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Advances in HPV vaccines: current progress and future directions

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Abstract. Human papillomavirus (HPV) is a significant contributor to cervical cancer and other malignancies, particularly in regions with limited access to healthcare. Globally, three licensed prophylactic vaccines, Cervarix™, Gardasil®4, and Gardasil®9, have achieved significant success in preventing HPV infections and decreasing the prevalence of HPV-related illnesses, including cervical cancer. These vaccines play a crucial role in public health efforts by targeting high-risk HPV types. Therapeutic vaccines are intended to activate immune response and offer a potential method to eradicate persistent infections by targeting oncoproteins E6 and E7, which are implicated in the occurance of HPV-associated tumors. In the following research, we deliver an in-depth description of the categorization, mechanisms, and trial outcomes of both prophylactic and therapeutic HPV vaccines, highlighting the successes and limitations of current approaches. By evaluating recent advancements, this review aims to inspire innovative strategies to improve the ability of HPV vaccines to produce the desired results in the contexts of both prevention and treatment.

Keywords: Human papillomavirus (HPV) vaccines, Cervical cancer prevention, Cancer immunotherapy.

1. Introduction

The human papillomavirus (HPV) is a common virus that is mainly spread through sexual contact. It has a high correlation with the emergence of numerous cancer forms, particularly cervical cancer. Cervical cancer ranks fourth globally among cancers to which women are susceptible, according to the World Health Organization (WHO), with approximately 311,000 fatalities and 570,000 cases reported in 2018. According to the WHO, high-risk HPV strains, especially types 16 and 18, are linked to the bulk of these instances and almost 70% of diagnoses of cervical cancer [1]. The creation of preventative HPV vaccinations has significantly contributed to the fight against cervical cancer and provides hope for a decline in the prevalence of HPV-related illnesses.

The efficacy and technology of vaccines have advanced significantly since the first HPV vaccine was made accessible in 2006. The prophylactic vaccinations currently available (Cervarix™ and Gardasil®) offer a very effective way to prevent infection with the most cancer-risk HPV types.

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According to studies, these vaccinations not only shield women against the risk of cervical cancer but also lower the prevalence of other illnesses and cancers linked to HPV, including vulvar, throat, and anal malignancies [2]. Even with these developments, further research and development are required to produce improved therapeutic results. In this review, we discuss the current status of HPV vaccines, with an emphasis on the mechanisms of preventive vaccines, the development of therapeutic vaccines, and future directions for improving the effectiveness of HPV vaccines. By looking at the progress made to date and identifying potential areas of innovation, this review emphasizes the importance of continued efforts in HPV vaccine research.

2. Prophylactic HPV vaccine

In recent years, the research of prophylactic human papillomavirus (HPV) vaccine has made remarkable progress. In 2014, the WHO issued guideline recommendations for the HPV vaccine, emphasizing the importance of vaccination.

Over the past decade, several distinct HPV vaccines have entered the market and have gained widespread usage. Among these, the primary vaccines utilized are the bivalent vaccine (Cervarix™), quadrivalent vaccine (Gardasil®4), and the nine-valent vaccine (Gardasil®9). These vaccines target various high-risk HPV types, particularly HPV types 16 and 18, which make up an estimated 70% of cervical cancer cases. The Gardasil®9 offers protection against nine HPV types following basic immunization, including the aforementioned two types as well as five more high-risk types (31, 33, 45, 52, 58), demonstrating an effective rate of up to 97% in clinical trials [3].

2.1. Cervarix™

Cervarix™ mainly targets HPV16 and HPV18, the two types of HPV known to cause roughly 70% of cervical cancer cases, and are highly effective clinically, significantly reducing the incidence of cervical cancer. The composition of Cervarix™ is that of virus-like particles (VLPs) found in HPV types 16 and 18, along with AS04 as an adjuvant [4]. The AS04 formulation contains lipid A and *aluminum* hydroxide. Additionally, monophosphoryl lipid A (MPL), which is a detoxified bacterial lipopolysaccharide and acts as an agonist for toll-like receptor 4, is included to cause the stimulation of both innate and adaptive immune responses. They also mentioned that in long-term trials evaluating the effectiveness of bivalent vaccines in combatting HPV16/18 infection in females between the ages of 18-25 years, Cervarix™ was 100% effective against CIN2+/CIN3, with cumulative efficiencies of 97.4% and 94.9%, respectively [4]. In the vaccine trial, there was a 50% reduction in HPV16/18 vulvar infections in about 1,000 women involved. Although Cervarix™ is less protective against both HPV types than Gardasil®4, they have a better preventive effect.

2.2. Gardasil®4

Gardasil®4 is a liquid vaccine administered via injection, produced using Saccharomyces cerevisiae. It contains purified L1 protein that has been truncated at the C-terminal and forms virus-like particles (VLPs), with amorphous aluminum hydroxyphosphate (AAHS) included as an adjuvant [4]. It extends the coverage of the HPV6 and HPV11on the basis of Cervarix™, which are associated with about 90% of genital warts. This expansion allows the quadrivalent vaccine to prevent cervical cancer while also helping to decrease genital warts incidence. Reviews on Gardasil®4 show that its effectiveness is as high as 93% among women aged 18 to 26, reducing the occurrence of cervical cancer lesions related to HPV. In this sample, participants demonstrated excellent immune responses to HPV types 6, 11, 16, and 18, all of which showed sustained antibody responses and maintained high levels of immune responses for more than five years after vaccination [5].

2.3. Gardasil®9

In recent research, the development of Gardasil®9, which was approved by the FDA in 2014, has received much attention with the use of amorphous aluminum hydroxyphosphate sulfate (AAHS) as an adjuvant. It covers nine HPV types, including HPV16, 18, 31, 33, 45, 52, 58, 6, and 11. This vaccine

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has been shown to prevent about 90% of cervical cancer cases [3]. It is mentioned that Gardasil®9 is indicated for the prevention of HPV-related diseases in women aged 9-45 years. In addition, Gardasil®9 is also indicated for men aged 9-45 years and can be used to prevent anal, oropharyngeal, oropharyngeal, head and neck cancers, precancerous lesions, dysplastic lesions and genital warts. This greatly broadens the scope of vaccine protection and becomes an important tool for cervical cancer prevention in China [6].

2.4. Immunological effects of prophylactic vaccines

In the field of vaccine development, recombinant DNA technology has been employed to enhance both the safety and efficacy of vaccines. Clinical studies indicate[4]that administration of the nine-valent HPV vaccine significantly increases protection against HPV infection and related lesions, with an effectiveness rate exceeding 90% observed particularly among uninfected individuals [5]. In addition, the HPV vaccination age has also been adjusted. In terms of the age of vaccination, existing guidelines recommend that women between the ages of 9 and 26 be vaccinated, but the age can be modestly advanced for younger women with high levels of education and many sexual partners. In terms of vaccination methods, intramuscular injection is recommended, which is usually a three-needle vaccination program, that is, the 0, 1 and 6 months. For Gardasil 9, recent studies also support its use in adults over 26 years of age, showing good immunogenicity and safety [5].

In terms of adverse reactions, the safety of HPV vaccine has been widely verified, and the vast majority of vaccinators have only mild discomfort, including pain, erythema or fever at the injection site, the incidence of severe adverse reactions is less likely. At the level of public health policy, immunization plans of various countries have been continuously improved to facilitate the extent to which vaccination of HPV vaccine is covered, achieve the effect of herd immunity, and further aid in the reduction of incidence of HPV-related diseases [7].

3. Therapeutic HPV Vaccine

While prophylactic vaccines like Gardasil are highly effective in preventing new HPV cases, they still fail address pre-existing infections. This shortcoming highlights the critical demand for therapeutic vaccines that can tackle HPV-related diseases and cancers associated with HPV, including those in the oropharynx and anus. Therapeutic vaccines for HPV work by triggering immune responses aimed at eliminating persistent HPV infections. Recent studies and experiments have seen notable successes in the development of therapeutic HPV vaccines. Various options, such as viral vector, DNA, and mRNA vaccines, are currently being evaluated in clinical trials for their potential to treat HPV-associated cancers.

3.1. Live Vector Based Vaccines

Live vector-based vaccines are mainly classified into bacterial and viral vector types. These vaccines use attenuated vectors to carry HPV-specific antigen genes into host cells, inducing a robust immune response. Viral vectors, particularly adenoviruses, vesicular stomatitis virus (VSV), and arenaviruses, have demonstrated considerable potential in targeting HPV-associated tumors due to their ability to induce strong immunogenic responses while maintaining a favourable safety profile. In contrast, bacterial vector vaccines have faced challenges related to safety and efficacy, particularly when the immune response against the bacterial vector overshadows the response to the HPV antigens. Viral vector vaccines, which are replication-deficient, have displayed potential in both preclinical and clinical trials, with ongoing research supporting their safe and effective application as treatments for HPV-related cancers[4].

3.2. Peptide Based Vaccines

Peptide-based vaccines utilize short amino acid sequences derived from HPV viral proteins to elicit a cell-mediated immune response. These vaccines can be improved in effectiveness via adjustments to their design. Methods include enhancing the ability of peptides in vaccines to bind to MHC molecules,

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or by fusing multiple epitopes into a composite formulation [4]. Peptide vaccines have significant advantages in real-life health care scenarios due to their excellent stability and ease of storage, as they do not require complex refrigeration conditions, thus allowing them to facilitate mass production and deployment in resource-poor areas. While peptide vaccines have logistical advantages, such as stability and ease of production, they also have drawbacks. First, antigen-presenting cells (APCs) do not recognize peptides in a timely manner, and thus peptides lack the capability to induce a strong immune response. Therefore, they are often used in combination with adjuvants or appropriate delivery systems (e.g., nanoparticles) to increase their effectiveness. On the other hand, the effectiveness of polypeptide vaccines may be affected by differences in human leukocyte antigen (HLA) polymorphisms between different individuals. This characteristic genetic variation may limit the widespread use of peptide vaccines in different populations [8].

Despite the above-stated problems, peptide vaccines, with improvements and in conjunction with its ease of logistics, can become a highly effective and implementable vaccine. Peptide vaccines developed to target the E7 oncoprotein have thus far shown significant therapeutic potential in clinical trials. For example, in a Phase II clinical study involving patients with cervical intraepithelial neoplasia, more than half of the participants experienced remission after being vaccinated with a peptide-based therapeutic vaccine (CIN) [9]. In preclinical models, researchers have further enhanced the efficacy of peptide vaccines by incorporating them into a nanoparticle delivery system, creating what is called a “nano-vaccine”. This innovative approach significantly improves the efficiency of antigen delivery and can induce a stronger cytotoxic T lymphocyte (CTL) response [10]. In addition, current research is investigating combinations of peptide vaccines with immune checkpoint inhibitors, such as PD-1 blockers, to address the challenge posed by tumor-induced immunosuppressive environments. Such instances demonstrate great promise for the field of immunotherapy.

3.3. Nucleic Acid Based Vaccines

Nucleic acid vaccines are mainly classified into DNA vaccines and RNA vaccines. In comparison to traditional vaccines, DNA vaccines have more stability and are safer, and they can be repeated for long-term protection as antibodies against vectors are not produced. However, they are mainly limited to weaker antigenicity. While RNA vaccines have strong self-replication ability, so that they can highly express antigens and produce strong immune responses, and even induce innate immune responses [3]. Whereas, due to the poor stability of RNA vaccines and the limitation of not spreading between cells, there are few clinical trials related to HPV.

3.4. Cell Based Vaccines

Another emerging approach is cell-based vaccines. These vaccines work by manually delivering HPV antigens to APCs, specifically dendritic cells that process the antigens and present them to cytotoxic T cells. These T cells are therefore activated and begin to recognize and destroy HPV-infected or HPV-transformed cells. By specifically targeting HPV-associated tumor antigens, cellular vaccines minimize the risk of autoimmune reactions and ensure a precise immune attack on cancer cells. In addition, they also show the potential for long-term immune memory, which is crucial for preventing cancer recurrence. However, clinical trials have reported mixed results, with many vaccines ineffective in patients with advanced cancer. This suggests that while cell-based vaccines are promising, further research and optimization are needed to overcome current limitations and tumor immune escape mechanisms [6].

4. Future Directions in HPV Vaccine Development

Although current prophylactic HPV vaccines (e.g., Gardasil® and Cervarix™) have shown promising results, future research must continue. There is still tremendous room for improvement by exploring new strategies to overcome the limitations of current vaccines, especially in targeting HPV-associated malignancies.

Plant extracts have shown great potential in HPV development. Curcumin and resveratrol are two plant polyphenols that have shown promising effects in HPV-associated cancer therapy. By modulating

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inflammatory pathways, curcumin inhibits cell proliferation and promotes apoptosis, especially in suppressing the expression of NF-κB and COX-2. In addition, the synergistic effect of curcumin with resveratrol produces inhibition of HPV-associated cancer tumor growth by targeting STAT3, Notch, and Wnt pathways [11][12]. These properties make them ideal candidates for enhancing immune responses to HPV vaccines.

The search for alternative antigenic targets is of equal interest. Current HPV vaccines primarily target the L1 protein, but other viral proteins such as the E6 and E7 oncoproteins, which are implicated in the transformation and maintenance of HPV-associated tumors, also require attention. By targeting these oncoproteins, therapeutic vaccines could be developed that not only prevent infection but also treat existing HPV-associated diseases. Such vaccines can activate a rigorous cytotoxic T-cell response to clear infected and transformed cells [13].

In Frontiers, researchers have combined HPV vaccines with immune checkpoint inhibition therapies to enhance the immune response against HPV-driven tumors by helping the immune system detect and attack cancer cells with higher success by combining inhibitors (e.g., PD-1 and CTLA-4 blockers) with HPV vaccines, which has been shown to be effective in therapeutic applications [14]. This combination strategy holds immense promise in significantly improving treatment for patients with HPV-related malignancies.

Taken together, these innovative strategies provide ideas for future HPV vaccine development. New vaccines in the future will enhance therapeutic efficacy and further strengthen the protection and treatment of HPV-associated diseases.

5. Conclusion

The development of an HPV vaccine has important implications for global public health. Cervarix and Gardasil, two prophylactic vaccines, have been shown to be conducive to the mitigation of high-risk HPV infected population. In particular, types associated with the majority of cervical cancer cases (i.e., 16 and 18) offer broad protection against multiple HPV strains and are the core of global cancer prevention strategies. Despite their successes, however, they do not solve existing HPV infections or related cancers. This limitation highlights the importance of therapeutic vaccines to address persistent infectious HPV and related malignancies, as is the current focus of vaccine research.

Therapeutic vaccines, with platforms on viral vectors, peptides, nucleic acids, and cells, are designed to activate cytotoxic T lymphocyte(CTL) responses against HPV-infected or transformed cells. Early clinical trials have shown positive outcomes in application of certain therapeutic vaccine candidates, including tumor regression and disease reduction in patients. Nevertheless, significant challenges remain, particularly in overcoming tumor immune evasion mechanisms and optimizing the delivery strategies for nucleic acid vaccines.

Future research in HPV vaccine is likely to center on the exploration of new antigen targets, integration of advanced delivery systems, and combination of vaccines with immune checkpoint inhibitors or plant-based compounds. These innovative approaches have demonstrated potential for improving vaccine efficacy and offer promising avenues for the subsequent development and application of HPV vaccines.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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