Update of international guidelines for cervical cancer screening

Abstract

Cervical cancer mainly affects women in developing countries, its incidence and mortality rates being closely related to the availability of programs of screening and vaccination against human papillomavirus (HPV). By 2020, the World Health Organization Global Strategy to eliminate the threshold of four cases of cervical cancer per 100,000 women per year by the end of the century implies achieving the following goals by 2030 and maintaining them: 90% of girls should be fully vaccinated for HPV by the age of 15; 70% of women should be screened by a high-performance test until the age of 35 and then again until the age of 45, so that each woman is tested at least twice in her lifetime, at a distance of maximum 10 years between tests; 90% of women identified with cervical pathology should receive treatment. In this article, we review the recommendations of the USA specialty societies regarding the cervical cancer screening in women with baseline risk, of the European guidelines on providing a quality screening for cervical cancer, and of the Australian guide.

Keywords: *cervical cancer, human papillomavirus (HPV), oncogenic strains, HPV testing*

Rezumat

Cancerul de col uterin afectează în principal femeile din țările în curs de dezvoltare, incidența și ratele mortalității sale fiind strâns legate de disponibilitatea programelor de screening și vaccinare împotriva virusului papiloma uman (HPV). Până în 2020, Strategia globală a Organizației Mondiale a Sănătății pentru eliminarea pragului de patru cazuri de cancer de col uterin la 100.000 de femei pe an până la sfârșitul secolului implică atingerea următoarelor obiective până în 2030 și menținerea acestora: 90% dintre adolescente ar trebui să fie complet vaccinate pentru HPV până la vârsta de 15 ani; 70% dintre femei ar trebui să fie supuse unui test performant până la vârsta de 35 de ani și apoi din nou până la vârsta de 45 de ani, astfel încât fiecare femeie să fie testată cel puțin de două ori pe parcursul vieții, la o distanță de maximum 10 ani între teste; 90% dintre femeile identificate cu patologie cervicală ar trebui să primească tratament. În această lucrare sunt revizuite recomandările societăților de specialitate din SUA privind screeningul cancerului de col uterin la femeile cu risc bazal, ale ghidurilor europene pentru asigurarea calității în screeningul cancerului de col uterin și ale ghidului australian.

Cuvinte-cheie: *cancer de col uterin, virusul papiloma uman (HPV), virusuri oncogene, testare HPV*

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Most cases of cervical cancer can be prevented by effectively treating precancerous lesions detected by cervical screening. The available methods for cervical cancer screening are the Pap test, primary HPV testing and co-testing, including cervical cytology and concomitant HPV testing; the infection with HPV oncogenic strains and the persistence of infection are the most important factors of cancer progression[1,2].

Primary HPV testing has a sensitivity of 75-100% in the detection of infection with 13 strains with high oncogenic risk, but a lower specificity compared to the Pap test (85-96%). Since 2004, reports from six European countries have compared the results of HPV and cytological tests as primary screening and, based on these reports, the European Guidelines for Quality Assurance in Cervical Cancer Screening were established. In 2020, the World Health Organization (WHO) certified the superiority of HPV testing as a screening method and published the guidelines for implementing this test in universal screening programs, 2021 being the year of publishing the update of the guidelines for screening and treatment of precursor lesions in the prevention of cervical cancer by the WHO[3].

Secondary testing includes cytology triage; women tested positive for oncogenic HPV in primary screening should be tested without delay by cervical cytology, the optimal cytology test being the one of using the sample collected during the HPV screening. Depending on the result of the cytology triage, the HPV-positive women may be recommended to repeat the test or undergo the colposcopic examination, the advice to undergo colposcopy of all HPV-positive patients not being recommended.

The benefits of screening for decreasing incidence and mortality outweigh the risk of false-positive tests that lead to unnecessary consecutive procedures, which

justify the screening programs around the world[4]. An example in this respect is a randomized trial from India, which demonstrates that a single screening with HPV testing reduces the number of cervical cancers diagnosed in advanced stage by 50% compared to the lack of any lifelong screening[5]. The United States of America adopted the Pap test screening in the 1950s and by the mid-1980s the incidence of cervical cancer had decreased by 70%[6].

The disadvantages of screening are the discomfort mainly due to extreme ages, the psychosocial consequences represented by anxiety associated with being referred to colposcopy, the increased costs of health systems, the false-positive results, and interventional risks on the prognosis of pregnancy, the ablation or excision of the cervical lesion being responsible for the high incidence of second-trimester abortion, premature and preterm rupture of membranes, premature birth and perinatal mortality.

Pap test screening is recommended to be repeated every three years, the detection rate being similar to the annual testing[7].

The primary HPV test, without cervical cytology, is recommended to be performed every five years, the US Food and Drug Administration (FDA) approving only COBAS and BD Onclarity tests for this purpose, while the WHO has pre-certified Cepheid Xpert HPV and Qiagen care HPP tests. Over time, countries such as Australia, the Netherlands and the United Kingdom have shifted their national cytology-based screening program to the use of HPV testing. The detection of the presence of a high-risk strain (HR-HPV) should be followed immediately by genotyping for HPV types 16 and 18 and Pap smear cytology test. HPV self-sampling is not FDA approved, but is available in the Netherlands and Australia, as well as in countries with limited resources. Co-testing is recommended to be repeated every five years, a significant number of tests being FDA approved and widely available in the United States (Aptima, Aptima HPV 16 and 18/ 45, Cervista HPVhr, Cervista HPV 16/18, Hybrid Capture 2). The HPV triage testing or the reflex HPV testing is recommended for the detection of atypical squamous cells of undetermined significance (ASC-US) on cytological examination, the testing being performed automatically from the sample that was collected for cervical cytology.

WHO guidelines confirm that screening even once in a lifetime is beneficial, and the interval between tests depends on the resources and infrastructure available in each country, leaving the decision regarding the age range and frequency of testing to each state, but also considering the local spread of the disease. The most critical period remains the 30-45 age range, which may be particularly relevant for the screening strategy in resource-limited countries[8].

Although the superiority of one of the three screening methods over the others in disease detection and incidence continues to be controversial, primary HPV testing is associated with an increase in the number of false-positive results compared to cervical cytology, leading to unnecessary procedures, especially in young patients, in whom the HPV infection often regresses spontaneously[9-12].

Routine screening is addressed to the population at baseline risk, defined by the following characteristics: age, lack of symptoms, immunocompetence and previous negative results of cervical cancer screening; patients under 25 years of age with ASC-US and HPV negative, patients under 25 years old with low-grade intraepithelial lesion (L-SIL) or ASC-US HPV positive followed by two consecutive negative cytology results, and patients over 25 years old with L-SIL, ASC-US HPV positive or patients who are HPV positive but negative for intraepithelial lesion or malignancy (NILM) in whom colposcopy was negative for CIN 2/CIN 2+, after obtaining three consecutive negative results of co-testing. High-risk patients are defined by the presence of the HIV infection, immunosuppression, or intrauterine exposure to diethylstilbestrol, requiring more frequent screening testing. They should benefit from screening initiated one year after the onset of sexual activity, but not later than 21 years old, by cervical cytology or co-testing and a colposcopic landmark at the first visit; cervical cytology should be repeated at intervals of at least 12 months for three years; the negative results may be followed by an increase in the testing interval to the standard of three years or by co-testing over the age of 30 years old, repeated annually for the first three years, and subsequently at three-year intervals if the results of the first tests were negative.

According to the United States Guidelines issued by the most important expert groups, the screening of patients at baseline risk is adapted according to age and summarized in Table 1.

- **Age <21 years old:** ACS does not recommend screening asymptomatic, immunocompetent patients under 21 years old, regardless of the age of onset of sexual activity[13], due to the very low incidence of cervical cancer at this age and the high possibility of the HPV infection to become negative. Although ASC-US and L-SIL lesions are significantly more common in adolescents compared to adults, 90-95% of these lesions and as many of the high-grade lesions regress spontaneously.
- **Age 21-29 years old:** for this age range, the recommendations of expert groups continue to be variable for asymptomatic and immunocompetent patients. The 2018 guidelines of the United States Preventive Services Task Force[14] recommend initiating screening at the age of 21 with repeated cervical cytological examination every three years. Another acceptable approach is to initiate screening at the age of 25 with primary HPV testing every five years, according to the ACS guidelines 2020[13]. The benefits of cytology for this age range are based on meta-analyses of randomized trials and observational studies that have shown false-positive rates of HPV testing due to the high incidence of transient infections in this

age group[11], although the screening recommendation was not adjusted for the effect of HPV vaccination to which 54% of the eligible population of the United States[15] or 70% of adolescents aged 13 to 17 years old[16] adhered.

- **Age 30-65 years old:** the continuous screening is recommended for all asymptomatic and immunocompetent women, either by primary HPV testing every five years, or by co-testing every five years, or by Pap test every three years, regardless of HPV vaccination status, ACS preferring primary HPV testing over other strategies[13]. Patients should be tested even in conditions of sexual abstinence.
- **Age >65 years old:** the decision to stop screening depends on the patient's previous screening results, life expectancy and preferences, in the form of a mutual informed agreement. Previous normal screening results (history of CIN2/CIN2+ absent in the last 25 years, two primary HPV tests/two negative co-testing in the last 10 years, the most recent testing performed in the last five years, three negative Pap tests in the last 10 years, the most recent test performed in the last three years) support the cessation of testing after 65 years old, although some clinicians continue to offer screening until the age of 74 to people whose life expectancy exceeds 10 years. Many clinicians believe that, if previous screening results were inadequate or unknown, patients over the age of 65 should continue the program with a co-testing or cytological examination performed annually for three years before increasing the interval at five years or to stop screening at the age of 80, depending on life expectancy and the patient's decision, given that a substantial number of cases of cervical cancer occur after the age of 65 years old.

In Australia, the country with the lowest cervical cancer mortality rate in the world due to the adoption of the cervical cancer screening program in 1991, the guidelines recommend starting screening at the age of 25 years old and stopping it after the age of 74. In December 2017, cervical cytology screening every two years was replaced with primary HPV testing every five years, followed by liquid-based reflex cytology of cases positive for oncogenic HPV[17,18].

The patients with hysterectomy and a history of cervical intraepithelial neoplasia (CIN) need supervision after this surgery; total hysterectomy without a history of CIN does not need further screening for cervical or vaginal cancer; subtotal hysterectomy patients have a similar risk of developing cervical cancer as patients who did not undergo this procedure.

The screening of HPV vaccinated patients for cervical cancer is being evaluated, given the impossibility of immunization against all oncogenic HPV strains and the potential infection prior to vaccination[13,19,20].

The European Guidelines for Quality Assurance in Cervical Cancer Screening[21] recommends the following cervical cancer screening strategy, which was also adopted in the development of the national screening program in our country: for asymptomatic women aged 25-65 years old, a test every 3-5 years, if normal. The women with subtotal hysterectomy for benign conditions are included in the screening; the discontinuation of screening after total hysterectomy for benign conditions is recommended due to the low screening efficiency and potential adverse effects due to false-positive results in this category of the population; total hysterectomy must be confirmed by medical documents or a clinical examination attesting the cervical absence, the screening being performed when the indications for hysterectomy are not clear. In Romania, the organized screening of cervical cancer is performed according to the criteria recommended by the European Guidelines, every five years, according to the *Joint Order MS 238/CNAS 538 from 2012 for the approval of the methodological norms on organizing and conducting screening in cervical cancer*. Thus, screening for cervical cancer by Pap test is recommended for all women aged between 25 and 65 years old who have no suggestive symptoms or a confirmed diagnosis of cervical cancer and did not undergo total hysterectomy for non-cancerous conditions.

Retesting within the National Cervical Cancer Screening Program in Romania takes place five years after the last normal result. The family doctor will recommend testing all eligible women aged 25-64 for whom a normal result that is more recent than five years cannot be documented. The family doctor will explain to the patient the significance of the test result and the conduct to be followed. In case of an unsatisfactory result or a negative result for intraepithelial or malignant lesions, but with non-neoplastic changes, it is recommended to repeat the test within 3-6 months. In case of a positive result for epithelial or glandular cell abnormalities, the general recommendation is the referral to a gynecologist/oncologist for evaluation and specialized intervention. In the specific case of changes indicating the presence of atypical squamous cells of undetermined significance (ASC-US) or a low-grade squamous intraepithelial lesion (LSIL), there is the option to repeat the test at six months. In case of persistence of changes, the referral to a gynecologist/oncologist for evaluation and specialized intervention is recommended.

A screening episode for cervical cancer ends either with the reintroduction into the screening program for routine screening every five years, or with the confirmation of the cancer diagnosis. The reintroduction of women who presented dysplastic abnormalities of squamous or glandular cells in the screening program is performed after obtaining three consecutive negative smears at an interval of six months. Patients with cervical cancer abnormalities as a result of screening belong to the cervical lesions monitoring program, which is not included in the screening program. Women with preinvasive lesions or severely altered cytological outcome (ASC-H – atypical squamous cells, high-grade squamous lesion cannot be ruled out; HSIL – high-grade squamous intraepithelial lesion; AIS – adenocarcinoma *in situ* or invasive adenocarcinoma) should be referred to colposcopy without any

Table 1 Recommendations of the United States specialty societies on cervical cancer screening in women at basal risk. ACS: American Cancer Society; ASCCP: American Society for Colposcopy and Cervical Pathology; ASCP: American Society for Clinical Pathology; SGO: Society of Gynecologic Oncology; USPSTF: United States Preventive Services Task Force; ACOG: American College of Obstetricians and Gynecologists; ACP: American College of Physicians (UpToDate, accessed in June 2021)

Society	Age of initiation (years)¶	Age of cessation (years)	Recommended screening test and frequency		Post-HT for benign pathology	HPV vaccination
USPSTF (2018)	21	65Δ	**Age between 21 and 29 years old:** ■ Pap test every 3 years	**Age ≥30 years old:** One of the tests: ■ Pap test every 3 years; ■ Primary HPV test◊ every 5 years; ■ Co-testing (Pap test and HPV test simultaneously) every 5 years.	Not recommended§	Similar recommendations for unvaccinated patients
ACS (2020)	25	65¥	**Age ≥25 years old** One of the tests: ■ Primary HPV test◊ every 5 years (preferably); ■ Co-testing (Pap test HPV test simultaneously) every 5 years; ■ Pap test every 3 years.		Not recommended‡	Similar recommendations for unvaccinated patients
			Age 21-29 years old	**Age ≥30 years old**		
ACOG (2016)	21	65Δ	One of the tests: ■ Pap test every 3 years; ■ Primary HPV test◊ may be considered every 3 years for patients ≥25 years of age.	One of the tests: ■ Co-testing (Pap test and HPV test simultaneously) every 5 years (preferably); ■ Pap test every 3 years; ■ Primary HPV test◊ may be considered every 3 years for patients ≥25 years of age.	Not recommended§	Similar recommendations for unvaccinated patients
ACP (2015)	21	65Δ	■ Pap test every 3 years	One of the tests: ■ Pap test every 3 years Alternative: Co-testing (Pap test and HPV test) every 5 years	Not recommended§	N/A
ASCCP/SGO (2015 guidelines)	21	N/A	Primary HPV test◊ may be considered every 3 years for patients ≥25 years of age	Primary HPV test◊ may be considered every 3 years	N/A	N/A
ACS/ASCCP/ ASCP (2012)	21¶	65†	■ Pap test every 3 years (preferably)	One of the tests: ■ Co-testing (Pap test and HPV test) every 5 years (preferably) ■ Pap test every 3 years	Not recommended**	Similar recommendations for unvaccinated patients

*¶ Regardless of the age of onset of sexual activity; Δ For patients without a history of CIN2/CIN2+ with proof of previous adequate testing (three or more negative results of consecutive cytological examinations or two consecutive negative co-testing in the last 10 years, the most recent being performed in the last 5 years). ◊ HP HPV tests approved by the United States Food and Drug Administration for primary HPV testing; § For patients who have undergone a total hysterectomy (TH) for benign conditions and which have a history of no CIN 2 or above lesions; ¥ For patients with proof of adequate negative screening performed (two consecutive negative primary HPV tests or co-testing in the last 10 years, the most recent being performed in the last 5 years, or three consecutive negative Pap tests in the last 10 years, the most recent being performed in the last 3 years) and without a history of CIN2/CIN2+ in the last 25 years. Screening should not be resumed for any reason, even if the woman has a new sexual partner. ‡ For patients who have undergone a total hysterectomy (TH) for benign conditions and have a history of no CIN2/CIN3 lesions in the last 25 years and have never had cervical cancer. † For patients with proof of adequate negative screening performed (consecutive negative cytology or two consecutive negative co-testing in the last 10 years, the most recent being performed in the last 5 years) and without a history of CIN2/CIN2+ in the last 20 years. Screening should not be resumed for any reason, even if the woman has a new sexual partner. ** For patients who have undergone a total hysterectomy (HT) for benign conditions and have a history of no CIN2/CIN3 lesions in the last 20 years and have never had cervical cancer.*

other observations or tests. In case of minor modified cytological result such as ASC-US (atypical squamous cells of undetermined significance), AGC (atypical glandular cells) or LSIL, the European Guidelines recommend HPV testing, after which retesting may be recommended preferably after 6-12 months or immediate referral to colposcopy. For women with negative cytology in the initial screening after a positive primary HPV test, cytological retesting should be performed at a shorter interval than usual, at most 6-12 months.

The referral to colposcopy of patients with negative cytology is not recommended. Primary HPV testing, absent from the National Cervical Cancer Screening Program in Romania until 2020, is found in the guidelines of WHO/IARC experts in the Applicant's Guidelines – Specific Conditions *"Be responsible for your health – regional programs of prevention, early detection, diagnosis and early treatment of cervical cancer – stage II"*, launched in December 2019 for the North-West, Center, South-Muntenia and North-East regions, being recommended as the main screening method for women over 30 years of age within the Cervical Cancer Clinical Guidelines of the Romanian Society of Obstetrics and Gynecology and the Romanian College of Physicians, approved by the Ministry of Health, published updated in 2019.

HPV testing, in addition to minor modified cytology result, is not among the procedures of the second-phase screening centers in Romania. Repeating the cytology at least 6-12 months is an acceptable alternative to performing the HPV test. Women with a positive HPV test and normal cytology in the primary screening could be retested for HPV with or without cytological triage at a preferable 12-month interval, being referred to colposcopy, and it is recommended that only patients with ASC-US or more severe results and positive HPV test be referred and tested. The European recommendations for patients with positive HPV and negative cytology provide the following options: presentation for repeated secondary testing after at least 12 months, presentation for colposcopy or return to routine screening in case of negativity of HPV test. Women who have a repeated negative HPV test should return into the normal screening program without the need for cytological triage for these cases. As a protocol for the use of single cytological testing, women with ASC-US or more severe results in repeated testing should be referred to colposcopy, and those with normal repeated cytology should receive the indication to return to routine screening. However, patients with a repeated positive HPV test receive an indication for colposcopy.

The clinical accuracy of the primary HPV test on samples collected by the patient for cervical screening is sufficient to conduct organized, population-based pilot programs for women who did not participate in the screening program despite personal invitation and individual alerting. A primary HPV test may be included in the cervical cancer screening program only if it demonstrates reproducibility and consistently high sensitivity to CIN2+ and CIN3+ and only if the minimal detection of transient lesions due to HPV infection is clinically irrelevant. Primary HPV screening programs should follow the rules established by the European guidelines that are guidelines for any cervical cancer screening program independent of the primary testing method used. The European recommendations refer to the organization of the program, planning, monitoring, evaluation, communication and quality assurance of the entire screening process, implicitly of sample collection, histopathological interpretation and classification of cervical tissue and management of detected lesions. Like cytological testing, HPV testing should only be performed on samples processed and analyzed in qualified laboratories, accredited by specialized authorities in compliance with international standards. These laboratories must analyze a minimum of 10,000 tests per year. Any decision regarding the implementation of primary HPV testing in cervical cancer screening must consider the economic factors of the healthcare system and implicitly the correct use of the test, as underlined in the instructions, in accordance with the recommendations set out in the Annex of the European Guidelines for Quality Assurance in Cervical Cancer Screening[21].

In 2019, together with the team of Micomi Clinic, we published an article dedicated to the analysis of the efficacy of using the dual system of immunocytochemical molecular markers p16/Ki-67 CINtec® PLUS (DS) compared to the HPV testing in the management of ASC-US lesions detected on cytological Pap test, in order to reduce unnecessary colposcopies and interventions with marked effects on the fertility of young women[22]. The average age of the patients with ASC-US lesions in the group analyzed in our country was 32 years old, 62% being young women who were tested for HPV by self-financing; in the age group under 30, the incidence of HR-HPV was 77%, higher than in the age group above 30 years old (62%), but the number of detected strains increased with advancing age, the most common strain present in combinations being HPV 16 (18%). In 36% of cases, CIN2+ lesions were due to a single HPV strain, in 10% of cases, they were due to coinfection with two strains, and in 20% of cases, more than two types of HPV were involved, 10% of CIN2+ patients being HPV-negative. Colposcopic positivity at 6-12 months after the initial negative colposcopy reveals that the detection of HPV and/or molecular changes induced by it precedes the appearance of pathologically identifiable pathological aspects with a significant time interval. Of the total of 140 patients who underwent the three tests, DS was positive in 59.2% of cases, and the prevalence of HPV infection was 75%. The sensitivity, specificity and predictive values of DS compared to the DNA test for HPV were evaluated relative to CIN2+ lesions confirmed by biopsy; HPV testing had a 98% sensitivity, 38% specificity, a positive predictive value of 46% and a negative predictive value of 97%, while the DS sensitivity was 100%, the specificity was 88%, the positive predictive value was 82%, and the negative predictive value was 100%. The risk of a person with ASC-US, DS+ to develop

the disease over the next six months is 11.1%, and over the next 12 months – 38.9%, the test accurately selecting patients who do not require colposcopy and reassessment earlier than one year, significantly decreasing the level of anxiety of patients, the number of invasive procedures in nulliparous and the diagnostic costs. In cervical cancer screening, double immunocytochemical staining can find its place in cytology-based programs as a strategy for the early detection of cervical lesions or as a triage test in the modern approach to screening based on primary HPV testing. ■

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