31 and 33 is found in 36%, 37%, 5% percent, 2%,2% of cases, respectively [2].

The most expected and most likely outcome in women infected with HPV is complete resolution of the infection within 2 years [50, 51]. The least expected result is the development of neoplasia [52] and it occurs as a result of persistent infection. Currently, there is no effective treatment for HPV persistence [53].

Spontaneous recovery of HPV infection is more likely in young women [6]. Low-grade lesions caused by HPV can be detected clinically when smears are used for screening, but they are usually temporary, however, HPV can become latent [54]. It may be reactivated in immunocompromised patients however, it is not known which HPV infections become latent and whether recurrent HPV infections carry a significant cancer risk. The possibility of pre-cancerous or cancerous lesions increases with persistent HPV infections. More than one HPV type can be positive in a woman. When women with multiple types of infection were compared with women who were positive for only one HPV type, no increased risk was identified. This suggests that each HPV type causes disease independently from the other [55].

Although HPV is the most powerful cause for cervical cancer development, the presence of HPV alone is not sufficient for cervical cancer, and additional factors are required. These factors can be causes such as smoking, endogenous and exogenous hormones. HPV is positive in 99% of patients diagnosed with cervical cancer. It is thought that an HPV virus type that causes cervical cancer is encountered around the age of 21 on average [56]. While HPV 16 is responsible for 50% of cervical cancer, HPV 18 is responsible for 20% [57]. The remaining cases (19%) are caused by HPV 31,33,45,52,58 [58]. While persistent HPV infection progressing to CIN3 in 5 years [59], CIN3 progresses to invasive cancer in 30% of patients after 30 years [60]. Factors such as smoking, multiparity, age at first birth, and the use of oral contraceptives facilitate the progression of HPV-infected epithelial cells to cancer [61].

Excessive viral load in the lesion does not mean that the lesion will progress to cancer, except for HPV 16 [62]. Very high dose viral load may be detected in some low-grade lesions, but these lesions may regress over time [8]. Therefore, viral load measurement is not useful in the clinic and does not provide any additional benefit [63].

4. HPV vaccination

Routine HPV vaccination is recommended for adolescents and young adults in many countries. HPV vaccination provides a direct benefit to both men and women by providing safe protection against cancers that may result from persistent HPV infection. This protective effect has been best demonstrated in cervical cancer, one of the most common women's cancers worldwide. Inactive HPV vaccination can prevent HPV infection and its sequelae. Vaccination status does not change recommendations for screening. HPV vaccine provides protection not only from cervical caser but also from vulvar, vaginal, oropharyngeal, anal cancers, and anogenital warts. There is also evidence of decreased genital warts among men of similar age in areas with a high proportion of vaccinated women [64].

The vaccine does not protect against 100 percent of the types known to cause cervical cancer since the most extensive vaccine protects against only 9 types of HPV. Therefore, women should continue to have cervical screening regardless of whether they are vaccinated or not. However, in societies that cannot include the HPV vaccine in the routine vaccination program due to economic concerns, it is recommended that public health efforts focus primarily on the vaccination of young women, the group with the absolute benefit and cost-effectiveness of HPV vaccination. However, none of the existing HPV vaccines will cure pre-existing vaccine-type HPV infections or related diseases [27], as the vaccine is effective if used in primary prevention. Sexually active individuals should be vaccinated consistently with recommendations specific to their age. Abnormal Papanicolaou test, genital warts, or a history of HPV infection is not a contraindication to HPV

vaccination [65]. The HPV vaccine is recommended for these patients as it can still protect against infection with HPV vaccine types that have not been encountered yet [66, 67]. However, if the individual is previously infected with any HPV type in the vaccine, it reduces the protection of the vaccine.

These vaccines contain virus-like particles, but without producing the effect of the virus, only activate the body's immune system, in other words, by initiating the production of HPV-type antibodies, enable the woman to become resistant to HPV for a long time. Many studies have reported that the prevalence and incidence of HPV infection and HPV-related disease decreased following the initiation of HPV vaccination [68–71].

The vaccine does not contain virus DNA, it contains capsid particles of the virus. The vaccine is produced against the L1 and L2 capsid proteins. L1 VLP vaccines strongly stimulate cellular and humoral immunity. There are three types of HPV vaccine, bivalent, quadrivalent, and 9-in-1 vaccine, although not all of them are available everywhere. Bivalent vaccine is protective against the HPV types 16 and 18, quadrivalent vaccine and 9-shot to vaccine to,HPV types 16,18,6,11, and HPV types 16,18,6,11,31,33,45,52,58 respectively. Although it is not available everywhere, it is more advantageous to be vaccinated with a 9-shot vaccine since it contains more HPV types that cause cervical cancer. Characteristics of the three human papillomaviruses (HPV) vaccines licensed for use in the United States are demonstrated in **Table 1** [72]. Therapeutic vaccines are under development but not clinically available [73].

The best time for HPV vaccination is before an individual has sexual intercourse. Clinical trial data on vaccine efficacy in men and women show that vaccination with the HPV vaccine is most effective among people not infected with HPV. Although it can be applied to individuals of all age groups, routine HPV vaccination is recommended between 11 and 12 years of age [66]. In this age group, the protection of the vaccine is almost 100% [74–77]. The resulting titers are generally higher in younger people than in older individuals [72]. There is no minimum threshold titer defined for protection. The natural history and the determinants of the immune response to HPV are still poorly understood [6]. The World Health Organization (WHO)

Characteristic	**Bivalent (2vHPV)**	**Quadrivalent (4vHPV)**	**9-valent (9vHPV)**
Brand name	Cervarix	Gardasil	Gardasil 9
VLPs	16, 18	6,11,16,18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc	Merck and Co., Inc
Manufacturing	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1	Saccharomyces cerevisiae (Baker's yeast), expressing L1
Adjuvant	500 μg aluminum hydroxide, 50 μg 3-O-desacyl-4′ monophosphoryl lipid A	225 μg amorphous aluminum hydroxyphosphate sulfate	500 μg amorphous aluminum hydroxyphosphate sulfate
Volume per dose	0.5 ml	0.5 ml	0.5 ml
Administration	Intramuscular	Intramuscular	Intramuscular

Table 1.
Characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States.

recommends that the primary target of HPV vaccination programs is women between the ages of 9 and 14 and that local public health programs only recommend that older women be vaccinated if it is cost-effective and does not divert resources from vaccinating the primary target population or cervical cancer screening [66]. It is recommended to vaccinate men between the ages of 16–26 [72]. The vaccine can be administered from the age of 9 years [72], but it is not recommended before the age of 9. Compensatory vaccination is recommended for adolescents and adults aged 13–26 who have not been vaccinated before or have not completed the vaccine series [78] and for males aged 13 through 21 years who have not been vaccinated previously or who have not completed the 3-dose series. Males aged 22 through 26 years may be vaccinated. ACIP recommends vaccination of men who have sex with men and immunocompromised persons through age 26 years if not vaccinated previously [72]. The decision to vaccinate individuals over the age of 26 should be made on an individual basis. Because in this age group, the protection of the vaccine decreases [79]. While the protection of the vaccine is 81% in individuals between the ages of 26–35, it decreases to 75% in individuals between the ages of 35–46. The rate of protection is 44% in individuals who have been previously infected with HPV [80]. In these cases, the vaccine protects against other types of HPV. Persons who are virgin under the age of 26 can have the 9-inoculation vaccine if they have had a bivalent or quadrivalent vaccine before. The HPV vaccine is not recommended during pregnancy due to limited safety information [72]. Those who were vaccinated by mistake during pregnancy do not need termination because no relationship has been shown between the HPV vaccine and abortion or poor fetal outcomes [81]. Women of reproductive age do not need a pregnancy test before vaccination [72]. If conception is achieved between doses, the remaining doses are postponed, the remaining doses are completed after pregnancy, and do not start over [82]. Vaccine is safe for nursing mothers because inactive vaccines do not affect the safety of breastfeeding. There is no need to screen the individual for HPV before HPV vaccination [67]. Measurement of post-vaccination antibody titers has no clinical use [6] since the protective titer is unknown.

In addition, studies are showing that HPV is present in the smoke that occurs during the surgical removal or ablation of HPV-infected tissues and that nasal or oropharyngeal HPV infection may develop if this smoke is inhaled by healthcare workers [83]. Therefore, it would be beneficial to vaccinate healthcare workers who are at risk of such exposure [84]. Studies have shown that the HPV vaccine protects women against high-grade lesions of the cervix, vulva, and vagina for 10 years, and persistent antibody levels have been found [85–87].

The vaccine is administered in 3 doses [72]. The peak immunity achieved with 3 doses of vaccination is greater than that of native HPV infection. After 2 years, the antibody level drops but is still higher than that of innate immunity [78]. There is no evidence of the additional benefit of a booster dose. For individuals under 15 years of age, 2 doses are sufficient (between 0 and 6–12 months). In this age group, if the second dose is administered less than five months after the first dose, the dose should be repeated at least 12 weeks after the second dose and at least five months after the first dose. It can be applied in 0,1 and 6 months or 0, 2, and 6 months. The interval between the first and second doses should be a minimum of 4 weeks. The interval between the second and third doses should be a minimum of 12 weeks. The minimum interval between the first and third doses should be 5 months. If a dose has been administered at a shorter interval, it should be repeated at the minimum recommended interval after the last dose has passed [66, 67, 88]. If the dosing schedule is got out of order the remaining doses are made quickly, not starting over [67, 72]. Vaccines that can provide the same protection after 1 dose are in the development phase. Such a vaccine could be an important breakthrough

for low-income countries to prevent disease. If possible, the vaccination should be continued with whatever type of vaccine it started. However, if there is a problem in accessing the vaccine or if the first vaccine is not known, it can be continued with other types of vaccines [72]. Although direct efficacy data on HPV vaccination in immunocompromised hosts are lacking, immunocompromised individuals can also be vaccinated in the same manner [66]. The HPV vaccine can be safely administered in a different anatomical region at the same time with other age-appropriate vaccines. Coadministration of HPV vaccine with other vaccines does not affect the immune response [83, 89].

Side effects of HPV vaccination are generally limited to mild local reactions (regional reaction, systemic malaise, fever) [72] and syncope. Mild injection site reactions were the most common side effects in studies [90]. Syncope is not specific to the HPV vaccine [90, 91]. None of the side effects already seen are characteristic of the HPV vaccine. Following HPV vaccination, a routine waiting period of 15 minutes in a sitting or supine position is recommended [67]. Other reported side effects include headache, nausea, vomiting, tiredness, dizziness, and weakness [43]. The adjuvant aluminum hydroxyphosphate found in the quadrivalent and 9-vaccine and the adjuvant aluminum hydroxide + monophosphoryl lipid found in the bivalent vaccine is used to increase the immunological response of the vaccine. The higher the amount of adjuvant in the vaccine, the more side effects it has. For this reason, since the 9-vaccine contains more adjuvant substances, its side effects occur more [72]. However, the protection of the 9-in-1 vaccine against HPV 16 and 18 is approximately as much as the quadrivalent vaccine [72].

5. Conclusions

Cervical cancer is preventable cancer worldwide with the organized and strict compliance of early screening methods, vaccination programs, and changing sexual behavior. Aggressive treatments of early or ambiguous cytologic lesions related to HPV may result in a decrease in rates of more advanced disease although increases in the incidence of cervical adenocarcinomas have been reported in several populations. Because cervical screening tests are insufficient in detecting adenocarcinoma. Since the HPV vaccine is protective against high-risk types, it is beneficial to apply it to the recommended age groups.

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Conflict of interest

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