

HPV Infection and Cervical Cancer. Prevention Opportunities

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Abstract

Cervical cancer remains a medical and social problem for our country and requires the implementation of effective strategy for its prevention. The etiopathogenesis of precancer lesions and cervical cancer is associated with the human papillomavirus infection. The proof of the biological significance of papillomavirus infection led to the need to identify the role of individual HPV types, and thus to the rapid development of various specialized virological techniques. The introduction of HPV vaccines does not waive the need of regular screening examinations with Pap smear. The widespread use of cytologic screening, improving the sensitivity of the screening test and the application of HPV vaccines are an actual opportunity to reduce cervical cancer incidence.

Keywords: *Human papillomavirus infection; Cervical cancer; Prevention opportunities*

Introduction

Cervical cancer (CC) is the fourth most common malignant tumor in women worldwide, with about 530000 new cases per year, accounting for almost 12% of all neoplasia in female population. Approximately 270000 deaths of CC are reported globally, representing thus 7.5% of all women who have died of cancer. If the current trend of increasing incidence of the disease continues, more than 1 million new cases may be expected in 2050 [1].

The significance of the problem is further confirmed by the fact that CC is included in the political declaration of the 2011 UN General Assembly Summit for Prevention and Control of Noncommunicable Diseases. In 2013 the World Health Assembly included CC among the priorities of the 2013 - 2020 Action Plan for Prevention and Control of Noncommunicable Diseases.

In Bulgaria, in the recent years, 1,100 new cases were diagnosed, and the death cases are over 350. Nationwide, it is one of the five most common malignancies in women, accounting for 6.5% of all neoplasia [2]. Another unfavorable indicator is the low frequency of pre-invasive forms, which is maintained during the recent years. This defines CC as a medical and social problem for our country and requires the implementation of effective strategy for its prevention.

In the last 30 years, the etiopathogenesis of precancer and cervical cancer is associated mainly with the Human papillomavirus (HPV) infection. In 1983 zur Hausen found HPV in precancer lesions, and in 1985 he described an active transcription of the virus in cancer cells, for which he was awarded the Nobel Prize for medicine in 2008 [3] that marked the beginning of numerous studies that confirmed the place of HPV in the etiology of anogenital neoplasma. Some authors found evidence of papilloma infection in 99% of cervical carcinoma cases [4,5].

Human papillomaviruses are DNA viruses hosted by squamous and metaplastic cells. Genital HPV infection is transmitted mainly by sexual intercourse and is usually observed in the beginning of the sexual life of individuals [6]. It is believed that about 60% of the female population encounter the papilloma virus at least once in their lives, while for most of them the infection is transient [7].

So far about 200 different types of HPVs have been reported, out of which approximately 50 affect the genital tract [8,9]. Their classification is made on the basis of phenotypic characteristics and their nucleotide sequence. Individual HPV types are defined through genomic analysis and actually represent genotypes [10,11].

The biological effects of papilloma viruses are determined mainly by their oncogenic significance. Most often, they are divided into two main groups. The first one includes HPV types associated with benign mucocutaneous changes - types 6 and 11. The second one is associated primarily with the appearance of precancerous and cancerous lesions, out of which 20 are associated directly with CC [13]. Out of them, 16 and 18 are responsible for 70% of cases with CC, 50% for high-grade intraepithelial lesions, and 4 - 25% for low-grade pre-cancerous changes of the cervix [11].

Most cervical changes caused by HPV infection will not progress to invasive carcinoma, even if they remain untreated. The variance between the high incidence of HPV infection and the relatively low incidence of CC shows stepwise gradient - of an increasing burden and decreasing frequency between these conditions. It is believed that in 3 - 10% of women elimination of the viral infection is not achieved, and it persists at a high risk to progress to CC [12].

The main task of primary prophylaxis is to prevent a disease and therefore it is applicable to these forms of malignant tumors, for which there are convincing evidence of their etiological factors [13].

Proving the viral etiology of a given disease is a prerequisite to focus the efforts on the development of specific antiviral vaccines for prevention and treatment [14].

Both authorized anti-HPV vaccines have been produced by using recombinant DNA technology. The antigen is L1 capsid HPV protein, while proteins self-assemble into noninfectious and non-oncogenic units called virus-like particles (VLP), which ensure required immune response through the proliferation of CD4 + and CD8 + T cells and Th1 and Th2 cytokines [13].

The target population of prophylactic vaccines are girls over 10 years of age, as the goal is to prevent the persistent infection, cytological and histological abnormalities associated with HPV 16/18 and ultimately - the development of CC.

The results of comprehensive clinical studies of authorized HPV vaccines convincingly demonstrate their high protective activity. They show efficacy of over 90% in terms of preventing precancerous changes and CC, causally related to vaccine oncogenic types. Data from clinical studies show that both vaccines feature a good immunogenicity and safety profile.

The main target group for vaccination are girls prior to sexual onset - the objective is the formed postvaccination antibodies to protect them against an oncogenic HPV infection by preventing the entering of the virus into the cells of the cervical epithelium [14].

The new WHO guide on cervical screening, accepted by the World Cancer Congress, Melbourne (2014), recommends vaccination with HPV vaccine to girls from the age of 9 to 13 years, with at least two doses. The vaccine prevents the infection with viruses responsible for most cases of CC, while studies have shown that the administration of two doses was as effective as three. According to WHO, this will facilitate the administration of the vaccine and will reduce the price [15].

The introduction of HPV vaccines does not waive the need of regular screening examinations with Pap smear due to the delayed effect of immunization. Furthermore, 30% of the cases of cervical cancer are caused by HPV types, which are not included in the vaccine.

The secondary prevention combines methods to detect malignant tumors at an early stage, or at a stage prior to the development of cancer. The most effective form of secondary prevention appear to be screening tests. They are actively targeted to different population groups, in the absence of a need for medical examination or signs of disease [13].

There are various types of screening. In CC, the organized, population based cytological screening is deemed effective. It may reduce cancer mortality, and in the cases when precancerous conditions are detected and treated – it may lower incidence. If a range of at least 70% of the underlying population is achieved, it is possible to reduce advanced cancers by more than 30% and the mortality rate - by more than 15% [13].

The classic cervical screening is carried out by applying the cytologic method of G.Papanicolaou-L.Koss, which has a sensitivity of 81 - 85% and specificity of 95 - 98% [13]. It is well known that the cytology test has a low diagnostic value for detection of HPV infection. Hence the interest in the detection of HPV to increase the effectiveness of CC screening programs [11].

The prevalence of subclinical and transient HPV infections makes the detection of the virus insufficiently effective means of identifying women at risk to develop CC. DNA-based methods to determine HPV show only the presence of the virus, but not its oncogenic activity, as it is impossible to distinguish between active and latent or transient infection. More recent techniques based on determining the expression of mRNA of the viral E6/ E7 oncogenes improve the diagnostic capabilities by showing the initiation of the process of malignant transformation of cells at a very early stage.

In recent years, the concept of cervical screening attempts to implement some new modern methods that can be summarized in the following directions:

- ✓ Cytology test: automated cytoanalysis and monolayer smears technique.
- ✓ Imaging diagnostic methods: visual inspection, digital cervicography, opto-electronic analysis.
- ✓ Molecular biomarkers: HPV-testing and other new genetic markers.

Conclusion

We may summarize that the widespread use of cytologic screening, improving the sensitivity of the screening test and the application of HPV vaccines are an actual opportunity to reduce CC incidence.

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