Review Article

Human papillomavirus-associated cancers: A growing global problem

Anshuma Bansal, Mini P Singh[1], Bhavana Rai

Departments of Radiotherapy and [1]Virology, PGIMER, Chandigarh, India

Abstract

Human papillomavirus (HPV) infection is linked with several cancers such as cancer cervix, vagina, vulva, head and neck, anal, and penile carcinomas. Although there is a proven association of HPV with these cancers, questions regarding HPV testing, vaccination, and treatment of HPV-related cancers continue to remain unanswered. The present article provides an overview of the HPV-associated cancers.

Key words: Human papillomavirus, human papilloma virus associated cancers, prevention

Submission: 30-10-2014 **Accepted:** 07-12-2015

Introduction

Among all human cancers, 15% are caused by viral infections. Human papillomavirus (HPV) accounts for approximately 600,000 cases of cancers of the cervix, oropharyngeal cancers, anal cancers, vulvovaginal and penile cancers, as well as a genital wart and recurrent papillomatosis of the lungs worldwide.[1] HPV has an exclusively intra-epithelial infectious cycle and infects both the cutaneous and mucosal squamous epithelium. HPV type 16 and 18 are the most common oncogenic viruses among the HPVs that cause cancer.[2]

Uterine cervical cancer, the third most common cancer in women worldwide and the second most common cancer in Indian women, is caused by infection with one of these oncogenic types. In general, HPV has been associated with more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 70% of oropharyngeal cancers and more than 60% of penile cancers.[1]

Address for correspondence: Dr. Bhavana Rai,
Department of Radiotherapy, PGIMER, Chandigarh, India.
E-mail: bhavana1035@gmail.com

Access this article online	
Quick Response Code:	Website: www.ijabmr.org
	DOI: 10.4103/2229-516X.179027

The HPVs belongs to the family *Papillomaviridae* that consists of small, nonenveloped deoxyribonucleic acid (DNA) viruses. The genome of HPV consists of double-stranded cDNA and encodes DNA sequences for six early (E1, E2, E4, E5, E6, and E7) and two late proteins (L1 and L2).[3] The E1 and E2 proteins are the early viral proteins required for replication and translation of virus, E2 also regulates the expression of E6 and E7, E4, and E5 helps in viral assembly and growth stimulation, whereas late proteins L1 and L2 forms minor and major capsid proteins.[3] There are more than 100 types of HPV and based on their sequence they can be divided into alpha, beta, gamma, delta and mu. Papillomavirus that infects cervix and oropharngeal mainly belongs to the genus alphavirus. Further, these viruses can be classified into high risk and low-risk HPV types depending on their oncogenic potential. HPV 16 is considered to have the highest ability to cause cancer.[4]

Biology of Human Papilloma Virus Associated Cancers

E6 and E7 gene product of HPV contributes to the pathogenesis of cancer.[1] The HPV virus integrates with

How to cite this article: Bansal A, Singh MP, Rai B. Human papillomavirus-associated cancers: A growing global problem. Int J App Basic Med Res 2016;6:84-9.

the DNA within the host cell nucleus and thereby dysregulates the expression of the oncoproteins E6 and E7.[5] Degradation of p53 is induced by E6 protein, leading to loss of p53 activity. Its degradation is accomplished through the formation of a complex among p53, E6, and E6AP. In the physiological state, p53 functions to arrest the cells in the G1 phase of the cell cycle and induces apoptosis to allow repair of host DNA. Further, the E7 binds to cyclin-dependent kinase inhibitor, which results in the loss of control over cell cycle.[4]

Pathogenesis

The HPV infects squamous epithelial cells, which have the capacity to proliferate, and get access to basal cell during trauma or abrasion. In the basal cells, HPV infection induces the expression of viral genes that helps in the viral replication. The interaction of HPV with the host cells occurs via surface receptors such as heparin sulfate proteoglycans and alpha 6 integrins. The early proteins E1 and E2 are required for the initiation of replication. The protein E2, being the transcriptional repressor of E6 and E7, controls the expression of E6 and E7. The mode of replication is the rolling circle mechanism during which the virus gets integrated into the human genome. The integration disturbs the E2 gene thereby resulting in a higher expression of E6 and E7 oncoproteins and leading to cell transformation. After the viral replication, the L1 and L2 gene products form the virus capsid and the mature virus is produced. Finally, the virus is released with the help of E4 protein.[5-7]

Mode of Infection

Although HPV is most commonly sexually transmitted, nonsexual transmission and occasionally transmission even through fomites has been known to occur.[8] The risk factors that can contribute to HPV acquisition can be early onset of sexual activity, multiple sexual partners, and use of oral contraceptives. In addition, low socioeconomic status and smoking habit of individuals have reported to increase the risk of acquiring the infection. However, in most of the cases, the infection is subclinical and is cleared by the immune system. The persistence of infection has been linked with oncogenesis.[9]

Molecular Diagnostics

The diagnostic modalities for HPV detection are based on target, signal, and probe amplification.

Target amplification

This technique is based on the duplication of the DNA fragments from a targeted gene sequence. The important one's include.

Polymerase chain reaction

The most important method in this regard is the polymerase chain reaction that uses the primer which is targeted to the viral capsid L1 gene. The commonly used 11 consequences primers are PGMY09/11, GP5+/6+ and SPF10. This can be followed by type specific polymerase chain reaction (PCR) for the amplification of the single genotype of HPV by targeting the type specific DNA sequence. Different types of HPV can be identified.

Amplicor human papilloma virus

This is based on PCR and can identify 13 high-risk HPV (hrHPV) types. This system is based on amplification of DNA, followed by hybridization of nucleic acid.

Linear array human papilloma virus genotyping test

This is a qualitative test for the detection of 37 high and low HPV genotypes. It has the additional capability to detect multiple infections which can occur in 35% of patient samples.[10]

Papillo check

This test is certified in the European Union as an *in vitro* diagnostic test for the qualitative identification of 24 HPV types. It can detect a total of 18 high-risk and 6 low-risk HPV types with a sensitivity of 98%.

Real time polymerase chain reaction

This technique helps to quantify the viral load of HPV. An association has been found between HPV 16 viral load and cervix dysplasia.[11] On the other hand, few studies have shown that low initial viral load implicates worst prognosis in patients with uterine cervical cancer treated with radiotherapy.[12]

APTIMA human papilloma virus assays

This test can be considered as the next generation in cervical cancer screening. It minimizes false positives and helps clinicians to guide the patients for colposcopy. In the negative for intraepithelial lesions or malignancy and clinical evaluation of APTIMA HPV RNA trials, this assay showed 24% less false positive results as compared to hybrid capture. This test is performed from thin prep liquid cytology samples routinely used for pap testing. Unlike other Food and Drug Administration (FDA) approved DNA-based test this detects mRNA overexpressed from E6 and E7 viral oncogenes that are entangled to carcinogenesis. In a cohort of 5006 women from Paris, France; the sensitivity and specificity reported with APTIMA HPV assay in the cohort with CIN III, was 95.7% and 90.3%, compared to 73.3% and 90.8% with liquid based cytology and 95.3% and 84.9% with hybrid capture 2 (HC2).[13]

Signal amplification techniques

This technique uses DNA technology or hybrid capture to increase the DNA signal to detectable levels. These include.

Hybrid capture

This test is based on hybridization in a solution of long synthetic RNA probes.[14]

Care human papilloma virus

This test takes 2½ h this short time test enables the patients to be followed up at the same visit.

Cervista

This is the first FDA-approved genotyping test that can detect 14 high-risk HPV types. These techniques involve signal amplification technique using two simultaneous isothermal reactions.[14] This offers an advantage over hybrid capture because it determines the presence of sufficient DNA for reliable results.[15]

The two assays widely used for detecting genital types are PCR and HC2 assay.[16] However, developing countries face several challenges in widespread adoption of these tests for screening purposes.

Human Papilloma Virus and Cancer Cervix

HPV DNA plays a central role in the etiology of cervical cancer. In one of the Indian population based studies the hrHPV types were found in 87.8% of squamous cell carcinomas (SCC) using PCR-based line blot assay and HPV typing was as follows, HPV 16 (66.7%), HPV 18 (19.4%), HPV 33 (5.6%), HPV 35 (5.6%), HPV 45 (4.6%), HPV 52 (2.8%), HPV 58 (2.8%), HPV 59 (2.8%) and HPV 73 (2.8%).[17,18] Although, hrHPV infection may result in CIN1, in the majority of instances spontaneous regression of the same is also known to occur. However, in those with HPV 16 or 18 infection, with a high viral load, the CIN may persist for a longer time and eventually progress to CIN2/3.[19-24] In this regard, HPV16 viral loads have been reported to be a stronger predictor for the persistence of lesions than the load of HPV-18, 31 and 33.[25] Severity of cervical neoplasia can be measured by HPV 16 loads.[26] Studies have shown that HPV-16 load increased with the increased lesion grade.[27,28] Viral load per unit amount of genomic DNA is a potential HPV-related biomarker, which could predict those at risk of cervical cancer development.[29] Quantitative real time assays utilized to estimate HPV loads have been shown to be specific and reproducible.[30,31]

The prognostic value of HPV genotypes has also been studied in patients with cervical cancer treated with radiotherapy. Wang *et al*. evaluated the significance of the HPV genotypes in 327 patients with cervical cancer treated with radiotherapy alone or concurrent chemo-radiation. Of the 22 genotypes detected in 98.8% patients, the most common genotypes were HPV 16, 58, 18, and 33. A significant improvement was reported in the chemoradiotherapy arm of patients with HPV 18 and HPV 58 positive tumors.[32] In another study by Kahla *et al*., the presence of HPV 16 and intactness of E2 gene was evaluated as a predictor of radiation response. PCR, using specific primers for the L1 region assessed the presence of HPV 16 and E2 disruption was detected by amplifying the entire E2 gene. An increased tendency of HPV 16 E2 negative tumors was observed in advanced stage disease as compared to HPV 16 L1 (75% and 20% respectively). Intact HPV 16 E2 was observed more frequently in untreated patients compared to those who received radiotherapy. The E2 disruption was reported in 75% patients receiving radiotherapy dose of 50 Gy, thus implying that viral DNA status could be of benefit as a marker for optimization of radiation treatment.[33]

Human Papilloma Virus and Incidence Trends for Head and Neck Cancer

Oral infection with HPV is recognized as an independent cause of oropharyngeal cancer. Although a low prevalence (4.5%) of oral HPV has been demonstrated in the general population, studies have shown that 95% of HPV-associated head and neck cancers are HPV 16 related.[34] HPV-associated oropharyngeal cancers typically develop near the base of the tongue and in the tonsils. Sixty-three percent of oropharyngeal cancers each year are associated with HPV infection.[35] A higher incidence of HPV-associated oropharynegeal cancers has been related to an increased number of sexual partners and younger adults. A 4-fold higher incidence has been observed in men as compared to women, and the association of sexual practices with HPV-associated oropharyngeal cancers suggest that sexual partners of cervical cancer patients may be at a higher risk of developing HPV-associated oropharyngeal cancers.[36,37]

HPV data have been retrospectively analyzed in a large randomized trial by Hong *et al*.[38] who examined 198 patients with locally advanced oropharyngeal SCC. Forty-two percent of cancers were HPV-positive. Among the patients treated by surgery with adjuvant radiotherapy (n = 110), definitive radiotherapy-alone (n = 24) and definitive radiotherapy with chemotherapy (n = 47) groups, patients with HPV-positive cancers had a better outcome when treated with radical radiotherapy ± chemotherapy or surgery and adjuvant radiation. The likelihood of loco-regional recurrence, an event or mortality from any cause was only one-third or less as compared to the HPV-negative patients.

Sathish *et al*. have shown that as compared to those with environmentally related cancers, patients with HPV oropharangeal cancer present with a better performance

status, are healthier and have a higher likelihood of a complete response to treatment.[39] Thus, HPV-associated cancers have a favorable outcome with radiotherapy and treatment may be optimized depending on the HPV status so as to achieve the best possible treatment outcome and circumvent treatment-related toxicity and morbidity. Hence, less intensive treatment regimens could be used to achieve a similar treatment efficacy along with decreased toxicity and an improved quality of life. Several ongoing clinical trials are currently under investigation to evaluate the possibility of de-escalation of radiotherapy doses in the treatment of HPV-associated oropharyngeal cancers.[40]

Anal, Penile, and Vulvo Vaginal Cancers

The association of HPV is well-documented in the development of anal cancers. However, an increase in the incidence of this relatively uncommon cancer has been reported over the last few decades. An increased risk of anal cancers has been reported in homosexual men and *Human immunodeficiency virus* (HIV) positive groups. Though there is emerging evidence that anal intra epithelial neoplasia (AIN) is a precursor of anal cancer and unlike cervical cancer, the evidence is mainly from small studies with a follow-up duration of only 5–10 years. Larger studies are required to evaluate the progression of AIN to anal cancers and to study its impact on treatment outcome.[41]

Similar to other HPV-related cancers, an increase in the incidence of vulvar cancers has been also been reported mainly in younger women and mechanisms similar to those of cervical cancer development have been documented. A systematic review has reported a progression rate of 3.3% from vulval intra-epithelial neoplasia to SCC of the vulva.[42] The role of HPV-related vaccine seems encouraging and the Females united to unilaterally reduce endo/ectocervical disease 1 (FUTURE) study has demonstrated a significant reduction of HPV-related anogenital diseases in young women.[43]

Human Papilloma Virus Infection in *Human Immunodeficiency Virus* Positive Host

An increased incidence of ano-genital HPV infection and HPV-associated precancerous lesions has been documented in sero-positive HIV patients compared to the common populace.[44] Both HPV-related cervical and anal cancers have been associated in individuals with HIV-seropositivity. Multiple mechanisms could be responsible for this. First, the HIV-mediated immune attenuation may alter the immune response to HPV. In that situation, tumor response to anti-retroviral treatment would be expected. However, since studies have shown a lack of response to the same, this implies that there might more explanations. HIV might up-regulate HPV gene expression, and HPV and HIV infection might both disrupt tight junctions of mucosal epithelium and facilitate infection with the viruses. Second, HPV clearance has been implicated in HIV acquisition, thereby suggesting an incursion of HPV clearance associated immune cells. Thus, HPV might not only cause cancers resulting in an increased morbidity and mortality through cause of squamous cell cancers but may also increase the risk of HIV infection. If that is so, logically, HPV vaccination could be used in the risk reduction of both HIV and HPV-associated cancers.[44,45]

Human Papilloma Virus Related Cancer Prevention

Two vaccines against HPV prevent the infection by inducing the production of neutralizing antibodies. These are the quadrivalent vaccine Gardasil, marketed by Merck, which protects against initial infection with HPV types 6, 11, 16 and 18. Another bivalent vaccine is Cervarix by GlaxoSmithKline that is, protective against HPV 16 and 18.[46]

So far, HPV vaccines have been used mainly in the prevention of cervical cancer. The vaccines provide little benefit to women already infected with HPV types 16 and 18, which includes most sexually active females. Hence, the ideal time for vaccination should be before the first exposure to HPV infection. Hence, the current recommendations are that this vaccine should be given to 11–12-year-old girls and to those who have not completed or started the series between 13 and 26 years of age.[46] Both vaccines are given over 6 months in three shots. They are approved for use in both males and females in the USA and UK. The vaccine is however not effective if infections or lesions in cervix have already been reportedly caused by HPV.[17,46]

FUTURE I and FUTURE II studies have evaluated the quadrivalent vaccine[47] Papilloma trial against cancer in young adults study and the Costa Rica HPV vaccine trial have evaluated the bivalent vaccine.[48,49] HPV 16 and 18 have been found to be efficacious against infection and cervical lesions associated with HPV16 and HPV18 up to 8.4 years and up to 5 years with the bivalent vaccine, and quadrivalent vaccine, respectively.[50] Cervical screening should be sought by women, even if she has received the vaccine. Furthermore, the recommendations for screening continue to remain the same even for females who have received the HPV vaccine. Since these vaccines have proven efficacy only against the common genotypes 16 and 18, its efficacy against the other genotypes like HPV 33 and other less common oncogenic

subtypes remains questionable. Thus, other preventive and cost-effective strategies continue to play an important role, especially in the context of developing countries.[51]

The two HPV vaccines, i.e. Gardasil and Cervarix approved for the use in cervical cancer prevention by the FDA have been also been approved for other indications. Gardasil is now approved for prevention of genital warts and the HPV-associated precancerous lesions in the anogenital region besides prevention of vulvar, vaginal, and anal cancers. Cervarix is approved for prevention of precancerous cervical lesions caused by HPV infection besides cervical cancer prevention. These vaccines have not been approved as yet in the prevention of penile or oropharyngeal cancer.

Therapeutic vaccines are also being developed to treat already established infections. These are being targeted to E6 and E7oncoproteins that are expressed throughout the life cycle of the virus.[52]

Conclusion

HPV-related cancers constitute a distinct entity compared to their non-HPV related counterparts and are usually associated with a favorable prognosis. Effective preventive measures could help reduce the burden of these cancers, which have shown an increase in the incidence over the last few decades. The knowledge regarding the same is largely based on Western literature and experience from developing countries is sparse. Large multicenter trials are required in order to study the biological behavior and formulate treatment strategies in the management of the same.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Arbyn M, de Sanjosé S, Saraiya M, Sideri M, Palefsky J, Lacey C, *et al.* EUROGIN 2011 roadmap on prevention and treatment of HPV-related disease. Int J Cancer 2012;131:1969-82.
2. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. Lancet 2007;370:890-907.
3. Nwokolo NC, Barton SE. Sexually transmitted diseases of the vulva. Ridley's The Vulva, Third Edition. 2009;6:44-70.
4. de Sanjosé S, Diaz M, Castellsagué X, Clifford G, Bruni L, Muñoz N, *et al.* Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: A meta-analysis. Lancet Infect Dis 2007;7:453-9.
5. Wiest T, Schwarz E, Enders C, Flechtenmacher C, Bosch FX. Involvement of intact HPV16 E6/E7 gene expression in head and neck cancers with unaltered p53 status and perturbed pRb cell cycle control. Oncogene 2002;21:1510-7.
6. Evander M, Frazer IH, Payne E, Qi YM, Hengst K, McMillan NA. Identification of the alpha6 integrin as a candidate receptor for papillomaviruses. J Virol 1997;71:2449-56.
7. Joyce JG, Tung JS, Przysiecki CT, Cook JC, Lehman ED, Sands JA, *et al.* The L1 major capsid protein of human papillomavirus type 11 recombinant virus-like particles interacts with heparin and cell-surface glycosaminoglycans on human keratinocytes. J Biol Chem 1999;274:5810-22.
8. Mayeaux EJ Jr. Reducing the economic burden of HPV-related diseases. J Am Osteopath Assoc 2008;108 4 Suppl 2:S2-7.
9. Scully C. Oral squamous cell carcinoma; from an hypothesis about a virus, to concern about possible sexual transmission. Oral Oncol 2002;38:227-34.
10. van Hamont D, van Ham MA, Bakkers JM, Massuger LF, Melchers WJ. Evaluation of the SPF10-INNO LiPA human papillomavirus (HPV) genotyping test and the roche linear array HPV genotyping test. J Clin Microbiol 2006;44:3122-9.
11. Khouadri S, Villa LL, Gagnon S, Koushik A, Richardson H, Matlashewski G, *et al.* Viral load of episomal and integrated forms of human papillomavirus type 33 in high-grade squamous intraepithelial lesions of the uterine cervix. Int J Cancer 2007;121:2674-81.
12. Kim JY, Park S, Nam BH, Roh JW, Lee CH, Kim YH, *et al.* Low initial human papilloma viral load implicates worse prognosis in patients with uterine cervical cancer treated with radiotherapy. J Clin Oncol 2009;27:5088-93.
13. Rebolj M, Preisler S, Ejegod DM, Bonde J, Rygaard C, Lynge E. Prevalence of human papillomavirus infection in unselected SurePath samples using the APTIMA HPV mRNA assay. J Mol Diagn 2013;15:670-7.
14. Wiwanitkit V. Cervista HPV HR test kit in cervical cancer screening. J Low Genit Tract Dis 2013;17:99.
15. Johnson LR, Starkey CR, Palmer J, Taylor J, Stout S, Holt S, *et al.* A comparison of two methods to determine the presence of high-risk HPV cervical infections. Am J Clin Pathol 2008;130:401-8.
16. Bhatla N, Moda N. The clinical utility of HPV DNA testing in cervical cancer screening strategies. Indian J Med Res 2009;130:261-5.
17. Arulponni TR, Janaki MG, Nirmala S, Ramesh BS, Rishi KS, Kirthi K. Carcinoma cervix treated with radiotherapy – Our experience with emphasis on our concern. J Obstet Gynecol India 2010;60:61-5.
18. Nandakumar A, Ramnath T, Chaturvedi M. The magnitude of cancer cervix in India. Indian J Med Res 2009;130:219-21.
19. Castle PE, Dockter J, Giachetti C, Garcia FA, McCormick MK, Mitchell AL, *et al.* A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer. Clin Cancer Res 2007;13:2599-605.
20. Hubbard RA. Human papillomavirus testing methods. Arch Pathol Lab Med 2003;127:940-5.
21. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, *et al.* The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst 2005;97:1072-9.
22. Dalstein V, Riethmuller D, Prétet JL, Le Bail Carval K, Sautière JL, Carbillet JP, *et al.* Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: A longitudinal French cohort study. Int J Cancer 2003;106:396-403.
23. Josefsson AM, Magnusson PK, Ylitalo N, Sørensen P, Qwarforth-Tubbin P, Andersen PK, *et al.* Viral load of human papilloma virus 16 as a determinant for development of cervical carcinoma *in situ*: A nested case-control study. Lancet 2000;355:2189-93.
24. Lillo FB, Lodini S, Ferrari D, Stayton C, Taccagni G, Galli L, *et al.* Determination of human papillomavirus (HPV) load and type in high-grade cervical lesions surgically resected from HIV-infected women during follow-up of HPV infection. Clin Infect Dis 2005;40:451-7.
25. Monnier-Benoit S, Dalstein V, Riethmuller D, Lalaoui N, Mougin C,

Prétet JL. Dynamics of HPV16 DNA load reflect the natural history of cervical HPV-associated lesions. J Clin Virol 2006;35:270-7.
26. van Duin M, Snijders PJ, Schrijnemakers HF, Voorhorst FJ, Rozendaal L, Nobbenhuis MA, *et al.* Human papillomavirus 16 load in normal and abnormal cervical scrapes: An indicator of CIN II/III and viral clearance. Int J Cancer 2002;98:590-5.
27. Cuzick J. Viral load as surrogate for persistence in cervical human papillomavirus infection. In: Development in Cervical Cancer Screening and Prevention. Oxford: Blackwell; 1997. p. 372-8.
28. Peitsaro P, Johansson B, Syrjänen S. Integrated human papillomavirus type 16 is frequently found in cervical cancer precursors as demonstrated by a novel quantitative real-time PCR technique. J Clin Microbiol 2002;40:886-91.
29. Saunier M, Monnier-Benoit S, Mauny F, Dalstein V, Briolat J, Riethmuller D, *et al.* Analysis of human papillomavirus type 16 (HPV16) DNA load and physical state for identification of HPV16-infected women with high-grade lesions or cervical carcinoma. J Clin Microbiol 2008;46:3678-85.
30. Dutta S, Begum R, Mazumder Indra D, Mandal SS, Mondal R, Biswas J, *et al.* Prevalence of human papillomavirus in women without cervical cancer: A population-based study in Eastern India. Int J Gynecol Pathol 2012;31:178-183.
31. Franco EL, Coutlée F. Prognostic value of measuring load of human papillomavirus DNA in cervical samples: An elusive target. J Natl Cancer Inst 2009;101:131-3.
32. Wang S, Wei H, Wang N, Zhang S, Zhang Y, Ruan Q, *et al.* The prevalence and role of human papillomavirus genotypes in primary cervical screening in the northeast of China. BMC Cancer 2012;12:160.
33. Kahla S, Kochbati L, Maalej M, Oueslati R. Situation of HPV16 E2 gene status during radiotherapy treatment of cervical carcinoma. Asian Pac J Cancer Prev 2014;15:2869-73.
34. Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, *et al.* Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: A population-based study in routine clinical practice. Lancet Oncol 2011;12:663-72.
35. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Semin Oncol 2004;31:744-54.
36. Gillison ML, Chaturvedi AK, Lowy DR. HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer 2008;113 10 Suppl: 3036-46.
37. D'Souza G, Dempsey A. The role of HPV in head and neck cancer and review of the HPV vaccine. Prev Med 2011;53 Suppl 1:S5-11.
38. Hong AM, Dobbins TA, Lee CS, Jones D, Harnett GB, Armstrong BK, *et al.* Human papillomavirus predicts outcome in oropharyngeal cancer in patients treated primarily with surgery or radiation therapy. Br J Cancer 2010;103:1510-7.
39. Sathish N, Wang X, Yuan Y. Human papillomavirus (HPV)-associated oral cancers and treatment strategies. J Dent Res 2014;93 7 Suppl: 29S-36S.
40. Mirghani H, Amen F, Blanchard P, Moreau F, Guigay J, Hartl DM, *et al.* Treatment de-escalation in HPV-positive oropharyngeal carcinoma: Ongoing trials, critical issues and perspectives. Int J Cancer 2015;136:1494-503.
41. Stanley MA, Winder DM, Sterling JC, Goon PK. HPV infection, anal intra-epithelial neoplasia (AIN) and anal cancer: Current issues. BMC Cancer 2012;12:398.
42. van Seters M, van Beurden M, de Craen AJ. Is the assumed natural history of vulvar intraepithelial neoplasia III based on enough evidence? A systematic review of 3322 published patients. Gynecol Oncol 2005;97:645-51.
43. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, *et al.* Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. N Engl J Med 2007;356:1928-43.
44. Wieland U, Kreuter A, Pfister H. Human papillomavirus and immunosuppression. Curr Probl Dermatol 2014;45:154-65.
45. Stanley MA, Sterling JC. Host responses to infection with human papillomavirus. Curr Probl Dermatol 2014;45:58-74.
46. Armstrong EP. Prophylaxis of cervical cancer and related cervical disease: A review of the cost-effectiveness of vaccination against oncogenic HPV types. J Manag Care Pharm 2010;16:217-30.
47. Harper DM. Current prophylactic HPV vaccines and gynecologic premalignancies. Curr Opin Obstet Gynecol 2009;21:457-64.
48. FUTURE I/II Study Group, Dillner J, Kjaer SK, Wheeler CM, Sigurdsson K, Iversen OE, *et al.* Four year efficacy of prophylactic human papillomavirus quadrivalent vaccine against low grade cervical, vulvar, and vaginal intraepithelial neoplasia and anogenital warts: Randomised controlled trial. BMJ 2010;341:c3493.
49. Paavonen J, Naud P, Salmerón J, Wheeler CM, Chow SN, Apter D, *et al.* Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted 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;374:301-14.
50. Herrero R, Wacholder S, Rodríguez AC, Solomon D, González P, Kreimer AR, *et al.* Prevention of persistent human papillomavirus infection by an HPV16/18 vaccine: A community-based randomized clinical trial in Guanacaste, Costa Rica. Cancer Discov 2011;1:408-19.
51. Nigam A, Saxena P, Acharya AS, Mishra A, Batra S. HPV vaccination in India: Critical appraisal. ISRN Obstet Gynecol 2014;2014:394595.
52. Tahamtan A, Ghaemi A, Gorji A, Kalhor HR, Sajadian A, Tabarraei A, *et al.* Antitumor effect of therapeutic HPV DNA vaccines with chitosan-based nanodelivery systems. J Biomed Sci 2014;21:69.