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Contemporary methods of prevention and early detection of cervical cancer - a review of the literature

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Abstract

Cervical carcinoma remains a significant health problem, despite the progressive fall in the mortality rate during the past 60 years. However, cervical carcinoma is still the most common cancer among women worldwide and the leading cancer cause of death in many countries. The primary strategy to reduce the incidence and death rate from cervical carcinoma is screening by cervical cytology. The knowledge that persistent human papillomavirus (HPV) infection is the main cause of cervical cancer has resulted in the development of prophylactic vaccines to prevent HPV infection and HPV assays that detect nucleic acids of the virus. This study is a review of currently available methods of prevention and early detection of cervical cancer.

Key words: cervical carcinoma, Human papillomavirus (HPV) vaccination, cytology, prevention, early detection.

Introduction

Cervical cancer is a serious oncological problem, mainly in developing countries, where about 80% of cases are recorded among all cases. According to data from the World Health Organization approximately 570 000 cases of cervical cancer and 311 000 deaths from the disease occurred in 2018. Cervical cancer was the fourth most common cancer in women, ranking after breast cancer (2·1 million cases), colorectal cancer (0·8 million) and lung cancer (0·7 million) and third cause of death in the world¹. Cervical cancer was the leading cause of cancer-related death in women in Africa, Melanesia, Southeast Asia, and Central and Eastern Europe². Globally, the average age at diagnosis of cervical cancer was 53 years, ranging from 44 years (Vanuatu) to 68 years (Singapore). The global average age at death from cervical cancer was 59 years, ranging from 45 years (Vanuatu) to 76 years (Martinique). Cervical cancer ranked in the top three cancers affecting women younger than 45 years in 146 (79%) of 185 countries assessed.

In Poland, cervical cancer accounted for 4% of all cancers in women. Over the past decades, their incidence has decreased by around 30%, despite this it remains higher than the European average by around 15%. Cervical cancer is the cause of 4% of cancer deaths among women in our country, mainly after the age of 50. Mortality due to it is in Poland 70% higher than the average for European Union countries³. This may be due to the low efficiency of screening tests, the high degree of progression at the time of diagnosis and / or the low effectiveness of the treatment used.

The main reason for the development of cervical cancer is infection with oncogenic HPV types, sexually transmitted pathogens. It is also responsible for the development of cancer of the vulva, vagina, penis, throat, mouth, anus. The risk of infection increases: early start of sex life, a large number of partners, a large number of pregnancies and births, smoking, use of hormonal contraceptives, low socioeconomic status, inflammation of the genital organs, other than HPV infection, HIV infection. Infection has no symptoms, which is why cytological screening is so important. A vaccine against carcinogenic HPV strains has also been available on the market in recent years

Prevention of cervical cancer

These are all actions taken to prevent the disease from rising, its severity, progression or recurrence and its spread. We can divide it into primary and secondary prevention.

Primary prevention, which is aimed at preventing papillomavirus infection, includes:

- Public education on risk factors for the development of cervical cancer.
- The vaccine.

Secondary prevention aims to diagnose precancerous and early forms of cervical cancer and their effective treatment. We include:

- Cytological examination.

HPV vaccines

It is estimated that 80% of women and men will be infected with HPV at least once during their entire lifetime. Most already as teenagers and young people. Usually, the infection occurs within a few months of starting sexual life. Most of them will be eliminated within a few months to 2 years thanks to a well-functioning immune system. Persistence of HPV

infection over 24 months is associated with high oncogenic potential of the virus. Cervical cancer most often develops in women 35-55 years old⁴. To prevent this, vaccines have been created. There are 3 vaccines registered and available in Poland to protect against HPV infection. They are all preparations of purified, virus-like particles of various HPV types. Those are:

- Cervarix, human papillomavirus 2-valent vaccine directed against types HPV-16, HPV-18,
- Gardasil, human papillomavirus 4-valent vaccine directed against types HPV-6, HPV-18, HPV-6 i HPV-11
- Gardasil 9, human papillomavirus 9-valent vaccine directed against types HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58.

Vaccines are given depending on age in 2 (9-14 years) or 3 (over 14 years) doses.

Primary prophylaxis by means of vaccination is recommended in the Polish vaccination calendar for girls and boys before sexual initiation in accordance with the schedule provided by the manufacturer. Vaccines are available free of charge for teenagers only in some preventive programs run by the local authority. Local programs are organized but their coverage probably does not exceed 10% in the 12–14-year-old cohort. Due to the high cost of the vaccine, few people decide to buy it themselves. The Ministry of Health in January this year announced that from 2021 the vaccine will be included in the mandatory vaccination calendar for girls⁵.

On June 28, 2019, the US Advisory Committee on Immunization Practices (ACIP) issued two recommendations on the use of the human papillomavirus (HPV) vaccine. First of all, the upper limit of the age indication is currently 26 for women. The age of 21 was left for men. It was also recommended that men and women aged 27 to 45 discuss the possibility of HPV infection with their physicians and receive the vaccine if they are considered at risk of infection. The recommendations did not include people aged > 45 years because the vaccine was not effective in this population⁶.

In 2017, WHO issued its position on preventive vaccinations against HPV. Recommends the introduction of compulsory vaccinations for people aged 9-14, and if additional vaccination measures up to 18 years are available due to their excellent safety profile, population efficiency and effectiveness⁷.

It is too early to assess whether the vaccine will actually reduce the incidence of invasive cervical cancer, as it develops for many years after infection with oncogenic HPV types. So far, population efficacy has been confirmed for HPV, condylomata and advanced cervical precancerous infections. These are changes that appear relatively quickly after contact with HPV (the period of incubation of condylomas and precancerous conditions of the cervix is from several to several months). In 2015, the results of a meta-analysis of 20 studies covering 140 million people were published in countries where > 50% of girls were vaccinated. The results of this meta-analysis indicate that the incidence of HPV types 16 and 18 decreased by 68% (relative risk [RR]: 0.32 [95% CI: 0.19-0.52]). The risk of HPV infection types 31, 33 and 45 also decreased (RR: 0.72 [95% CI: 0.54-0.96]), suggesting cross-protection. In contrast, the incidence of condylomas in girls aged 13–19 years decreased by 61% (RR: 0.39 [95% CI: 0.22–0.71]). In addition, there was a decrease in condyloma in men <20. years of age (RR: 0.66 [95% CI: 0.47–0.91]) and in women aged 20–39 years (RR: 0.68 [95% CI:

0.51-0.89]), which indicates the creation of population immunity⁸. Evidence of the population's effectiveness of the vaccine in the prevention of cervical cancer is dependent on the incidence of endothelial cervical neoplasia in the United States, Australia, Denmark, Sweden⁹

Vaccination does not, however, release you from further cytological screening because vaccines do not protect against all types of HPV viruses that are responsible for cervical cancer¹⁰. According to available data, they can prevent the development of 90% of cancers caused by oncogenic types of HPV¹¹.

As numerous studies have shown, all HPV vaccines have a high safety profile. However, there is a risk of side effects such as soreness, redness or swelling at the puncture site, fatigue, headache or fever¹². Vaccines are contraindicated in some situations:

- girls under 10 years of age due to a lack of data on safety and immunogenicity in this age group,
- pregnancy due to the lack of research aimed at administering the vaccine to pregnant women,
- people who are allergic to any of the ingredients of the vaccine,
- people who have a high fever; low fever or upper respiratory tract infection is not a contraindication to vaccination,
- the vaccine may be used during breast-feeding only if the potential benefits outweigh its potential risks,
- no data are available on the use of the vaccine in immunocompromised persons, e.g. patients with HIV or receiving immunosuppressants¹³.

Cytological examination

In Poland, secondary prevention by cytological screening has been present for around four decades as an opportunistic intervention and since 2006/2007 as an organized screening program recommended by the European Union¹⁴. Countrywide organized screening program was introduced in 2006/2007 with a target age group 25–59 years of age and a 3-year screening interval¹⁵. Current recommendations of the Polish Society of Gynecology (PTG) indicate the need for annual cytological control of women after 25 years of age. At the time of early sexual intercourse, a cytological examination should be performed no later than three years after sexual initiation. If the results of cytological smears are correct and there are no risk factors for cervical cancer, then screening may be carried out every three years¹⁶. It is a microscopic examination that allows you to assess the state of the cell, its structure and characteristics. Preventive cytological examination is performed after menstruation, in the first phase of the cycle¹⁷. The tool used for collecting cyanological material is the Cervex-Brush. The advantage of this type of brush is the use of one tool, which is used to collect material from the vaginal part and cervical canal and to make a smear on one slide. Cytological smear is assessed according to the Bethesda system. Such a diagnosis is a descriptive diagnosis and includes: smear quality assessment, description of the cells found, presentation of the probable histological picture of the lesion being assessed and suggestions regarding patient management¹⁸. Cytological examination does not prevent infection with the

human papillomavirus HPV, which causes cervical cancer. It only helps to identify early signs of disease that may suggest infection.

The role of new cytological techniques that can be used in population cervical cancer screening in recent years increases. These include thin-layer cytology, also known as liquid-based cytology (LBC), which is a modification of the traditional method of cytological examination. The exfoliated epithelial cells obtained from the disc and cervical canal are transferred to a tube with a fixative fluid (liquid transport medium). During laboratory treatment, the collected material is filtered and automatically distributed on the surface of the microscope slide, and then dyed. This technique allows filtering and separating most of the impurities from the suspension (blood, inflammatory cumen), reducing the error of material collection and reading¹⁹.

The ASC (American Cancer Society) guidelines of 2002 recommend performing liquid cytology in a group of women under 30 years old at two-year intervals or conventional cytology annually. In a population of thirty-year-old and older women who had three consecutive cytological test results negative, these tests may be performed once every three years²⁰.

The Polish Gynecological Society recommends that in the diagnosis of cervical cancer use cytological examination and HPV DNA test as two complementary elements of a multistage cervical cancer prevention program.

According to Reksy, only 20–35% of women at screening age (30–59 years) perform a cytological examination²¹.

New technologies in cervical cancer screening - Human papillomavirus-based cervical cancer screening

Cervical cancer screening has traditionally been based on cervical cytology. Given the aetiological relationship between human papillomavirus (HPV) infection and cervical carcinogenesis, HPV testing has been proposed as an alternative screening test. The use of amplification techniques in epidemiological studies has shown that cervical cancer samples have 90 to 100% presence of HPV DNA. In the same female population, without HPV lesions, the presence of HPV DNA is detected in 5-20% of cases²².

Virolological diagnostics has been included in the stage of an in-depth preventive screening program. It is implemented when a woman receives a test result with an ASC-US diagnosis.

Further diagnoses may change in patients with diagnosed ASC-US. In most of them, clinical pathology will not be present, and in some, there may even be a significant degree of endothelial epithelial lesions usually detected in subsequent studies. Such women go for colposcopic examination along with a biopsy, which perform a verification function in this system. In another situation, it is recommended to repeat the cytological examination after 6 and 12 months. Due to the costs of further tests and patient anxiety, it is reasonable to perform a selection test in women with ASC-US before referring them for colposcopy²³.

Based on scientific research on the usefulness of HPV DNA tests compared to repeated cytological tests in the selection of patients with ASC-US before colposcopic examination, it was found that three serial cytological tests performed every six months in patients with ASC-US have the same sensitivity to detect CIN2 as and a single HPV DNA test (HC II) performed immediately after the original ASC-US result. Women who are negative for high risk HPV

are excluded from further testing, and women who are positive are referred directly for colposcopy or biopsy if necessary. An alternative to the HPV test is cytology every six months for two years or direct colposcopy.

HPV tests are used to detect the presence of DNA or mRNA of high-oncogenic human papillomaviruses. Tests do not detect CIN changes and cancer. Their role is to verify the abnormal results of the cytological examination, and thus to determine the risk of developing precancerous changes and cervical cancer. A negative HR HPV DNA test result assessing known high-oncogenic types of papillomavirus excludes the presence of CIN 3 and cervical cancer and indicates that the examined woman will not develop cervical cancer within six years. A negative test result, however, does not exclude CIN1 and CIN2, as these changes can be caused by viruses with low oncogenic potential. A single positive test result indicates the presence of viral DNA in the sample, but does not allow for the assessment of the duration of infection²⁴.

For detection of endothelial neoplasia, it is recommended to combine two methods: cytological and molecular (DNA / mRNA) testing, which allows achieving almost 100% certainty that in the coming years the development of cancer is unlikely in such a patient.

Summary

Based on the data presented in the future, detection of cervical cancer may be much more effective due to the use of modern diagnostic methods. Modern diagnostics will detect early precancerous lesions that are easily treatable. The most important element of success is the early application of women for cytological examination and their participation in the Prevention and Early Diagnosis Programs of Cervical Cancer. Vaccination can reduce the number of people infected with oncogenic HPV.

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