

THE DEVELOPMENT OF HUMAN PAPILLOMA VIRUS (HPV) VACCINES

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Abstract. The discovery that human papilloma virus (HPV) causes the vast majority of cervical cancers opens new possibilities for controlling this disease, which is the second most common cancer among women worldwide. Research centers around the world are actively involved in developing HPV vaccines. The paper presents the latest information regarding both prophylactic and therapeutic vaccines.

Key words: human papiloma virus, vaccine, cervical cancer

Rezumat. Descoperirea etiologiei legate de papilomavirus a cancerului cervical deschide noi oportunități pentru controlul acestei maladii, cea de-a doua formă de cancer al femeii din punct de vedere al frecvenței pe plan mondial. Centrele de cercetare sunt în prezent activ implicate în dezvoltarea și elaborarea vaccinurilor anti HPV. Articolul prezintă cele mai recente informații privind atât vaccinurile profilactice cât și cele terapeutice.

Cuvinte cheie: virusul papilomului, vaccin, cancer cervical

Cervical cancer is one of the most common causes of cancer-related death in women. Cervical cancer begins with abnormal changes in the cervical tissue. The risk of developing these abnormal changes has been associated with certain factors, including previous infection with human papilloma virus (HPV), early sexual contact, multiple sexual partners, cigarette smoking, and oral contraceptive use. The papilloma virus is relatively small—just two strands of DNA contained in a round shell, or envelope, that looks like a golf ball when enlarged under an electron microscope. DNA testing has identified nearly 20 papilloma types that primarily infect the cervix, vulva and vagina in women, the penis in

men, and the urethra and anus in both sexes. Of these, only four are most often found within cervical cancer cells. Type 16 accounts for about half the cases in the United States and Europe. In Latin America, by contrast, types 39 and 59 are the most prevalent types, while in West Africa, type 45 is common (1).

It is estimated that for every 1 million women infected, 10% (about 100,000) will develop precancerous changes in their cervical tissue (dysplasia). Of these, about 8% (8,000 women) will develop early cancer limited to the outer layers of the cervical cells (carcinoma *in situ* [CIS]) and roughly 1,600 will develop invasive cancer unless the precancerous lesions and CIS are detected and treated (1).

Currently there is no treatment for HPV infection; therefore, once infected a person is most likely infected for life. In most cases an active infection is controlled by the immune system and with time becomes dormant; however, it is not possible to predict whether or when the virus will become active again. These observations form a compelling rationale for the development of vaccine therapy to combat HPV infections (2).

HPV vaccine, if administered prior to initiation of sexual activity, theoretically would prevent women from developing cervical cancer later in life.

A safe, effective and affordable vaccine to prevent cervical cancer must meet several expectations. First, it must be multivalent, being effective against several of the most common types of HPV associated with cervical cancer. Second, the vaccine must offer long-lasting protection against HPV infections. Third, ideally this vaccine should have low production costs, a long life, would require only a single dose and should be administered orally or via a nasal spray rather than by injection.

There are some special features of the HPV system that strongly influence the concept of HPV vaccine development. Some difficulties occur:

- Because HPV does not cause disease in animals, it is difficult to conduct the animal research for vaccine development (3).
- Scientists do not know precisely which elements of the human immune system are important in

preventing or resolving HPV infections. Although there is evidence that immune response does play a role in controlling HPV infections, it is not known why HPV infections persist in some individuals and regress naturally in others (4).

- HPV enters the body via mucosal membranes and does not spread systemically. The mucosal immune response is less understood than the systemic immune system.
- At the moment there are identified approximately 90 types of HPV. Preventing cervical cancer will require a multivalent vaccine, that is a combination vaccine effective against the common carcinogenic types of HPV (including types 16, 18, 31 and 45).

HPV do not grow adequately in tissue/culture systems; therefore DNA recombinant technology has to be used for HPV vaccine development. Researchers are investigating the following five approaches to producing HPV antigens:

1. Recombinant live vector vaccines- a harmless virus or bacteria is genetically engineered to produce an HPV antigen. The immune system responds both to the host organism and the HPV antigen.
2. Protein and vaccine proteins > capsid proteins L1, L2 and the oncoproteins E6 and E7.
3. Virus-like particles (VLPs).
4. "Naked" DNA vaccines: HPV genetic material is inserted into bacterial plasmids. When these circular DNA structures are used in a vaccine, the DNA is expressed

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in human cells that than produce HPV antigen.

There are two types of HPV vaccines: prophylactic and therapeutic.

Prophylactic vaccines are designed to prevent the development of HPV infection. A prophylactic vaccine would work primarily by stimulating antibody-mediated immunity, therefore inducing neutralizing antibodies and inactivating HPV before the virus infects host cells. This strategy requires sustained, high levels of antibodies at mucosal surfaces over long period of time. Different sources of virus structural proteins, i.e., L1 and L2 are being considered. For vaccines, most of the present attention is being directed to virus-like particles (VLPs) composed of L1 or both L1 and L2 proteins. Virus-like particles mimic the authentic virus not only morphologically, but also by their ability to bind to cell surface. They present conformational epitopes required for eliciting neutralizing antibody (5). Prophylactic vaccine cannot make an immediate impact on the prevalence of cervical cancer, which usually takes 20 years or longer to develop after initial infection with HPV. Other potential vaccines include DAN vaccines, i.e, plasmid with genes coding for structural proteins (6).

A prophylactic vaccine would need to be administered before children become sexually active. Because HPV is sexually transmitted, a vaccine to prevent cervical cancer will be more effective if it is administered to boys as well as girls.

In contrast, a **therapeutic vaccine** could help women who are already infected with HPV. Such a vaccine could:

1. prevent low-grade disease to evolve to high-grade disease;
2. cause existing lesions to regress;
3. control the spread of metastatic cancer;
4. prevent recurrence of cervical cancer after treatment.

Therapeutic vaccine could also be divided:

1. *therapeutic vaccine designed to suppress virus replication*

Whereas prophylactic vaccine are aimed at prevention of virus infection, this first type of therapeutic vaccine (also called secondary prophylactic vaccine) is intended for treating subjects already infected. Virus replication needs E1 and E2 proteins in the distal layers of the epithelium. A therapeutic vaccine containing these two proteins should induce or enhance cell-mediated immunity to these proteins, which should limit virus growth (7).

2. *therapeutic vaccine designed for treatment of cervical neoplasia.*

The strategy is based on the fact that virus- induced tumors express well-defined antigens of viral origin. They are “nonself” and thus more easily recognized by the immune system than tumors of nonviral origin. E6 and E7 proteins are the virus proteins express in HPV associated carcinoma, so they are the natural targets of immune reactions. Therapeutic vaccine against

cervical neoplasia should induce cytotoxic lymphocytes that recognize tumor-associated antigen and destroy the cells that carry it. Recombinant viruses expressing E6 and E7 proteins could be efficient antitumoral vaccines (8).

At present, the greatest expectations center on chimeric VLPs. There are several clinical studies in progress or in preparation with these chimeric VLPs (9, 10, 11).

Therapeutic vaccines based on genetic modification of the tumor cells are also being considered (12).

As already mentioned, decades have to pass before the anticancer effect of prophylactic HPV vaccines can be determined unequivocally. A significant reduction in the occurrence of cervical lesions in vaccinated population as compared with that in non-vaccinated women would indicate a protective effect. Another possibility to monitor the efficacy of this vaccine is to search for cervical HPV infections in vaccinated and non-vaccinated populations.

Information on the clinical efficacy of therapeutic vaccine will be obtained more rapidly. Correlation between the immune response (marked by cytotoxic lymphocytes) and clinical outcome may provide helpful clues on vaccine dosing and the most advantageous way to administer it.

In summary, HPV development holds great promise for reducing the impact of cervical cancer. Given the current state of technology, however many experts believe that it could be between 10 and 20 years before an effective, affordable and acceptable

vaccine will be available for widespread use in cervical cancer prevention programs.

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