HPV Vaccines

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ABSTRACT
According to the literature, viruses cause about 20% of cancer cases. Human Papilloma Virus is very good known oncogenic virus. HPV causing majority of cervical cancer cases, but this virus also causes other cancers, e.g. anal or head and neck cancers. In recent years, the subject of anti-HPV vaccines have become popular. First vaccine was approved by FDA in 2006. Currently, there are three anti-HPV vaccines available on the market. First results of effectiveness evaluation are very optimistic.

Keywords: HPV, vaccination, oncogenic virus, cervical cancer, Cervarix, Silgard, Gardasil

1. INTRODUCTION – WHAT IS HPV?

Human Papilloma Virus (HPV) is one of seven known group of viruses that cause cancer [1]. More than 100 types of this virus have been identified so far, but only 40 types are associated with cancer [2]. Papilloma viruses are small dsDNA-viruses, which causes benign epithelial lesions (warts) [3]. Virion size is 55 nm in diameter [4]. This group of viruses infects various animals, including humans [4]. Papillomaviruses preferentially infect differentiating squamous epithelium, every part of human skin can be infected [3]. Some types of HPVs, such as HPV-16, HPV-18, and HPV-31, have been identified as causal factors of cervical carcinoma and rectal cancer [4]. The ability for HPV oncogenesis was discovered...
and described by a Polish researcher and professor of medicine Stefania Jabłońska in 1972 [5].


*Papillomaviridae* family is divided into over 50 groups. Four main groups are *Alphapapillomavirus, Betapapillomavirus, Gammapapillomavirus* and *Deltapapillomavirus*. The characteristics of each group are shown in the Table 1.

**Table 1.** Classification and characteristics groups of *Papillomaviridae* [6]

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species (examples)</th>
<th>Characteristics</th>
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<tr>
<td></td>
<td></td>
<td>• genetics: E5 ORF region is located between the early and late coding regions</td>
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<tr>
<td>Betapapillomavirus</td>
<td><em>HP</em>-5, <em>HP</em>-9, <em>HP</em>-49, <em>HP</em>-cand92</td>
<td>• preferentially infect human skin;</td>
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<td></td>
<td></td>
<td>• genetics: absent E5 ORF region</td>
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<tr>
<td></td>
<td></td>
<td>• histologically recognizable by cytoplasmic inclusion bodies;</td>
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<td></td>
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<td>• genetics: absent E5 ORF region</td>
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<tr>
<td>Deltapapillomavirus</td>
<td><em>Bovine papillomavirus 1</em>, <em>European elk papillomavirus</em>, <em>Ovine papillomavirus 1</em></td>
<td>• inducel fibropapillomas (hosts: ungulate);</td>
</tr>
<tr>
<td></td>
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<td>• genetics: E5 ORF region is located between the early and late coding regions</td>
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1. 2. Oncogenic potential, epidemiology

HPV viruses with oncogenic potential can be divided into two groups: low oncogenic viruses (e.g. HPV 6, 11, 42, 43, 44) and highly oncogenic viruses (e.g. HPV 16, 18, 31, 33, 35, 39, 45, 46, 51, 52, 56, 58, 67) [2].

Around 75% of sexually active women are infected with HPV at some point in their lives [7,8]. In many cases, the virus usually resolves spontaneously after a few (on average 5.9) months, but the chronic form of infection affects 20% of the women [7,8].
1. 3. Mechanism of oncogenesis

In HPV oncogenesis the E5, E6 and E7 genes are thought to play causative roles [9,10]. Expression of E5 causes increased activity of epidermal growth factor receptor (EGFR) [10]. Protein E6, through interaction with E6AP (an E3 ubiquitin ligase), promotes the degradation of p53 factor [9]. Protein E7 can bind to the retinoblastoma protein (pRb). After binding, E7 disrupts its complex formation with E2F transcription factors [9].

Very important for oncogenesis initiation is integration viral DNA into the host genome. Expression of early HPV genes E1 and E2 is compulsory for later E6 and E7 activity [10].

**Figure 1.** HPV genome (from: Wikipedia)

1. 4. HPV life cycle [9-12]

1) Penetration into the host cell initiated by viral protein L1 (clatrin-associated endocytosis);
2) Transport L2-viral DNA complex to the host-cell nucleus;
3) Uncoating;
4) Maintenance viral DNA as an episome (by expression of proteins E1 and E2);
5) Expression of E6 and E7 proteins (controlled by E1 and E2);
6) (from this point only in keratinocytes) Stimulation expression of E1, E2, E4 and E5 proteins;
7) Viral genome replication;
8) Synthesis of late proteins – L1 and L2;
9) Assembly and release of the virus.

2. OTHER ONCOGENIC VIRUSES

<table>
<thead>
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<th>Table 2. Oncogenic viruses – basic information [13-19]</th>
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<tr>
<td>Genetic material</td>
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<tr>
<td>DNA</td>
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According to the literature, viruses cause about 20% of cancer cases [2]. There are different forms of viruses and different oncogenic mechanisms. Table 2. is presenting basic information about these viruses.

3. VACCINES AGAINST HPV

In recent years, the topic of vaccination against HPV has become very popular. Vaccines contain human papillomavirus virus-like particles (HPV VLP), which can be generate by synthesis in vitro the major virus capsid protein L1 [20]. Particles are antigenically almost identical to native virions [20]. Animal studies indicate that the administration of HPV VLP induces high levels of serum IgG anti-L1 antibodies [20]. It has also been shown that such vaccines can also cause resistance to other types of HPV virus, but it is significantly lower [20].

HPV vaccines are a relatively new product. First anti-HPV vaccine was developed by Professor Ian Frazer and Dr Jian Zhou in University of Queensland in Australia in 1991 and approved by FDA in 2006 [21]. This vaccine marketed by Merck & Co. is known as Gardasil or Silgard. In 2011 Gardasil was approved in 121 countries [22].

Gardasil is tetravalent vaccine – protects from HPV-6/11/16/18. Types 16 and 18 of virus are responsible for about 70% cases of cervical cancer [23]. Types 6 and 11 are not oncogenic, but are responsible for about 90% cases of genital warts [23]. To achieve the highest efficiency, it is recommended to vaccination girls who have not yet taken sexual activity. Tetravalent Gardasil is recommended for men aged 9-26 too, because is giving a protection against warts.

In 2009 FDA approved second anti-HPV vaccine – Cervarix [24]. This bivalent vaccine (anti-HPV-16/18) is marketed by GlaxoSmithKline concern. Cervarix contains AS04, an adjuvant that has been found to boost the immune system response [25]. In the USA, Cervarix is approved for females 10 through 25 years old. Cervarix not protects from warts – this is vaccination against only two types of oncogenic viruses. Same as Gardasil, is recommended to vaccination girls who have not yet taken sexual activity, but not recommended for men – types 16 and 18 do not cause warts [25].

The newest anti-HPV vaccine is Gardasil-9. This vaccine has been approved in 2014 [26]. It protects against 5 additional types of HPV (HPV-31, HPV-33, HPV-45, HPV-52, and HPV-58) compared to the first-generation Gardasil [26]. These types are responsible for 20% cases of cervical cancer [26].

4. RESULTS OF VACCINATION PROGRAMMES, FUTURE

By August 2014, 58 countries (30%) had accepted HPV vaccine in their national vaccination programme for girls [27]. Some countries had accepted this vaccine also for boys [27]. The newest data about effectiveness of vaccination are very optimistic. In USA, 6 years after vaccine introduction, there was a 64% decrease in 4vHPV type prevalence among young females (aged 14 to 19 years) and a 34% decrease among females aged 20 to 24 years [28]. The high efficacy of vaccination has also been proven for other than cervical carcinoma caused by HPV [29]. Three dose efficacy, which prevent CIN 2 or worse by any HPV type is
about 62% for both vaccines Cervarix and Gardsail-9; the three dose efficacy which prevent CIN 3 or worse by any HPV type is 93% for Cervarix and 43% for Gardasil-4, no data for Gardasil-9 [29]. These optimistic results let us suppose that universal vaccination programs will prevent many of the HPV-induced cancers in the future [29]. However, the screening programmes are still the most important [29].

5. CONCLUSIONS

- The effectiveness of HPV vaccines makes it possible to look optimally in the future: widespread vaccination would probably drastically reduce cervical cancer incidence.
- Today's important challenge seems to convince the public that universal vaccination against HPV should be an important objective.

References


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