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Beyond cervical cancer: Human papillomaviruses infection-related neoplasms and their prevention

Več kot le rak materničnega vratu: neoplazme v povezavi z okužbo s človeškimi papilomavirusi in njihovo preprečevanje

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Abstract

Human papillomaviruses (HPV) are a very heterogenic group of viruses, which are etiologically related to many benign and malignant neoplastic lesions of squamous epithelium. They are also involved in adenocarcinoma carcinogenesis. It is wrong to believe that cervical cancer represents the only neoplasm that HPV is connected to. Studies have confirmed the connection between HPV infection and anogenital warts, respiratory and laryngeal papillomatosis, head and neck carcinomas and, last but not least, vulvar and vaginal carcinoma, rectal carcinoma and penile cancer. HPV infection is known as the most common sexually transmitted disease in developed countries, nearly all sexually active people will get HPV at some time in their life. Late age of sexual debut, low number of sexual partners and protective behaviour can prevent from acquiring the HPV infection. At the moment, there is no specific antiviral treatment for the HPV. The best-known method that can prevent HPV infection is vaccination. Vaccination against most common genotypes is considered as the most successful preventive measure to prevent most of the severe precancerous changes, cervical cancer and other benign and malignant lesions caused by HPV infection.

Izvleček

Človeški (humani) papilomavirusi (HPV) so heterogena skupina virusov, ki jih etiološko povezujemo z benignimi in malignimi novotvorbami ploščatoceličnega epitela. Prav tako pa se vpletajo tudi v karcinogenezo adenokarcinomov. Zmotno je prepričanje, da je okužba s HPV povezana zgolj z rakom materničnega vratu. Številne raziskave so potrdile povezavo med okužbo s HPV in nastankom anogenitalnih bradavic, papilomatoze grla, raka glave in vratu ter nenazadnje novotvorb zunanjega spolovila, nožnice, anusa in penisa. Okužba s HPV je danes v razvitih državah poznana kot najpogostejša spolno prenosljiva bolezen. Z njo se okuži večina spolno aktivnih ljudi vsaj enkrat v življenju. Pred okužbo se lahko zaščitimo s splošnimi ukrepi, kot so manjše število spolnih partnerjev, kasnejši začetek spolnega življenja ter varno in odgovorno vedenje. Trenutno ne poznamo specifičnega protivirusnega zdravljenja okužbe s HPV. Najuspešnejša metoda, s katero lahko preprečimo okužbo s HPV, je cepljenje. Z obstoječimi cepivi lahko preprečimo večino hujših predrakavih sprememb in raka materničnega vratu ter druge benigne in maligne neoplazme, povzročene z okužbo z virusi HPV.

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1 Introduction

Research has shown that as much as 15% of all human cancer cases are related to viral diseases. Both DNA and RNA viruses can cause malignant changes in the human body. Among the viruses that can cause malignant lesions, the group of human papillomaviruses (HPV) stands out. HPV are mainly associated with cervical cancer (CC). It is incorrect to believe that CC is the only neoplasm caused by HPV. Soon after the discovery of HPV, a causal link was established between individual disease changes of squamous epithelium in the genitals, on the skin, in other organs and the infection caused by certain types of HPV. HPV is also associated with precancerous changes in the glands and adenocarcinomas of the cervix. The association is less pronounced than in squamous cell carcinoma, but research by the Swedish Cancer Registry has confirmed a link between HPV and cervical adenocarcinoma in 131 cases (1-4).

Infections with low-risk HPV genotypes are believed to cause the majority of genital warts and throat papillomas, while infections with high-risk HPV genotypes are believed to cause the occurrence of a certain proportion of head and neck carcinomas, rectal carcinoma, vaginal carcinoma, vulvar carcinoma, and penile cancer, in addition to cervical cancer (5).

In Slovenia, 8–16 cases of laryngeal papillomas are newly discovered per year, most often in children under five years of age. In Slovenia, laryngeal papillomas – as well as anogenital warts, which are the most common sexually transmitted infections – are most commonly caused by HPV 6 and HPV 11 (5,6).

2 Human papillomavirus (HPV)

HPVs are a very heterogeneous group of DNA viruses that are thought to have a causal link to a number of benign and malignant changes in squamous epithelium and, to a lesser extent, glandular epithelium. They belong to the family *Papillomaviridae*, genus *Papillomavirus* (7). These are small viruses, about 55 nm in diameter. They are nonenveloped, and their genome is a circular, closed, double-stranded DNA molecule composed of a coding and a non-coding region. The coding region is divided into early region (E) and late region (L). The E region contains protein genes important for regulating viral DNA replication and viral gene expression, and for interacting with host cell proteins. Most HPV genotypes identified so far have at least six different E genes. The E6 and E7 genes are the most researched, as they play the most important role in the oncogenesis of lesions associated with the HPV infection (5).

Among the HPV genotypes (there are more than 200), about 40 infect the epithelium of the anogenital area. According to their oncogenic potential, they are divided into low- and high-risk genotypes. Low-risk genotypes (HPV 6, 11, 26, 30, 34, 40, 42, 43, 44, 53, 55, 57, 61, 62, 63, 69, 70, 72, 73, 77, 79 and 82) are most commonly associated with genital warts (3), and high-risk genotypes (16, 18, 31, 33, 35, 39,

45, 51, 52, 56, 58, 59, 66, 68) with precancerous and cancerous changes in the cervix and other areas.

Different genera of HPV are transmitted in different ways, but most commonly through sexual intercourse. Most sexually active people become infected with HPV at least once in their lives (8). The prevalence of HPV infections is highest in people under 25, but in some countries, the incidence of infections increases again in people over 45 (9). The incidence of infection with genus Alpha HPV in men is similar to that of women. In both sexes, HPV infection is most often asymptomatic. Infection begins with the entry of the virus through damaged epithelium of the skin or mucous membranes and with infection of the basal cells of the multilayered squamous epithelium. It can then be productive or incomplete (abortive). Most infections are transient, with an average duration of 6–12 months (5,10,11).

Tumour development is thought to take place in three stages. During the first stage, the virus infects the cell. In the second stage, other carcinogenic substances, such as cigarette smoke (smoking), UV rays, radiation, various chemical factors, and so on, play an important role in addition to viruse infection. The third and key stage of lesion formation consists of the incorporation (integration) of viral DNA in the vicinity of certain cellular proto-oncogenes or tumour suppressor genes. According to research, the physical state of HPV DNA in benign and malignant neoplastic lesions is different. In benign changes, viral DNA is almost always present in the extrachromosomal, i.e. episomal form. Copies of DNA are numerous. In malignant neoplastic lesions – unlike in the benign ones – viral DNA is almost always included in the host genome. The tendency to integrate into the human genome is shown mainly by high-risk HPV, while among the low-risk types, integration into the human genome is rare. The described model presents the basic characteristics of oncogenesis associated with HPV infection. Among many infected people, only a few develop malignant neoplastic lesions; the time interval between infection and the appearance of tumour is relatively long. However, the connection between the HPV infection and other carcinogenic factors is obvious (2).

3 Cervical cancer and its precursors

Cervical cancer (CC) is the first malignancy which has been found to have a causal link to HPV infection and is still the fourth most common cancer in women worldwide. Infection with high-risk HPV genotypes is a necessary but not sufficient factor for the development of CC. Additional risk factors include sexual habits, long-term use of contraceptives, smoking and low socioeconomic status. Following HPV infection, the disease develops slowly from low-grade squamous intraepithelial lesion (LGSIL) through high-grade squamous intraepithelial lesion (HGSIL) to CC. The time interval from the onset of precancerous changes to the onset of cervical cancer can last several years. Therefore, with regular preventive gynaecological examinations and Pap tests, most precancerous changes can be detected and treated promptly. Since the introduction of the organized national screening programme ZORA in 2003, when 211 new cases of cervical cancer were recorded, the age-standardized incidence rate has halved and in 2018 with 106 new cases amounted to 6.6/100,000 (12). The positive result can be attributed to the high number of women being screened, which in 2018 exceeded 70%. The screening could be further increased

by the possibility of self-sampling for HPV at home for women who do not respond to the screening programme, as we proved in a recent Slovenian study (13). High-quality cytological examination of Pap tests, followed by an HPV test in case of a pathological result is also important. According to the results of a recent study, p16/Ki67 dual immunocytochemical staining may be of great help in the case of unclear Pap test results (14-16). The cancer management process requires constant monitoring of the quality of one's work and critical analysis of the results (17). Our results place Slovenia among the countries with the lowest cervical cancer incidence and mortality in Europe and the world.

4 HPV-associated changes in the anogenital area

Anogenital HPV infections are considered the most common sexually transmitted infections in both the developed and underdeveloped world. Most anogenital infections are asymptomatic, clinically unexpressed or subclinical. In 2017, 336 cases of anogenital warts were reported in Slovenia; the incidence was 16.3/100,000 inhabitants, but the actual incidence is most likely greatly underestimated. In the United States, the incidence of genital warts is between 100–170/100,000 inhabitants. The infection is most common between the ages of 15 and 40 and is equally common among men and women (3,11).

Infection with low-risk HPV genotypes is associated with the development of benign tumours such as anogenital warts and papillomas. These genotypes are rarely found in dysplasias and invasive anogenital cancers. In these neoplastic lesions, the HPV 6 and HPV 11 genotypes, which are thought to cause 80–90% of all cases of genital warts, are particularly important (18,19,20). In 2010, a Slovenian study found that at least 20.9% of women aged 20–64 were infected with HPV 6 or HPV 11 (21). In 2017, genital warts most often appeared in the 20–24 age group (84.4/100,000 inhabitants). Among women aged 20–24, the incidence was 101.2/100,000, and among men, the infection was most common in the 25–29 age group (83.0/100,000). In both sexes, genital warts or condyloma, called *condylomata acuminata*, are most common form of benign neoplastic lesions (3,11).

No specific antiviral drug is known. Milder forms of changes are treated with destructive procedures such as laser vaporization or cryotherapy. Patients with genital warts are prescribed podophyllotoxin and imiquimod (Aldara®). Genital warts can disappear spontaneously and often recur despite treatment (11).

High-risk HPV genotypes are causally associated with more than 99% of cervical cancer, 40% of vulvar carcinoma, 70–90% of vaginal and rectal carcinoma, 25–30% of oral cancer and 47% of penile cancer cases (22,23).

The incidence of rectal carcinoma has been increasing in recent years and is mainly related to genotypes 16 and 18. According to the Cancer Registry of the Republic of Slovenia, there are 1438 new cases per year in Slovenia (24). An increase in incidence is present mainly in the "at-risk populations" (23).

Vulvar carcinoma can be divided into two groups according to the predisposing factors themselves. The first type is associated with HPV infection and occurs mainly in younger women. The second type is not associated with HPV and occurs in elderly patients without epithelial neoplasia. The most common malignant tumour of the vulva is squamous cell carcinoma (95%) (25).

In the study of women with vulvar intraepithelial neoplasia (VIN), HPV DNA

was isolated in 48% of all cases, of which 96% were high-risk HPV genotypes 16 and 18. If VIN was not treated and reached stage III, vulvar carcinoma developed in 80% of cases. Risk factors for developing VIN and vulvar carcinoma, which may develop later, include HPV infection (the genotype that causes anogenital warts), low economic status, smoking and an increased number of sexual partners, which directly increases the risk of infection with various HPV genotypes (25).

Vaginal intraepithelial neoplasia (VaIN) is a rare disease. As with precancerous vulvar and cervical lesions, oncogenic HPV strains are also involved in the formation of VaIN. Malignant tumours of the vagina represent a small proportion among cases of vaginal carcinoma (1.2%). Vaginal carcinoma mainly affects postmenopausal women between the ages of 55 and 65. The most common histological form is squamous cell carcinoma with a developmental stage of VaIN (11).

Squamous cell carcinoma is more common in women diagnosed with cervical cancer, anogenital cancer, and infections with the HPV 16 genotype. HPV DNA was isolated in 55–64% of vaginal carcinoma cases. The high-risk genotypes 16 and 18 are most commonly found in association with vaginal carcinoma. Risk factors for developing vaginal carcinoma are also risk factors for HPV infection.

The prognosis and survival of patients with vaginal carcinoma also differ depending on the presence of HPV infection. A study showed that the 5-year survival rate of patients with HPV-positive vaginal carcinoma was 57.4%, whereas for patients with HPV-negative vaginal carcinoma it was 35.7% (26).

Penile cancer is a rare disease caused by several factors. The following have been identified: phimosis, poor hygiene, smoking and chronic inflammation (27).

Kidd and colleagues found one of the high-risk HPV genotypes in 31% of penile cancer cases; the HPV 16 genotype was most commonly isolated (27). They found that the progression of HPV 16 infection to penile intraepithelial neoplasia (PeIN), a precursor to the development of squamous cell carcinoma of the penis, is relatively slow. Among those infected with the HPV 16 genotype, more than 19 months elapsed between infection and development of PeIN in 50% of cases (27).

According to the Cancer Registry of the Republic of Slovenia, an average of 45 cases of vulvar carcinoma, 10 cases of vaginal carcinoma, 13 cases of penile cancer and 10 cases of rectal cancer in women and 3 in men per year were recorded from 2011 to 2015 in Slovenia (24).

5 Recurrent respiratory papillomatosis

Recurrent respiratory papillomatosis is often mentioned in connection with HPV infection. In the respiratory tract, small wart-like papillomas grow as a result of infection with HPV genotypes. Recurrent respiratory papillomatosis is divided into two subtypes: the juvenile form and the adult form. The juvenile form occurs before the age of 12 and is predominantly more aggressive with more recurrences than in adults. The HPV 6 and HPV 11 genotypes are "responsible" for more than 90% cases of recurrent respiratory papillomatosis. The remaining few per cent of the disease is caused by infection with the HPV 16 and HPV 18 genotypes. Children are most often infected with these genotypes during birth while travelling through the birth canal of an infected mother, and some cases of HPV infection are thought to occur even before birth – *in utero*. Additional risk factors, both immunological and genetic, are thought to

be important for the development of the disease. Papillomas can develop anywhere in the respiratory tract, but they are most commonly found in the throat area, where we talk about laryngeal papillomatosis (28).

The incidence of spontaneous malignant transformation of laryngeal papillomas is approximately 2%. It is higher in immunocompromised patients, in those treated with radiation or chemotherapy and in HIV-positive patients, where it can reach 10%. In case of malignant transformation, the prognosis of the outcome is poor. Treatment is most often surgical (2,28).

6 Carcinomas of the head, neck, and nasal and paranasal sinuses associated with HPV infection

Squamous cell carcinoma (SCC) of the head and neck is one of the most common cancers in the world (3). Oropharyngeal squamous cell carcinoma includes cancers of the tonsil, the base and posterior third of the tongue, the soft palate, and posterior and lateral walls of the pharynx. Squamous cell carcinoma accounts for more than 95% of all oropharyngeal cancers. The development of cancer is closely linked to alcohol abuse and smoking, and recently, HPV infection has been increasingly cited as a cause of cancer (29).

The male-to-female incidence ratio is 2.7:1. Researchers have already discovered a high incidence of infections with high-risk HPV genotypes in certain areas of the head and neck in the past. HPV was found in the oropharynx, especially in the tonsils, in 50% of cases. In the sinus and nasal area, HPV infection in association with squamous cell carcinoma was confirmed in 20%. Squamous cell carcinoma in association with HPV infection develops through a number of oncogenic pathways. Epidemiological studies have shown that HPV-associated squamous cell carcinoma is more likely to develop in the younger population and has a higher incidence among young women. If the sinus and nasal areas are affected, the nasal cavities are more commonly affected, as opposed to non-HPV-associated squamous cell carcinomas, in which the maxillary sinus is most commonly affected (3).

The most commonly isolated genotype associated with squamous cell carcinoma is HPV 16, which causes about 60% of oropharyngeal cancers. The risk of developing oropharyngeal cancer is 16 times higher in HPV-positive patients than in those without HPV infection. In both Europe and America, HPV infection accounts for 70–80% of oropharyngeal cancers (29).

Cancer associated with HPV infection has a better prognosis than non-HPV-related cancer. It is characterized by increased sensitivity to chemotherapy and radiotherapy (3,29).

The incidence of head and neck cancer in Slovenia has been stable in recent years: approximately 442 people are diagnosed with head and neck cancer in Slovenia every year (24). In 2015, the World Health Organization (WHO) identified ten histological types of head and neck tumours, and about 90% of these tumours were grouped into the category of conventional types of head and neck cancer with the abbreviation HNSCC (Head and Neck Squamous Cell Carcinomas). Within this category, two groups were formed according to risk factors, disease development, and treatment. The first group includes keratinized HNSCC, which occurs mainly in older men, heavy smokers, and spirit drinkers who are not infected with HPV 16. This tumour is characterized by frequent mutations in the TP53 gene found in 50% of keratinized HNSCC. There is

also a positive reaction to the p53 protein and a negative reaction to the p16 protein. The disease caused by these tumours is more severe and has a worse outcome. The second group includes non-keratinized HNSCC, which occurs in younger men between the ages of 40 and 60, non-smokers, people who do not drink alcohol excessively but are infected with HPV 16. Tumours are positive for p16 protein and negative for the p53 protein. The prognosis of the outcome of the disease development is better. Risk factors for developing head and neck cancer connected with HPV infection include multiple sexual partners, oral-genital and oral-anal sexual intercourse and marijuana use. Less common forms of HNSCC include papillary and lymphoepithelial carcinomas, which are most likely to be associated with HPV 16 infection, while spindle cell and acantholytic carcinomas are most likely to be associated with smoking and alcohol abuse (3).

Other high-risk HPV genotypes, such as HPV 18, 31, or 33, are also associated with head and neck cancer but are less common than the HPV 16 genotype (30).

According to the Cancer Registry of the Republic of Slovenia, an average of about 100 cases per year of oropharyngeal cancer, including the base of the tongue and tonsils, were recorded in Slovenia from 2011 to 2015 (24).

De Martel and colleagues found that infections with high-risk HPV genotypes could be attributed to 26% of all oropharyngeal cancer cases (22).

7 HPV vaccination

There are currently no specific antiviral treatments for HPV infection (8). While safe sexual behaviour can reduce the risk of HPV infection, it cannot prevent it. Regular gynaecological examinations and responding to the invitation of the ZORA screening programme contribute to the timely detection and treatment of precancerous changes and cervical cancer. However, due to the possible skin to skin transmission of the virus, condoms do not protect against infection. The most successful method by which HPV infection can be prevented is vaccination. Vaccination with existing vaccines is considered the most successful measure for preventing the most severe precancerous changes and cervical cancer as well as other benign and malignant neoplastic lesions caused by HPV infection. The virus-like particles in the vaccine do not contain viral DNA and therefore cannot infect human cells, nor can they multiply in them or cause disease (11,31).

Three types of vaccine are licensed for general use in Europe; a bivalent vaccine containing the HPV 16 and HPV 18 genotypes; a quadrivalent vaccine containing the HPV 6, HPV 11, HPV 16 and HPV 18 genotypes and a vaccine containing nine HPV genotypes (HPV 6, HPV 11, HPV 16, HPV 18, HPV 31, HPV 33, HPV 45, HPV 52 and HPV 58) (32).

Vaccination with a bivalent vaccine prevents precancerous anogenital changes (on the cervix, vulva, vagina and rectum) as well as CC and rectal cancer. In addition to the above stated, the quadrivalent vaccine also prevents the formation of genital warts (condyloma acuminatum), which are causally linked to specific HPV genotypes (33). As with a 2- or 4-valent vaccine, vaccination with a 9-valent vaccine is intended for ages nine and up and prevents precancerous changes and CC, vulvar, vaginal and rectal carcinomas, as well as genital warts (condyloma acuminatum) caused by specific HPV genotypes (34).

Vaccination is given in two or three doses, depending on the age when the first dose was given. People aged between 9 to

14 are vaccinated with two doses of the vaccine (0.6 months). For those older than 15, vaccination with three doses of the vaccine is required (0, 2 and 6 months for the tetravalent and 9-valent vaccines or 0, 1, 6 months for the bivalent vaccine) (35).

The HPV vaccine has been available in Slovenia since 2007. Since the 2009/2010 school year, vaccination has been carried out as recommended, and it is free for girls in the 6th grade of primary school. Girls who have not been vaccinated in the 6th grade of primary school can be vaccinated later at the expense of compulsory health insurance (36).

Until the 2013/2014 school year, girls were vaccinated with a tetravalent vaccine according to the 0, 2, 6 month schedule, and from the 2014/2015 school year on, with two doses of the vaccine according to the 0, 6 month schedule. With the 2016/2017 school year, the vaccination programme for 6th-grade primary school girls began to use the nine-valent vaccine. For the rest of the population, vaccination in Slovenia is currently a self-payment option (36).

The proportion of vaccinated sixth-graders in Slovenia ranges between 44% and 55%, but it has been below 50% in most years. In the 2018/2019 school year, in Slovenia, vaccination with the second dose amounted to 59.3% and was thus the highest so far (37). There are large differences in the proportion of vaccination coverage between health regions. The highest proportion of vaccinated girls was achieved in Murska Sobota in the 2010/2011 school year (87.3%) and the lowest in the Ljubljana region in the 2014/2015 school year (29.7%) (38).

The immunogenicity of all three vaccines is good. Namely, the antibody response to the genotypes the vaccine contains is between 93% and 100% in women and 99% and 100% in men. Antibody levels are higher in younger individuals (39). All three vaccines have a good safety profile (40). The vaccine is most effective in girls and boys prior to their first sexual intercourse before being exposed to the possibility of HPV infection (41). Vaccination does not only offer protection to vaccinated people. With a high proportion of vaccinated individuals, collective protection is also created (42,43).

A systematic review of research and a meta-analysis published in June 2019 published the results of the efficacy of HPV vaccination in reducing the prevalence of HPV infections and the incidence of CIN 2 among girls and women and anogenital warts among girls, women, boys and men. In the first four years after HPV vaccination, the prevalence of HPV 16 and 18 decreased significantly in 13–19-year-old girls and 20–24 year old women, compared to the prevalence of HPV genotypes 16 and 18 in the pre-vaccination period. Somewhere between 5 to 8 years after vaccination, the prevalence of these genotypes decreased by 83% in 13–19-year-old girls and 66% in 20–24-year-old women. The prevalence of HPV 16 and 18 did not change significantly in the first four years after vaccination in 25–29-year-old women. 5 to 8 years after vaccination, the prevalence in this group also decreased by 37% (44).

In the four years after vaccination, the prevalence of HPV genotypes 31, 33, and 45 decreased only minimally in 13–19-year-old girls. Within 5–8 years of vaccine introduction, there was a 54% prevalence decrease. In women aged 20–24, the prevalence for the genotypes mentioned above decreased by 28%. In women aged 25–29, the change in prevalence was not significant four years after vaccination or later (44). Only two studies are available for investigating HPV infection and changes in the prevalence of HPV genotypes among

boys and men. They found an insignificant decrease in the prevalence of HPV 16 and 18 and 31, 33, 45 among boys aged 16–19. The decrease in prevalence was minimal both in the first four years after vaccination and later. No significant changes in the prevalence were observed in men aged 20–24 (44).

Within 5–9 years of vaccine introduction, the incidence of cervical intraepithelial neoplasia (CIN) 2 and of higher grade decreased by 51% among girls aged 15–19 and by 31% among women aged 20–24. The proportion of diagnosed anogenital warts decreased by 67% in girls aged 15–19, by 54% in 20–24-year-old girls, and 31% in women aged 25–29. The incidence of anogenital warts was 48% lower in boys aged 15–19 and 32% lower in men aged 20–24 (44).

8 Conclusion

HPVs are certainly one of the most important and at the same time least known groups of viruses, which significantly influence the occurrence of many neoplasms. It is incorrect to think that only cervical cancer (CC) is associated with HPV infection. As shown in the article, HPV is associated with many other neoplasms, both benign and malignant, that significantly affect patients' quality of life. Therefore, it is essential to make young people aware of the possibility of infection during sexual intercourse and the importance of preventing infection through vaccination. Vaccination remains the best-known way to prevent HPV infection. Therefore, HPV-related neoplasms are currently the only ones against which we can actively protect ourselves and prevent their formation. Although vaccination in Slovenia is part of the vaccination programme for children and adolescents, the vaccination rate is still low. Both healthcare professionals and the National Institute of Public Health (NIJZ) are working on increasing this number over the years to reduce the number of HPV-related neoplasms.

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