VACCINATION AGAINST THE HPV – POSSIBLE PRIMARY PREVENTION FOR NEOPLASIA

Raluca Gabriela Ioan, Gabriela Adriana Dincă, Mioara Ionescu
"Professor Dr. Alfred Rusescu" Institute for Mother and Child Protection, Bucharest

ABSTRACT

The frequency of different types of cancer (among which the cervical cancer covers 55%) etiologically correlated with the Human Papillomavirus (HPV) infection is worrying particularly amongst early ages. Demonstrating the presence and the oncogene role of some HPV types opened the way to prophylaxis by vaccination in a significantly high percentage of cases. Vaccination against HPV was first used in 2006 and it remarkably brought down the infection prevalence, with a good immunologic response and durable protection.

Key words: papillomavirus, cancer, vaccination

The *Papillomavirus* (HPV) infection affects almost all sexually active persons, and approximately 40% of them are infected during the first 2 years of sexual activity. Out of the over 120 HPV types approximately 40 infect mucosa. 16 and 18 types have a high oncogene risk and have been reported in women (from the USA) with a frequency of 25% at the age of 14-19, 43% at 20-24, 30% at 30-39, 28% at 40-49 and 24% at 50-59 (1). The frequency of different types of cancer etiologically correlated with HPV infection is worrying; out of 20,413 women the following results were reported: 4% vagina, 15% vulva, 55% cervical, 11% oropharyngeal, and 15% anal cancer. The frequency of cancer in men (on a total group of 12,000) was 14% anal, 80% penile, 78% oropharyngeal (2).

The mucosa infection with 6-11 HPV types produces genital warts which develop and reoccur causing a psycho – social stigma, recurrent papilomatosis laringea and cervical intraepithelial neoplasia.

In cutaneous infections about 80 HPV types are etiologically incriminated of producing common warts on the arms and legs.

In 2008 professor Dr. Harald Zur Hausen received the Nobel Prize for Medicine for his contribution to proving HPV's role in cervical cancer genesis.

In 1976 he isolated the viral types from genital warts and in 1983 he separated the two HPV types (16 and 18) that are incriminated of producing cervical cancer. He was thus able to develop curative therapies or cervical cancer prevention.

After identifying 18 HPV DNA, Harald Zur Hausen proved that the two types – 16 and 18 are present in 82% of the invasive cancer cases. (3)

HPV is a heterogeneous group of DNA viruses, capsidless and icosahedral, with a 52-55 nm diameter, of small dimensions, with two DNA chains.

Papillomaviruses have a small size. They lack the cover and are composed of 72 capsomeres disposed in an icosahedral simetry. Their genome is made up of a circular molecule of double catenary with about 800 bases pairs. The genetic information is located on only one DNA spiral and consists of at least 8 phases.

The viral genome can be divided into 3 parts: (4)

- LCR – long control region – representing 7-11%; it is located between sequences L1

Coresponding author:
Dr. Raluca Gabriela Ioan, "Professor Dr. Alfred Rusescu" Institute for Mother and Child Protection, 120 Lacul Tei Bv., Bucharest
e-mail: ioan_raluca@yahoo.com

and E6/E7 and contains the promoters of the precocious genes P97 for HPV 16 and P105 for HPV 18; it contains the regulating sequences for replication and viral transcription.

- The precocious region – large (E), containing 50% of the genome length that encodes proteins involved in cell transformation (E6, E7, E5);
- The Late Region – late (L) encoding the capsid proteins, the major ones L1 and the minor ones L2.

THE ONCOLOGIC ROLE OF HUMAN PAPILLOMAVIRUS

In the presence of micro-lesions HPV infects the basal cells of the skin or of the mucosa membranes. 10% of these infections generate condylomas, papillomas or dysplasia. It is known that some types of HPV are etiological agents specific both to cervical cancer and preneuroplasic lesions. (5) HPV with a high oncogene risk associated with cervical cancer produces 2 oncoproteins E6 and E7 that interact with proteins of cell P53 and pRB (6). The virally and endogenically derived proteins interact and produce the regulation of the cell cycle progression by developing the cervical cancer. The basal cells do not allow HPV replication, but as the keratinocyte differentiation progresses, replication of HPV DNA and synthesis of HPV structured proteins are initiated in the superior structures of the epithelia. Malign tumors induced by HPV are monoclonal and the time between the HPV infection and the carcinoma development varies between several months and over 13 years. (7)

THE RISK FACTORS

Among the assembly of mechanisms connected to the cervical carcinogenesis there are a few factors with a relatively well defined role categorized as risk factors: smoking, nutritional factors (lack of carotene and vitamin A), long term contraception, pregnancy (first birth at a very young age (16), as well as parity, immunosuppression, genetic factors or infected partner.

– *HPV infection*. The cervix cancer is first of all caused by oncogene HPV infection. After analyzing 932 samples from women coming from 22 countries, it was proved that DNA prevails in HPV in cervical cancer cases worldwide.

– *The young age* is one of the most important risk factors. Induced HPV intraepithelial cervical neoplasia is most frequently seen in women aged between 18 and 35. There is such an exposure to the virus during teenage (12-16 years) that conditions the occurrence of ICN after 18 (8). The first contact with the virus at an early age is a decisive element for the upcoming development. Nowadays the age girls begin their sex life is considered to be between 14 and 16, that is why the HPV infection frequency is very high under the age of 20. The frequently studied local conditions (ectopy) for sexually active young women can explain the high receptivity to infections (9). This assessment goes along with the epidemiologic data for cervical cancer risk the earlier the first sexual contacts happen – during childhood and teenage. Contracted HPV can produce minimal cervical lesions, it can progress towards intraepithelial cervical lesions (around the age of 20) or cancer (around the age of 40) (10).

Other risk factors: high parity and very young age of the first birth, the high number of sexual partners, smoking, oral contraceptives, immunosuppression, genetic factors, infected partner, lack of betacarotene and vitamin A.

Cervical cancer represents a major health problem with almost 500,000 new cases and approximately 200,000 deaths per year at a worldwide level (11); it is the second malign cause in the world and the most frequent neoplasia in the developed countries. (12). In this context the possibility of finding a way of prevention in a high percentage of genital cancers (almost 44%) means hope.

Vaccination against HPV was first used in 2006 and approved by FDA both for the bivalent vaccine and for the tetravalent one. As HPV infection can occur even in the case of a single sexual partner vaccination before the beginning of the sexual life is recommended.

The vaccination age for girls and boys is around 11-12 (it can start at 9) with 3 doses in 6 months (the second dose 1-2 months after the first, and the third dose 6 months after the first one). Persons who haven't completed the vaccination (with 3 doses) will do it between 13 and 26 years old for girls and between 13 and 21 years old for boys. 22-26 aged men will also be included if they had sexual intercourse with other men, are HIV infected or suffer from other diseases that require immunosuppressive treatment.

In the USA the ACIP (Advisory Community on Immunization Practices) recommends HPV vaccination at the age of 10-14, because after vaccination antibodies titers are obtained with a double level of both HPV 16 and 18, compared to the one specific to the age group of 15-25.

Types 16 and 18 are the most common in sexually active women; the age for starting the sexual life differs from a country to another (according to the culture, social and socio-economic status) and the recommendation for vaccination against HPV was introduced to Europe in 2007.

Based on clinical studies the vaccine is immunogenic for both girls and women aged between 10 and 55.

According to the numbers reported by CDC referring to the vaccinated population, the decline of the infection occurrence for the HPV types contained by the vaccine was remarkable and the recommended age for the vaccination provides a good immunologic response and a durable protection. There are no records of the protective effect of the HPV vaccine when only one or two doses were applied.

It is TO REMEMBER that the current vaccines do not protect against all HPV types. There is still a risk of 30% for the vaccinated women to develop cervical cancer that is why the Pap test is obligatory.

Other measures of prevention against the cervical cancer are added to a correct Pap test: the use of condoms, limiting the sexual partners or having a partner with a low number of previous sexual partners. It is not recommended to apply the vaccine to: people suffering from allergies to vaccine components or from severe allergies (high attention to the yeast), pregnant women or people suffering from other diseases associated with a moderate or severe evolution.

During 6 years of HPV vaccine use in the USA undesired effects were reported: moderate or low fever, headaches and nervous behavior that can be prevented by asking the patient to sit or lay down for 15 minutes after the vaccination. Monitoring the vaccinated person will be done similarly to any other vaccination.

The vaccine "is not good" is a phrase that lacks any medical coverage, clinical studies demonstrate that it has a good safety profile, no differences were noticed regarding the local or general adverse reactions, or the adverse effects compared to other vaccine types.

CONCLUSIONS

Acquiring specific protective antibodies by vaccinating the teenagers, young adults and persons with a high risk reduces the burden of neoplasia induced by the virus types contained in the HPV vaccines.

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