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The role of HPV in the development of cervical intraepithelial neoplasia and cervical cancer

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Abstract: Despite impressive achievements in the field of molecular biology, which made it possible to reveal the main mechanisms and stages of carcinogenesis and to significantly improve the capabilities of instrumental diagnostics, every year there is a disappointing trend in the world towards an increase in the number of patients with oncological diseases.

Keywords: Oncological diseases, stages of carcinogenesis.

Introduction: Despite impressive achievements in the field of molecular biology, which made it possible to reveal the main mechanisms and stages of carcinogenesis and to significantly improve the capabilities of instrumental diagnostics, every year there is a disappointing trend in the world towards an increase in the number of patients with oncological diseases.

According to the World Health Organization (WHO), the average annual increase in human papillomavirus infection exceeds 2.5-3 million, the frequency of asymptomatic virus carriage in the world is high and amounts to 15.5% in Russia; in the USA - 28.6%; in Europe - 2-12%. HPV-associated cervical cancer is the third most common cancer among women in the world, with -70% of cases due to infection with HPV types 16 and 18. Compared to other gynecological diseases, cervical cancer is more common in young women, with an average age of about 49 years. Over the past 50 years, the introduction of "... Pap smear testing and HPV vaccination in developed countries has reduced morbidity and mortality by 75% ...". Despite widely implemented prevention programs, the prevalence of cervical cancer continues to remain high.

Cervical cancer is a dangerous disease, the second most common type of cancer among women in Uzbekistan. In 2021, 1,827 new cases were identified, 997 women died. Morbidity and mortality are steadily increasing, and cervical cancer is projected to cause 2,100 new cases and 1,300 deaths per year by 2030. [1].

In Karakalpakstan, the incidence of cervical cancer ranks second after breast cancer among the female population. A malignant tumor of the cervix in 2020 claimed the life of 71 women in Karakalpakstan.

Despite the widespread use in clinical practice of various destructive and excisional methods of treatment of cervical intraepithelial neoplasia (CIN) and carcinoma in situ, a number of patients subsequently revealed the persistence of human papillomavirus (HPV) of high carcinogenic risk, which contributes to the recurrence of the disease and repeated surgical interventions on the cervix [9; 10].

In order to accurately diagnose the severity of CIN, assess the prognosis of the course of small forms of cervical lesions, and select the most optimal management tactics for patients, it is necessary to search for effective biomarkers with high diagnostic and prognostic significance.

Currently, the human genome and transcriptome are widely studied to search for biomarkers of CIN and PCM [2;3].

The purpose of the study

To develop differentiated approaches to the management of patients with cervical intraepithelial neoplasia of varying severity based on the study of clinical, morphological methods.

METHODS

According to the inclusion and exclusion criteria, 110 patients were recruited into a single-stage prospective

cohort study. Depending on the results of histological examination of cervical biopsies, 4 groups were formed: chronic cervicitis in combination with HPV infection (n=30), LSIL (n=30), HSIL (n=30) and cervical cancer (n=20).

Research methods

Mandatory research methods:

1. A clinical study that includes the collection of complaints, anamnesis, assessment of reproductive function and risk factors for HPV-associated cervical diseases, general examination and gynecological examination, calculation of body mass index (BMI), examination and palpation of the mammary glands.

2. Cytological method (liquid cytology).

3. Molecular genetic methods (genotyping of 21 HPV types with determination of viral load by real-time PCR).

4. Advanced colposcopy.

Table 1

Classification of HPV depending on oncogenicity (IARC, 2003)

The degree of oncogenicity of HPV	Type of HPV
Highly oncogenic	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Low-oncogenic	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81
Medium oncogenic	26, 53, 66

In 2012, the IARC identified 3 groups of oncogenic HPV: group 1 - high carcinogenic risk, group 2 A - probable carcinogenic risk, group 2B - possible carcinogenic risk (Table 2).

It is known that the human papillomavirus plays a key role in the development of breast cancer. In 2008, German physician and scientist Harald zur Hausen was awarded the Nobel Prize in Physiology or Medicine for his study of HPV and its role in the pathogenesis of breast cancer.

Carcinogenic risk groups depending on the type of HPV (IARC, 2012)

Carcinogenic risk group	Type of HPV
1	HPV 16, HPV 18, HPV 31, HPV 33, PO 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58 and HPV 59
2A	HPV 68
2B	P 26, PCH 30, PCH 34, PCH 53, PCH 66, PCH 67, PCH 69, PCH 70, PCH 73, PCH 82, HPV 85, HPV 97

In August 2020, the World Health Assembly adopted the Global Strategy for cervical cancer elimination. The WHO has set up global 90-70-90 targets to be reached by 2030: 90% of girls fully vaccinated with the human papillomavirus (HPV) vaccine by age 15; 70% of women are screened by 35, and again by 45 years of age; and 90% of women identified with cervical disease receive treatment.

Cervical endometriosis (Figure 1) was detected in 12% of cases. Cervical endometriosis was most often found in patients who underwent knife conization, DEC and CO2 laser vaporization of the cervix - 23%. Less often, endometriosis was detected after the use of radio wave treatment (19%) and cryodestruction of the cervix (12%).

The results of a retrospective analysis showed that in 30% of women, after excision and/or destructive treatment of the cervix, pregnancy was complicated by ICN, in connection with which such patients had stitches on the cervix (67%), obstetric pessaries were also used (33%). An analysis of the obstetric history showed that premature birth was observed in 15% of pregnant women who underwent cervical surgery, and most often they were operative (cesarean section in 60% of cases). A case of very early premature birth at the age of 27 weeks of pregnancy in a patient 4 years after cervical electroconization for HSIL deserves attention. As a result of this complication, the patient had a child with cerebral palsy (cerebral palsy).

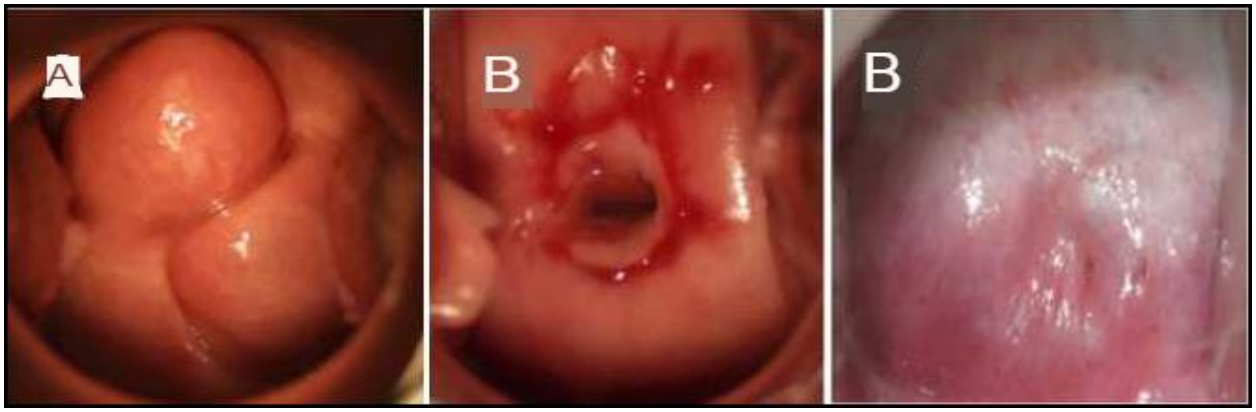

Figure 1. Consequences of surgical treatment of the cervix:

A) scarring of the cervix, B) endometriosis of the cervix, C) complete stenosis of the external pharynx of the cervix

68% of excisional and destructive interventions on the cervix were performed outside the Republican Specialized Scientific and practical Medical Center of Oncology and Radiology. It should be noted that before surgical treatment of the cervix, as well as in the process of monitoring its condition after treatment outside the walls of the Republican Specialized Scientific and practical Medical Center of Oncology and RadiologyAGP, most patients were not typed for HPV, therefore it is not possible to assess the persistence of a certain type of HPV or reinfection with other types in these patients. According to the results of HPV testing, HPV infection was detected in almost half (48%) of the patients. Of these, HPV BP was detected in 96% of cases. The most common type of HPV was type 16 (33%). Then we met 33 (7%), 52 (7%), 56 (7%), 59 (7%) types of HPV. 35 and 39 HPV types were detected with a frequency of 6% each. HPV 31, 44(55), 45, 51, 58 The types were identified with the same frequency - 4%. There were also 68 (3%) and 18 (3%) HPV types in patients with HPV infection. Type 82 HPV was detected in 1% of patients with HPV infection (Figure 10). From a cytological point of view, chronic cervicitis consists of cells of flat, cylindrical and metaplastic epithelium, elements of chronic inflammation (lymphocytes, histiocytes, cells of the plasma and fibroblastic series), non-specific signs such as acanthosis, hyper- and parakeratosis were often noted (Figure 2).

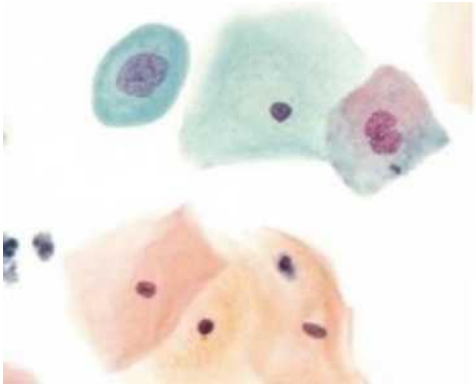

Figure 2. Cytological picture of chronic cervicitis in combination with HPV infection

The cytological picture in ASCUS was characterized by the presence of single squamous epithelial cells with signs of atypia, the interpretation of which caused difficulty. Coilocytes were often found - cells of the intermediate layer with enlarged nuclei, an uneven membrane and hyperchromia, with the presence of an extensive perinuclear zone of enlightenment, clearly delimited from the peripheral parts of the cytoplasm, which were stained more evenly and intensively. The perinuclear zone of enlightenment is the result of degenerative changes, necrosis of the cytoplasm, which begins with the nucleus with a gradual spread to the periphery.

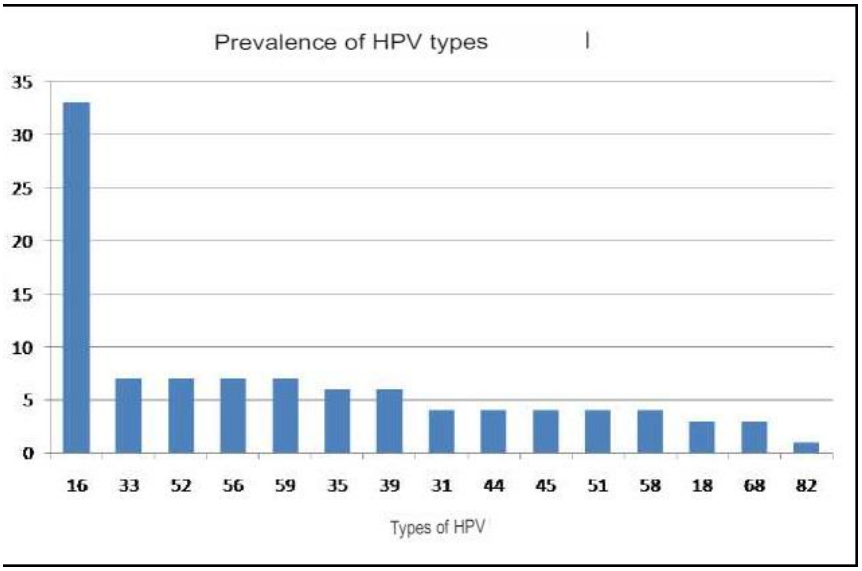

Figure 3. The prevalence of various types of HPV in patients with a history of cervical surgery

CONCLUSION

Thus, the presence of relapses of SIL and breast cancer (22%) indicates the use of excessively gentle, non-excisional HSIL treatment methods with the lack of adequate colposcopic control, as well as the subsequent persistence of HPV BP, the timely diagnosis of which was not given sufficient attention. The results of simultaneous HPV testing revealed a high incidence of HPV infection (48%), including HPV BP 96% in patients who had previously undergone destructive and excisional interventions on the cervix for precancerous and malignant diseases. Thus, HPV testing is advisable to use in addition to annual cytological screening in patients who have undergone cervical surgery to identify risk groups for the development of HSIL and breast cancer relapses.

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