KING SAUD UNIVERSITY

Human papillomavirus (HPV)

MIC 450

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Medical Virology

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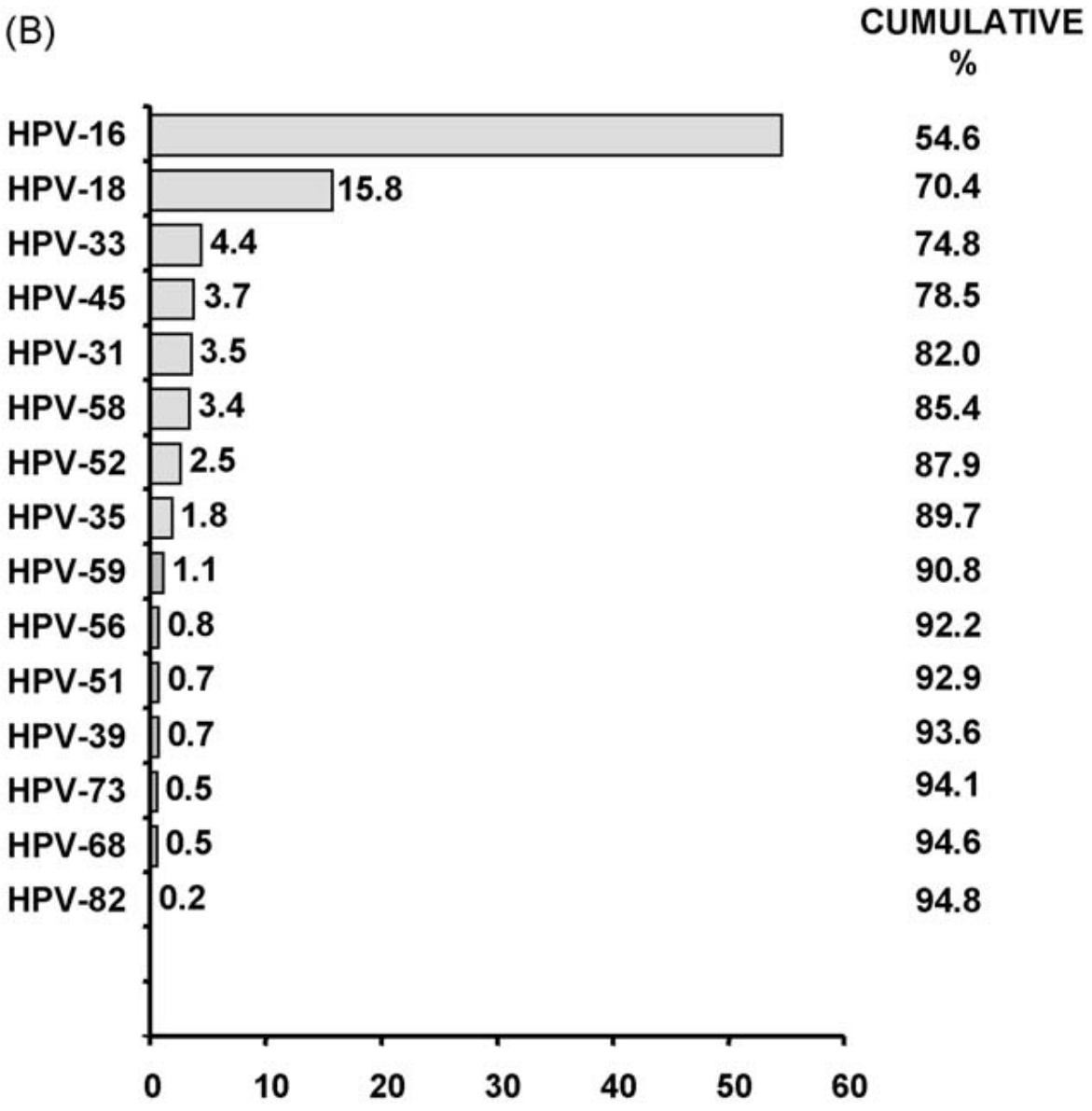
Human papillomavirus (HPV)

Introduction:

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States. The relationship of cervical cancer and sexual behavior was suspected for more than 100 years and was established by epidemiologic studies in the 1960s. In the early 1980s, cervical cancer cells were demonstrated to contain HPV DNA. Epidemiologic studies showing a consistent association between HPV and cervical cancer were published in the 1990s. The first vaccine to prevent infection with four types of HPV was licensed in 2006.[*1]HPV is so common that nearly all sexually active men and women get it at some point in their lives. There are many different types of HPV. Some types can cause health problems including genital warts and cancers. But there are vaccines that can stop these health problems from happening. Human papillomaviruses are small, double-stranded DNA viruses that infect the epithelium. More than 120 HPV types have been identified; they are differentiated by the genetic sequence of the outer capsid protein . Most HPV types infect the cutaneous epithelium and can cause common skin warts. About 40 types infect the mucosal epithelium; these are categorized according to their epidemiologic association with cervical cancer.[*2]This meta-analysiswas recently updated to include more than 14,500 cases from studies published up to January 2006 The most common HPV types identified were, in order of decreasing prevalence, HPV-16, -18, -33, -45, -31, -58, -52, -35, -59, -56, -51, -39, -6, -68, -73, -66 and -70. The prevalence of high-risk HPV types obtained from the most recent metaanalysis is shown in Fig. 1B.HPV-16 and -18 accounted for 70% of all cervical cancer cases worldwide, and the eight most common types (HPV-16, -18, -33, -45, -31, -58, -52 and -35) accounted for 90% of cases**.**[*3]


(B)
CUMULATIVE %
HPV-16
HPV-18
HPV-33
HPV-45
HPV-31
HPV-58
HPV-52
HPV-35
HPV-59
HPV-56
HPV-51
HPV-39
HPV-73
HPV-68
HPV-82
54.6
15.8
70.4
4.4
74.8
3.7
78.5
3.5
82.0
3.4
85.4
2.5
87.9
1.8
89.7
1.1
90.8
0.8
92.2
0.7
92.9
0.7
93.6
0.5
94.1
0.5
94.6
0.2
94.8
0
10
20
30
40
50
60

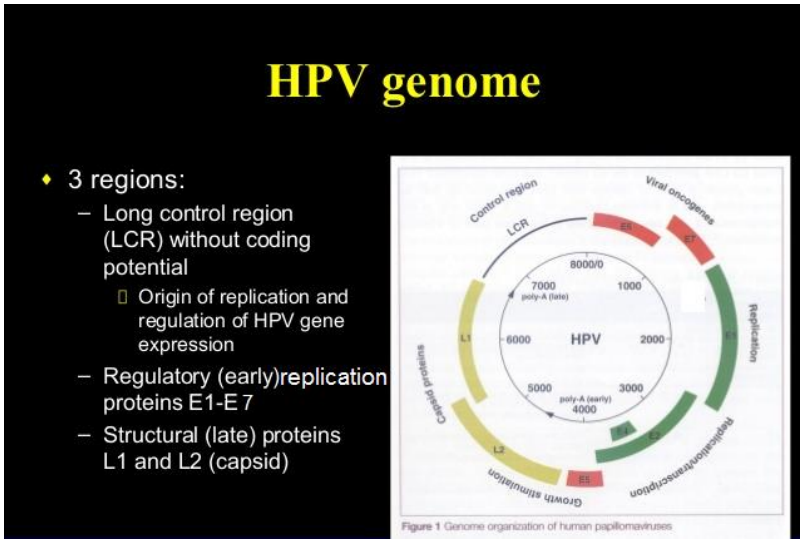
Considering the annual rate of infection, it is apparent that many cases are cleared from detectable levels after some time.[6] A study of 608 college women in 1998 discovered that 70% of new HPV infections were cleared within 12 months, and 91% were cleared by 24 months after the time of initial infection. It was determined that the median duration of HPV infection in this cohort was approximately 8 months, depending on various factors regarding immune function and virus type. High-risk (oncogenic) HPV types, such as 16, 18, 61 and 73 were more likely to persist than nononcogenic types; however, the majority of high-risk HPV infections were cleared within 24 months.*4

Classification in virus :

Order : *Unassigned*
Family : *popillumaviriade*
Gene : *popillumavirus*. *5

Structure and genome :

Shape : icosahedral symmetry .
Size: small size and small DNA viruses (50-55 nm)
Enveloped: They are non-enveloped viruses.
Nucleic acid: about 8000 base pairs (8Kb) of double-stranded, circular DNA.*6



Proteins (Virulence factors):

The virulence factors include proteins E6 and E7 of high-risk serotypes of HPV. These proteins have been shown to inactivate the host's tumor suppressor proteins p53 and Rb. This inactivation of tumor suppresser proteins results in the host cells dividing at rate that cannot be regulated and malignant (cancerous) transformation of these cells.[*7] The viral oncogenes, E6 and E7 are thought to modify the cell cycle so as to retain the differentiating host keratinocyte in a state that is favourable to the amplification of viral genome replication and consequent late gene expression. E6 in association with host E6 associated protein, which has ubiquitin ligase activity, act to ubiquitinate p53, leading to its proteosomal degradation. E7 (in oncogenic HPVs) acts as the primary transforming protein. E7 competes for retinoblastoma protein (pRb) binding, freeing the transcription factor E2F to transactivate its targets, thus pushing the cell cycle forwards. All HPV can induce transient proliferation, but only 16 and 18 can immortalise cell intes (in vitro).

Transmission :

HPV is transmitted through intimate skin-to-skin contact.

1) You can get HPV by having vaginal, anal, or oral sex with someone who has the virus. It is most commonly spread during vaginal or anal sex. Anyone who is sexually active can get HPV, even if you have had sex with only one person. HPV is so common that nearly all sexually active men and women get it at some point in their lives. HPV can be passed even when an infected person has no signs or symptoms. You can develop symptoms years after you have sex with someone who is infected, making it hard to know when you first became infected.

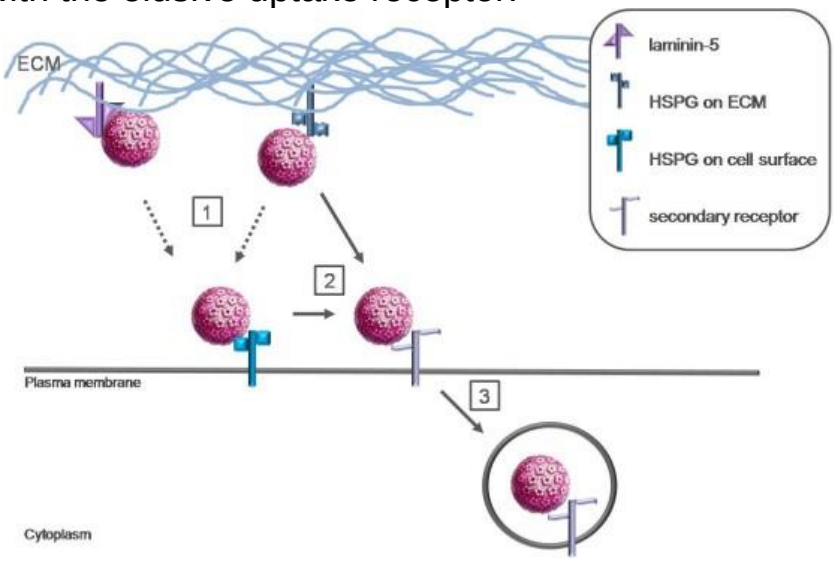
2) fomites (rare) Fomites are inanimate objects that may harbor the infectious organism and transmit it when the fomite is introduced to a non-infected person.

3)Some experts believe that in rare cases HPV may be transmitted through shared bath towels.

4) Very rarely, a pregnant woman with genital HPV can pass HPV to her baby during delivery. In these cases, the child can develop RRP or recurrent respiratory papillomatosis.[*8]

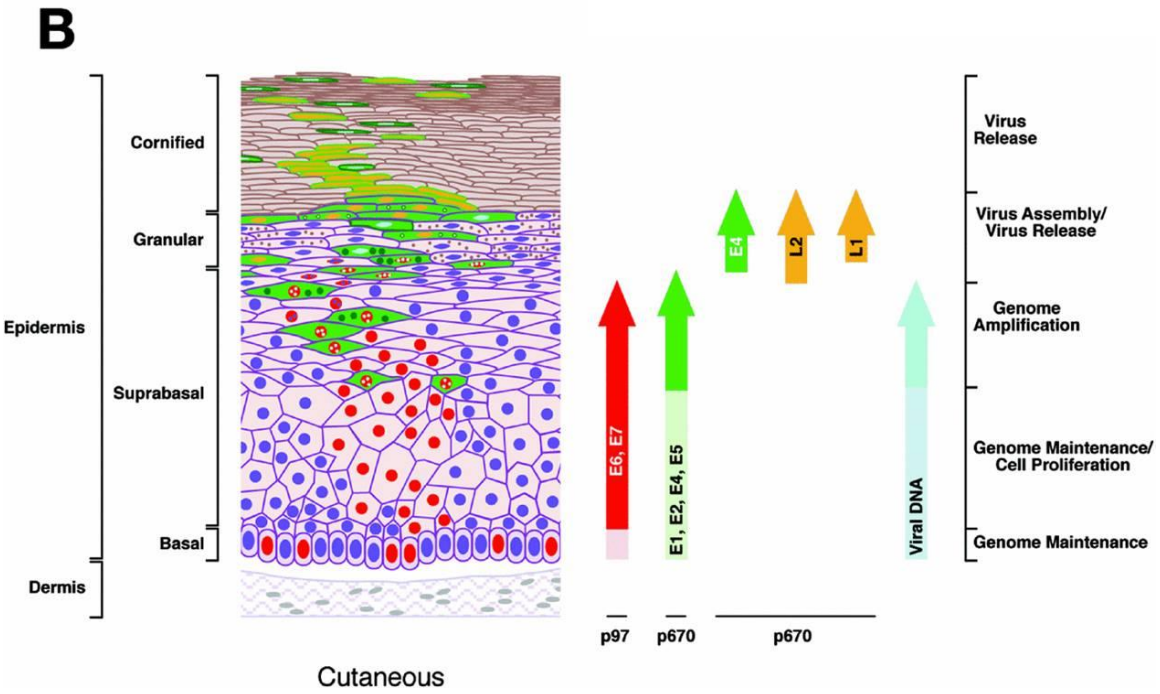
Penetration and the target organ:

HPVs are restricted in their host range to humans, and primarily infect stratified epithelia at either cutaneous or mucosal sites. Mucosotropic HPVs can be further subdivided into high- and low-risk types depending upon their degree of association with human malignancy.*[9]Host cell entry of HPV is initiated by binding of the virus particle to cell surface receptors It has been suggested that virions bind initially to the basement membrane prior to transfer to the basal keratinocyte cell surface*[10] (HPVs) must deliver their genetic material into the nucleus of the target cell. The viral capsid has evolved to fulfil various roles that are critical to establish viral infection. The particle interacts with the cell surface via interaction of the major capsid protein, L1, with heparan sulfate proteoglycans. Moreover, accumulating evidence suggests the involvement of a secondary receptor and a possible role for the minor capsid protein, L2, in cell surface interactions.The entry of HPV in vitro is initiated by binding to a cell surface receptor in contrast to the in vivo situation where the basement membrane has recently been identified as the primary site of virus binding. Binding of HPV triggers conformational changes, which affect both capsid proteins L1 and L2, and such changes are a prerequisite for interaction with the elusive uptake receptor.*[11]



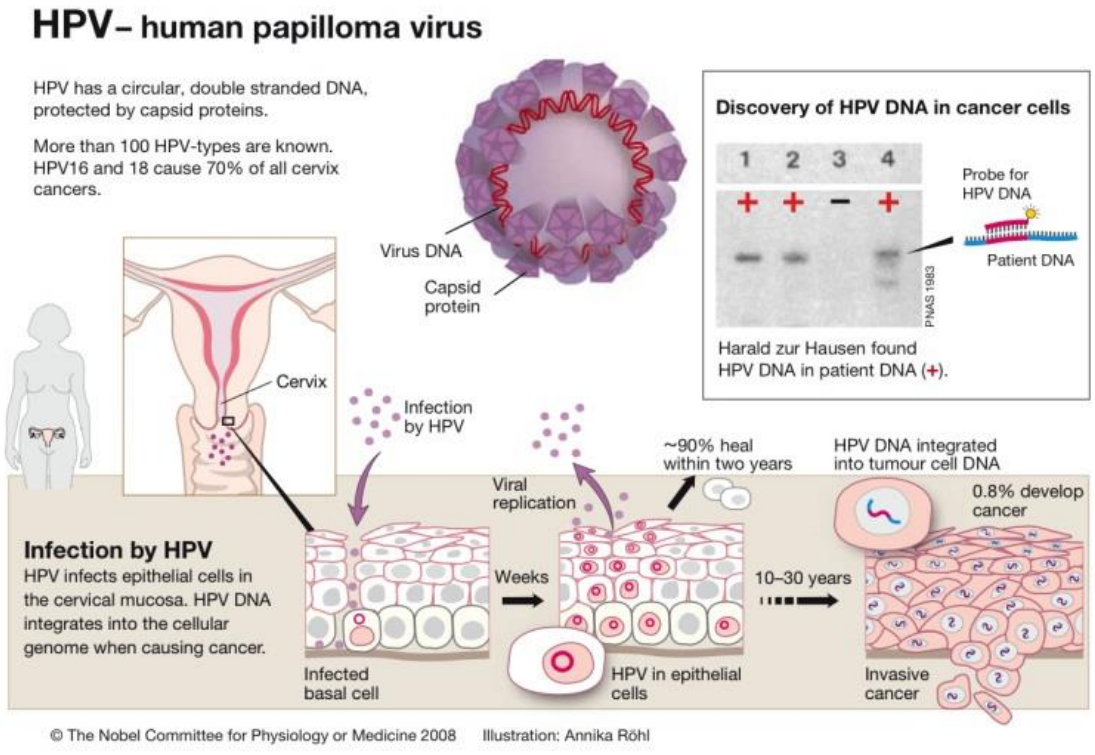
Replication cycle:

solely in keratinocytes, or keratin-producing epithelial cells, the differentiation of which is critical to the papillomavirus's own development. The virus first infects keratinocyte stem cells, which live in the basal layer of the epithelium, through a breach in the upper layers of the epithelium. Upon infection, the virus takes advantage of the cell's replication machinery to reproduce its genome several times, so that each infected cell contains a low viral load of about 50 copies. As the cells proliferate, they move towards the outer layers of the epithelium; the viruses proliferate as well, but do not amplify their genome to escape detection by the immune system. When the host keratinocyte reaches S-phase in the differentiation compartment of the epithelium, the papillomavirus replicates its genome to the critical limit of about 1000 copies. In fact, the virus releases growth promoters E6 and E7 at this stage in order to stimulate the host's movement into this phase. When the keratinocyte reaches the superficial epithelium and dies, the genomes are repackaged into capsids and shed from the cell.[*12]



Assembly :

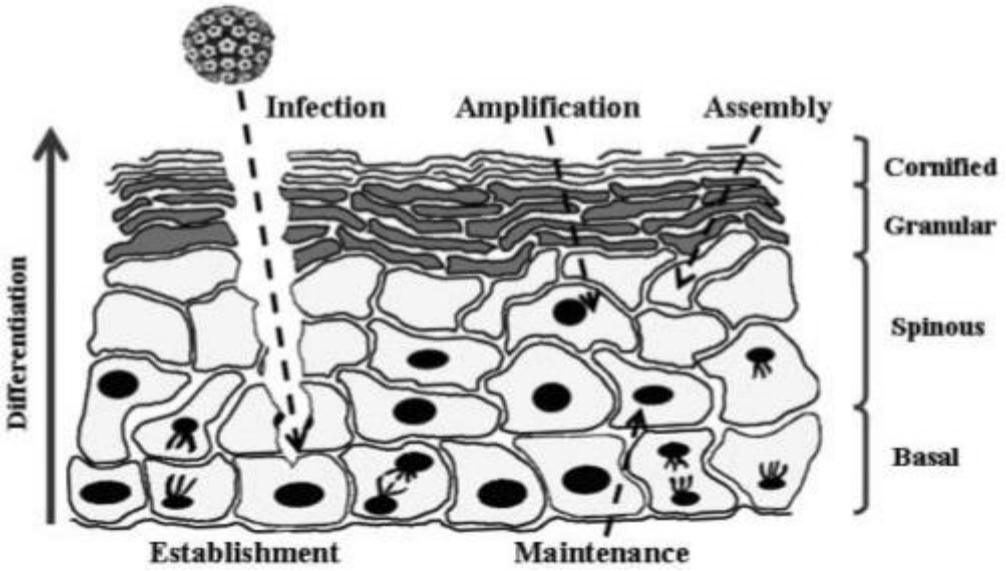
Human papillomaviruses (HPVs) are small dsDNA tumor viruses, which are the etiologic agents of most cervical cancers and are associated with a growing percentage of oropharyngeal cancers. The HPV capsid is non-enveloped, having a T=7 icosahedral symmetry formed *via* the interaction among 72 pentamers of the major capsid protein, L1. The minor capsid protein L2 associates with L1 pentamers, although it is not known if each L1 pentamer contains a single L2 protein. The HPV life cycle strictly adheres to the host cell differentiation program, and as such, native HPV virions are only produced *in vivo* or in organotypic "raft" culture. Research producing synthetic papillomavirus particles—such as virus-like particles (VLPs), papillomavirus-based gene transfer vectors, known as pseudovirions (PsV), and papillomavirus genome-containing *quasi*virions (QV)—has bypassed the need for stratifying and differentiating host tissue in viral assembly and has allowed for the rapid analysis of HPV infectivity pathways, transmission, immunogenicity, and viral structure.[*13]



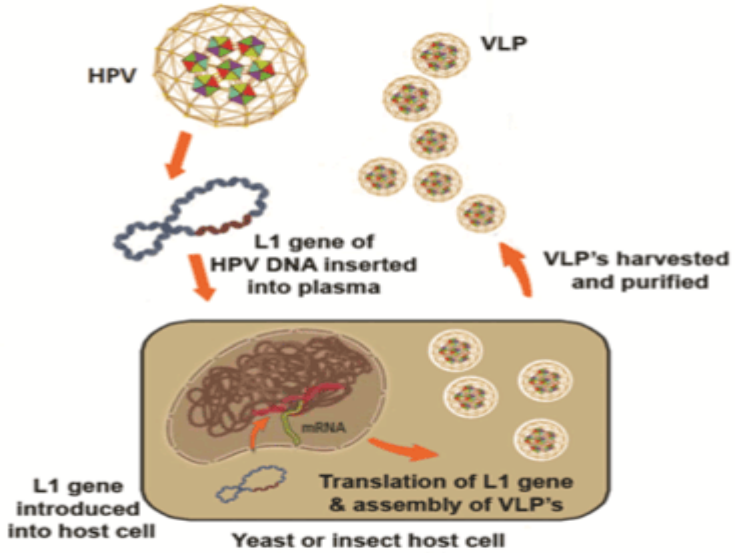
High-risk HPV types initiate the majority of transcription Via 2 major viral promoters. The first, or early, promoter initiates upstream from the E6 ORF, and synthesizes transcripts that are translated early in the viral life cycle. Since the early promoter functions independently from differentiation,

it can initiate prior to the productive phase of the viral life cycle. In HPV16 the early promoter is referred to as p97, in HPV31 the early promoter is referred to as p99, and in HPV18 it is referred to as p105. The second, or late, promoter is initiated in a differentiation-dependent manner, and thus is activated only when cells are grown in the host's stratifying/differentiating tissue, or in vitro through the use of methylcellulose or organotypic culture techniques. Once acti-vated, the late promoter directstranscription from a heteroge-neous set of start sites which are clustered around nucleotide 742 (p742) in HPV31. A late promoter has been identified in HPV16 (p670), and evidence suggests that a late promoter exists in HPV18 as well the late promoter specifically serves to produce a set of transcripts that facilitate the translation of L1 and L2 proteins.
The life cycle of HPV is strictly linked to the differentiation program of the host keratinocyte, whereby the assembly of mature virions is restricted to terminally differentiated suprabasal cells, limited in part by the differentiation dependence of the late promoter . Initial infection by HPVs is thought to occur through micro-abrasions of the epithelial tissue, thus allowing entry of the HPV particle into cells of the basal layer . Basal layer cells consist mainly of stem cells and transit-amplifying cells, and it is the epithelial stem cells that must be infected for a lesion to be maintained. These cells continuously divide and replenish cells that are lost due to desquamation.[*14] Controversies exist as to the primary and/or secondary receptors for HPV entry, with alpha integrin and heparin sulfate as key possibilities, in addition to a role for laminin 5. Heparin sulfate appears important for adsorption and infection of a variety of HPV-typed VLPs, PsV, and native virions in non-host and transformed cell lines, whereas HPV31b organotypic culture-derived native virions (OTNV) do not require heparin sulfate for infection of HaCat or N/Tert-1 human keratinocytes, but do require it for infection of non-host and transformed cell
lines. Post-adsorption to the cell surface, internalization of virions has been shown to take many hours, and, depending on the papillomavi-rus type, virions can enter via clathrin-coated pits or caveolae . Recent studies involving entry pathways (e.g., clathrin- vs. caveolar-mediated endocytosis) and entry kinetics (e.g., few vs. many hours) of HPV have suffered due to a lack of consistency . This may be due to the use of multiple types of synthetic papilloma-virus particles and cell lines, in addition to the use of native virions, and cross-talk between clathrin and caveolar pathways . Recent discoveries with polyomaviruses suggest that controver-sies over papillomavirus entry may be from the initial usage of clathrin-mediated endocytosis and later exploitation of caveolar endocytic machinery within the cell .While many details are lacking regarding the delivery of the viral genome into the nucleus, it is thought that the N-terminus of L2 is cleaved within the endosomal compartment via the cel-lular protease, furin, thus releasing an L2/genome complex into the cytosol . The L2/genome complex may then interact with syntaxin 18, which fer-ries the complex to a perinuclear site . L2 may then trans-locate the genome into the

nucleus through its NLS . Once in the nucleus, a sophisticated cascade of viral gene expression occurs which serves to maintain a minimum number of viral DNA copies per cell .E1 and E2 are among the first early proteins that are expressed, assisting in the establishment of 20 to 100 episomal copies per basal cell . These 2 proteins form a complex with the viral origin of replication and recruit cellular polymerases and the necessary accessory proteins to facilitate replication. E2 is a DNA-binding protein that recruits E1 to the origin of replication, but also serves to regulate transcription of E6 and E7 from the early promoter . The E6 and E7 proteins from high-risk, but not low-risk, HPV types are oncoproteins. High-risk E6 is able to bind the tumor suppressor protein, p53, forming a trimeric complex along with the cellular ubiquitin ligase, E6AP. The ubiquitin ligase activity of E6AP leads to the rapid turnover of p53 . High-risk E7 is able to bind to and modulate a variety of proteins, such as the retinoblastoma (Rb) family of tumor suppressors, and cell-cycle regulatory proteins, leading to enhanced cellular replication .As HPV-infected basal cells divide, each new daughter cell is replete with a set of viral genomes as the genomes are equally partitioned during mitosis. Recent studies suggest that both Brd4-dependent and independent partitioning of viral genomes into daughter cells can occur, depending on the papillomavirus type studied . Post-mitosis, one cell remains attached to the basal layer, while the other cell is detached from the basal layer and begins to migrate up through the suprabasal layers . During migration of the cell up through the strata, the cell begins a process of terminal differentiation



In non-HPV-infected epithelia, cells normally exit the cell cycle once they detach from the basal layer, and this is often accompanied by the loss of nuclei in differentiating suprabasal cells . In the case of HPV-infected epithelia, detached cells remain mitotically active due to the oncogenic properties of the E7 protein . Because of this, infected cells that have already differentiated can re-enter the S phase and enhance the expression of cellular replication factors that are required for concomitant viral genome amplification, and late gene expression . While designated 'early proteins', E1^E4 and E5 are both translated in a differentiation-dependent manner, both of which may affect the replication of viral genomes through the inhibition of G2-to-M transition, and stimulation of cell-cycle progression, respectively . Similarly, the L1 and L2 capsid proteins are expressed only in terminally differentiated keratinocytes . Studies with both papillomaviruses and polyomaviruses suggest that, once expressed, capsid proteins assemble into icosahedral capsids *via* assistance from chaperone proteins . It is unknown if encapsidation of the viral genome takes place during capsid assembly or after; however, encapsidation is assisted by L2 and may be facilitated by E2 proteins . In the cornified envelope, E1^E4 proteins are thought to interact with cellular keratin networks, causing their collapse, thus allowing mature virions to escape from the cornified cells . Mechanistic details concerning the host cell differentiation program that leads to the productive phase of the HPV life cycle are unclear. It is also unclear as to the regulated molecular interactions that must take place for individual capsid proteins to assemble into higher-ordered structures over the time-course of stratification and differentiation of the host keratinocyte.[*15]

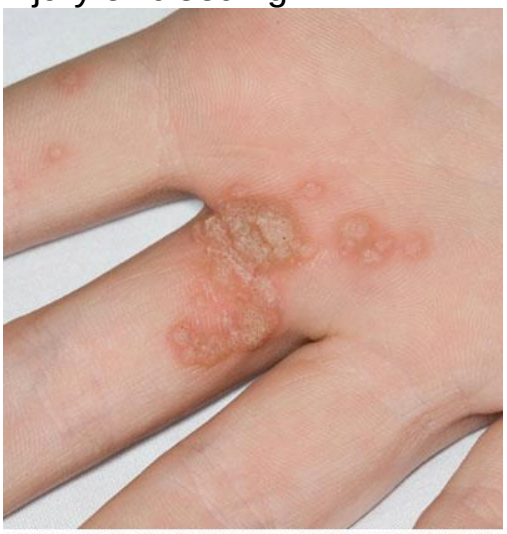


video https://www.youtube.com/watch?v=XYtV034mQvQ

Symptoms HPV: In many cases, HPV causes no symptoms ,when they do occur most people feel fine even when they have cell changes caused by HPV, the most common symptom is warts in the genital area. Signs of infection can appear weeks, months, or even years after the person has been infected with the virus.

1- Genital warts become present, they may appear as a small bump, cluster of bumps or stem-like protrusions. They can range in size and appearance and be large, small, flat or cauliflower shaped and may be white or flesh tone.[*16]

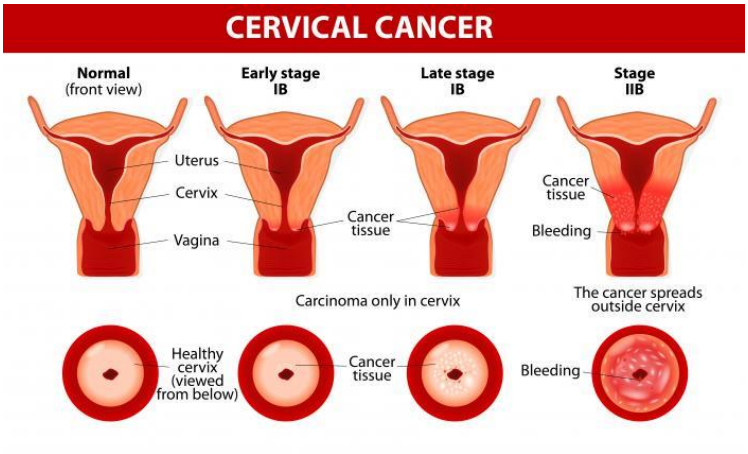
2- Common warts. Common warts appear as rough, raised bumps that usually occur on the hands, fingers or elbows. In most cases, common warts are simply a nuisance because of their appearance, but they may also be painful or susceptible to injury or bleeding.



3- Plantar warts. Plantar warts are hard, grainy growths that usually appear on the heels or balls of your feet, areas that feel the most pressure. These warts may cause discomfort or pain.[*17]

4- **Flat warts**, which generally affect children, adolescents and young adults, appear as flat-topped slightly raised lesions which are darker than normal skin color and are most commonly found on the face, neck or areas having been scratched.

If HPV has contributed to the development of cancer, a person may become symptomatic of the cancer itself in the later stages of the disease.[1] These cancers include cancer of the cervix, vulva, vagina, penis, anus and oropharynx.[*16]



Diagnosis and Cytopathic effect:

*DIAGNOSIS

HPV has not been cultured by conventional methods. Infection is identified by detection of HPV DNA from clinical samples. Assays for HPV detection differ considerably in their sensitivity and type specificity, and detection is also affected by the anatomic region sampled as well as the method of specimen collection.(CDC,2015) Several HPV tests have been approved by the Food and Drug Administration (FDA) and detect 13-14 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Test results are reported as positive or negative for any of the types; some tests specifically identify HPV 16 and 18. These tests are approved for triage of Papanicolaou (Pap) test results (ASC-US, atypical cells of undetermined significance) and in combination with the Pap test for cervical cancer screening in women 30 years of age and older. The tests are not clinically indicated nor approved for use in men. Epidemiologic and basic research studies of HPV generally use nucleic acid amplification methods that generate type-specific results. The polymerase chain reaction (PCR) assays used most commonly in epidemiologic studies target genetically conserved regions in the L1 gene.*[18]

*CYTOPATHIC EFFECT

Cytopathic effects related to the human papillomavirus (HPV) infection are more frequently found in cervical intraepithelial neoplasia (CIN) 1; however, there are indications that at least half the histological diagnoses of CIN2 and CIN3 include koilocytosis areas. The objective of this study was to evaluate the frequency of the cytological criteria suggestive of HPV infection in the cervical smears of women with a histological diagnosis of CIN. One hundred and sixty-two women with abnormal cervical smears and a diagnosis of CIN confirmed by histopathology were selected, including 46 cases of CIN 1, 42 of CIN 2 and 74 cases of CIN 3.Koilocytosis was found in 63% of the smears from women with a histopathological diagnosis of CIN 1. This sign was observed in 26.2% and 25.7% of smears of women with a diagnosis of CIN 2 and CIN 3, respectively. Cytomegaly also was frequent in cervical smears of women with histopathological diagnosis of CIN 1(71.8%). On the other hand, spindle cells and atypical metaplasia were more frequent in women with CIN 2 and CIN 3. Atypical parakeratosis showed similar frequency in all grades of CIN diagnosis. Koilocytois and cytomegaly were inversely correlated with

the diagnosis of CIN2 or CIN 3, with OR values respectively of 0.30 (95%CI 0.13–0.68) and 0.26 (95%CI 0.11–0.58). The others signs analyzed did not show any significant association. Koilocitosis andcytomegaly can provides good reassurance that a patient with atypical cervical smear have CIN 1**.**[*19]

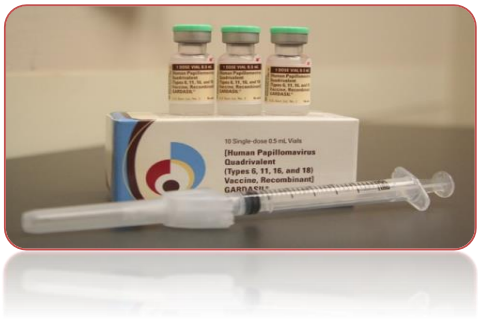
Control the virus and Prevention:

1- vaccine :The FDA has approved two vaccines (Cervarix and Gardasil) to protect females against the types of HPV that cause most cervical cancers.

Gardasil vaccine :

its First vaccine to prevent cervical cancer, also protects against most Types 6, 11, 16, 18. It's best to be vaccinated before becoming sexually active.

Its recombinant vaccine .The vaccine is recommended for girls and women ages 9 to 26, but it can be given to older women as well. Gardasil also protects males against genital warts and is approved for boys and males ages 9 to 26. The FDA recently approved Gardasil for the prevention of anal cancer in both males and females ages 9 to 26. But the HPV vaccine does not protect against all types of HPV. Women aren't protected if they have already been infected with the HPV type(s) that are covered by the vaccine prior to vaccination .two pharmaceutical companies, Merck and GlaxoSmithKline, have recently reported a remarkable degree of protection by candidate prophylactic HPV vaccines . The vaccines that both companies are developing are subunit virus-like particle (VLP) vaccines composed of a single viral protein, L1, which is the major structural (capsid) protein of the virus and contains the immunodominant neutralization epitopes of the virus. The vaccines are based primarily on preclinical research showing that (a) when expressed in cells, L1 has the intrinsic ability to self-assemble into VLPs that can induce high levels of neutralizing antibodies ; (b) in animal models of animal papillomavirus infection, parenteral vaccination with L1 VLPs protects from high-dose challenge with homologous virus , while animals are not protected by systemic immunization with denatured L1 or L1 VLPs from a heterologous papillomavirus because L1 neutralization epitopes are conformationally dependent and predominantly type specific; and (c) protection can be passively transferred by immune IgG . The VLPs from the Merck vaccine are produced in yeast , while the VLPs from the GlaxoSmithKline vaccine are produced in insect cells via recombinant baculovirus.

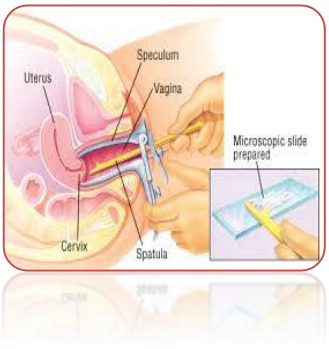


2- Use a Condom

using a condom can help lower the risk of HPV transmission. It is important to use a condom from start to finish of every sex act, including oral and anal sex. HPV is transmitted by skin-to-skin contact. Because HPV can infect areas that are not covered by the condom, condoms will not fully protect you against contracting HPV, but condoms do help in HPV prevention. Also, never reuse a condom.

3- Get the Pap Test

It's important for women to have regular check-ups, which include Pap smears to look for cervical cancer in its earliest stages — when it is most treatable. The Pap smear is a test that checks for abnormalities in the cells that line the cervix and is one of the best ways to detect cervical cancer.Trent says that the Pap test is now emerging as an important screening test for men at risk for anal lesions. Men at risk include gay, bisexual men,



Important notes :

- Schedule a day when you won't be having your period.
- Avoid sexual intercourse 48 hours before the test.
- Do not use vaginal creams, foams, films or other jellies for 48 hours before the test.

4- Consider Abstinence

The only 100 percent effective way to prevent HPV transmission is abstinence from any sexual contact, including oral, anal, and vaginal sex. However, for most adults, complete abstinence is not a realistic option. There are other effective ways to prevent HPV from spreading and infecting you and your sexual partners.*[20]

Treatments:

There is no treatment for the virus itself. However, there are treatments for the health problems that HPV can cause on the symptoms of the infection. Symptoms include genital warts associated with low-risk HPV types (which don't generally lead to cancers) and the precancerous changes sometimes associated with the high-risk types of HPV:

Genital warts can be treated by you or your physician. If left untreated, genital warts may go away, stay the same, or grow in size or number of cells .
Cervical precancer can be treated. Women who get routine Pap tests and follow up as needed can identify problems *before* cancer develops. Prevention is always better than treatment.Other HPV-related cancers are also more treatable when diagnosed and treated early.[*21] there are other HPV treatment options. as more males and females are vaccinated against HPV, the rates of infection may be greatly reduced. There are currently three vaccines currently available: Cervarix, Gardasil, and Gardasil-9.[*22].And for Pregnant women, or women trying to conceive, should consult closely with their doctor before starting treatment. HPV treatments can affect pregnancy, so doctors may want to delay treatment until after childbirth.[*22]

Recent discoveries :

Papillomaviruses are an ideal model system for the study of DNA virus evolution. On several levels, phylogenetic trees of papillomaviruses reflect the relationship of their hosts. Papillomaviruses isolated from remotely related vertebrates form major branches. One branch of human papillomaviruses (HPVs) includes an ape and two monkey papillomaviruses, possibly because the diversification of the viruses predated the separation of the infected-primate taxa. This hypothesis predicts that the root of the evolution of some if not all HPV types should point to Africa, since humans evolved from nonhuman primates in this continent. We tested this hypothesis and compared the genomic sequences of HPV type 18 (HPV-18) isolates from four continents. Diversity within HPV-18 correlates with patterns of the evolution and spread of Homo sapiens: HPV-18 variants, just like HPV-16 variants, are specific for the major human races, with maximal diversity in Africa. Outgroup rooting of the HPV-18 tree against HPV-45, which is closely related to HPV-18, identifies African HPV-18 variants at the root of the tree. The identification of an African HPV-45 isolate further reduces the evolutionary distance between HPV-18 and HPV-45. HPV-18 variants from Amazonian Indians are

the closest relatives to those from Japanese and Chinese patients and suggest that a single point mutation in the phylogenetically evaluated genomic segment represents at least 12,000 years of evolution. We estimate that diversity within HPV-18 and probably within other HPV types evolved over a period of more than 200,000 years and that diversity between HPV types evolved over several million years.

Reverences :

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