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HPV virus as the main cause of cervical cancer, vaccination - literature review
Wirus HPV jako główna przyczyna raka szyjki macicy, szczepienia - przegląd literatury

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ABSTRACT

HPV infection is one of the most common viral infection of the female and male reproductive tract worldwide. Most of the human papillomavirus infections cause no symptoms and go away on their own. Some infections develop into persistent infection, which can lead to the development of cancer of the cervix, anogenital, oral cavity and pharynx.In this paper, we focused on cervical cancer, which is the second most common cancer in the world among women. More than 300,000 women died from this cancer in 2020. The invention and introduction of prophylactic HPV vaccines has played a significant role in reducing the number of viral infections, thus reducing the incidence of benign and malignant diseases caused by them and the mortality resulting from them. There are three vaccines on the pharmaceutical marketfor prevention of specific HPV infection. They are: a bivalent vaccine Cervarix, a tetravalent vaccine Gardasil and a nonavalent vaccine Gardasil 9. These vaccines are safe because they do not contain an attenuated virus particle, but their production is based on a virus-like particle of the main capsid protein L1-VLP. Gardasil 9 targets nine HPV types andcomparing to the other two vaccines it is the most effective at preventing the development of preinvasive cervical cancer. WHO recommends administering them to girls aged 9 to 14 in a two-dose schedule or from 15 years of age in a three-dose schedule. The side effects of the above-mentioned vaccines were mostly associated with a cutaneous reactions around the site of injection (pain, redness, swelling), and some people also experienced systemic symptoms such as a headache, a fever, vomiting, a dizziness, muscle pain and a diarrhea. The following article is an analysis of the current knowledge on the effectiveness and safety of prophylactic HPV vaccines based on publications available in the Pubmed and Google Scholar databases.

Key words: HPV; HPV vaccine;cervical cancer; high-risk HPV; human papillomavirus.

INTRODUCTION

HPV virus causes 57,000 new cancers in women and 60,000 new cancers in men annually[1,2].In total, HPV leads to the development of 5% of all human cancers [2,3]. It mainly leads to the development of a cancer of the cervix, anogenital, oral cavity and pharynx[4-7]. Until now, there are 200 varieties of HPV classified[8,9].
It is transmitted by contact with the skin or mucous membranes[10,11]. HPV types are often referred to as "non-oncogenic" (low-risk) or "oncogenic" (high risk, cancer-causing). Non-oncogenic HPV types are: 6, 11, 40, 42, 43, 44, 54, 61, 72 i 82, and oncogenic HPV types are: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. High-risk types 16 and 18 are the most oncogenic and occur most often[12]. They are associated with an increased risk of developing vulvar, anal, vaginal, penile, oropharyngeal cancer, while genotypes classified as low risk, i.e. 6 and 11, correlate with the development of genital warts[1,13,14].High-risk subtypes are more common in developing countries than in the US and Europe, but when it comes to oncogenic virus types, other than HPV 16 and HPV 18 are more common there[1].

The following article is an analysis of the current medical knowledge regarding the relationship between HPV virus and cervical cancer, as well as the effectiveness and safety of existing vaccines against the most common types of the virus, based on available publications. In order to search for the latest reports in the literature, the following keywords were used: HPV; HPV vaccine; cervical cancer; high-risk HPV; human papillomavirus.

HPV	
"non oncogenic"(low risk)	"oncogenic"(high risk)
6,11,40,42,43,44,54,61,72,82	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

Table 1. HPV types[12].

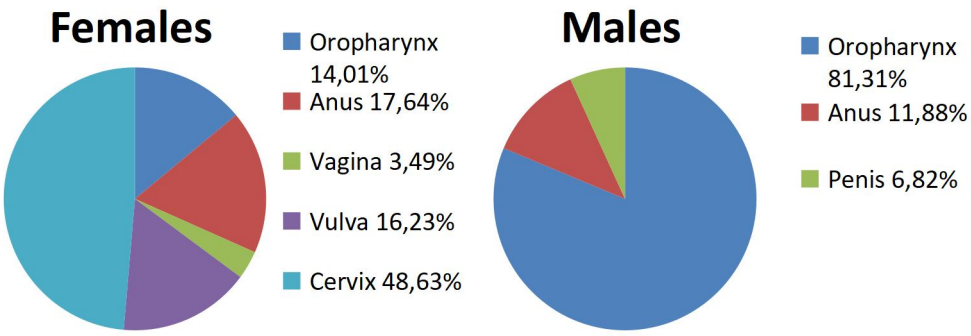

Figure 1. Percentage of different HPV-associated cancers in women and men according to the WHO and the CDC.

BASIC VIROLOGY

HPV are small, non-enveloped, double-stranded DNA viruses belonging to the Papillomaviridae family[15]. The human papilloma virus capsid is approximately 50 nm in diameter. It has the shape of an icosahedron consisting of 72 L1 protein pentamer. The second protein making up the capsid L2 is in the center of each of the pentamer and quantitatively, the quantitative ratio of L2 to L1 is 1:5-1:10[16]. The genome consists of approximately 8,000 base-pairs and encodes early regulatory proteins (E1,E2,E4,E5,E6,E7) and late structural proteins (L1 and L2)[17]. The genetic information of the virus consists of three regions: early one (E),a coding protein (E1,E2,E4,E5,E6,E7); a late region (L), that is built by late genes (L1 and L2) and encodes two viral capsid proteins (L1 and L2); an upstream regulatory region that has a regulatory function over the replication and transcription of its genetic information[15].

GENES	ACTIVITY
L1	Major Capsid protein
L2	Minor Capsid protein
E1	Replication of Viral genome and its mantenance
E2	Initiation of viral DNA replication; regulates transcription od E6 and E7
E4	Release of viral particles
E5	Enhances growth factor signaling pathways
E6	Inhibits p53 and causes loss in cell cycle regulation
E7	pRb mediated deregulation of cell cycle

Table 2. Organization and structure of HPV genome[17].

CERVICAL CANCER

Cervical cancer is the second most common cancer in women worldwide and it is estimated to affect approximately 1.4 million women[18]. The 5-year death rate is estimated at 24%, and in 2020, 340,000 women died of cervical cancer worldwide[13,19,20].Due to the prevalence of the virus in society, most sexually active women will be infected with HPV at some point in their lives. These infections are asymptomatic and cleared by the immune system. However, some may develop persistent HPV infection, which may progress to low-grade or high-grade cervical intraepithelial neoplasia (CIN), cervical cancer, or regress at any stage of development[21,22]. It has been proven that virus genotypes with high oncogenic risk, i.e. 16, 18, 26, 31, 33, 35, 39, 45, 51.53, 56, 58, 59, 66, 68, 70, 73 and 82 more often lead to progression infection into cancer[23]. Infected cells can be detected using cytology. Normal cervical epithelium can transform into high-risk atypical squamous cells (ASC-H), atypical glandular cells (AGC), low-grade dysplastic intraepithelial changes (LSIL) and high-grade dysplastic intraepithelial changes (HSIL). Changed cells can be examined by colposcopy or by collecting the material by curettage of the cervix. Abnormal lesions are classified as cervical intraepithelial neoplasia (CIN I-III) or adenoma in situ (AIS). The highest incidence of cervical cancer falls on two periods: 35-40 years and 65-80 years[13,19].

CERVICAL CANCER SCREENING

It consists in performing a cytological examination and genotyping of the HPV virus. The American Cancer Society published guidelines in 2020 suggesting cytology every 3 years or together with genotyping every 5 years. These tests should be performed on every woman between the ages of 25 and 65[24].Tests are widely available, but still 14% of women in the United States have never used them[25]. Pap smear has a very low sensitivity in detecting HPV infection, from 30-50% of precancerous lesions may be missed[26,27].The HPV-DNA test is much more sensitive than cytology. A single performance is 90% effective in detecting precancerous changes or cervical cancer[28]. Primary and secondary prevention effectively prevent the development of cervical cancer.

VACCINES - EFFICACY, TYPES

Human papillomavirus is very widespread around the world, the development of a vaccine against it has become one of the leading public health activities. These vaccines owe their effectiveness to targeting the main protein that builds the capsid of the virus - the L1 protein[29,30]. However, their action is focused on preventing infection in healthy patients, and they are not able to treat existing infections and changes caused by the presence of the virus in the body[29,31]. Currently existing HPV vaccines are preventive vaccines. Scientists are currently working on inventing therapeutic vaccines that would help fight existing infections or cancers by stimulating the immune system[32]. So far, none of them have proven to be effective[33].

At the moment there are three vaccines: bivalent (Cervarix) which protects against infection with HPV 16 and 18, a tetravalent vaccine (Gardasil) which prevents infection with HPV 6,11,16,18 and a nonavalent vaccine (Gardasil 9) which protects against HPV infection by types 6,11,16,18,31,33,45,52,58. Their production is based on a VLP-virus-like particle of the aforementioned main L1 capsid protein[34]. This protein is produced in yeast, bacteria or insect cells. They are safer than the attenuated vaccine because they do not contain the viral genome as a protein[35]. Cervarix consists of HPV16, HPV18, MPL(monophosphoryl lipid A) and aluminum hydroxide adjuvant (collectively referred to as adjuvant system 04, AS04)[36]. Gardasil has a VLP structure directed against HPV 6, HPV 11, HPV16 and HPV18, while Gardasil 9 also has HPV 31, HPV 33, HPV 45, HPV 52 and HPV 58[37].Both have only aluminum hydroxide as an adjuvant, therefore they are not able to induce such levels of antibodies as Cervarix due to the content of MPL, which is a TLR4 agonist.

TYPE OF VACCINE	PROTECTION AGAINST INFECTION
Cervarix	HPV 16, HPV 18
Gardasil	HPV 6, HPV 11, HPV 16, HPV 18
Gardasil 9	HPV 6, HPV 11, HPV 16, HPV 18, HPV 31, HPV 33,HPV 45, HPV 52, HPV 58

Table 3. Types of vaccine.

EFFECTIVENESS

The first HPV vaccine licensed for use is the tetravalent Gardasil. Studies have shown that this vaccine is highly effective in preventing cervical infections, pre-invasive lesions of cervical cancer, genital, anal, vulvar, penile and oral warts caused by the HPV types it targets [39,39,40,41,42].The vaccine is more than 90% effective in preventing the development of pre-invasive conditions caused by HPV16 and HPV18: cervical cancer (CIN2, CIN2+, CIN3+) and vaginal cancer (VIN/VaIN 2)[11,43]. The decrease in the incidence of CIN2+ and CIN3+ after using Gardasil caused by other types of virus ranged from 20%-50%.

Cervarix, once injected into the body, can protect the body against infection for a minimum of 10 years[44,45]. Adoption of the HPV 16 and 18 vaccine in the period before exposure to these types of virus prevents the development of cervical adenocarcinoma, precancerous changes and other abnormal changes that infection can lead to. In a follow-up study conducted in girls aged 10-14, which tested the efficacy and safety of the vaccine after three administrations, more than 85% of participants showed long-term cross-protection against infection with HPV types 31 and 45[45]. In contrast, another randomized clinical trial conducted in Costa Rica showed that the incidence of oropharyngeal cancers caused by human papillomaviruses 16 and 18 decreased by 93% 4 years after vaccination[46].

In 2014, the FDA approved the nonavalent Gardasil 9 vaccine for use. Because this vaccine covers five additional types of HPV: 33,35,45,52,58 it protects against the development of an additional 20% of cervical cancer compared to the tetravalentvaccine[13].This vaccine is most effective in preventing the development of non-invasive cervical cancer compared to the other two vaccines[47].
It also achieved the highest effectiveness in preventing the development of diseases of the vulva (85%) and vagina (90%) caused by the human papilloma virus[48,49,50].Adoption of the vaccine after exposure to the virus and after the infection has been treated can effectively prevent their recurrence. Three doses of the vaccine are required to achieve a high enough antibody level to provide protection. A study conducted in 2019 showed that after administration of the vaccine, induced antibodies can cross the placenta and thus protect the fetus against infection with HPV types 6 and 11[51].Gardasil 9, on the other hand, is characterized by low effectiveness against other types of viruses and low cross-resistance.

WHEN TO GET VACCINATED?

WHO recommends vaccinating girls at the age of 9. A two-dose vaccination schedule is recommended for people under 15 years old with an interval of 6 months between doses. The three-dose vaccination schedule is recommended for girls who receive the first dose from the age of 15 years and for those immunodeficient in the vaccination schedule(0, 1 to 2 month, 6 month schedule).

VACCINE SAFETY

Studies have shown that the most common side effects of the vaccines were injection site reactions such as swelling, redness, pain[52]. In addition, a nonavalent vaccine, due to the presence of aluminum as an adjuvant and more than twice the size of the virus-like particle than the tetravalentvaccine, was shown to have more systemic and local adverse reactions[53]. Cervarix was more likely to cause headache, fever, vomiting, dizziness, myalgia and diarrhoea, approximately 60% of those reporting side effects were headache and fatigue predominating [52,54]. The risk of an anaphylactic reaction to the components of the vaccine taken has been estimated at 0.3-3 cases per million doses[55,56,57].There have been several large meta-analyses that have found no association between vaccine intake and autoimmune disease and other serious medical conditions[58,59].In 2013, a cohort study of 1 million Danish and Swedish girls who took Gardasil was conducted. It did not cause neurological, immune or thromboembolic side effects[60].

SUMMARY

There are oncogenic and non-oncogenic types of the virus. Methods that help us protect ourselves against cervical cancer include: regular screening tests and prophylactic vaccinations.The incidence of cervical cancer and related mortality has decreased in recent years, mainly due to the widespread implementation of screening programmes. Adoption of the prophylactic vaccine in the period before an exposure to the virus has so far been the most effective protection against the development of precancerous conditions of the cervix, cancer of the penis, vulva, vagina, anus, oral cavity, but also against papillomatous changes on the skin and genitals. Adoption is associated with minor side effects, mainly related to the local injection of the vaccine, and with a

lower frequency of systemic symptoms.At the moment, unfortunately, there are no methods that effectively treat existing persistent infections, but the work is still ongoing.

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