

## Preventing Cervical Cancer Through HPV Vaccination: A Review Article

Shokoufeh Gholamreza Fahimi<sup>1</sup>, Haniye Fayezi<sup>2\*</sup>

1. Department of Microbiology, Faculty of Biological Sciences, Islamic Azad University, Tehran North Branch, Tehran, Iran.

2. Kimia Andisheh Teb Medical and Molecular Laboratory Research Co., Tehran, Iran.

\* Corresponding author: Haniye Fayezi Email: Fayezi.haniye@gmail.com



Shokoufeh Gholamreza Fahimi  
Ph.D. candidate

### Article Type:

Review Article

### Article Info:

**Received:** 21 January . 2025

**Revised:** 29 January. 2025

**Accepted:** 5 February. 2025

**ePublished:** 4 March. 2025

**Key words:** prevention, cervical malignancy, papillomavirus vaccine, human papillomavirus

### Abstract

Cervical cancer ranks as the fourth most common malignant disease among women worldwide and is one of the leading causes of death among women of reproductive age in developing countries. Human Papillomavirus (HPV), the most common sexually transmitted infection, is associated with 95% of cervical cancer cases. While HPV infection is typically self-limiting, it can cause pre-malignant oral-anal lesions in both men and women that may progress to malignancy. HPV vaccination has emerged as a crucial preventive measure against HPV infection and its associated complications, including oral, anal, and cervical cancers, as well as genital warts. Studies have demonstrated that HPV vaccines exhibit high efficacy and immunogenicity, producing acceptable immune responses. The Gardasil vaccine has shown remarkable effectiveness, providing up to 90% protection against cervical cancer. Moreover, the newer nine-valent vaccine demonstrates even greater efficacy, offering up to 97% protection against high-grade malignant cervical and vulvar cancers. Enhanced public awareness about HPV's prevalence, transmission routes, pathogenesis, and treatment options, coupled with widespread vaccination programs, is crucial for improved disease control. These efforts collectively contribute to managing the virus's consequences and potentially eradicating cervical cancer in the coming decades. This study aims to investigate the vital role of vaccination in preventing both HPV infection and cervical cancer, ultimately working toward reducing the global burden of this significant public health concern.

## 1. Introduction

The human papillomavirus (HPV), a member of the Papillomaviridae family, weaves a complex tale as a DNA virus often caught in the web of sexually transmitted infections. To date, researchers have uncovered over 40 HPV distinct subtypes with the potential to infect both males and

females in the intimate realms of the body. Each subtype tells its own story, affecting various areas, yet a mere 15 have been linked specifically to the rise of cervical cancer. Notably, the notorious HPV 16 genotype is responsible for a staggering 70% of these cases, marking it as a key player in this serious narrative (1)

genotype is responsible for a staggering 70% of these cases, marking it as a key player in this serious narrative (1). While the links between lifestyle factors—such as the indulgence in alcohol, the habit of smoking, and ongoing exposure to the sun's rays and other forms of radiation—are well-documented in the cancer conversation, many remain unaware of the considerable impact of infectious diseases on the global cancer burden (2). Epidemiological investigations reveal that elements like education, income levels, and a host of sexual and reproductive factors, alongside specific health behaviours and lifestyle choices, all contribute to the unfolding saga of cervical cancer. In this intricate tale of prevention and awareness, knowledge is our strongest ally (3). HPV 16 is classified as a high-risk type of HPV and serves as a significant contributor to the development of invasive cervical cancer. Preventing persistent HPV infection could lead to a notable reduction in cervical cancer cases. Key strategies include promoting health care, educating patients, and providing counseling on safe sexual practices, such as delaying first intercourse, encouraging male circumcision, and ensuring early diagnosis and treatment of any vaginal infections (4). Cervical cancer is most commonly diagnosed in women aged 50 to 55 years old, with the highest mortality rates observed in those aged 75 and older. This pattern indicates a gradual progression of the disease after an earlier infection (5). Additionally, low socioeconomic status significantly increases the risk of developing cervical cancer. This is evident, as approximately 85% of cases occur in underdeveloped countries (4). Notably, India, where 16-17% of the world's female population resides, accounts for a staggering 27% of global cervical cancer cases (6).

Understanding the link between HPV and cervical cancer opens the door to effective prevention strategies, such as vaccination and regular screening. Research overwhelmingly shows that HPV vaccination during early adolescence significantly reduces the risk of vaccine-type HPV infections, precancerous conditions, and cervical cancer later in life. If the current vaccines confer lifelong immunity, we could see cervical cancer rates drop by an impressive 85% among those vaccinated before they encounter oncogenic HPV (7). Furthermore, studies reveal that HPV vaccination not only protects individuals but also lowers the prevalence of HPV infections and associated diseases throughout

the progression towards cancer. When administered prior to an individual's first sexual encounter, the vaccine can decrease the likelihood of virus infections by over 90%. Additionally, unvaccinated individuals also start experiencing some protection through herd immunity once vaccination rates surpass the 50% mark (8-10). As vaccination programs were rolled out, studies showed a significant decrease in genital warts among vaccinated groups. Additionally, there was strong evidence suggesting that high vaccination rates in females offered protection to unvaccinated males (11). Another key finding is the reduction in cervical precancer rates within vaccinated populations (12-14), with noticeable differences when comparing vaccinated individuals to those who were not vaccinated (15, 16). Perhaps the most crucial point is the decline in cancers related to HPV. This decline was first noted in long-term follow-ups of participants from the initial vaccine trials, beginning around seven years post-vaccination (17). More recently, invasive cancer rates among 15- to 24-year-olds in the United States have dropped significantly since the introduction of the vaccine (18).

## **2. Role of the HPV Genes on the Viral Replication and Cervical Carcinogenesis**

Human papillomavirus (HPV) is one of the main causes of cervical cancer, mostly caused by its ability to reproduce and induce genetic changes in epithelial cells. HPV genes, especially E6 and E7 genes, play a key role in viral replication processes and carcinogenesis (19, 20). By binding to the p53 protein and breaking it down, the E6 gene prevents the cell cycle from stopping if there is DNA damage. Similarly, the E7 gene increases the proliferation of infected cells by banding to Rb proteins and activating the cell cycle (21). These two genes allow HPV-infected cells to divide uncontrolled, and eventually genetic mutations lead to cell changes that can lead to cancer. In addition, L1 and L2 genes also play a role in making viral coverage and spreading the virus from infected cells. Recent research has shown that high-risk HPVs (such as HPV 16 and 18) are more likely to lead to cervical cancers than low-risk types. Studies have also shown that chronic HPV infection, especially in people with weakened immune systems, can increase the risk of cancer. Understanding the exact role of HPV genes in viral replication and carcinogenesis can help develop targeted therapies (22).

### 3. Immune Response and Immune Evasion

In cervical cancer, the immune system is usually unable to identify and destroy cancer cells, as tumors have various mechanisms to escape the immune response. One of the most important of these mechanisms is the use of the human papillomavirus (HPV) in interference with the immune response (23). By producing proteins such as E6 and E7, HPV can disrupt the function of immunosuppressive proteins such as p53 and Rb and prevent the removal of cancer cells by natural killer cells (NK cells) and T cells (24). Also, in cervical cancer, tumors can prevent the immune system from identifying T cells by changes in the level of MHC class I molecules (25, 26). In addition, changes in the tumor microenvironment, such as the presence of inflammatory factors and immunosuppressive cells, contribute to the creation of a suppressed immune environment that allows the tumor to grow. These processes prevent the body from identifying and destroying the tumor by the immune response, and therefore immune therapies such as immunotherapy can be used as an approach to dealing with cervical cancer (27).

### 4. Epidemiology of HPV and Cervical Cancer

Epidemiology of human papillomavirus (HPV) and cervical cancer shows that HPV is the main cause of this type of cancer. More than 200 types of HPV are known, some of which, such as HPV 16 and 18, are specifically associated with cervical cancers. Chronic infections with these viruses, especially in women with weakened immune systems or people with high-risk sexual behavior, increase the risk of cervical cancer (28). The prevalence of HPV infection in different societies varies depending on socioeconomic factors, so that in developing countries, this type of cancer is more common due to limited access to health services (29). On the other hand, despite preventive vaccines such as Gardasil, which are effective against high-risk types of HPV, new cases of cervical cancer have decreased in developed communities. However, reducing the incidence of cancer requires continued preventive measures and regular screenings (30-32).

### 5. Human Papillomavirus (HPV) and Cervical Cancer

Human papillomavirus (HPV) is one of the main causes of cervical cancer. More than 200 types of HPV are known, some of which are closely associated with cervical cancer, especially types 16 and 18. These viruses are typically transmitted through sexual contact, and in many cases, the infections caused by them disappear spontaneously (33). But in some people, chronic infections with high-risk types of HPV can lead to cell changes and genetic mutations that eventually lead to cervical cancer. Research has shown that HPV vaccines can effectively prevent high-risk types of viruses, and a significant decrease in the incidence of cervical cancer has been observed in developed countries following the use of these vaccines. However, regular screening and early detection continue to be essential for the Prevention of this cancer in various communities (31, 34, 35).

### 6. Pathophysiology and mechanism of HPV infection

Human papillomavirus (HPV) is a two-stranded DNA virus that is transmitted especially through sexual contact. The virus has several types, divided into two categories: "low-risk" and "high-risk". High-risk HPV types include 16, 18, 31, and 45 types, especially associated with cervical, anal, and some other cancers (36). In the infection mechanism, HPV enters the epithelial cells of the skin and mucosa of the body, disrupting some cellular regulation processes with the help of proteins E6 and E7. E6 protein causes the destruction of p53 protein, which leads to the Prevention of normal cell death and increased cell proliferation (37). Also, the E7 protein inhibits the proteins of the retinoblastoma family (Rb), which causes the cell cycle to continue uncontrollably (38). The Natural History of infection with HPV typically involves several stages. Initially, the virus enters the surface of the epithelium and may in many cases be destroyed by the immune system. In some people, infection persists chronically and can lead to precancerous cell changes, such as cell lesions with changes in DNA and cell function (39). These changes can gradually lead to cervical cancer. Usually, this process takes several years, and during this time, the HPV genome may cause mutational changes in host cells that eventually lead to cancer (36-39).

In the field of carcinogenicity, high-risk viruses such as HPV 16 and 18 play a major role. These viruses are able to stimulate carcinogenic processes due to their ability to alter cellular signaling pathways and prevent cell cycle stops. In later stages, cells with HPV may develop chromosomal abnormalities that contribute to the development of cancer (40). In general, understanding the exact mechanisms of HPV infection and its progress towards cancer can help develop new ways to prevent and treat cervical cancer (36-40).

## 7. Impact on Cervical Cancer Prevention

Studies show that the vaccine can have a significant effect on reducing the burden of cervical cancer. Human papillomavirus (HPV) is the leading cause of cervical cancer, which is considered one of the most common cancers in many countries. Vaccination against HPV can significantly reduce the risk of cancer by preventing chronic infections caused by the virus (41). According to other research, HPV vaccination can prevent up to 70 percent of cervical cancer cases. The vaccine, which is most commonly administered in adolescence, produces protective antibodies against various types of HPV, especially types 16 and 18, which are the main causes of cancer in women. In addition, extensive vaccination programs, such as those implemented in Scandinavia and Australia, have shown significant success in reducing the incidence of this cancer (34). Recent studies have also shown that HPV vaccination effectively reduces the risk of pre-cancerous lesions in the cervix. This reduces the need for invasive treatments and the cost of cancer-related treatment (42). Therefore, investing in this vaccine not only benefits public health, but can also help reduce the economic burden caused by the disease (43).

## 8. HPV Vaccination

### 8.1 Molecular Aspects of FDA Approved Vaccines

Vaccination stands out as one of the most effective methods globally for reducing the incidence of cancers and infections related to HPV. However, the persistent high rates of diseases stemming from HPV infections remain a significant challenge,

with cervical cancer being the fourth most prevalent cancer among women across the world (1). Many countries have launched vaccine campaigns as a viable approach to curbing HPV-related diseases. Despite these efforts, the desired reduction in incidence has not been fully realized. The reasons behind this are more intricate than they may initially seem. In particular, the context in Latin American countries presents its own set of challenges, influenced by various factors. Before examining the current landscape in Latin America and the hurdles faced in reaching vaccination goals, it's essential to first outline the key prophylactic vaccines that are commonly administered today (1). Cervarix® (GSK), Gardasil® (Merck), and Gardasil 9® (Merck) are preventive vaccines targeting specific serotypes of HPV. These vaccines utilize virus-like particles (VLP), which mimic the outer structure of HPV without any infectious material inside, ensuring a safer vaccination process (44). The VLPs are composed of L1 viral proteins created through recombinant technology, and they play a key role in triggering immune responses. This enables the body to produce antibodies that can protect against future infections (45-47). Cervarix® (GSK), which received FDA approval in 2009, is a bivalent vaccine designed to combat HPV types 16 and 18, responsible for about 70% of cervical cancers (CC) (48). Studies have shown that Cervarix can provide up to 10 years of protection by maintaining levels of antibodies against HPV 16 and 18 (49, 50). Additionally, women who have been vaccinated exhibit significantly lower HPV prevalence after four years, underscoring the vaccine's potential in preventing HPV-related oropharyngeal cancers (51). Gardasil® (Merck) is a quadrivalent vaccine designed to protect against infections caused by HPV types 6, 11, 16, and 18. These types are responsible for most cases of skin lesions and cervical cancers (52). Moreover, this vaccine has also shown effectiveness in decreasing HPV infections in the oral cavity, as well as in the penis, vulva, and anus (53-55). In addition to the quadrivalent vaccine, there's another option available, Gardasil 9® from Merck. This vaccine targets nine HPV serotypes HPV-6, 11, 16, 18, 31, 33, 45, 53, and 58 offering protection against about 90% of cervical cancers (56).

While prophylactic vaccines are the most widely known for preventing HPV infections, it's important to note that there are also therapeutic vaccines. These are specifically designed to help treat individuals who are already infected and showing symptoms related to the virus.

### 8.1.1 Peptide- and Protein-Based Vaccines

Vaccines that utilize peptides and proteins leverage fragments of human papillomavirus (HPV) proteins to encourage an immune response. Some of these proteins and peptides have been found to have lower levels of antigenicity, leading to enhanced effects when combined with adjuvants (57, 58). Delivering a peptide vaccine directly to a specific site enables a localized effect, helping to inhibit tumor cells that have been activated by either specific or non-specific antigen-presenting cells (APC) (57). Clinical observations show that these vaccines can provoke immunogenic responses in cervical cancer (CC) patients, generating targeted immune reactions against HPV. Numerous clinical studies underscore their beneficial outcomes, particularly in promoting the regression of precancerous lesions and combating HPV-related cancers (59-62).

### 8.1.2 Live Vector Vaccines

bacterial and viral live vectors have the unique ability to produce numerous copies of specific antigenic genes or proteins within a host, with the output largely determined by the size of the molecule delivered (57). Vaccines that utilize live vectors, like *Listeria monocytogenes* and *Lactococcus lactis*, act as adjuvants, enhancing the efficacy of HPV vaccines. These vectors stimulate an immune response by aiding in antigen processing within macrophages. A notable clinical trial demonstrated the effectiveness of a *Listeria monocytogenes*-based vaccine for patients with cervical cancer, showing positive results in 40% of participants (63, 64).

### 8.1.3 Nucleic Acid-Based Vaccines

On a different note, nucleic acid-based vaccines, including both DNA and RNA types, aim to trigger a focused immune response against HPV. These vaccines have

shown promising immunogenic effects in patients with precancerous lesions, fostering both cellular and humoral immunity (65). Among them, the DNA vaccine pNGVL4aCRT-E7 has been evaluated in various clinical trials targeting women with Cervical Intraepithelial Neoplasia (CIN) 2–3. This plasmid DNA vaccine, associated with calreticulin, produced an immune response in 69% of participants, leading to a reduction in the severity of the affected tissues following treatment (66).

### 8.1.4 Whole Cell-Based Vaccines

Cell-based therapeutic vaccines hold promise for reversing HPV-related diseases. These innovative vaccines function by isolating and targeting specific cells, such as T lymphocytes or dendritic cells (DCs), sourced from infected tissues or relevant pathological samples (67). Tissues obtained through biopsy from tumors and associated vascular systems are nurtured in laboratory environments, where they are engineered to generate immunomodulatory cytokines. Following this modification, these cells are reintroduced into the patient's body, with the goal of prompting the regression of the infection (68-70). In general, these diverse HPV vaccination approaches have demonstrated immunogenic effects and the capacity to elicit targeted responses against the virus in individuals with precancerous lesions and cervical cancer (CC). Nonetheless, additional clinical research is essential to assess the long-term efficacy and safety of these vaccines.

## 9. Future Perspectives

There is significant focus on the potential for cross-protection against other HPV types and on extending vaccination efforts to older populations (71). Additionally, the development of next-generation vaccines, particularly therapeutic options for those already infected, holds great promise for improving preventive measures. Staying updated on these advancements is crucial to leading the charge against cervical cancer and ensuring new findings are incorporated into effective public health strategies (72). Innovative technologies are playing a key role in the future of HPV prevention.

detection of HPV and related health issues are being developed, allowing for more focused and personalized approaches. Moreover, advances in telemedicine and digital health are improving vaccine delivery systems, including remote monitoring and follow-ups, making the process more efficient and effective (73). Incorporating artificial intelligence (AI) and machine learning into cervical cancer screening and vaccination initiatives can significantly improve accuracy, optimize procedures, and more precisely pinpoint high-risk groups. Staying updated on these technological advancements is essential for enhancing their effectiveness in cervical cancer prevention and promoting women's health (74). The global community is increasingly coming together to tackle cervical cancer head-on. With international organizations, governments, and NGOs uniting their efforts, significant strides are being made towards eliminating this disease. Key initiatives include the launch of vaccination programs, enhancements to screening facilities, and the creation of international collaborations aimed at bridging gaps in access to preventive care (75). The WHO's recent global call to action emphasizes the shared dedication to eradicating cervical cancer as a public health issue by the century's end. It is vital that we continue to monitor and support these global initiatives to ensure resources are mobilized efficiently, policies are aligned, and progress remains steady in the fight against cervical cancer (76).

## 10. Conclusions

Over the years, significant research has highlighted the link between HPV and cervical cancer, leading to the development of effective prevention strategies. Now, we have the tools to nearly eliminate cases of this disease. Cervical cancer prevention is evolving beyond the previous one-size-fits-all approach of annual exams for all adult women. Instead, primary prevention starts in adolescence with universal HPV vaccination, which helps prevent future infections. Since many adults have likely been exposed to high-risk HPV types, secondary prevention through regular screenings becomes essential for this group. By integrating HPV testing into screening processes, healthcare providers can

better allocate resources to those at higher risk, thereby minimizing unnecessary procedures for those at lower risk. This strategy is both efficient and effective, but it does require a commitment of time and resources to establish strong population management systems that can effectively track and remind patients about necessary screenings and interventions. It's also important to note that cervical cancer often affects individuals who have not been screened adequately. Therefore, it is vital that all adolescents receive their HPV vaccinations and that adults with a cervix undergo regular screenings and follow-up care. These actions are crucial steps toward reducing cervical cancer rates.

## Reference

1. Cutts F, Franceschi S, Goldie S, Castellsague Xd, De Sanjose S, Garnett G, et al. Human papillomavirus and HPV vaccines: a review. *Bulletin of the World Health Organization*. 2007;85:719-26.
2. Shapiro GK. HPV vaccination: an underused strategy for the prevention of cancer. *Current Oncology*. 2022;29(5):3780-92.
3. Bahmanyar ER, Paavonen J, Naud P, Salmerón J, Chow S-N, Apter D, et al. Prevalence and risk factors for cervical HPV infection and abnormalities in young adult women at enrolment in the multinational PATRICIA trial. *Gynecologic oncology*. 2012;127(3):440-50.
4. Chatterjee S, Chattopadhyay A, Samanta L. HPV and cervical cancer epidemiology-current status of HPV vaccination in India. *Asian Pacific Journal of Cancer Prevention*. 2016;17(8):3663-73.
5. Kamolratanakul S, Pitisuttithum P. Human papillomavirus vaccine efficacy and effectiveness against cancer. *Vaccines*. 2021;9(12):1413.
6. Shankar A, Roy S, Rath GK, Chakraborty A, Kamal VK, Biswas AS. Impact of cancer awareness drive on generating awareness of and improving screening for cervical cancer: a study among schoolteachers in India. *Journal of global oncology*. 2018;4:1-7.

7. Hariri S, Unger ER, Schafer S, Niccolai LM, Park IU, Bloch KC, et al. HPV type attribution in high-grade cervical lesions: assessing the potential benefits of vaccines in a population-based evaluation in the United States. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;24(2):393-9.
8. Group FIS. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine*. 2007;356(19):1915-27.
9. Oliver SE, Unger ER, Lewis R., et al. Prevalence of human papillomavirus among females after vaccine introduction—National Health and Nutrition Examination Survey, United States, 2003–2014. *The Journal of infectious diseases*. 2017;216(5):594-603.
10. Drolet M, Bénard É, Boily M-C, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. *The Lancet infectious diseases*. 2015;15(5):565-80.
11. Ali H, Donovan B, Wand H, Read TR, Regan DG, Grulich AE, et al. Genital warts in young Australians five years into national human papillomavirus vaccination programme: national surveillance data. *Bmj*. 2013;346.
12. Brotherton JM, Fridman M, May CL, Chappell G, Saville AM, Gertig DM. Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study. *The Lancet*. 2011;377(9783):2085-92.
13. Gertig DM, Brotherton JM, Budd AC, Drennan K, Chappell G, Saville AM. Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study. *BMC medicine*. 2013;11:1-12.
14. Ueda Y, Yagi A, Nakayama T, Hirai K, Ikeda S, Sekine M, et al. Dynamic changes in Japan's prevalence of abnormal findings in cervical cytology depending on birth year. *Scientific reports*. 2018;8(1):5612.
15. Dorton BJ, Vitonis AF, Feldman S. Comparing cervical cytology and histology among human papillomavirus–vaccinated and–unvaccinated women in an academic colposcopy clinic. *Obstetrics & Gynecology*. 2015;126(4):785-91.
16. Brogly SB, Perkins RB, Zepf D, Longtine J, Yang S. Human papillomavirus vaccination and cervical cytology in young minority women. *Sexually Transmitted Diseases*. 2014;41(8):511-4.
17. Luostarinen T, Apter D, Dillner J, Eriksson T, Harjula K, Natunen K, et al. Vaccination protects against invasive HPV-associated cancers. *International journal of cancer*. 2018;142(10):2186-7.
18. Guo F, Cofie LE, Berenson AB. Cervical cancer incidence in young US females after human papillomavirus vaccine introduction. *American journal of preventive medicine*. 2018;55(2):197-204.
19. Wei T, Grace M, Uberoi A, Romero-Masters JC, Lee D, Lambert PF, et al. The Mus musculus papillomavirus type 1 E7 protein binds to the retinoblastoma tumor suppressor: implications for viral pathogenesis. *Mbio*. 2021;12(4):10.1128/mbio.02277-21.
20. Balasubramaniam SD, et al. Key molecular events in cervical cancer development. *Medicina*. 2019;55(7):384.
21. Squarzanti DF, Sorrentino R, et al. Human papillomavirus type 16 E6 and E7 oncoproteins interact with the nuclear p53-binding protein 1 in an in vitro reconstructed 3D epithelium: new insights for the virus-induced DNA damage response. *Virology journal*. 2018;15:1-13.
22. Kajitani N, Schwartz S, editors. *The role of RNA-binding proteins in the processing of mRNAs produced by carcinogenic papillomaviruses*. *Seminars in Cancer Biology*; 2022: Elsevier.

23. Chitsike L, Duerksen-Hughes P. The potential of immune checkpoint blockade in cervical cancer: Can combinatorial regimens maximize response? A review of the literature. *Current Treatment Options in Oncology*. 2020;21(12):95.
24. Castro-Muñoz LJ, Rocha-Zavaleta L, Lizano M, Ramírez-Alcántara KM, Madrid-Marina V, Manzo-Merino J. Alteration of the IFN-pathway by human papillomavirus proteins: antiviral immune response evasion mechanism. *Biomedicines*. 2022;10(11):2965.
25. Shklovskaya E, Rizos H. MHC class I deficiency in solid tumors and therapeutic strategies to overcome it. *International journal of molecular sciences*. 2021;22(13):6741.
26. Jongasma M, Neefjes J, Spaapen R. Playing hide and seek: Tumor cells in control of MHC class I antigen presentation. *Molecular Immunology*. 2021;136:36-44.
27. Chaberek K, Mrowiec M, Kaczmarek M, Dutsch-Wicherek M. The creation of the suppressive cancer microenvironment in patients with HPV-positive cervical cancer. *Diagnostics*. 2022;12(8):1906.
28. Ahmed W, Zaib S, Ullah S, Fatima A, Zaib Z, Haseeb Azam MA, et al. Role of human Papillomavirus in various cancers: epidemiology, screening and prevention. *Mini Reviews in Medicinal Chemistry*. 2023;23(10):1079-89.
29. Nweke MC, Okolo CA, Daous Y, Esan OA. Challenges of human papillomavirus infection and associated diseases in low-resource countries. *Archives of Pathology & Laboratory Medicine*. 2018;142(6):696-9.
30. Zhang J, Fan J, Skwarczynski M, Stephenson RJ, Toth I, Hussein WM. Peptide-based nanovaccines in the treatment of cervical cancer: a review of recent advances. *International Journal of Nanomedicine*. 2022:869-900.
31. Ngoma M, Autier P. Cancer prevention: cervical cancer. *Ecancermedicalscience*. 2019;13.
32. Safaeian M, Solomon D, Castle PE. Cervical cancer prevention—cervical screening: science in evolution. *Obstetrics and gynecology clinics of North America*. 2007;34(4):739-60.
33. Ahmed HG, Bensumaidea SH, Alshammari FD, Alenazi FSH, ALmutlaq BA, Alturkstani MZ, et al. Prevalence of human papillomavirus subtypes 16 and 18 among Yemeni patients with cervical cancer. *Asian Pacific journal of cancer prevention: APJCP*. 2017;18(6):1543.
34. Sankaranarayanan R. HPV vaccination: The most pragmatic cervical cancer primary prevention strategy. *International Journal of Gynecology & Obstetrics*. 2015;131:S33-S5.
35. Chan CK, Aimagambetova G, Ukybassova T, Kongrtay K, Azizan A. Human papillomavirus infection and cervical cancer: epidemiology, screening, and vaccination—review of current perspectives. *Journal of oncology*. 2019;2019(1):3257939.
36. Wolf J, Kist LF, Pereira SB, Quessada MA, Petek H, Pille A, et al. Human papillomavirus infection: Epidemiology, biology, host interactions, cancer development, prevention, and therapeutics. *Reviews in Medical Virology*. 2024;34(3):e2537.
37. Vats A, Trejo-Cerro O, Massimi P, Banks L. Regulation of HPV E7 stability by E6-associated protein (E6AP). *Journal of Virology*. 2022;96(16):e00663-22.
38. Nor Rashid N, Yong ZL, Yusof R, Watson RJ. HPV 16E7 and 48E7 proteins use different mechanisms to target p130 to overcome cell cycle block. *Virology Journal*. 2016;13:1-8.
39. Kang SD, Chatterjee S, Alam S, Salzberg AC, Milici J, Van Der Burg SH, et al. Effect of productive human papillomavirus 16 infection on global gene expression in cervical epithelium. *Journal of virology*. 2018;92(20):10.1128/jvi. 01261-18.

40. Pešut E, Đukić A, Lulić L, et al. Human papillomaviruses-associated cancers: an update of current knowledge. *Viruses*. 2021;13(11):2234.
41. de Sanjosé S, Bruni L, Alemany L. HPV in genital cancers (at the exception of cervical cancer) and anal cancers. *La Presse Médicale*. 2014;43(12):e423-e8.
42. Ntanasis-Stathopoulos I, Kyriazoglou A, Liontos M, Dimopoulos MA, Gavriatopoulou M. Current trends in the management and prevention of human papillomavirus (HPV) infection. *J buon*. 2020;25(3):1281-5.
43. Nandi A, Shet A. Why vaccines matter: understanding the broader health, economic, and child development benefits of routine vaccination. *Human vaccines & immunotherapeutics*. 2020;16(8):1900-4.
44. Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology*. 1991;185(1):251-7.
45. Schiller J, Chackerian B. Why HIV virions have low numbers of envelope spikes: implications for vaccine development. *PLoS pathogens*. 2014;10(8):e1004254.
46. Amanna IJ, Slifka MK. Mechanisms that determine plasma cell lifespan and the duration of humoral immunity. *Immunological reviews*. 2010;236(1):125-38.
47. Schiller J, Lowy D. Explanations for the high potency of HPV prophylactic vaccines. *Vaccine*. 2018;36(32):4768-73.
48. Silviade S, Steiner I, Felix A, Ordi J, Jain A, Lima M, et al. Human papillomavirus genotype attribution in invasive cervical cancer. *Aristotle University of Thessaloniki*; 2010.
49. Schwarz TF, Huang L-M, Valencia A, Panzer F, Chiu C-H, Decreux A, et al. A ten-year study of immunogenicity and safety of the AS04-HPV-16/18 vaccine in adolescent girls aged 10-14 years. *Human vaccines & immunotherapeutics*. 2019;15(7-8):1970-9.
50. Malagón T, Drolet M, Boily M-C, et al. Cross-protective efficacy of two human papillomavirus vaccines: a systematic review and meta-analysis. *The Lancet infectious diseases*. 2012;12(10):781-9.
51. Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PloS one*. 2013;8(7):e68329.
52. Garland SM, Steben M, Sings HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus vaccine. *The Journal of infectious diseases*. 2009;199(6):805-14.
53. Schlecht NF, Masika M, Diaz A, et al. Risk of oral human papillomavirus infection among sexually active female adolescents receiving the quadrivalent vaccine. *JAMA network open*. 2019;2(10):e1914031-e.
54. Olsson S-E, Kjaer SK, Sigurdsson K, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. *Human vaccines*. 2009;5(10):696-704.
55. Wilkin TJ, Chen H, , et al. A randomized, placebo-controlled trial of the quadrivalent human papillomavirus vaccine in human immunodeficiency virus-infected adults aged 27 years or older: AIDS Clinical Trials Group Protocol A5298. *Clinical Infectious Diseases*. 2018;67(9):1339-46.
56. Yang DY, Bracken K. Update on the new 9-valent vaccine for human papillomavirus prevention. *Canadian Family Physician*. 2016;62(5):399-402.

57. Barra F, Della Corte L, Noberasco G, Foreste V, Riemma G, Di Filippo C, et al. Advances in therapeutic vaccines for treating human papillomavirus-related cervical intraepithelial neoplasia. *Journal of Obstetrics and Gynaecology Research*. 2020;46(7):989-1006.
58. Yang Y, Che Y, Zhao Y, Wang X. Prevention and treatment of cervical cancer by a single administration of human papillomavirus peptide vaccine with CpG oligodeoxynucleotides as an adjuvant in vivo. *International immunopharmacology*. 2019;69:279-88.
59. Coleman HN, Greenfield WW, et al. Human papillomavirus type 16 viral load is decreased following a therapeutic vaccination. *Cancer Immunology, Immunotherapy*. 2016;65:563-73.
60. Van Damme P, Bouillette-Marussig M, Hens A, De Coster I, Depuydt C, Goubier A, et al. GTL001, A therapeutic vaccine for women infected with human papillomavirus 16 or 18 and normal cervical cytology: results of a phase I clinical trial. *Clinical Cancer Research*. 2016;22(13):3238-48.
61. Welters MJ, van der Sluis TC, van Meir H, Loof NM, van Ham VJ, van Duikeren S, et al. Vaccination during myeloid cell depletion by cancer chemotherapy fosters robust T cell responses. *Science translational medicine*. 2016;8(334):334ra52-ra52.
62. van Poelgeest MI, Welters MJ, et al. HPV16 synthetic long peptide (HPV16-SLP) vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carcinoma, a phase II trial. *Journal of translational medicine*. 2013;11:1-14.
63. Maciag PC, Radulovic S, Rothman J. The first clinical use of a live-attenuated *Listeria monocytogenes* vaccine: a Phase I safety study of Lm-LLO-E7 in patients with advanced carcinoma of the cervix. *Vaccine*. 2009;27(30):3975-83.
64. Vici P, Pizzuti L, Mariani L, Zampa G, Santini D, Di Lauro L, et al. Targeting immune response with therapeutic vaccines in premalignant lesions and cervical cancer: hope or reality from clinical studies. *Expert review of vaccines*. 2016;15(10):1327-36.
65. Yang A, Jeang J, Cheng K, Cheng T, Yang B, Wu T-C, et al. Current state in the development of candidate therapeutic HPV vaccines. *Expert review of vaccines*. 2016;15(8):989-1007.
66. Alvarez RD, Huh WK, Bae S, Lamb Jr LS, Conner MG, Boyer J, et al. A pilot study of pNGVL4a-CRT/E7 (detox) for the treatment of patients with HPV16+ cervical intraepithelial neoplasia 2/3 (CIN2/3). *Gynecologic oncology*. 2016;140(2):245-52.
67. Shibata T, Shah S, Evans T, Coleman H, Lieblong BJ, Spencer HJ, et al. Expansion of human papillomavirus-specific T cells in periphery and cervix in a therapeutic vaccine recipient whose cervical high-grade squamous intraepithelial lesion regressed. *Frontiers in Immunology*. 2021;12:645299.
68. Ayesha N, Aboulaghras S, Jahangeer M, Riasat A, Ramzan R, Fatima R, et al. Physiopathology and effectiveness of therapeutic vaccines against human papillomavirus. *Environmental Science and Pollution Research*. 2021;28:47752-72.
69. Chang EY, Chen CH, Ji H, Wang TL, Hung K, Lee BP, et al. Antigen-specific cancer immunotherapy using a GM-CSF secreting allogeneic tumor cell-based vaccine. *International journal of cancer*. 2000;86(5):725-30.
70. Mikysková R, Indrová M, Símová J, et al. Treatment of minimal residual disease after surgery or chemotherapy in mice carrying HPV16-associated tumours: Cytokine and gene therapy with IL-2 and GM-CSF. *International journal of oncology*. 2004;24(1):161-7.

- 71.Cheng L, Wang Y, Du J. Human papilloma-virus vaccines: an updated review. *Vaccines*. 2020;8(3):391.
- 72.Nayereh KG, Khadem G. Preventive and therapeutic vaccines against human papillomaviruses associated cervical cancers. *Iranian Journal of Basic Medical Sciences*. 2012;15(1):585.
- 73.Osei EA. Innovations in healthcare delivery: Human papilloma virus self sampling diagnostics and participatory innovations for CCS. *Cancer Medicine*. 2023;12(14):15544-51.
- 74.Hou X, Shen G, Zhou L, Li Y, Wang T, Ma X. Artificial intelligence in cervical cancer screening and diagnosis. *Frontiers in oncology*. 2022;12:851367.
- 75.Rathod S, Potdar J, Gupta A, Sethi N, Dande A. Empowering women's Health: insights Into HPV vaccination and the prevention of invasive cervical cancer. *Cureus*. 2023;15(11).
- 76.Organization WH. Global strategy to accelerate the elimination of cervical cancer as a public health problem: World Health Organization; 2020.