

# HPV infections, related diseases and prevention methods

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**Summary** HPV diseases are common infections that affect the urogenital and pharyngeal mucous membranes. Persistent infection with oncogenic strains leads to tumorigenesis. Diagnosis and treatment of HPV-related disease is often difficult to manage from perspective of the patient and family physician because it refers to symptomatic treatment of the clinical manifestation of the disease in the form of warts or genital warts. Additional treatment generally requires specialised care. The oncogene effect of HPV infection on the development of cervical, anal, vaginal, vulvar, penile, oral cavity and laryngeal cancers has been demonstrated. Each year, more than 300,000 women die worldwide from cervical cancer. At the same time, over 3,000 cases of cervical cancer are diagnosed in Poland. The primary role in limiting HPV infections is that of preventive vaccination. In Poland, the vaccination is burdened with many restrictions, and thus the vaccination ratio is significantly lower than in other European countries. Only a proper definition of limitations and a detailed attempt to spread treatment will help reduce the incidence of HPV-related cancers. In Poland, only about 20,000 HPV vaccines are performed annually. This vaccination is recommended but no reimbursement. Lack of a common immunisation programme and the high price of vaccines, as well as low public awareness, are major contributors to the low vaccination rates. General practitioners have a fundamental influence on the promotion of health.

**Key words:** human papillomavirus, infections, cancers, treatment, prophylaxis, HPV vaccination coverages, National Health Policy.

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## Human papillomavirus and related diseases

Human papillomaviruses (HPVs) are a large group of DNA viruses comprising more than 170 types infecting epithelial basal cells and which are exposed by micro-tears or epithelial wounds [1]. They fall broadly into two groups. The first group of viruses infects the skin or cutaneous surfaces, and the second infects the flat surfaces of the mucous membrane, especially the genital tract [2]. The virus is a common pathogen among men and women, and HPV infections are perceived as the most frequent sexually transmitted disease [3]. However, the virus can also be transmitted vertically and perinatally [4, 5]. A study in Finland showed the presence of the virus in 44% of infants aged from 2 days to 3 years [4].

The worldwide number of HPV infections is assessed to be around 660 million [6]. Most are related with HPV types 1, causing skin warts, and types 6 or 11, which lead to genital warts. However, persistent infection with HPV types 16 and 18, and their close relatives 31, 33, 35, 52, 58, 39, 45, 59, 56 and 51, may cause carcinogenesis [7].

The virus enters the cell as a result of endocytosis and is then transported to the nucleus, where the transcription of genes encoding the E1 and E2 proteins necessary for viral DNA replication begins [7, 8]. This leads to the synthesis of six oncoproteins: E1, E2, E4, E5, E6 and E7 [9]. The expression of E6 and E7 inhibits the tumour suppressor proteins p53 and the retinoblastoma protein (pRb), which leads to carcinogenesis [10]. Episomal expressions E2, E4 and E5 may also spontaneously cause cancer [11]. Saraiya et al. [12] discovered the presence of HPV DNA in 91% of cervical, 91% of anal, 75% of vaginal, 70% of oropharyngeal, 60% of vulvar, 63% of penile, 32% of oral cavity and 21% of laryngeal cancers. The pathology is often clinically silent for a long time, and late diagnosis hinders the therapeutic process.

Cervical cancer is the leading HPV-related neoplasm and is second after breast cancer, the leading cause of tumour death among women under 65, totalling over 300,000 deaths annually [13]. Every year, more than 3,000 cases of cervical cancer are diagnosed in Poland, and they constitute about 4% of all malignant tumours among women [13]. Despite an observable decline in morbidity over the past 30 years, the incidence of cervical cancer is 15% higher than the average for European Union countries [14].

## Diagnosis of HPV-related diseases

HPV infection can be difficult to diagnose as it often remains asymptomatic for a long time. The clinical manifestation of condyloma or skin warts is mostly clustered lumps. They may proliferate to cauliflower-like plaques on the skin in urogenital area and present symptoms such as itching or burning [15]. These are the first symptoms a patient usually presents with to their primary care physician. The clinical manifestation of HPV as cutaneous or genital warts is easy to diagnose in comparison to oncological processes, which, apart from testing for cervical cancer, do not have screening programmes in Poland and are usually diagnosed as lesions with the presence of HPV.

Accurate diagnosis is also difficult due to the unavailability of virological and genetic methods in outpatient clinics. Therefore, the family physician should primarily carry out educational and preventive activities and diagnostics with oncological vigilance, provide initial treatment and encourage specialist consultation in situations requiring intensive treatment or additional diagnostics. Further diagnosis of lesions is usually performed by specialists, mainly gynaecologists and dermatologists. In fact, only gynaecologists usually perform an HPV screening diagnosis in Poland. A Papanicolaou test (Pap Test, Pap Smear) is vital for the early detection of the presence of abnormal cervical



squamous epithelial cells [16]. The role of the family physician should be to recommend the patient for an appointment with an examination and Pap Smear. This effectively reduces the risk of cervical cancer if the cancer can be detected and treated early enough, and cure rates can be as high as 70–90% [17]. According to the Polish Society of Gynaecologists and Obstetricians, a Pap Test should be performed regularly for every woman after the onset of sexual activity and not later than the third year after first intercourses [9, 18]. If a woman has not started having intercourses, she should have her first examination at the age of 25. Thereafter, the frequency of testing varies depending on the woman's age and the result of the previous test. If the previous result was normal and the woman is healthy, then the next test is performed in 3 years. In certain situations, it is necessary to have the test every year, such as patients with compromised immune systems, HIV-positive patients and those with abnormal previous Pap Test results. In the case of finding abnormal cells in the tissue that lines the outer part of the cervix (atypical squamous cells of undetermined significance: ASC-US) or a low- or high-grade squamous intraepithelial lesion (LSIL or HSIL), colposcopy with biopsy, P16/Ki-67 immunohistochemistry or HPV DNA HR test detecting DNA of 12 high-oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) are recommended [18].

The diagnosis of other HPV-related diseases is also based primarily on a detailed history, physical examination and search for precancerous conditions associated with papillary lesions. Anal cancers may be diagnosed through defecation problems and by performing an anorectal examination [19]. The search for HPV infection in penile cancer is often based on actions secondary to the disease process [20].

The limited possibility of screening among men and the lack of guidelines make infections in the male population much more difficult to detect, and infections are simultaneously often overlooked or downplayed by the patients themselves. This is a particularly important as it has been proven that transmission capacity and risk of infection for men are almost similar to women [21]. Moreover, the infection may also have a negative effect on male fertility [22].

## Treatment

The likelihood of spontaneous remission of warts is low; therefore, treatment is recommended to prevent progression of the disease to invasive lesions [15]. Pharmacotherapy is used as the first method of choice and is available to the family physician. It includes antimetabolic drugs, like podophyllotoxin 0.5% solution or ointments containing green-tea extracts with anticarcinogenic and immune-stimulatory effects, like sinecatechins [23]. 5% imoquimod used overnight for 2 weeks is also widely utilised to treat genital HPV lesions [24]. The gold standard is invasive treatment, carried out in Poland mainly by a specialist and which includes cryotherapy, surgical excision, curettage, electrocoagulation or ablative laser treatments (CO<sub>2</sub>, Nd:YAG and Er:YAG lasers) [25].

Treatment of lesions in the cervix uteri consists primarily of surgical methods. They concern patients who have HSIL, cervical intraepithelial neoplasia (CIN) with positive HPV DNA and the persistence or progression of the lesion during a 2-year follow-up, including a follow-up colposcopy and positive HPV tests, including CIN [18]. The most common is diagnostic excision of the lesion with the use of the Loop Electrosurgical Excision Procedure or Large Loop Excision of the Transformation Zone (LEEP/LLETZ – procedures to excise the cone from the cervix using a specialised loop), electroconisation (removal of diseased parts of the cervix using electricity), conisation (removal of diseased parts of the cervix) with a surgical knife, conisation with a laser beam and surgical amputation of the cervix [18]. However, these are symptomatic methods that will not eliminate the whole presence of the virus in the body, while only temporarily reducing the oncological risk.

## Prophylaxis

Vaccination has been perceived as the only effective method in preventing HPV infection. The first registered vaccine in the USA was in 2006, and nowadays, there are three types of vaccines available on market: 2-valent, against HPV-16 and HPV-18 (the two HPV genotypes that cause approximately 70% of cervical cancer); 4-valent, preventing HPV-6, HPV-11, HPV-16 and HPV-18 (as well as against genital warts) and 9-valent, protecting against HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58 (also contains the most frequent oncogenic HPV DNA strains to prevent cervical, vulvar, vaginal, anal, oropharyngeal and other head and neck cancers, as well as genital warts) [26–29].

By 2018, nearly a hundred countries had implemented a HPV vaccination programme [30]. The vaccination rate varies in many countries but is significant higher in countries where HPV vaccination is a part of the national programme of vaccination, e.g. Malta 84%, Italy 67%, Spain 83% and Sweden 76% [31]. Among European Union countries, only Poland, Estonia and Romania have not introduced universal vaccination against HPV [31]. In Poland, vaccination coverage is difficult to estimate, though it is less than 10%, and according to the data of United Nations Children's Fund (UNICEF), only 22,341 people were vaccinated against HPV in Poland in 2018 [32]. At present, Poland has no HPV national vaccination programme. However, the HPV vaccination is recommended for girls and boys, especially in those between 9–14 years of age, in 2 or 3 doses, before they become sexually active [33]. This vaccination is not reimbursed in Poland; however, there are actions by local governments regarding financial support for HPV vaccination [33].

Over the past several years, more than 100 million doses of the vaccine have been administered, and studies to date have demonstrated a positive safety profile for HPV vaccination and no serious adverse events have been reported [34]. The Vaccine Adverse Event Reporting System and Vaccine Safety Database did not identify reports of questionable safety or an increased risk of specific adverse events globally [35, 36]. Only post-dose syncope and local skin reactions were noted [36]. Long-term use of the vaccine has also allowed for the first observations of effectiveness [37, 38].

The reasons for low vaccination coverage in different countries vary, and the problem is complex. In Poland, due to the lack of a national vaccination programme against HPV, all factors encouraging to HPV vaccination are particularly important in building positive attitudes towards the vaccination and the desire in parents to vaccinate their children against HPV.

First of all, society is not fully aware of the dangers of HPV infection [39]. Lack of knowledge fosters vaccine-avoidance and generates negative views of the vaccine, e.g. parents believe their children have no risk of HPV infection, question the usefulness of the vaccination at such an early age, worry that their children will engage in riskier sexual behaviour, and they also believe that the vaccination promotes an earlier age of sexual initiation [39–41]. Parents are also afraid of side effects of the vaccine [42]. Moreover, the media is not promoting enough the importance of HPV-related diseases and it causes a false perception of the risk associated with HPV infection, which is a proven factor in questioning the validity of HPV vaccination [43].

Medical recommendations are essential in building acceptance of prophylaxis. A conversation with a health provider and their recommendations significantly improve awareness and help parents decide more often to perform vaccinations [43, 44]. However, doctors rarely recommend or inform about HPV vaccines [39]. Doctors themselves are also aware of this problem, and more than half of Polish paediatricians recommend vaccination as little as a few times a year [45]. Lack of time, discomfort in talking about sex and sexually transmitted infections,

the high cost of HPV vaccines and doubts about the quality of treatment due to limited education are the main limitations according to health providers [45, 46]. Doctors are less likely to promote HPV vaccination among boys as well [46]. As a result, parents often have to rely on unverified sources of medical knowledge from the Internet or TV [39]. There is also a significant increase in refusal of vaccinations, from 4,893 in 2007 to 23,147 in 2016 [47]. In the opinion of health care professionals, a national vaccination programme with reimbursement seems necessary to increase the HPV vaccination rate in Poland [45].

## Conclusions

The diagnosis and treatment of HPV-related diseases is difficult and, due to advanced treatment methods, often beyond the means of the family physician. Therefore, effective prophylaxis by means of available preventive vaccinations and patient education encouraging self-control and screenings are of primary importance. Introduction of a vaccination programme, reducing the cost through reimbursement and extensive promotion will increase access, increase awareness and reduce HPV-related infections.

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