 International Standard Serial Number (ISSN): 2319-8141

International Journal of Universal Pharmacy and Bio Sciences 8(4): July-August 2019

INTERNATIONAL JOURNAL OF UNIVERSAL PHARMACY AND BIO SCIENCES

*IMPACT FACTOR 4.018****

*ICV 6.16****

Pharmaceutical Sciences **Review Article……!!!**

HUMAN PAPILLOMAVIRUS VACCINATION FOR CERVICAL CANCER : CURRENT STATUS IN INDIA

POOJA SHARDA, PRIYA SHARMA, PARMINDER NAIN*, JASPREET KAUR

Department of Pharmacy Practice, M.M. College of Pharmacy, Maharishi Markandeshwar (Deemed To Be University), Mullana-Ambala (Haryana).

KEYWORDS:

Cervical cancer, Human papillomavirus, vaccines.

FOR CORRESPONDENCE:

Dr. Parminder Nain *

ADDRESS:

Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana-Ambala – 133207 (Haryana).

ABSTRACT

Cervical cancer, in women, is second most common cancer worldwide, next to the breast cancer. Worldwide 247,000 deaths are there just because of cervical cancer. India has a population of approximately 365.71 million women above 15 years of age, who are at risk of developing cancer. In India, cervical cancer is the most common and frequent cancer in woman. Human papillomavirus (HPV) infection is the major risk factor for cervical cancer. Treatment of cervical cancer depends on the type of cancer, stage of the cancer and patient's age. The death rate from cervical cancer can be reduced by vaccination system available for the prevention of HPV infection. According to morbidity and mortality weekly report, in year 2017, HPV vaccination initiation has increased an average of 5.1% points annually since 2013. In India there are two types of HPV vaccines available. Since the vaccines are costly, so people generally refused for vaccines, but they should be educated that cost for cervical cancer chemotherapy is more than vaccination.

INTRODUCTION:

There are more than hundred types of cancers, including breast cancer, skin cancer, lung cancer, cervical cancer, colon cancer, prostate cancer, and lymphoma. The cancer mostly affects middle aged women (40-55years) specially form the low economic status who fail to carry out regular health check-ups due to financial inadequacy. Human papillomavirus (HPV) causes various types of cancer among which cervical cancer, ranked second cancer in women worldwide, accounts for 528,000 cases in the world and it causes 247,000 estimated deaths annually globally. In India, an estimated 122,800 new cases and 67,500 deaths annually due to cervical cancer. Globally about 85% of burden is from less developed regions which constitutes around 12% of all female cancer.[1] On an average HPV infection shows no symptoms but persistent genital HPV infection can cause cervical cancer in women. If one linked cervical cancer with HPV, data gives concluded information that 99% of cervical cancer is caused by HPV. Other than cervical cancer HPV also cause anogenital cancer, head and neck cancers, and genital warts in both men and women. HPV infections are transmitted through sexual contact. There is no current treatment for HPV caused cancer, but empirically radiation therapy, chemotherapy, targeted therapy are given according to stage.[2] Intravaginal application of 5% 5-fluorouracil (5-FU) was found to be an effective treatment for cervical intraepithelial neoplasia (CIN-2) in a prospective, non-blinded, randomized controlled study of 60 women. At six-month follow-up, disease regression was observed in 26 of 28 women (93%) who were treated with 5-FU and in 15 of 27 women (56%) in an observation-only group.[3]

Different Type of Cancer Caused By HPV-

Cervical cancer- HPV type 16 and 18 are responsible for 70% cervical cancer.

Anal cancer- Anal cancers cause by HPV 16.

Oropharyngeal cancer- 70% Oropharyngeal cancer caused by HPV 16.

Rare cancer- HPV 16 cause about 65% of vaginal cancers, 50% vulvar cancer, 35% penile cancer.

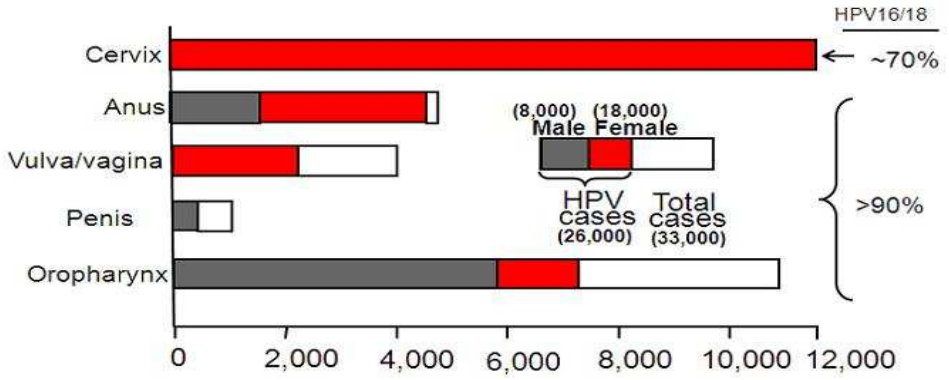

Figure 1: Different type of cancer caused by HPV

Infection with low-risk or nononcogenic types, such as type 6 and 11 can cause benign cancers or genital warts and laryngeal papillomas.[4]

Sign and Symptoms of Cervical Cancer [5]

- Loss of libido
- Severe menstrual cramps
- Irregular menstruation
- Constipation
- Blood in your urine
- Loss of bladder control (urinary incontinence)
- Bone pain
- Swelling of one of your legs

Screening of Cervical Cancer

Cervical cancer screening is testing for pre-cancer and cancer among the women who have no symptoms. When screening detects pre-cancerous lesions, these can be easily treated and cancer can be avoided.

Different Screening Methods are-

- PAP smear test
- Liquid based cytology
- Visual inspection with acetic acid (VIA)

Epidemiological Data of Cervical Cancer in India – According to official report by WHO, Indian has on top in comparative ranking bases of death per year by cervical cancer. The current estimates indicate approximately 132,000 new cases diagnosed and 74,000 deaths annually in India accounting to nearly 1/3rd of the cervical cancer deaths. Indian women prone to face 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer. At any given time 6.6% of women in the general population are estimated to harbour cervical HPV infection. HPV serotypes 16 and 18 account for nearly 76.7% of cervical in Indian. Genital warts have been reported in 2-25% of sexually transmitted disease clinics attendees in India. The national cancer registry programme, established by the Indian Council of medical research, as a surveillance system for cancer in India. It collects data in active manner, visiting government and private sector hospitals, specialised cancer hospitals and pathology laboratories to get information on the types and magnitude of cancer cases. The cancer registry in India doesn't cover entire country actively collects information only from a few urban and rural registries established in the country. There has been a regular campaign against cervical cancer for 30 years in India ranking 4th worldwide. The number of deaths due to cervical cancer is estimated to rise to 79,000 by the year

2010.[5] In urban areas, cancer of cervix account for 40% of cancers while in rural areas it accounts for 65% of cancers as per the information from the cancer registry in Barshi. The reliability indices show that the registry is of an acceptable standard. The registry activity has increased cancer awareness in this population ($p < 0.01$), increased the frequency of early cervical cancers (stages I and IIa) by more than 2-fold during the past 16 years and significantly decreased the relative risk of death (hazard ratio 0.7 [0.5-0.9]). [6]

Pathogenesis's - HPV Virus

HPV infections are most common sexually transmitted infections worldwide. Genital HPV is foremost sexually transmitted virus. About 14 million new genital HPV infections occur each year only in US. In fact, the centres for disease control (CDC) estimates those more than 90% males and 80% females are infected once with HPV. [7]

Human papilloma virus are small, gram negative, double stranded DNA virus that infect the epithelium. There are around 100 types of HPV and are differentiated by the genetic sequence of the outer capsid protein L-1 (table no-1). More than 40 HPV types can be easily spread through direct sexual contact, from the skin and mucous membranes of infected people to the skin and mucous membranes of their partners. They can be transmitted sexually. Other HPV types are responsible for non-genital warts, which are not sexually transmitted. Sexually transmitted HPV types are- Low- risk HPV and High-risk HPV.[8]

- Low risk HPV does not cause cancer but can cause skin warts (so known as *codylomata acuminata*) on or around genitals, anus, mouth or throat. For example, HPV types 6 and 11 cause 90% of all genital warts. HPV types 6 and 11 also cause recurrent respiratory papillomatosis, a disease in which benign tumours grow in the air passage leading from nose and mouth into the lungs
- High risk HPV which can cause cancer. About a dozen high risk HPV types have been identified. Two of these, HPV types 16 and 18 are responsible for most HPV caused cancers.

Table 1 : Different type of protein function-

E1	Viral DNA replication
E2	Control of viral transcription, DNA replication, and segregation of viral genomes.
E4	Favor and support the HPV genome amplification, besides regulating the expression of late genes, controlling the virus maturation, and facilitating the release of virions

E5	Enhance the transforming activity of E6 and E7; Promotes fusion between cells, generating aneuploidy and chromosomal instability; Contribute to immune response evasion.
E6	Bind and degrade the tumor-suppressor protein p53, inhibiting apoptosis; Interact with proteins of the innate immune response, contributing to immune evasion and persistence of virus;Activate the expression of telomerase.
E7	Bind and degrade the tumor-suppressor protein pRB; Increase cdk activity; Affects the expression of S phase genes by directly interacting with E2F factors and with histone deacetylases; Induce a peripheral tolerance in cytotoxic T lymphocytes (CTL) and Downregulate the expression of TLR9, contributing to immune response evasion
L1	Major capsid protein; contains the major determinant required for attachment to cell surface receptors. It is highly immunogenic and has conformational epitopes that induce the production of neutralizing type-specific antibodies against the virus.
L2	Minor capsid protein; L2 contributes to the binding of virion in the cell receptor, favoring its uptake, transport to the nucleus, and delivery of viral DNA to replication centers. Besides, E2 helps the packaging of viral DNA into capsids

Immune Response to HPV Infection

Immune response generated to HPV infection can be explained by different models. In natural infection, HPVs cause invasion by following a minor abrasion or breakdown of squamous epithelium, firstly binding to the basement membrane. The formed complex interact and results in confirmational change of the L1 epitope, before HPV enters the keratinocyte by a novel endocytic pathway. On the basal cell the L1 portion of the HPV virion protein coat binds to heparan sulfate proteoglycans which appear to be the primary (1°) attachment factor. However, the steps involved in virion internalization are not completely known. The mechanism behind the immune response to HPV can be explained with the help of murine challenge model .In this model there is the observation in which capsids undergo a conformational change while bound to the basement membrane that results in L2 cleavage, followed by the exposure of an N-terminal cross-neutralization L2 epitope and transfer of the capsids to the epithelial surface. Basal cells are also relatively accessible in transformation zones (TZ) where

mutilayered squamous epithelia meet a simple glandular epithelia. This is the same region where squamous metaplasia occurs (a process whereby glandular epithelium is replaced by squamous). As a result of this junction, and the metaplastic process, immature basal cells are accessible in the TZ.[9-11]

After basal cells get infected, HPV undergoes a low-level replication to about 100 copies of viral DNA per cell. As the cells undergo normal differentiation and migrate towards the epithelial surface, viral DNA replication is upregulated resulting in several thousands of copies of HPV DNA per cell. This high-level replication is dependent on host-cell replication enzymes but is mediated by HPV proteins E1/E2 as well as E6/E7. The HPV E1 protein is a DNA helicase that binds to the viral of and unwinds the double-stranded DNA. The E2 protein both regulates viral expression and binds to the E1 protein, increasing the binding affinity of the E1/E2 complex to the origin of viral replication. E6 and E7 prolong the lifespan of the host replication enzymes. Although incident infection may be entirely undetected, productive infections of the cervix results in lesions detected as low-grade squamous intraepithelial lesions (LSIL), or equivocal Pap tests are actually the viral cytopathic manifestations of incident HPV infection. On biopsy, these lesions are recognized as CIN1. The cyto-histologic feature of koilocytosis is characteristic, but not diagnostic, of productive HPV infection. These lesions are likely to be cleared as a result of cell-mediated immune responses directed to HPV proteins. These responses are eventually followed by antibody generation to HPV L1 in approximately half of those in whom an HPV DNA is detected (figure-2). This is a slow and generally weak response to L1 and many women do not seroconvert. [12-15]

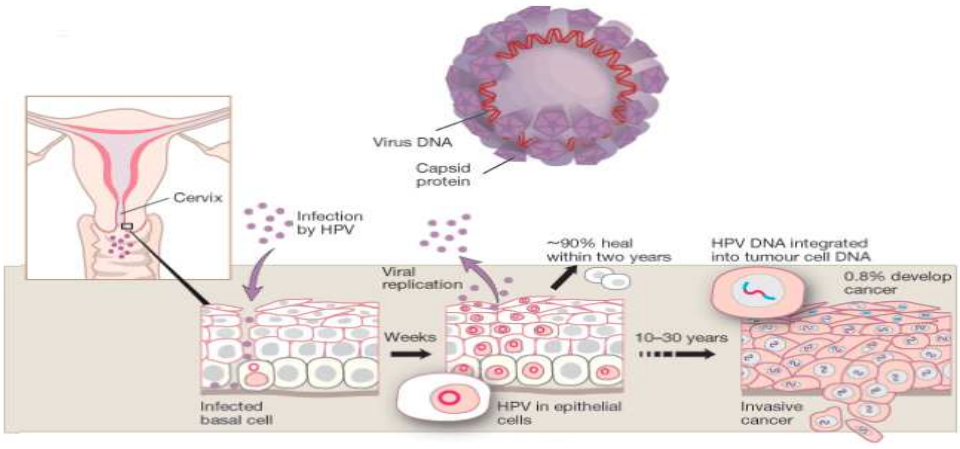

Figure 2 : Pathogenesis of HPV cause cervical cancer

Vaccination For HPV

Vaccines for HPV are introduced in the market in order to prevent the individuals from deadly infection since it can resulted to cervical cancer. Currently there are three vaccines available worldwide. In India

only two vaccines are available in market- a bivalent and quadrivalent vaccine. These vaccines are efficacious and effective against infection as well as preventing precancerous cervical lesions with virus types 16 and 18, which constitutes about 70% of cervical cancer cases globally. The quadrivalent vaccines apart from virus type 16 and 18 also provide prevention against several other HPV types like type 6 and type 11 that are responsible for anogenital warts. The monovalent the third type of vaccine provides additional protection against HPV types 31, 33, 45, 52 and 58. Data generated from various clinical trial conducted in various continents shows safety of HPV vaccines. The primary target group in most of the countries recommending HPV vaccination is young adolescent girls, aged 9-14. For all three vaccines, the vaccination schedule depends on the age of the vaccine recipient.[16-18]

Mechanism of Action

The mechanism by which HPV vaccines protect against HPV infection and disease has not been fully defined. Preclinical studies suggest that L1 VLP vaccine efficacy is mediated by humoral and cell mediated immunity. In studies on dogs, cows and rabbits, immunization with L1 VLPs induced high serum titers of type-specific neutralizing antibodies, which prevented infection after challenge with large amounts of the relevant animal papillomavirus type .The mechanisms of action of the HPV L1 vaccines are not known. Vaccines shows protection against HPV infection in humans by neutralizing serum immunoglobulin G (IgG) induced by VLP-based HPV vaccination. Neutralizing serum IgG may transudate from capillaries to basal stem cells in the genital epithelial mucosa and bind to viral particles. A serologic correlate of protection has not been identified, and the minimum antibody level required for clinical protection is unknown. Therefore, many national regulatory authorities have not accepted immunogenicity comparisons to infer overall efficacy or duration of protection, except in populations in which efficacy studies are not feasible (e.g. young girls and boys).[19-22]

Dosing and Schedule

HPV vaccine should be administered in 3 separate intramuscular injections (0.5 ml) in the deltoid region of the upper arm over 6-month period with the first dose, the second dose 2 months after the first dose, and the third dose 6 months after the first dose. The recommended age for administration is 9-12 years. Catch-up vaccination is permitted up to age of 26 years. A total of three doses of 0.5 ml in 6 months are recommended for HPV vaccine. HPV vaccine can simultaneously with other vaccines such as hepatitis B and tDAP.[23]

CONCLUSION:

The human papillomavirus is the most common sexually transmitted infection in the India and is the cause of cervical cancer and genital warts. The quadrivalent HPV vaccine is 99% effective at preventing the high-grade cervical lesions caused by HPV types 16 and 18 that are precursors to

cervical cancer. It is equally effective at preventing HPV 6 and 11-related genital warts when given to HPV-naive individuals. It can also reduce a significant number of infections when given to women with some prior HPV exposure. But if we considering the population perception, due to high cost of vaccines Indian population refused for vaccination, but they should guide for the severe consequences and cost of expenditure for cervical cancer . Since vaccine costs around 2000.-3000 but the treatment for cervical cancer can ranges from 2 lakhs -5 lakhs. According to MMWR (Morbidity and mortality weekly report), in year 2017 the coverage among adolescents (13-17) years there is increased in the HPV vaccination. HPV vaccination initiation has increased an average of 5.1% points annually since 2013. This should be increased more with proper education among people. Another best option to overcome the incidence of cervical cancer is HPV vaccination that should be mandatory in vaccination schedule by national immunization programme (NIP), Ministries of Health (India) to preventing, disability, and death in children and adults.

ACKNOWLEDGEMENT;

The authors would like to thanks Maharishi Markandeshwar (Deemed to be University) and Department of Pharmacy Practice, M.M. College of Pharmacy.

REFERENCES:

1. Nwabichie CC, Rosliza AM, Suriani I. Global burden of cervical cancer: A literature review. International Journal of Public Health and Clinical Sciences 2017; 4(2): 10-18.
2. Deverakonda A, and Gupta N. Diagnosis and Treatment of Cervical Cancer: A Review. Research and Reviews Journal of Nursing and Health Sciences 2016; 2(3): 1-11.
3. Primavesi F, Stattner S, Jager T, Gobel G, Presl J, Tomanova K. *et al*., Progressive oncological surgery is associated with increased curative resection rates and improved survival in metastatic colorectal cancer. Cancers 2019; 11(2): 1-22.
4. Lowy DR, and Schiller JT. Reducing HPV-Associated Cancer Globally. Cancer Prev Res (Phila). 2012; 5(1): 18–23.
5. Kaarthigeyan, K. Cervical cancer in India and HPV vaccination. Indian J Med Paediatr Oncol. 2012; 33(1): 7-12.
6. Jayant K1, Nene BM, Badwe RA, Panse NS, Thorat RV, Khan FY. Rural cancer registry at Barshi, Maharashtra and its impact on cancer control. The National Medical Journal of India 2010; 23(5): 274-277.
7. Bruni L, Albero G, Serrano B, Mena M, Gomez D, Munoz J. *et al*., ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in India. 2019; (10): 21-89.

8. IARC Monographs on the evaluation of carcinogen risk to human. (Human Papillomaviruses) WHO, International Agency for Research on Cancer 2017; 90: 64-67.
9. Day PM, Gambhira R, Roden RB, Lowy DR, Schiller JT. Mechanisms of human papillomavirus type 16 neutralization by L-2 cross-neutralizing and L-1 type-specific antibodies. Journal of Virology 2008, 82(9): 4638–4646.
10. Culp TD, Budgeon LR, Christensen ND. Human papillomaviruses bind a basal extracellular matrix component secreted by keratinocytes which is distinct from a membrane-associated receptor. Virology 2006; 3479(1):147–159.
11. Roberts JN, Buck CB, Thompson CD, Kines R, Bernardo M, Choyke PL. *et al*., Genital transmission of HPV in a mouse model is potentiated by nonoxynol-9 and inhibited by carrageenan. Nature Medicine 2007; 13(7): 857–861.
12. Kines RC, Thompson CD, Lowy DR, Schiller JT, Day PM. The initial steps leading to papillomavirus infection occur on the basement membrane prior to cell surface binding. Proceedings of the National Academy of Sciences of the United States of America 2009, 106 (48): 20458–20463.
13. 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 glucosamine glycans on human keratinocytes. The Journal of Biological Chemistry 1999; 274(9): 5810–5822.
14. Giroglou T, Florin L, Schafer F, Streeck RE, Sapp M. Human papillomavirus infection requires cell surface heparin sulphate. Journal of Virology 2001; 75(3): 1565–1570.
15. Shafti-Keramat S, Handisurya A, Kriehuber E, Meneguzzi G, Slupetzky K, Kirnbauer R. Different heparin sulphate proteoglycans serve as cellular receptors for human papillomaviruses. Journal of Virology 2003; 77(24): 13125–13135.
16. World Health Organization. Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals. Geneva, 2007.
17. Olsson SE, Villa LL, Costa RL, Petta CA, Andrade RP, Malm C, *et al.*, Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine. Vaccine. 2007; 5(26): 4931-9.
18. Villa LL. Overview of the clinical development and results of a quadrivalent HPV (types 6, 11, 16, 18) vaccine. Int J Infect Dis. 2007; 11(2): S17-25.
19. Stanley M, Lowy DR, Frazer I. Chapter 12: Prophylactic HPV vaccines: Underlying Mechanisms. Vaccine 2006; 24 (Suppl. 3): S106–S113.

20. Stanley MA, Sudenga SL, Giuliano AR. Alternative dosage schedules with HPV virus□like particle vaccines. Expert Review of Vaccines 2014; 13(8): 1027□38.

21. Bachmann MF, and Kopf M. On the role of the innate immunity in autoimmune disease. The Journal of Experimental Medicine 2001; 193(12): F47–F50.

22. Uthaisangsook A, Day NK, Bahna SL, Good RA, Haraguchi S. Innate immunity and its role against infection. Annals of Allergy, Asthma and Immunology 2002; 253–264.

23. Stanley M. Immune responses to human papillomavirus. Vaccine 2006; 24(Suppl.1): S16–S22.