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Strategy of cervical cancer primary and secondary prevention

The lack of screening programs and high prevalence of human papilloma virus (HPV) are the major factors of high of risk of cervical cancer (CC) in low-income and developing countries. The discovery by Harald zur Hausen of connection between chronic persistence of oncogenic HPV (high-risk HPV) and the development of CC marked the beginning of the organization of primary prevention of CC through the creation of vaccines against high-risk HPV, and the development of HPV testing as an emerging strategy for secondary prevention of cervical cancer.

Keywords: pcervical cancer, human papilloma virus, screening, vaccination.

Relevance. Cervical cancer (CC) is one of the most common cancers. It ranks fourth among female cancers and seventh among all malignant tumours. 528,000 new cases of CC were registered during 2012. East Africa (42.7 per 100,000), South Africa (31.5 per 100,000), and Latin America (20.0 per 100,000) have high incidence of CC – more than 30 cases per 100,000 [1]. North America (10.2 per 100,000), Western Europe (8.0 per 100,000), Australia (5.5 per 100,000), New Zealand (5.5 per 100,000), and West Asia (4.4 per 100,000) have the lowest incidence rates [1].

Despite the introduced preventive measures, the mortality remains high. In 2012, Globocan reports about 445,000 deaths related to this disease, with the most part of it (230,000) – in low-income countries. The highest mortality was in East Africa (27.6) – more than 20 cases per 100,000 [1].

Human Papilloma Virus

The human papilloma virus (HPV) is the causative agent of CC [3]. This family of heterogeneous viruses includes more than 200 genotypes; more than 40 types of HPV are transmitted sexually. [4]. Fourteen of HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) are pathogenic or «of high risk» and foster the CC [5, 6].

Although most of the sexually active women get infected with HPV once in life [7], less than 10% of women get chronically infected [8]. Such «chronic» infection with a highly oncogenic HPV genotype contributes to CC [8-10].

The HPV particles were first visualized in the middle of 1900s; in the late 1990s the oncogenic genotypes of HPV were named as a major risk factor for CC. HPV virology is important for understanding the CC development.

HPV belongs to the family of papilloma viruses. Its classification has a clinical significance for the following reasons: (1) only one specific HPV genus is associated with CC; (2) different HPV genotypes have different pathogenicity. HPV are grouped into five genera (α, β, γ, μ and η). A-HPV includes HPV genotypes which infect both the genitals and the oral mucosa [11]. HPV is also grouped in «high risk» and «low risk» categories based on their oncogenic potential. Among the 14 high-risk HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), the two most common types – HPV 16 and 18 – are responsible for 71% cases of CC [12]. Two low-risk HPV types (6 and 11) contribute to the formation of pointed condylomas most of which require specialized treatment [12].

According to the US Centres for Disease Control and Prevention (CDC), about 6.2 million new cases of HPV are registered each year in the US, with about 20 mln people infected today [13]. It is sexually transmitted and widely spread among all sexually active groups of population. The CDC believes that at least half of all sexually active people will be infected with HPV at a certain moment; at that, at least 80% of women are infected at the age of 50 [13]. In the US, 10% of the population has an active HPV infection; in 4%, the infection has caused cytological abnormalities; and in another 1% it has caused genital condylomas [14].

The peak incidence of HPV infection is observed in juniors and adolescents, with 80%-90% probability of infection. The HPV incidence decreases with the age. HPV infection persists in 5%-15% of infected women, while 85%-90% of infections become laboratory-undetectable within two years [15]. Chronic persistence of HPV 16 and 18 causes 70%-75% of CC cases [16]. HIV-infected women are at higher risk of recurrent HPV infection despite ongoing antiretroviral therapy and have a higher risk of cervical neoplasia.

The carcinogenesis in CC includes four stages: the HPV infection of the cervical transformation zone, the persistence of infection, the increase and transformation of HPV infected cells into the cervical intraepithelial neoplasia (CIN III) or adenocarcinoma in-situ (AIS), and progression into an invasive cancer [17]. Minor cell abnormalities, such as abnormal squamous changes of unclear significance (ASCUS), low-grade squamous intraepithelial lesions (LSIL) or abnormal glandular changes in indeterminate significance (AGUS) in cytological smears, or cervical intraepithelial low-grade lesions (CIN I) in histological response may be observed within several months after infection with HPV [17]. With untimely treatment, 40%-50% of CIN III and AIS cases can progress to cervical cancer within 5-30 years [16, 18, 19]. The time between HPV infection and the development of CIN III is shorter than the progression of CIN III to invasive cervical cancer. Despite the improvement of socio-economic status, awareness of the population, the empowerment of women in the fields of education and science, healthy lifestyles, and improved hygiene which promote the reduction of risk of CC, the preventive vaccination of teenage girls against HPV before their first sexual

contact is an economically beneficial and effective primary prevention strategy [20, 21].

Prevention of Cervical Cancer.

The awareness of the chronic infection with high-risk HPV being the reason of almost all cases of CC has led to the development of primary and secondary CC prevention strategy. The strategy includes primary prevention by vaccination of teenage girls before their first sexual contact to prevent HPV infection, and secondary prevention through the detection of precancerous lesions of cervix, such as CIN III and AIS by screening & HPV testing of women above 30 years. Two recombinant HPV vaccines available today – a four-valent HPV vaccine against types 16, 18, 6, and 11; and a bivalent vaccine against HPV types 16 and 18 – contain real viral particles [22]. Both vaccines showed high immunogenicity and significant protection against chronic HPV infection, CIN III, and intraepithelial neoplasia of the anus for women aged 15-26 [22]. In the vaccinated population, both vaccines protect against 70% of cases of CC [25]. The efficacy of vaccines against persistent infection, investigated in phase III clinical trials, exceeded 99% [22]. The vaccine studies showed strong enough immunogenicity and excellent safety in adolescence, although clinical trials did not include girls below 9 years old who are the main target group of the national vaccination program [22]. Evidence on vaccine safety and efficacy in clinical trials, as well as public health guidelines recommend the inclusion of HPV vaccination in the national immunization programs. The most common adverse reactions following vaccination against HPV included pain at the injection site from mild to moderate, headache and fatigue [20].

Vaccination against HPV targeting mainly teenage girls is now a part of the national immunization program in 62 countries [20, 21, 23]. The research on cost-effectiveness supports the vaccination of teenage girls against HPV before their first sexual contact, also in the low-income and developing countries, subject to the availability of vaccines; the cost-effectiveness of vaccination largely depends on cost per HPV vaccine [24, 25]. Even with a significant reduction in the cost of vaccines over the past few years, the cost of vaccines remains a serious problem for low-income countries. In terms of the economic benefits of vaccination, the efficacy and safety of vaccines, the government shall consider the inclusion of a two-dose vaccination against HPV in the national immunization program in developing and low-income countries that can implement this program at affordable prices through multi-level pricing, as well as through the Gavi vaccine alliance or the PAHO (Pan American Health Organization) foundation.

The vaccination of 58 million of 12-year-old girls in 179 countries worth $ 4 B shall prevent 690,000 cases of CC and 420,000 deaths. The vaccination against HPV (adjusted for annual disability and taking into account the cost of GDP per capita) was considered economically efficient in 156 (87%) out of 179 countries [21]. Still, various studies recommend different optimal age for teenage girls' vaccination [26]. Some studies also substantiate the vaccination of boys against HPV [20, 27].

The immunogenicity after two-dose vaccination of teenage girls was close to the three-dose regimen with a proven efficacy against persistent infection and precancerous lesions [28-32]. As the immune effect of two doses for 9-14 year-old girls was comparable to the effect of three doses, the EMA and 10 countries in Central and North America, Africa and Asia got a license for a two-dose vaccination regimen. Canada, Chile, Colombia, Mexico, South Africa, the UK and Switzerland now use a two-dose regimen, while most of the national immunization programs include a three-dose regimen.

In some developed countries, where vaccination was introduced four or five years ago, the preliminary assessment of HPV vaccination programs showed a notable reduction of HPV infection, genital lesions associated with HPV infection, and cervical precancer in the vaccinated population [33-35]. In April 2007, Australia introduced a quadrivalent HPV vaccine for girls aged 12-13 years. More than 70% of the main target group was covered with a three-dose vaccination regime.

The incidence of HPV types 16/18/6/11 has decreased by 77% after the inclusion of HPV vaccination in the national program. In the vaccinated target age group of Australia, the development of condylomas acuminates has decreased by 90%, the CIN III and AIS – by 48% [33, 36]. The population cross-sectional study in Scotland has shown a significant reduction in the prevalence of HPV types 16 and 18 among HPV vaccinated women: 13.6% compared to 29.5% among unvaccinated women [38]. Since the introduction of HPV vaccination in Denmark in 2006, the risk of atypia, or CIN II-CIN III, has decreased among vaccinated women significantly – by 44% [34].

Among the female population of Kazakhstan, CC ranks second after breast cancer. 2 women day from CC daily what causes a significant economic harm to the national economy.

Since 2005, preventive examinations take place in women's health consulting rooms all over the country. In 2008, the order of the Ministry of Health of the Republic of Kazakhstan No. 607 was issued «On the improvement of preventive examinations of certain categories of adult population»; the order No. 665 of 2009 «On Approval of the Rules for Conducting Preventive Medical Examinations of Target Populations» was reissued on 29.12.2014 under № 361. Since 2008, there is a national CC screening program using PAP test and Bethesda classification. [37]. All women aged 30 to 60 years are screened every 5 years. The program was introduced in stages starting from training of specialists, arrangement of women's health consulting rooms and their fitting with vaginoscopes [38]. Liquid cytology was actively introduced since 2011 to provide a number of advantages vs. the traditional method. It is a quick method of investigation and easy way to obtain samples; it also highly sensitive for mild and severe pathologies.

Conclusion. Today, WHO recommends a two-dose vaccination regimen for girls with a minimum interval of six months between doses if the vaccination starts before the age of 15 [34]. This recommendation increases availability of HPV vaccination more affordable in comparison to the three-dose regimen. A three-dose regimen of 0, 1-2 and 6 months is required for girls not vaccinated till the age of 15, as well as for people with weakened immune systems, including HIV infected people. As far as HPV vaccination reduces the prevalence of infection and the development of cervical neoplasia, the screening will reduce mortality from CC among women not vaccinated against HPV. The long-term impact of vaccination on the CC screening will be country-specific and will

depend on immunization, coverage of vaccination, the impact of population immunity, and the starting age for screening.

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