ACADEMICIA: An International Multidisciplinary Research Journal
ISSN: 2249-7137 Vol. 11, Issue 12, December 2021 SJIF 2021 = 7.492
A peer reviewed journal

TESTING THE HUMAN PAPILLOMAVIRUS IN THE PRIMARY SCREENING OF THE CERVICAL DISEASE

Doniyorbek Shuxratbekovich Khasanov*; Dilfuzahon Zakirzhanovna Mamarasulova**

* PhD, Docent,
Department of Oncology and Medical Radiology,
Andijan State Medical Institute, Andijan, UZBEKISTAN

**Associate Professor,
Doctor of Medical Sciences,
Department of Oncology and Medical Radiology,
Andijan State Medical Institute, Andijan, UZBEKISTAN
Email id: dilya2580559@gmail.com

DOI: 10.5958/2249-7137.2021.02740.3

ABSTRACT

This article discusses the issues of HPV testing by cytological screening. The combination of cytology and HPV testing is considered the mainstay of screening. These methods complement each other since cytological examination has high specificity, but low sensitivity, while HPV testing, on the contrary, is characterized by low specificity and high sensitivity.

KEYWORDS: *Cervical Cancer, Screening, Cytology.*

INTRODUCTION

Human papillomavirus (HPV) is a DNA virus that infects epithelial cells. More than 200 types of HPV are isolated, which clinical manifestations of infection with which range from asymptomatic, the development of simple papillomas and genital warts to squamous cell and invasive carcinomas of the mucous membranes. All types of HPV are divided into 3 groups according to oncogenic potential:

- Non-oncogenic, i.e. not capable of causing the development of a tumor;

- Optionally oncogenic or with low oncogenic potential, capable of causing the development of neoplasia under certain conditions;

- oncogenic, with a high risk of developing tumors, including invasive cancer.

The probable mechanism linking HPV infection and the development of cervical cancer is the ability of the virus to epigenetically inhibit the tumor suppressor gene **[1, 2, 6, 8]** and disrupt the regulation of mitotic activity of cells, affecting the G1 phase of the cell cycle [**1, 3]** by methylation of cell DNA **[4, 7, 9].** Also, HPV, like other viruses, penetrating into the cells of the immune system, trigger methylation of signaling proteins, changing their informative function and disrupting a complex cascade of interactions of specific immunity effectors **[12, 15, 10].**

The prevalence of HPV is up to 40% in the general population, peaks between the ages of 14 and 30, when transient HPV infection predominates, and decreases with age. Among patients with cervical cancer, the incidence of HPV is 99.7% **[1, 2, 5].**

Primary screening programs in many countries are now reorganizing towards high-risk HPV testing (hrHPV), especially in women over 30 years of age.

Advantages and disadvantages

The use of hrHPV tests as the primary screening for cervical cancer has several advantages. Randomized controlled trials and meta-analyzes of randomized data demonstrate level of evidence A that the HPV test has a higher sensitivity and negative predictive value in detecting advanced stages of the disease compared to cytological research. Screening based on HPV is 60-70% more informative in terms of detecting invasive cervical cancer in women over 30 years old compared to cytology **[3, 7, 6].** This advantage is especially pronounced for glandular lesions. Higher sensitivity allows the inter-screening interval to be lengthened: usually 5 years in case of a negative result, compared to 3-5 years and even more often for cytological screening. vrHPV is an objective test with high inter- and intra-variability. The test can be carried out in centralized laboratories to ensure quality control. Also, the test requires practically no special technical skills to assess the result. This reduces the requirements for staff, in particular the presence of a cytopathologist with specific skills that require periodic retraining and re-certification. hrHPV test allows to reduce the number of unsatisfactory screening results, it is possible to independently collect material with a sensitivity comparable to a medical procedure, with a slightly lower specificity. Self-collection of material is a good alternative for countries with a low level of healthcare organization, as well as for women living in remote and hard-to-reach regions **[13, 7].**

The main disadvantage of the hrHPV test is its very low age-dependent specificity compared to cytological examination, since the test can detect transient HPV infection without real carcinogenic potential **[2, 5, 10].** The use of hrHPV in women under 30 years of age as a primary screening is not recommended, due to the high incidence of hrHPV infection in this group of women **[9, 8].** In addition, HPV has an oncogenic potential for all epithelial tumors; therefore, its specificity in terms of cervical cancer is low **[11, 15].** To increase the specificity and minimize the need for colposcopy, "key" tests are needed to detect an infection that tends to persist and is associated with carcinogenesis **[13, 1].** The cost of HPVH, which was initially high, is now significantly reduced; in some regions, during tenders, it has reached a lower level than cytological examination. A cost-benefit study has shown that primary screening using the h-HPV test is more cost-effective than screening based on a cytological study, since the high cost of h-HPV testing is balanced by its high sensitivity and safe lengthening of inter-screening intervals **[16, 15, 2].** A positive HPV test can have negative psychological consequences due to cultural and religious factors **[4, 17].**

Kits for vaginal h-HPV DNA determination can be used by women on their own, which makes screening affordable for women who do not participate in regular screening programs. Meta-analyzes demonstrates that self-sampling using PCR kits has the same accuracy as a medical sampling procedure **[14, 12].**

Characteristics of HPV tests

Most HPV tests are based on PCR (except Hybrid Capture 2 and Cervista). Most PCR tests use viral DNA amplification (except APTIMA, which amplifies RNA). Most tests identify 13 types of HPV with a high carcinogenic risk, in particular, the risk of cervical cancer. Most tests have

comparable sensitivity and specificity characteristics.

Which hrHPV test to use

In the course of screening programs, it is preferable to use hrHPV tests with clinically proven reproducibility, high sensitivity for CIN2 +, CIN3 + and minimal, clinically insignificant sensitivity for detecting transient HPV infection. Processing and analysis of the collected sample should be carried out in a high-tech laboratory, accredited by the relevant authorities, equipped and operating in accordance with international standards **[14, 3].** A laboratory involved in the cervical cancer screening program must conduct at least 10 thousand tests per year [**11, 18].**

By December 2019, 253 commercial alpha HPV tests and 452 variants of the original tests were available in the world **[8, 10, 9].** However, more than 60% of the developed tests have no confirmed diagnostic sensitivity and are not reflected in refereed presumed publications **[13].**

Since there are many test options available, it is important to regularly evaluate them for use in screening programs.A recent systematic review **[12]** has listed hrHPV VLK tests that have been validated and validated in randomized trials that have shown a low incidence of cervical cancer in women with negative test results **[11, 10],** or meet equivalent international criteria based on cross-sectional analysis of data **[9, 16].** International criteria are based on a comparison of the sensitivity of new HPV tests and one or two "standard" comparison tests (GP5 + / 6 + PCR-EIA or HC2) using the same molecular markers (in particular, hrHPVDNA). Tests are considered to be eligible if they demonstrate results that are not lower than standard tests.

By December 2019, a sufficient number of developed commercial tests have been validated for use as components of cervical cancer screening programs.

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