

CORRESPONDENCE: LETTERS TO THE EDITOR

THE INCIDENCE OF PENILE CANCER

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Questions:

1. How to explain the fact that genital neoplasms in women (affecting the cervix, vagina or vulva) are much more common (incidence of 25 per 100,000 in Romania compared to 10/100,000 women worldwide, ranking second after breast cancer), while penile cancer is very rare (representing less than 1% of man's malignancies)?

Keywords:

HPV infection, cancer, uterine cervix, penis

Papilloma virus (HPV) infection is involved 100% in the etiology of genital neoplasms in women and, respectively, 40% in the determinism of penis cancer. As HPV infection is a sexually transmitted disease, a higher incidence of penile cancer would be expected.

Infection with genital papilloma viruses correlates with the occurrence of precancerous lesions in the mucosa and skin of the vulva, vagina, cervix, rectum, perineal floor, or, respectively, in men, in the mucosa and skin of the penis, scrotum, anus and perineal floor.

2. The incidence of penile cancer is extremely low compared to cervix cancer. What is the explanation?

Anti-HPV vaccination for the primary prophylaxis of genital cancer in women is addressed not only to girls aged 10-11 years, but in some countries, during the last 2 years, even to boys aged 10-12 years in order to prevent the occurrence of penile cancer.

It should be mentioned that, in Romania, this preventive approach failed, the vaccination rate of the target population being below 3%.

If anti-HPV vaccination were performed optimally, the incidence of cervical cancer could fall below 70%, further reducing the incidence of penile cancer.

It is necessary that pro-vaccination messages in the media (based on the logic of statistics) consistently prevail over anti-vaccination messages, that are based on emotional logic.

ANSWER: ASSOC.PROF. DR. VASILE NIȚESCU

Keywords:

genome, HPV, viral oncoproteins, integrin alpha-6, koilocytes, penis cancer

Molecular biology studies have revealed the causal relationship between HPV infection and the determinism of genital neoplasms in both partners involved in a heterosexual act, the incidence of cervical cancer being significantly higher than that of penile cancer.

HPV strains classified as “low risk” cause genital warts (Fig.1a,b) while those considered as “high risk” are responsible for the squamous epithelial lesions.

Infection of the genitals with high-risk oncogenic strains of HPV is a sexually transmitted disease encountered with high frequency, being demonstrated, in the initial

stage, by the presence of koilocytes on the genital secretion smear.

According to Kjaer and Kyrgioum, in over 70% of patients with cervical cytological lesions, HPV 16 and 18 genotypes were identified, followed, in frequency, by genotypes 33,45,31,51.

According to Munoz and collaborators, quoted by Nițescu V, HPV infection - genotypes 16 and 18 - is responsible for about 65-77% of cases of cervical cancer caused by these viral strains (Fig.2).

The viral load of a cell with the mentioned oncogenic genotypes, respectively non-oncogenic HPV genotypes, in conditions of coinfection with herpes virus or cytomegalovirus, increases the risk of intraepithelial malignancy of the cervix, as evidenced by the sensitivity and specificity of molecular detection methods such as Real Time PCR, Multi-



Fig. 1a



Fig. 1b

Fig. 1a Anogenital warts by infection with HPV genotype 6;
1b Condylomata acuminata positioned beneath the clitoral gland; (5)

plex PCR, “in situ” hybridization techniques or double, simultaneous qualitative detection of p16 and Ki-67 proteins.

The oncoproteins E6 and E7, which are under the control of the protein encoded by the E2 gene, cause, in the infected person, an immune response to the antibodies determined by E6 and E7.

Viral proteins become effective in the genesis of cancerous tissue by blocking the p53 (tumor-suppressor protein) gene, which is responsible for maintaining the integrity of the cell genome, and, abnormally, produce mutations that induce malignant cell formation and growth.

I mention that the alpha-6 integrin of cervical cells is the main receptor for HPV genotype 16, the very cause of clinical forms associated with intraepithelial squamous lesions (pre-malignancy), bowenoid papulosis and invasive cervical cancer.

Adenocarcinomas and adenosquamous carcinomas are usually associated with the HPV genotype 18.

In 90% of cases, according to Giuliano AR et al. (2002), the modifications determined in the cellular structure of the cervix diminish in the next 1-3 years depending on the HPV viral load, by eliminating the virus by the immune system, a phenomenon proven by local gynecological examination and laboratory tests.

Peculiarities of genital infection in women with oncogenic HPV genotypes

In women, HPV infection due to sexual intercourse causes cervical, vulvo-vaginal, perineal, anal and oropharyngeal cancer.

Of the more than 120 genotypes of HPV, the 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 strains have an oncogenic risk, of which genotype 16 is the most difficult to remove (to be cured), (Fig.3).

After contacting any oncogenic HPV genotype, the severity of genital infection may be amplified by the genetic polymorphism, or by the presence of other local infections or comorbidities, or by the pathology of the genital microbiota, or by age over 55 (that decreases immune defense), or by the use of hormonal contraceptives HPV regulatory region), or smoking (suppressing immunity through mutagenic activity of cigarette compounds).

The incidence of cervical cancer is significantly higher than that of penile cancer, sexual intercourse being often performed at a young age, with multiple partners, a context in which a large number of pregnancies and abortions occur.

The HPV inoculation is done directly on the external orifice of the cervix and periorificial, the virus reaching, together with the sperm, on this surface.

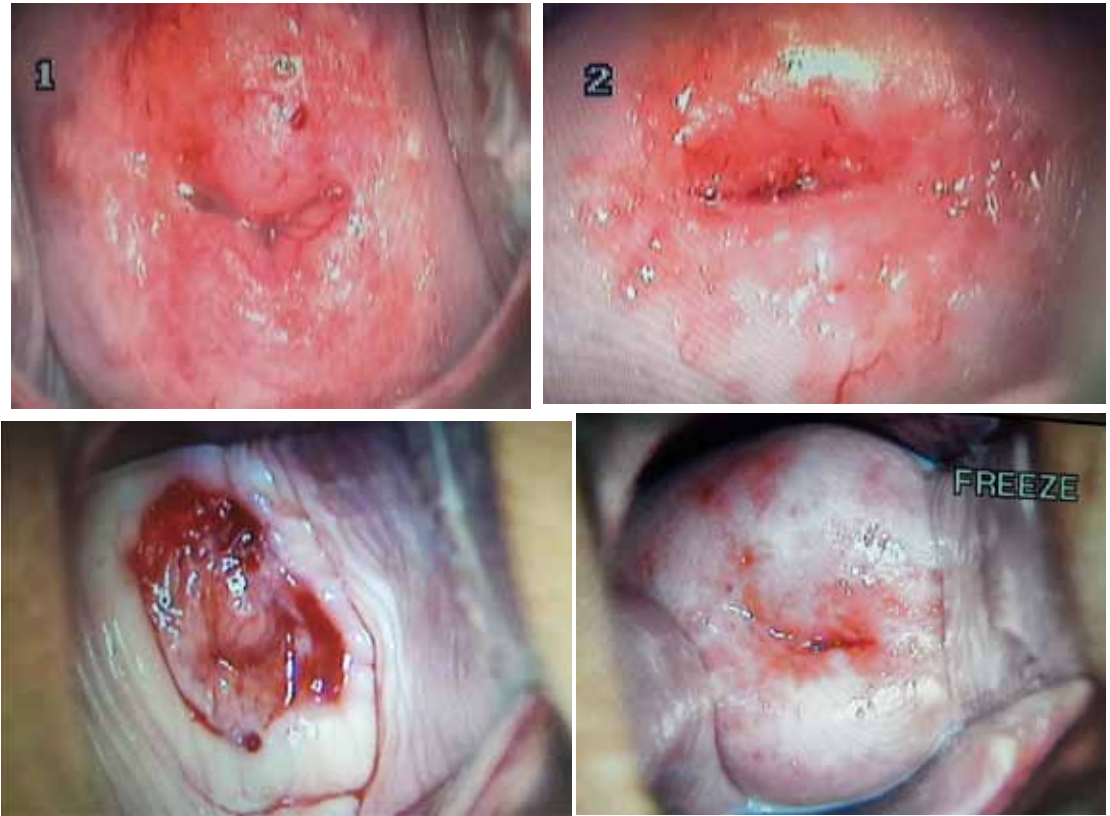


Fig. 2 The appearance of the cervix in HPV infection, various oncogenic strains (from left to right): 18,16, 51 and IS39, 68

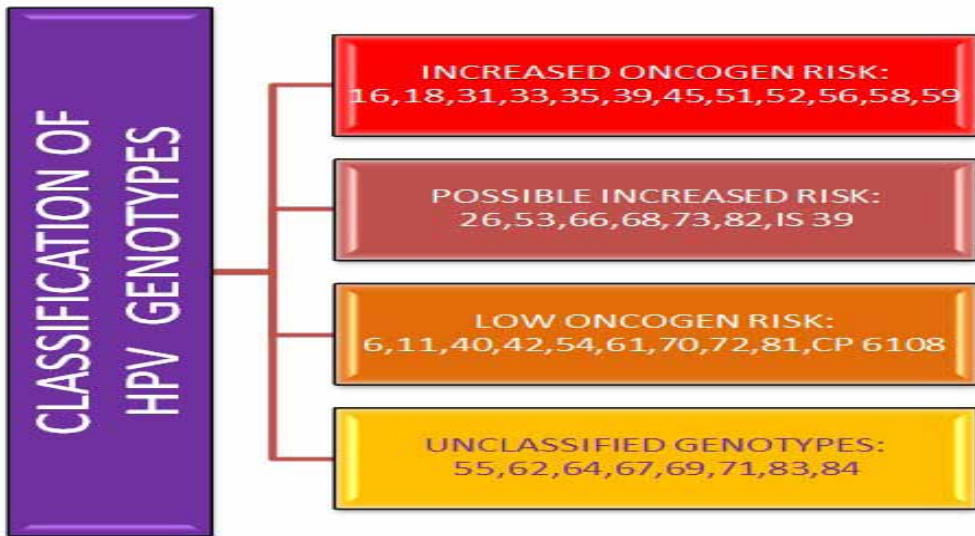


Fig. 3 Classification of HPV strains, adapted after A.Tropé

During intercourse, the contraction of the uterine body eliminates secretions from the cervical canal and performs the aspiration of HPV and sperm fluid from the vagina, which reach, in large quantities, the surface of the cervix. The aspiration of HPV-infected vaginal contents is also done by chemotactism of vaginal discharge.

The forward-backward movement of the uterus, which is fixed between its insertion on the vaginal dome and the elements of suspension and support of the uterus, intensifies local blood circulation, stimulating the cellular receptors located in the cervical transformation area during squamous metaplasia, that is very vulnerable to determination of cervical neoplasms by oncogenic HPV genotypes.

Genital warts are much more common in women, being the consequence of infection with HPV genotypes with low oncogenic risk, in most cases due to genotypes 6 and 11, less often strains 40, 42, 43, 44.

As a clinical practitioner, I observed another peculiarity of HPV infection in a number of 13 pregnant women aged between 17 and 35 years, who presented for the termination of the pregnancy of up to 12 weeks of gestation, patients who were curetted and the genital warts they they had disappeared spontaneously about two weeks after the medical abortion.

This situation can be explained by the pregnancy-associated immunosuppression, which predisposes to easier infection and the persistence of existing infections.

The risk of acuminate warts is 2-3 times higher during pregnancy, in the context of immuno-suppression caused by increased progesterone, which has a cortisone-like action.

During pregnancy, warts appear at the vulvar, perineal and anal level, and may have a cauliflower appearance (Fig.1a), or on the pubic area, of the labia minor and labia major, in the vagina or cervix, some of which may undergo a malignant transformation.

Peculiarities of genital infection in men with oncogenic HPV genotypes

Sexually contracted HPV infection is much rarer in men, a context in which anti-L1-HPV antibodies are also low, compared to women.

The man is an asymptomatic reservoir of the HPV virus, being a donor of this infection to the sexual partner. It is estimated that, in men, 70% of these infections disappear within a year.

The incidence of anal cancer in homosexual men is higher than that of anal cancer in women.

Penile cancer is most often due -in over 60% of cases- to the HPV 16 genotype, followed by genotype 18 -in over 13% of cases.

The prevalence of viral DNA in genital HPV in men varies between 2% and 75%, depending on the site of harvesting and the method of detection (ano-genital, paraurethral, endourethral, balano-preputial, from the lesions or mixed sampling).

Anal cancer is more common in women in heterosexual relationships, but the risk of developing anal cancer is higher in homosexual men, in whom genotype 16 is involved in 60.2% of cases, genotype 18 in 13.3% and genotypes 6 and 11 in 8.13% of patients (Costin Cernescu).

Penile and anal cancers represent less than 0.5% of the locations of malignant disease in men, in male homosexuals being a tendency to increase this percentage.

In men, HPV rarely causes severe conditions. There is no treatment to remove the virus in order to prevent sexual transmission.

The length of the urethra in men is much longer than that of women, a context in which it is an obstacle to the dissemination of HPV infection. The symptoms caused by HPV infection in the glans or urethra are reduced (Fig.4a).

Usually, the man requests a medical consultation when he finds out that his sexual partner is infected with HPV.

The sperm liquid discharge during ejaculation cleanses endourethral impurities, a situation in which the pathology of the penis due to HPV infection is reduced. HPV infection of the external genitalia and of anus is significantly lower than HPV infection of the uterine cervix.

In men, HPV DNA is identified in the lesions of the glans and the body of the penis, respectively in the balano-preputial groove and in the urethra (Fig.4b).

Buletin de rezultate

Nume pacient: [redacted] Prenume pacient: [redacted] Data nasterii: 19/07/1989 CNP: [redacted] Varsta: 31 ani 7 luni Sex: M MRN: [redacted] Adresa: [redacted] Data recoltarii: 22/02/2021 16:40	Contract: CMI "DR. NITESCU VASILE - ORS" Cod de bare: 1004429708 Data inregistrarii: 22/02/2021 Numar cerere: 31021792653 Recoltat: *External Punct de recoltare: Adresa: Data rezultat: 12/03/2021 <small>Valori in afara limitelor admise pentru varsta si sexul respectiv</small>
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Denumire	Rezultat	UM	Interval de referinta
IMD Germania			
14 HPV genotipare - uretra			
Secrete genitale / Multiplicare prin Real time PCR			
ADN - HPV risc crescut	Poativ		Nedetectabil
Comentariu1			
A fost identificat tipul HPV 39			
<small>Au fost testate urmatoarele tipuri HPV cu risc crescut: 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 66, 68, 69, 73, 82</small>			
ADN - HPV risc scazut	Nedetectabil		Nedetectabil
Comentariu2			
<small>Un rezultat nedetectabil indica faptul ca in probe de secrete uretrale nu a fost identificat nici unul din urmatoarele tipuri de HPV cu risc scazut. Testate: 6, 11, 40, 42, 43, 44, 54, 51, 70.</small>			
Medic de laborator			
[redacted]			

14 - Buletin de rezultate de laborator
 Rezultatele se vor interpreta in context clinic de catre medicul trimittator.

Fig. 4a HPV DNA urethra, genotype 39

According to some authors (Cernescu), in men there would be an annual regression of 5% of HPV infection. Studies performed by USA authors have found that HPV infection is much more common in male homosexual partners. According to Auvert, the presence of HPV infection, as well as of other sexually transmitted diseases, is lower in circumcised men.

As in the case of other sexually transmitted diseases, HPV infection is more easily transmitted from male to female sex partners respectively more difficult from woman to man, according to the data mentioned above. In monogamous couples, HPV infection was confirmed in 75% of women and in 20% of men (Cernescu).

Conflict of interest

The authors do not report any conflict of interest.



Fig. 4b HPV genotype 42- associated with herpes lesions

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