



Cervical cancer – risk factors and new opportunities for prevention in Poland

Rak szyjki macicy – czynniki ryzyka i nowe możliwości profilaktyki w Polsce

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Abstract

Introduction and Objective. Cervical cancer is the fourth most frequently diagnosed cancer among women worldwide. In 2020 alone, there were more than 604,000 new cases of this cancer, with a total of more than 340,000 deaths. Despite visible improvements, cervical cancer is still a major global problem. The aim of this review is to analyze the key risk factors associated with the development of cervical cancer, evaluate existing prevention method, and present new opportunities for prevention in Poland.

Brief description of the state of knowledge. The main risk factor for cervical cancer is HPV infection. Other factors, such as HIV and *Chlamydia Trachomatis* infection, oral contraceptives, smoking and multiple sexual contacts, also predispose to the development of this cancer. The recurrence of the disease often depends on the presence of a history of miscarriage, tclinical severity and the treatment used. Prevention includes HPV vaccination, population-based cytological screening of women and HPV testing. In June 2023, Poland enabled the possibility of free HPV vaccination for children aged 12 and 13.

Summary. Cervical cancer remains a major challenge for modern medicine. Statistics have improved significantly in recent years due to the introduction of immunization and greater availability of screening tests. The free vaccination programme in Poland is another step toward developing primary prevention in our country. It is hoped that the situation will also improve in the poorer countries of the world.

Key words

cervical cancer, cervical cancer risk factors, cervical cancer prevention

Streszczenie

Wprowadzenie i cel pracy. Rak szyjki macicy jest czwartym pod względem częstości rozpoznania nowotworem wśród kobiet na świecie. W samym 2020 roku odnotowano ponad 604 tys. nowych przypadków zachorowania na ten nowotwór, zaś liczba zgonów wyniosła ponad 340 tys. Pomimo widocznej poprawy w zakresie leczenia tej choroby rak szyjki macicy wciąż stanowi poważny globalny problem. Celem niniejszej pracy jest analiza kluczowych czynników ryzyka związanych z rozwojem raka szyjki macicy, przedstawienie nowych możliwości prewencji tej choroby w Polsce, jak i ocena istniejących już sposobów jej zapobiegania.

Opis stanu wiedzy. Głównym czynnikiem ryzyka raka szyjki macicy jest zakażenie wirusem HPV. Do rozwoju tego nowotworu predysponują również inne czynniki, takie jak zakażenie HIV i *Chlamydia Trachomatis*, przyjmowanie doustnych środków antykoncepcyjnych, palenie papierosów czy podejmowanie licznych kontaktów seksualnych. Wywiady przeprowadzone z pacjentkami prowadzą do wniosku, że nawrót raka szyjki macicy często zależy od doświadczenia poronienia, stopnia zaawansowania klinicznego choroby oraz zastosowanego leczenia. Profilaktyka obejmuje szczepienia przeciw HPV, populacyjne badania cytologiczne kobiet oraz testy na obecność HPV. W czerwcu 2023 roku wprowadzono w Polsce możliwość darmowego szczepienia przeciw HPV dla dzieci w wieku 12 i 13 lat.

Podsumowanie. Rak szyjki macicy wciąż pozostaje poważnym wyzwaniem dla współczesnej medycyny. W ostatnich latach statystyki uległy znacznej poprawie dzięki wprowadzeniu szczepień ochronnych i większej dostępności badań przesiewowych. Program darmowych szczepień w Polsce to kolejny krok w kierunku rozwijania profilaktyki pierwotnej w naszym kraju. Pozostaje mieć nadzieję, że sytuacja na tym polu ulegnie poprawie również w biedniejszych krajach świata.

Słowa kluczowe

rak szyjki macicy, profilaktyka raka szyjki macicy, czynniki ryzyka raka szyjki macicy

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INTRODUCTION AND OBJECTIVE

Cervical cancer (CC) is the 4th most commonly diagnosed cancer in women worldwide [1]. In 2020 alone, there were more than 604,000 new cases of this cancer, and the number of deaths was more than 340,000 [2]. Current estimates indicate that every year in Poland 3,862 women are diagnosed with cervical cancer and 2,137 die from the disease [3]. Despite visible improvements, cervical cancer is still a major global problem. It is mainly faced in developing countries which lead the way in both morbidity and mortality associated with the disease [4]. The situation is different in developed countries where screening programmes over the last 30 years have reduced the number of new cases and deaths by more than half [5]. Two genotypes of the human papillomavirus (HPV) are mostly responsible for cervical cancer – HPV 16 and 18. Understanding the risk factors and prevention options is crucial in combating the global problem associated with this disease. The aim of the review is to identify risk factors, assess the impact of public education on the risk of developing this disease, as well as analyze available and present new prevention methods for young Polish women and men.

STATE OF KNOWLEDGE

Risk factors – Human papillomavirus (HPV) infection.

Persistent HPV is responsible for 99.7% of cervical cancer cases [6], 70% of which can be attributed to types 16 and 18, and type 16 alone is responsible for 50% of squamous cell carcinomas [7]. The mechanism involves infection of the epithelium of the skin mucosa and production of virus particles in mature epithelial cells. This disrupts the cell cycle and promotes uncontrolled cell division. It is said that more than 70% of sexually active men and women will become infected at some point in their lives [8]. Infection occurs mainly through skin-to-skin contact, with the peak period of infection occurring shortly after the onset of sexual activity. In most cases, the infection resolves spontaneously within two years. Most infections are benign, only a small proportion can persist and lead to cancer. In addition to sexual activity, age is also a factor determining infection. This is due to the highest metaplastic activity, which decreases with age and facilitates HPV infection. The infection most often affects sexually active women aged 19–30. The later stage of cancer occurrence indicates its slow progression [9]. At the same time, it should be remembered that HPV infections which have a longer course are more common with the oncogenic types, and are always an alarming sign.

Oral contraceptives. Already in the 1970s, a connection between OC and the development of CC was suspected. The effect of high-dose preparations was assessed in 300 women with cervical dysplasia compared to healthy women. In the examined women, an increase in the conversion of cervical lesions from dysplasia to CIN was observed [10]. A 2005 report by the International Agency for Research on Cancer (IARC) showed that combined oral contraceptives increase the risk of breast, cervical and liver cancer [11]. There is strong evidence of correlations between the use of oral contraceptives and the risk of CC. An increased risk of cervical cancer and breast cancer has been observed in women who had recently used oral contraception [12], and

the length of its use was also significant. It was observed that among those taking oral contraceptives, the risk of developing CC increased along with the increasing duration of use, and decreased after they stopped taking the drugs. After more than 10 years, it returned to the level found in those who never used them [13].

Chlamydia Trachomatis infection. Research shows that Chlamydia Trachomatis infection may also predispose to the development of cervical cancer. In a multivariate analysis conducted among women with baseline HPV type 16 or 18 infection, women with cervical trachomatis infection were 1.82 times more likely to develop CIN2, compared to women without infection [14]. The reasons for this phenomenon are not well understood. The increased risk may be due to changes in the apoptosis pathway and the DNA repair system, which secondarily may lead to the development of CC [15].

Smoking. It has been known for a long time that cigarette smoke is carcinogenic. It is no different in the case of cervical cancer. According to studies, both active and passive smoking contribute to the development of this cancer. Tobacco smoke as a co-factor affects many signalling pathways involved in cancer initiation and progression [16]. Research limited to HPV-positive women has shown an increased risk of cervical cancer in smokers compared to non-smokers [17]. The problem is the strong correlation between smoking and exposure to sexually-transmitted diseases and the oncogenic role of HPV, which makes it difficult to verify the separate role of cigarette smoking in cervical carcinogenesis. A good method for measuring nicotine intake is to test the level of cotinine, the main component of the distribution of this substance in the human body. Kapeu et al. evaluated the connection between serum cotinine levels and CC risk. They noted that the risk of cervical cancer increased with increasing cotinine intake and age of diagnosis. Based on this, cigarette smoking was identified as an independent risk factor for invasive cervical cancer [18].

Human immunodeficiency virus (HIV). Analyses have shown a noticeable association between HIV infection and cervical cancer risk. At the same time, it should be remembered that HIV-infected women are more likely to develop HPV-related infections [19]. Weakening due to the immunodeficiency virus, in turn, can make it even more difficult to control HPV infection. The role of screening in HIV-positive individuals is also worth emphasizing. This does not look too optimistic in poorer countries. Najjuka et al. conducted a study on this topic in Uganda where 98% of HIV-positive women were aware of CC screening. However, of these, on examining the percentage of those tested, it was only 44%, of whom only 16% had been tested within the last year [20]. In addition, women infected with human immunodeficiency virus were diagnosed earlier with cervical cancer [21].

Sexual behaviour. The effect of multiple sexual contacts on the development of cervical cancer has been a research topic attracting attention for a long time, because sexual behaviour plays a role in cervical cancer risk. Studies have shown that having multiple sexual partners is associated with an increased risk of cervical cancer [22]. It is likely that high exposure to human papillomavirus infection, a major factor

in the incidence of cervical cancer, plays a large role [23]. In addition, starting sexual activity at a young age is another risk factor for CC [24].

Risk factors for recurrence. One meta-analysis showed that miscarriage, clinical stage, and the treatment used had a significant impact on disease recovery. More specifically, the risk of recurrence in patients who have miscarried three or more times increased by as much as 65%, compared to patients without a history of miscarriage. The higher the clinical stage, the greater the chance of relapse. The probability of recurrence in those receiving chemotherapy alone, compared to those treated with surgery alone, was more than three times higher [25].

Situation in Poland. Risk factors in Poland do not differ from those observed worldwide, but the morbidity and mortality rate is one of the highest in Europe [26]. This may be influenced by the fact that 40% of new cases of cervical cancer in Polish women are diagnosed at a more advanced stage [27]. The percentage of people attending screening is also low. Research was conducted on the education of students about the risk factors and prevention of cervical cancer. The majority of students knew that the main risk factor for cervical cancer is infection with the human papillomavirus, while only 40% of students knew that in Poland, the Population-based Prevention and Early Diagnosis Programme is implemented every three years in women aged 25–59 [28]. This shows that prevention education should be a priority in the fight against CC.

Primary prevention. Primary prevention mainly involves avoiding HPV infection. This can be achieved by reducing the number of sexual contacts, or using condoms, but a much more effective way is vaccination against HPV. The United States Food and Drug Administration (FDA) currently approves 3 vaccines to protect against human papillomavirus infection. They are: Gardasil, Gardasil 9 and Cervarix. Each protects against HPV genotypes 16 and 18. Gardasil vaccines also protect against HPV 6 and 11, which are responsible for 90% of genital wart cases, and Gardasil 9 alone even protects against genotypes 31, 33, 45, 52, 58. It is also the only vaccine used in the USA [29]. The other two are still available worldwide. Current recommendations are to vaccinate men and women between the ages of 9–26, and even up to the age of 45 if indicated [30]. Vaccination rates are much higher in wealthier countries where, in 2014, about 32% of women under the age of 20 were fully vaccinated [31]. Research has shown that vaccination prior to first sexual contact provides more than 90% protection against targeted infections and HPV-related complications, while vaccination after exposure to HPV provides only about 50% protection [32].

It has also been reported recently that Gardasil 9-induced antibodies can cross the placenta which potentially protects the infant from HPV genotypes 6 and 11 [33]. Earlier vaccination of the population against HPV before changing sexual behaviour is likely to have a positive impact on outcomes [34]. Research has shown that cancer-causing HPV types, as well as vaccine efficacy, vary by region [35].

New opportunities for prevention in Poland. An interesting new proposal for preventing the development of cervical cancer is undoubtedly the free human papillomavirus

vaccination programme launched in Poland in June 2023 [36]. Previously, vaccinations against HPV have been provided for a fee as part of the recommended vaccination programme, but due to the high costs of vaccines, many parents were forced to give up this type of prevention. In 2021, a 50% refund was introduced, but only free vaccinations maximize the possibilities of protection against HPV infection. An important change is the voluntary nature of vaccination. In doing so, it was necessary to transform the existing law and establish a new fund, which further prolonged the entire implementation process [37]. The vaccination covers girls and boys aged 12 and 13, i.e. adolescents born after 31 December 2009 and up to their 14th birthday. Two types of vaccines are available: 2-valent Cervarix and 9-valent Gardasil [38].

Not just vaccines. Evidence has been provided that a high intake of carotenoids (α -carotene, β -carotene, lutein, zeaxanthin) reduces the risk of CC, especially in people exposed to second hand smoke [39]. Also, vitamin E is a strong antioxidant with anticancer effects in the cervix, which works by preventing reactive oxygen species from oxidizing cellular proteins and DNA. In this case, a meta-analysis showed a significant preventive effect on cervical cancer (cervical dysplasia, cervical cancer *in situ* and invasive cancer) in the highest intake group [40].

The preceding examples effectively demonstrate the positive impact of a healthy diet and supplementation on human health. At the same time, it is important to remember that, despite everything, it is vaccination that is at the forefront when it comes to primary prevention of cervical cancer.

Secondary prevention. Organized screening programmes have reduced the incidence of cervical cancer by up to 80% [41]. Unequal access to screening is a major reason for the significant differences in CC incidence and mortality in rich and poor countries [42]. For decades, cervical cytology has been the mainstay of cervical screening, but recently HPV testing has become increasingly important [43].

Cervical cytology. Involves examining the cervix with a speculum and taking a sample of cells. Examination of the cells allows visualization of normal-looking, low-grade and high-grade abnormalities. Low-grade abnormalities are atypical squamous cells of undetermined significance or squamous cell lesions, and usually indicate HPV infection but do not suggest a precancerous lesion. High-grade abnormalities include atypical squamous cells suggesting a high degree of malignancy and atypical glandular cells. Such lesions require urgent surgical treatment. The specificity of this test is high, while the sensitivity leaves much to be desired. It is important to repeat examinations regularly and frequently [44].

HPV tests. These tests have a higher sensitivity than cytology and a single test can detect about 90% of precancerous conditions and cancers [45]. This allows for safer screening intervals. Researchers suggest that testing for HPV at 5-year intervals results in a lower risk of cancer than a cytology test performed every 3 years [46]. Despite its many advantages, HPV tests have a higher rate of abnormal results relative to cytology. This is said to be about 10% compared to 6% [47]. The golden mean seems to be Co-testing tests, which are a combination of cytology and an HPV test. Co-testing

slightly increases the sensitivity of detecting precancerous lesions and invasive cervical cancer compared to HPV tests [48].

DISCUSSION

The review paper aimed to present in the best possible way the problem of cervical cancer. However, it should be remembered that the data contained in publications do not allow the ideal representation of the situation in Poland and worldwide. Scientific evolution means that information often loses its validity quickly so it is necessary to approach the issue objectively.

SUMMARY

Cervical cancer continues to be a major challenge for modern medicine. In recent years, numerous screening programmes and greater contributions to public education have significantly improved the situation. The free vaccination programme is a good initiative for young Polish women and men, allowing a considerable expansion of prevention options in Poland. Unfortunately, the biggest problem is still in the least developed countries where health care finances do not allow such expenditure. It is to be hoped that in those countries new opportunities will also be created to prevent such a severe disease, as many human lives can still be saved.

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