THE RELATIONSHIP BETWEEN HUMAN PAPILLOMA VIRUSES AND CERVICAL CARCINOMA

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Abstract. Cervical carcinoma with squamous cells has many of the characteristics of a venereal disease: high incidence (over 500.000 cases every year), an increased frequency for the women with multiple sex partners and the presence of one of the papillomavirus genotypes with a high carcinogenic risk (HPV 16, 18, 31 and 45) in 100% of the cases. **Material and methods.** In the period of time 2001-2012, in the Department of Obstetrics and Gynecology belonging to “Sf. Apostol Andrei” Emergency Hospital in Galaţi, 5047 women were hospitalized under the suspicion of having cervical neoplasia. As part of the screening programme, the women belonging to the high risk group are tested for HPV by using Hybrid Capture 2 (HC2). **Results and discussions.** The seropositive women’s risk of having a persistent HPV infection is 7 times higher than in the case of the seronegative ones, with the same age. This risk is double for the women with CD4 lymphocytes below 200/mmc. Infection with cancer-causing HPV types is limited to the epithelium of the uterine exocervix and it does not spread to other parts of the body. **Conclusions.** Cervical cancer is caused by the oncogenic types of HPV, types 16 and 18 being responsible for over 70% of the cases. It represents the second cause of mortality by cancer for the women between 15 and 44 years old. Anti-HPV vaccination comes as a partner of the screening programmes aiming to reduce the incidence and mortality by cervical cancer.

INTRODUCTION

HPV is an extremely contagious virus and this type of infection is frequently met. There are over 100 strains of HPV, and the infections caused are asymptomatic ones; about 40 strains are sexually transmitted, with tropism for the genital mucosa and they can be classified into two large categories: *oncogenic HPV and HPV with low risk.* Persistent infection with oncogenic types can cause precancerous intraepithelial lesions of high degree, or even cervical cancer, while the types with low risk can cause a number of other benign conditions and warts (8, 9, 12, 13, 14).

According to The Communicable Disease Centre in the United States of America, the risk of getting this kind of infection along their lives is at least 50% for sexually active women and men.

From the over 30 Human Papilloma Virus (HPV) isolated from the genital tract, HPV 16 is responsible for 50% of the cervical cancers, and the other 3 genotypes add up to other 30%. Longitudinal studies have shown that pre-cancerous lesions in cervical cancer are associated with a persistent HPV infection (5, 10, 12, 15).

The mechanism of induced viral transformation is mediated by the early proteins of HPV- E6 and E7. In most cancers HPV genome is integrated in the cellular genome. The integration has the effect of annihilating the viral protein E2 and hyper expressing the oncoproteins E6 and E7. Oncoproteins form complexes with cellular anti-oncoproteins: E6 with p53, and E7 with Rb protein (retinoblastoma) (1, 2, 3, 6, 7, 10, 16, 20).

Viral oncoproteins E6 and E7 of the HPV genotypes with a high carcinogen risk make more effective anti cellular oncoproteins than the proteins of the other HPV genotypes. Antioncoproteines cell inactivation results in disruption of cell division cycle and the occurrence of chromosomal damage, especially on chromosome 3 (6, 17, 18).

The most common lesion is the acquisition of genomic material in the q segment of chromosome 3 and the loss in 3 p. Genes E6 and E7 are situated at the end of the early region of 5' and they are translated from a polycistronic ARNm. The two ORF are spaced by a very short variable distance (2 pb at HPV16 and 8 pb at HPV18). E6 proteins of some HPV with genital location are associated with the tumour suppressor protein p53, inducing its ubicuitin-dependent degradation (and leading to the elimination of cell cycle control p53) or they can repress/activate the transcription from the homologous and heterologous promoters via basal transcriptional initiation complex (1, 2, 3, 6, 7, 10, 16, 17, 18, 20).

Immunology and HPV oncogenes (cancer-causing)

The infection with the HPV types that cause cancer is limited to the epithelium that wraps the cervix and does not spread to other body parts.

Most people that get infected with oncogenic HPV strains do not synthesize effective and protective antibodies that are able to block the infection; generally, a previous infection does not result in immunity against subsequent infections.

A vaccine would boost the immune system to recognize and destroy the virus once it has entered the body, before the settlement of the infection.

Prevention by vaccination, together with screening, is the optimum way of protection for women against cervical cancer (3, 12, 19).

Together with screening, vaccination will ensure a further reduction in the risk of cervical cancer and will significantly reduce the number of abnormal screening results, which requires subsequent follow-up.

The best possible protection against cervical cancer will be obtained through the vaccine that provides the broadest protection against cancer-causing viruses and also the longest duration of protection. Most of the times, cervical cancer is caused by HPV (Human Papilloma Virus). In our country there is a vaccine against it that is produced by Silgard, that had a broad information campaign. This implies the administration of three doses within 6 months. This vaccine should not be given to pregnant women (19).

MATERIALS AND METHODS

In the period of time between 2001-2012, in the Department of Obstetrics and Gynecology belonging to "Sf. Apostol Andrei" Emergency Hospital in Galaţi, there were 5047 women hospitalized under suspicion of having cervical neoplasia, with a peak frequency in 2007 and also with a slightly increasing tendency after this year.
The frequency of genital inflammatory diseases is high (12.9%) and it exposes the population in this area to an increased risk of getting cervical cancer.
In the program of screening women over 30 in the high-risk group are HPV tested using Hybrid Capture 2 (HC2). The women who were HPV negative after a Pap smear normal test were retested in 5 years.
The women who were HPV positive and had a modified Pap smear test (II, III, IV, V) were subjected to colposcopic examination. The women who were HPV positive with a normal Pap smear test repeated this test after 6 months and the HC2 test after 12 months.
The women who were HPV negative and had a modified Pap smear test, repeated this test after 3 months and they were also subjected to colposcopic examination if the Pap smear test remained modified for more than 9 months or if the patient showed signs of Cervical Intraepitelial Neoplasia (CIN).
HPV testing must be performed with a test that is clinically validated in order to make sure of the results objectivity and their reproducibility. We practiced HPV typing for the types 16, 18 and 45.

RESULTS AND DISCUSSIONS

HPV infection was present in 7,1% of the patients in the study lot with a relative risk 4.58 ori higher for the patients under 45 years old, 2.73 times higher for the patients who come from the urban area and 5,53 times higher for the patients who are not married. The risk of transmitting the infection is higher in the case of the people with multiple sexual partners (RR=4.31). The cumulative risk in HPV infection on age groups shows the predominance of the patients aged between 15 and 19 (17.6 $^{o}/_{oo}$) (fig. 1).

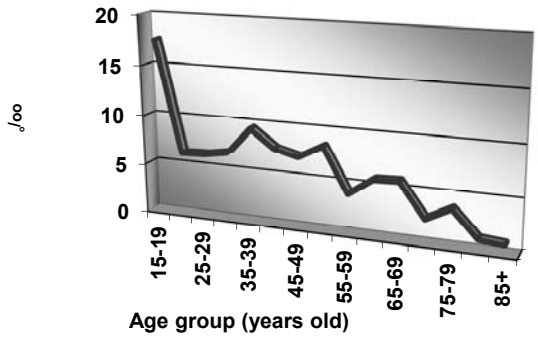

Fig. 1. Cumulative risk on age groups in HPV infection

Increasing cumulative prevalence is faster in women with advanced immunosuppression. HIV-positive women have a 7 times higher risk of having a persistent HPV infection than seronegative women of the same age. This risk doubles for the women with CD4 lymphocytes below 200/mmc.

Biochemical parameters investigated show average values of hemoglobin below 8 mg/dl, average values of leukocytes well above normal values (10,700/mmc) and increased VSH (>21 mm/1h).
HPV infections were also involved in other anogenital cancers.
The most frequent locations were the vulva, vagina, perineum, anus, penis; among these locations, vulvar squamous cell carcinoma is rare and often not associated with persistent infection.
Even if the etiological role is not unanimously recognized, there are over 20 types of papilloma viruses (HPV) that are associated with cervical cancer. The role of the viral agents continues to be controversial (4, 5, 8, 10, 12, 15). Based on epidemiological, clinical and laboratory evidence, it was found that there is a direct causal link between human papillomaviruses (HPV) and cervical cancer. It was proven that the DNA belonging to the oncogenic types of HPV is present in 99.7% of the tissue samples harvested from the malignant cervical tumours, all over the world. Actually, the infection with oncogenic HPV is “the necessary cause” of cervical cancer (5, 8, 13, 15, 17).

HPV transmission mechanism

It is notable that that most people are unaware of the infection and can spread the virus through:

a) sexual contact:

- sexual intercourse;
- genital-genital, manual-genital, oral-genital;
- HPV infection is rare among the virgins, but it can result from non-penetrative sexual contact;
- the proper use of condoms reduces the risk, but it does not provide complete protection against the infection.

b) non-sexual ways:

- mother-newborn (vertical transmission);
- iatrogenic (for example surgical gloves, instruments used for biopsy), hypothetical mechanism, not enough documented (seems rather rare).

Although most infections are eliminated by using their immunity infected individuals are unaware of the presence of HPV and can spread the virus.
When the patient’s own immune system cannot eliminate the infection, the persistence of the viral oncogenic strains in the cervical mucosa can lead to the appearance of the pre-cancer lesions.
The maximum risk of getting an HPV infection is recorded for the age group 15-19 years old.
Cervical cancer is caused by the oncogenic types of HPV, types 16 and 18 being responsible for over 70% of the cases.
This is the second cause of death by cancer for the women between 15 and 44 years old.
Unfortunately, Romania ranks first in Europe in terms of mortality from cervical cancer.
Anti-HPV vaccination comes as a partner of the screening programmes because it reduces the incidence and mortality from cervical cancer.

The current approach to preventing HPV infection:

- total abstinence from any genital contact is the most efficient method of preventing the HPV infection (practically unfeasible);
- mutual monogamy throughout a person’s life; still, if one of the partners was not monogamous, they are both subject to risk;

- condom use can reduce the risk, but does not provide complete protection;
- the risk of HPV infection is reduced in circumcised men (arguably).

The analysis of the samples taken from 932 women from 22 countries indicates a prevalence of 99.7% of HPV DNA in cervical cancer worldwide. Tissue samples were tested for DNA -HPV through 3 PCR tests, and the presence of the malignant cells was confirmed on adjacent tissue sections (7, 10, 14).

HPV groups with oncogenic potential:

- low oncogenic potential - types 6, 11, 41, 42, 43, 44;
- high oncogenic potential - types 16, 18, 45, 56;
- intermediary oncogenic potential - types 31, 33, 35, 51, 52.

Here are the factors that can reduce HPV exposure to the immune system:

- there is no blood stage of the infection (without viraemia);
- late and limited expression of the viral capsid proteins;
- HPV did not lyse keratinocytes (so there is no pro-inflammatory cytokine release and the tissue destruction caused by HPV is low);
- E6 and E7 suppresses the activation of the interferon required for the cellular immune response;
- there is no activation of the antigen producing cells (APCs).

The detectable serum antibodies for HPV are not a reliable marker for the infection and natural immunity because:

- the response in antibodies to HPV infection is weak and slow:
  - for the 588 women infected with HPV 16, 18 and 6, the average time of seroconversion was about 12 months after the moment they got infected;
  - it did not appear for all the women;
  - only 54-69% showed seroconversion in the first 18 months since getting infected.
- the immune response varies according to the HPV type;
- the levels of antibodies are inconstant for the patients with cervical cancer.

Most HPV infections heal with the body's natural cellular immune response.

CONCLUSIONS

The lifelong risk of HPV infection is at least 50% for the people who are sexually active.

Although most infections are eliminated thanks to people's own immunity, the infected people are not aware of the presence of HPV and they can spread the virus.

When immune system cannot eliminate the infection, the persistence of the viral oncogenic strains in the cervical mucosa can lead to pre-cancer lesions.

The maximum risk of HPV infection is in the age group 15-19 years old.

Cervical cancer is caused by the oncogenic types of HPV, types 16 and 18 being responsible for over 70% of the cases.

It represents the second cause of mortality by cancer for the women between 15 and 44 years old.

Unfortunately, Romania ranks first in Europe in terms of mortality by cervical cancer.

Anti-HPV vaccination comes as a partner of the screening programmes aiming to reduce the incidence and mortality by cervical cancer.

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