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HPV – Relevance, Oncogenesis and Diagnosis (A Review)

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A B S T R A C T
According to authoritative sources, 660 million people are registered worldwide as infected with the human papillomavirus, otherwise HPV. Three-quarters of the sexually active part of the population becomes infected with HPV throughout their lives, between the ages of 18 and 30 years. Of this number, more than 300,000 people die every year from oncological diseases, while the initiating factor in the carcinogenesis of the above diseases is HPV [6]. To date, more than 600 strains of HPV have been identified, with each strain genetically different from another closely related type by approximately 10%. Strains No. 16 and 18 have the highest oncogenic potential. Only these two HPV strains account for up to 95% of oral cavity cancer. In addition, in total, these types cause up to 92% of anal cancers, 89% of oropharyngeal cancers, 80% of vulvar and vaginal cancers, also 70% of cervical cancers and 63% of penis cancers. These figures show how wide the scope of clinical problems is, and how relevant the problem of early diagnosis is for the prevention of malignant neoplasms caused by HPV.

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Introduction. The human papillomavirus is not the only type of virus that affects humans, it is a whole group of pathogenic and genetically heterogeneous DNA-containing viruses, of which about a hundred strains affect the epithelium and mucous membranes of people. HPV is practically the only one of the studied human viruses that does not enter the human bloodstream or even if the virus enters the bloodstream, then in a very small amount. As a result, the infectious process during infection with HPV, due to the limited contact of the virus with immune cells, proceeds without a pronounced development of the inflammatory response of the human body.

All this, of course, contributes to a very low rate of seroconversion, the titer of antibodies to HPV in the blood is very low, which affects both the diagnosis of the disease and does not prevent infection with other HPV strains later.

HPVs are obligate epitheliotropic viruses, and in the process of infection they affect the basal layer of the epithelium of the skin and mucous membranes, primarily the mucous membrane of the genital organs. The basal layer of infected cells (genitals, larynx, oral cavity, eyes, etc.) further becomes a source of constant infection of neighboring epithelial cells.

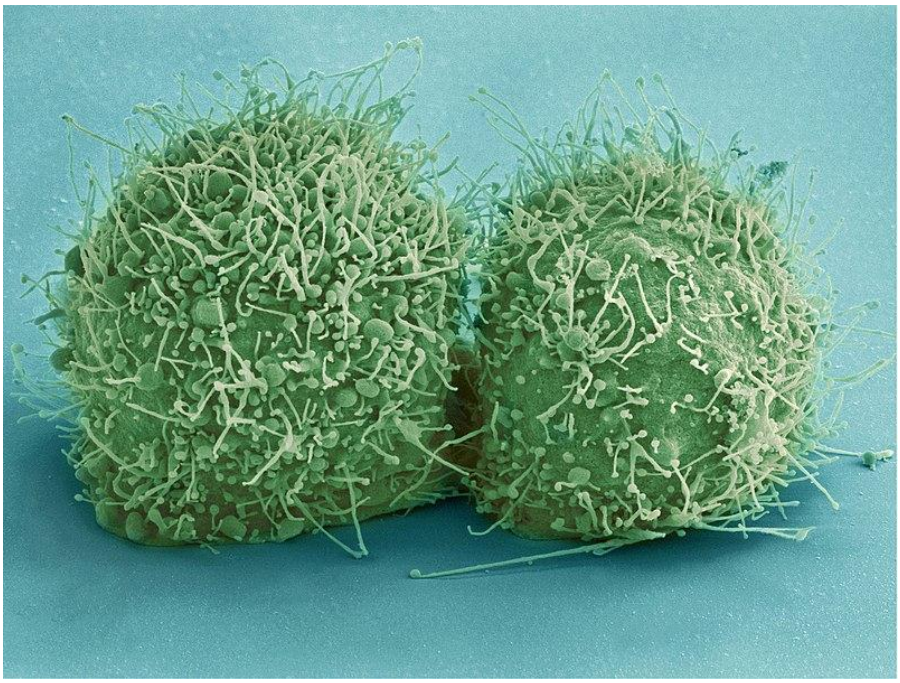
HPV genetic material is embedded in squamous endothelial cells (most often of the genital tract) or stratified skin epithelium, the so-called virogeny process. The reproductive cycle of HPV is directly related to the differentiation of epithelial cells. The doubling of the nucleic acid of the human papillomavirus occurs in the cells of the basal layer, while in the cells of other layers of the epidermis, the viral particles only persist for a long time. HPV refers to simple or non-enveloped viruses, that is, they have a 20-sided capsid without an additional lipoprotein layer - supercapsid. The virus has double-

stranded DNA in the form of a closed ring. The nucleic acid of a virus is tuned to produce its proteins repeatedly, as the life cycle of a virus requires pieces of DNA to be torn off.

The basis for the development of oncological processes during HPV infection is the expression of oncoproteins of the E6 and E7 types. These proteins interfere with the functioning of key host cell proteins that are responsible for proper division. In the future, this leads to uncontrolled cell division and the accumulation of cellular DNA mutations [**9**]. For the life support of the genetic material of viruses and their reproduction, the organelles of the host cells are used, while the epithelial tissue undergoes vacuolar degeneration. Thus, in the future, this leads to deformations of the epithelium, the appearance of papillomas, condylomata, and, of course, cancerous degeneration should be considered the most formidable complication of human papillomavirus infection.

A case in point is the story of a patient named Henrietta Lacks, who died of cervical cancer less than a year after her diagnosis.

The researchers were able to develop a whole cell line from a single cancer cell in Henrietta's tumor formation, called HeLa, after the initial letters of Henrietta Lacks' name. For 70 years, scientists have grown about 200 tons of HeLa cells, which is 400 times the body weight of Henrietta Lacks herself. These cells have made a splash in science, because due to the "immortality" discovered in them, they are widely used in various scientific experiments.



Scanning electron micrograph of just-divided HeLa cells.

They are called "immortal" because HeLa cells can divide an unlimited number of times, unlike normal cells, which have a Hayflick limit. HeLa cells have an abnormal set of chromosomes from 49 to 78, unusual for the human karyotype, in various sublines. Initially, HeLa cells were infected with human papillomavirus type 18 (HPV18). Researchers attribute the immortality of HeLa cells to the consequences of infection with the human papillomavirus HPV18. The virus caused triploidy of chromosomes, that is, the formation of three copies of chromosomes instead of the usual pair, followed by the splitting of some of them into fragments. In addition, as a result of infection, the activity of the telomerase enzyme increased which builds up telomeres at the ends of chromosome DNA, and also increased the expression of the c-Myc gene, which produces specific products that have a stimulating effect on cell division processes [**2**].

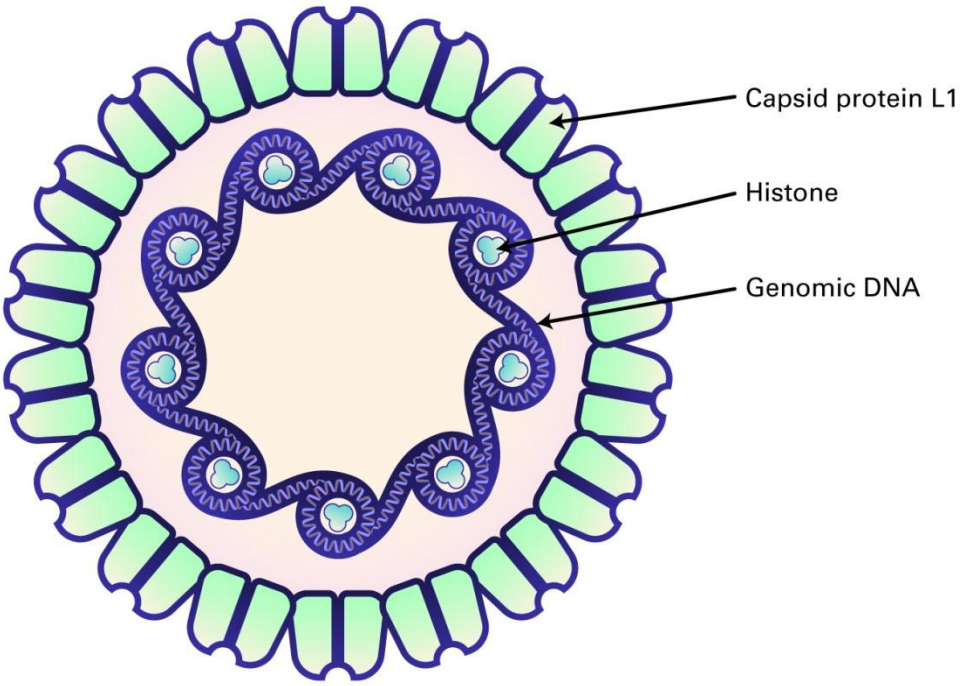
Main part. The source of the causative agent of HPV infection is a sick person or carrier. The main route of transmission is sexual contact, and a condom does not protect 100% from HPV. In addition, there is the possibility of infection with papillomavirus in newborns during childbirth, a vertical route of transmission. And finally, there is a contact-household transmission route. The fact is that

papillomaviruses can easily exist in a warm, humid environment for weeks, months, and even years. Thus, infection can occur in toilets, baths, swimming pools, gyms, and recreational places, open water bodies, widely visited by people during summer holidays, are not excluded. After all, it is known that poorly treated domestic and industrial waters are a source of various infectious diseases [**7**].

The entrance gates of infection are various microtraumas of the skin and mucous membranes, this can occur through direct contact or the use of personal hygiene items. HPV is often associated with sexual transmission, in fact, as we can see; HPV infection does not mean proof of sexual contact. It's just that the standard life cycle of the virus is designed for infection through microcracks in the skin. Infection through the mucous membranes is only more effective, and if we may say so, more contagious and therefore more often observed [**10**].

Nevertheless, the sexual route has been and remains the main one in HPV infection. According to the study, in the USA, Russia and many other countries, HPV is the most common sexually transmitted disease [**8**]. It has been established that promiscuity leads to the development of cervical cancer and penile cancer, women who have an early sexual life and often change sexual partners have an increased risk of developing cervical cancer. Indirect evidence is also the fact that nuns rarely develop cervical cancer.

With regards to infection by contact-household HPV through household items and even with a normal handshake, this is facilitated by the extreme resistance of the virus to antiseptics [**1**]. The resistance to antiseptics of the virus is provided by its capsid, due to which many classical medical antiseptics are ineffective against papillomaviruses. Dehydration also does not have a significant effect on the viability of the virus, so after a week with complete dehydration and room temperature, about one third of papillomaviruses survive [**3**].



Structure of HPV

The high resistance of papillomaviruses to various disinfectants creates many medical difficulties. Broad-spectrum antiseptics against HPV are ineffective, for example, 95% ethanol kills up to 86% of viruses, and widely used 75% ethanol affects only 16% of papillomaviruses [**4**]. Modern research has shown that the extreme resistance of HPV to conventional disinfectants often leads to cases of HPV infection during gynecological examinations due to the fact that some gynecological instruments are reusable and cannot be sterilized in autoclaves due to heat damage [**5**].

According to WHO, 50-80% of the population of our planet is infected with HPV, but only 5-10% of infected individuals have clinical symptoms of the disease, that is, characteristic genital warts, which are

small flesh-colored outgrowths in the anogenital zone.

Condyloma acuminate

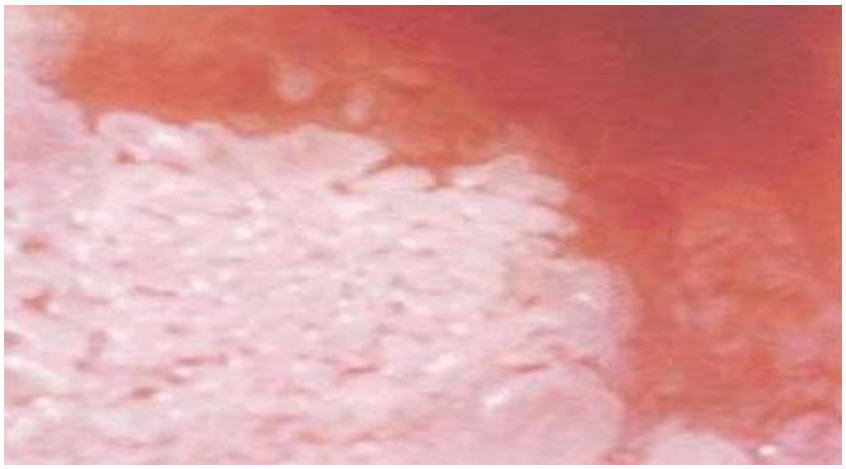
At the moment, there is no specific treatment for HPV, that is, there are no drugs and methods that would completely eliminate the virus from the human body. Doctors mainly use destructive methods - electrocoagulation, laser destruction, radiosurgical destruction, cryodestruction aimed at treating the effects of the virus, that is, warts and tissues with cellular changes are removed. It is also possible to use non-specific antiviral drugs in combination with immunomodulators (α-interferon preparations). In 2006, Merck & Co. developed the vaccine Gardasil, which showed almost 100% effectiveness in protecting against precancerous changes in cervical cancer caused by HPV types 16 and 18. This vaccine is for girls and women aged 9 to 26, and boys aged 9 to 17. Gardasil protects against infection by the 4 most dangerous types of human papillomavirus: 6, 11, 16, 18, and thus prevents the oncological diseases associated with these viruses.

Papillomavirus infection is so widespread and its consequences are so serious that, given the costs of diagnosing and treating all the pathologies associated with it, in developed countries it is considered the most "expensive" infection after HIV.

The material for the study of HPV are scrapings of the urogenital and anogenital zones (urethra, cervix, vagina, rectum), scrapings of the oral cavity, from the conjunctiva of the eyes. In addition, urine, semen and cerebrospinal fluid are used as biomaterial. Blood is not considered a universal material for the diagnosis of HPV, since it is much more important to take material from places of direct infection with the virus (scrapings of the endothelium of the urinary and genital tract or histological material from papillomas and condylomata).

The main methods for diagnosing papillomaviruses remain nucleic acid amplification methods, that is, PCR. This molecular biological technique is well suited for the detection of a latent (hidden) infection, especially viruses located in the cells of the basal layer. The subclinical form of papillomavirus infection with mild symptoms, in addition to PCR, is detected using colposcopy, cytological and morphological examination of tissues affected by the virus.

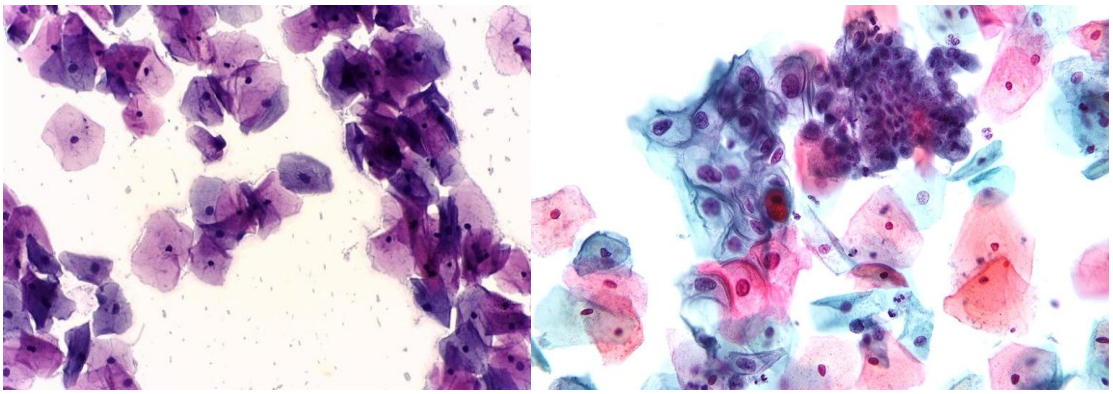
In a colposcopic examination, to improve the visualization of anogenital warts, a 3% acetic acid test is performed, which narrows the unchanged vessels of the treated tissue, normal vessels, as a rule, disappear for a short time when treated with acetic acid, and atypical ones do not change. The test is considered positive when white areas (acetowhite areas) are detected on the cervix, which are different from the rest of the surface of the cervix. The more intense the tissue whitens after treatment with acetic acid and the longer this effect persists, the more serious and deeper the lesion. On the contrary, the absence of white areas on the cervix after treatment with 3% vinegar indicates the opposite result.



White areas, cervical tissue affected by HPV

Changes in the epithelium of the cervix caused by HPV can be detected by cytological microscopy of desquamated cells. There are various classifications for the study of abnormal precancerous cells, but the most common is atypical squamous cells of undetermined significance (ASCUS). The most common cause of atypical squamous epithelial cells of undetermined significance in humans is the human papillomavirus. These abnormal cells are detected with a Pap test or Pap smear.

The Pap test is aimed at detecting early cervical cancer and active HPV. For women over 30 years of age and, especially with the presence of HPV types 16 and 18, this method of examination is mandatory. Biomaterial is taken from the cervical canal - scraping of the epithelium. Subsequently, an imprint smear is prepared, which is fixed with 96% alcohol for 5 minutes. Next, slides with fixed smears to be studied are sequentially immersed in containers with various dyes and fixing compounds. After a series of stainings, atypical cells are detected by microscopy. The fact is that normal and atypical cells react differently to staining - due to this, it is possible to more accurately determine the presence of altered (atypical) cells, estimate their number and predict the development of malignant tumors. Normally, if there are no atypical cells, that is, all cells of the same shape and size, the test is considered negative. The presence of cells of different shapes and sizes, as well as cells with abnormal nuclei and cytoplasm, indicates a positive Pap test.



a **b**

a) Micrograph of a normal Pap smear b) Micrograph of a Pap test showing a low-grade intraepithelial lesion (LSIL) and benign endocervical mucosa

Conclusion. In terms of prevalence, HPV ranks first among all sexually transmitted infections of viral etiology. According to forecasts, the number of cases of cervical cancer caused by HPV by 2030 will reach 700 thousand cases, while the death rate will be about 400 thousand. Similar growth is expected in the coming years, especially in developing countries. The lack of quality medical care and diagnostics in third world countries will lead to a surge in HPV-related cancers. High oncogenicity, "secrecy" of clinical symptoms, diagnostic complexity makes HPV the object of close attention of laboratory doctors, infectious disease specialists, oncologists, gynecologists and a host of other health workers. One thing is certain; the study of the human papillomavirus in connection with its exceptional carcinogenicity is of

great medical and social importance.

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