Review Article

A review on Human Papilloma virus

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ABSTRACT

Human Papilloma virus (**HPV**) is a virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. Recently, HPV has been linked with an increased risk of cardiovascular diseases. In addition, HPV 16 and 18 infections are strongly associated with an increased odds ratio of developing oropharyngeal (throat) cancer. Papillomaviruses are a group of small non-enveloped DNA tumor viruses with a vision size of 55 nm in diameter. This group of viruses infects various animals from birds to mammals, including humans. There is now an HPV test for women, which can be used as part of cervical cancer screening and management. This test is not a general check for HPV, and it is not designed to find HPV in men. In men, genital warts may appear around the anus or on the penis, scrotum (testicles), groin or thighs. Even men who have never had anal sex can get warts around the anus. Warts may appear within weeks or months after sexual contact with an infected person, or not at all. A person can have the type of HPV that causes genital warts, but never develop any warts. In present review the attempt are made to focus on detail information about Human Papilloma virus.

Keywords: Human Pappilloma Virus, Oropharyngeal, Warts, Mammals.

1. INTRODCTION TO HUMAN PAPPILOMA VIRUS

Human Papilloma virus (**HPV**) is a virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. While the majority of the known types of HPV cause no symptoms in most people, some types can cause warts (verrucae), while others can – in a minority of cases – lead to cancers of the cervix, vulva, vagina, penis, oropharynx and anus. Recently, HPV has been linked with an increased risk of cardiovascular diseases. In addition, HPV 16 and 18 infections are strongly associated with an increased odds ratio of developing oropharyngeal (throat) cancer.

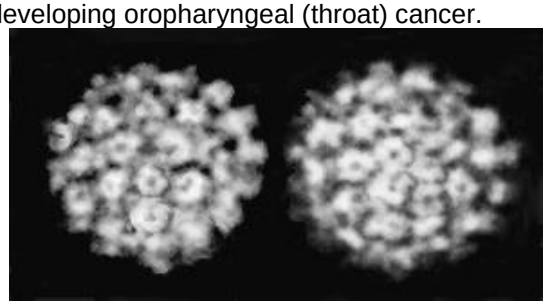


Fig. 1 Morphology of HPV

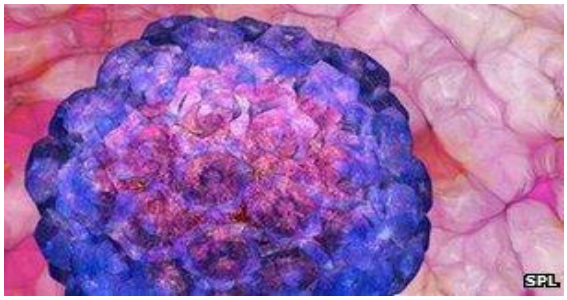


Fig. 2 HPV Infection in Cervical

More than 30 to 40 types of HPV are typically transmitted through sexual contact. Some sexually transmitted HPV types may cause genital warts. Persistent infection with "high-risk" HPV types — different from the ones that cause skin warts — may progress to precancerous lesions and invasive cancer. HPV infection is a cause of nearly all cases of cervical cancer however; most infections with these types do not cause disease.

Most HPV infections in young females are temporary and have little long-term significance. Seventy percent of infections are gone in 1 year and ninety percent in 2 years. However, when the infection persists — in 5% to 10% of infected

women — there is high risk of developing precancerous lesions of the cervix, which can progress to invasive cervical cancer. This process usually takes 10–15 years, providing many opportunities for detection and treatment of the pre-cancerous lesion. Progression to invasive cancer can be almost always prevented when standard prevention strategies are applied, but the lesions still cause considerable burden necessitating preventive surgeries, which do in many cases involve loss of fertility[1-4]
In more developed countries, cervical screening using a Papanicolaou (Pap) test or liquid-based cytology is used to detect abnormal cells that may develop into cancer. If abnormal cells are found, women are invited to have a colposcopy. During a colposcopic inspection, biopsies can be taken and abnormal areas can be removed with a simple procedure, typically with a cauterizing loop or, more commonly in the developing world by freezing (cryotherapy). Treating abnormal cells in this way can prevent them from developing into cervical cancer. [1, 2, 4]
Pap smears have reduced the incidence and fatalities of cervical cancer in the developed world, but even so there were 11,000 cases and 3,900 deaths in the U.S. in 2008. Cervical cancer has substantial mortality in resource-poor areas; worldwide, there are an estimated 490,000 cases and 270,000 deaths each year.
The circular HPV DNA is 6800 to 8000 base pairs in length and codes for eight genes - E6, E7, E1, E2, E4, E5, L1 and L2. The first six are "early" viral genes which code for proteins produced during the early phase of infection in the basal cell layer. They result in enhanced proliferation of the infected cells and their lateral expansion. [5] The E5 Protein has been shown to complex with epidermal-growth-factor receptor, platelet-derived-growth factor receptor and the colony-stimulating factor-1 receptor, which promotes growth. [6] E5 also appears to inhibit programmed cell death. [7] Nevertheless the fact that the viral E5 gene is often deleted during the process of viral DNA integration with the host cell genome suggests a dispensable role in oncogenesis. E6 and E7 genes and their proteins appear to have a central role in HPV-induced cervical cancer. They are expressed in cervical cancers and are individually able to immortalise various human cell lines in vitro but when expressed together their efficiency is enhanced.8 The E6 Protein has significant effects by virtue of its interaction with, and degradation of, p53.9 p53 is also known as the "guardian of the genome" and is crucial in protecting normal cells when exposed to stress (e.g. radiation, UV light or chemicals). In such cells it causes cell cycle arrest preventing a cell with damaged DNA from multiplying, and allowing the cellular repair systems to fix any damaged DNA. If repair is not feasible then p53 induces apoptosis (programmed cell death). Since all cancers arise on a background of DNA mutations, p53 has a key role in preventing carcinogenesis and unsurprisingly 50-60% of all cancers have p53 mutations. Other effects of the E6 protein include degradation of the pro-apoptotic BAK protein which is involved in the intrinsic (mitochondrial) death pathway. BAK has a physiological role in the cellular response to stress, in that it can promote opening of the mitochondrial permeability pores releasing intra-mitochondrial cytochrome-c which induces apoptosis. E6 also activates telomerase and stabilises active Src-family kinases involved in enhanced cell survival, proliferation, and motility. The E7 Protein binds to and degrades the Retinoblastoma (Rb) protein.10 The RB gene, initially identified as the gene responsible for childhood eye tumours, was one of the first tumour suppressor genes to be discovered and led to Knudson's famous "two-hit" hypothesis of cancer development.11 The Rb protein normally inhibits proliferation by binding to the E2F transcription factor – a key player controlling the G1/S phase checkpoint of the cell cycle. Loss of Rb by HPV E7 protein can therefore result in uncontrolled cell division. A- Normal cell would react to excessive E2F-mediated growth signals by p53-dependent apoptosis, however the presence of E6 protein counteracts this by p53 and BAK degradation which prevents apoptosis. The end result of their combined action is host cell DNA which is prone to accumulate chance errors unchecked by physiological repair or programmed cell death. [7]
Papillomaviruses are a group of small non-enveloped DNA tumor viruses whose infection usually causes benign epithelial lesions (warts). Certain types of HPVs, such as HPV-16, HPV-18, and HPV-31, have been recognized as causative agents of cervical cancer and anal cancer and their infections, which arise via sexual transmission, are associated with more than 95% of cervical cancer. Papillomaviruses infect keratinocytes in the basal layer of stratified squamous epithelia and replicate in the nucleus of infected keratinocytes in a differentiation-dependent manner. Viral gene expression in infected cells depends on cell differentiation and is tightly regulated at the transcriptional and

post-transcriptional levels. A noteworthy feature of all papillomavirus transcripts is that they are transcribed as a bicistronic or polycistronic form containing two or more ORFs and are polyadenylated at either an early or late poly(A) site. In the past ten years, remarkable progress has been made in understanding how this complex viral gene expression is regulated at the level of transcription (such as via DNA methylation) and particularly post-transcription (including RNA splicing, polyadenylation, and translation). Current knowledge of papillomavirus mRNA structure and RNA processing has provided some clues on how to control viral oncogene expression. However, we still have little knowledge about which mRNAs are used to translate each viral protein. Continuing research on post-transcriptional regulation of papillomavirus infection will remain as a future focus to provide more insights into papillomavirus-host interactions, the virus life-cycle, and viral oncogenesis.

Papillomaviruses are a group of small non-enveloped DNA tumor viruses with a vision size of 55 nm in diameter. This group of viruses infects various animals from birds to mammals, including humans. Papillomaviruses usually cause benign tumor but sometimes also cause malignancies. To date, more than one hundred human and animal papillomavirus genotypes (types) have been completely sequenced. It is likely that additional types will be added as additional papillomavirus genomes are cloned and sequenced. Recently, the International Committee on the Taxonomy of Viruses (ICTV) has accepted that papillomaviruses are a distinct taxonomic family, the Papillomaviridae, and are unrelated to the polyomaviruses and SV40. The taxonomic status of papillomavirus types, subtypes, and variants is based on the sequence of their L1 genes which differ from each other by at least 10%, 2-10%, and maximally 2%, respectively The bovine papillomavirus type 1 (BPV-1) and human papillomavirus type 1a (HPV-1a) genomes were the first papillomavirus genomes to be completely sequenced For the past two decades, BPV-1 has served as a prototype for studies of the molecular biology of papillomaviruses. [4]

Papillomaviruses replicate and assemble exclusively in the nucleus. Virus infects the keratinocytes in the basal layers of a stratified squamous epithelium. However, viral gene expression and replication proceed in a tightly controlled fashion regulated by keratinocyte differentiation. Although the mechanism on how keratinocyte differentiation regulates HPV gene expression is not fully understood, there is general agreement that viral gene expression leads to the expression of six nonstructural viral regulatory proteins (E1, E2, E4, E5, E6 and E7) from the early region of the viral genome in undifferentiated or intermediately differentiated keratinocytes and two structural viral capsid proteins (L1 and L2) from the late region of the genome in keratinocytes undergoing terminal differentiation The E4 protein continues to be expressed in the terminally differentiated keratinocytes. E1 and E2 are involved in viral DNA replication and the regulation of early transcription. E4 expressed in a productive infection associates with cytokeratin filament collapse. E5, E6, and E7 are viral oncogenes and their expression induces cell immortalization and transformation. In particular, E6 and E7 are two viral oncoproteins that inactivate, respectively, p53 and pRb, two cellular tumor suppressor proteins.

Although papillomavirus infections usually result in benign lesions, human papillomavirus (HPV) infection sometimes progresses to the development of malignant lesions. Certain types of HPVs, such as HPV-16, HPV-18, and HPV-31, which are designated “high-risk” or “oncogenic,” have been recognized as causative agents of cervical and anal cancers. These sexually transmitted viruses are associated with more than 95% of cervical cancer. Among those high-risk HPVs, HPV-16 alone is responsible for development of 58.9% of cervical cancer.This knowledge has led to the development not only of HPV vaccines but also of cervical cancer screening strategies which incorporate HPV testing. A characteristic consequence of cancer associated with persistent infection by these high-risk.

HPV vaccines (Cervarix and Gardasil), which prevent infection with the HPV types (16 and 18) that cause 70% of cervical cancer, may lead to further decreases. [8, 12]

- HPV stands for human papillomavirus.
- There are more than 100 types of HPV.
- HPV is so common that three out of four people will have it at some point in their lives.
- Some types of HPV produce warts on the hands or feet.
- About 40 types of HPV can infect the genital area — the vulva, vagina, cervix, rectum, anus, penis, or scrotum.

- These types are transmitted through vaginal, anal, or oral, sex and other skin-to-skin contact.
- Papillomaviruses are small, approximately 52-55nm in diameter.
- They are non-enveloped, icosahedra particles. This shape is made up of 12 pentameric and 60 hexameric capsomers arranged on a T=7 lattice.
- Their carpsid is composed of two proteins, a major (L1) and minor (L2).
- They are DNA viruses.
- HPV is part of the family known as Papovaviruses, which was named for it's three main members: PApillomavirus, POlyomavirus, and simian Vacuolating Agent. They are found in many vertebrates, and exhibit high species specificity.
- This family contains two genera of oncogenic viruses, Papilloma and Polyoma viruses.
- The Papillomavirus' genome is circular, d/s DNA approximately 8,000bp in size.
- 77 subtypes or genotypes (Genus A Papovaviridae).
- 23 subtypes infect the ano-genital region.
- Most people exposed develop a subclinical infection.
- All develop some type of humoral response.
- 30% develop a clinical infection: condyloma or dysplasia.
- 15-35 years of age most susceptible.
- Only epithelial cells infected.
- 90% will clear high risk types.
- DNA virus with double stranded, circular DNA.
- Genome = 8,000 base pairs.
- 12-15 genes identified.
- Genotypes are based on a greater than 10% difference in DNA structure of E6, E7, or L1 genes.
- Icosohederal capsid outer shell
- HPV is the virus that causes warts.
- More than 100 different kinds, 30-some of this cause genital HPV.
- Spread by sexual contact or from mother to baby.
- Genital warts appear 6 weeks to 8 months after contact with an HPV infected person.
- The most common sexually transmitted disease worldwide.
- Certain types of HPV are linked with cervical cancer.
- Divided into 2 subcategories: Genital Warts and Cervical Dysplasia.
- Most people do not know they have it.
- There are high risk and low risk types of it. [11]

2. HISTORY 0F HUMAN PAPILLOMA VIRUS[9, 13]

The papillomaviruses are part of the PAPOVAVIRIDAE family of DNA tumor viruses.

First discovered in the early 40's. Gained notoriety in the early 80's when it was discovered that some types of HPV caused cervical cancer.

1894-1924: Ciufo, Variot and others show that genital and skin warts can be transmitted between individuals by a filterable infectious agent 1933 (Shope) rabbit papillomas have viral etiology, 1935 (Rous) papillomas can progress to carcinoma

Papillomaviruses found to cause skin warts and other tumors in vertebrates ranging from birds to people.

1928: Georgious Papanicolaou develops the "Pap smear" technique for microscopic detection of cervical cancer and pre-cancer

1942: Rigoni-Stern reports that prostitutes have much higher incidence of cervical cancer than nuns

1951: George Otto Gey establishes in vitro culture of HeLa (Henrietta Lacks) cells derived from a lethal cervical cancer.

1983: Harald zur Hausen discovers new HPV types (types 16 and 18) lurking in HeLa cells and other cervical cancer cells.

2008: Harald zur Hausen wins Nobel Prize for his work establishing a causal link between HPVs and cervical cancer.

3. TRANSCRIPTION OF HUMAN PAPPILOMA VIRUS:- [7, 14]

All papillomaviruses contain a double-stranded, circular DNA genome approximately 8 kb in size that can be divided, in general, into three major regions: early, late, and a long control region (LCR or noncoding region [NCR]). The three regions in all papillomaviruses are separated by two polyadenylation (pA) sites: early pA (A_E) and late pA (A_L) sites .The early region of papillomavirus genomes occupies over 50% of the virus genome from its 5′ half and encodes six common open reading frames (E1, E2, E4, E5, E6 and E7) that translate individual proteins as briefly described above. Two other ORFs, E3

and E8, were also assigned to this region initially, but only the E8 ORF in BPV-1 and HPV-31 .has been proven to encode a protein, a spliced E8^E2C fusion protein, which functions as a negative regulator of viral transcription and replication. Unlike BPV-1 and HPV-31, E8 in several rabbit papillomaviruses have been characterized as an oncogene, with features similar to those of the E5 of both BPV-1 and several HPVsHPV-31. The late region of all papillomavirus genomes, covering almost 40% of the virus genome, lies downstream of the early region and encodes L1 and L2 ORFs for translation of a major (L1) and a minor (L2) capsid protein. The LCR region, a segment of about 850 bp (10% of the HPV genome), has no protein-coding function, but bears the origin of replication as well as multiple transcription factor binding sites that are important in regulation of RNA polymerase II-initiated transcription from viral early as well as late promoters. How these transcription factor binding sites are involved in regulation of papillomavirus gene expression has been summarized in a recent comprehensive review. Genome structure and transcription map of HPV-16. The bracket line in the middle of the panel represents a linear form of the virus genome for better presentation of head-to-tail junction, promoters (arrows), and early (A_E) and late (A_L) polyadenylation.

In general, each ORF in a papillomavirus genome is often referred to as a gene. However, a gene, in molecular terms, is defined as the entire nucleic acid sequence that is necessary for the synthesis of a functional transcript. According to this definition, a gene is not equivalent to an ORF. In eukaryotes and many viruses, a gene usually contains axons and introns. An ORF encoding a polypeptide is usually spread across multiple axons from various parts of the genome which are combined into a full-length ORF through RNA splicing. This is particularly true in papillomaviruses even though only one ORF (E1^E4) in papillomaviruses spans two separate axons. In fact, extensive mRNA mapping and analysis of BPV-1 transformed C127 cells as well as productively infected bovine fibropapillomas has led to the conclusion that each transcript from the BPV-1 genome could be bicistronic, tricistronic, or even polycistronic with two or more ORFs. On the other hand, a particular ORF could exist in multiple mRNAs transcribed from different promoters. Until today, the transcription map of BPV-1 has been the best known map for our understanding of the complexity of papillomavirus gene expression and has been summarized in the HPV compendium. However, to determine which transcripts encode which viral proteins has been a challenge and we still have only a very limited knowledge of which proteins are translated from each transcript. Recent HPV-16 transcript mapping and gene expression studies have shed some light on this problem. [1, 8]

Although there has been some recent progress on characterization of new promoters and minor transcripts from HPV-11 and HPV-31, this review will emphasize HPV-16 and update the HPV-16 transcription map. The HPV-16 genome contains two major promoters. The P97 promoter lies upstream of the E6 ORF and is responsible for almost all early gene expression .The P670 promoter lies within the E7 ORF region and is responsible for late gene expression. Although other minor promoters in the early regions of the genome have been described, their activities in the context of an episomal HPV genome remains unknown. The HPV-16 P97 promoter, equivalent to P99 in HPV-31 and P105 in HPV-18, is very potent and tightly controlled, primarily by upstream cis-elements in the LCR. These cis-elements, including four consensus E2-binding sites (E2-BSs), ACC (N_6)GGT , interact with cellular transcription factors and the viral transactivator/repressor E2 and regulate the transcription of P97 from undifferentiated basal cells to highly differentiated keratinocytes. However, recent studies indicate that E2 functions as a repressor for P97 transcription at steps after TBP or TFIID binding and its transcriptional repression only occurs in cells harboring integrated, but not episomal HPV-16 DNA . The resulting early primary transcripts (pre-mRNAs) all have three exons and two introns, which undergo alternative RNA splicing and are polyadenylated at nt 4215. As shown in the, each intron of the early transcripts could be spliced out through utilization of three alternative 3′ splice sites at nt 409, 526 or 742 in intron 1, and three other alternative 3′ ss at nt 2582, 2709, 3358 in intron, leading to the production of at least 14 species of mRNA transcripts with various coding potential.

The HPV-16 P670 promoter is a late-promoter. Its activity can be induced only in differentiated keratinocytes. The similar activity of late promoter P742 in HPV-31 could be induced during vegetative replication of HPV-31 in raft cultures. In other DNA viruses, the late promoter activation always requires viral lytic DNA

replication. Although transcription of late promoter P742 in HPV-31 has been related to the protein kinase C pathway, it remains puzzling on how the late promoter is activated. A recent study suggests that cell differentiation signals alone are sufficient to activate transcription from the late promoter P742, although DNA amplification is also required for maximal activity of the late promoter . A cis element located in the E6 and E7 coding region appears to regulate the late promoter. Nevertheless, both the late P670 promoter in HPV-16 and P742 in HPV-31 are positioned in the E7 coding region and transcription from the late promoter has to bypass the early pA site to allow expression of the late region. As a result, a true late pre-mRNA is a chimeric transcript of early and late regions, with the early region in its 5′ half and the late region in its 3′ half. This late pre-mRNA can be processed into early region transcripts which are cleaved and polyadenylated at the early poly (A) site (transcripts P and Q) and late region transcripts which are cleaved and polyadenylated at the late poly(A) site (transcripts R, S, and T). In contrast to early transcripts, the late region transcripts are detectable only in differentiated keratinocytes with vegetative DNA replication.[4]

4. STRUCTURE OF THE HUMAN PAPPILOMA VIRUS[7, 9]

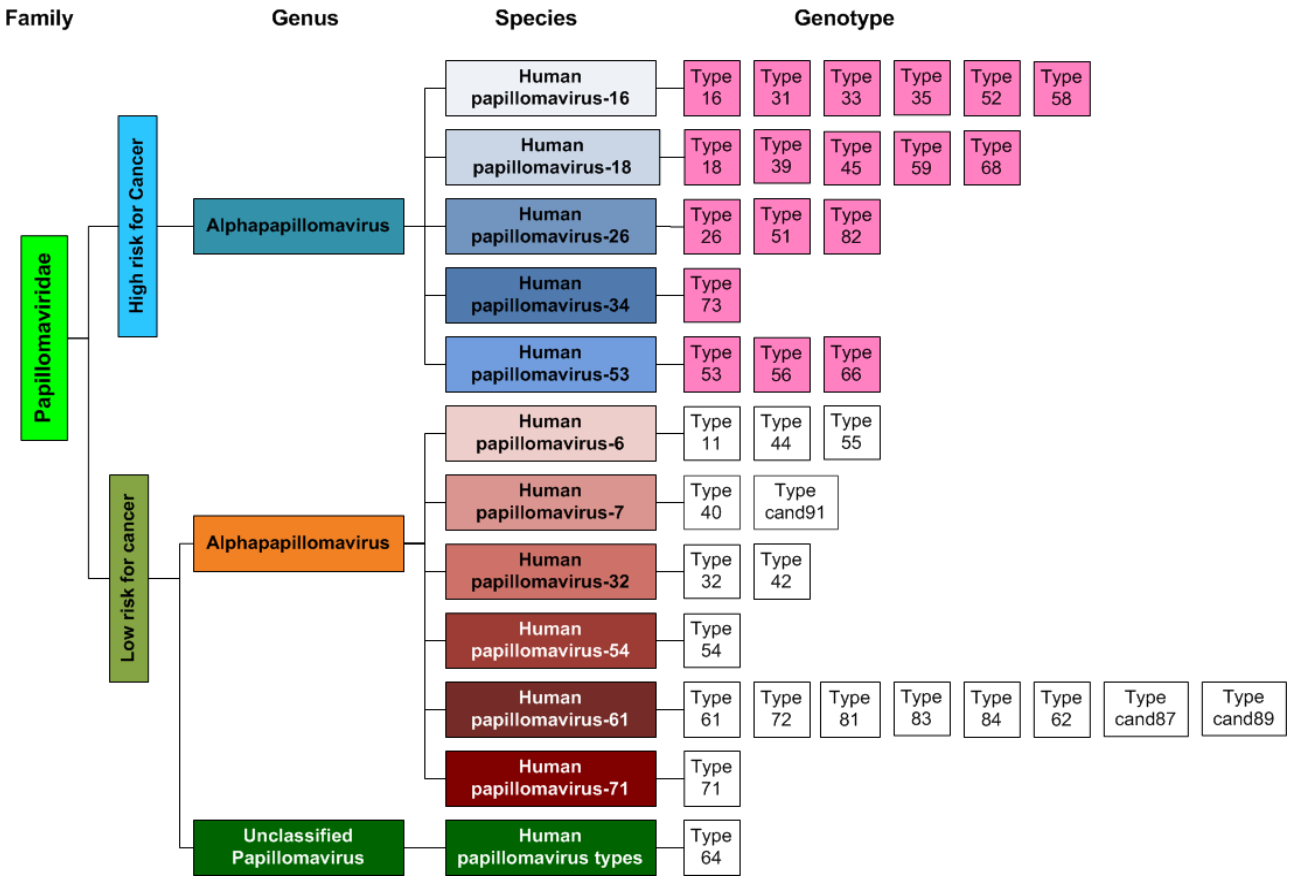
(1) Viral components and physical properties

Papillomaviruses are small, non-enveloped, icosahedral DNA viruses that have a diameter of 52–55 nm. The viral particles consist of a single double-stranded DNA molecule of about 8000 base-pairs (bp) that is bound to cellular histones and contained in a protein capsid composed of 72 pentameric capsomers. The capsid contains two structural proteins — late (L)1 (55 kDa in size; 80% of total viral protein) and L2 (70 kDa) — which are both virally encoded. Virus-like particles (VLPs) can be produced by the expression of L1, alone or in combination with L2, in mammalian or non-mammalian expression systems. The intact virion has a density of 1.34 g/mL in cesium chloride and a sedimentation coefficient (S20, W) of 300 (Kirnbauer et al., 1992; Hagensee et al., 1993a).

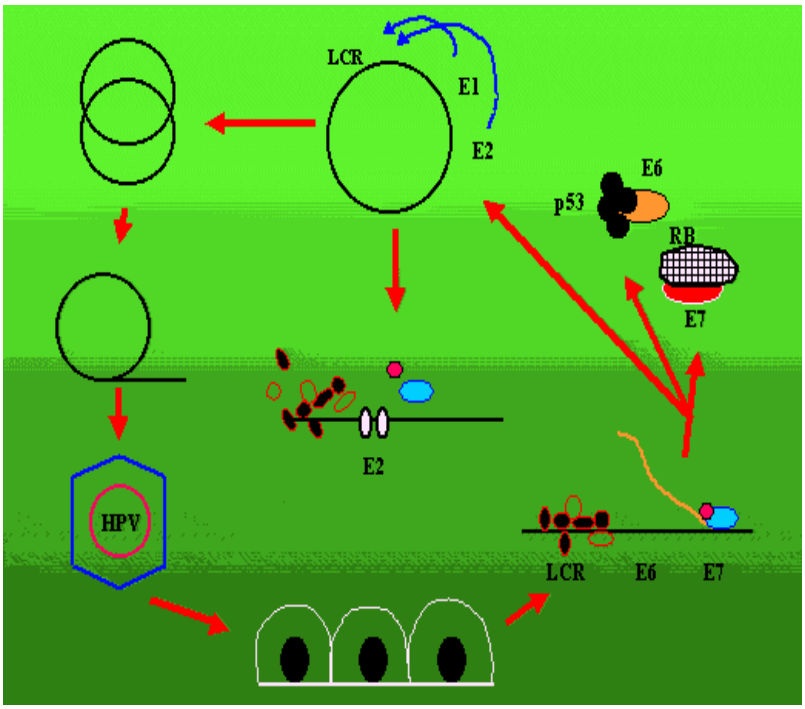
(2) HPV genome, proteins and life cycle

The genomes of all HPV types contain approximately eight ORFs that are all transcribed from a single DNA strand. The ORF can be divided into three functional parts: the early (E) region that encodes proteins (E1–E7) necessary for viral replication; the late (L) region that encodes the structural proteins (L1–L2) that are required for virion assembly; and a largely non-coding part that is referred to as the long control region (LCR), which contains cis elements that are necessary for the replication and transcription of viral DNA. The viral E proteins are transcribed from the early promoter (e.g. P97 in HPV 31) whereas the L proteins are transcribed principally from the late promoter (P742 in HPV 31) (see Figure 1) (Fehrmann & Laimins, 2003). The E1 and E2 proteins of HPV act as factors that recognize the origin of replication; E2 protein is also the main regulator of viral gene transcription. E4, despite its name, is believed to be involved in the late stages of the life cycle of the virus and E5 may function during both early and late phases. The E6 and E7 proteins target a number of negative regulators of the cell cycle, primarily p105Rb and p53, respectively. During the viral life cycle, E6 and E7 facilitate stable maintenance of viral episomes and stimulate differentiating cells to re-enter the S phase. The L1 and L2 proteins assemble in capsomers, which form icosahedral capsids around the viral genome during the generation of progeny virions (Fehrmann & Laimins, 2003). [12]

5. CLASSIFICATION OF HUMAN PAPPILOMA VIRUS[16]



6. LIFE CYCLE OF HUMAN PAPPILOMA VIRUS[3, 9]



Starts with the infection of the host cell

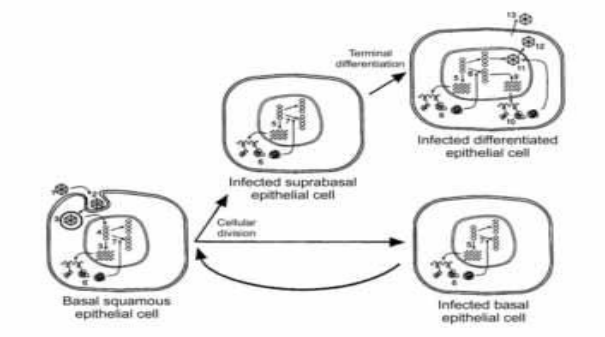
The virus DNA is released within the nucleus. Numerous cellular transcription factors interact with the non-coding viral regulatory region (LCR), starting transcription of the two hpv-16 transforming early genes (E6 and E7). The transforming proteins interact with the cellular antioncogenic regulator p53 disrupting the cell cycle. Infection requires entry to non-differentiated basal cells Virus binds to heparin and α_6-integrin.

Virions are taken in by endocytosis Genome ends up inside nucleus Stays as circular DNA Does not incorporate itself into host genome. Replication of genome occurs generating 50-100 copies Every cell division genome is duplicated and split equally between parent and daughter cell. This type of division is referred to as 'plasmid replication.When Basal Cells become Keratinocytes burst of viral replication occurs.

This burst is called vegetative replication. During this same period L1 and L2 genes are expressed producing capsids. Release of assembled virions occurs during cell death.

The HPV life cycle consists of initial infection, uncoating, genome maintenance, genome amplification, and packaging to form new viral particles. Most of the work in this area and its associated genetic events has focused on HPV type 16 (HPV16) which is a major cause of cervical cancer. Initial infection is thought to require viral access to cells in the basal layer of the epithelium, via breaks, abrasions or other micro-traumas in the stratified epithelium. Hair follicles seem to have abundant amounts of viral DNA15 leading to suggestions that epithelial stem cells may be an important target for the virus.16 The virus attaches to the basal epithelial cells via specific cell surface receptors17 leading to internalisation of the virus followed by uncoating of the viral particles and release of the viral genome. It has therefore been suggested that E7 functions to promote S-phase entry in a subset of suprabasal cells with intrinsically low levels of p21/p27 or alternatively high levels of E7 expression. Amplification of viral genome occurs in the mid to upper epithelial layers and requires the activity of E1, E1, E4 and E5 proteins. The exact details are still to be elucidated but key events include up-regulation of a promoter present within the E7 open reading frame and increased E1/E2 expression. The freshly replicated genome can act as a template for further gene expression leading top increased amounts of E1/E2 and other replication proteins. The minor (L2) and major (L1) capsid proteins are expressed.

7. REPLICATION CYCLE OF HUMAN PAPPILOMA VIRUS[11,13,15]



8. SYMPTOMS OF HUMAN PAPPILOMA VIRUS[8, 12]

Most men who get genital HPV do not have any symptoms. However, some types of HPV can cause genital warts. Genital warts are single or multiple growths that appear in the genital area. They may be raised, flat, or cauliflower shaped.

In men, genital warts may appear around the anus or on the penis, scrotum (testicles), groin or thighs. Even men who have never had anal sex can get warts around the anus. Warts may appear within weeks or months after sexual contact with an infected person, or not at all. A person can have the type of HPV that causes genital warts, but never develop any warts.

Genital HPV is passed on through genital contact –such as vaginal and anal sex. Both men and women can get HPV – and pass it on - without even realizing it. Genital warts can also be passed on by a person who has HPV but no visible warts. Since the virus can be "silent" for a long time, people can have genital HPV even if years have passed since they have had sex.

Certain types of HPV have been linked to cancer of the anus and penis in men. These cancers are rare –especially in men with healthy immune systems. The types of HPV that can cause genital warts are not the same as the types that can cause penile or anal cancer.

Over half of sexually active men in the United States (U.S.) will have HPV at some time in their lives.

- About 1% of sexually active men in the U.S. have genital warts at any one time.

The American Cancer Society (ACS) estimates that about 1,530 men will be diagnosed with penile cancer in the U.S. in 2006. In this country, penile cancer accounts for about 0.2% of all

cancers in men. It is especially rare in circumcised men.

ACS estimates that about 1,910 men will be diagnosed with anal cancer in 2006. The risk for anal cancer is 17 times higher among gay and bisexual men than among heterosexual men. The risk is also higher among men with compromised immune systems, including those with HIV. At the moment, there is no test approved to detect HPV in men. However, there are ways to detect the most common problem caused by HPV in men, genital warts. Genital warts are usually diagnosed by visual inspection. Some health care providers may use a vinegar solution to help identify flat warts, although this test is not specific for warts. That means the test may falsely identify normal skin as a wart.

There are currently no tests approved to detect early evidence of HPV-associated cancers in men, as there are for women (Pap tests). Nonetheless, since anal cancer is more common in gay, bisexual, and HIV-positive men, some experts recommend routine anal Pap tests for those populations. The anal Pap test is used to find abnormal cells in the anus (caused by HPV) that could turn into cancer over time. However, it is not yet clear that finding and removing abnormal cells from the anus will effectively prevent anal cancer from developing in the future. CDC does not recommend anal cancer screening.

There is no treatment or cure for HPV. But there are ways to treat the health conditions associated with HPV in men, including genital warts, penile cancer and anal cancer. Visible genital warts can be treated with medication, surgically removed, or frozen off. Some of these treatments can be applied by the patient, while others must be performed by a health care provider. No one treatment is best. Warts might return, especially in the first 3 months after treatment. (Genital Warts Treatment)

It is not known whether treatment of genital warts will reduce the chance of passing the virus on to a sex partner. If left untreated, genital warts may go away, remain unchanged, or increase in size or number. They will not turn into cancer. For these reasons, some individuals may choose not to get treated, but to see if the warts will disappear on their own.

No. HPV is not like other sexually transmitted infections (STIs), which need to be detected and treated. HPV is a virus that lives in the skin, rather than in your body. There is no clear health benefit to knowing you have this virus since HPV is unlikely to affect your health and cannot be treated. For most men, there would be no need to treat HPV, even if treatment were available since it usually goes away on its own.

While most men will not develop health problems from HPV, some men are at higher risk of disease from HPV. HIV positive men are more likely to get severe and prolonged cases of genital warts, which may be more resistant to treatment. They are also more likely to develop anal cancer. It is also important for men to realize that they can unknowingly transmit HPV to their female sex partners. Compared to heterosexual men, women are at higher risk of developing disease from HPV most notably, cervical cancer. Cervical cancer in women is much more common than anal or penile cancer in men. According to ACS, more than 9,700 women will be diagnosed with cervical cancer in the U.S. in 2006.

Because HPV is so common but usually invisible, the only sure ways to prevent it are not to have sex, or to have sex with only one uninfected person, who is only having sex with you. You can lower your risk by limiting your number of sex partners and choosing partners who have had few or no sex partners. Condoms may also lower your risk of HPV-associated conditions. Condoms may provide some but not complete protection against HPV, since HPV can infect skin that is not covered by a condom. Condoms have been shown to reduce the risk of genital warts and cervical cancer. Condoms can also reduce the risk of HIV and some other sexually transmitted infections, when used all the time and the right way.

There is now an HPV test for women, which can be used as part of cervical cancer screening and management. This test is not a general check for HPV, and it is not designed to find HPV in men. Partners usually share HPV. If you have been partners for a long time, it is likely that you already have HPV. The types of HPV that put a woman at risk for cervical cancer very rarely cause any health problems for heterosexual men. This probably means she has a type of HPV on her cervix that could put her at risk for cervical cancer. HPV is not a sign that you or your partner has been unfaithful in the relationship. HPV can be silent in the body for many years before it is found on a test. She may have had HPV for many years, and there is no way.

HOW DOES HUMAN PAPPILOMA VIRUS WORKS? [4]

HPV infects the basal cells of the dermal layer, and early gene expression occurs in these cells.

- Late gene expression and high copy DNA synthesis occurs only in terminally differentiated epidermal cells.
- This implies a link between differentiation and gene expression, although the nature of this link is unknown.
- Some strains of HPV are able to transform host cells on their own, whereas others require cofactors.
- **Signs of HPV infection**
  1) Cervical cancer
  2) Genital organ cancer

9. DIAGNOSIS TESTS OF HUMAN PAPPILOMA VIRUS [8,15,16]

1) Non-molecular techniques for the detection of genital HPV infection
   (a) Visual inspection techniques
   (b) Colposcopy

Genital HPV infections other than HPV-associated cervical neoplasia

ii)Non-genital HPV infection

   (c) Cytology and histology
2) Detection of HPV proteins in infected tissues
3) Detection of HPV nucleic acids
   (a) PCR-based methods
   (b) Commercial nucleic acid hybridization methods
   (c) Southern and northern blot hybridization
   (d) In-situ hybridization
   (e) Comparison of HPV testing methods
4) Detection of HPV infections and HPV-associated cancers by serological Assays
   (a) Detection of capsid antibody
   (b) Neutralization assays
   (c) Detection of antibodies to E6 and E7
   (d) Detection of antibodies to E1, E2, E4 and E5

10. TREATMENT FOR HUMAN PAPPILOMA VIRUS[4, 8, 10, 14, 15]

Most people with HPV have no signs or symptoms and HPV will clear up by itself.

Unlike other sexually transmitted infections, HPV is caused by a virus and viruses cannot be cured with antibiotics. There is currently no medical cure to eliminate the HPV virus. Four types of HPV cause the majority of genital warts (types 6 and 11) and most cases of cervical cancer (types 16 and 18). Two vaccines are now available in Canada; one protects against types 16 and 18 and the other against all four types. You should speak to your physician about this option. Treatment depends on the type of HPV virus you have contracted. If you have contracted the low risk types of HPV that cause genital warts, the warts can be removed with treatment at home or at your physician's office. If you have contracted high risk types of HPV that cause cervical, anal or other genital cancer, the treatment will depend on the stage of development at the time of diagnosis.

Treatment of genital and anal warts

There are home therapies available and some treatment options are available in the doctor's office. The average timeframe required for the successful treatment of cervical, anal and genital warts are approximately eight (8) months. Eliminating the visible aspect of the warts will not always eliminate the HPV virus completely and the warts can reappear. If there are too many warts or they are bulky your physician may recommend one of the following treatment options:

- Chemical treatment methods (cryotherapy) can be painful, embarrassing and may cause scarring. Direct application of two powerful chemicals (podophyllin and trichloroacetic acid) can destroy external genital and anal warts, but this must be repeated several times.
- A new product, imiquimod cream (Aldara) is now available and has some success at stimulating the immune system to fight the virus when it causes external genital and anal warts. There are factors that will affect the successful treatment of genital and anal warts such as smoking, having a diet deficient in Vitamin A or having another sexually transmitted infection.

Treatment of pre-cancerous lesions

Pre-cancerous lesions rarely cause any noticeable symptoms. These are usually detected through a Pap test (smear) or a colposcopy. It does take many years (as much as 10 years) for pre-cancerous cells to develop into cancer, so having a regular Pap test will ensure that any abnormal cells are detected

early. The most common reason a woman develops cervical cancer is because she did not have a Pap test. Pre-cancerous lesions can usually be treated successfully. Options at this stage can include loop electrosurgical excision procedure (LEEP) which involves the removal of a tissue using a wire loop. Other treatments include laser therapy or cryotherapy.

Treatment of HPV related cancer

Once you have been diagnosed with cervical cancer, it means there is invasive cancer in the deeper layers of the cervix and has spread to the uterus. If the cancer is limited to the cervix, it can be treated with the removal of the uterus hysterectomy Genital warts can be treated by a doctor and by different methods.

Podofilox gel: A patient-applied treatment for external genital warts.

Imiquimod cream: A patient-applied treatment. Chemical treatments (including trichloracetic acid and podophyllin), which must be applied by a trained health care provider to destroy warts.

Cryotherapy: Uses liquid nitrogen to freeze off the warts.

Laser therapy: Uses a laser beam or intense lights to destroy the warts.

Electrosurgery: Uses and electric current to burn off the warts.

Surgery: Can cut away the wart in one office visit .

Interferon: an antiviral drug, which can be injected directly into warts.

The development of a vaccine against HPV is under way, but is still not available.

If left untreated, some genital warts may regress on their own.

ROUTINE VACCINATION

• This HPV vaccine is recommended for girls and boys 11 or 12 years of age. It *may* be given starting at age 9.

11. PHARMACOLOGICAL DRUGS USED IN HUMAN PAPPILOMA VIRUS[16]

- There are top 5 drugs that works on Human Pappiloma Virus
  1) **Gardasil:-** It is one of the top drug for the HPV virus. It is non-infectious quadrivalent recombinant vaccine, with highly purified virus-like particles, in combination with an Al-contaning vaccine adjuvant.
  2) **Imiquimod (Aldara):**- It is a prescription medication that acts as an immune response modifier. Imiquimod is a patient-applied cream used to treat certain diseases of the skin as well as HPV.
  3) **Podofilox (Condilox):-** It is a drug used to treat HPV virus. It is non alkaloid toxic lignin extracted from the roots & rhizomes of the Podophyllum species. It is topical gel used for the treatment of external genital.
  4) **Tricholoacetic acid:**- It is analogue of acetic acid in which 3 hydrogen atom of the methyl group have all been replaced by chlorine atom. Solution containing tricholoro acetic acid used for treatment of genital warts.
  5) **Vaccine:-** It is used for the protects against the sexually transmitted virus that cause cervical cancer it also helps in genital warts.

12. MARKETED PREPARATIONS USED IN HUMAN PAPPILOMA VIRUS[16]

1) **Nog Divine** (Natural Forming Liquid, Initiative Lubricant).
2) **Bioglide** (Meditional Lubricating Gel).
3) **Carageenan** (Natural Personal Lubricant).

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