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Human *papillomavirus* (HPV)

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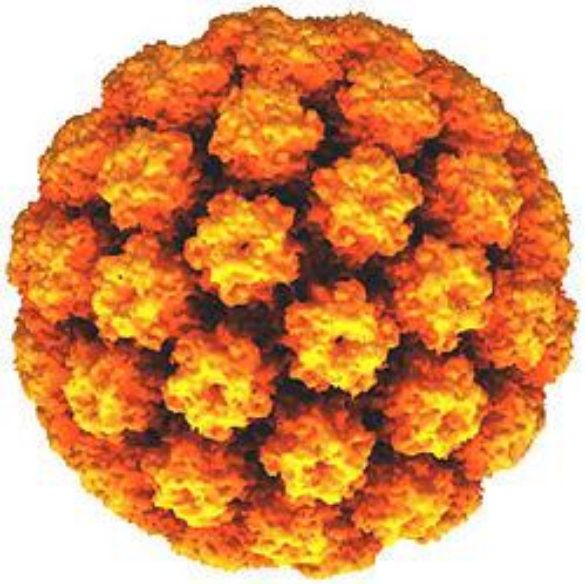
What is HPV?

- The **Human papillomavirus** (HPV) is a virus that can infect mucus membranes (like the genitals, or inside the mouth) or the skin .
- They cause **warts.** Some of them may cause **cancer.**
- There are over **100** different virus types in this group.
- Most cases of cervical, oral and throat cancers are caused by HPV.
- Most cases of HPV can be prevented by a **vaccine** which also would stop the HPV from causing cancer.



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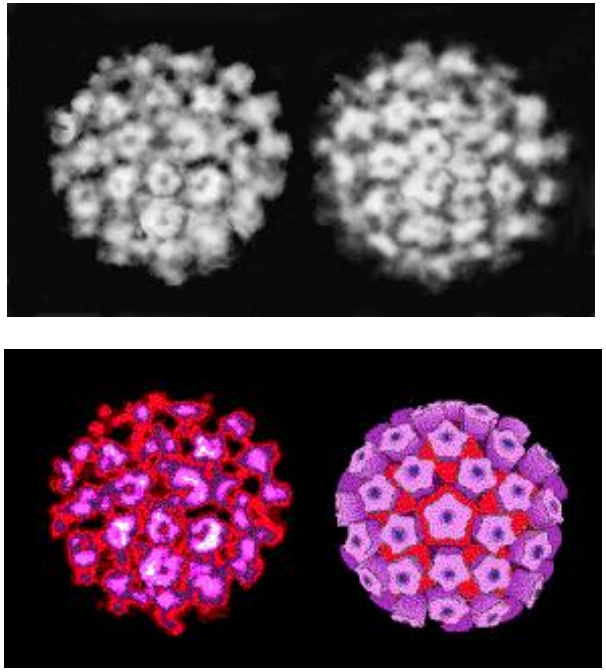
- HPV is part of the family known as **Papovaviruses**, which was named for it's three main members:
- **Papillomavirus, Polyomavirus**, and **simian Vacuolating agent**.

- They are found in many vertebrates, and exhibit high species specificity.
- This family contains two genera of oncogenic viruses, Papilloma and Polyoma viruses.

- Tropism for **squamous epithelium**.
- Associated with warts and papillomas.

- Papillomaviruses are small, approximately 52-55nm in diameter.
- They are **non-enveloped**, **icosahedral particles**.

- Their capsid is composed of two proteins, **a major (L1)** and **minor (L2).**



SEM image of a Human Papilloma Virus and a computer model showing the structure of the virus.

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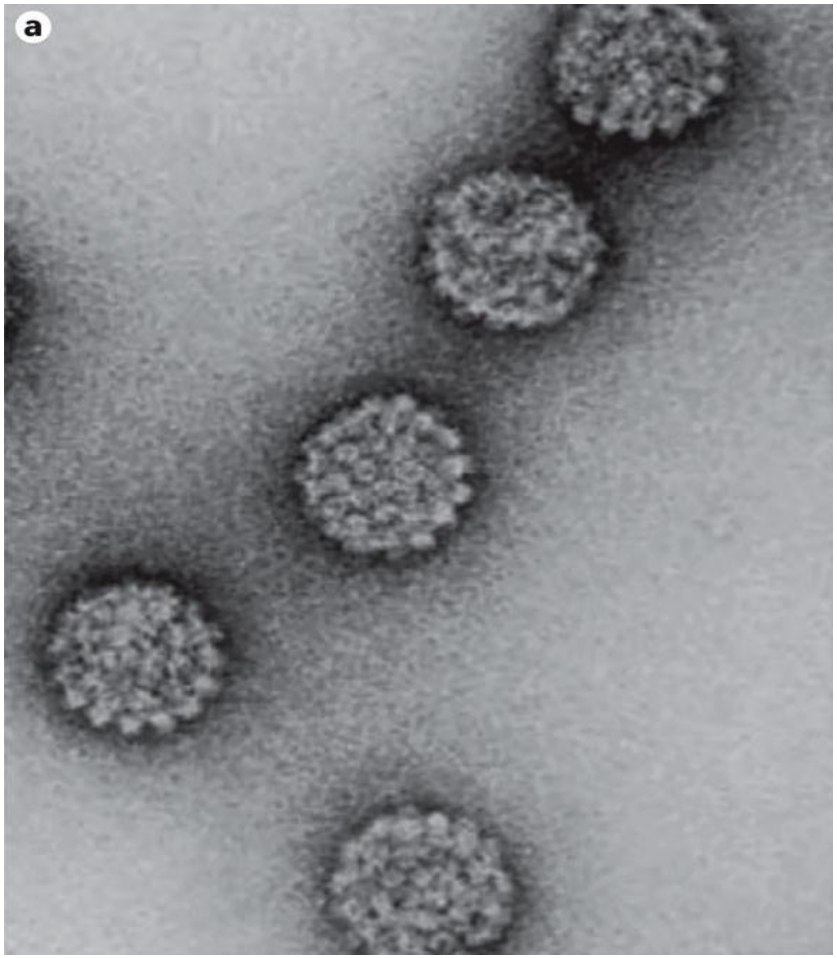

Human papillomavirus (HPV) particles (55 nm in diameter) are shown in the negatively stained transmission electron micrograph.

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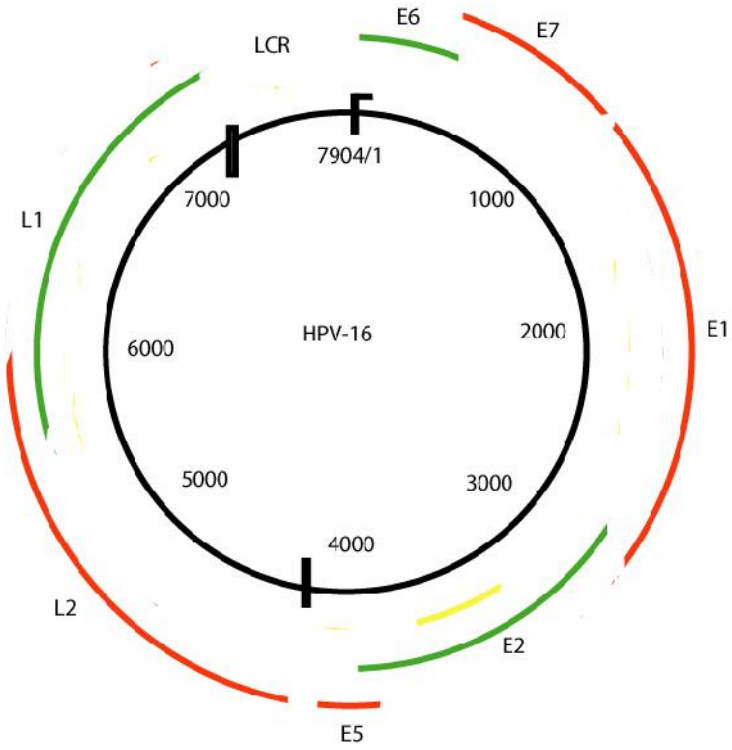
Genome Organization

- They are **DNA viruses**.
- The Papillomavirus' genome is **circular, d/s DNA** approximately **8,000bp** in size.
- Similar for all papillomaviruses: Many of the HPV genomes have been sequenced and have a genetic organization similar to that of HPV-16, one of the oncogenic strains.
- Only **one strand** transcribed
- Open reading frames (ORFs) named in relation to bovine papillomavirus genes
  - **"Early"** genes E1-E7 (but no E3 in HPV)
  - "**Late"** genes L1 and L2, coding for major and minor capsid proteins



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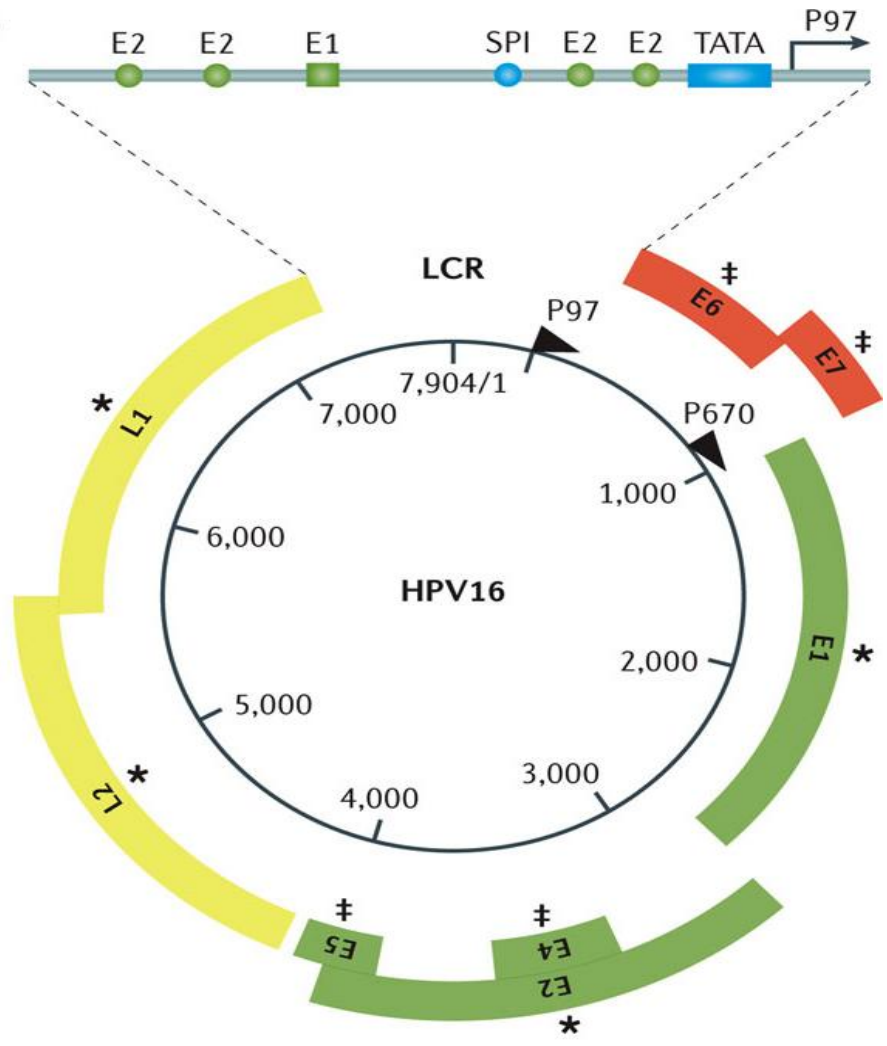
The early **(P97)** and late **(P670)** promoters are marked by arrowheads.

The six **early open reading frames (ORFs)**, namely E1, E2, E4 and E5 (in green) and E6 and E7 (in red), are expressed from the **different promoters at different stages during epithelial cell differentiation.**

The **late ORFs** (L1 and L2 (in yellow)) are expressed from the P670 promoter in the **upper epithelial layers** as a result of changes in splicing.

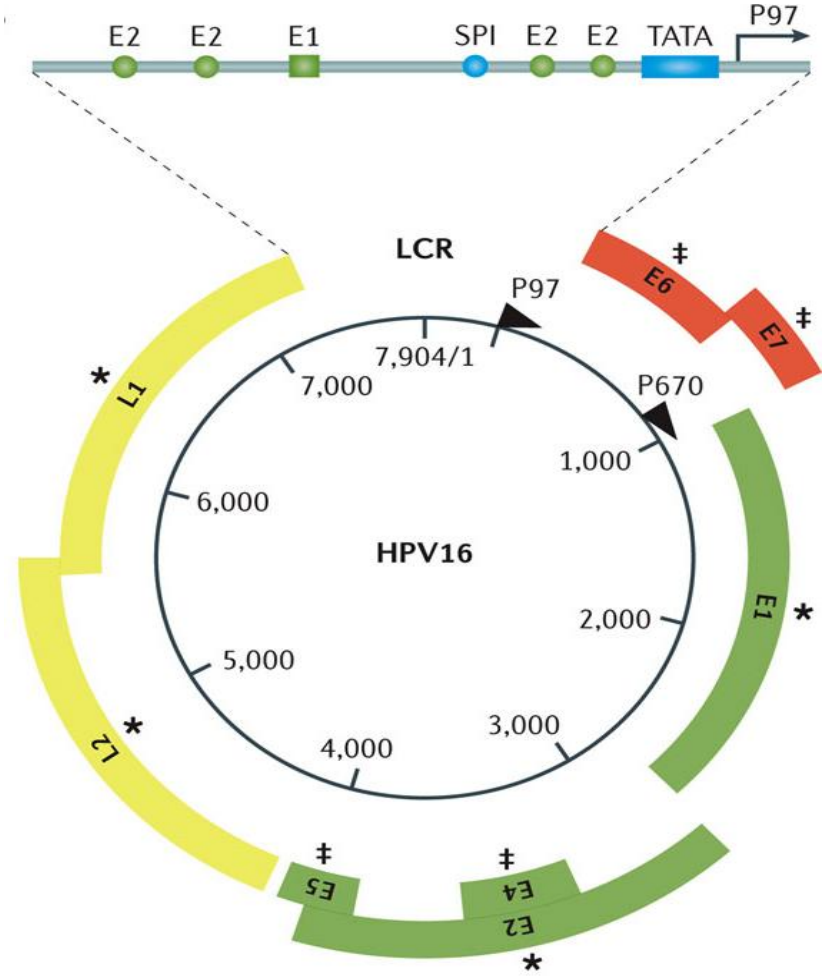


The genome organization of the high-risk Alpha HPV types, illustrated as HPV16.

The long control region (LCR, sometimes referred to as the upstream regulatory region or non-coding region (NCR) is a non-coding region of the genome that contains origin of replication, as well as post-transcriptional control sequences and replication regulatory elements that contribute to **viral gene expression**.

Also, **non-coding region (NCR)**, or, **upstream regulatory region (URR)**, is a segment of about 850 bp (10% of the HPV genome). It contains the **origin of replication** and multiple transcription binding sites.

The binding sites for the E1 and E2 viral gene products and the SP1 transcription factor are shown. The gene products (denoted with an asterisk (*)) are core viral proteins that are required for genome replication, viral assembly and release; those denoted by a double dagger (‡) are accessory proteins with functions that include cell cycle entry and immune evasion.



The genome organization of the high-risk Alpha HPV types, illustrated as HPV16.

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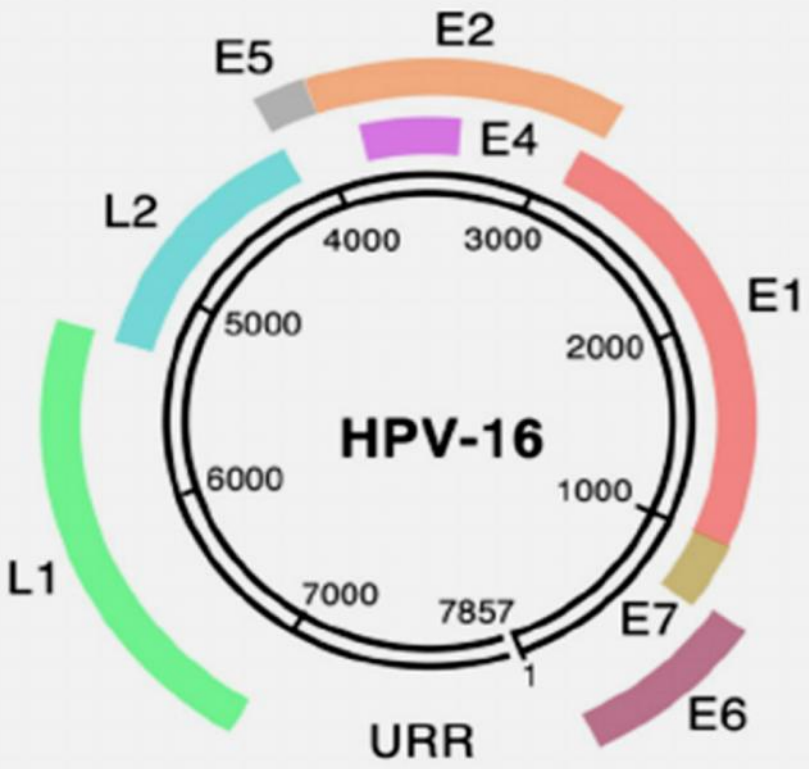
HPV Genome structure and function



Gene	Function
L1	Major capsid protein.
L2	Minor capsid protein.
E1	Transcription factor, helicase activity. Mediates episomal DNA replication.
E2	Transcription factor. Regulates viral copy number.
E4	Facilitates virion release.
E5	Stimulates cell proliferation and prevents differentiation. Downregulates surface MHC class I expression.
E6	Deregulates cell cycle control through p53 inactivation/degradation. Induces malignant transformation together with E7.
E7	Keeps cells active in the cell cycle through Rb inactivation. Induces malignant transformation alone and together with E6.

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How Does HPV "Cause" Cancer?

In high-risk HPV strains 16, 18, 31, 39, 45 and 59:

- Protein E6 **interacts with p53(Apoptosis inducer)** in the host cell and promotes it's degradation via the ubiquitin dependent pathway.
- Protein E7 complexes with **retinioblastoma protein (Rb)** (Cell cycle checkpoint and DNA repair), thereby inactivating it.
- Rb and p53 are both **tumor suppressors,** involved in DNA repair and apoptosis.

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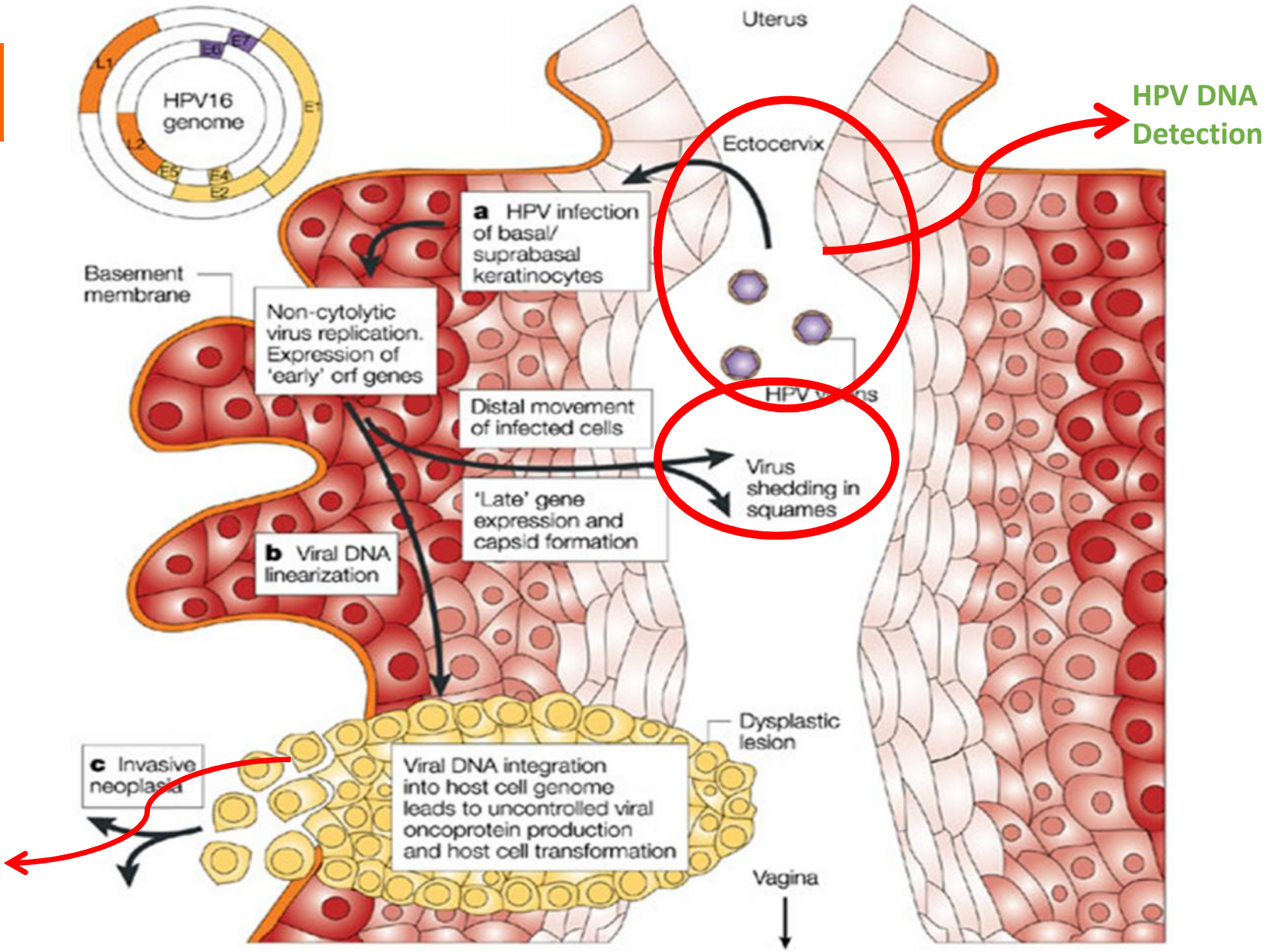
HPV Genome features

- Dependent on host cell for replication, transcription and translation so out of the host is inactivated.

- Viral functions tightly linked to cellular differentiation

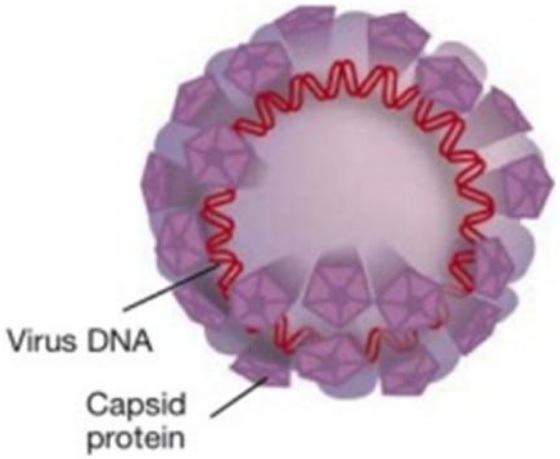
HPV life cycle



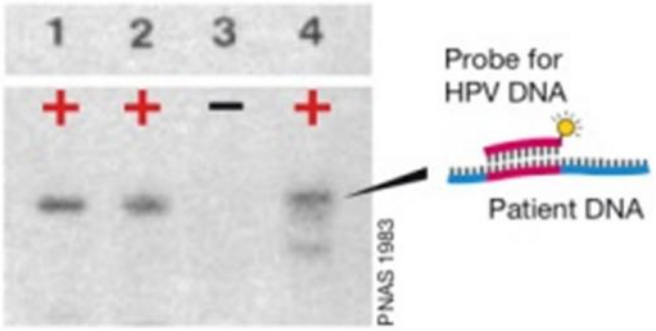
HPV– human papilloma virus

HPV has a circular, double stranded DNA, protected by capsid proteins.

More than 100 HPV-types are known. HPV16 and 18 cause 70% of all cervix cancers.



Discovery of HPV DNA in cancer cells



Harald zur Hausen found HPV DNA in patient DNA (+).

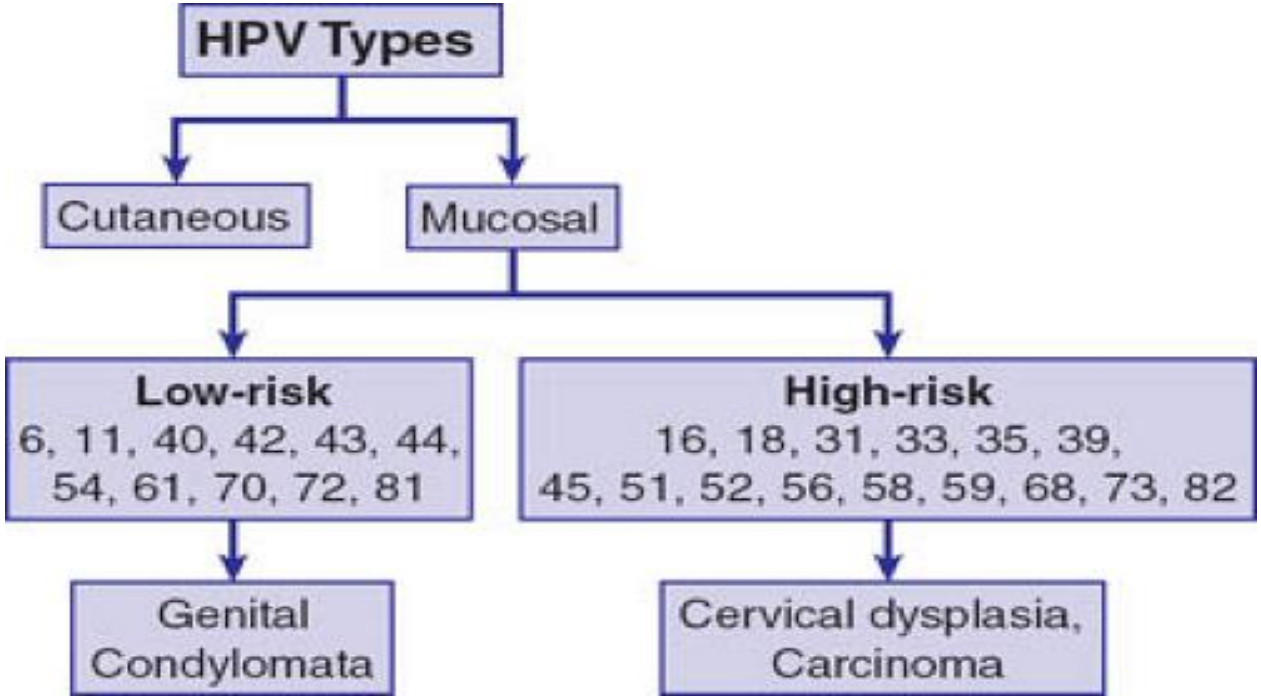
Infection by HPV

HPV infects epithelial cells in the cervical mucosa. HPV DNA integrates into the cellular genome when causing cancer.

HPV Types

- There are ≥150 type.
- Typing based on nucleic acid sequence
  - sequence variation >10% = new type;
  - sequence variation : 2-10% = subtype,
  - sequence variation <2% = variant
- Types assigned sequential number based on order of discovery
  - No relation to phylogeny
- Two major phylogenetic branches, differing affinities for site of infection
- **Cutaneous**: Keratinized squamous epithelium
- **Mucosal**: Non-keratinized squamous epithelium

HPV Mucosal Types and Variants



- More than 30 types found in anogenital tract
  - “Low risk” types: rarely found in cancers
  - “High risk” types: frequently found in cancers

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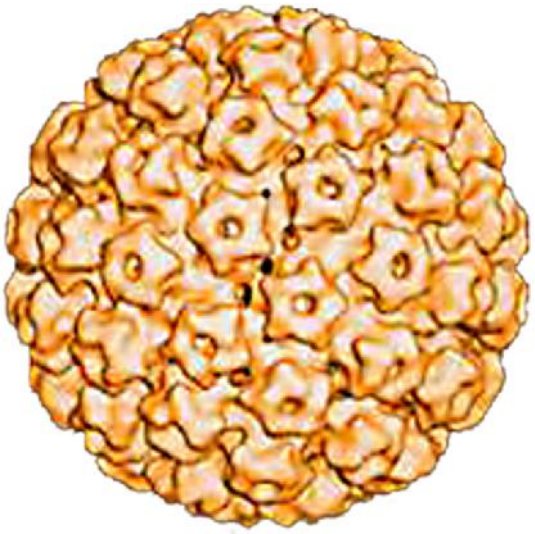
HPV is a necessary cause of cervical cancer – 99.7%[4]

HPV

Cancer causing Types[1,2,4]

- HPV 16
- HPV 18



Non-cancer causing types[1,2]

- HPV 6
- HPV 11

- >75% of Cervical Cancer[5]
- >50% of Vaginal & Vulvar Cancer[5]

90% of Anogenital warts[5]

1.Schiffman M, Castle PE. *Arch Pathol Lab Med*. 2003;127:930–934. 2. Wiley DJ, Douglas J, Beutner K, et al. *Clin Infect Dis*. 2002;35(suppl 2):S210–S224. 3. Muñoz N, Bosch FX, Castellsagué X, et al. *Int J Cancer*. 2004;111:278–285. Reprinted from *J Virol*. 1994;68:4503–4505 with permission from the American Society for Microbiology Journals Department. 4. Walboomers JM, Jacobs MV, Manos MM, et al. J Pathol. 1999;189:12–19. 5. X. Castellsagué, S. de Sanjose, T. Aguado, K. S. Louie, L. Bruni, J.Muñoz, M. Diaz, K. Irwin, M. Gacic, O. Beauvais, G. Albero, E. Ferrer, S. Byrne,F. X. Bosch. HPV and Cervical Cancer in the World. 2007 Report. WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Available at: www.who.int/hpvcentre

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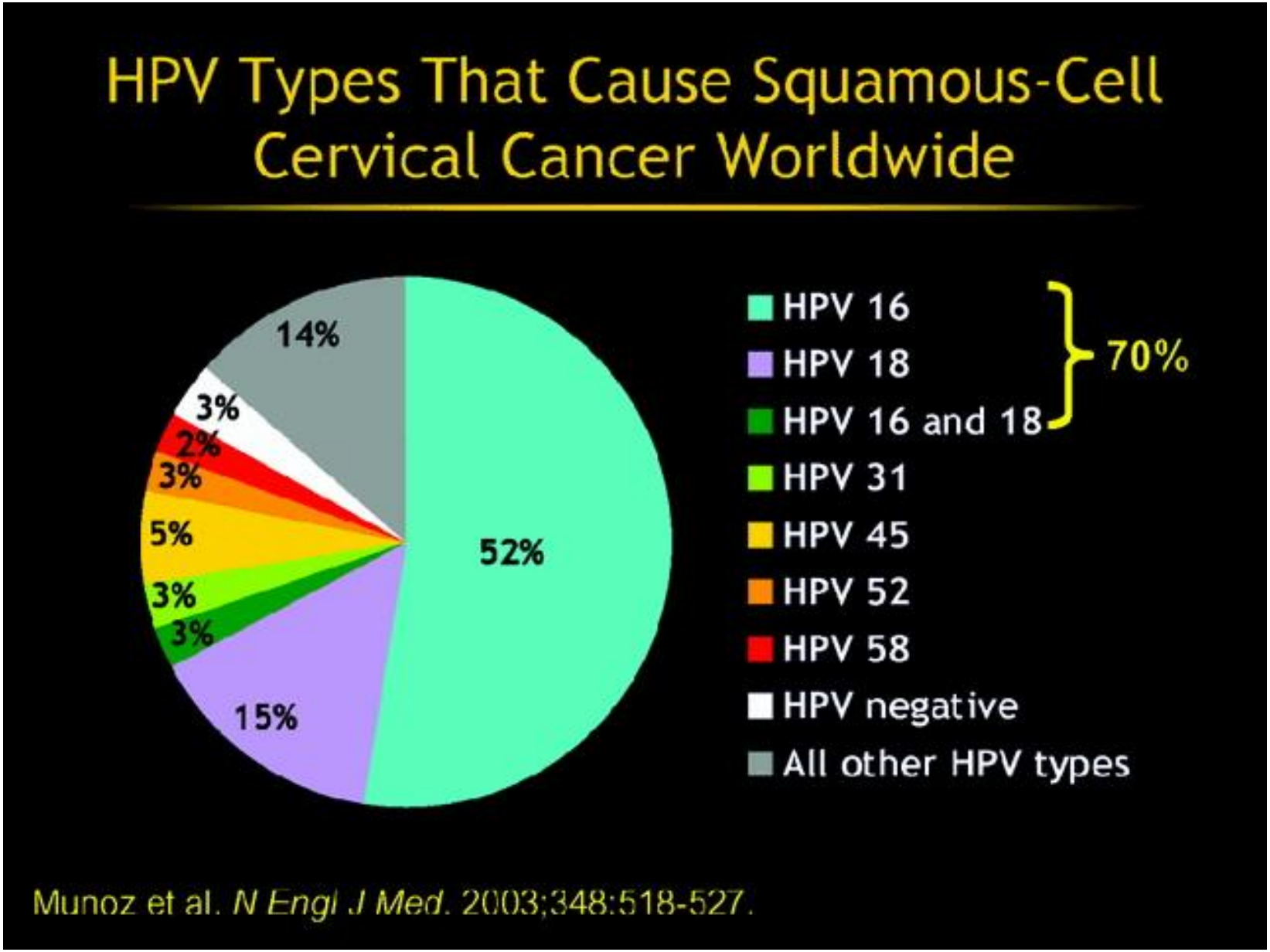

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Can HPV Cause Other Types of Cancer?

A 2005 study entitled "*Sensitive detection of Human Papillomavirus in cervical, head/neck, and schistosomiasis-associated bladder malignancies"* found that:

- "Virtually all tested **cervical cancers** and **schistosomiasis-associated bladder cancers**, and a **plurality of head/neck cancers** are associated with HPV DNA in the tumor."
- HPV DNA was present in 35%of head and neck cancers analyzed (253 samples).
- HPV DNA was present in 98%of cervical cancers analyzed.
- HPV DNA was present in all 27 samples of schistosomiasis-associated bladder cancer analyzed.
- In another study, HPV DNA was found in 25 of 29 samples of **breast carcinoma**. Strains 11 and 6 were most prevalent.

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Unique features of HPV

- No simple in vitro culture method
- Antibody based methods lack sensitivity
- Diagnosing infection requires detection of HPV genetic information


Thanks for your kindly attention

Association with cervical cancer[1]	Genotypes	Most likely clinical conditions
Low-risk	• Most common: 6 and 11 • 40, 42, 43, 44, 54, 61, 70, 72, 81 and CP6108	Condylomata acuminata
Probable high-risk	• 26, 53 and 66	Precancerous or cancerous lesions
High-risk	• Most common: 16, 18 • 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82	Precancerous or cancerous lesions

- 99.7% of all cervical cancer cases are associated with persistent infection with high-risk HPV types.

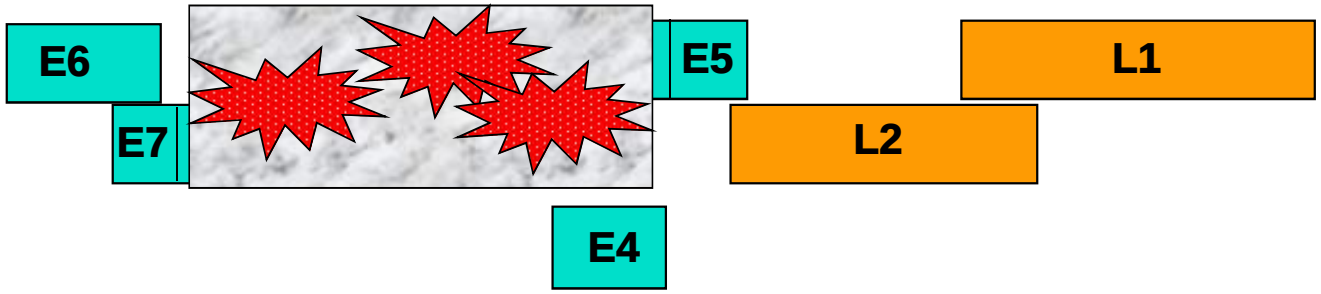
- HPV types 16 and 18 are the most common high-risk types and account for 70% of all cervical cancer cases worldwide.

  -50% as a result of HPV-16 infection .

  -20% as a result of HPV-18 infection.

Viral Integration

- Not part of normal viral life-cycle
- Occurs randomly in host chromosomes
- Characteristic breakpoint in viral genome
  - E1-E2 disruption
  - Abnormally regulated E6/E7 expression
- Associated with oncogenesis but not required



- disruption of E1 to E2 of variable sizes, results loosing checkpoint for cell proliferation and transcription.

- integration occurs at chromosome ”fragile sites”