Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/33/20240903

Research and future directions of HPV-related vaccines

Xiaofei Wu

School of Life Science and Technology, China Pharmaceutical University, Nanjing, Jiangsu, 211198, China

2020200358@stu.cpu.edu.cn

Abstract. Human papillomavirus (HPV) infection is a major cause of cervical lesions such as cervical cancer in women. Prophylactic vaccines developed against HPV have been widely used, but these vaccines are only effective against certain types of HPV and do not work in people who are already infected. Therefore, the development of therapeutic vaccines is also particularly important. The use of the modified poxvirus (MVA) as a vector for HPV vaccinations has garnered attention in recent years. It has been found that modified poxvirus vaccines are able to combat human papillomavirus infection and have significant safety and efficacy profiles. Based on the study of the distribution of HPV types in different regions and populations, this paper finds that there are differences in the prevalence of high-risk HPV subtypes in different regions, and that a large number of infected people need more effective treatments. At the same time, by comparing the advantages and disadvantages of preventive and therapeutic vaccines, we recognize that both have roles that cannot be replaced by the other in the task of fighting HPV, and that the two vaccines need to be developed together and complement each other in order to minimize the harm of HPV. Based on these findings, this paper provides a constructive reference for future targeted prevention and treatment of HPV in different regions of the world with different HPV distributions.

Keywords: Human papillomavirus (HPV), cervix, protective vaccine, therapeutic vaccine.

1. Introduction

Cervical cancer is the second most prevalent cancer affecting women worldwide, with human papillomavirus (HPV) infection being its primary cause. The most common strains responsible for cervical cancer are HPV16 and HPV18, which have a consistent distribution across different regions, except for HPV58 that shows a higher prevalence in Asia. Currently, the majority of HPV vaccines being used clinically are preventive vaccines that target HPV L1 and L2 viral particles, stimulating the production of specific antibodies. However, these vaccines are only effective in females who have not been infected with HPV or have not yet developed cervical lesions. Consequently, the development of therapeutic vaccines targeting high-risk HPV-infected females is of great significance for enhancing women's health and safety, and eradicating the widespread threat of HPV-related cervical cancer. Human papillomavirus (HPV) is an enveloped, double-stranded circular DNA virus with a diameter of about 55nm. There are over 200 types of HPV that can infect humans, with more than 40 types causing different epithelial-related diseases. The eight open reading frames (ORFs) that make up the majority of the HPV genome are classified as follows: the early region, which controls DNA replication outside of chromosomes; the late region (encoding L1 and L2), which forms the structural elements of the viral

DOI: 10.54254/2753-8818/33/20240903

shell; and the non-coding region, also known as the upstream regulatory region, which is involved in upstream regulation.

According to the International Agency for Research on Cancer (IARC), The risk of cervical cancer determines which HPV varieties are considered high-risk or low-risk. There are twelve high-risk varieties among them, including HPV 16, 18, 58, and other more prevalent high-risk strains. Of them, kinds 16 and 18 are the most carcinogenic.

2. HPV

Low-risk HPV often causes low-grade squamous intraepithelial lesions (LSIL) and benign genital warts, while high-risk HPV can lead to high-grade squamous intraepithelial lesions (HSIL) and cervical cancer. HPV primarily infects skin and mucosal tissues, and in most cases, HPV infection does not exhibit obvious clinical symptoms. However, persistent infection with certain HPV types can cause epithelial hyperplasia and eventually lead to cancer. Clinically, this manifests as different types of epithelial warts and malignant tumors such as cervical and anal cancer. The progression from HPV infection to cervical cancer is a relatively long process, which may take several years to over a decade. HPV-induced cervical epithelial tissue lesions are classified into several stages: cervical intraepithelial neoplasia (CIN) stages Ⅰ, Ⅱ, and Ⅲ, cervical carcinoma in situ, and invasive cancer. During the early stages of infection, the viral genome exists in a free form, with weak protein expression that does not cause cell or tissue damage. When cells infected with HPV begin to grow and differentiate, proteins such as E1, E2, E6, and E7 are expressed, promoting the synthesis of viral proteins, assembly of viral particles, and release. In usual circumstances, the immune system of the infected individual eliminates all viruses within several months to a few years. However, a very small percentage of infected individuals are unable to clear all the virus, causing HPV to no longer be restricted by cell differentiation and allowing the expression of E6 and E7 proteins, leading to morphological changes in cells, uncontrolled proliferation, and entry into the CIN stage. 1% of CIN Ⅰ, 5% of CIN Ⅱ, and 12% of CIN Ⅲ will eventually progress to cervical cancer [1].

3. The HPV infection rates among different populations in various regions.

Cervical cancer is a prevalent malignant tumor that poses a hazard to women's health globally. Every year, there are about 604000 fresh cases of cervical cancer occurring worldwide, and the illness causes 342,000 deaths. 85% of these cases occur in less developed countries [2]. China, as the world's largest developing country, currently has a 16.8% HPV infection rate among women. In China, between 70 and 80 percent of women have had at least one HPV infection in their lives; most of these infections are transient and go away in eight to twelve months. Nonetheless, a tiny percentage of women with high-risk HPV infections go on to have persistent infections, which can result in cervical intraepithelial neoplasia (CIN) or even cervical cancer. Studies have shown that rural women have a higher risk of high-risk HPV infection compared to urban women, which may be related to lower personal hygiene and health awareness in rural areas [3-4]. In certain urban areas such as Yichang in Hubei and Zunyi in Inner Mongolia, Compared to other parts of China, women have greater rates of HPV infection and cervical cancer [5-6]. Furthermore, research has indicated that the distribution of HPV infection among women is also related to age. Due to changes in the female body's environment and immune system, both adolescence (10-19 years old) and the menopausal transition period (starting around 40 years old, lasting 1-2 years, and potentially up to 10-20 years) are peak periods for HPV infection [7].

4. Distribution of HPV Genotypes in Different Cervical Lesions

According to a retrospective analysis conducted by the Zhejiang Cancer Hospital in China [8], the higher rates of HR-HPV infection in different stages of HPV infection is shown in figure 1.

DOI: 10.54254/2753-8818/33/20240903

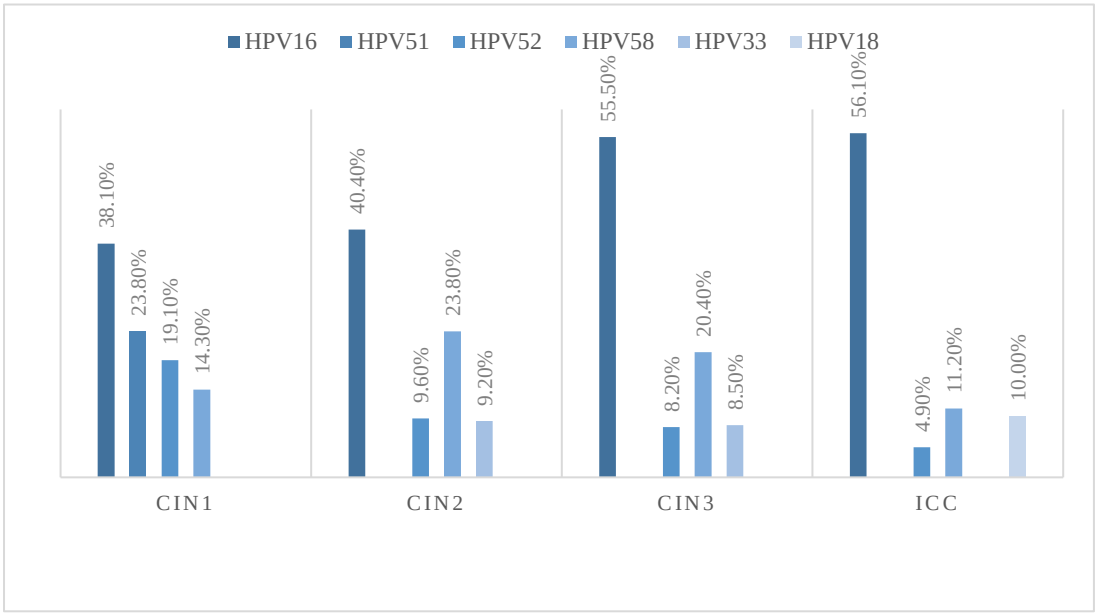

Figure 1. Distribution of HR-HPV types with higher prevalence at different stages of infection.

In addition, Wang et al. [9] conducted an analysis in 2023 that examined the prevalence of HPV infection among women in the Xinjiang region of China. The results of the analysis showed that of 3,870 local women who came to the clinic, 1,281 were detected with HPV infection.85.95% of the cases were of the high-risk kinds, and the most common genotypes were 16, 52, and 58, with the majority of infections being single infections. With aging, the HPV infection rate had a U-shaped curve distribution, with maxima at the ages of 25 and 55. The results indicate that among women in China, the highest infection rates are associated with these four types of H-R HPV: HPV16, 58, 18, and 52.

5. Preventive vaccines

Currently, most of the vaccines used clinically are therapeutic vaccines. This includes bivalent, quadrivalent, and nine-valent HPV vaccines, which are already being used globally [10]. These vaccines have high immunogenicity and immunoreactivity, effectively activating the immune system and eliciting an immune response, which can prevent HPV infection in 80% of vaccinated individuals.

To date, there have been three HPV vaccines available on the global market. Merck developed the quadrivalent vaccine, known as Gardasil, which covers HPV strains 6, 11, 16, and 18. Additionally, Merck has also created a nine-valent vaccine called Gardasil 9, which includes HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58. GSK, on the other hand, developed the bivalent vaccine Cervarix, targeting HPV strains 16 and 18.

These vaccines are developed using HPV VLPs as antigens. The L1 and L2 proteins expressed by recombinant genes in the carrier can form particles similar to the HPV virus under certain conditions. They are highly immunogenic and closely resemble the wild-type HPV virus, capable of eliciting significant immune responses in the human body, thus preventing HPV. Furthermore, the vaccine composition only includes the shell proteins and does not contain viral DNA or express carcinogenic proteins. As a result, it does not possess infectivity or carcinogenicity, ensuring its safety. In animal experiments and clinical trials that have been completed, VLPs have demonstrated high safety and good immunogenicity, inducing significant specific humoral immune responses in the body to effectively prevent relevant types of HPV [11]. Cervarix, Gardasil, and Gardasil9 have been on the market for many years, with Cervarix and Gardasil being available for a decade. Extensive clinical data and long-term post-marketing surveillance data have fully demonstrated their efficacy and safety, making outstanding contributions to the safety and health of women worldwide.

DOI: 10.54254/2753-8818/33/20240903

6. Therapeutic vaccines

preventive vaccines mentioned above can only target certain types of HPV and are not effective against other types. Additionally, since they target the free HPV before it integrates into cells, they have no effect on patients who are already infected or have developed lesions. Therefore, the development of therapeutic vaccines that can target multiple types of HPV and treat infected patients has become the focus of research. Therapeutic vaccines work by recognizing viral antigen epitopes within infected cells, thereby triggering an immune response, killing infected cells, and preventing further viral replication and disease progression. They can be used to treat infected patients.

6.1. Peptide vaccine

Synthetic peptide vaccines are a safe and novel type of vaccine. They mainly use attenuated or inactivated microorganisms as carriers and artificially synthesize protective short peptides according to the amino acid sequence of natural proteins, and add adjuvants to make vaccines. Typically, human leukocyte antigen (HLA)-restricted epitope peptides are used, which can induce specific CD8+ cytotoxic T lymphocyte (CTL) responses under in vitro and in vivo conditions, leading to the killing of tumor cells and exhibiting good specificity. The limitation of peptide vaccines lies in the fact that they need to match specific HLA types, significantly restricting their range of clinical applications [12]. Synthetic peptide vaccines are safer, more stable, and easier to make than conventional vaccinations, but they have a lower immunogenicity and need adjuvants to work. Al(OH)3 is the only approved adjuvant currently used, but it mainly enhances antibody-mediated humoral immunity and has little effect on cellular immunity. Therapeutic vaccines developed with HPV16 E6 and E7 proteins have shown good progress in clinical trials. In recent years, HPV16 synthetic long peptide (HPV16-SLP) has been widely used in clinical research [13], as it can induce long-lasting immune responses in low-grade cervical lesions

6.2. Protein vaccine

Protein vaccines, because they use complete proteins, possess all antigenic epitopes without HLA restrictions. However, similar to peptide vaccines, they also have the issue of weak immunogenicity, requiring the use of adjuvants to enhance the immune response. Currently, the proteins E6 and E7 remain hot topics of research. However, E6 and E7 proteins themselves are the culprits that cause cancer, so before developing protein vaccines, it is necessary to delete or mutate the carcinogenic sites of these proteins.

Heat shock proteins (HSPs) are a class of functional proteins that widely exist in eukaryotes. They are highly conserved and have significant roles as adjuvants in anti-tumor therapy. Previous studies mainly focused on the HSPs of Mycobacterium tuberculosis, while recently it has been found that human HSPs have a stronger effect compared to those of Mycobacterium tuberculosis [14].

The fusion protein E7-mHSP70, formed by cloning the gene HSP70 from rat liver cells and fusing with the E7 protein, can even produce significant anti-tumor effects without the need for adjuvants [15].

6.3. Viral vector vaccine

Because of their high infectivity, recombinant viruses may express antigens in huge quantities in infected cells, which qualifies them as carriers for the development of therapeutic HPV vaccines. To date, therapeutic HPV vaccines have been created using adenoviruses, baculoviruses, and vaccinia viruses.

Adenovirus is a non-pathogenic single-stranded DNA-defective virus that can infect various cells. Recombinant adenoviruses are non-pathogenic wild-type adenoviruses with a range of host cell tropism, minimal immunogenicity, and a prolonged half-life of exogenous gene expression in the body. Therefore, it is considered a suitable choice as a tumor vaccine vector.

Tan [16] et al. generated adenovirus expressing the fusion proteins of HPV16, HPV18, and HPV58 mE6E7 (Ad-HPV16/18,/58mE6E7), which induced antigen-specific immune responses. These cellular and humoral immune reactions effectively protected mice from tumor suppression.

DOI: 10.54254/2753-8818/33/20240903

Zhou [17] et al. sensitized dendritic cells (DC) and examined their capacity to elicit antigenic immune responses using reassembled adenoviruses that expressed the combined protein of HPV16 E6, as well as E7 (Ad-ofE6E7). They found that the E6E7-sensitized DC vaccine, when co-cultured with splenocytes, effectively induced tumor-specific CTL responses and was able to kill TC-1 cells. These results suggest that the HPV16 E6E7 sensitized DC vaccine can play a beneficial role in immune therapy for cervical cancer.

In recent years, people have started paying attention to the modified vaccinia Ankara virus (MVA) as a carrier for the HPV vaccine. The MVA E2 vaccine has demonstrated remarkable safety and efficacy. It is a suspension of MVA TG8042 particles and contains attenuated recombinant MVA, which includes sequence-coded modified HPV16 E6, E7, and interleukin-2. Additionally, it can encourage the generation of CD8+ T cells, suppress E2 expression, and exhibit significant anti-tumor effects against HPV infection. The MVA E2 vaccine has entered phase III clinical trials.

7. Advantages and disadvantages of preventive versus therapeutic vaccines

The prophylactic HPV vaccine needs to be administered in the absence of HPV infection in order to be effective; therefore, routine vaccination is usually administered before puberty, preferably before sexual activity has begun. Moreover, the therapeutic vaccine is able to provide broad-spectrum protection to the vaccinated individual. In addition to being effective against the high-risk strains 16 and 18, it is also effective against some sub-strains of HPV that can also cause lesions, and the period of protection lasts for more than 10 years. After more than ten years of extensive vaccination and research, the safety of the prophylactic HPV vaccine has also been proven. However, the prophylactic HPV vaccine does not provide 100% protection against the virus and does not have any therapeutic ability for those who are already infected, or even have developed the disease. The therapeutic HPV vaccine is still in the research phase and is not yet available on a large scale, but it has shown some benefits in clinical trials. The therapeutic HPV vaccine is designed to help patients who have already been infected by boosting their immune system's ability to attack the virus. The therapeutic vaccine also boosts the immune system's immunity to the virus, reducing the likelihood of recurrence. However, compared with the broad-spectrum prophylactic vaccine, the therapeutic vaccine can only be used for specific subtypes of patients, the vaccine has a slower onset of action, and more clinical data are needed to prove its safety.

8. Conclusion

Although HPV is the culprit for cervical lesions in women worldwide, the dominant local HPV subtypes are not exactly the same depending on the region. In the vast poor and backward areas, women are more susceptible to infection and all kinds of related diseases due to lack of hygiene knowledge and conditions. The current mainstream therapeutic HPV vaccine has protected thousands of women from the disease by virtue of its excellent preventive ability. However,the limitations can be seen, and in order to better protect against the threat of HPV, researchers need to vigorously promote the research of therapeutic vaccine, together with the advanced pathological analysis technology, in order to achieve a more targeted, more effective Treatment. Different types of vaccines can be selected for individuals at various stages and in different regions, alongside the implementation of regular and dependable HPV testing. In underdeveloped areas, efforts can be made to widely promote fundamental education on safety and health, while ensuring availability of essential hygiene products. In the future, as the development of biotechnology, a broader-spectrum and effective preventive vaccine and a safe and reliable therapeutic vaccine is expected to be developed.

References

[1] Ostorag 1993 Natural history of cervical intraepithelial neoplasia:a critical review Int J Gynecol Pathol 12(2) 186-192

[2] Nurbia A Perdam N Zumiran R Guzaili N 2023 Current awareness of cervical cancer prevention and comprehensive sexual health among women in Kashgar area Effect of educational intervention Chinese Maternal and Child Health Research 34 (09) 47-51

DOI: 10.54254/2753-8818/33/20240903

[3] Li JKang L Li B et al 2015 Effect of a group educational interven tion on rural Chinese women's knowledge and attitudes about hu man papillomavirus (HPV)and HPV vaccines BMC Cancer15:691
[4] Li JHuang RSchmidt JE et al 2013 Epidemiological features of human papillomavirus (HPV)infection among women living in Ma inland China Asian Pac J Cancer Pre14(7) 4015-4023
[5] Xueli L Xiangui Z Hongying L 2015 Analysis on the characteristics of human papillomavirus infection among women in Yichang area Chinese Journal of Cancer Prevention and Treatment 22(16) 1261-1265
[6] Yanbo S Shaoming W Dan D etc 2016 Comparative study on cervical cancer screening using liquid-based cytology and human papillomavirus typing in Inner Mongolia Chinese Clinical Journal of Obstetrics and Gynecology 17(1) 10-13
[7] Hui W; Changhong Z 2022 Characteristic analysis of infection types and cervical lesions in HPV-infected patients of different ages Journal of Bengbu Medical College 47(05) 642-645
[8] Xu XXZhou JSYuan SHet al 2015 Distribution of HPV genotype in invasive cervical carcinoma and cervical intraepithelial neoplasia in Zhejiang ProvinceSoutheast China: establishing the baseline for surveillance Int J Environ Res Public Health12 (9) 10794-10805
[9] Danping W Jiadi Z Wei W et al 2023 Analysis of HPV infection and genotype distribution among women undergoing physical examination in Urumqi Xinjiang Xinjiang Medicine 53(03)
[10] Yih WK Kulldorff M Dashevsky I et al 2021 A Broad Safety Assessment of the 9-Valent Human Papillomavirus VaccineAm J Epidemiol 190(7) 1253-1259
[11] Thones N Herreinera Schadlich L et al 2008 A Direct comparison of human papillomavirus type 16 L1 particles reveals a lower immunogenicity of capsomeres than virus like particles with respect to the induced antibody response J Virol82(11) 5472-485
[12] Kanodia S Kast WM 2008 Peptide-based vaccines for cancer: Reali zing their potential Expert Rev Vaccines 7(10) 1533-1545
[13] van Poelgeest MIE Welters MJvan Esch EMet al 2013 HPV16 syn thetic long peptide(HPV16-SLP)vaccination therapy of patients with advanced or recurrent HPV16-induced gynecological carci nomaa phase II trial J Transl Med11:88
[14] Songdong M 2017 The mechanism of action of heat shock protein gp96 as a new vaccine adjuvant in cellular immunity and humoral immune response Institute of Microbiology Chinese Academy of Sciences 12-01
[15] Li YL Liu J Liu J N et al 2011 Immunization of protein HPV16 E7 in fusion with mouse HSP70 inhibits the growth of TC-1 cells in tumor bearing miceVaccine29(35) 5959-5962
[16] Lu Q 2019 Study on the immune effect of AD-HPV16/18/58mE6E7 trivalent recombinant adenovirus vector therapeutic vaccine Guangxi Medical University
[17] Zhou ZX Li D Guan SS et al 2015 Immunotherapeutic effects of den dritic cells pulsed with a coden-optimized HPV 16 E6 and E7 fusion gene in vivo and in vitroAsian Pac J Cancer Prev16(9) 3843-3847