OBSTETRICS AND GYNAECOLOGY

HPV-ASSOCIATED CERVICAL CANCER: CURRENT STATUS AND PROSPECTS

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ABSTRACT

Every year, 570,000 new cases of cervical cancer (CC) are diagnosed in the world, and 311,000 people die from this disease. CC is the fourth most common type of cancer and therefore the fourth leading cause of cancer death in women worldwide. Numerous data on the occurrence and development of cervical cancer indicate an association in most cases (up to 90 %) with human papillomaviruses (HPV) of high carcinogenic risk (HCR).

CC prevention strategies are based on screening, and deaths from this oncopathology can be prevented through vaccination and treatment with early detection of the disease.

In this review, much attention is paid to current issues of detection and prevention of HPV-associated pathologies, and cervical cancer in particular, aiming to summarize and analyze the latest international literature data on this issue.

As a result of this study, it was shown that for countries implementing the National program of vaccination against HPV of high carcinogenic risk, a decrease in the incidence of both cervical pathologies of varying severity and other cancers associated with the HPV carriage was registered.

While effective implementation of actual experience and future advances in human papillomavirus vaccine prophylaxis may make it possible for all countries to move to the high levels of vaccination coverage required to eliminate HPV-associated pathologies, the results also suggest that the path to complete cervical cancer elimination as a global public health problem can be extremely difficult due to a number of existing limitations.

Key words: *cervical pathology, cervical cancer, HPV, screening, prevention, vaccination*

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ВПЧ-АССОЦИИРОВАННЫЙ РАК ШЕЙКИ МАТКИ: СОВРЕМЕННОЕ СОСТОЯНИЕ И ПЕРСПЕКТИВЫ

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РЕЗЮМЕ

Ежегодно в мире диагностируется 570 000 новых случаев рака шейки матки (РШМ), и 311 000 человек погибают от этого заболевания. РШМ – четвёртый по распространённости вид рака и, соответственно, четвёртая по распространённости причина смерти от рака у женщин во всём мире. Многочисленные данные о возникновении и развитии РШМ свидетельствуют об ассоциации в большинстве случаев (до 90 %) с вирусами папилломы человека (ВПЧ) высокого канцерогенного риска (ВКР).

В свою очередь стратегии профилактики РШМ основаны на скрининге, а смертельные исходы от данной онкопатологии представляется возможным предотвратить путём проведения вакцинопрофилактики и лечения при раннем обнаружении заболевания.

В представленном обзоре большое внимание уделяется актуальным в настоящее время вопросам выявления и профилактики ВПЧ-ассоциированных патологий, в частности рака шейки матки, с целью обобщения и анализа последних международных литературных данных по данной проблематике. В результате проведения настоящего исследования показано, что для стран, реализующих Национальную программу вакцинации против ВПЧ ВКР, зарегистрировано снижение заболеваемости как патологиями шейки матки различной степени тяжести, так и другими онкозаболеваниями, ассоциированными с носительством данного вируса.

Несмотря на то, что эффективное использование накопленного на сегодняшний день опыта и будущих достижений вакцинопрофилактики папилломавирусной инфекции может позволить всем странам перейти к высокому уровню охвата, который необходим для окончательной ликвидации ВПЧ-ассоциированной патологии, полученные результаты также свидетельствуют о том, что путь к полной ликвидации рака шейки матки как глобальной проблемы общественного здравоохранения может оказаться чрезвычайно трудным в силу ряда существующих ограничений.

Ключевые слова: *патология шейки матки, рак шейки матки, ВПЧ, скрининг, профилактика, вакцинация*

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1. INTRODUCTION

According to the World Health Organisation (WHO), malignant neoplasms are one of the most common causes of death worldwide [1].

According to GLOBOCAN, there were 604,127 new cases and 341,831 deaths from cervical cancer in 2020 [2].

Currently, high incidence and mortality rates from cervical cancer (CC) remain an urgent problem, the solution to which is of great importance in improving the demographic situation both in the Russian Federation and worldwide. We used the joint WHO and IARC-GLOBOCAN project, which provides annual data on cancer incidence worldwide, in order to estimate CC incidence for this literature review (Fig. 1).

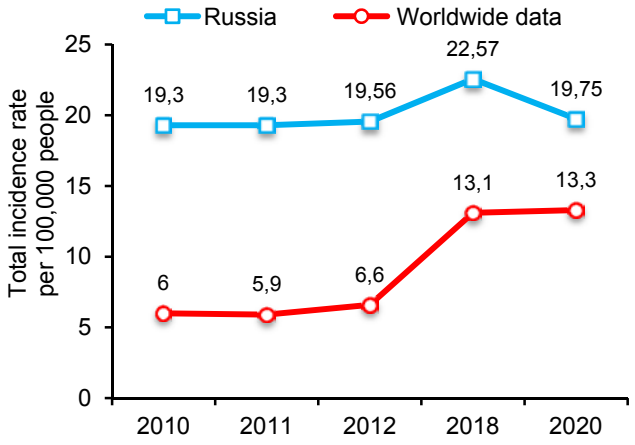

FIG. 1.

Dynamics of standardized worldwide incidence rates of cervical cancer through 2010 to 2020

Over the past two decades, it has become evident that viruses are significant for the development of human malignant neoplasms [3]. Human papillomavirus (HPV) with high carcinogenic risk (HCR) is considered a major cause of CC [4]. CC precursors are premalignant diseases (cervical dysplastic changes of varying severity), as well as various inflammatory conditions and damage to the squamous epithelium of the cervical mucous membrane – cervicitis and cervical erosion, respectively. In this case, human papillomavirus contributes to the acceleration of malignant transformation of the damaged epithelium into malignant pathology. Thus, it is important to perform testing for HPV infection when performing secondary prevention.

As a result of timely detection and treatment of cervical pathology from the moment of HPV initiation, it is possible to prevent the occurrence of both the premalignancy (dysplastic changes of varying severity) and further progression to the development of malignant neoplasm.

The aim of this study is to review the course of HPV infection from infection of female patients without morphological changes in the cervical epithelium to progression to malignancy and to discuss surveillance approaches for monitoring and implementation of public health programs (in particular HPV vaccination for high carcinogenic risk HPV and CC prevention programs) to achieve control and eventual elimination of this cancer.

Methods. A literature search was conducted in PubMed and Google Scholar databases using different variations of the following keywords: cervical pathology, cervical cancer, human papillomavirus, HPV, prevention, vaccination, screening. Full-text articles from 2014 to 2022 were included in the study. The language of the studies was not an obstacle to inclusion in this literature review. A total of 81 references are included in the review.

2. HPV INFECTION

A large body of research in the world literature is devoted to the influence of HPV on the emergence and development of premalignant and malignant processes in various morphological changes of the cervical epithelium. This section summarizes literature data on HPV in female patient groups ranging from healthy patients to CC patients.

The healthy group includes female patients without morphological changes in the cervical epithelium. Worldwide, 10.4 % of women with normal cervical cytological findings are HPV carriers [4]. Higher prevalence was found in less developed regions (22.1 % in Africa, 20.4 % in Central America and Mexico) compared to North America (11.3 %), Europe (8.1 %), Asia (8.0 %) [4]. A study of women with normal cytology published in 2010 showed the highest prevalence of HPV (23.2 %) among women under 25 years of age [4]. HPV 16 was the most common type [5]. For example, the prevalence of this virus in a study of high-risk HPV infection among healthy women in Tehran, Iran, was 5.1 %. HPV 16 was also the most frequently detected genotype. However, it should be noted that in recent years, HPV 31, 33, 45 and 58 have been most commonly detected in many East Asian countries in a cohort of healthy women [6].

Background pathologies of the cervix include diseases such as cervicitis, cervical erosion and endocervical polyps.

Cervicitis is an extremely common gynecological disease among women (30–40 % of cases) aged 20–40 years, characterized by inflammation of the cervix, which increases the risk of sexually transmitted infections [7]. This background cervical disease can cause a number of reproductive system disorders such as endometritis, salpingitis, pelvic inflammatory disease, chorioamnionitis and other complications. Chronic cervicitis was reported to be associated with various stages of cervical cancer progression, including cellular transformation and stimulation of proliferation, invasion, angiogenesis, and metastasis [7].

Depending on the nature of the course of inflammation, viral cervicitis caused by the human papillomavirus is distinguished. In Beijing, China, the prevalence of HPV

among patients with cervicitis was reported to be 75.8 %, among which HPV 16, 18, and 52, three most common HPV types, were detected with an incidence rate of 19 %, 11.6 %, and 15.2 %, respectively [8].

According to epidemiological data, 5–15 % of HPV patients are diagnosed with *chronic* HPV-associated cervicitis. The most frequent unfavorable course and outcome of the disease is noted among women with viral-bacterial or viral-fungal infection of the lower genital tract. In addition, these associations lead to a protracted course of the disease with numerous recurrences. Thus, chronic exo- and endocervicitis, high prevalence of HPV create prerequisites for the formation of premalignant cervical diseases [9]. The International Papillomavirus Society (IPVS; http://ipvsoc.org/) considers HPV-associated cervicitis as a primary marker of cervical premalignancy.

Cervical erosion is a chronic inflammation with the highest incidence of cervical lesions in recent years [10] and is one of the frequent gynecological problems (15–30 % of cases). Erosion occurs as a consequence of cervical infection and represents the basis for cancer, as there is a high risk of HPV contact with basal cells. Currently, data on HPV incidence for this pathology are not presented in the world literature [10, 11].

Endocervical polyps. The etiology of cervical polyps remains unknown, but many theories have been presented. One theory suggests that they can be the result of cervical vascular thrombosis and can disrupt blood flow resulting in the formation of a polyp. Other theories describe that they occur due to infection or chronic inflammation of the cervix [12]. One case study on the association of HPV with endocervical polyps has been mentioned in the literature. It was found that among HPV-positive women, endocervical polyps were present in 6.9 % of cases. However, the most frequent genotypes of HPV-positive samples are HPV 16 and 18 [13].

Cervical dysplasia is divided into two subtypes: low and high malignancy – which are associated with HPV infections to varying degrees.

LSIL (CIN1, cervical intraepithelial neoplasia I) is a low grade squamous intraepithelial lesion [14]. A diagnosis of CIN is not a reason for screening and initiation of treatment, as CIN1 suggests a low risk for the development of severe dysplastic changes [15]. The association between CIN1 and HPV remains controversial. However, there are studies suggesting that CIN1 is mainly caused by HPV of low carcinogenic risk. There is also evidence that HPV of high carcinogenic risk is closely associated with CIN1 [16]. HPV 16 and 18 cause 25 % of CIN1 cases [17]. According to a study conducted in China, HPV 16, 52 and 18 are the most common HPV genotypes in CIN1 [18].

Differences in HPV infection risk and CIN1 outcomes may be related to regional differences in populations [16].

HSIL (CIN2 + (CIN3 + *In situ*)) is a high grade squamous intraepithelial lesion [14].

Preinvasive cervical cancer is a stage of malignant neoplasm in which malignant changes are localized only in the cervical epithelium. In this case, the malignant cells have not yet broken through the basement membrane and therefore have not penetrated even into the subepithelial tissue. Therefore, this stage of the disease is referred to as intraepithelial, null or carcinoma *in situ* [19].

HPV 16 and HPV 18 are known to cause up to 50 % of CIN3, but oncogenic HPV types such as HPV 31, 33, 45, 52 and 58 pose a risk of developing CIN3 equivalent to the risk of HPV 18 [19, 20]. Moreover, a mixed infection of HPV 31 and 33 among women over 30 years of age exceeds the oncogenic risk of HPV 16 [20, 21]. According to a study conducted by Chinese scientists, CIN2 and CIN3 are characterized by the presence of HPV 52, 16, 58, 33 and 18 [18]. It should be noted that genotypes HPV 39, 56, 58 and 68 are associated with a lower risk of progression to CIN3 [21]. HPV 16 is known to have the strongest impact on the development of cervical cancer *in situ* [22].

It is worth noting that **cervical cancer** is a preventable disease. However, it is limited by social and economic status and education level. Most women are poorly informed about the causes, risk factors, prevention and treatment of CC. CC incidence in developed countries remains lower than in less developed countries. In fact, approximately 95 % of deaths from cervical cancer occur in low-income countries. HPV infection is the most significant predominant factor in the development of cervical cancer [23]. According to the literature, HPV 16, 18, 45, 31, 33, 52, 58, and 35 are the most common HPV types among women with CC in descending order of frequency. They account for 91 % of invasive CC cases [9]. However, it is worth noting that worldwide, the percentage of cervical cancer cases caused by HPV 16 and 18 is about 70 % [19]. HPV 68, 26, 66, 67, 73 and 82 are rarely detected in women with CC, but the carcinogen classification system is constantly being updated [24].

3. ONCOGENESIS OF CERVICAL CANCER

3.1. Infection

The cervix is formed by a simple columnar secretory epithelium. The vaginal cavity is lined by a multilayered non-keratinizing squamous epithelium. The epithelium is the area where more than 90 % of lower genital tract malignancies are initiated; it is also particularly vulnerable to high-risk HPV [25].

The process of carcinogenesis, starting with cellular changes caused by HPV infection and ending with CC, can take from 10 to 40 years (but in rare cases CC can also develop in 1–2 years), which provides a window for clinical prevention, diagnosis and treatment [25].

Cervical cancer is a result of a continuous process: normal cervical epithelium after infection with HPV progresses to CIN, then transforms into invasive squamous cell carcinoma (ISC) [26].

A viral infection caused by HPV begins with the virus entering the cervical epithelium through microcracks. HPV genomes then migrate into vesicular nuclei together with L2 protein, where they become low-copy episomes. Once in the host cell nucleus, HPV genomes rapidly replicate to 10–200 copies per cell, marking the initial phase of

amplification and leading to the establishment of infection. During this initial phase, only the early viral promoter is transcriptionally active, leading to the expression of early HPV proteins: E1, E2, E6 and E7.

The expression of E1 and E2 proteins then leads to the regulation of virus replication in infected cells, which leads to the expression of other early-stage proteins. Further, the expression of E5, E6 and E7 oncoproteins starts, which promotes cell survival and uncontrolled proliferation [27].

The presence of E5 leads to inappropriate activation of the epidermal growth factor receptor (EGFR), triggering a series of events followed by the production of vascular endothelial growth factor (VEGF), thereby promoting angiogenesis, which is one of the hallmarks of cancer progression. E6 production leads to repression of several signaling systems. E6 and E6AP can form a complex capable of tagging the p53 protein for its degradation, thereby reducing levels of this tumor suppressor protein. p53 degradation leads to dysregulation of Bcl-2 (a regulator of apoptosis) expression and inhibition of Bak. Moreover, E6 can mark the degradation of Bak, an important pro-apoptotic protein, and bind to p300, thus inhibiting its p53 activation mechanism. In addition, E6 can bind to FAS ("death receptor" whose activation leads to apoptosis) and accelerate its degradation. All these mechanisms triggered by E6 result in apoptosis defense. E7 has the ability to bind to pRB (retinoblastoma protein) of tumor suppressors p107 and p130, which are E2F regulators (transcription factor). This binding releases E2F, which in turn can continuously induce cell cycle progression. In general, interference of HPV proteins leads to uncontrolled cell overgrowth [27].

3.2. Viral persistence and integration

During persistent high-risk HPV infection, HPV integration events known to cause genome instability can often be detected. There is a growing number of studies suggesting that integration of high-risk HPV DNA may be a prerequisite and/or driving force for HPV carcinogenesis, maintenance of a malignant phenotype, and development of cervical cancer [28]. Ongoing studies have established the association of HPV integration with cervical CIN levels, which could potentially be used as a marker to assess the risk of cervical cancer among patients with HPV infection [28]. Numerous studies have shown that HPV integration typically involves disruption of the open reading frames of the viral E1 and E2 regions, leading to activation of the E6 and E7 oncogenes. The E6 and E7 oncogenes have several cellular targets that promote malignant transformation with the mechanism described above, accompanied by increased ubiquitin degradation of p53, Bak, inhibition of pRb and activation of cyclin-dependent kinases [1, 29, 30].

During the infectious process, the virus may be present in episomal, integrated or combined (mixed) form in the host cell genome. In its integrated form, the virus can cause changes in cellular functions that promote replication of viral particles and malignant cell transformation. Currently, there are several hypotheses regarding the correlation between viral status and lesion stage. It has been suggested that the virus is fully integrated into the genome in advanced malignant lesions. Other studies have failed to establish a definite stage of full integration [31]. HPV genome integration has been found in two types: as a single integrated genome and as multiple tandem repeats of the viral genome into the cellular genome [32].

The correlation between structural variations in the host genome and HPV integration is poorly studied. In particular, it is unclear whether tandem integration is preceded by chromosome aberrations that facilitate HPV integration or whether HPV integration causes more extensive chromosomal changes. However, there is information in the literature that the integration of HPV DNA into the human genome causes various genetic alterations such as amplification of oncogenes, inactivation of tumor suppressor genes, inter- or intrachromosomal rearrangements, and genetic instability [33]. While host cell genome instability and HPV genome integration are more common in invasive tumor diseases compared to CIN lesions, it is unknown whether genome instability differs between integrated and non-integrated forms of HPV [34].

3.3. Elimination

Most HPV infections do not cause symptoms and pass spontaneously within 1–2 years due to rapid immune clearance. The immune system eliminates the virus within six months in 50 % of infected women and in 90 % of women within two years of persistence [35]. Approximately 90 % of patients with HPV infection have innate and humoral immune-mediated virus clearance within a few months after viral infection [36].

Only if the infection persists, it can lead to the development of a premalignant CIN lesion (1–2 years) and progression to CC can take up to 10–15 years [37, 38]. Many factors contributing to HPV persistence and triggering carcinogenic pathways remain elusive [39].

During the progression of a premalignant lesion, the host immune system detects infiltration of $CD4^+$-, $CD8^+$-lymphocytes (a type of T-lymphocytes) and macrophages, increase in pro-inflammatory cytokines and induction of neutralizing antibodies [40]. A slow immune response to infection causes a decrease in antibody titers. Neutralizing antibodies (Nab) are triggered after viral infection and target only viral particles and not virus-infected cells, which thus cannot cure the infection. In addition, the role of macrophages and natural killers (NK) involved in the immune response is unclear. Langerhans cells, major antigen presenting cells (APC) in the epithelium, play an important role in the recognition of HPV infection and induction of the cellular immune response [36].

A combination of innate and adaptive immunity prevents HPV infection. Effector T cells targeting early viral proteins can eliminate virus-infected cells. However, the immune response that can protect against re-infection with the same or even a different type of HPV is dis-

puted. Studies attempting to investigate whether antibodies developed after natural HPV infection provide protection against re-infection have provided conflicting results [36]. A US study showed that there was no evidence of homologous immunity against any of the HPV types studied, suggesting that intratype competition is weak or absent [41]. At the same time, according to previous results obtained by these scientists, it has been shown that HPV 16 viral particles can induce low levels of neutralizing antibodies against HPV 31. Clinical trial data have shown that vaccines targeting HPV 16 provide partial protection against HPV 31 [41].

During the HPV persistence phase, during which the host immune system cannot eliminate the virus, expression of E6 and E7 proteins may contribute to lesion progression, which usually results from E2 promoter methylation and viral integration, contributing to immune abnormalities [36].

The development of cervical cancer depends not only on negative regulation of cell cycle control and accumulation of genetic damage by viral oncoproteins, but also on immune evasion [25]. Mechanisms of immune system evasion by HPV include:

• suppression of the antigen presentation mechanism (antigen presentation is the process of presenting a fragment of antigen to a T lymphocyte in order to trigger a T cell response);

• resistance to cytotoxicity mediated by cytotoxic T lymphocytes (CTL);

• recruitment of immune cells that inhibit the immune response, such as immature dendritic cells (DC), tolerogenic DCs, T regulatory cells (Treg), tumor-associated macrophages (TAM) and myeloid-derived suppressor cells (MDSC).

In addition, overexpression of E6 and E7 proteins impairs cellular DNA repair, resulting in genome instability and immune escape [42].

4. POTENTIAL BIOMARKERS OF CERVICAL CANCER

The results of a study published in 2021 involving more than 40,000 women showed that E6/E7 mRNA detection has the highest sensitivity compared to conventional cytological examination and p16/Ki-67 testing [43]. Considering these results, the E6/E7 mRNA assay seems to be a very good candidate for ultrasensitive screening. Scientific consensus on the optimal sensitivity of tests used in cervical cancer screening remains open [43].

TABLE 1

POTENTIAL BIOMARKERS OF CERVICAL CANCER

CC Biomarkers	Sensitivity / specificity, %	Conclusion	Source
miR-9	67.3 % / 80 %		
miR-21	82.7 % / 72 %	miR-9, miR-21 and miR-155 may be prospective biomarkers for the diagnosis of HPV-associated cervical cancer	Park S. et al. (2017) [45]
miR-155	65.4 % / 96 %		
SIM1	38.5 % / 100 %	*SIM1* methylation status may be a potential diagnostic biomarker of cervical cancer	Kim H.J. et al (2018) [46]
SEPT9	89.5 % / 63.3 %	*SEPT9* promoter methylation is a potential biomarker for early detection of cervical cancer and its overexpression may determine radioresistance	Jiao X. et al. (2019) [47]
ZNF582	71 % / 81 %	*ZNF582* can be used as a potential biomarker for CIN3 prognosis	Li N. et al. (2019) [48]
PAX1	86 % / 85 %	Diagnosis of *PAX1* methylation can be included in the cervical cancer screening diagram	Fang C. et al. (2019) [49]
SOX1	96 % / 99 %	*SOX1* sensitivity and specificity make it suitable for use in cervical cancer early detection programs	Zhang L. et al. (2020) [50]

Currently, potential highly sensitive biomarkers for cervical cancer also include *SOX14*. It belongs to a group of genes involved in the binding of high mobility group domains to DNA, which stimulates the differentiation process in the cell cycle. Regarding cervical cancer, *SOX14* potentiates cell proliferation and invasiveness. Detection of *SOX14* allowed differential diagnosis of precancerous lesions and cervical cancer with a sensitivity of 94.12 % and specificity of 86.46 % [44].

In addition to the examples described above, potential biomarkers of premalignant lesions and CC presented in the references are summarized in Table 1.

The JAK/STAT pathway, with which the E6/E7 oncoproteins interact, has been highlighted among the numerous cells signaling pathways involved in cervical cancer carcinogenesis. Signal transmission in this pathway contributes to the tumor progression and the development of metastases. Currently, JAK/STAT pathway inhibitors are known to be of interest in ongoing clinical trials. However, it is important to focus on the evaluation of the recurrence-free period and overall survival of CC patients [51]. Notch is another pathway which is important for cervical cancer progression. This signaling pathway is associated with differentiation of epithelial cells with HPV. Most invasive cases of cervical cancer show cytoplasmic localization of Notch1, with Notch1 in the cell nucleus correlating with worse treatment outcomes [52].

The role of HPV in the development of CC is undeniable. However, the *HLA* (Human Leukocyte Antigen) gene, probably responsible for genetic predisposition to cervical cancer, has attracted the attention of researchers. Several studies in recent years have found independent risk variants associated with the 6p21.3 locus of the *HLA* gene. The estimated inherited susceptibility to cervical cancer infection ranges up to 7 %. However, the authors conclude that studies on larger populations of HPV-negative cases of cervical cancer, which are diagnosed statistically later than HPV-positive cases and correlate with poorer survival, are needed to verify these findings [53].

5. HPV VACCINATION: RESULTS AND PROSPECTS

By understanding the role of HPV in the development of cervical cancer, researchers have focused on developing suitable strategies to detect and prevent this disease [27]. The ultimate goal of HPV vaccination is to reduce the occurrence of cervical premalignancies and inflammatory diseases by preventing infection with the major oncogenic HPV types [54].

Currently, there are three commercially available preventive vaccines that vary in the number of HPV types and target (some are not available in certain countries). Cervarix is a bivalent vaccine targeting HPV 16 and 18; Gardasil is a quadrivalent vaccine against HPV 6, 11, 16, 18; Gardasil 9 is a 9-valent vaccine targeting the same HPV types as the quadrivalent vaccine (6, 11, 16, 18) as well as types 31, 33, 45, 52 and 58 [55, 56]. Quadri- and bivalent first-generation HPV vaccines have been available since 2006 and 2007, respectively [57]. The target group for vaccination recommended by WHO is girls aged 9 to 14 years who are not sexually active because they have a better immune response to the vaccine than adolescents [56].

Large international clinical trials have shown that HPV vaccines are safe and highly effective against persistent vaccine-type infection and premalignant cervical lesions in women (vaccine efficacy ≥ 93 %) [55].

Data demonstrating the high efficacy of HPV vaccination have recently been published for Australia [58]. Due to the success of the HPV vaccination programme, the introduction of vaccination for both sexes, the recent switch to a two-dose vaccination schedule, and the 2017 changes to the National Cervical Screening Programme, estimates suggest that an incidence rate of less than 4 CC cases per 1,000,000 women is likely to be achieved by 2035 if current vaccination coverage rates can be maintained. Therefore, it is likely that Australia will be the first country in the world to eliminate cervical cancer as a public health problem. However, other countries are expected to follow suit within the next decade or two [58].

In addition, HPV vaccination is also effective in preventing cervical diseases [56]. For example, Scotland researchers show a reduction in low and high CIN associated with high utilization of bivalent HPV vaccine at the population level [59]. Results from a recent Japanese study showed that women aged 20–24 years who received HPV vaccine had significantly lower rates of abnormal cervical cytological examination results compared to those who did not receive the vaccine [60]. An Australian study showed that vaccination with quadrivalent HPV vaccine also helps to reduce the incidence of HSIL and LSIL among women [61]. Results of Canadian studies show that HPV vaccination was moderately effective in preventing HSIL among adolescents, but much less effective in older age groups, especially among those with a history of abnormal cytological findings [62]. These two vaccines also protect against HPV 6 and 11, which cause anogenital warts [56].

In 2014, estimated HPV vaccination coverage rates for young and adolescent girls were more than 30 % in developed countries but less than 3 % in less developed regions [58].

In 2018, WHO called for action to achieve global elimination of cervical cancer, and to develop a strategic plan that includes goals and targets for scaling up HPV vaccination, cervical screening, and treatment of premalignant and malignant diseases [58].

Worldwide, at least one dose has been administered to nearly 118 million women [63]. Global vaccination coverage is estimated at 15 % and 40 % in high-income countries. In Europe, full vaccination coverage is estimated at 35 % [64]. 90 % of global CC deaths occur in low- and middle-income countries, which struggle to implement effective prevention programs due to lack of financial resources and low public awareness. However, it is important to note that the situation in these countries should

improve annually. As of mid-2020, 41 % of all low- and middle-income countries have initiated national HPV vaccination programs [65]. The dissemination of vaccination faces a number of challenges such as the cost of the vaccine (in the absence of a national vaccination programme), the lack of information on HPV vaccine, and the difficulty of completing vaccination [66]. The COVID-19 pandemic is expected to increase the above-mentioned challenges to HPV vaccination [67].

Thus, discussions about cervical cancer elimination have largely focused on the opportunities and challenges of vaccination programme scale-up. These disparities in HPV vaccination coverage may explain differences in the incidence, prevalence, and mortality associated with CC around the world.

In countries that have achieved high vaccination coverage, a 73–85 % reduction in vaccine-type HPV prevalence has been noted [55]. It is worth noting that as of December 2019, 124 countries and territories have implemented national immunization programs for HPV vaccination [54].

It has been estimated that current achieved vaccination coverage could potentially prevent up to 12.5–13.4 million cases of cervical cancer by 2069 and could achieve an average cervical cancer incidence of approximately 4 per 100,000 women per year [58].

TABLE 2

IMPLEMENTATION OF CERVICAL CANCER PREVENTION PROGRAMS IN SOME COUNTRIES

Country	National cervical cancer screening programme	National HPV vaccination programme	Source
Russian Federation	No As part of the medical check-up it is mandatory to perform the Pap (Papanicolaou) test that involves collecting cervical cells from the group of women 21–29 years old once every 3 years; group of women 30–65 years old – the Pap test + HPV testing every 5 years.	No	Cervical intraepithelial neoplasia, erosion and ectropion (2022) [70]
Austria	The Pap test (after the age of 18)	Yes, for girls and boys	Sroczynski G. et al. (2020) [71]
Belgium	The Pap test every 3 years, possibility of HPV DNA test	Yes	Jolidon V. et al. (2020) [72]
Czech Republic	Girls over the age of 15 should have the Pap test every year	Yes	Altova A. et al. (2021) [73]
Denmark	Women aged 23 to 49 should have the Pap test every 3 years, women aged 50 to 59 years – every 5 years. HPV test for women aged 60 to 64 – once.	Yes, girls ≥ 12 years old	Pedersen K. et al. (2018) [74]
Estonia	Women aged 30 to 55 should have the Pap test every 5 years	Yes, girls aged 12 to 14	Ojamaa K. et al. (2018) [75]
France	Women aged 25 to 65 should have the Pap test every 3 years	Yes, girls aged 11 to 14. Additional vaccination option for girls aged 15 to 19	de Rycke Y. et al. (2020) [76]
Netherlands	Women aged 30 to 60 should have HPV test every 5 years	Yes, vaccination for girls at the age of 12	de Munter A.C. et al. (2021) [77]
Germany	The Pap test – before the age of 35, co-testing – at ages 35 to 65	Yes, for boys and girls aged 9 to 14	Osowiecka K. et al. (2021) [78]
Australia	The Pap test every 2 years, HPV DNA test every 5 years	Yes, girls aged 12 to 17	Kramer J. (2021) [79]
Portugal	Determined in certain regions of the country (HPV test, the Pap test), performed every 3 years or every 5 years for the age groups of 25–60, 25–64 and 30–65	Yes, girls under the age of 13	Fernandes C. et al. (2022) [80]

6. CERVICAL CANCER PREVENTION PROGRAMS

In 1993, the European Guidelines for Quality Assurance and Principles for this screening were published. This year was the key date for the introduction of cervical cancer screening in Europe [68].

After 2015, the criteria for the screening programme were clearly defined: the age of the target group; the time intervals for the screening test; the algorithm for further management of the patient depending on the results [69]. Table 2 presents current information on the implementation of cervical cancer prevention programs in some countries.

Both screening and HPV vaccination programs do not yet have a unified regime. Most of the countries listed above base CC screening on the Pap tests every 3 years. HPV testing is used in Belgium, Denmark and parts of Portugal. The Netherlands is the only country in Europe where cytology has been completely replaced by HPV testing. A programme based on HPV testing was launched in the country in 2017 [81].

TABLE 3

AGE-STANDARDIZED CERVICAL CANCER INCIDENCE AND MORTALITY RATES PER 100,000 FEMALE POPULATION IN EUROPEAN COUNTRIES IN 2020

Country	Incidence	Mortality
Russian Federation	20.5	8.8
Austria	7.7	2.6
Belgium	11.1	2.9
Czech Republic	13.5	5.2
Denmark	14.8	3.2
Estonia	26.9	6.3
France	10.1	3.2
Netherlands	10.0	2.1
Germany	11.1	3.2
Portugal	15.6	4.6
Australia	6.0	1.7

Many countries have HPV vaccination programs. In Austria and Germany, boys are also vaccinated. Differences in approaches to CC prevention are reflected in the incidence and mortality rates presented in each country. The incidence and mortality rates for cervical cancer, based on data published by the International Agency for Research on Cancer, are presented in Table 3.

The lack of a national HPV vaccination programme speaks volumes. The lowest risk of death among the countries included in this review is noted in Australia, where cytological scrape screening is used in addition to the HPV vaccination programme.

Based on the above, it seems reasonable to standardize recommendations for CC prevention programs. There is both an urgent need to fund HPV vaccination in countries where it is not available and to include HPV HCR vaccination in mandatory National Preventive Vaccination Calendars.

8. SUMMARY AND CONCLUSIONS

In recent years, scientific publications have increasingly drawn conclusions about the need for timely screening measures for the most accurate and effective detection of women with premalignant cervical lesions for early intervention and prevention of malignant neoplasm. It is believed that cervical screening, differentiated management of patients with HPV-associated cervical disease and HPV vaccination will be complementary synergistic strategies for CC prevention in the coming decades.

However, the above arguments suggest that the complete elimination of cervical cancer as a global public health problem may be extremely difficult to achieve due to the following reasons: lack of uniform standards for CC prevention, lack of implementation of a publicly funded HPV vaccination programme in some countries (e. g., the Russian Federation).

In addition to the above, in order to improve the implementation of CC prevention, it is important to highlight the following areas: accelerated evaluation of the clinical efficacy of new diagnostic tools, development of HPV vaccines with wider genotype coverage and shorter dosing regimens.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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