

INFECTION WITH HUMAN PAPILLOMA VIRUS IN CERVICAL NEOPLASIA

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Abstract: The purpose of this study was to establish if the infection with human papilloma virus (HPV) presents a potential irreversible evolution towards malignancy. Materials and methods. The study was made on a number of 1885 patients that were suspected to have cervical neoplasia, which were monitored between 2001-2010 in „Elena-Doamna” Clinical Hospital of Obstetrics and Gynecology in Iași, the Military Hospital Galați, the County Hospital Galați and the Emergency Hospital Buzau. Results and discussions. The study proved that the risk of contacting a genital infection with HPV and cervical cancer is influenced by the sexual activity, the risk of getting infected with HPV during a person’s lifetime is at least 50% for those sexually active. Conclusions. The patients benefited from colposcopy and biopsy only if the repeated cytology suggested more severe changes. The conservative conduct is represented by a repeated cytology when the patients are admitted into the lot (the initial cytology is performed before this moment).

INTRODUCTION

There have been 35 types of HPV described for humans, classified according to the sequence of the nucleotides from the viral ADN by using methods of recombining them (Southern Blot Hybridisation) (10). Types 16, 18, 31 and 35 are oncogenic. About 1-2% of the women who are sexually active have a HPV cervical infection (Bernstein, 1985).

Branca (1995) correlates the risk degree of HPV cervicitis with the association with HIV (Human immunodeficiency virus); 47% of the women who are HIV positive had HPV lesions at their colposcopic and/or cytologic examination, and for 40% of them there was some form of CIN (cervical intraepithelial neoplasia): CIN I, CIN II and CIN III; 37% of the cases with CIN I and CIN II developed rapidly towards CIN III. In the cases with negative HIV only 23% had HPV lesions, and 26% of these cases were associated with CIN I, CIN II or CIN III; only one case had a fast development (after a year) from CIN I to CIN III.

Remmink (1995) monitored a group of women for 3-4 months by cervical cytology, colposcopy and HPV tests. The cases that had progressive lesions of CIN were always positive for HPV, and the biopsy confirmed the stage of CIN III. The author thinks that the effect of HPV on the progression of CIN type lesions is also increased by other risk factors (age, number of sexual partners, smoking, etc.).

The present stage of the research creates premises for selecting the cases of CIN with an irreversible evolutionary potential towards malignancy separately from those with a benign evolution. The infections with oncogene types (16, 18, 31, 35) would require a more aggressive treatment with the purpose of blocking the progression towards CIN types with high malignancy (1, 10).

The literature of speciality underlines the fact that the risk of getting an HPV genital infection and cervical cancer is influenced by the sexual activity, the risk of infection with HPV during a lifetime for people who are sexually active being of at least 50% (1, 7). Although most infections are eliminated by their own immunity, the infected people are not aware of the HPV presence and they can spread the virus. HPV is transmitted through direct contact between tegument - mucous. That is why this infection can occur in the case of virgins with sexual exposure, too. The infection can also be transmitted in other ways than sexually, for example by fomites (8).

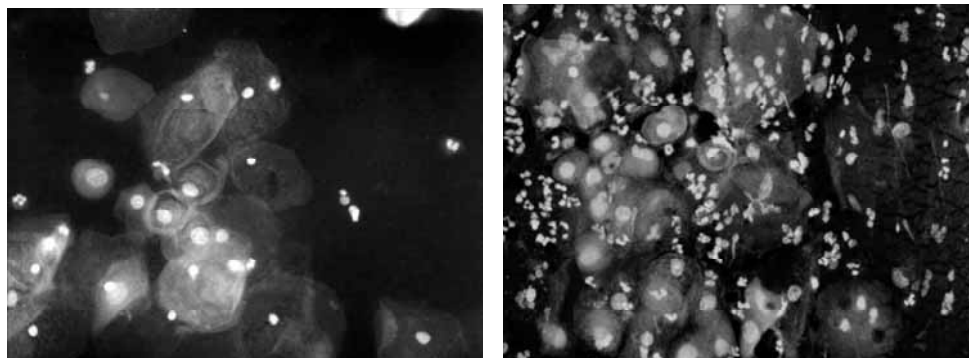
The phenotypic expression of HPV infection depends on 3 factors:

1. types of virus – the simple presence of an infection with oncogene types does not mean. For a woman to develop cervical cancer some other additional factors need to act together.
2. local factors of environment
 - a. exposure of basal and parabasal cells to the virus
 - b. trauma

In the case of immuno-depressed patients (kidney transplant, HIV, treatment with cortisone) the probability of developing a persistent infection and a cancer respectively is higher.

3. the immune response of the host – the immune system
The primary immune response of the host has a decisive importance in the evolution of infection. In the case of HPV infection we are talking about cellular immunity; the immunity of the host being the one that is able to eliminate most infections. When a person’s own immune system is not able to eliminate the

infection, the persistence of the viral oncogenic strains in the cervical mucus can lead to the appearance of pre-cancerous lesions.



**Figure 1. LSIL - Low grade squamous intraepithelial lesion with cytopathic effect HPV
(col. Pap x 20)**

The Collection in the Pathologic Anatomy Lab
“Elena Doamna” Clinical Hospital of Obstetrics Gynaecology Iasi

There are many types of HPV infection:

1. latent forms in the inferior genital tract without any clinical or colposcopic manifestations;
2. subclincic forms: abnormal smears, colposcopic lesions, histopathologic lesions revealed in biopsy;
3. clinical forms: ano-genital warts (acuminate).

THE PURPOSE OF THE STUDY

The purpose of this study was to establish if the infection with human papilloma virus (HPV) has a potential irreversible evolution towards malignancy.

MATERIAL AND METHODS

During 2001–2010, 1885 women were investigated through specific examinations for suspicion of cervical neoplasia.

The data of the present study come from a thorough analysis of the case files or the observation sheets of the patients diagnosed with such a pathology, where we focused on/researched the following aspects according to a previously established protocol:

- epidemiologic (the distribution of cases on years of study, age groups, sex, area of residence, combination of co-morbidities, HPV infection);
- addressability to a doctor. analysis of statistical indicators in Family planning offices in Iasi, Galați and Buzău;
- establishing the profile of the patient with pre-invasive cervical lesions;
- possibilities of detecting the pre-invasive lesions of the cervix by cytology, colposcopy, biopsy;
- therapeutic possibilities (prophylactic and curative conduct);
- clinical-progressive manifestations;
- studying the prognostic factors.

RESULTS AND DISCUSSIONS

According to the cases we studied, the HPV infection was present in 7,1% of the patients in the present group that is studied.

In terms of epidemiological characteristics sought we ascertained the following aspects (fig. 2):

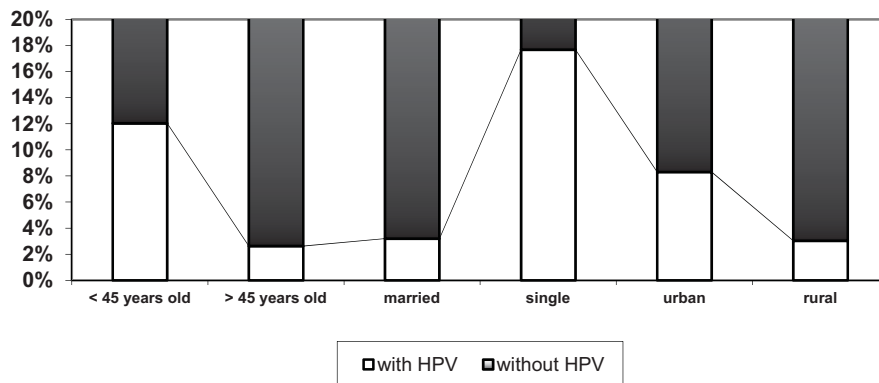


Figure 2. The distribution of the patients in the group that is studied with HPV according to the epidemiologic characteristics

- HPV is present with a predictive positive value of 80,6% for the patients under 45 years old, for whom it represents a risk that is relatively 4,58 times higher than for the patients over 45 (RR=4,58; IC95%: 3,01÷6,95);
- For the single patients the predictive positive value of HPV presence is of 67,2%, with a relative risk 5,53 times higher when compared with married patients (RR=5,53; IC95%: 3,91÷7,81);
- The patients coming from towns or cities have a positive predictive value of the HPV presence of 90,3%, with a relative risk 2,73 times higher than for the patients coming from the rural area (RR=2,73; IC95%: 1,56÷4,80).

Table I. The distribution of cases according to the vaginal examination with valves

Vaginal examination with valves (VEV)	
This type of examination was performed to all the patients in the group studied.	
>	Soft parts:
	▪ episiotomy – 1617 cases (85,8%);
>	vagina:
	▪ condiloma/warts – 145 cases(7,7%)
	▪ cystorectocele – 397cases (21,1%)
	▪ vaginitis – 1521 cases (80,7%)
	▪ stenosis – 1 case (0,05%)
>	cervix:
	▪ multiparous cervix – 481 patients (25,5%)
	▪ nulliparous cervix – 127 patients(6,7%)
	▪ chronic cervicitis – 378 cases (20,1%)
	▪ bleeding exo-cervicitis – 366 cases (19,4%)
>	discharge/secretion:
	▪ purulent – 175 cases (9,3%);
	▪ serosanguineous – 69 cases (3,7%).

Table II. Distribution of cases according to the digital vaginal examination

Digital vaginal examination (DVE)	
The digital vaginal examination is recommended to be used cautiously for the patients who are bleeding, and that is why this kind of examination was only performed to 1282 patients (68%), with the following results:	
➤ uterine body:	
▪	fibroid uterus – 300 cases (15,9%);
➤ cervix	
▪	multiparous cervix – 481 cases (25,5%)
➤ vagina	
▪	cistorectocele – 397 cases (21,1%)
➤ annexes	
▪	normal – 102 cases (5,4%)

As an immediate result of realizing the gravity of the illness and the long term consequences that are caused by cervical neoplasia following the screening performed (2, 3, 4, 11), during 2010 – 2011 274 people accepted having a vaccine (14,5%), as it follows:

- 224 with Silgard vaccine
- 50 with Cervarix vaccine

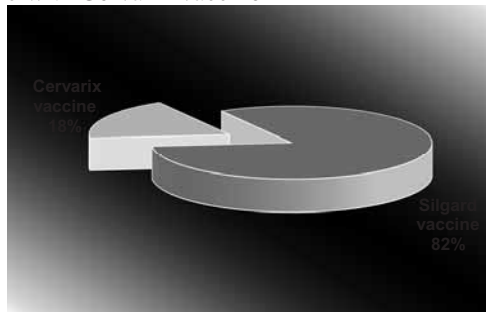


Figure 3. The distribution of patients who accepted vaccination according to the type of the vaccine

The distribution of the vaccinated patients on age groups showed the maximum frequency for the group between 31-35 years old:

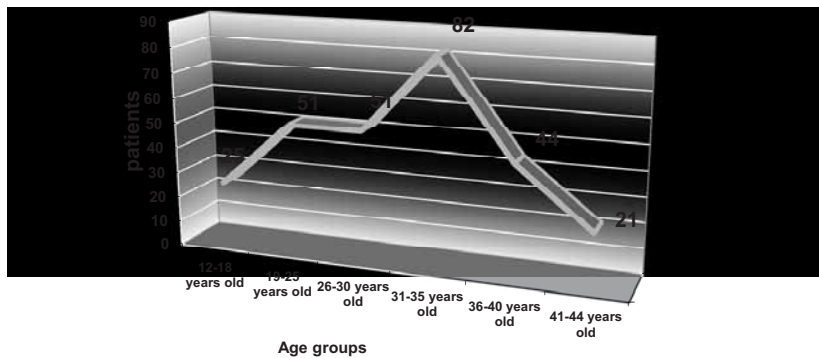


Figure 4. The distribution of vaccinated patients on age groups

There were 35 people from the rural area (12,8%) significantly less than those coming from the urban area (87,2%) ($p=0,00003$), and 152 people were married (55,5%), a significantly increased share when compared with those who are not married ($p<0,001$).

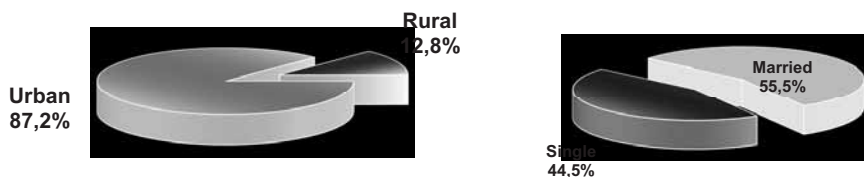


Figure 5. Distribution of vaccinated patients according to their area of origin and marital status

In simple words, the lesions with a low degree are transitory HPV infections that can cause certain cellular changes, but which in most cases disappear spontaneously. Sometimes the HPV infection persists and generates more cellular and tissular abnormalities, which are the high degree lesions. Their presence shows that there was no spontaneous disappearing of the viral infection and hence these lesions must be recognized and treated in order to stop the possibility of developing a cervical cancer (2, 3, 5, 6).

If there is no lesion present, we recommend, if this is possible, to review all the cytologic, colposcopic and eventually histopathologic evaluations made (1, 2, 9).

The patients with ASCUS (Atypical squamous cells of undetermined significance) cytology, who are in the post menopause period, can repeat the cytology at about a week after they have followed local estrogenic treatment. If the patients show clinical or cytological signs of atrophy and do not have any restrictions/contraindications they will use estrogenotherapy. In this case, the clinician can meet the following situations:

- the repeated cytology is negative for a malignant intraepithelial lesion – it is recommended to repeat the cytology every 4-6 months; after 2 negative cytologies the patient will enter a programme of routine screening;
- one of the repeated cytologies is ASCUS type or even more significant than that – colposcopy is recommended here.

For the patients with ASCUS type cytology and also with immunodepressive syndrome, no matter what the viral charge is, antiviral associated therapy is the recommended attitude, followed by an immediate colposcopy.

According to Bethesda 2001 indications regarding clinical conduct, we recommend specifically to investigate ASCH type cytology (Atypical squamous cells - cannot exclude) identical with H-SIL (High grade squamous intraepithelial lesion) smears. However, when the patients with ASCH have a negative histology which does not confirm the existence of the intraepithelial lesion cytologically suspected (because of the equivocal nature of the category ASCH), the doctor must re-assess the colposcopic and histologic aspects (3) before moving on to a more aggressive treatment (electro-surgical procedure of excision).

When facing a cytologic result - type ASCH the recommended conduct is to send it for a colposcopic assessment immediately, no matter if the doctor uses the conventional technique or cytology in a liquid environment.

If the presence of a CIN is confirmed by biopsy, the therapeutic procedure about to be applied will be established according to the severity of the intraepithelial lesion.

If the pluri-disciplinary re-assessment of the case leads to different interpretations, the conduct must change depending on these results.

If the interpretation of the cytologic smear is H-SIL type again, or in the case when it is not possible to re-assess the smear, it is better to choose an excisional diagnosis procedure, especially for the patients who are not pregnant.

The omission of sampling for assessing the endo-cervix is acceptable when it is intended to use an excisional diagnosis procedure immediately.

For women with H-SIL, where the colposcopy suggests a lesion of high degree, the initial assessment made using an excisional diagnosis procedure is also acceptable (British version „*see & treat*” - treatment at first consult following an abnormal cytology) (5).

The sorting that uses either the repeating of the cytology or ADN-HPV determination is not acceptable. The exception to these recommendations are the young patients, of reproductive age (with a satisfactory colposcopy, without the confirmation of a high degree CIN by biopsy and with a negative endocervix assessment), who accept and take the risk of having an occult lesion present that can be supervised for 1 year by colposcopy doubled by cytology repeated every 4-6 months (8, 12).

The excisional diagnosis procedure is recommended if, during one of the examinations, the colposcopy shows a lesion which progresses towards a suggestive aspect of high degree lesion or if the cytology continues to be H-SIL type.

CONCLUSIONS

HPV represents a relative risk 3 times bigger for women under 45 years old, single, coming from the urban area.

The patients benefited from colposcopy and biopsy only if the repeated cytology suggested more severe changes. The conservative conduct is represented by performing a new cytology when accepting the patients in the group (the initial cytology is performed before this moment).

HPV sorting was used in association with a cytologic result, in order to appreciate its effectiveness in selecting the patients with ASCUS, who need colposcopy.

If the cytology showed more severe changes and if the presence of HPV with a high oncogenic risk was proven, the patients were sent to have a colposcopy.

During 2010-2011, following the screening performed, as an immediate result of the fact that people realized the seriousness of this illness and the long term consequences caused by the cervical neoplasia, 274 people accepted vaccination (14,5%).

Considering the scientific evidence concerning HPV infection, the international practice guides and the situation of the morbidity and mortality by cervical cancer in Romania, an ideal screening should cover all women, after a maximum of 3 years after the moment they start their sexual life.

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