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THE PROBLEM OF HUMAN PAPILLOMAVIRUS AND THE PREVENTION OF CERVICAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *The human papillomavirus (HPV) is the most common infection transmitted worldwide. It has high oncogenic activity and is the main reason for the development of cervical cancer. Cervical cancer is the leading cancer in women, especially in developing countries. Preventive measures, like vaccination, are of special significance in light of HPV's high prevalence and its connection with cancer.*

The study aimed to *examine current literature data on the role of HPV vaccination in the prevention of cervical cancer.*

Methods: *The analyzed data were obtained from scientific publications, clinical research, and systematic reviews on HPV and cervical cancer prevention. More than 120 full-text sources were examined, of which 27 publications were selected for inclusion in the review.*

Results: *An analysis of numerous epidemiological and clinical studies showed the high effectiveness of HPV vaccination in preventing HPV-associated diseases, including cervical cancer.*

Conclusion: *HPV vaccination is a powerful instrument of primary prevention of cervical cancer and other HPV-associated diseases. The widespread implementation of vaccination, especially in adolescence before the start of sexual activity, has the potential to significantly reduce the global burden of the RSM. However, given the long latent period of disease development, screening programs remain important and should be carried out in parallel with vaccination.*

Keywords: *Human papillomavirus (HPV), vaccination, cancer prevention, cervical cancer.*

Introduction: Human papillomavirus (HPV) is one of the most common sexually transmitted infections. According to epidemiological studies, almost every sexually active person encounters an HPV infection during their lifetime. The highest incidence of infection is observed between the ages of 15 and 25, which coincides with the first years of sexual activity. HPV can cause various diseases - from benign warts to malignant neoplasms, including cervical cancer (CC), anal canal, oropharynx, and other anogenital localizations [1].

Of particular concern is the oncogenic potential of certain HPV genotypes, of which types 16 and 18 are responsible for approximately 70% of cervical cancer cases worldwide. In this regard, primary prevention is of key importance, particularly HPV vaccination, which can prevent the development of malignant diseases associated with persistent viral infections.

The study aimed to examine current literature data on the role of HPV vaccination in the prevention of cervical cancer.

Materials and methods: A search and selection of articles was conducted in the PubMed, Web of Science, Scopus, and RSCI Up to Date databases using the main keywords and phrases: " *human papillomavirus* ", " *cervical cancer* ", " *cervical cancer prevention* ". The review included articles no more than 10 years old and related to the topic of this review. Reports of individual observations, correspondence, letters, and studies not conducted on humans were excluded from the review. To achieve the study's objective, an analysis of data from scientific publications, clinical trials, and systematic reviews on HPV vaccination and cervical cancer prevention was conducted. The following materials were used: the results of randomized controlled trials of HPV vaccines, data on the long-term effects of vaccination, including a reduction in the incidence of cervical cancer and other HPV-associated diseases, systematic reviews, and meta-analyses assessing the effectiveness of vaccines and the results of screening programs. More than 120 full-text sources were studied; the review included data from 27 publications.

Results: According to most authors, more than 88% of patients with invasive cervical cancer are HPV-infected. The etiological structure is dominated by HPV types 16 (70-72%), 18 (13-15%), and 45 (5-7%). Failure to detect high-risk HPV (HRHPV) in cervical cancer is associated, among other things, with false-negative test results. The conducted literature analysis revealed a relationship between HPV status and age, morphological form of the tumor, vi-

ral load, HRHV genotype, presence of deep stromal invasion, and metastatic lesions in the lymph nodes. Regarding the molecular genetic parameters of HPV HCR, such as viral load and HPV DNA integration, the association with prognostically important clinical indicators of cervical tumors, including disease stage, locoregional tumor process prevalence, and tumor histological type, remains a subject of discussion [2].

Many publications state the presence of a correlation between the HPV status and the HPV genotype of the HCR, with such an important factor influencing the results of cervical cancer treatment as the morphological form of the tumor. Ambiguous conclusions on the presence of a relationship between several molecular genetic parameters of HPV infection and the main prognostic factor - the stage of the disease (caused by both the heterogeneity of samples, the use of various test systems, and insufficiently complete consideration of the main parameters of HPV infection, primarily data on the integration of viral DNA), make it advisable to conduct further studies on a representative group of patients with homogeneous diagnostic protocols for determining the most complete spectrum of HPV parameters of the HCR. In addition, the conducted analysis of the literature showed the promise of searching for predictors of the effectiveness of specialized treatment of patients with cervical cancer among such HPV infection parameters as HPV status, HPV genotype of the HCR, and the significantly associated physical status of viral DNA [2].

However, recent research findings suggest opportunities for cervical cancer prevention in resource-limited settings by adopting a combined vaccination and screening strategy, which has been proven to be cost-effective in several low- and middle-income countries. The 2020 American Cancer Society guidelines update recommends that women initiate cervical cancer screening at age 25 years and undergo primary HPV testing every 5 years until age 65 years as the preferred option [3].

Further studies are needed to clarify the prognostic value of HPV DNA integration and other molecular parameters of these HPV genotypes. The relevance of this issue is likely to increase over time with widespread HPV vaccination, which is expected to reduce the prevalence of the more aggressive HPV genotypes 16 and 18 in cervical cancer [4].

Recently, three large Chinese cohort studies showed that 7.5-15.5% of patients with cervical carcinoma had negative HCR HPV test results on previous cytology specimens. These studies raise the question of whether these negative HCR HPV results represent true HCR HPV-negative carcinomas or false-negative HCR HPV test results due to limitations in cytology specimen testing. This is an increasingly important issue with the increasing push to use only HCR HPV testing for CC screening. This study shows that negative HPV testing on cervicovaginal cytology specimens in women subsequently diagnosed with cervical carcinoma can be explained by the occurrence of true HPV-negative carcinomas in more than half of the patients. These results should be considered in developing future CC screening guidelines [5].

Testing is more sensitive than cytology for the detection of cervical cancer and its precursors. However, there are limited and conflicting data on the efficacy of combining these two methods for screening cervical adenocarcinoma. This multicenter retrospective study examined the screening results of a cohort of Chinese patients subsequently diagnosed with invasive cervical adenocarcinoma to determine the optimal screening method for cervical adenocarcinoma. Both cytology and HCR HPV testing alone showed low screening efficacy, whereas their combination notably improved the primary screening efficacy for cervical adenocarcinoma. Thus, cytology and combined HCR HPV testing may be the most effective screening method for cervical adenocarcinoma [6].

Although cervical cancer is primarily caused by HPV infection, some types of cervical cancer test negative for HPV. Since these HPV-negative types of cervical cancer are often diagnosed at an advanced stage and have a poor prognosis, it is important to understand their molecular pathology. Although cervical cancer treatment is currently not stratified based on HPV positivity, there are cases of HPV-negative cervical cancer that have a worse prognosis than HPV-positive cervical cancer. For example, HPV-negative cervical cancer has been reported to have worse survival than HPV-positive cervical cancer [6]. However, false-negative HPV tests should also be considered, especially those due to improper specimen handling. In addition, metastasis to the cervix from cancers arising from other organs should be excluded, as treatment options vary widely. With the increased availability of HPV vaccines, the number of deaths from HPV-positive cervical cancer has steadily decreased. However, HPV-negative CC is expected to persist in the post-vaccination era, requiring intensive research into carcinogenic pathways and therapeutic targets [7].

Current estimates of HPV infection rates in China vary by geographic region (9.6-23.6%), with two age-specific prevalence peaks in women aged ≤20-25 years and 50-60 years. The most commonly detected HPV genotypes in the Chinese population are HPV-16, 52, and 58. Five HPV vaccines are licensed in China, and several others are in clinical trials. Although modeling studies in China suggest that HPV vaccination is cost-effective, population coverage and uptake are relatively low. Various policies have been implemented to raise awareness and increase vaccination coverage, with the long-term goal of eliminating cervical cancer in China [8, 9].

Most HPV genotypes are characterized by self-limiting infection, with the virus being eliminated by the immune system within 6–12 months. However, if the virus persists in cells, especially those with high oncogenic risk geno-

types, the likelihood of integrating the viral genome into the host DNA increases. This, in turn, can destabilize the cell cycle, disrupt apoptosis, and, potentially, lead to the development of malignant neoplasms [10-12].

Human Papillomavirus Epidemiology and Typification. HPV infection is one of the most common sexually transmitted viral infections. According to the World Health Organization, during their lifetime, up to 80–90% of sexually active men and women encounter infection with one or more types of the virus. The highest peak of infection occurs in the age range of 15–25 years, especially in the first years after the onset of sexual activity.

The human papillomavirus is a heterogeneous group comprising over 200 genotypes, of which about 40 affect the anogenital tract. Depending on the oncogenic potential, HPV is usually divided into types:

– high oncogenic risk (oncogenic) – 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68;

– low oncogenic risk (non-oncogenic) – 6, 11, 40, 42, 43, 44, 54, and others.

The most significant in terms of oncogenic potential are types **16 and 18,** causing about 70% of all cases of cervical cancer. Additionally, about 20% of cases are associated with types 31, 33, 45, 52, and 58. The remaining 10% are less common, but also dangerous types, such as 35, 39, 51, 56, 59, and 68 [13,14].

Types 6 and 11, in turn, do not have oncogenic potential, but are responsible for approximately 90% of cases of anogenital warts, as well as respiratory papillomatosis. The geographic distribution of HPV genotypes can vary, as can the frequency of occurrence of different types depending on the age group and sexual behavior of the population. This makes local epidemiological monitoring relevant, especially in countries with a high incidence of cervical cancer.

Thus, the high prevalence of HPV, the diversity of its types, and the direct link with the development of oncological diseases emphasize the need for large-scale preventive programs, primarily vaccination.

The Role of Human Papillomavirus in Cervical Cancer Development. Cervical cancer is one of the leading cancers in women worldwide. According to the International Agency for Research on Cancer, almost all cases of cervical cancer are associated with persistent HPV infection, mainly oncogenic types. Of these, HPV types 16 and 18 are found in approximately 70% of cases, while the remaining types comprise 31, 33, 45, 52, 58, and others [14,15].

Oncogenic HPV types cause high-grade squamous intraepithelial lesions that, if untreated, can progress to invasive cancer. The key event in the development of neoplasia is viral persistence, i.e., the long-term presence of the virus in epithelial cells without elimination by the immune system. Typically, the infection is eliminated within 6–12 months; however, during persistence, the virus can integrate into the host cell genome, disrupting cell cycle regulation. Integration of the viral genome leads to the overexpression of the E6 and E7 oncoproteins, which diminish the p53 and Rb tumor-suppressing functions, respectively. This contributes to uncontrolled cell division, disruption of apoptotic mechanisms, and accumulation of genetic mutations, which, in turn, lead to malignancy. The median age of detection of precancerous changes in the cervix is approximately 10 years after the onset of sexual activity, which emphasizes the long-term nature of infection progression. At the same time, early diagnosis (for example, using a Pap test and HPV testing) allows for the detection of pathological changes at the preclinical stage and significantly reduces mortality from cervical cancer [14-16].

It is also worth noting that oncogenic HPV types are involved not only in the pathogenesis of cervical cancer, but also other malignant neoplasms: anal cancer (up to 90% of cases - type 16), cancer of the oropharynx, vulva, vagina, and penis. This further increases the importance of combating HPV infection as a global medical and social problem [15,16].

Thus, the presence of persistent HPV VCR is a necessary, although not the only, condition for the development of cervical cancer. Prevention of infection through vaccination is an effective strategy for the primary prevention of this disease.

Vaccination as a Primary Method to Prevent Human Papillomavirus and Cervical Cancer. Vaccination against HPV is currently recognized as the most effective method of primary prevention of cervical cancer and other HPV-associated diseases. Vaccines are developed based on virus-like particles containing the capsid protein L1, which does not carry viral DNA, ensuring the safety and high immunogenicity of the vaccine.

There are three main groups of HPV vaccines on the market:

– The bivalent vaccine (Cervarix) is designed to protect against types 16 and 18;

– The quadrivalent vaccine (Gardasil) affects types 6, 11, 16, and 18;

– The nine-valent vaccine (Gardasil 9) protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The bivalent and quadrivalent vaccines have shown high efficacy in preventing infections and precancerous lesions caused by the corresponding HPV types. The nonavalent vaccine significantly expands the spectrum of protection, covering up to 90% of cervical cancer cases.

Clinical studies and meta-analyses have shown that vaccination:

– reduces the incidence of HPV infection;

– significantly reduces the prevalence of cervical intraepithelial neoplasia (CIN 2/3);

– reduces the incidence of anogenital warts;

– demonstrates a pronounced effect at the population level due to herd immunity.

Vaccines are most effective when administered before the onset of sexual activity. Vaccination is recommended for girls and boys aged 9 to 14 years, and in some countries is also administered to extended age groups up to 26 years and older.

Vaccination coverage of both sexes is of particular importance. Although the direct burden of HPV-associated diseases is higher in women, men are an important link in the chain of transmission of the infection. In addition, they are also susceptible to developing HPV-related cancers of the anus, oropharynx, and penis.

In several countries, there has been a decrease in the incidence of HPV infection and its complications 10–12 years after the introduction of mass vaccination. However, experts emphasize that the effect of vaccination does not appear immediately, and during the transition period, there remains a need for secondary prevention programs, including regular screening and testing for HPV.

Thus, vaccination is an effective, scientifically proven, and safe strategy for the primary prevention of cervical cancer and other diseases caused by HPV. Its widespread implementation allows for a significant reduction in HPV-related morbidity and mortality and is of great importance for public health.

Limitations of Vaccination and the Role of Secondary Prevention. The vaccine is most effective when administered before the onset of sexual activity, which limits protection among adults already infected with the virus.

Even the nine-valent vaccine does not cover *all* oncogenic HPV types. High-risk genotypes not included in the vaccine composition (e.g., 35, 39, 51, 56, 59, 68) continue to circulate worldwide, which, although less frequently, can also cause malignant transformations. And although there is a possibility of cross-protection due to antigenic similarity between types, it is not complete.

Additional limitations include: 1) *low vaccination coverage,* particularly in low- and middle-income countries; 2) *lack of gender parity* in vaccination (in many countries, only girls are vaccinated); 3) *lack of mass revaccination programmes* or antibody titer monitoring; 4) *hesitancy and low public awareness* of the importance of vaccination.

Given these factors, *secondary prevention* continues to play an important role in reducing morbidity and mortality from cervical cancer. The main methods of secondary prevention are: *Pap test* – to detect cellular atypia; *HPV testing* – to determine the presence of HPV HCR; *colposcopy and biopsy* – if the screening results are suspicious.

Early detection of precancerous changes in the cervical epithelium helps prevent the development of invasive cancer, even in the case of HPV infection.

Vaccination should be considered as part of a comprehensive approach to cervical cancer prevention, combined with regular screening, education, and improved access to health care.

Discussion: All are prophylactic vaccines designed to prevent primary HPV infection and subsequent HPV-associated lesions. In the United States, the 9-valent vaccine is specifically approved for the prevention of cancers and precancerous lesions of the cervix, vulva, vagina, anus, oropharynx, head and neck, and genital warts in women and for the prevention of anal, oropharyngeal, and other head and neck cancers, precancerous and dysplastic lesions of the anus, and genital warts in men [17].

Various models have shown that vaccinating both men and women is more beneficial in reducing HPV infection and disease than vaccinating women only, although vaccinating men is less cost-effective than vaccinating women [17,18]. However, cost-effectiveness analyses are limited by not including an estimate of the benefit of reducing other HPV-related diseases [1] in men, as discussed above, and by uncertainty about various variables that influence the impact of vaccinating men. These include vaccination coverage among women, the effect of herd immunity, the range of health outcomes included, and the impact of HPV-related diseases on quality of life [19,20].

According to the Advisory Committee on Immunization Practices (ACIP) guidelines, routine HPV vaccination is recommended for all women and men in the following age ranges in the United States:

– Routine HPV vaccination is recommended between the ages of 11 and 12. It can be administered starting at age 9.

– For adolescents and adults aged 13 to 26 years who have not previously received or completed the vaccination series, catch-up vaccination is recommended.

– For adults aged 27 years and older, catch-up vaccination is generally not recommended [1, 21].

It is noted that the decision to vaccinate people in this age group should be made on an individual basis. The likelihood of prior exposure to HPV vaccine types increases with age; thus, the population benefit and cost-effectiveness of HPV vaccination are lower among older patients [22, 23].

Recommendations from other expert groups for resource-limited settings vary somewhat. The World Health Organization (WHO) recommends that the primary target of HPV vaccination programmes should be girls aged 9–14 years, and that local public health programmes should recommend vaccination of older women only if it is available, cost-effective, and does not divert resources from vaccination of the key target population or screening for cervical cancer [24, 25].

Vaccination at a younger age is also supported by observational studies, which suggest that it is associated with a greater reduction in cervical cancer incidence compared to vaccination at a later age [26-28].

Conclusion: HPV is the leading cause of cervical cancer, as well as other anogenital and oropharyngeal malignancies. Its high prevalence, oncogenic potential of individu-

al genotypes, and ability to persist in the body for a long time make the problem of HPV infection relevant both in clinical and epidemiological terms. Analysis of world literature indicates high efficiency of HPV vaccination as a method of primary prevention of cervical cancer. In countries with high vaccination coverage, there is a reliable decrease in morbidity and mortality.

Modern HPV vaccines are an effective and safe tool for primary prevention. They help prevent infection with the most dangerous types of the virus, significantly reducing the risk of precancerous and malignant changes. However, the full effectiveness of vaccination requires broad population coverage, the start of immunization before the onset of sexual activity, and a gender-neutral approach to vaccination programs.

Limited vaccine coverage, the lack of universal immunity to all HPV types, and the impossibility of treating existing infections highlight the need for a comprehensive approach. In these circumstances, secondary prevention remains important – regular screening examinations aimed at early detection and treatment of precancerous lesions.

Thus, the fight against HPV-associated diseases should be based on the integration of primary and secondary prevention measures, as well as on raising awareness among the population and health workers. Only such an approach allows us to count on a sustainable reduction in morbidity and mortality from cervical cancer on a global scale.

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АҢДАТПА

АДАМ ПАПИЛЛОМАВИРУСЫНЫҢ ПРОБЛЕМАСЫ ЖӘНЕ ЖАТЫР МОЙНЫ ОБЫРЫНЫҢ АЛДЫН АЛУ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Адам папилломасы вирусы (HPV) – әлемде берілетін ең көп кездесетін инфекция. Онда онкогендік белсенділігі жоғары және жатыр мойны обырын дамытудың негізгі себебі болып табылады. Жатыр мойны обырын әйелдерде, әсіресе дамушы елдерде қатерлі ісік аурулары арасындағы жетекші орындардың бірін алады. HPV-нің биік таралуы және оның қатерлі ісікпен байланысы аясында профилактикалық шараларды, мысалы, вакцинацияны енгізу ерекше мәнге ие болады.*

Зерттеудің мақсаты *– жатыр мойны обырының алдын алудағы HPV вакцинациясының рөлі туралы қазіргі әдебиет деректерін зерттеу.*

Әдістері: *Зерттеу мақсатына жету үшін ғылыми жарияланымдардан, клиникалық зерттеулерден және HPV-ге арналған клиникалық зерттеулер мен жүйелік шолулар мен жатыр мойны обырының алдын-алу бойынша мәліметтерді талдау жүргізілді. 120-дан астам толық мәтіндер зерттелді, шолулар 27 жарияланымнан мәліметтерді қамтыды.*

Нәтижелері: *Көптеген эпидемиологиялық және клиникалық зерттеулерді талдау HPV-аспиратталған аурулардың алдын-алу, оның ішінде жатыр мойны обырының алдын-алудағы адам папиллома вирусына қарсы вакцинацияның жоғары тиімділігін көрсетті.*

Қорытынды: *HPV вакцинациясы жатыр мойны обырының және басқа да HPV-аспиратталған аурулардың алғашқы алдын-алудың қуатты құралы болып табылады. Вакцинацияның, әсіресе жыныстық қатынас басталғанға дейін, әсіресе жасөспірімдерде Жасөспірімге дейін жатыр мойын обырынің жаһандық ауыртпалығын едәуір азайтуға мүмкіндігі бар. Алайда, аурудың ұзақ жасырын кезеңі, скринингтік бағдарламалар маңызды болып қала береді және вакцинациямен қатар жүргізілуі керек.*

Түйінді сөздер: *адам папилломавирусы, вакцинация, қатерлі ісіктің алдын алу, жатыр мойны обыры.*

АННОТАЦИЯ

ПРОБЛЕМА ВИРУСА ПАПИЛЛОМЫ ЧЕЛОВЕКА И ПРОФИЛАКТИКА РАКА ШЕЙКИ МАТКИ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Вирус папилломы человека (ВПЧ) является самой распространенной инфекцией в мире, передающейся половым путем. Данный вирус имеет высокую онкогенную активность и считается главной причиной развития рака шейки матки (РШМ).*

РШМ занимает одно из ведущих мест среди онкологических заболеваний у женщин, особенно в развивающихся странах. В свете высокой распространенности ВПЧ и его связи с онкологическими заболеваниями, внедрение профилактических мер, таких как вакцинация, приобретает особую значимость.

***Цель исследования** – изучение актуальных данных литературы о роли вакцинации против ВПЧ в профилактике рака шейки матки.*

***Методы:** Для достижения цели исследования был проведён анализ данных научных публикаций, клинических исследований и систематических обзоров, посвящённых ВПЧ и профилактике РШМ. Было изучено более 120 полнотекстовых источников, в обзор вошли данные 29 публикаций.*

***Результаты:** Анализ многочисленных эпидемиологических и клинических исследований показал высокую эффективность вакцинации против ВПЧ в профилактике ВПЧ-ассоциированных заболеваний, в том числе РШМ.*

***Заключение:** Вакцинация против ВПЧ является мощным инструментом первичной профилактики РШМ и других ВПЧ-ассоциированных заболеваний. Широкое внедрение вакцинации, особенно в подростковом возрасте до начала половой жизни, имеет потенциал существенно снизить глобальное бремя РШМ. Однако, учитывая длительный латентный период развития заболевания, программы скрининга остаются важными и должны проводиться параллельно с вакцинацией.*

***Ключевые слова:** вирус папилломы человека (ВПЧ), вакцинация, профилактика рака, рак шейки матки (РШМ).*

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