Connecticut Cancer Partnership
HPV Vaccination: Progress & Challenges

HPV-related oral and oropharyngeal disease

Patient education and prevention: an oral healthcare perspective

Easwar Natarajan BDS, DMSc
Associate Professor, Oral Pathology
UConn School of Dental Medicine
Natarajan@uchc.edu

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Oral Healthcare Providers

Capabilities & Responsibilities

- Educate patients about HPV-related disease
  - Warts/ squamous papilloma
  - Oropharyngeal cancer (tonsillar/throat cancer) & other cancers
- HPV infection and differences between viral strains
- Pathobiology/ mechanism of disease
- **Educate patients about rationale for HPV vaccination:**
  - **Gardasil 9™** – nine-valent cross reactive to **HPV strains 6,11,16,18,31,33,45,52,58**

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Two Clinical Situations

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Patient 1

A 9-year-old girl presents with a painless gum growth

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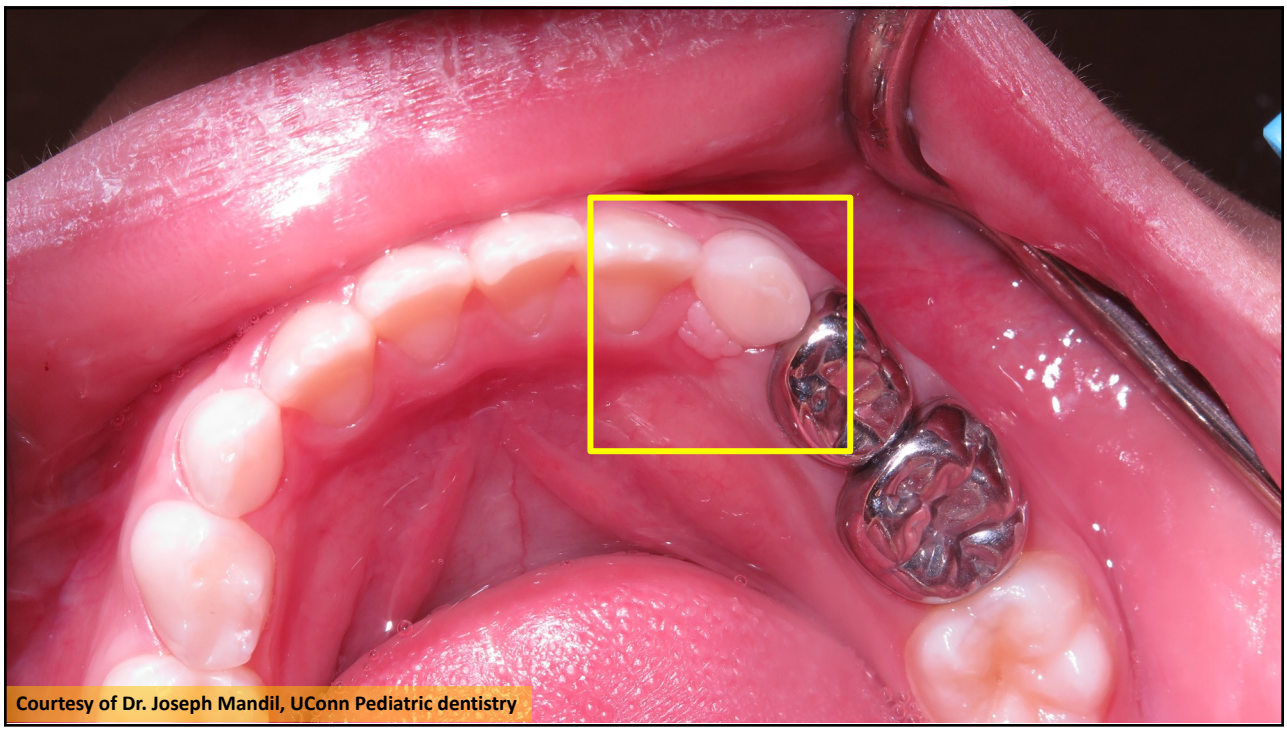
Courtesy of Dr. Joseph Mandil, UConn Pediatric dentistry

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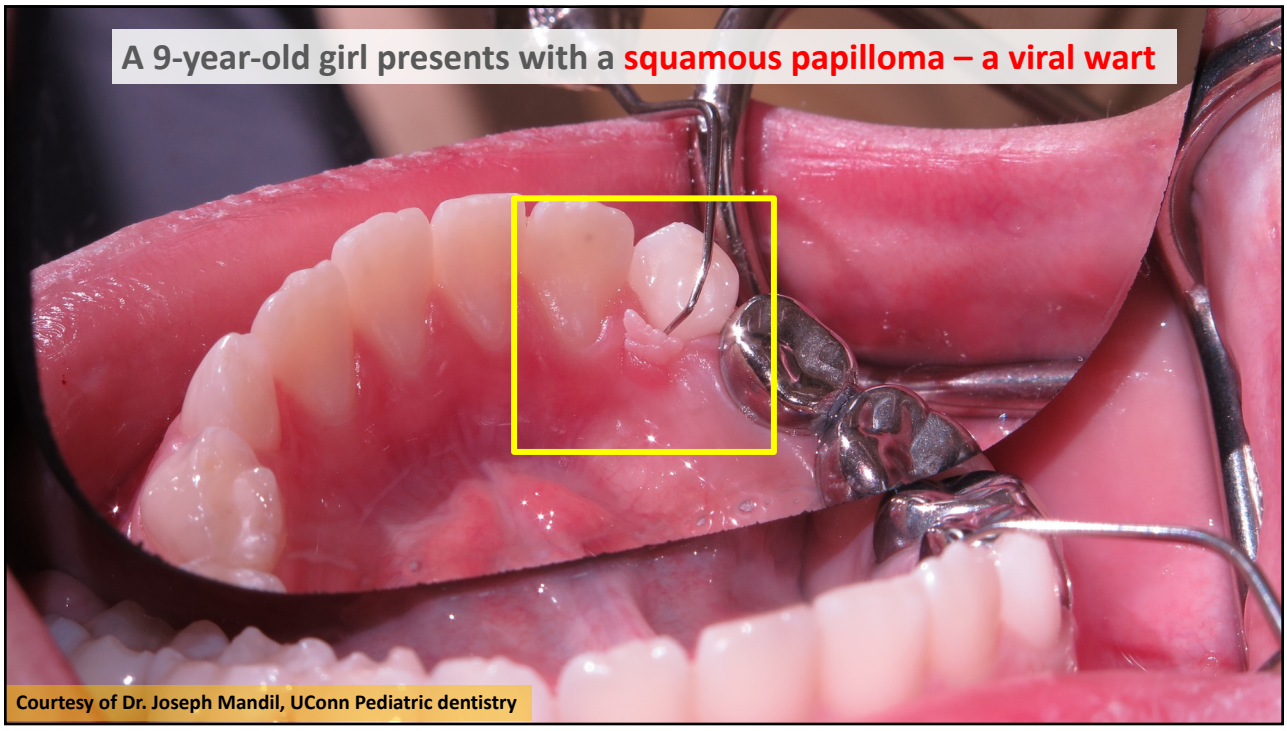
A 9-year-old girl presents with a squamous papilloma – a viral wart
Courtesy of Dr. Joseph Mandil, UConn Pediatric dentistry

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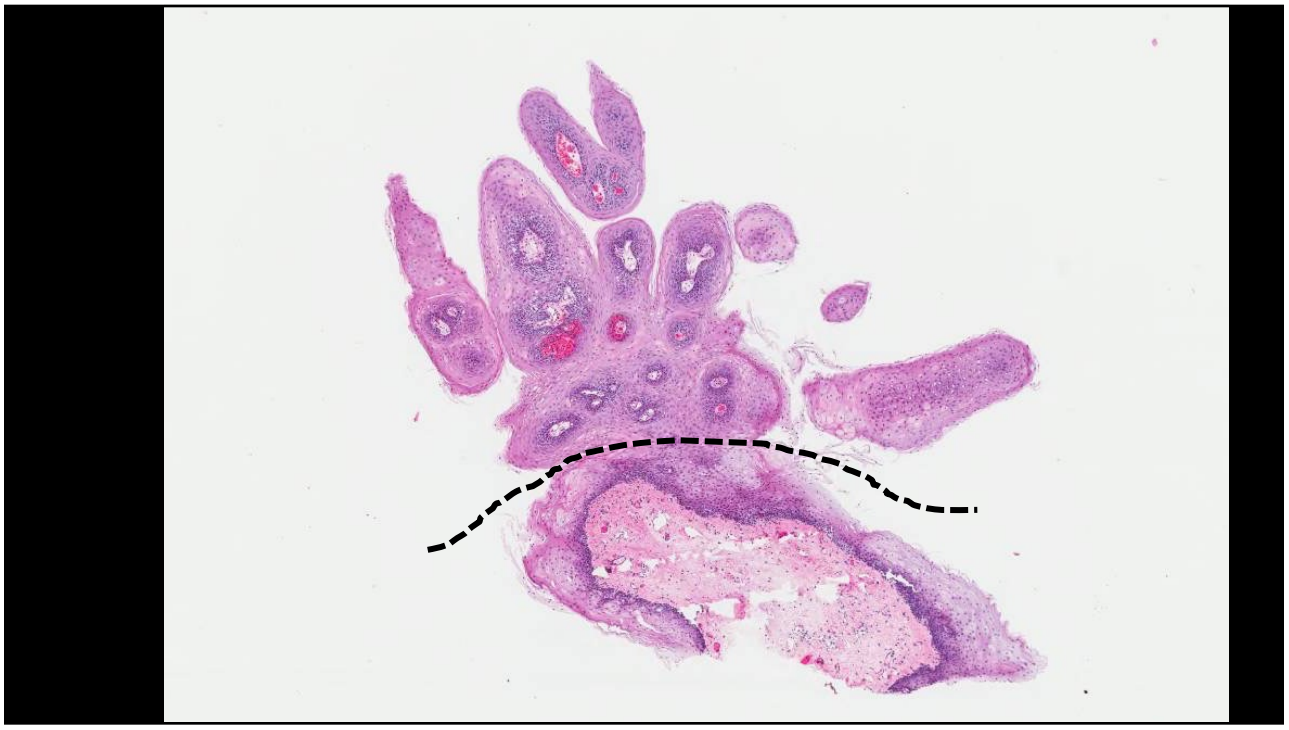

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What is a Wart/ Papilloma?

A virally induced benign neoplasm

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Clinical Scenario

A patient with a squamous papilloma/ HPV - viral wart

Questions:

1. How does HPV cause a benign neoplasm?
2. Are HPV-related warts sexually transmitted? STD?
3. Is our patient at risk of developing **oral (mouth) cancer**?
4. Is our patient at risk for **oropharyngeal (throat) cancer**?
5. Is our 9-year-old patient a candidate for the **HPV vaccine**?
6. What role does an oral healthcare provider have in vaccine awareness/ education?

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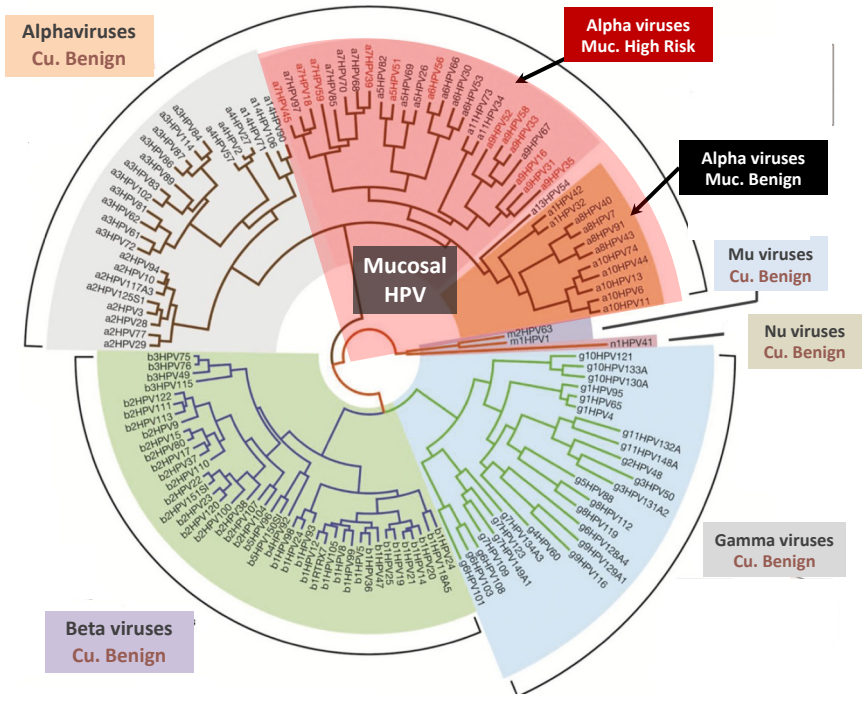
HPV > 200 strains

Cutaneous

Mucosal



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Benign HPV related disease/ warts

- **Naked capsid DNA virus;** **> 200 strains of HPV**
- **Host cell:** **Basal epithelial cells (epidermis, mucosa)**
- **Mode of transmission:** contact, abrasion (portal of entry)
- **Replication of HPV is linked to epithelial life cycle**
- Cause **benign neoplasms** of keratinocytes in squamous epithelia
- HPV 6 and 11; 2, 4 and 40 associated with benign warts
- **Common – 3% of all biopsies**

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Human papilloma virus Pathogenesis

How does the virus cause epithelial proliferation?

*HPV tricks the body into **producing viral protein***
*by causing **epithelial cell division**!*

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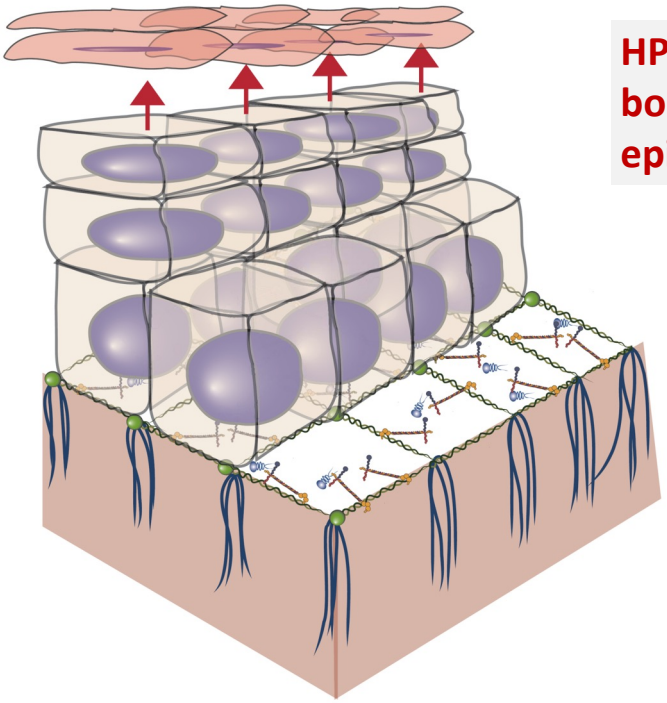

HPV's life cycle is bound to an epithelium's life-cycle

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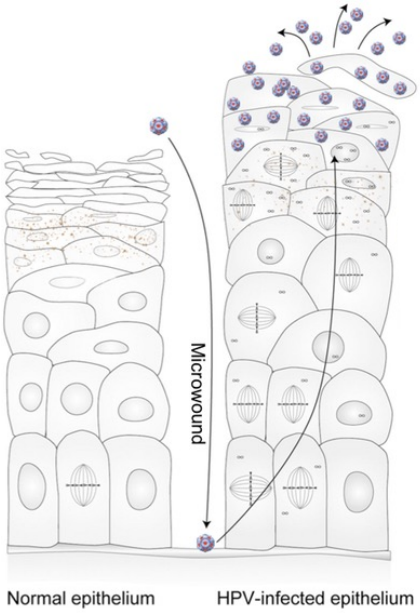

HPV Portal of Entry

Wounds/ Microwounds

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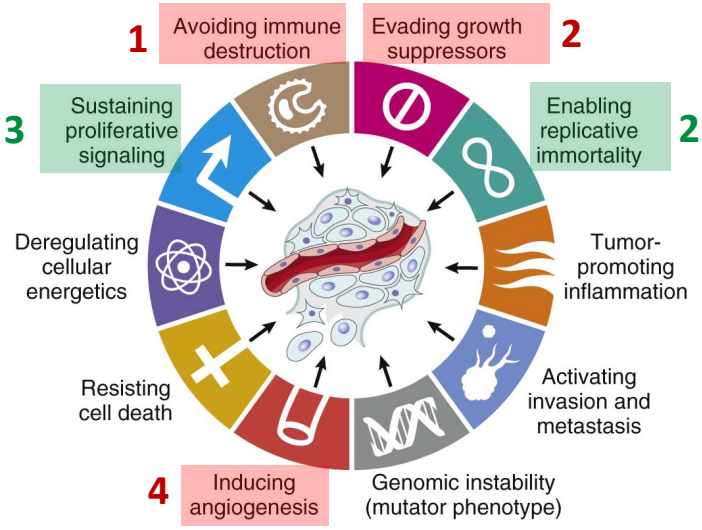
Neoplastic progression
How does HPV cause neoplasia?



Hanahan & Weinberg, Cell (2011) 144: 646-74

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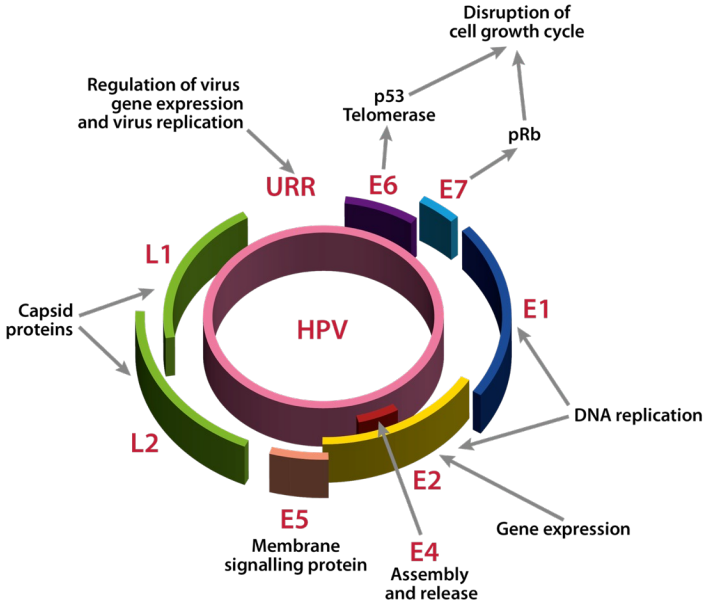
HPV tricks the body into producing viral protein



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HPV – Host Entry and Infection

1. **Portal of entry – epithelial tropism *(productive infection)***
   - Basal layer of stratified squamous epithelium- wounds, microwounds

2. **Binding of virus** to ECM components **(L1 capsid)****
   - Heparan sulfate proteoglycans
   - Laminin 332; Integrins & basement membrane proteins

3. **L1 and L2** conformational change
   - **Host protease mediated** opening up of capsid

** **HPV Vaccines contain virus-like particles of L1 major capsid protein**

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HPV infection

Sequence of Events

4. **Internalization and uncoating -** 2-12 hours
   - L2 exposure & binding to uptake receptor complex
   - Partial degradation of L1 by lysosomes
5. **Microtubular transport** to trans-golgi network (TGN)
   - L2 binding to microtubule dynein
6. **Epithelial mitosis (prophase to pro-metaphase)**
   - HPV harboring vesicles cross the Lamin nuclear barrier
7. **Following mitosis viral complex dissociates**
   - HPV DNA associates with nuclear bodies
   - **Cell is now suprabasal or in spinous layer**

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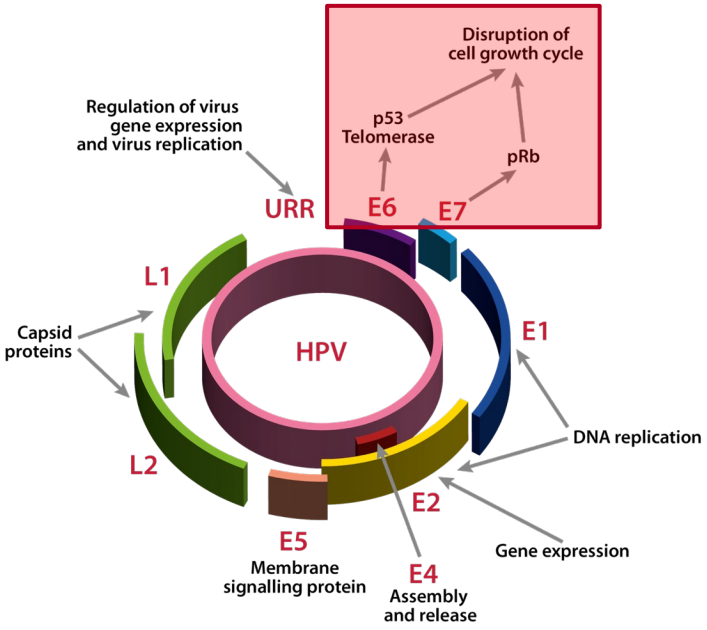
HPV-related pathogenesis

E6 & E7 push cells over cell cycle checkpoints



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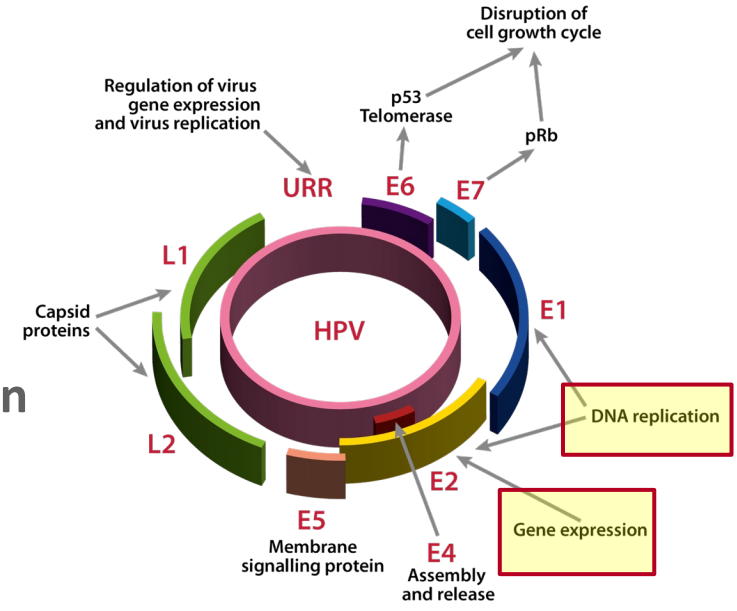
HPV-related pathogenesis

E1 and E2 drive Viral gene expression & replication



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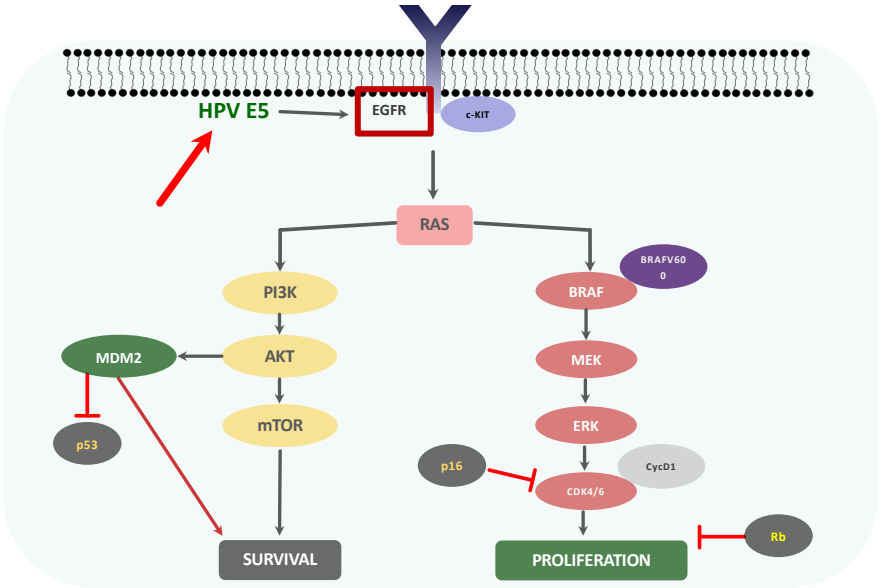
HPV mediated RTK pathway deregulation



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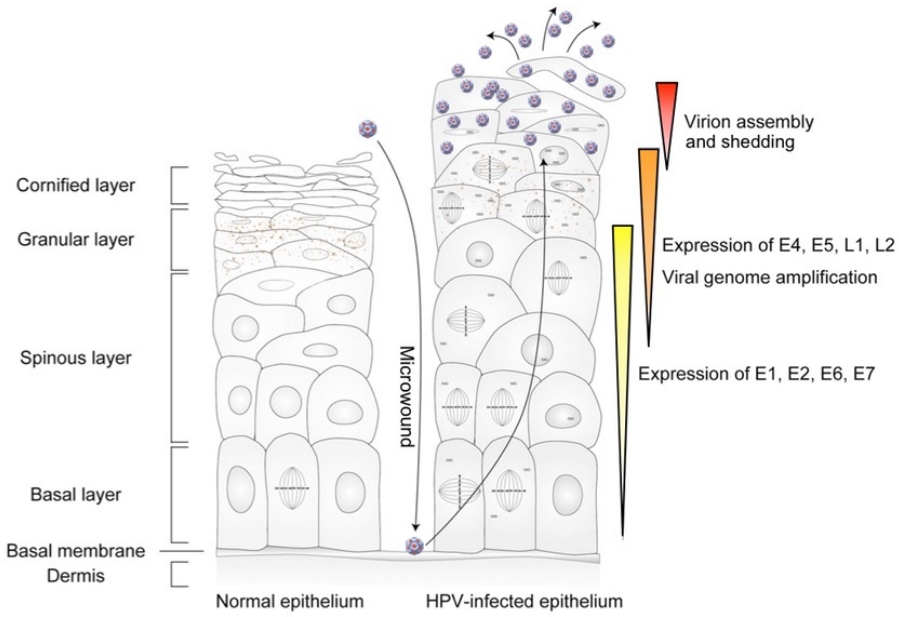
HPV transcription and replication



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Oral warts are benign
Squamous papillomas/ warts are exophytic

- E1, E2 activity is intact causing **viral replication** and epithelial proliferation
- **E6, E7 activity kick-starts the cell cycle and silenced**
- **E5 stabilizes EGFR, promotes angiogenesis, and aids immune evasion**
- Epithelial proliferation causes the **exophytic papillary appearance**
- Capsid assembly and viral shedding is seen toward the surface **(warts are contagious)**

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Squamous papilloma/ verruca vulgaris

Management

- Surgical excision – preferably cold steel (not lasers)
- Multiple warts – selected surgical excision

Prognosis:

Patients can develop multiple warts/ recurrences OR not

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Clinical Scenario

A patient with a squamous papilloma/ HPV - viral wart

Questions:

1. Is it benign? **YES**
2. Are oral HPV-related warts STDs? **Possible, but commonly NOT!**
3. Is our patient at risk of developing **oral** (mouth) cancer? **NO**
4. Is our patient at risk of developing **oropharyngeal** (throat) cancer? **NO**
5. Is our 9-year old patient a candidate for the HPV vaccine? **YES**

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HR-HPV-related oropharyngeal SCC
HPV-related-Cervical SCC
Tobacco-related-Oral Cavity SCC
UV exposure-related-Skin and Lip SCC

Different diseases
that share a name

****SCC = squamous cell carcinoma**

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Patient 2

- **A 52-year-old man with an incidentally discovered neck lymph node swelling**
- **Fluctuant & non-tender on palpation**
- Present for 3 months and growing in size
- No pain; no symptoms of discomfort
- No difficulty swallowing or voice changes/ hoarseness
- **NO oral findings or complaints**

Medical history & social history:

- Diabetes, hypertension (controlled with medications
- Negative for tobacco use; occasional alcohol

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Samples obtained
FNAC & Tissue biopsy

Fine needle aspirate:

- Basaloid squamous epithelial cells
- p16 immunoexpression positive

Scoping + biopsy of small tonsillar nodule

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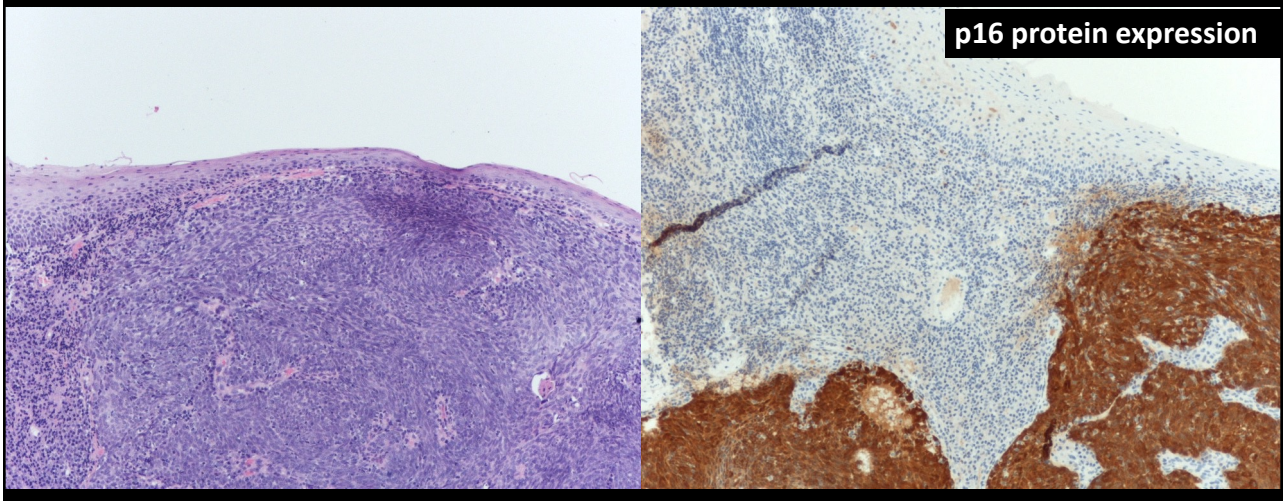
Diagnosis: HR-HPV oropharyngeal squamous cell carcinoma
p16 positive



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HR-HPV and Oropharyngeal Cancer

A real and emerging epidemic

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Primers and promoters

Risk factors for Oropharyngeal SCC

- Tobacco
  - Smoking – cigarette, cigar, pipe, reverse smoking
- Alcohol
- Age

Traditional Risk factors for "throat cancer"

OPSCC used share many of the same risk factors as oral, esophageal, and lung cancer

BUT

HR-HPV is NOW the # 1 RISK FACTOR

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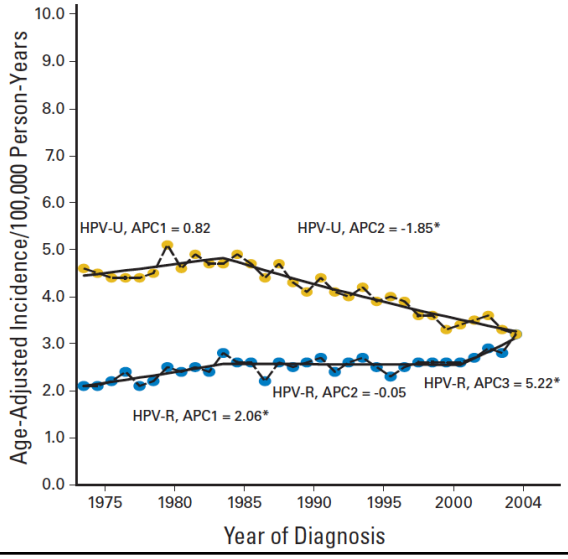
Oropharyngeal cancer

Changing trends in pathogenesis

Smoking related

HPV- related



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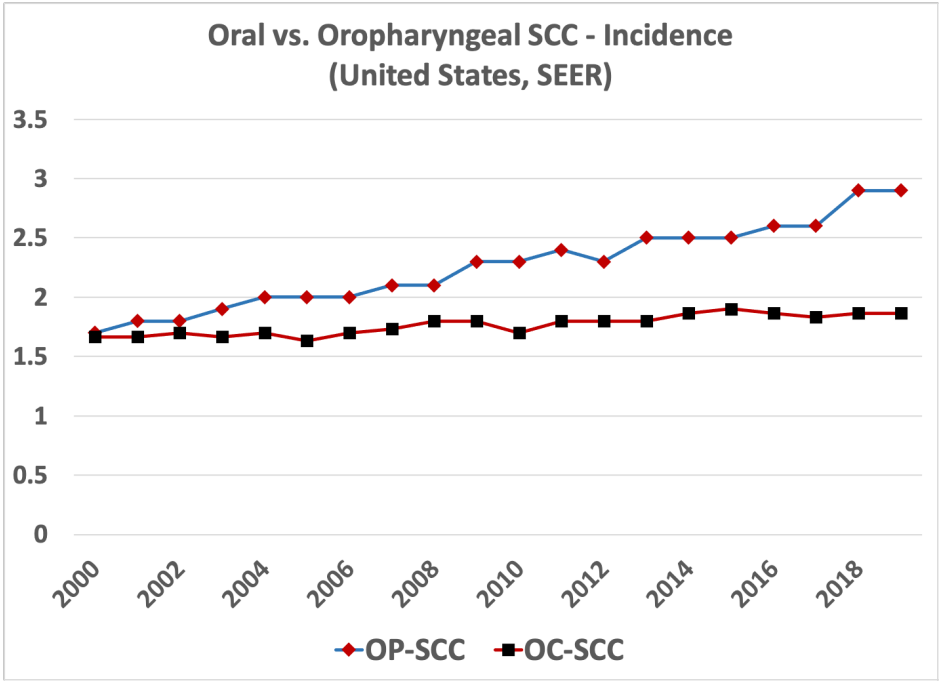

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HPV Carcinogenesis

Site and strain specific

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HPV Strains - High Risk

High risk HPV strains

- **Types 16, 18**, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.
- **HPV 16 and 18** - 70 percent of cervical and anal carcinoma
- **HPV 16** accounts for **> 90% of oropharyngeal SCC**

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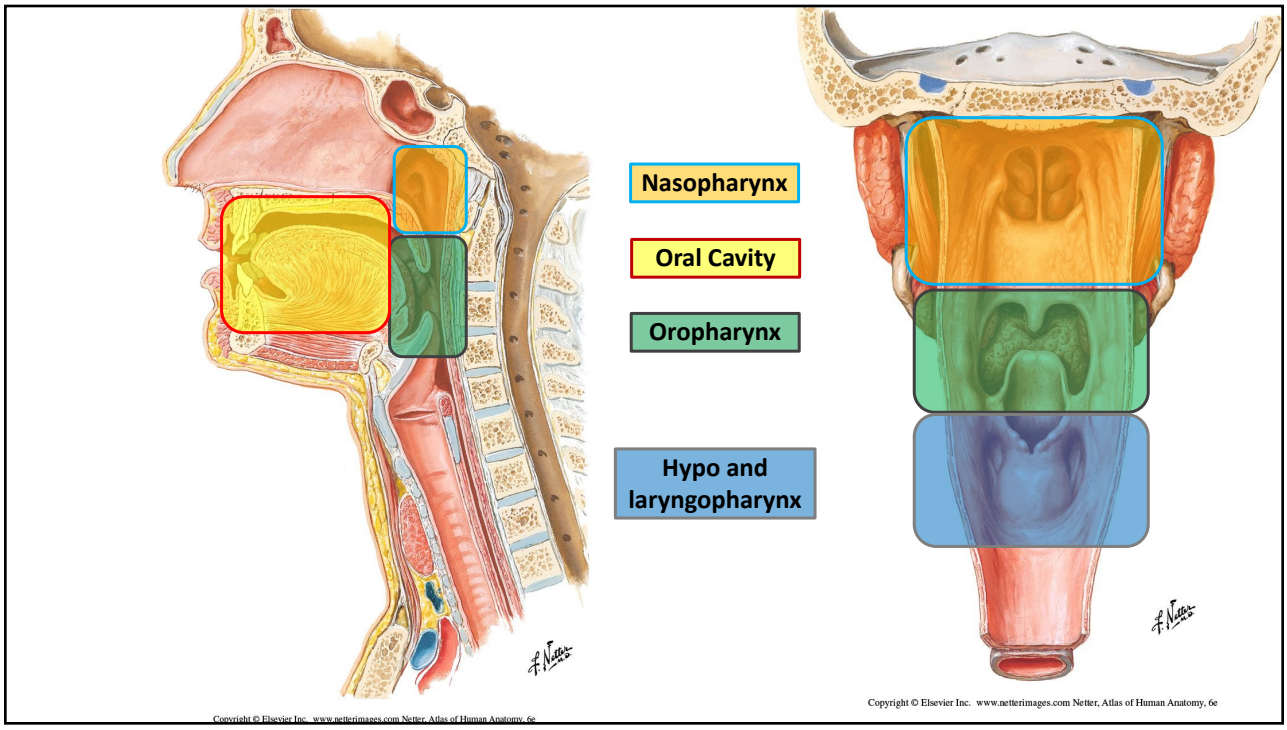

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Oropharynx – Anatomical considerations

Endodermally derived

- **Superior border:** nasopharynx; **Inferior border:** hypopharynx

Parts of the oropharynx:

Pharyngeal wall: bounded by the soft palate & vallecula

Tonsils: palatine & lingual tonsils

Base of tongue: posterior 1/3rd of tongue to base of the epiglottis

Soft palate & uvula

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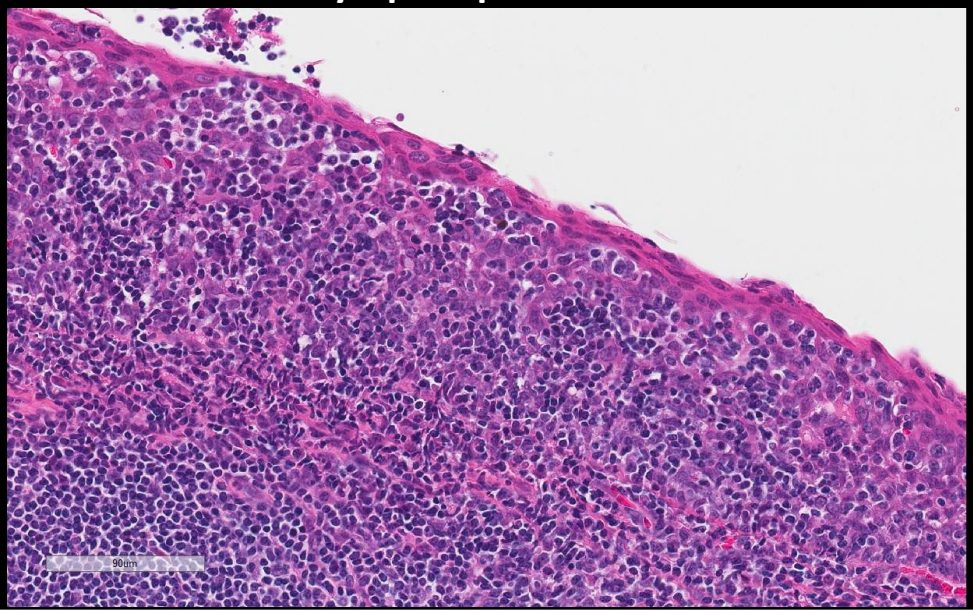
Reticulated stratified squamous epithelium or Lymphoepithelium



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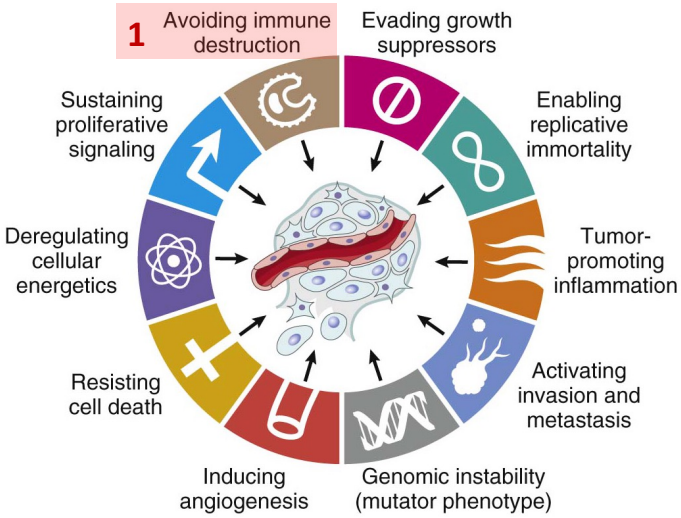
Hallmarks of OPSCC

How did we get here?



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HPV – Immune Evasion

Silence is success

1. **Physical barriers:** binding to ECM leads to internalization
   - **Protected from immune-cells in superficial epithelial layers**
2. **Innate immunity**
   - **E5 transcription suppresses Langerhans cells**
3. **Adaptive response:**
   - Evasion **immune-privileged tonsillar/ oropharyngeal mucosa (checkpoints)**
4. **Latency:**
   - HPV remains **undetected** in basal cells for years & **reactivation from latency is possible**

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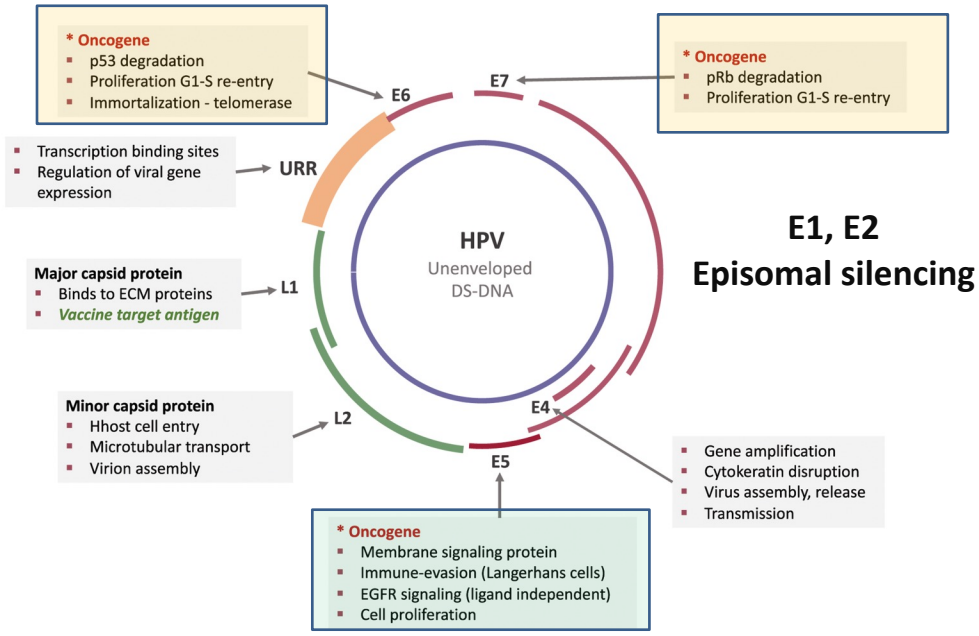
HPV genome and carcinogenesis



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HPV related carcinogenesis

No mutations or deletions

- **E1, E2** silencing/ inactivation - no viral replication
- **E6, E7** DNA integration
  - **E6 binds + inactivates p53** (compromising G1/S and G2/M)
  - **E7 neutralizes Rb** at G1/S
- **E5 is a critical player** in carcinogenesis
  - **stabilizes EGFR; stabilizes MAPK pathway**
  - neutralizes interferon activity
  - **stimulates angiogenesis along with E4**

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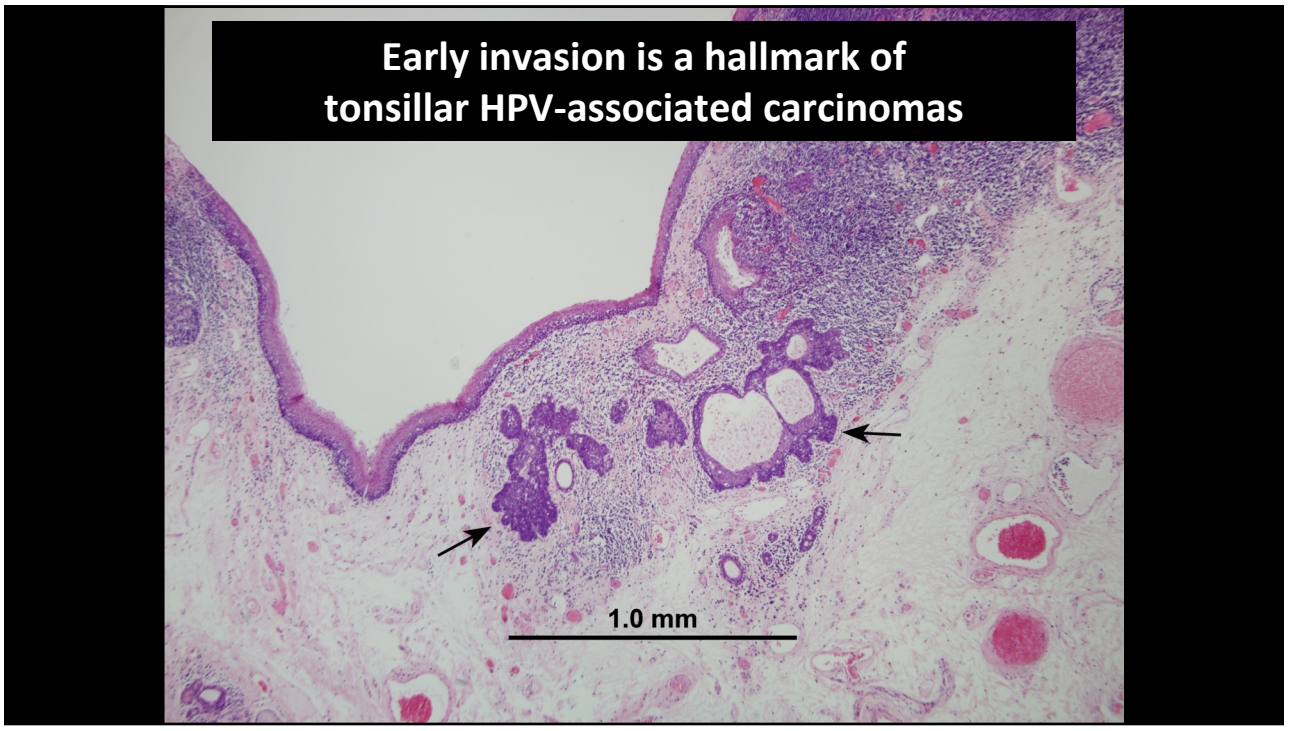

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HPV-related oropharyngeal cancer

Unique clinical features (unlike oral cancers or warts)

- **Young men/ women**
- Initial presentation
  - **painless cervical lymph node**
  - frequently incidental discovery
  - **no evidence of precancerous white changes**/ mass on oral exam
  - surface changes are rarely seen (white/ red changes)
- **Biopsies show SCC within lymph nodes** triggering work-up to identify primary site

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Two Clinical Situations

Patient 1: Squamous papilloma/ wart

Patient 2: Oropharyngeal squamous cell carcinoma

HPV-related neoplasms

Benign

Malignant / Cancer

Similarities in mechanism?

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HPV vaccines - rationale

Deploy the immune-system at the portal of entry

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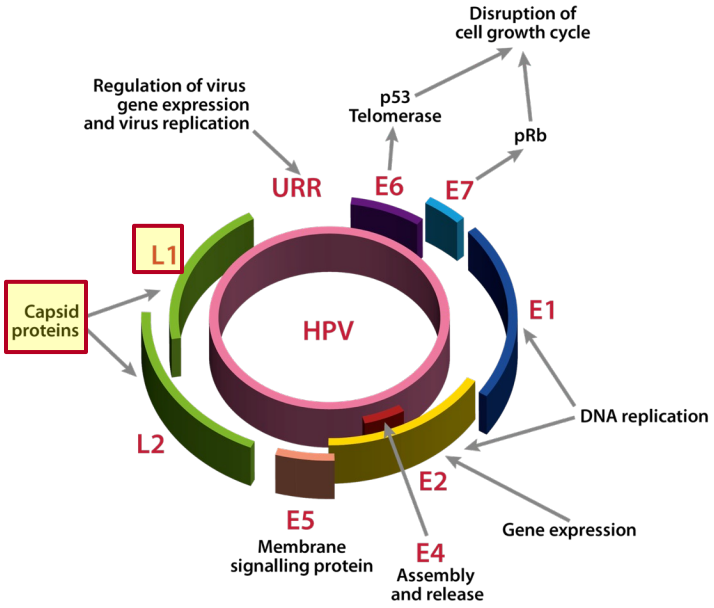
HPV vaccines target packaged L1 capsid viral-like proteins



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HPV vaccines

- Vaccines contain virus-like particles of **L1 major capsid protein**
- Immunization against HR-HPV strains **HPV-16, 18 to prevent cervical/ oropharyngeal/ anorectal cancer**
- **Gardasil™ (original)** – tetravalent cross reactive with **HPV 6,11**
- **Gardasil 9™ (current)** – nine-valent cross reactive **HPV 6,11,31,33,45,52,58**
- **Children – boys & girls aged 11 to 12 years; can be started at 9 years**
- **Adolescents & adults – aged 13 to 26 years; catch up vaccines**
- **Adults older than 27 years: selected situations/ routine?**

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Oral Healthcare Providers

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- Educate patients about HPV-related disease
  - **Warts/ squamous papilloma**
  - **Oropharyngeal cancer (tonsillar/throat cancer)**
- HPV infection and differences between viral strains
- Pathobiology/ mechanism of disease
- **Educate patients about rationale for vaccines:**
  - **Gardasil 9™** – nine-valent cross reactive to **HPV strains 6,11,16,18,31,33,45,52,58**

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Oral Healthcare Providers

Capabilities & Responsibilities

- **HPV vaccines protect against LR- & HR-HPV:**
  - **Warts, oropharyngeal, cervical, and anorectal cancer**
- **Dentists/ orthodontists/ hygienists see patients & their families frequently:**
  - **Vaccine Education**
  - **Vaccine Administration?**

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Thank you!

Natarajan@uchc.edu

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