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A Review on Role of Human Papilloma Virus (HPV) in Health-Related Diseases

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Abstract

Human Papilloma Virus (HPV) is a DNA tumor virus with double stranded and non-enveloped DNA of 8 kilobase. Its genome is covered by capsid protein with icosahedral symmetry and a diameter of 55nm. It induces proliferative lesions in mucosal and cutaneous epithelia. It is ubiquitous in nature and have been detected in both animals and humans and well adapted to their host. More than 100 types of HPVs are present and they all are involved in causing infection in squamous epithelial cells of skin and mucosa, this eventually leads to papilloma's or warts benign type. The continuous infection with high risk HPV type causes cervical cancers and also anal cancer, vulvar, vaginal, penile and laryngeal papillomatosis. The HPV with cervical cancer association increase with elevation in number of squamous cell carcinoma at the sites of lesions in people. This infection is frequently noticed in a population with suppressed immune system. The HPV infects immature squamous epithelium at the squamocolumnal junction of cervix. The relation of HPV with non-melanoma skin cancer (NMSC) is clinically important as it is most common form of malignancy among fair skinned populations. This results in cytopathological changes induced by the virus which cytology and histology clearly diagnose as precancerous lesions which eventually result to become cancer. The HPV can be diagnosed by several techniques mainly Hybrid Capture 2, Polymerase chain reaction (PCR) and Real time Polymerase chain reaction (RT-PCR). The HPV infection can be prevented by vaccination and currently two preventive HPV vaccines based on VLPs are authorized for application. They are totally efficient in preventing infections of HPV 16 and 18 which are mainly high risk HPVs involved in causing genital infections in women .This review reveals the diseases associated with HPV diagnosis, the transmission of HPV and their prevention through effective vaccination.

Keywords: Sexually Transmitted Virus (STDs), Non-sexual transmission, Polymerase Chain Reaction (PCR), HPV Vaccination, Warts.

INTRODUCTION

The HPV is associated with many health-related disease but it more frequently causes cervical cancer, occurring mainly through sexual transmission in both men (oral cancer) and women (cervical cancer). It is a ubiquitous virus detected in wide variety of animals and human specific for their respective host. The HPV on the basis of its genomic sequence consist of many types and it has been classified into two group's high grade and low grade. Some authors also refer few HPV types as intermediate due to the reason that these subtype types are less frequently found in the disease.

The HPV belongs to Papovaviridae family and is small non-enveloped capsid of 55 nm in diameter, consisting of 72 capsomers. These capsomers contain at least 2 proteins L1 and L2. The major protein L1 is present in capsomer and each virion contains several copies of minor L2 protein.[1] This virus has resemblance with golf ball when seen through microscope. Its genome is functionally divided into 3 regions.

Non-coding upstream regulatory region 400 to 1,000 bp, this regulatory region contains promoter, enhancer, silencer sequence which enables the regulation of DNA replication. The regulatory region has vast variability in the genome.[2]

The next 2 region is early region contains proteins involved in replicating the DNA and also inducing oncogenesis E1-E7.

Third region consisting of late region encodes the structural protein L1, L2 for virus capsid.

This virus genome has circular double stranded DNA which consists of early genes E1 and E7 and late gene L1 and L2. Among all early genes, few perform transcription and replication of virus for increasing its copy number and some of them play important in transforming characteristics of oncogenes. The oncogene E6 binds to tumor suppressor gene p53 and

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E7 to pRb respectively. This leads to inhibition of tumor suppressor genes. These Oncogene, late gene and Open reading frame (ORF) all lie on one strand of DNA. The late gene codes capsid protein and E1 and E4 genes perform function in releasing newly formed virus from epithelial cells.[3,4] HPV is a DNA tumor virus responsible for causing epithelial proliferation at cutaneous surfaces. There exist more than 100 types of HPV infecting human genital tract. There are few oncogenic or high-risk type associated with cervical, vulvar, vaginal and anal cancer and other are non-oncogenic or low risk types associated with genital warts or anogenital condyloma.[5,6] Genital warts are although not life-threatening conditions but a major cause of morbidity as well as psycho-social distress and embarrassment. The HPV infection mostly spreads through penetrative vaginal or anal intercourse.

The natural history of HPV infection reveals that majority of HPV infection is not constant. Bierman R *et al*. have investigated that approximately 70% of young age women became HPV negative within 1 year and 90% of them became HPV negative within 2 years with a median time interval of infection of 8 months.[7] Thus, majority of these infections become clear but HPV16 are associated with increased rate of persistence and the factors for persistent infection of HPV are age older than 30 years, parity, immunosuppressive, smoking and oral contraceptive use.

The risk factors for HPV infection investigated by epidemiological studies reveal the infection key determinants are first intercourse age and number sexual partners and at least 1 sexual partner with HPV carrier.[8] Castellsague *et al*. reported many exogenous and endogenous factors responsible for HPV related disease rather than HPV infection alone.[9]

HPV infection and mode of transmission

HPV infection occurs widely but can be prevented, among all the type of HPV infection the HPV of genital type are most prevalent sexually transferred viral infection. As the main factor many of HPV infection of genital type is age of first sexual intercourse, relative number of sexual partner. This was also reported by Bosch F X, *et al*. in study a conducted by them in which they observed that in both male and females, the HPV-DNA of genital type rises with increase in number of sexual partners and first sexual intercourse in younger age.[10,11]

These all evidences reveal the transmission of HPV occurs predominantly through sexual transmission but there are some overwhelming evidence documenting the other ways of HPV transmission.

Perinatal Transmission

This type of HPV transmission incidence is low as shown by the study conducted in women with a known HPV status in their infants examined from birth till the age of three years. Perinatal transmission is clearly described for laryngeal papillomatosis, which spreads through tracheobronchial tree and progress first to pulmonary papillomatosis and then to fetal chest infection. The juvenile papillamatosis is probably associated with HPV infection which has been acquired from mother with genital warts or other infections. The juvenile form of laryngeal papillomatosis is higher in first born infant delivered vaginally to adolescent mothers as compared to adults. Cason J reported first case of non-sexual transmission in 1956 in child (boy) born from mother having condyloma. This child developed laryngeal papillomatosis in 3 months and penile wart in 6 months of after his birth, since then perinatal transmission cases started accumulating.[12]

Transplancental transmission

This type of transmission was revealed by a study conducted in amniotic fluid sample of the women with abnormal cytological reports and HPV positivity examined by PCR. Showing the presence of HPV-16 in cord blood sample of infants born to the mother with HPV-16 positive test. Afterwards, different types of HPV were detected in aminiotic fluid, placenta, cervical scrapes and epidermodysplasia verruciformis.[13]

Horizontal Transmission

This type of transmission was reported for HPV 2 in warts, anus and hand in a 5 year old boy. Other cases have also been identified for the low grade type of HPV involved in horizontal transmission of HPV. The HPV with penile infection has also been detected in nail brush of men and same type of HPV has also been found in genital and hand sample. All these evidences increase the probability of person with genital warts can transmit genital type of HPV not only through sexual transmission but also from touching their family members and children.

Transmission by other factors

HPV transmission through blood has never been detected, the reason behind it is that the blood does not consist of viremic phase. HPV infection transmission to infants from breast feeding by mothers have also not been discovered. Although, HPV DNA in medical instrument has occasionally be isolated, till now there are no such evidences of HPV-DNA can initiate with any carrier i.e. *de novo* initiation.

In conclusion, it can be said that a) HPV infection of genital type including genital warts can also happen in sexually inactive or naïve population such as infants, children, young and adult persons.

b) The transmission of perinatal type in child exist from mother but the incidence rate is low.

c) HPV of high risk type have been found in non-genital mucosae eg, oropharynx conjunctiva, mucosae of mouth and also these HPV are involved in few oral, oropharynx and cervical cancer.

HPV is divided into three main groups in context of health disease and also according to the area of body in which infection is seen anogenital and oral regions, external skin. They are mucocutaneous, cutaneous and also rare autosomal recessive disorder like Epidermodysplasia verruciformis.

HPV association with skin disease

The HPV association with health disease was first established with skin cancer in 1978 by Jablonska and Gerard Orth at Pasteur Institute. The association of HPV with skin disease in external surface causes warts which were mentioned earlier in Greek times, as sudden appearance or disappearance of skin lesions associated with magic or multitude of folk cures in early times. The warts of cutaneous type are transmitted either from directly or by contaminated surfaces and objects indirectly. Through contaminated objects the transmission occurs by minute break in the epidermal barrier. In children, HPV infection transmits through oral region by chewing fingers and through playing and from hand to face through minor abrasions of elbow and knees. The prevalence rate for this disease varies according to age, prevalence rate being high in children and adolescents as estimated in a study conducted by Williams *et al*. in 1993. Examination of warts histologically showed malignant lesions with overgrowth in all the layers of dermis which results in acanthasis, papillomatosis and hyperkeratosis (thickening, folding, increase in horny layer respectively). Sometimes in upper layer vacuolation of cells occurs and also inclusion bodies are observed. Croissant *et al*. in 1998 reported various cutaneous type of warts showing characteristics changes.

These warts usually disappear but sometimes it may persist because of presence of virus in the skin surrounding the original wart, the ascending evidences had shown the association of cutaneous HPV types in the causation of skin cancer. The most important environmental carcinogen for human is solar radiation specifically UV-B in spectrum. In genomic and mitochondrial DNA, UV-B has been known to induce mutagen. This makes it most important factor in developing non-melanoma skin cancer (NMSC).[15-17]

HPV association with NMSCs developed especially at site which are exposed to sunlight plays a role of co-factor for virus in developing Carcinogenesis. It is one of the most favorable ways the virus participates in developing NMSC. The HPV of both cutaneous and anogenital types encodes proteins of early gene are similar and are involved in developing lesions. Hence, it is conspicuous that the target of virally encoded proteins for cells is different. The anogenital cancers consist of 1 copy of HPV genome at least per cell and for sustaining the transformed phenotype viral gene expression is also necessary.[18] The cutaneous associated cancers show the presence of HPV-DNA virus in only 1 of 5000 cells.[19] All these observations intimate a new pattern for understanding HPV association with NMSC.

The association of HPV with cutaneous carcinoma was described by Lewandowsky *et al.* in 1992 as Epidermodysplasia verruciformis (EV) which is a rare heritable disease. The first evidence of HPV infection involvement in development of skin cancer was identified by these investigations.[20] This disease has been characterized by the tendency to infect from specific HPV types, called EV HPV types currently named as beta-HPV types, including HPV types 5, 8, 9, 12, 14, 15, 17. As in benign lesions, multiple types of HPV are present, HPV 5 or 8 and 14, 17, 20, 47 as found in Squamous cell carcinoma are of high-risk types.[21] It is presented that by the fourth decade a maximum 60% of patients will develop SCC at body exposed to sunlight.[22] This disorder is specific in its inability of controlling HPV infection of the keratinocyte level because of inability of patient's immune system in rejection of EV-HPV harming cell and hence the beta HPV infection persists. In Immune system, a partial defect in cell mediated immunity results in natural killer cells and cytotoxic T-cells inhibition have been observed in patients of EV and also interacting immunogenic and environmental factors especially UV radiation.[23,24] The HPV and other lesions related to epidermis in addition to being strongly associated in cervical carcinogenesis, high risk mucosal HPVs are involved in development of other specific epidermal cancers. HPV of type 16 is commonly found in vulval disease, the p16INK4a, a surrogate marker helps in diagnosis of cancerous and non-cancerous lesions of vulva and also other NMSCs.[25,26]

The HPV 16 and other mucosal associated viruses are also involved in developing periungual lesions (defects occurring around fingernail or toenail). Investigating the mechanism of mucosal HPV in causing cancer provides the valuable understanding of skin carcinogenesis in the future. Cutaneous HPVs involved in causing cancer are also detected and involved in developing other skin disease like psoriasis (skin disease marked by red, itchy, scaly patches).[27] The EV-HPV types, especially of types 5 and 36, were detected at higher frequency in children with psoriasis. Additionally, other studies reveal. The presence of HPV-5 at higher frequency in psoriatic plaques and HPV DNA positivity has also been observed in plucked hairs from psoriatic patients who are undergoing Psoralen and Ultraviolet A (PUVA) treatment.[28]

- **Verrucae vulgares, Verrucae plantares**

This skin disease mainly effects hands and feet but can also occur elsewhere on the body. The cutaneous HPV type 1, 2, 4, 27, 57, 65 results in benign warts on skin. Wart of this disease is skin colored characterized by the flat dome-shaped papules as the rough hyperkeratotic surface and sharp borders. These warts are usually asymptomatic, but sites which are exposed to pressure such as the soles of the feet, endophytic growth can be vulnerable. These appear as cluster lesions, regression of warts occurs spontaneously after several months or even years and multiple verrucae at different sites have been found to simultaneously resolve. The entire resolving lesions have mononuclear inflammatory infiltrate, which indicates that a cellular immune response is responsible for this reverting of the lesions.

- **Verrucae planae**

There morphology are reddish, flat, skin colored papules which mainly infect adults with the involvement of hand or distal forearms. They are primarily caused by HPV of cutaneous types 3, 10, 28 and 41.

- **Periungual warts**

These warts occur at the nail fold of finger or toe and are often painful. The treatment of this wart is not easy because it causes damage of nail matrix. If it lasts for long time or if the clinical appearance raises any integration, then biopsy has to be performed to exclude invasive carcinoma or Bowen's disease.

- **Butcher's warts**

This is one of the less well known human papillomavirus infections. These warts are caused by HPV-7. Prior reports suggest that HPV-7 may be transmitted from animal tissue to humans and from person to person. Mainly it is caused by a person who handles meat at work. A combination of maceration (soften tissues after death soaking and by enzymatic digestions) and trauma seems to be a predisposition factor.

- **Squamous cell carcinoma of finger**

It can be caused by mucosal high risk HPV type mainly type-16 and also HPV 31, 33, 35, 52 affecting fingers as special entities. Often same type of HPV can be isolated from squamous cells of finger and from lesions affecting genital mucosa, suggesting digital-genital transmission pattern. The mechanism responsible for the wider tissue tropism of genital HPV and involvement of finger is not known. In Human Immunodeficiency Virus (HIV) patients, the type26 of HPV can be the risk factor in developing squamous cell carcinoma of the finger.

- **Condylomata acuminata**

This disease is often recurrent but self-controlled and can occur on both external or internal genetalia and also perianally in anal canal. Clinical appearances often include flat, multiple or raised exophytic papilloma's. These lesions may be fleshy colored, brown and macerated and the keratinized surface of skin warts is absent. Condylomata can occur in large groups of lesions. Usually this infection has self-controlling power but it may occasionally persist for years or may reappear after treatment. This infection is caused by low risk HPV types (HPV6 or 11) and co-infection with other multiple types are also common.

• Buschke-lowenstein tumor (BLTs)

BLTs tumor are also called as Giant Condylome accuminatum and was identified and named on Buschke and Lowenstein in 1925. These are slow growing tumors appears like cauliflower exophytic neoplasia affecting the anogential regions. It can also affect other genital parts (vulva, anus). This disease has highly differentiating power with Ackerman carcinoma (low grade variant of squamous cell carcinoma), also classified as separate entity between condylomata and squamous cell carcinoma. They are invasive and invade genital growth involving anus and surrounding tissues and musculature of the pelvis. All this can result in organ destruction, but no metastasis occurs. In BLTs, low risk HPV6 and 11 may be detected, there are not any evidence for revealing what conduct BLTs. The risk factors for this disease are mainly hygiene, chronic irritation, alcohol abuse and immunosuppression.

• Bowenoid papulosis

This is a rare form of intraepithelial neoplasia as it is a precancerous skin condition present as a single or in group as small, flat, pigmented papules, red brown or flesh-colored spots or patches on external genitals of males and females. This disease is associated with HPV-16 and probability of spontaneous regression is greater in younger patients and progression to carcinoma have been not find frequently.

• Erythroplasia of Queyrat (EQ)

EQ is a squamous cell carcinoma of penis, glans (head penis) and prepuce (foreskin) are most commonly involved in this disease. This is seen exclusively in uncircumcised men. This disease was identified by Tarnovsky in 1891 and later by Fournier and Darier in 1893 termed who it as penile disease. The progression to invasive carcinoma may occur and spontaneous regression is unlikely to occur.

• Laryngeal papillomatosis

This disease occurs rarely but can severely affect the breathing capacity of individual. It consist of 2 variants juvenile and adult laryngeal usually HPV6 and 11 is diagnosed with the latter causing more serious effects. In, laryngeal papillomatosis HPV6 and 11 are mainly involved in causing severe dysplasia and carcinoma. The mothers with Condylomata are associated with 231 times of developing laryngeal papillomatosis than mothers without condylomata. Initial symptoms of the disease are hoarseness (Obstruction of the airway in small larynx and trachea) Stridor (indicates airway obstruction and it may be associated with voice changes and swallowing defect in voice). The single or multiple lesions preferred to be in vocal cords, lungs, nose, trachea and oral cavity. Due to higher regression rate, repeated surgery or laser removal is essential as the therapy but it has been find difficult to perform.

• Florid oral papillomatosis (Heck's disease)

Oral papillomatosis mainly occurs in children, but middle and young age adults also get affected with some lesions. There is no gender basis prediction in this disease. The sites mainly involved in the disease include labial, buccal and lingual mucosae, gingival and tonsillar lesions. Heck's disease causes infection in oral mucosa and HPV involved are of type-13 or less often HPV-32. The characteristics of this infection are multiple papilloma's on the oral mucosa usually on lower lips and buccal mucosa with no necessary symptoms. Occurrence of this disease is worldwide but is more common in indigenous population. Individual lesions of this disease are slightly elevated or broad. These lesions are papillary, smooth-surface, flat-topped in nature commonly as observed.

• Head Neck

Carcinogenesis of Head and skin mainly arise from mucosal lining and aerodigestive tract. The high-risk HPV types have recently been demonstrated in pathogenesis and infections of Head neck carcinogenesis. Risk factors for both parts are tobacco and alcohol consumption. The 30% of the head neck carcinogenesis are caused by HPV, mainly HPV-16. Head and neck associated tumors mainly occurs in tonsils, oropharynx and tongue. A special form for head neck disease is oral verrucous carcinoma. Lesions associated with the disease mostly affects oral cavity, larynx etc and these lesions are destructive but not metastasize and HPV involved in this disease are low-risk HPV of genital types.[29]

• HPV in cervical cancer

Carcinoma of cervix is second most common cancer found in women worldwide. The HPV has been most important agent in developing cervical cancer the correlation between them was established by Dr. Hausen and Durst (1983). They identified it by isolating HPV of type 16 and 18 and several other high risk types of HPV (51,52,56,58,59) from the cervical scrap[30,31] also HPV and tar together was found to have induced squamous cell carcinoma as demonstrated by Peyton Rous in (1934). Tar is obtained from cigarette and smoke from burning wood.[32] The HPV type showing high tendency of causing cervical cancer are high risk human papillomavirus. The HPV virus infects immature squamous epithelial cells in basal layer which could be found easily in areas of squamous metaplasia in squamocolumnar junction or erosion of the cervix. Almost 80% of low grade squamous intraepithelial (LSIL) and 90% of high grade squamous intraepithelial lesions (HSIL) are involved in HPV infections, many lesions clear itself, but clearance rate differs according to severity of lesion. The HSIL have greater rate of progression of cervical cancer. Further 60% of Cervical intraepithelial neoplasia (CIN) regressed and only 10% are likely to progress to CIN-3 and only 10% progress to invasive cancer. The infection that persist for more than 3 years approximately, will leads to number of structural changes (koilocyte) in cervical epithelium.[33] In this stage, premalignant lesion will develop which can be diagnosed by Papanicolaou smear test. Now there are many possibilities of eliminating a significant proportion of cervical cancer worldwide. Zhai *et al*. showed that the 9-valent HPV vaccine would provide protection against HPV type responsible in cervical cancer. The HPV causes cervical cancer by infecting squamous epithelium and integrating its DNA into DNA of the squamous epithelium cells.[34] The oncoproteins of HPV (E6 and E7) are responsible for causing the oncogenic process in cervical epithelium. The morphological changes caused by this virus seen in infected cells reveal structural changes in epithelium.

Diagnosis of HPV related health disease

The preliminary method used for HPV detection was western blot and southern blot by directly hybridization of probe. Both techniques were time consuming with less sensitivity and also required large quantity of DNA for detecting HPV. Now both of this technique is displaced by Amplification technique, it contains less amount of sample for detection of HPV and time consumption is also low. The methods now a day's used for HPV diagnosis are PCR and Hybrid Capture 2 HC2 for HPV detection.

Hybrid Capture2 (HC2)

The Hybrid Capture (HC2) technology is a hybridization based assay and performed in a solution containing RNA probe of two types A and B (stretch of RNA sequence) which has a complementary sequence for genome of high risk and low risk HPV type. The RNA probe A detects low risk HPV and RNA probe B detects high risk type of HPV in an individual

reaction. Then these HPV-DNA-RNA hybrids formed are interacted by antibody coated well of microtitire plate, which recognizes the HPV-DNA-RNA hybrid. These immobilized hybrids can be detected by sequence of reaction, the reaction generates luminescent product which are measured in a luminometer. As there is not any specific test for examining infectious in specimen, hence molecular techniques are used for detecting viral DNA. The commonly used tests is for HPV-DNA detection is hybrid capture (HC2) test, in this test alkaline lysis is performed followed by DNA hybridization with RNA probes which is detected by Chemiluminescence. The Cutaneous type of HPV are not detected by this assay.

Colposcopy, anoscopy/protoscopy, urethroscopy/meatoscopy

All these tests are used in detection of neoplasias often occurring at various sites in anogenital tract. In guidance with gynecologists, protoncologist and urologist, condylomas and dysplasia's can be diagnosed in various location by usage of colposcopy, anoscopy, urethroscopy of high resolution. If necessary, then set specific biopsy should be performed with adequate treatment.

Polymerase Chain Reaction (PCR)

This is a molecular technology performed for amplification of target DNA capable in enhancing exponentially and reproducible increase in HPV DNA sequence of samples.

While performing this assay, one should take care of avoiding false-positive results, which occur through cross-contamination of samples or reagents with PCR products of previously performed rounds. As, this problem happens in laboratories when PCR was first perform, many of the lab had implemented protocols to overcome this. Specificity and sensitivity regarding this technique can be different, it depends on the DNA isolation procedures, site and kind of clinical sample, primers the size of PCR product and also performance of enzyme (DNA Polymerase) used in PCR reaction, it shows the spectrum of amplified HPV DNA and capacity of detecting variant types of HPV-DNA. From this assay we can detect even minute quantity of viral genome of tissue or smear of the samples. Other than PCR a highly advanced technique for detecting HPV in samples is Real-time PCR (RT-PCR) which can determine the HPV genome copies per cell using simultaneous amplification of constituently expressed gene like housekeeping genes.

Papanicolaou Screening Test

The screening of cervical HPV infection is done by Papanicolaou smear test. This is a most common method of screening the infection associated with cervix. The method was introduced in 1949 and named after George Papanicolaou before the cause of cervical cancer was discovered in 1976. Cervical cancer caused HPV infection can be prevented by early screening program and helps in declining the incidence of cervix related lesions mainly in the countries with well-organized screening programme. The cytological changes caused in cervical epithelial cells by high risk HPV infection like those in transformation zone can be detected by the conventional method of cytology.[35]

Another method of processing specimen for Pap test is monolayer cytology. This technique forms uniform monolayer and prevents drying artefacts and contaminating mucus, RBCs, proteins and yeast are removed. Primary screening of Pap smear is done by Autopap has been approved and rescreening of cervical lesions are approved to perform by rescreening and Papnet. In both procedures abnormalities in cells can be viewed on the screen for analysis. Infection of oncogenic HPVs which persist, develop virtually to form all HSIL or neoplasia. Presence of HPV-DNA in cervical smears can be used as tumor marker for cervical carcinogenesis. Several studies showed that HPV-DNA testing have greater sensitivity for predicting high grade cervical dysplasia than cytology. In currently published reports different HPV genotypes have been evaluated. In which it was seen that patients with HPV16 positive infection are significantly higher risk of developing high grade abnormalities in 2 year of follow up duration than who test HPV positive for other oncogenic types. Goldie *et al.* studied several strategies of screening in 30-year age of population and used mathematical model for revealing clinical and economic outcomes for these methods. He concluded that HPV and cytology performed together are more useful in declining cervical cancer incidence and being more economically reliable than conventional cytology method.[36]

HPV vaccination

HPV prevention is possible through vaccination which has widely been accepted for prevention or elimination of infectious disease caused by HPV. Development of HPV vaccine has been considered advance in part for the production of virus like particles (VLPs). It imitates HPV virion structure of but do not have genetic material can be produced through exogenous expression of late gene in various types of cells, including bacteria, yeast and mammalian cells.[37] The VLP vaccine which provides protection against commonly occurring infection from HPV type are currently under clinical trials but initial reports have shown that HPV vaccines are effective in prevention of HPV related diseases and infections. Various studies regarding HPV vaccination showed that vaccination of HPV will be most effective if inoculated in initial phase of sexual activity and vaccine will target pre-adult and adolescents population.

The VLPs are not oncocogenic and infectious, these features make them ideal candidate for participating in vaccine production against HPV. They are concentrated, purified and then distributed in aliquots and combined with a substance which helps in enhancing the capacity of VLPs by combining with it called adjuvant.[38] Studies regarding monovalent vaccine against HPV16 revealed that this vaccine produces strong immune response against late gene of HPV virus in animals and humoral immunity in mammals.[39] Examination of vaccine in other test revealed that of VLP vaccine booster induced protective level of antibodies. The HPV 16 VLP vaccine as shown by principle studies is safe, well tolerated and induced higher antibodies titer levels than produce in response of natural infection.[40] Therefore, this observation was not powered for accessing the vaccine efficiency in prevention of clinical disease. In a population vaccine was administered the recipients of vaccine showed fewer cervical lesions than placebo (a substance that has no therapeutic effect used as control in testing new vaccine). The VLP vaccine helps in reducing cervical lesions and invasive cancer incidence.[41]

CONCLUSION

The HPV associated health diseases are known to be commonly transmitted through sexual transmission. These diseases causes many types of infections like genital warts and cervix lesions which if persist can cause cancer. Inspire of immense evidence regarding genital type of HPV transmitted through sexual transmission, there are few epidemiological observation reveals that non-sexual transmission of genital types also exist. The HPV infection is proceeded by HPV encoded oncogenic proteins which destroy a number of cellular network and cell cycle regulated genes. Their primary function is to elevate its viral life cycle through replication. Although, these irregularities cause defect in cellular system which ultimately generates a favorable

condition for initiation of tumor and invasive metastasis or progression. Various studies on molecular mechanism reveal complicated and varying events of epigenetic and genetic changes which will leads to the specific cancer with different etiology. In non-melanoma skin cancer, the UV is a primary etiological factor and now it has been cleared that HPV plays role of co-carcinogen with Ultraviolet in occurrence of NMSC disease. The range of infections involved in HPV, precancerous and malignancies continues to grow. Primary focus of worldwide in HPV context is to eradicate the potential of cervical cancer through HPV vaccination program by targeting pre-sexually active females. This virus have both of the properties it is highly effective as a pathogen and also as carcinogens, well adapted to their ecological niche and have capacity of avoiding immune response and challenging to eliminate it. All these findings have resulted in better understanding of the HPV transmission, infection, detection and vaccination.

CONFLICT OF INTEREST

The authors declare no Conflict of interest.

ABBREVIATIONS

DNA: Deoxyribonucleic acid; **PCR:** Polymerase Chain Reaction; **RT-PCR:** Real time Polymerase Chain reaction; **HPV:** Human Papilloma Virus; **STDs:** Sexually Transmitted DNA; **ORF:** Open reading frame; **NMSC:** Non-Melanoma Skin Cancer; **EV:** Epidermodysplasia; **PUVA:** Psoralen and Ultraviolet A; **BLTs:** Buschke-lowenstein tumor; **HSIL:** High grade Squamous intraepithelial lesions; **LSIL:** Low grade Squamous intraepithelial lesions; **CIN:** Cervical Intraepithelial neoplasia; **EQ:** Erthroplasia of Queyrat; **hc2:** Hybrid capture2; **UV:** Ultraviolet;

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