Human Papillomavirus (HPV): The Most Common Sexually Transmitted Disease

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ABSTRACT: Human Papillomavirus are small non-enveloped DNA virus, thediameter of ~55 nm whose infection causes benign lesion or warts persistent infection of HPV can cause amalignant tumor. HPV classified in two typeslow-risk and high-risk type of HPV. Low-risk type of HPV 6 and 11 causes benign lesion or warts (benign condylomata acuminate), the high-risk type of HPV 16 and 18 causes cervical cancer. HPV infection is sexually transmitted disease, there are vaccines that can prevent HPV infection such are Gardasil, Gardasil 9, and Cervarixwas it is also called has bivalent and quadrivalent vaccines. Food and Drug Administration has approved these drugs and other product from carrageenan lubricant, which can prevent from HPV infection.Future study, a Bioinformatics approach was considered to analysis the gene expression of HPV.

Keywords: Cervarix,Gardasil, Gardasil 9,Human papillomavirus (HPV),Gene expression

INTRODUCTION

Human papillomavirus (HPV) is one of the prevailing sexually transmitted diseases or sexually transmitted infection (STI) in the world. A Recent report from Centers for Disease Control and Prevention (CDC), almost 6.2 million people affected every year and around 20 million people already affected over the world [1]. Human papillomavirus is the double stranded, circular DNA around eight in size from the family papillomaviridae. They usually infect the squamous epithelial cells of skin or mucous. There are more than 100 types of HPV, which infects genital. HPVs classified as two types such as high risk because of their oncogenic potential or causes cancer and low risk, which does not cause cancer but cause benign lesion or warts. Thirteen types of HPV classified as high risk [2, 3]

HPVs have circular genome enclosed by a capsid protein, it has two structural viral capsid proteins (L1 and L2) from late genome differentiation and HPV viral gene expression leads to expression of six nonstructural viral protein such as (E1-E7) from early region of the viral genome [4]. The genes E6 and E7 are the oncogenes which are related to carcinogenesis where E stance for early. HPV 16 and 18 are the most common type that causes cervical cancer or genital cancer [2, 3].

Human papillomavirus infects the keratinocytes in the basal layer of stratified squamous epithelium where there is differentiation in theepithelium (which will not divide to stay in active state or stable state of thecell cycle). At this stage, the differentiation cell amplifies the viral genome that results in exophytic epithelial neoplastic when cells desquamate the virions are released, the cell exhibit abnormal and uncontrolled growth where thehigh-risk type of HPVs integrate into to the chromosome, which results in cellular immortalization and deregulated proliferation [5].

Infection caused by Human papillomavirus (HPV) is one of the main causative agents for cervical cancer in women and other anogenital cancers. HPV 16 and 18 are the usual cause of cervical cancers [6].

Structure of Human papillomavirus

HPVs relatively have a circular genome with double-stranded DNA, associated with histone proteins and enclosed by capsid proteins, which formed by two late proteins that are L1 and L2. Each capsid formed by 72 capsomeres, where each of them has five monomeric 55kDa that form a pentamer [7]. There are three regions in papillomavirus, separated by two polyadenylation sites (pA) such as early (A_E) and late polyadenylation (A_L) sites [4].

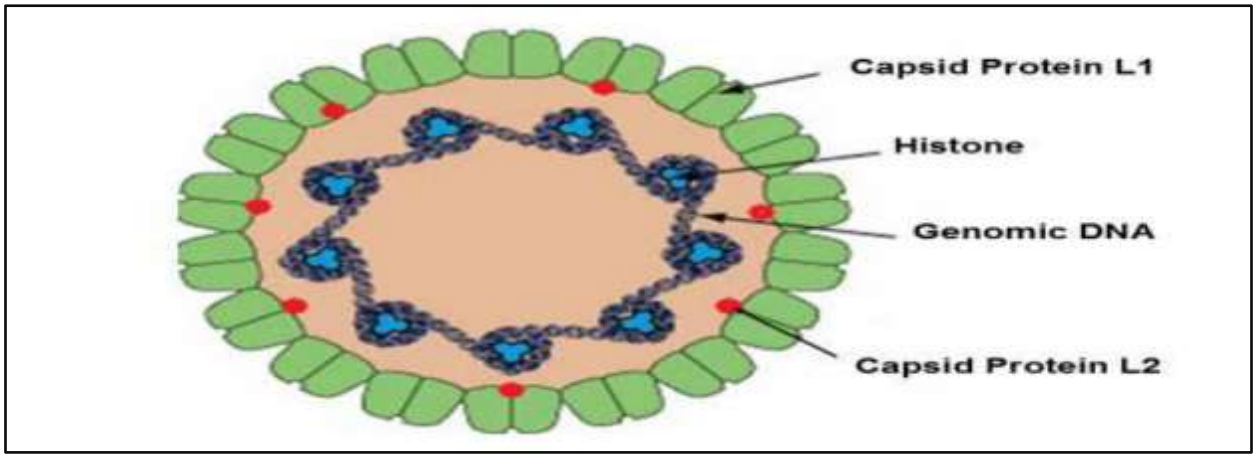

Figure 1: The structure of HPV.

In HPV, there are six non-structural proteins such as E1, E2, E4, E5, E6, E7 and two structural viral capsid proteins such as L1 and L2 [8].

Functions of viral proteins

E1 Protein- Viral DNA replication and early transcription. **E2 Protein-** E2 proteins regulates the viral transcription and DNA replication and separation of viral genomes. **E4 Protein-** HPV genome amplification are favored and supported regulates the viral maturation and it aids the release of virions. **E5 Protein-** E5 increases the transforming activity of E6 and E7. **E6 Protein-** It helps in degradation and bind to protein p53, suppress apoptosis, stimulates the expression of telomerase. **E7 Protein-** It helps to bind and impair to pRB, inflation in CDK activity. **L1 Protein-** It is a major capsid protein, which enhances the attachment of the cell surface receptors. **L2 Protein-** It is a minor capsid protein it helps in thebinding of thevirus to areceptor of the cell and it helps in transport to the nucleus and pass the viral DNA replication to the centers, however, it also helps in thepacking of viral DNA replication into the capsids [3].

Types of HPV

HPVs are classified has two types high risk and low risk where high risk is considered has oncogenic which may lead to cancer and low risk causes a lesion or warts [2].

Phylogenetic Classification	Epidemiologic Classification	
	High risk	Low risk
High risk	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 82, 26,* 53,* 66*	70
Low risk	73	6, 11, 40, 42, 43, 44, 54, 61, 72, 81, CP6108

Figure 1: Epidemiologic classification of Human papillomavirus

Outbreak of HPV

Cervical cancer is the most frequent cancer in women in India. Women above 15 years of age are at the risk developing cancer in India [8]. Current estimation indicates that every year 122844 are diagnosed with HPV infection and 67477 dies from cervical cancer. Cervical cancer ranks 2nd in India [8]. 2.5% of Indian women face alifetime risk of HPV infection and about 1.4% of the population face risk of cervical cancer deaths. 2-25% of people are infected with warts have been reported. Cervical cancer research programs havebeen developed in India. National cancer registry program, organized by Indian council of medical research, it collects information for cancer in India. Cancer registry collects information in certain rural and urban parts of India [9].Cervical incidence in India starts in peak age of 55-59 years [10]HPV infection worldwide were 50,000 cases every year reported, 250000 of cervical deaths reported. Around 50% of men and women are infected by HPV infection in their lifetime [10].

Table 1: Cervical infection in India

	No. Tested	% (95% CI)
HPV prevalence in women with normal cytology	35349	7.0 (6.7-7.2)
HPV 16/18 prevalence:		
Normal cytology	8845	5.0 (4.6-5.5)
Low-grade cervical lesions	177	28.2 (22.1-35.3)
High-grade cervical lesions	253	62.8 (56.7-68.6)
Cervical cancer	1745	82.7 (80.8-84.4)

HPV infection

HPVs infects epithelium cells but usually, they affect cervical cancer. [11].There are 2 types of basal layers existing in cervix, the first layer consists of transit-amplifying (TA) cells, which propagates and capable of undergoing terminal differentiation. The second type of cells are the stem cells that propagates infinite, which segregate and replenish the transit amplifying cells and serve as reserve cells for maintenance of the tissue [12,13]. The infection ties to heparan sulfate proteoglycans (HSPGs) on the cellar film (BM) which are visible after the conveyance, which actuates a conformational change, where it uncovered the site of L2, which makes it inclined for proprotein convertase. At that point there is L2 cleavage, the L2 killing epitope is uncovered and L1 that was not presented ties to the auxiliary receptor and attacks the edge of epithelial cells [14].

Essential official to HSPGs and furin cleavage, the infection expelling to the unidentified receptor on the cell surface. The infection enters the cell through endocytic pathway and limits in early endosome by 4 hours after the fact by 12 hours the infection uncoats inside the late endosome, the genome of viral, which complexed with L2 discharged. The intricate transport over the cytoplasm, by means of microtubules and the unpredictable, enters the core by 24 hours, the complex enter the atomic co-confines with ND10 and RNA interpretation starts[15].

HPV infection lasts for almost 12-18 months; the infection are taken care by the immune system eventually [16,17], but most of the women fail to clear the infection due to this there is enduring infection because of the enduring infection of HPV from warts or lesion which may lead to cancer (cervical cancer) [17, 18]. The clearance of HPV infection by the immune system are unidentified, either it protects for life long is unidentified [19]. Most cases there is thereappearance of HPV infection but they are most probably the benign lesion or warts [13, 17].

Constant persistent infection by HPV and it integrates insidethe cell, which increases the danger of causing cancerous lesion. E7 and E6 proteins are oncogenic proteins, which induces abnormal changes in thecentrosome, and there is reduplication were led to an abnormal number of centrosomes. In addition, they target p53 and pRB with the retention of cells with their chromosomal abnormalities [17, 20]. This may result in some genetic changes that may result in genetic abnormalities, which can result in cancer development [21].

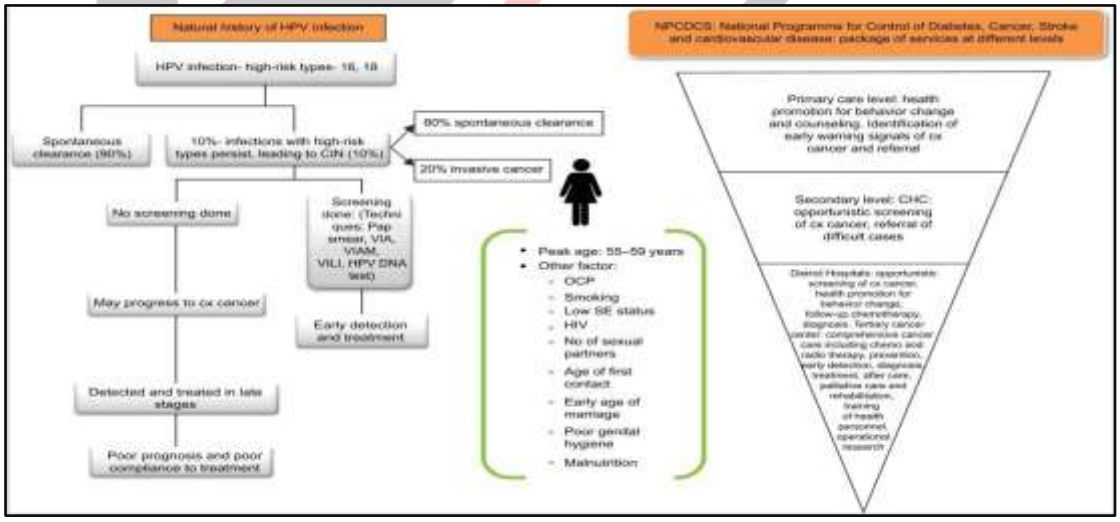

Figure 2: Epidemiology of cervical cancer

Screening of cervical cancer

Screening techniques for cervical cancer includes such as conventional exfoliative cervicovaginal cytology, neuro-medical systems, pap smear, automated cervical screening techniques, fluid sampling techniques with automated thin layer preparation

(liquid based cytology), , HPV testing, polar probe, laser induced fluorescence, speculoscopy and cervicography, visual inspection of the cervix [22].

Pap smear

Pap smear is one of the simple technique that is widely accepted for screening pre-malignant lesion of cervical cancer cells through cytological examining the cervical cells [22, 23].

HPV DNA Detection

HPV DNA testing considered more sensitive than the cytology screening of pre-malignant lesion. HPV DNA testing was been proved that it is a better technique than the Pap smear technique, visual analysis through acetic acid technique. HPV DNA testing and cytology are one of approved test in the US for screening women of aged 30 years and older [22, 24]. The HPV DNA testing benefits after 10 years were the women infected are in 20 and 30 years where thewomen are in chronic infection of HPV were it is a lifetime risk of developing cervical cancer [22, 25].

Acetic acid or lugol's iodine

This visual inspection of acetic acid (VIA) method is very simple technique same as the Pap smear test was the cervix washed with theacetic acid of 3 to 5% then it's checked for any indication of pre-malignant lesions. It is very low-cost technique; immediate results are available there is follow-up therapy in this technique compared to the Pap smear test [22].

Optical imaging and spectroscopy

Optical imaging and spectroscopy are the non–invasive technique for diagnosing the morphologic and any biochemical changes of the pre-cancerous cells. Technologies as such can improve the diagnosis of the cervix cancer with accuracy. Digital cameras can show wide areas with high resolution [22, 26].

Molecular methods for detecting HPV Infection

HPV infection cannot be proliferated in tissue culture and henceforth it depends on molecular techniques. Human papillomavirus double stranded DNA with 8000bp and well-known structure and gene organization, therefore, the choice of testing or screening considered is nuclear probe technology [27]. The screening of HPV can be inferred on the morphological, serological and clinical findings, the diagnosis of HPV depends on molecular techniques [28].Currently, nucleic acid hybridization assays, signal amplification assay, nucleic acid amplification are available [29,30].

Prevention of HPV

HPV transmission is asexual activity where one type of HPV is affecting almost 75% of sexually active adults. Most of them are usually resolved themselves without any risk very few progress into cancer. World health organization endorse some common approach to preventing cervical cancer or HPV infection. Primary prevention is vaccination and secondary prevention is screening and treatment. Women should undergo periodic screening, it can prevent from invasive cervical cancer, by periodic screening early pre-cancerous lesion and cervical cancer can be treated, five years interval of screening should be done by women in age group 30-65 years [31]. Long-term usage of contraceptive pills should be avoidedmultiple sexual partners, tobacco smoking, low socioeconomic status, poor hygiene, and diet low antioxidants and other probable factors. Usage of condoms can reduce the HPV transmission but condoms are unlikely to protect the HPV infection [32, 33]. Sometimes genetic factor can be responsible, which is unidentified [9].

HPV Vaccination

HPV infections are prevented by vaccination, Food and Drug Administration (FDA) approved three vaccines which are used against the HPV infection such asGardasil, Gardasil9, and Cervarix these three vaccines prevent HPV infection. The three vaccines prevent HPV 16, 18 and other associated HPV infection [34, 35]. HPV types 6 and 11 prevented by Gardasil, which prevents almost 90% of warts, Gardasil 9 also prevents high-risk types of HPV (30, 33, 45, and 52) [36]. The Gardasil and Cervarix vaccine is aquadrivalent and bivalent vaccine. The quadrivalent vaccine gives more protection, it protects from HPV 16 and 18 that majorly causes cervical cancer and it protects from HPV 6 and 11 that causes warts and lesions [30, 31]. Recently they have been exploring thestrategy of prevention using microbicides, Carrageenan a compound extracted from seaweed have been found that is used to inhibit HPV infection. Clinical trials are ongoing to check whether microbicide prevents HPV infection [37]. In US Food and Drug Administration have been approved a carrageenan lubricant which is atotally new approach to inhibiting HPV infection [38].

Discussion

HPV is one of the most common sexually transmitted diseases, where it causes warts or lesions persistent infection by Human papillomavirus can lead to cancer such as cervical cancer. HPV 16 and 18 type are the most common, which causes cervical cancer, HPV 6, and 11 strain cause genital warts or lesions. Screening of HPV infections using different techniques such as Pap smear, acetic acid test, HPV DNA testing and optical imaging and spectroscopy, molecular techniques are majorly used to detect the HPV infection. Vaccines are approved by FDA which are used to prevent HPV infection, bivalent and quadrivalent vaccines.

A tropical microbicidecarrageenan hasbeen used to inhibit HPV infection, in US FDA has approved a lubricant from carrageenan to inhibit HPV infection including cancer.

Future Perspective

Papillomavirus infection is the major cause for cervix cancer. Persistent infection of HPV without a diagnosis or treatment, which may lead to cancer. The high- risk type of HPV such as HPV 16 are responsible for cervical cancer. Ninety- eight percentage of cervical cancer are caused by HPV-16, E6 oncoprotein are responsible. Vaccines are present for HPV infection, which can prevent but complete protection by the present invention of vaccines, which does not give a complete protection for all HPV types hence it makes the current objective of the study [31]. Hence, a bioinformatics approach was considered to analysis the gene expression of HPV.

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