Cervical cancer screening

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Abstract

Cervical cancer remains an important public health issue even after the discovery of Papanicolaou screening test (1940) that facilitated the early detection of the illness. Identifying the human papillomavirus (HPV) as a leading cause, alongside with developments in molecular HPV screening and HVP vaccines, resulted in an important decrease in cervical cancer mortality rates. For developing the best screening method, there are still ongoing studies which assess the performance of existing methods and implementation of vaccines. The early detection of uterine cancer in the body is solely based on screening programs that require HPV testing.

Keywords: *human papillomavirus, cervical cytology, cervical cancer, HPV testing*

Rezumat

Cancerul de col uterin rămâne o problemă importantă de sănătate publică, dar care beneficiază, de la descoperirea testului Papanicolau în anul 1940, de un sistem de screening ce face ca boala să fie identificată într-un stadiu în care soluțiile terapeutice sunt la îndemână. Identificarea papilomavirusului uman (HPV) ca agent etiologic principal al acestei patologii, împreună cu dezvoltarea screeningului molecular HPV și a vaccinului HPV au dus la scăderea incidenței și mortalității prin cancer de col uterin. În vederea conceperii celei mai bune strategii de screening, încă se cercetează performanța metodelor actuale, dar și implementarea vaccinării împotriva HPV. Actualitatea în depistarea precoce a cancerului de col uterin privește tranziția spre programe de screening bazate pe testarea primară a HPV.

Cuvinte-cheie: *papilomavirus uman, citologie cervicală, cancer de col uterin, testare HPV*

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1. Introduction

Even though it has the best developed screening system, cervical cancer is the most frequent type of gynecological cancer, still ranking the first places regarding incidence and mortality in the developing countries. Almost all cases are related to human papillomavirus (HPV) infections, which are sexually transmitted and explain the high incidence of cervix cancer among the population. Most of the infections are self-limited, only a few become persistent, causing malignant lesions.

There is no treatment for HPV infection – there only exists a primary prevention by vaccination. HPV vaccination was implemented in various countries, its efficacy being demonstrated in Australia, New Zeeland, USA, Canada and Denmark.

The secondary prevention – cervical cancer screening – is used for the early detection of lesions and is represented by the Papanicolaou test (Pap test), which is recommended both for vaccinated and unvaccinated women.

With the appropriate approach, through prevention, screening and treatment, this disease can be eradicated as a health public issue.

2. Epidemiology

2.1. The incidence and mortality of cervical cancer

In 2018, cervical cancer ranked fourth in the world as frequency among women, with approximately 570,000 new cases and representing 6.6% of women's cancers[(1)]. The significantly lower incidence in the developed countries highlights the screening programs success in which Pap cytology test is performed.

2.1.1. Global estimates in 2018

According to the estimates, cervical cancer is the fourth cause of cancer among women worldwide[(2)]. Regarding cancer's global mortality, cervical cancer is on the third place among women, after breast cancer and lung cancer[(2)].

2.1.2. Romania's estimates in 2018

Romania ranks first in Europe regarding incidence, being 3.5 times higher than Europe's average. Cervical cancer was the second most frequent type in women aged between 15 and 44 years old[(3)].

2.2. The natural evolution of the disease

Squamous cell carcinoma occurs most frequently at the squamocylindrical junction from a preexistent dysplasic lesion – due to HPV infection (Bosch, 2002) – and leads to carcinoma *in situ* and then to an invasive malignant lesion. The local tumor progression can be exophytic, endophytic and infiltrative (when necrosis is involved). Subsequently, the tumor invades the ganglia near the cardinal ligaments, the anterior and posterior parameters. Once the local tumor proliferation starts, the lymphatic dissemination expands and the invasion becomes extensive to the parameters and bladder. The cervical cancer's metastasis spreads *via* the blood to the lungs, ovaries and liver.

2.3. Risk factors

Cervical cancer results from persistent genital infection with HPV, rarely from other causes. Thereupon, the major risk factors identified in the epidemiologic

studies are the early onset of the sexual life, multiple sexual partners, multiparity and smoking.

Genital HPV infection is the main cause associated with cervical cancer. The infection can be transitory or persistent, the last one causing premalignant or malignant modifications.

2.4. Evidence of the efficiency of the cervical cancer screening

The most frequently used screening test is known as Pap test, developed by Dr. George Papanicolaou in 1943, when he described that the sampled cells can be colored in order to evaluate the cytological abnormalities from the cervix. Although Pap test is still the main element used to discover the early cervical lesions, it is not yet widely used.

The specificity of the PAP test is approximately 86-100%[4], but the sensitivity is variable, that's why the test is recommended repeatedly throughout a woman's life.

2.5. The age group for which the cervical cancer screening is recommended

Because HPV has different manifestations on young women than in older women, The American College of Obstetricians and Gynecologists (ACOG) recommends starting the routine screening in all 21-year-old women, regardless their sexual behaviors and risk factors, with some exceptions such as HIV-positive cases, organ transplant or immunosuppressive therapy. In this cases, the first screening is recommended only at the beginning of sexual life, even before 21 years old, including two Pap tests at the interval of six months, and then annually[5].

2.6. Screening interval

For women between 21 and 29 years old, it is recommended to perform the Pap cytology test in a liquid-based cytology medium or conventional, every two years[6]. Routine screening, including HPV test, is not recommended for this age group because the most HPV lesions regress spontaneously especially in adolescents and young women. Women between 30 and 65 years old can be examined using Pap test or HPV co-testing. In cases with negative results at three consecutive Pap tests, the screening may be repeated every three years. In women with negative results of the cytology and HPV test, it is recommended to repeat the co-testing every five years[5].

Women with CIN 2 or CIN 3 case history must continue the cytological screening annually for at least 20 years[7].

Stopping the screening is recommended for women over 65 years old with three consecutive negative results at Pap test in the last 10 years[7]. The guides recommend stopping the screening in women who have experienced total hysterectomy regardless their age.

3. Organizing cervical cancer screening programs

3.1. Romanian screening policy

In Romania, the organized screening for cervical cancer is made according to the recommended criteria by the European Quality Assurance Guide in Cervical Cancer Screening, every five years, for all women between 25 and 65 years old, asymptomatic, without a confirmed diagnosis of cervical cancer and with no hysterectomy.

3.2. European screening policy

The European Quality Assurance Guide in Cervical Cancer Screening recommends:

- annual testing for the age group 25-35 years old; in case of a positive result, HPV testing;
- follow-up of the HPV persistent infection, for the age group 35-65 years old; in case of a positive result, cytological sorting.

4. Covering a larger numbers of patients in screening programs

To cover as many patients as possible into the screening programs, it is essential that the population is informed correctly and completely, understands the causes of the disease and knows the means of the available prevention.

5. The cervical screening test

Cervical cytology is a procedure which involves cervical cells exfoliation which are then fixed and analyzed under a microscope. The developed coloring method offers a polychromatic definition of the nucleus and cytoplasm's characteristics. The test enables the evaluation of the nuclear chromatin changes and the assessment of the cellular degeneration degree. Ideally, Pap test should be performed when the patient is outside the menstrual bleeding. Also, there must be avoided the sexual contacts, the intravaginal showers, the internal tampons and the contraceptive or pharmaceutical creams for at least 24-48 hours before the test.

It is filled out a standard form with information that include the last menstrual period, the presence of pregnancy, the use of exogenous hormonal therapy, the menopause status, the existence of the abnormal uterine bleeding or a personal history of cancer or dysplasia, and the presence of intrauterine devices.

5.1. Cervical brush

To detect macroscopic and squamocolumnar junction lesions, it is essential to have a proper view of the cervix. Sampling is done from the transformation area. When an infection is suspected, an additional sample may be procured to detect the infection after the Pap sampling. There are three types of devices used for cervical brush: spatula, plastic brush and endocervical brushes.

Spatula is used for preferential sampling from the ectocervix. It is oriented by the cervical outline and the cervix surface is scraped by at least one complete rotation.

The plastic brush with long bristles is surrounded by short bristles. With this type of device it is recommended to perform approximately five complete rotations in the same direction.

The endocervical brush is used together with the spatula, only after the ectocervix sample was prelevated with the spatula. The brush is inserted endocervically, leaving only the last layer of bristles visible. The brush should be rotated so that it makes contact with the entire wall of the cervix canal.

5.2. The quality of cervical brushing

The sample can be evaluated when it has an adequate number of squamous cells, cells from the transformation zone. A probe is considered unsatisfactory if in the cervical smear the squamous epithelial component is inappropriate or insufficient.

5.3. Liquid medium sampling

Sampling in liquid medium is performed with special devices which have a detachable tip and are transferred to a container with conservation solution and then sent to the laboratory.

6. Interpretation of cervical cytology results. Description of all types of cytological results according to Bethesda classification

Bethesda reporting system components (2001)[8]:

- Specimen type – conventional Pap test/liquid medium cytology on a thin layer.
- The specimen relevance – satisfactory for evaluation/unsatisfactory for evaluation.
- General categories – negative for malignant or intraepithelial lesions/epithelial cells abnormalities/other findings leading to increased risk.
- Interpretation of results – negative for malignant or intraepithelial lesions/organisms.
- Other nonmalignant findings – reactive cellular changes (inflammation, regeneration, irradiation)/posthysterectomy glandular cells/atrophy.
- Epithelial cells abnormalities – squamous cells/glandular cells.
- Other findings – endometrial cells in women over 40 years old/automatic verification and auxiliary tests as appropriate/notes and educational recommendations.

Atypical squamous cells of undetermined significance (ASC-US) represents an epithelial abnormality diagnosed when the degree of nuclear atypia is not sufficient for intraepithelial squamous lesions. For ASC-US evaluation, the patient needs to perform HPV testing, colposcopy and repeat cytology at 6 and 12 months.

Atypical squamous cells cannot exclude a high-grade lesion (ASC-H). This type of result describe cellular changes which do not meet the cytological criteria for a high-grade intraepithelial squamous lesion, but such a lesion cannot be excluded.

Low-grade intraepithelial squamous lesions (LSIL) suggest mild dysplasia or CIN 1 or cytological aspects of HPV infection. Studies regarding the natural evolution of this type of lesion suggest that approximately 50% will regress in the next two years, 20% will progress to HSIL, and 0.2% will progress to cervical cancer[9].

High-grade intraepithelial squamous lesions (HSIL): this type of result shows moderate and severe dysplastic lesions corresponding to hystological CIN 2, CIN 3 and *in situ* carcinoma. These lesions have a lower probability of regression in the next 24 months, approximately 35%. Twenty-three percent of them remain persistent and 1.4% progress to invasive cancer[9].

The glandular cells abnormalities (AGC) observed on cytological samples can be associated to glandular or squamous cells abnormalities, including cervical or endometrial adenocarcinoma.

Nonmalignant lesions. Some changes may guide the diagnosis for the presence of microorganisms such as *Trichomonas vaginalis*, *Candida*, *Actinomyces* and herpes simplex virus, or suggestive changes for bacterial vaginitis.

7. Colposcopy

Colposcopy is a procedure which allows the examination of the inferior anogenital tract with the help of a binocular microscope, in order to identify preinvasive and invasive neoplastic lesions with subsequent biopsy. It represents the gold standard in the evaluation of the patients with abnormal cytological results. Under colposcopic observation, the ectocervix suspected lesions can be biopsied using the Tischler biopsy forceps. The biopsy should be taken from places where emergency hemostasis can be provided.

8. Monitoring and reevaluation

Monitoring ASC-US patients. In this case, there are recommended to repeat the cytology after 6 and 12 months, colposcopy and HPV testing. If it turns negative, co-testing is repeated after three years. If it turns positive, the patient is directed to colposcopy.

Monitoring LSIL patients. Colposcopy is recommended. In case of adolescents, the cytology is repeated yearly, and in women who have reached menopause there are recommended HPV testing and repeating the cytology after 6 and 12 months.

Monitoring ASC-H, HSIL and squamous cancer patients. Colposcopy is recommended.

Monitoring AGC, AIS and adenocarcinoma patients. In this case (AGC), colposcopy, endocervical curettage and HPV testing are recommended. For women over 35 years old with bleeding or atypical endometrial cells, endometrial biopsy is recommended.

9. Modern methods of screening

9.1. Primary screening by HPV testing

Developing HPV testing is more precise and sensitive than cytology and led to major changes. According to the World Health Organization, HPV testing is now proposed as the main screening instrument for cervical cancer. Thereby, European guidelines recommend a screening interval of five years for HPV testing, which can be prolonged to 10 years depending on the patient's age and previous screening[10]. Another factor expected to help establish primary HPV screening as a more cost-efficient option is HPV vaccination. In a study made for evaluating the efficacy of the cervical cancer prevention, the most cost-effective strategy was to combine the vaccination with an organized screening program, using primary HPV testing with cytological sorting every five years[11].

The age when HPV testing can be stopped is important. European guidelines suggest that primary HPV screening may be stopped at the same recommended age

as cytology, 65 years old, if the most recent screening test is negative.

9.2. The follow-up of HPV-positive patients by cervical cytology and colposcopy depending on the presence or absence of high-risk strains

European guidelines recommend that in case of HPV-positive patients, cytology should be performed as the main triage test, which decreases the excessive number of requests for colposcopy. Thereby, only HPV-positive patients with cytological abnormalities are immediately directed to colposcopy. If primary HPV testing uses HPV 16 and HPV 18 genotyping, then the immediate attitude is colposcopy without previous cytology. If HPV testing is positive but negative for 16/18 strains, the patients are invited to make a cytological cervical exam, and if this is negative, screening will be repeated after 12 months.

10. The performance of the screening test

False negative results may appear due to incorrect sampling, incorrect display on the glass slide (conventional test), incorrect processing in the cytology laboratory, or to incorrect interpretation by the cytologist. ■

Conflict of interests: The authors declare no conflict of interests.

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