

EARLY DIAGNOSIS OF HPV-ASSOCIATED CERVICAL CANCER AND  
PRECANCER IN WOMEN AGED 30 AND OLDER

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**Relevance.** The study showed that carcinogenesis and morphogenesis of HPV-associated squamous cell carcinoma of the cervix is a multistage process that is associated with the sequential development of structural changes characterized by the formation of Oct4-positive reparative, neoplastic and cancerous SEMS.

**Keywords:** human papillomavirus, cervical cancer, cervical intraepithelial neoplasia.

**Abstract.** Long-term studies have established that the human papillomavirus (HPV), which belongs to the papovaviridae family and has a tropism for stratified squamous epithelium, plays a significant role in the etiology of cervical precancer and cancer [2,5]. Most scientists believe that during HPV infection, the viral oncoproteins E6 and E7 lead to genetic instability and epigenetic abnormalities in infected cells, which triggers the process of carcinogenesis and the development of cervical cancer [1,2,4,6]. HPV has been detected in almost 99.8% of cases of invasive cervical carcinoma and in more than 60% of cases of cervical intraepithelial neoplasia [1,3,7]. The period from the primary viral infection to the development of cervical cancer is quite long – 5-10 years, therefore, cervical cancer prevention can be carried out not only by preventing HPV infection (vaccination), but also by early diagnosis of precancerous processes and systemic screening. In those countries where vaccination is carried out, where the quality and prevalence of screening is high, a 90% decrease in the incidence of invasive cervical cancer is noted [2,8,9]. To date, questions about the frequency of screening, the use of markers and methods for diagnosing cervical cancer, especially in the case of transient infection, remain open. The American Society for Colposcopy and Cervical Pathology recommends starting the cervical cancer screening program for women from the age of 21. In Denmark, the age at which screening for cervical cancer begins is 23 years, in France – 25 years, in Finland – 30 years. The issue of the specifics of cervical cancer screening in women under 30 and over 30 years of age remains controversial. To conduct an effective screening test and early diagnosis of cervical cancer, it is necessary to find methods with high specificity and sensitivity. In countries with organized cervical cancer screening based on cytological examination, a decrease in morbidity and mortality from cervical cancer has been shown [2,10]. Cytological examination reveals a large number of patients with L-SIL with ASC-US (squamous epithelial cells with atypia of unknown genesis), L-SIL (low-grade squamous intraepithelial lesions) with a relatively low risk of developing cervical cancer. Detection of H-SIL (high-grade squamous intraepithelial lesions) in patients requires further examination [1,11,12]. It has been established that immunohistochemical (ICC) and immunocytochemical (ICC) studies using double antibodies to p16/Ki67 play an important role in the differential diagnosis of these changes. HPV testing has proven effective in screening women with ASC-US and L-SIL. However, it has been found that HPV infection is unstable in most women under 30 [3,13,14], limiting its use as a primary method for detecting precancerous changes in the cervix. Cervical cancer carcinogenesis is currently understood in terms of the formation of cancer stem cells (CSCs) and spheroid epithelial-mesenchymal structures (SEMS) in tissue.

Study objective: To evaluate the effectiveness of cytological, immunocytochemical, and HPV testing for detecting cervical precancer and cancer in the presence of HPV infection.

Study material and method. All 201 women were examined according to a generally accepted protocol: clinical examination, collection of smears in SurePath vials (BD, USA), preparation of cytological preparations stained according to Papanicolaou using the TriPath processor (BD, USA), and evaluation of smears using the Bethesda system [1,15]. As a result, 3 groups of women were selected: 1) 91 women to evaluate the effectiveness of HPV testing using the PCR-NV method and liquid cytology in detecting HPV-associated cervical pathology in women aged 30 years and older.

2) 49 women to evaluate the effectiveness of a combination of methods: liquid-based cytology, p16/Ki67 double immunostaining, and HPV testing using the NR-PCR method for HPV-associated cervical pathology.

3) 61 women to study the morphological and immunohistological features of different types of SEMS.

Histological diagnosis was considered the gold standard for assessing the effectiveness of HPV testing using the NR-PCR method on a Cobas 4800 system and liquid-based cytology. The second stage assessed the sensitivity and specificity of the p16/Ki67 double immunostaining methods. In 148 cases with detected cervical pathology, in addition to cytological analysis, molecular biology testing was performed to study the expression of p16/Ki67 markers in cytological preparations prepared from residual material.

Study Results. During cytological examination, a diagnosis of high-grade squamous intraepithelial lesion (H-SIL) was made based on the detection of large clusters of scattered atypical squamous epithelial cells with a polymorphic appearance and pronounced dyskaryosis, as well as mitotic figures. L-SIL reveals squamous epithelial cells with mild dyskaryosis combined with the presence of intact mature cells in the parabasal and superficial layers. A diagnosis of ASC-US was made based on the presence of isolated groups of squamous epithelial cells with enlarged and hyperchromic nuclei in smears against a background of inflammation. ASC-US-H revealed clusters and isolated atypical squamous epithelial cells with enlarged and hyperchromic nuclei, suspicious for H-SIL. Negative smears for intraepithelial lesion contained isolated koilocytes, leukocytes, and sheets of squamous and columnar epithelium with reactive changes and leukopenia. Atypical cells were absent, consistent with a diagnosis of NILM. Cytological examination of cervical smears revealed the following changes: H-SIL in 21 women (5 women under 30 and 16 over 30), L-SIL in 23 women (10 and 13, respectively), ASC-US in 15 women (7 and 8, respectively), and NILM in 32 women (13 and 19, respectively).

Next, HPV DNA was detected in the cytological material using the Cobas 4800 PCR test and compared with the histological findings. HPV DNA was detected in 63 of the 91 women (69.2%), including 35 women under 30 and 28 over 30. Moreover, the presence of HPV in the absence of atypical cells was detected twice as often in women under 30 (69.2%) compared to women over 30 (32.1%). These results confirm the data of other researchers [3].

In NILM, HPV DNA was detected more frequently in women under 30 than in older women. This can be explained by the temporary presence of the virus in the body, specifically its transient nature in young women under 30. In this case, the treating physician is only required to monitor the patient and administer antiviral therapy.

**Conclusions.** 1.Reparative SEMS are found in chronic cervicitis and L-SIL. They are characterized by the absence of cellular atypia and expression of p16, p53, and CD34. Low expression of the proliferation marker Ki67, the stemness marker ALDH1, and moderate expression of Vim, the tumor marker C-MYC, and the hypoxia marker HIF-1 are detected. 2.Early diagnosis of cervical precancer and cancer should be based on a combination of methods: liquid-based cytology, HPV testing using the PCR-NV method, and ICC with dual p16/Ki67 staining. This significantly increases their sensitivity and specificity.

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