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REVIEW ARTICLE

Primary prevention of cervical cancer: prophylactic human papillomavirus vaccines

A. Mandic

Oncology Institute of Vojvodina, Department of Gynecologic Oncology, Sremska Kamenica, Serbia

Summary

Human papillomavirus (HPV) is one of the most common sexually transmitted diseases worldwide. Cervical and anal intraepithelial neoplasia, genital warts, and recurrent respiratory papillomatosis such as cervical and other anogenital cancers, are HPV-associated diseases.

Prophylactic HPV vaccines are composed of HPV L1 capsid protein that self-assembles into virus-like particles (VLPs) when expressed in recombinant systems. The two types of prophylactic vaccines are designed a bivalent vaccine to protect against high-risk HPV types 16 and 18 and a quadrivalent vaccine designed to protect against HPV 16 and 18, and low-risk, genital wart-causing HPV 6 and 11.

Proof-of-principle trials have suggested that intramuscular injections of VLPs result in strong adaptive immune responses that are capable of neutralizing subsequent natural infections.

Recent research on the safety and efficacy of candidate prophylactic vaccines against HPV have shown very promising results with nearly 100% efficacy in preventing the development of persistent infections and cervical precancerous lesions in vaccinated individuals.

Key words: cervical cancer, human papillomavirus, vaccines

Introduction

Cervical cancer is a major cause of death in women of reproductive age in parts of the developing world [1]. In developed countries, incidence and mortality rates for cervical cancer have declined, due to the effectiveness of screening programs that assess cervical cytology by Papanicolaou smear method [2]. Approximately 80% of women will acquire a HPV infection in their life time [3]. Cervical cancer of both squamous and adenocarcinoma types is considered to be 100% attributable to persistent infection with oncogenic HPV types [3-5].

HPV

Papillomaviruses are small DNA viruses of the Papillomaviridae family, that infect epithelial tissues. Whether cutaneous or mucosal, the more than 100 types of HPV described have in common a circular DNA genome of about 8000 base pairs. These small genomes are organized into an early, a late, and a long control region. The products of 2 genes from the early control region, genes *E6* and *E7*, are essential in the HPV-induced processes of cellular transformation and immortalization, and 2 genes from the late control region, genes L1 and L2, encode the viral capsid proteins (Figure 1).

There are many studies showing the importance of persistent HPV infections as a major risk for developing cervical intraepithelial neoplasia (CIN), characterized by dysplastic changes with varying degrees of disordered maturation. CIN is classified as either CIN I or low-grade squamous intraepithelial lesions (LSIL) or CIN II/III or high-grade squamous intraepithelial lesions (HSIL).

These precursor lesions may last continually for several years until some of these HSIL lesions progress into invasive form [6-10]. HPV is one of the most common sexually transmitted diseases worldwide. Clinical manifestations of HPV infection are exceedingly common, and subclinical infection is widespread.

More than 100 types of HPV have been identified

Correspondence to: Aljosa Mandic, MD, PhD. Department of Gynecologic Oncology, Oncology Institute of Vojvodina, Institutski put 4, 21204 Sremska Kamenica, Serbia. Tel: +381 21 48 05548, Fax: +381 21 6613 741, E-mail: aljosa.m@eunet.rs

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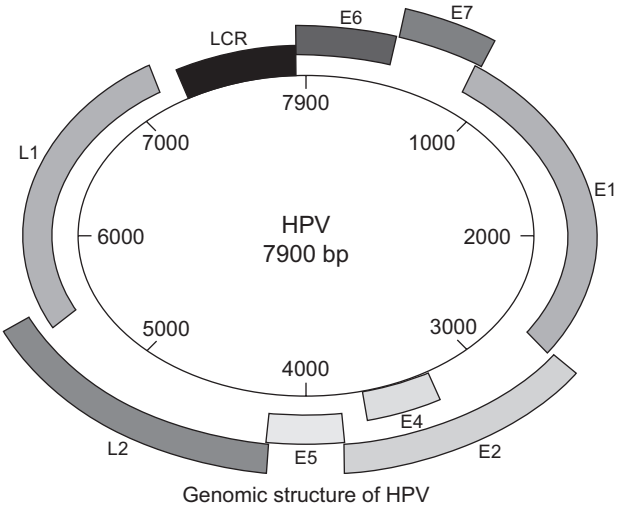

Figure 1. Genomic structure of HPV (Prendiville W et al. HPV Handbook 2004).

up until now, and up to 40 types affect the anogenital region and are divided into 2 groups (Table 1).

Four HPV types are implicated in the majority of HPV-related diseases. These 4 types have been the focus of vaccine development efforts. HPV 6 and 11 are low-risk types associated with the majority of cases of genital warts (90%), and HPV 16 and 18 are high-risk types implicated in approximately 50% of the cases of high-grade CIN, invasive cancer at a variety of anogenital sites, and 60-72% of cervical cancers [9,11].

Vaccine as primary prevention of cervical cancer

Vaccines are major weapons against many serious human pathogens that cause infective diseases, and represent one of the most important discoveries in the history of medicine in general. Following the confirmation that cervical cancer is mostly caused by persistent HPV infection, it was therefore reasonable to assume that a vaccine could prevent HPV infection will reduce the incidence of precancerous or cancerous lesions of the cervix by preventing the major risk factor i.e. a persistent HPV infection. The L1 capsid protein has been targeted for neutralizing antibody formation [12]. Empty VLPs were considered as leading candidates for prophylactic vaccine. Purified VLPs are morphologically identical to natural HPV virions [13,14]. VLPs were found to bind strongly to human and mouse immune cells that expressed markers of antigen-presenting cells (APCs), such as MHC class II, CD80 and CD86, including dendritic cells, macrophages and B cells. Because VLPs do not contain viral genetic material, there is no risk of oncogenic progression or productive infection associated with vaccination [15,16].

Table 1. Main low- and high-risk types of HPV

High risk types	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82
Low risk types	6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

Two pharmaceutical companies, GlaxoSmith-Kline (GSK) and Merck&Co., Inc. have led mainly the research and development in prophylactic HPV vaccines. During the last 10 years both companies put forward great efforts to acquire and publish results about the prophylactic effects of two HPV vaccines, bivalent by GSK and quadrivalent by Merck&Co. The main goals of these studies were to get information about the efficacy, immunogenicity and safety of these vaccines. At the beginning of the first decade of the 21st century 2 randomized controlled trials were published with highly promising proof-of-principle results [17,18]. Vaccine efficacy was almost 100% in preventing acquisition of persistent HPV infection (of the target types) in both studies. Both studies also showed encouraging results concerning prevention of CIN but the precision of the estimates of efficacy were much lower, given that these trials had not been designed with sufficient power to detect reduction in CIN incidence [19]. During the next few years several trials were carried out to prove the benefits of both prophylactic vaccines in general populations [20-22].

High-grade CIN (CIN2/3) is accepted as the immediate precursor of invasive cervical cancer and for vaccine licensing; the endpoint of CIN 2/3 or worse has been accepted widely as an ethically acceptable proxy for cervical cancer [23].

Efficacy of vaccination

In women who have no evidence of exposure or infection to the HPV genotypes in the vaccine, both vaccines show high efficacy, with more than 90% reduction in persistent infection (HPV DNA of the same type detected on 2 successive occasions 6-12 months apart in a woman previously being HPV DNA-negative) and 100% reduction in high-grade cervical lesions [24,25]. In the according-to-protocol (ATP) groups in the phase II trial of the bivalent vaccine, there was 100% efficacy against the development of HPV16/18-associated high-grade CIN2/3, despite the small numbers of the accrued individuals [14]. For both the bivalent and quadrivalent vaccines, results of different trials allow for the examination of broad trends in efficacy to prevent HPV 6/11/16/18-related disease in several groups of patients classified according to their HPV status at baseline. The quadrivalent vaccine was 98.2% effective in reduc-

ing the incidence of HPV 6/11/16/18-related disease in women who were serologically and DNA PCR negative at baseline to the relevant HPV type (per-protocol population), as well as in women who had been previously exposed to at least 1 HPV type vaccine at enrollment, but had no ongoing HPV infection [24,25]. Vaccine efficacy against of HPV 6/11/16/18-related disease in an intention-to-treat population was 51.5%, and for high-grade vaginal and vulvar lesions the vaccine efficacy in the per-protocol and intention-to-treat population was 100 and 79%, respectively [26]. Furthermore, the vaccine was shown to reduce the risk of developing disease by 27-28% in those individuals who were post-vaccination PCR positive and seronegative to the same HPV type for an average follow-up of 3 years [26,27] (Table 2).

Similar results were obtained for the bivalent vaccine [21]. Vaccination of HPV16/18 DNA positive women does not enhance clearance of the viral infection [28,29]. In the PATRICIA study with mean follow-up of 34.9 months after the 3rd dose, vaccine efficacy against CIN2+ associated with HPV16/18 was 92.9% (95% CI 79.9-98.3) in the primary analysis and 98.1% (95% CI 88.4-100) in an analysis in which the probable causality to HPV type was assigned in lesions infected with multiple oncogenic types in the according-to-protocol cohort (ATP-E cohort). Vaccine efficacy against CIN2+ irrespective of HPV DNA in lesions was 30.4% (95% CI 16.4-42.1) in the total vaccinated cohort (TVC), that included all women receiving at least one vaccine dose, regardless of their baseline HPV status. In the TVC-naive (no evidence of oncogenic HPV infection at baseline; represents women before sexual debut) the vaccine efficacy was 70.2% (95% CI 54.7-80.9). The corresponding values against CIN3+ were 33.4% (95% CI 9.1-51.5) in the TVC and 87% (95% CI 54.9-97.7) in the TVC-naive individuals. The vaccine efficacy against CIN2+ associated with 12 non-vaccine oncogenic types was 54.0% (95% CI 34.0-68.4; ATP-E) [30] (Table 3).

Immunogenicity

The measurement of specific serum immunoglobulin G (IgG) anti-L1 VLP antibodies by immunoassays in vaccinated and unvaccinated individuals is the main parameter used in the current vaccine trials to monitor vaccine-induced immune responses. VLPs are highly immunogenic and, in VLP-immunised individuals, the peak anti-VLP antibody responses are substantially greater than those made at seroconversion in natural infections [17,31]. Investigators have reported that 60 months post-vaccination the serum concentrations of antibody were falling from the peak level achieved after the 3rd immunization but they were still at least 10-20 times higher compared with antibody concentrations levels after natural HPV infection [21,22]. The long-term duration of protection depends on immune memory and there is evidence that both vaccines induce good immune memory. Increased numbers of circulating memory cells are generated after immunisation with the bivalent vaccine and this is attributed to the novel adjuvant ASO_4 [32]. Early results from a challenge study, in

Table 2. Quadrivalent HPV-6/11/16/18 L1 VLPs vaccine [28]

Concentration	20 µg HP-V6, 40 µg HPV-11, 40 µg HPV-16, 20 µg HPV-18
Adjuvant	Aluminum hydroxyphosphate sulfate
Dose, administration	0.5 ml, intramuscular
Schedule	0, 2 and 6 months
Trial size	9087 vaccinees, 9087 placebo
Age range of participants	16-26 years
Key eligibility requirements	No history of cervical lesions, few sexual partners
Duration	Up to 42 months
Per-protocol	
Efficacy by CIN2 and worse (range)	98% (93-100)
By HPV type: 6/11/16/18	100% / 100% / 97.6% / 100%
Intention-to-treat	
Efficacy by CIN2 and worse (range)	51.5% (41-61)
By HPV type: 6/11/16/18	91% / 100% / 46% / 85%
Per-protocol	
Efficacy by VIN2, VaIN2 and worse (range)	100% (83-100)
By HPV type: 6/11/16/18	100% / 100% / 100% / 100%
Intention-to-treat	
Efficacy by VIN2, VaIN2 and worse (range)	79% (56-91)
By HPV type: 6/11/16/18	89% / 100% / 78% / 67%

HPV: human papillomavirus, VLP: virus-like particle, CIN: cervical intraepithelial neoplasia, VIN: vulvar intraepithelial neoplasia, VaIN: vaginal intraepithelial neoplasia

Table 3. Bivalent HPV-16/18 L1 VLPs vaccine-phase III randomised, double-blind, controlled PApilloma TRIal against Cancer In young Adults (PATRICIA)

Concentration	20 µg HPV-16, 20 µg HPV-18
Adjuvant	AS04; comprised of 3-O-desacyl-4'-monophosphoryl lipid A [MPL] and aluminum hydroxide salt
Dose, administration	0.5 ml, intramuscular
Schedule	0, 1 and 6 months
Trial size	8093 vaccinees, 8069 placebo
Age range of participants	16-25 years
Key eligibility requirements	No more than 6 lifetime sexual partners before study enrolment, had an intact cervix were eligible for inclusion. Women were excluded if they had a history of colposcopy, were pregnant or breastfeeding, or had chronic or autoimmune disease or immunodeficiency
Duration	Mean follow-up 34 months after the third dose
ATP-E	
Efficacy by CIN2 and worse associated with HPV-16/18	92.9%
By HPV type: 16/18	95.7% / 86.7%
TVC-E	
Efficacy by CIN2 and worse associated with HPV-16/18	94.5%
By HPV type: 16/18	95.9% / 91.6%
TVC-naive	
Efficacy by CIN2 and worse associated with HPV-16/18	98.4%

TVC (total vaccinated cohort): included all women who were given at least one vaccine dose and were evaluable for efficacy (ie, had a baseline PCR or cytology sample and one further sample available) irrespective of other criteria, and was intended to represent the general population of young women, including those who are sexually active; TVC-E (Total vaccinated cohort for efficacy): included all women who were given at least one vaccine dose, had normal or low-grade cytology at baseline (ie, negative, atypical squamous cells of undetermined significance or low-grade squamous intraepithelial lesion), and were evaluable for efficacy; ATP-E (According-to-protocol cohort for efficacy) included all evaluable women (ie, those meeting all eligibility criteria, complying with the protocol procedures, without any protocol violations) who were given three vaccine doses, had normal or low-grade cytology at baseline, and were evaluable for efficacy; TVC-naive (Total vaccinated naive cohort): included women who were given at least one vaccine dose, were evaluable for efficacy, and at baseline had normal cytology, were DNA negative for all 14 oncogenic HPV types investigated, and were seronegative for HPV-16 and HPV-18; HPV: human papillomavirus, VLP: virus-like particle, CIN: cervical intraepithelial neoplasia

which 241 vaccinated women were given a boost dose 5 years after enrollment, showed rapid and enhanced antibody responses after the fourth immunisation, characteristic of an anamnestic response [22].

Adverse events

Trials have shown that the bivalent vaccine was very safe, and the adverse events were both mild and transient. The vaccine group had significantly more injection-site reactions than did the placebo group, but these symptoms were transient and mild. General symptoms such as fatigue, gastrointestinal complaints, headache, itching, and rash, were equally distributed between the placebo and vaccine groups.

The quadrivalent vaccine was well tolerated. Injection site reactions were more common in women receiving active vaccine injection, with injection-site pain being the most common adverse event. Headache was the most frequent systemic adverse event. The vast majority of adverse events were mild or moderate (94%), and there were no vaccine-related serious adverse events. Only one patient discontinued treatment due to an adverse event, and this patient was in the placebo group [22,33,34].

Cross-neutralization

There is preliminary evidence that the vaccines may offer some degree of cross protection against types phylogenetically related to the target types, such as HPV-45 (related to HPV-18), HPV-31 (related to HPV-16), HPV-33, HPV-52, and HPV-58, although at antibody concentrations that are 1-2 logs lower than the dominant type-specific neutralizing antibodies [30] (Table 4).

In second-generation vaccines some researchers are considering modifying the L1 molecules that make up the VLPs in such a way that the particle surface induces more broadly neutralizing antibodies. Until now, there are two ways to try to get such a vaccine; using pools of randomly mutagenized L1 genes for the direct ("genetic") immunization of mice, or using the minor structural protein L2. The isolated protein, L2 or specific L2-derived epitopes (e.g., of HPV-16) induce antibodies that neutralize infection by other HPV types but the titers induced by L2 are at least 1000-fold lower than when L1 VLPs are used. Multimerizing the immunogenic epitopes or engineering them onto the surface loops of L1 VLPs have improved the L2-specific immunogenicity, albeit not yet to a satisfactory level. With the introduction of rationally designed and highly efficient

Table 4. Vaccine efficacy against CIN2+ or more associated with HPV types [32]

ATP-E	
Efficacy by CIN2 and worse associated with HPV-31/33/45/52/58	50.3%
By any HPV type except HPV-16/18	54%
By any HPV type	61.9%
By HPV type 31/33/45/52/58	92% / 51.9% / 100% / 14.3% / 64.5%
TVC-naive	
Efficacy by CIN2 and worse irrespective of DNA in the lesion	70.2%
TVC-E	
Efficacy by CIN2 and worse irrespective of DNA in the lesion	30.4%

HPV: human papillomavirus, VLP: Virus-like particle, CIN: cervical intraepithelial neoplasia, ATP-E: the according-to-protocol cohort for efficacy, TVC-naive: the total vaccinated naive cohort, TVC-E: the total vaccinated cohort for efficacy

adjuvants, the antibody titers can be further increased to the point where they may become relevant [35].

Bivalent and quadrivalent HPV vaccines-comparison of immunogenicity and safety

Based on the high efficacy observed for both licensed vaccines in prelicensing studies, any differences in clinical efficacy associated with waning protection between prophylactic HPV vaccines, if they exist, are unlikely to become apparent for many years. Einstein et al. [36]. published their study that was undertaken to compare the immune response to the two prophylactic HPV vaccines using the same methodology for immune response assessment and safety through one month after completion of the three-dose vaccination course in healthy women aged 18-45 years. In the according-to-protocol cohort who were seronegative/DNA negative before vaccination for the HPV type analyzed, became seroconverted for HPV-16 and HPV-18 serum neutralizing antibodies, as measured by pseudovirion-based neutralization assay (PBNA), except two women aged 27-35 years in the quadrivalent HPV vaccine group who did not seroconvert for HPV-18 (98%). Geometric mean titers of serum neutralizing antibodies ranged from 2.3-4.8-fold higher for HPV-16 and 6.8-9.1-fold higher for HPV-18 after vaccination with the bivalent compared with the quadrivalent HPV vaccine, across all age strata. Positivity rates for anti-HPV-16 and -18 neutralizing antibodies in cervicovaginal secretions and circulating HPV-16 and -18 specific memory B-cell frequencies were also higher in the bivalent HPV vaccine group compared with the quadrivalent group. Both vaccines were generally well tolerated. Injection site reactions being most common in the bivalent vaccine group and compliance rates with the three-dose schedules were similarly high (≥ 84%) for both vaccines. The authors concluded that the importance of differences in the magnitude of the immune response between these vaccines is unknown and long-term studies evaluating the duration of efficacy after vaccination are needed for both vaccines [36].

Conclusions

Two HPV L1 VLP vaccines have been developed: a quadrivalent HPV6/11/16/18 and a bivalent HPV16/18, highly immunogenic and well tolerated. Several trials have shown that these vaccines are effective at preventing infection and diseases related to the vaccine HPV genotypes in women who were HPV DNA-PCR-negative at baseline. The protection generated by the vaccines persists for at least 5 years since the antibody levels remain high after 5 years. HPV vaccines are now licensed in more than 100 countries. National and regional immunization programmes aimed at young adolescent girls have been widely implemented, and include catch-up programmes in some countries up to the age of 18 years or older. Incorporation of HPV vaccination in the public health sector is still to be seen in the developing world, mostly due to the vaccine cost.

Despite the good efficacy of vaccines, the secondary screening with Pap test (or HPV DNA testing) will still be required to detect cervical cancers and pre-cancers caused by non-vaccine HPV types. The vaccines do not protect against all high-risk types of HPV and the prophylactic vaccination has no therapeutic effects on pre-existing precancerous lesions or cervical cancer.

The durability of these vaccines has been evaluated only for up to 5 years. Monitoring of antibody levels and high grade disease caused by the HPV vaccine types in sentinel groups of immunized individuals will be required over the next decades.

Education of physicians, policy makers, parents and adolescents will be crucial for adopting HPV vaccines, which ultimately will result in the reduction of cervical cancer rates and other HPV-related diseases worldwide.

References

1. Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer Statistics, 2001. CA Cancer J Clin 2001; 50: 7-33.
2. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002, Cancer Incidence, Mortality and Prevalence worldwide. IARC CancerBase No. 5, version 2.0, Lyon: IARC Press, 2004.
3. Baseman JG, Koutsky LA. The epidemiology of human papillomavirus infections. J Clin Virol 2005; 32 (Suppl 1): S16-24.
4. Walboomers JM, Jacobs MV, Manos MM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 1999; 189: 12-19.
5. Zur Hausen H. Human papillomavirus in the pathogenesis of anogenital cancer. Mini-review. Virology 1991; 184: 9-13.
6. Koutsky L. Epidemiology of genital human papillomavirus infection. Am J Med 1997; 102: 3-8.
7. Mandic A, Vujkov T. Human papillomavirus vaccine as a new way of preventing cervical cancer: a dream or the future? Ann Oncol 2004; 15: 197-200.
8. Koshiol J, Lindsay L, Pimenta JM, Poole C, Jenkins D, Smith JS. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. Am J Epidemiol 2008; 168: 123-137.
9. Bosch FX, Burchell AN, Schiffman M et al. Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. Vaccine 2008; 26S: K1-16.
10. Trottier H, Mahmud SM, Lindsay L et al. Persistence of an incident human papillomavirus infection and timing of cervical lesions in previously unexposed young women. Cancer Epidemiol Biomarkers Prev 2009; 18: 854-862.
11. Bosch FX, de Sanjose S. Chapter 1: Human papillomavirus and cervical cancer-burden and assessment of causality. J Natl Cancer Inst Monogr 2003; 31: 3-13.
12. Donnelly JJ, Martinez D, Jansen KU et al. Protection against papillomavirus with a polynucleotide vaccine. J Infect Dis 1996; 173: 314-320.
13. Cramer DW, Cutler SJ. Incidence and histopathology of malignancies of the female genital organs in the United States. Am J Obstet Gynecol 1974; 118: 443-460.
14. Kjaer SK, van den Brule AJC, Paull G et al. Type specific persistence of high risk human papillomavirus (HPV) as indicator of high grade cervical squamous intraepithelial lesions in young women: population based prospective follow up study. Br Med J 2002; 325: 1-7.
15. Jansen KU, Shaw AR. Human papillomavirus vaccines and prevention of cervical cancer. Annu Rev Med 2004; 55: 319-331.
16. Lowy DR, Frazer IH. Prophylactic human papillomavirus vaccines. J Natl Cancer Inst Monogr 2003: 111-116 (Ch 16).
17. Koutsky LA, Ault KA, Wheeler CM et al. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med 2002; 347: 1645-1651.
18. Harper DM, Franco EL, Wheeler C et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. Lancet 2004; 364: 1757-1765.
19. Franco EL, Harper DM. Vaccination against human papillomavirus infection: a new paradigm in cervical cancer control. Vaccine 2005; 23: 2388-2394.
20. Stanley M. HPV vaccines. Best Pract Res Clin Obstet Gynaecol 2006; 20: 279-293.
21. Harper DM, Franco EL, Wheeler CM et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. Lancet 2006; 367: 1247-1255.
22. Villa LL, Costa RL, Petta CA et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. Br J Cancer 2006; 95: 1459-1466.
23. Stanley M. Prophylactic HPV vaccines. Clin Pathol 2007; 60: 961-965.
24. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007; 356: 1915-1927.
25. Garland SM, Hernandez-Avila M, Wheeler CM et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) I Investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007; 356: 1928-1943.
26. Kjaer SK, Sigurdsson K, Iversen O-K et al. A pooled analysis of continued prophylactic efficacy of quadrivalent human papillomavirus (types 6/11/16/18) vaccine against high-grade cervical and extra genital lesions. Cancer Prev Res 2009; 2: 868-877.
27. Ault KA; Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007; 369(9576): 1861-1868.
28. Joura EA, Leodolter S, Hernandez-Avila M et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulvar and vaginal lesions: a combined analysis of three randomised clinical trials. Lancet 2007; 369(9574): 1693-1702.
29. Hildesheim A, Herrero R, Wacholder S et al. HPV Vaccine Trial Group. Effect of human papillomavirus 16/18 L1 virus like particle vaccine among young women with preexisting infection: a randomized trial. JAMA 2007; 298: 743-753.
30. Paavonen J, Naud P, Salmerón J et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvant vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. Lancet 2009; 374: 301-314.
31. Harro CD, Pang YY, Roden RB. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. J Natl Cancer Inst 2001; 93: 284-922.
32. Giannini SL, Hanon E, Moris P et al. Enhanced humoral and memory B cellular immunity using HPV16/18 L1 VLP vaccine formulated with the MPL/aluminium salt combination (AS04) compared to aluminium salt only. Vaccine 2006; 24: 5937-5949.
33. Ferenczy A, Franco EL. Prophylactic human papillomavirus vaccines: potential for sea change. Expert Rev Vaccines 2007; 6: 511-525.
34. Mandic A, Petrovic V. Vaccine as new way of prevention of HPV infections, precancerous and cancerous lesions of low female genital tract. Oncology Institute of Vojvodina; Sremska Kamenica, Zamurovic Publ, 2007, pp 9-69.
35. Gissman L. Cross-neutralization. HPV-Today 2009; 18: 6-7.
36. Einstein MH, Baron M, Levin MJ et al. Comparison of the immunogenicity and safety of CervarixTM and Gardasil® human papillomavirus (hPV) cervical cancer vaccines in healthy women aged 18-45 years. Hum Vaccines 2009; 5: 1-15.