Human papillomavirus

Human papillomavirus (HPV) - a DNA virus , family *Papillomaviridae* - is now considered the leading cause of cervical cancer (by some sources the only cause). However, statistically we can say that cervical cancer is a rare complication of a common infection. Vaccination is available - in the Czech Republic Cervarix (for type 16 and 18), Silgard (type 6, 11, 16, 18) and Gardasil9 (6, 11, 16, 18, 31, 33, 45, 52, 58)

Biology and genetics

The virus attacks the stem cells of the epidermis and undergoes its own cycle and replication with their differentiation . Different types of HPV infect the skin or mucous membranes. HPV viruses are divided into two main classes according to clinical risks : HPV-HR (high risk), which potentiates malignant cell transformation (eg HPV 16 and 18) and HPV-LR (low risk), which cause benign lesions (eg HPV 6 and 11).

Only HPV-HR virus DNA can be incorporated into stem cell DNA and induce malignant transformation. Depending on the virus cycle, the cell expresses different oncoproteins . The best known are E6 and E7 (which are expressed at the stem cell level and are caused by HPV-HR) and L1 and L2 , which are expressed at the epidermal surface cell level and are found in both HPV-HR and HPV-LR infection.

HPV-LR

- It leads to a condylomata accuminata lesion in 50% of infected women within 2-8 months after infection;
- multifocal lesions on the cervix, dam, around the anus, vulva (or penis);
- oncogenic;
- transmission by sexual contact or contact with contaminated laundry (semen, vaginal secretion);
- incidence age around 25 years;
- high infectivity.

HPV-HR

- The most common cause of cervical cancer;
- unifocal lesions (CIN 1-3 and invasive cancer);
- transmission by sexual contact, low infectivity;
- specific immunity has high protection;
- age of occurrence: 35 years (CIN 3) and 45 years (cancer);
- after infection, CIN 3 appears with an 18-month to five-year delay / cancer after 15-20 years;
- 80-90% of women eliminate the virus spontaneously (due to immunity) within 8-16 months;
- 10–20% who do not eliminate the virus: 20% will develop CIN 3 within 5 years, 5% will develop cancer within 15–20 years (only 1% of women with regular screening will develop cancer).

Epidemiology

HPV is transmitted through sexual contact (a condom does not always protect against infection). During their lifetime, 70-80% of women become infected .

The infection is most common in young women under 30 and then the incidence increases again after 55 years. In the group under 30 we find 30% of HPV positive, while over 30 it is only 10%.

This is explained by:

- *in young people* - more sexual partners and the beginning of sexual life at a younger age (immaturity of the cervical epidermis and therefore higher vulnerability to the virus). With one partner, about 28% of women become infected, and with ten sexual partners, 68% of women become infected;
- *in those over 55 years of age* - decreased immunity and hormonal changes (which change the properties of the tissues of the cervix).

In addition to the early onset of sexual life, and the number of partners, the other contributing risk factors are; long-term use of hormonal contraception , nutritional status, immune status, smoking, genital infections and BRCA 1 and BRCA 2 mutations.

In the **Czech** population, the incidence of cervical malignancies is **20 cases per 100,000 women per year and the mortality rate is 7 per 100,000**. Only less than 50% of women come to the doctor with operable cancer (most women with cervical cancer do not go for regular check-ups).

HPV 16 and 18 are more frequent and more persistent than other types. The persistence of the virus precedes micro- and macroscopic lesions on the cervix (which in practice means that the HPV test is more sensitive to determining the pathologies present than the cervical smear). Several studies have been performed showing a majority of HPV-HR virus in patients with precancerous or cervical cancer (HPV test negative excludes 99% precancerous and high-grade lesions).

Tab.1: Findings in individual virus strains.

	Condylomata acuminata	CIN 2–3	Invasive cancer
Typ HPV	6, 11	mostly 16 and 18	mostly 16 and 18
Histological finding	koilocytosis, papillomatosis, parakeratosis, absence of atypical mitoses	superficial koilocytosis, intraepithelial hyperplasia , atypical mitoses	stromal infiltration by neoplastic mass
Colposcopic finding	no necrosis or irregular proliferation	anomalies in the transformation zone	atypical vessels, ulceration
Relation to oncouppressor genes	none	rare	constantly - mainly p53 and pRb

Cytological findings and biopsies

Today, the screening of choice is the cervical smear. In the Czech Republic, it is paid once a year for prevention (the frequency of smears in Europe varies - for example, in Finland, it is done every 5 years for over 90% of women, so their incidence of cancer is the lowest in Europe). The target site of the swab is the junctional zone of the epithelium of the uterus and cervix.

The smear of cells from the surface of the cervix and uterus can be sent to the laboratory on a slide (so-called conventional smear) or as a liquid-based cell cytology (the smear is transferred from the brush to a vial with a solution . In the Czech Republic, a conventional smear is used, the liquid-based is used in France, Belgium and Switzerland. The result of the smear roughly corresponds to reality. For conventional smears, the sensitivity is about 70% (for LBC it is 88%), the general specificity of smears is 96%. False positive results are published in 2–8%, false negative results in approx. 5–10%. In case of finding ASCUS or worse (or in case of ambiguity), we perform a biopsy . In France and Belgium, the HPV test is still being used (if negative, the patient is only being monitored).

Tab.2: Relationship between cytological and histological findings:

Cytological results	Definition	Comment	Histological results
Normal		HPV test with normal colposcopy and smear does not make sense.	Maybe a false smear negativity.
ASCUS	Atypical Squamous Cells of Undetermined Significance	30% are HPV-HR positive	10-20% (Joseph Monsonego states up to 55% in his book) CIN 1 5-12% CIN 3 (carcinoma in situ to invasive cancer)
LSIL	Low grade squamous intraepitelial lesions	Highest incidence 25–32 years, overall incidence in the population 2.8% (Brussels 2008)	10% normal (dystrophy only) 70% CIN 1 20% CIN 3 and worse
ASCH	Atypical squamous cells		30 % dystrofie 30% CIN1 40% CIN 2 a 3
HSIL	High grade squamous intraepitelial lesions		4 % dystrofie 4 % CIN 1 92% CIN 2 and 3 (of which 1% already invasive or microinvasive cancer)

Histology (Richart division): CIN 1 (mild dysplasia) / CIN 2 (moderate) / CIN 3 (carcinoma in situ) / invasive carcinoma

Disadvantages of classical screening : The smear reveals 90% of high-grade lesions and 95% of invasive cancers. Therefore, it is suitably supplemented in case of diagnostic doubts by colposcopy (colposcopy is not a screening method). The difficulty of the biopsy lies in the possibility of not revealing the main pathology (there may be a finding of CIN 1 and next to CIN 2 and we will only diagnose CIN 1). However, these shortcomings are not significant and in practice these methods are sufficient.

Clinical manifestations

Patients may not have any problems. The patient's subjective difficulties usually correlate with the severity of the finding.

- Pain (during or after sexual intercourse);

- chronic discharge (there may be many other etiologies or bacterial superinfection , candidiasis), rather white in color
- bleeding outside the menstrual cycle ;
- difficulty urinating (beware of many other etiologies);
- in advanced cases general signs of malignant process - cachexia , fatigue, etc.

Therapy of patients with LSIL, ASCH and HSIL

We send patients for biopsy under colposcopic control (a small incision of the cervical tissue at a sufficient depth, performed on an outpatient basis, de facto painlessly, is possible as part of a routine hospital examination).

According to the results of histology:

- CIN 1 - follow-up with six-month swabs and biopsies, most regressing;
- CIN 2 - is considered a high risk lesion and is treated by excision of the lesion (local antivirals were tested , which had a therapeutic effect, but in addition to excision insufficient), or we can perform an HPV test and in case of negativity only monitor;
- CIN 3 - foci excision (in specific cases extrafascial hysterectomy), regression is in about 30% of cases, others persist or progress;
- Invasive cancer - surgical treatment in the early stages, more advanced - concomitant chemoradiotherapy.

Immunology and vaccination

CD4 + and CD8 + T cells are responsible for the spontaneous regression of HPV lesions. Immunity to HPV-HR and HPV-LR has the same level of efficacy. We can detect CD4 + T cells up to the stage of aggressive lesions. But in general, it is difficult to monitor the immune response.

So far, 14 oncogenic types of HPV have been found. Type 16 is the most oncogenic, followed by types 18, 33 and 45. According to French research, type 16 is found in 35.7% of CIN 3 and type 18 is found in 1.8% of CIN 3 (which implies that vaccination prevention in these patients would help about 40% of them). The proportion of types 6 and 11 in precancerous lesions is de facto zero. In 1.8% CIN 3, the HPV test was negative. Vaccines against types 16 and 18 (Cervarix) or 6, 11, 16 and 18 (Silgard) are available.

It is vaccinated with three doses of recombinant absorbed vaccine : at 1 month and 6 months for the 3rd dose (depending on the country - in Canada the first in about 10 years, the second in 6 months and the third in 5 years). In most European countries considered general prevention and is paid (at least until a certain age) by the state. In the Czech Republic, it was still paid by the patient at the end of 2009.

The general recommendation is to vaccinate girls before the beginning of sexual life (suitable time is around 9-10 years). Vaccination after the beginning of sexual life is also possible. If a woman has a persistent infection, the vaccine will not work.

If a woman is HPV negative (she has not yet become infected or has eliminated the infection), then she has the same "status" as a girl who has not yet started having sex. If a woman is in the phase of elimination (she is infected, but her immune system manages to eliminate the virus), vaccination will be effective in preventing the future infection and help eliminate the current infection.

(note: the last sentence is based on a consultation with HPV expert Prof. Philippe Simon of Hopital Erasme Brussels, although this approach is vague according to the textbook, because persistent infections precede lesions, so colposcopic examination and cytology do not determine whether if the woman is HPV negative or positive and whether it is a eliminating virus or a persistent virus without lesions yet, it can still work in practice)

We can simply divide these patients into groups- we put patients with colposcopically negative findings and negative cytology into the group "uninfected or successfully eliminating" and we can vaccinate them (this is a practice from Brussels, but it would be more accurate to do an HPV test and vaccinate only HPV negative, see note above).

We do not vaccinate patients with any findings (although in North America they also vaccinate as part of the treatment). We treat the lesions and vaccinate only when the findings normalize.

The situation (more precisely, the circumstances during vaccination) vary greatly from country to country. In the Czech Republic, by being reimbursed by the patient, by the fact that many first-line doctors do not have up-to-date information and lack of centralized vaccination (telling when to be vaccinated), general information is a bit chaotic and it is possible to get vaccinated almost anytime. Doctor acknowledges American research or adheres to European research or has a personal relationship with a pharmaceutical company).

The question of vaccinating boys: HPV is also involved in other pathologies - such as papillomatosis of the vocal cords and carcinomatous laryngeal degeneration (very rare), from urology boys are threatened by warts. There are not many rational reasons for vaccinating boys (with the exception of warts) (protection of a partner - anal HPV). Recent US economic calculations have shown that vaccinating boys (as opposed to girls) is uneconomical.

What to tell the patient

HPV causes cancer - all patients know that. However, they usually don't know the difference between the types of lesions, HPV-HR or HPV-LR, and any lesion on the cervix can be frightening. We explain everything to the patient in layman's terms ("LSIL - that's pretty good" is not enough) and assure her that cancer is a rare complication of this infection and has been developing for years (up to decades). We can recommend general advice for increasing immunity (psychologically it can help - the patient does something for herself and is actively involved). And we will prepare for vaccination issues (our and world literature, meta-analytical studies, etc.).

Summary video

Links

External links

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Reference

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Note: *Article consulted in Belgium at the Erasme Hospital in Brussels with Professor Philippe Simon, main information from French literature*
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