

Oral and Tonsillar Cancer What about HPV?

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Conflict of Interest

- I have no conflicts to declare

Outline

- Examination of the dental patient
- Precancerous oral lesions, high-risk features
- Oral vs tonsillar Ca: epidemiology and trends
- HPV vaccines and their potential impact on tonsillar (oropharyngeal) cancer

Patient Examination

- Permits detection and documentation of pathology or unusual anatomic variants
- Guides patient triage
- Key features:
 - Standard technique
 - Recording of findings (if not, was it ever found?)

Conventional Visual and Tactile Examination (CVTE)

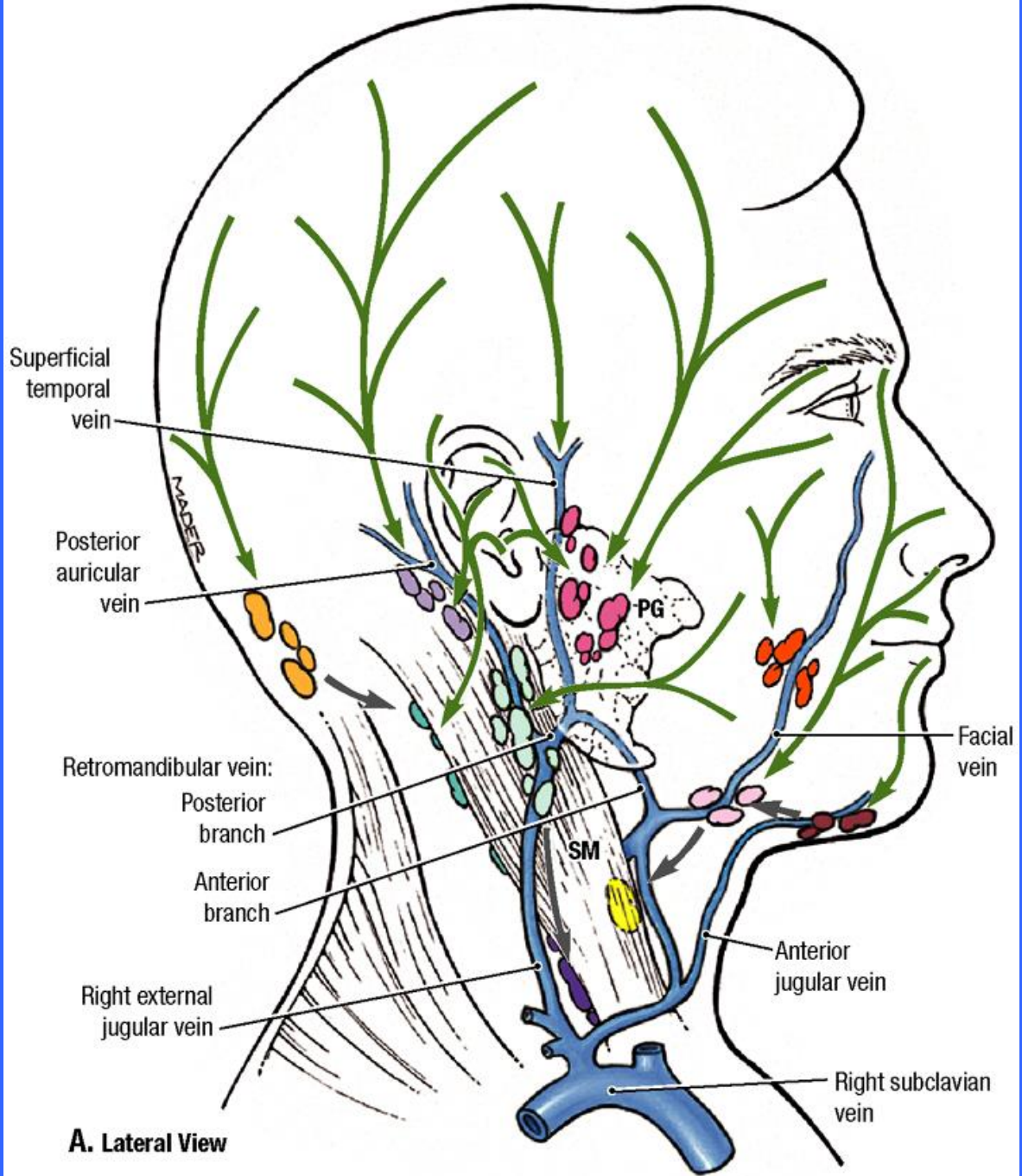
- Standard technique
- Recording of findings
- Knowledge of anatomy
- Knowledge of disease/pathology

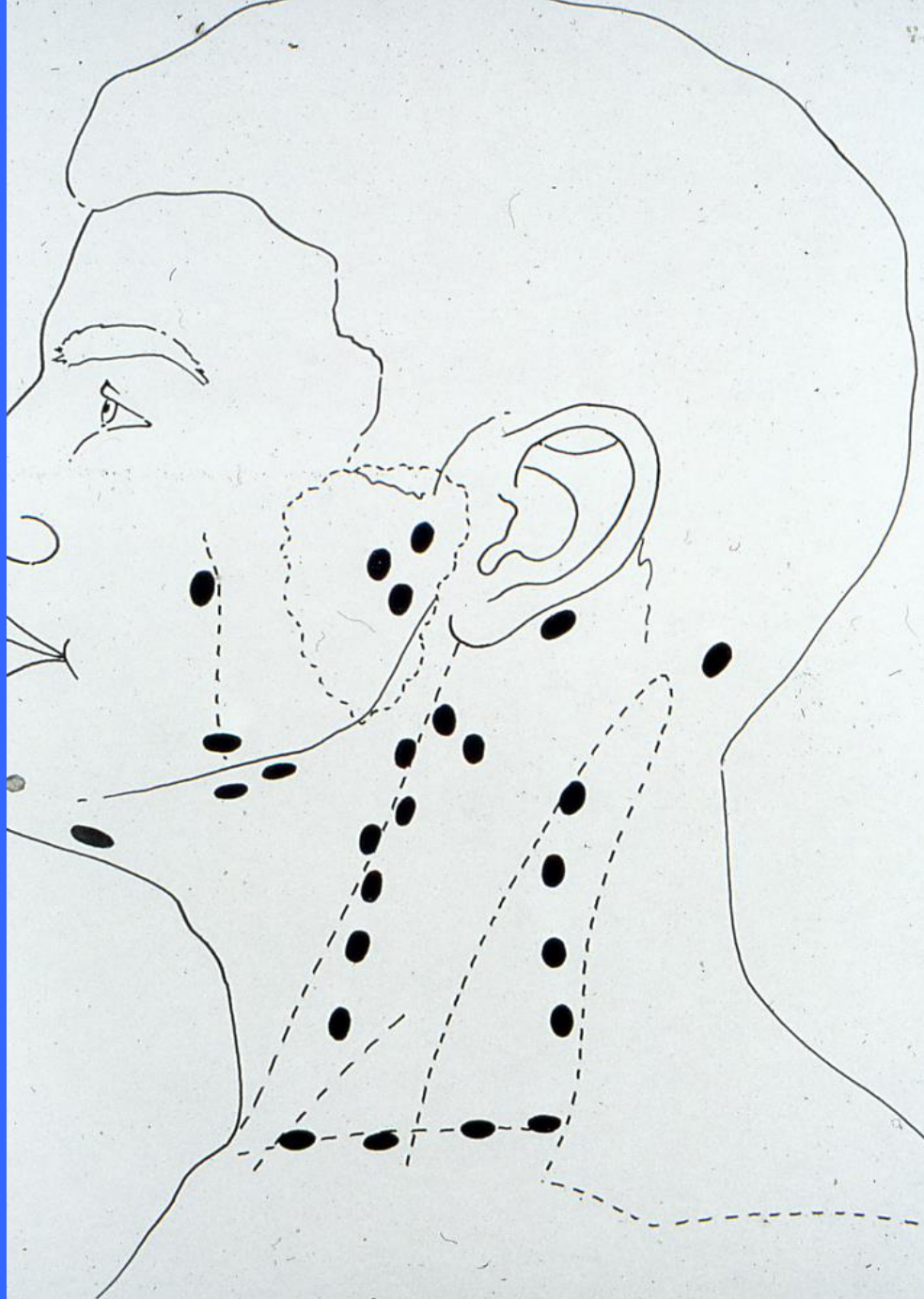
CVTE of Head and Neck: Equipment

- Operatory light
- Dental mirror
- Examination gloves
- Gauze
- Periodontal probe/measuring device

Head & Neck CVTE

- Neck & face: **standard** visual exam for color/surface changes plus tactile assessment (palpation) for lymph nodes/mass lesions
- Oral tissues: **standard** visual & tactile exam



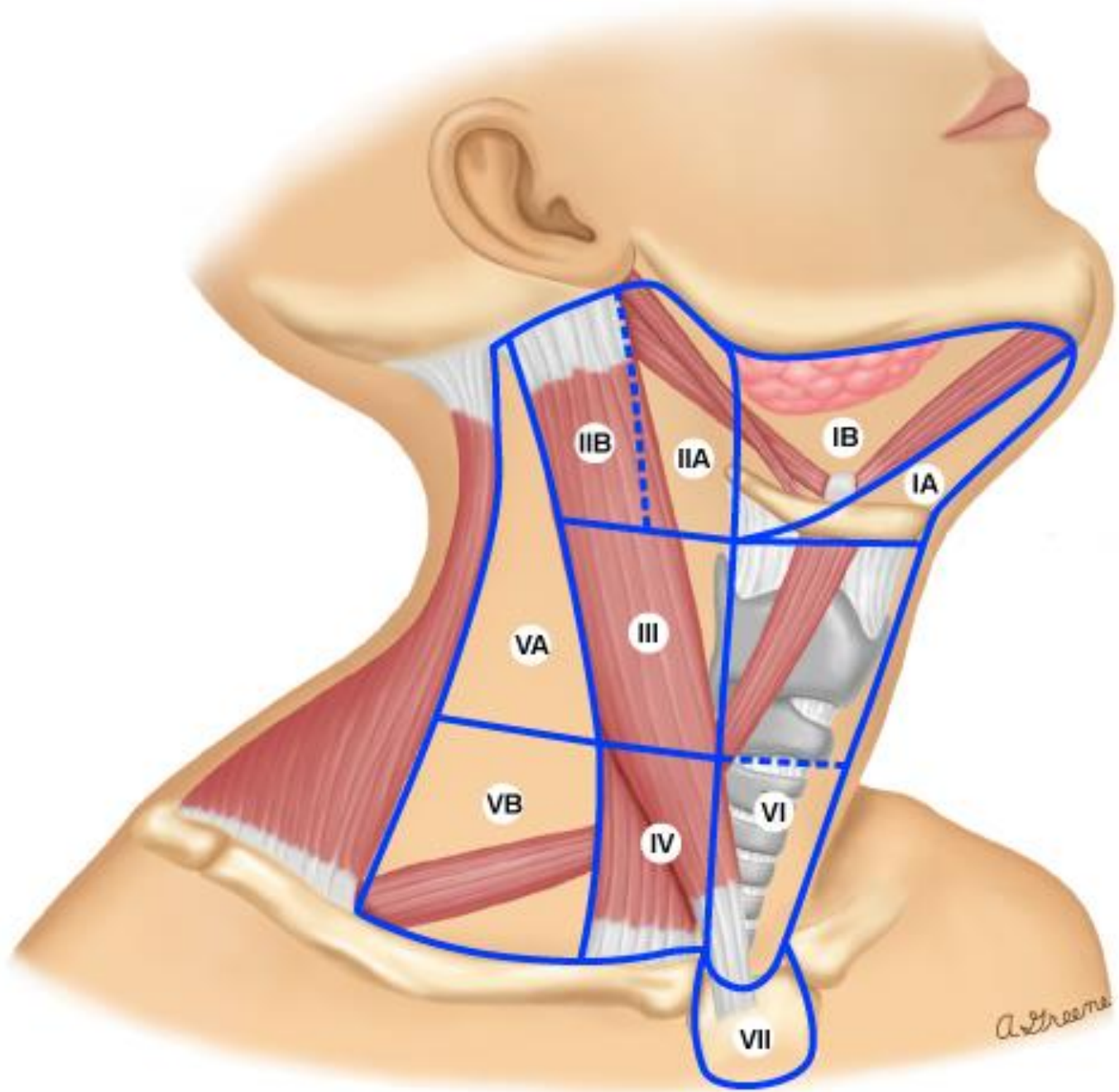






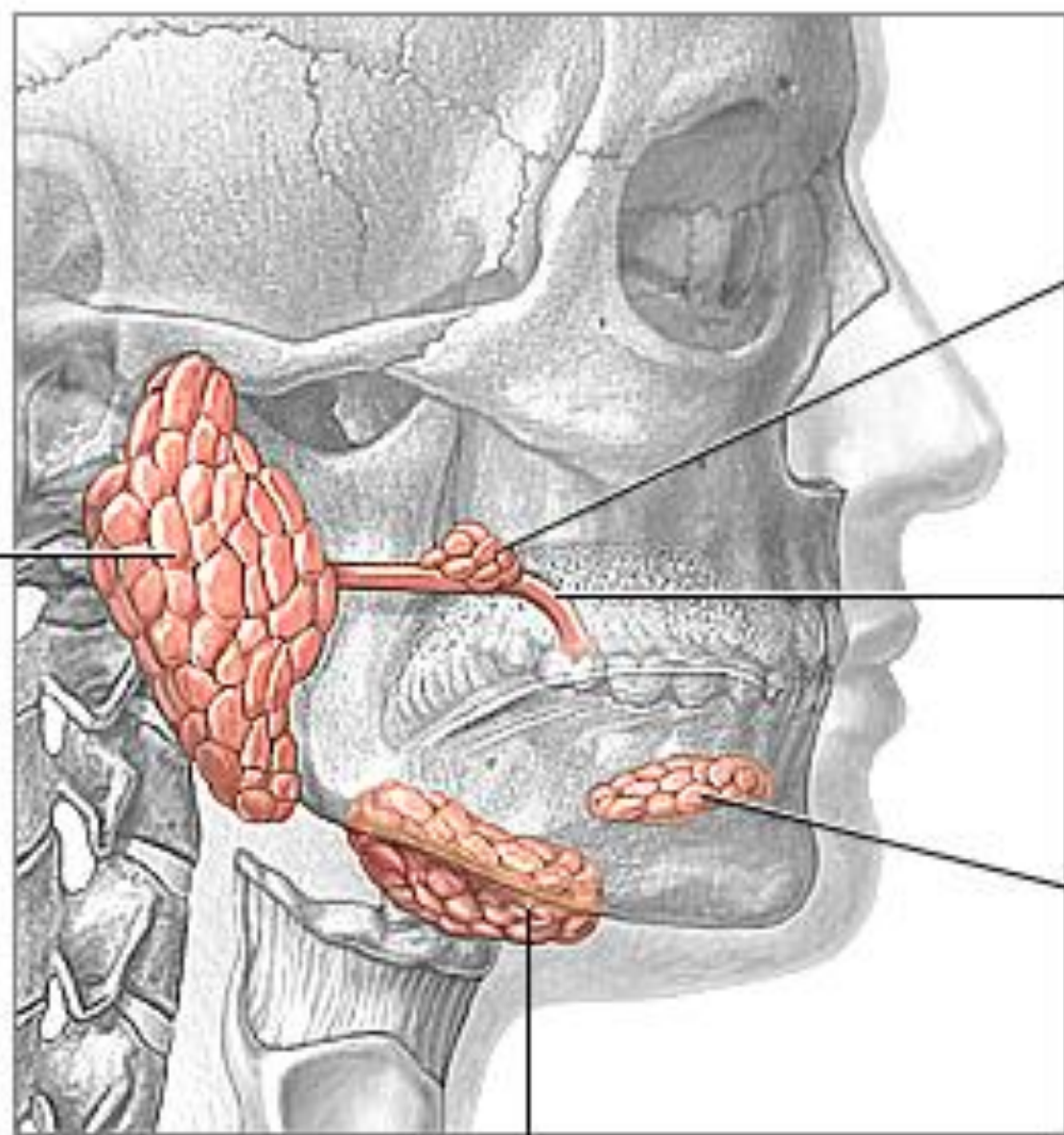








Parotid gland



Accessory
parotid gland

Parotid duct

Sublingual
gland

Submandibular gland

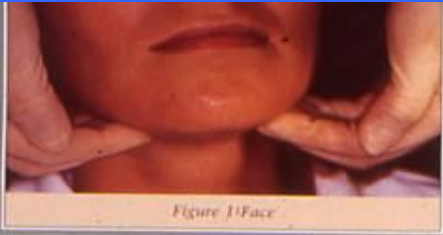


Figure 1-Face



Figure 2-Lips



Figure 3-Labial mucosa



Figure 4-Labial mucosa



Figure 5-Right Buccal mucosa



Figure 6-Left Buccal mucosa



Figure 7-Gingiva

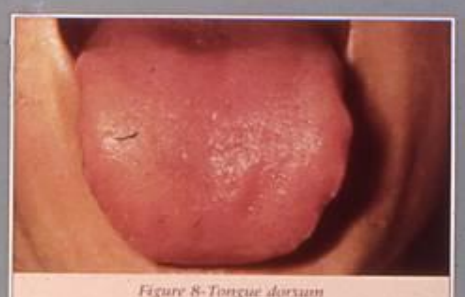


Figure 8-Tongue dorsum

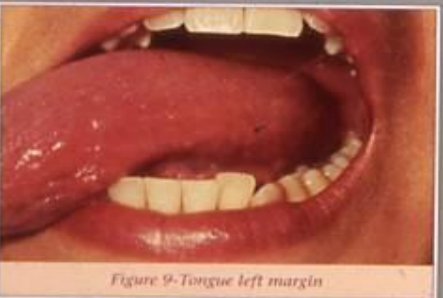


Figure 9-Tongue left margin



Figure 10-Tongue right margin

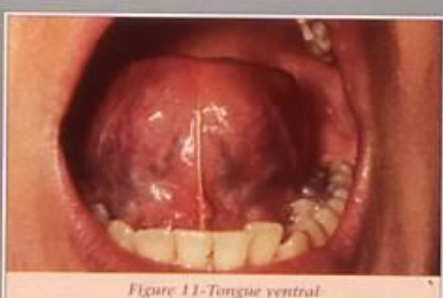


Figure 11-Tongue ventral







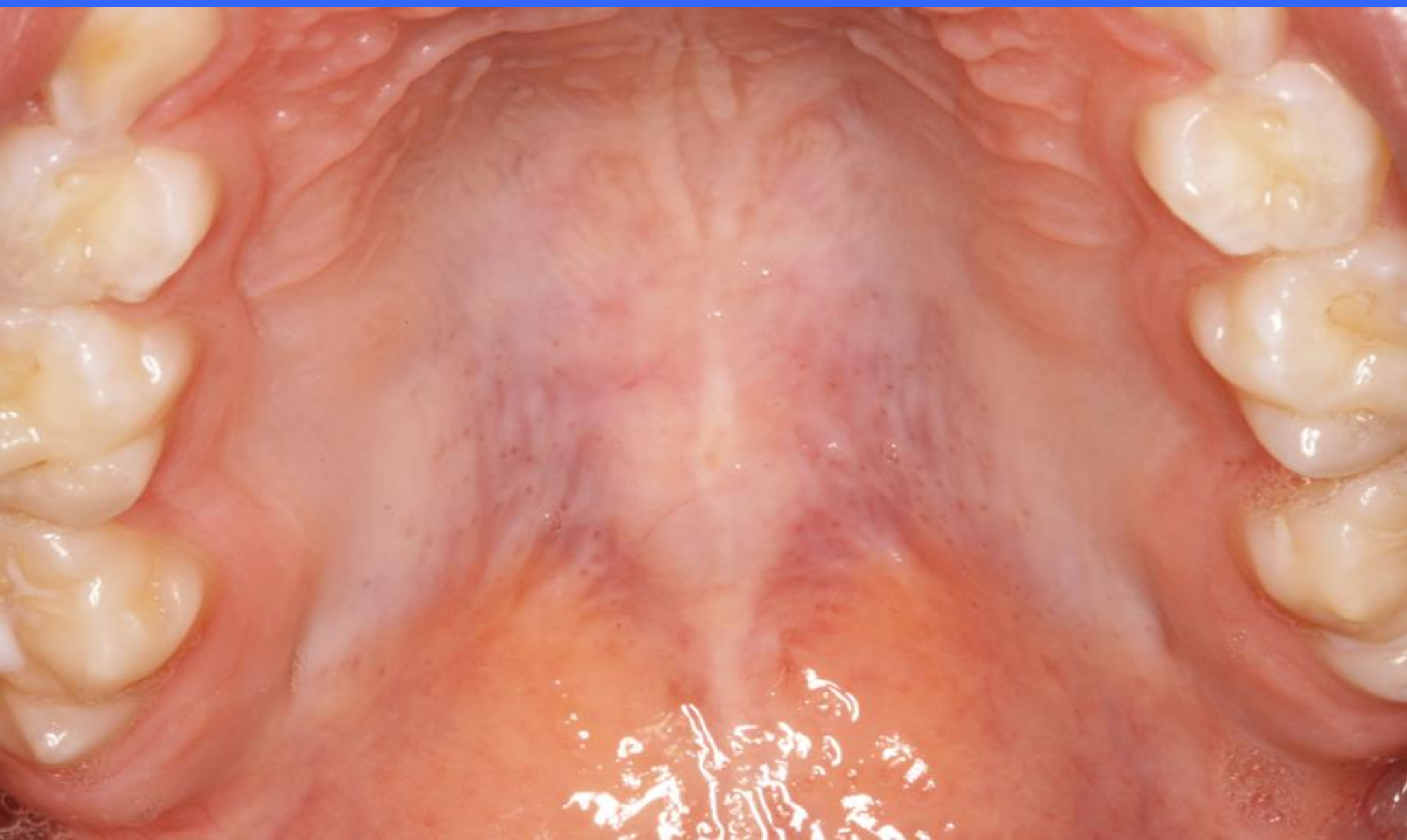








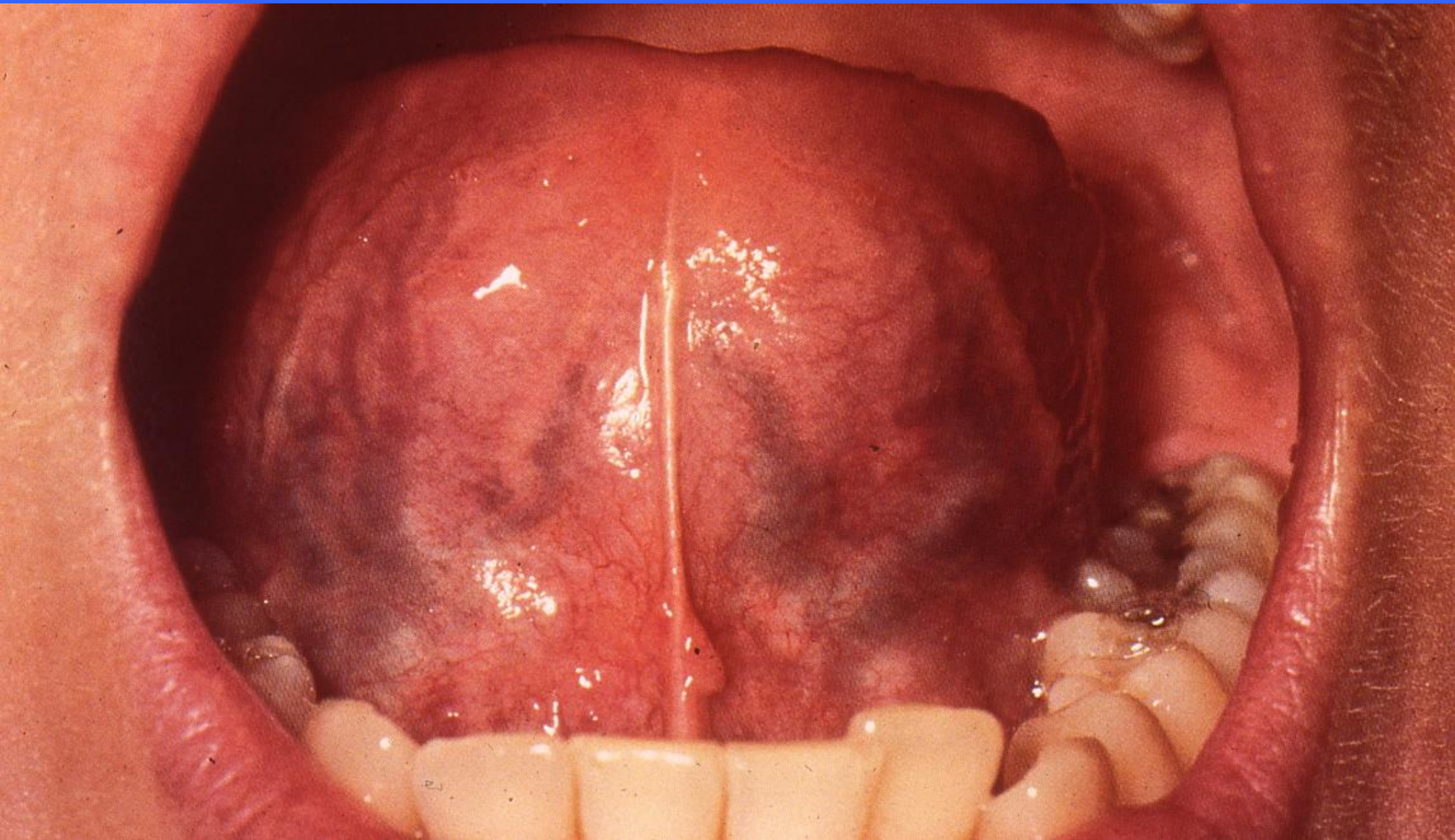


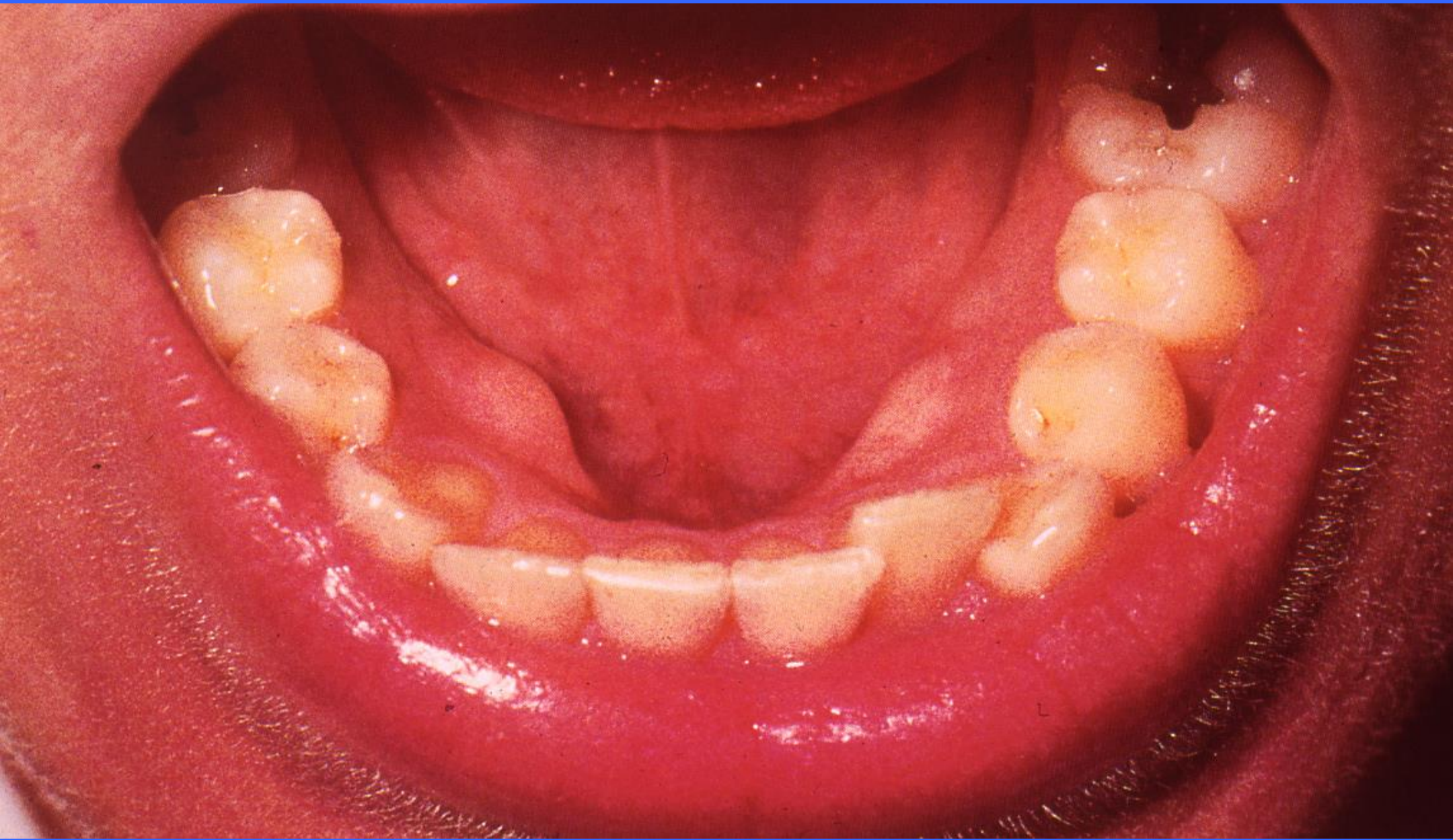


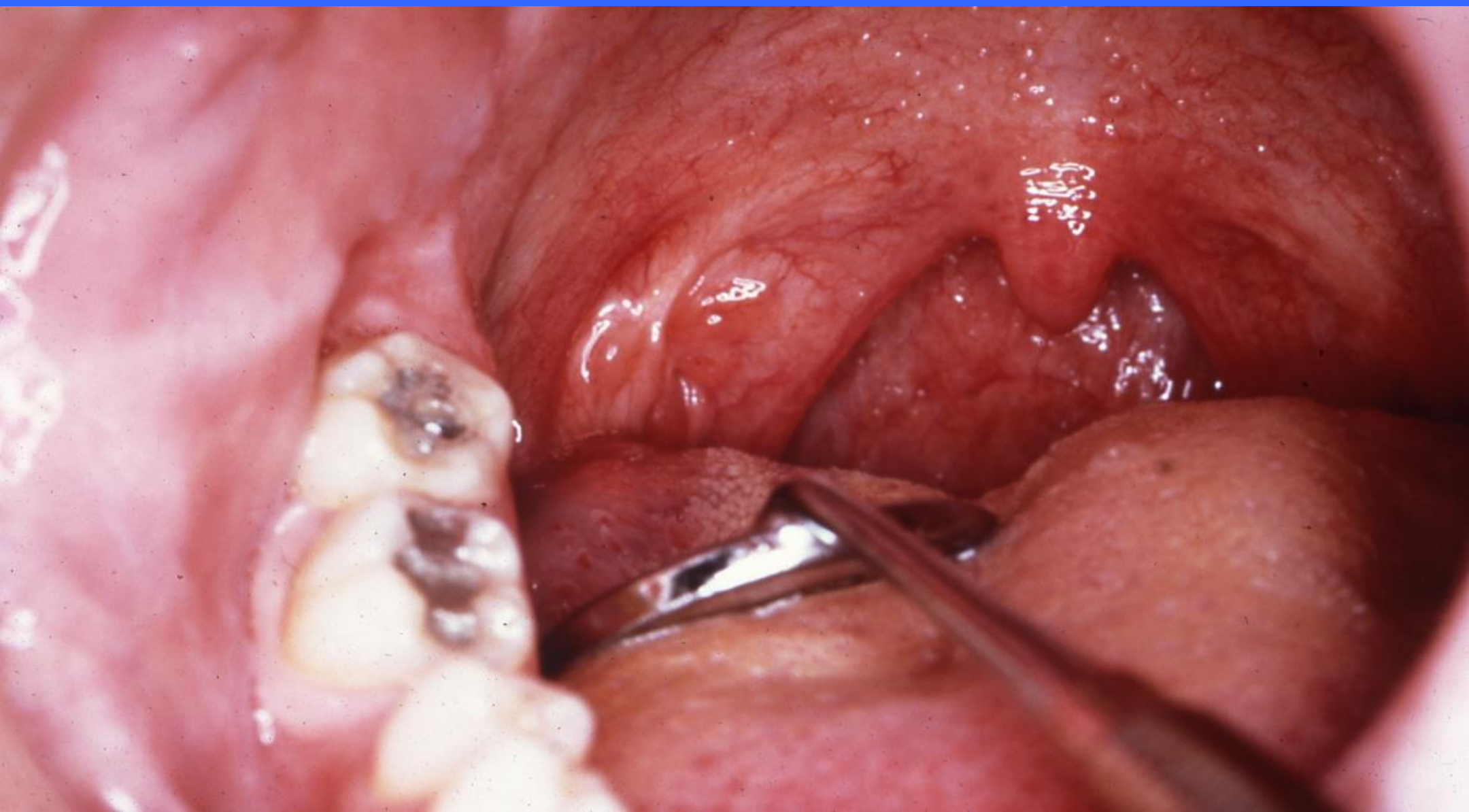














Recording of findings

- Site
- Size
- Character (flat, raised, depressed)
- Color (uniform, variable)
- Surface morphology (texture)
- Border (sharp?, smooth vs irregular)
- Consistency (palpation)
- Local symptoms
- Distribution (if multiple)

Oral pathology documentation

- Record lesional attributes
 - size, location, texture, consistency, etc.
 - *quality, close-up photographs*
- Discuss findings with patient: working diagnosis, differential diagnosis, risks, alternatives and plan for follow-up



Follow-up evaluation

- Has lesion changed?
- If initial therapy was used, did it help reduce signs/symptoms?
- When diagnosis still uncertain, the option of surgical biopsy should be discussed with patient/guardian

Follow-up protocol

- Initial: 7-21 days (+/- conservative therapy)
- If no progression, follow-up at 1, 3, 6 and 12 months. Then, every 6-12 months (or normal recall intervals)
- With lesion progression/worsening: biopsy
- Treat as determined by biopsy diagnosis
- If no evidence of epithelial precancer/cancer (OMF pathologist), follow and document as above

Oral biopsy?

Oral pathology!



Oral & Oropharyngeal Cancer

- In 2020, 53,260 new cases of oral and pharyngeal cancer in USA (10,750 deaths)
- Oral cavity: 35,310 cases (7110 deaths)
 - Pancreas: 57,600 cases (47,050 deaths)
 - Multiple myeloma: 32,270 (12,830 deaths)
- 90% are squamous cell carcinoma (SCCa)
- 97% patients \geq 35 years of age; M>F (2:1)

Oral & Oropharyngeal Cancer

- In 2022, 54,000 new cases of oral & oropharyngeal cancer in USA (11,230 deaths)
- Oral cavity: 34,730 cases (7250 deaths)
 - Pancreas: 62,210 cases (49,830 deaths)
 - Multiple myeloma: 34,470 (12,640 deaths)
- 90% are squamous cell carcinoma (SCCa)
- 97% patients \geq 35 years of age; M>F (2:1)

Oral & Oropharyngeal Cancer

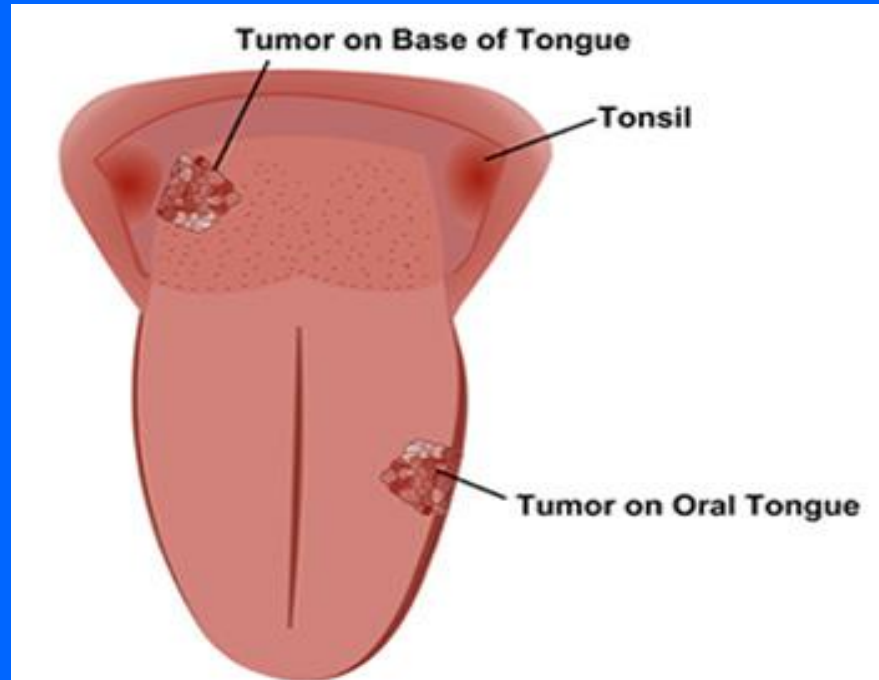
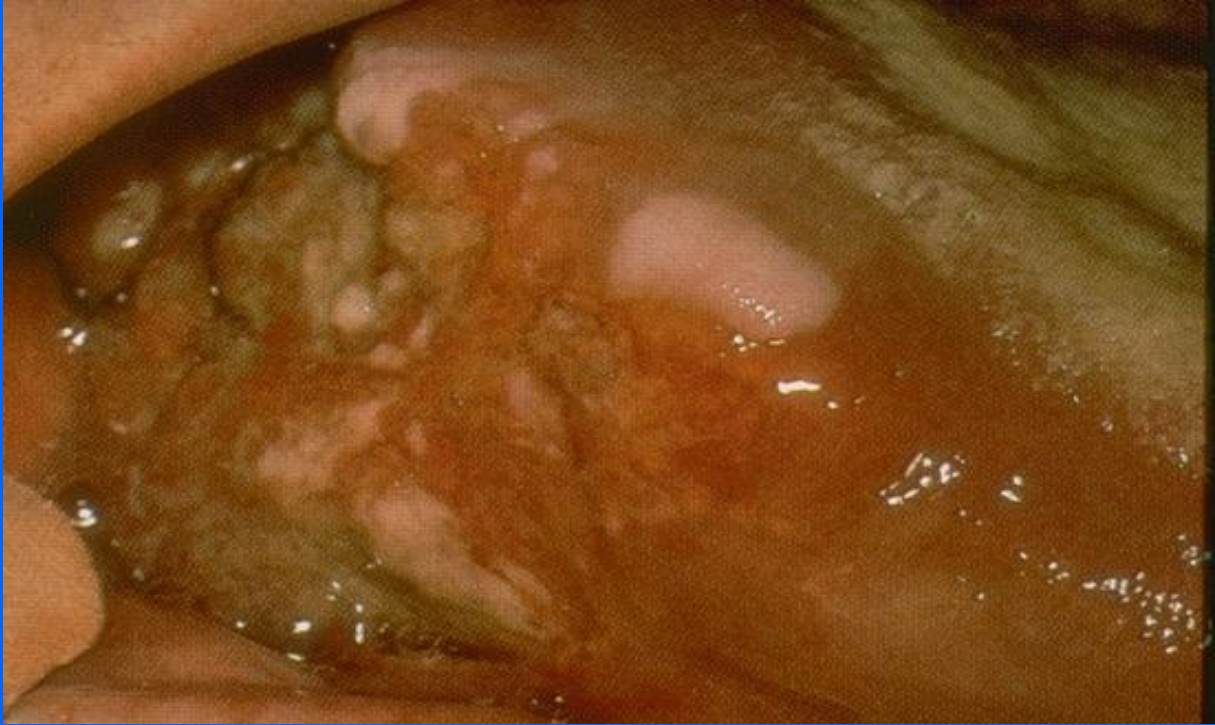
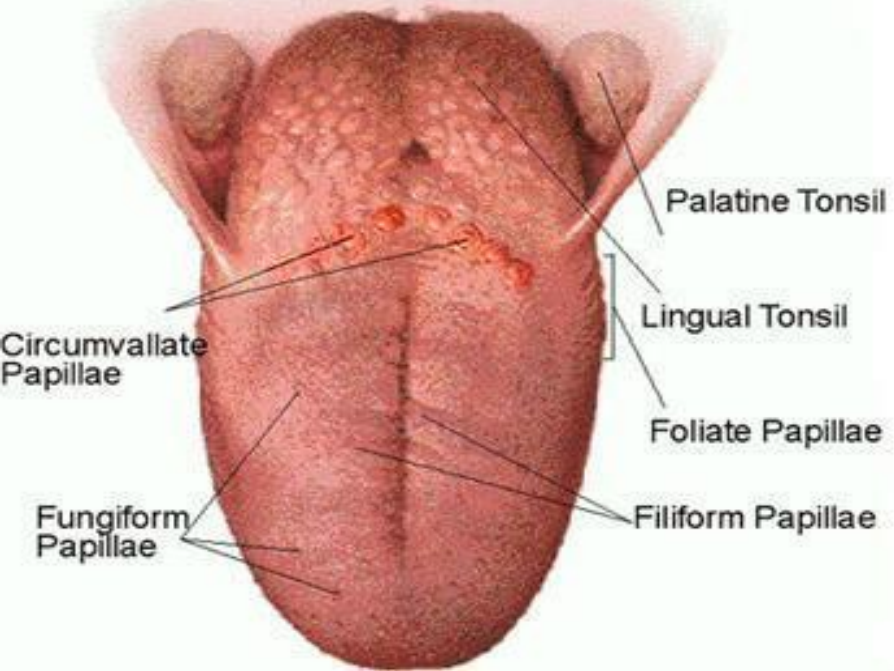
- In 2023, 54,540 new cases of oral & oropharyngeal cancer in USA (11,580 deaths)
- Oral cavity: 34,470 cases (7,440 deaths)
 - Pancreas: 64,050 cases (50,550 deaths)
 - Multiple myeloma: 35,730 (12,590 deaths)
- 90% are squamous cell carcinoma (SCCa)
- 97% patients \geq 35 years of age; M>F (2:1)

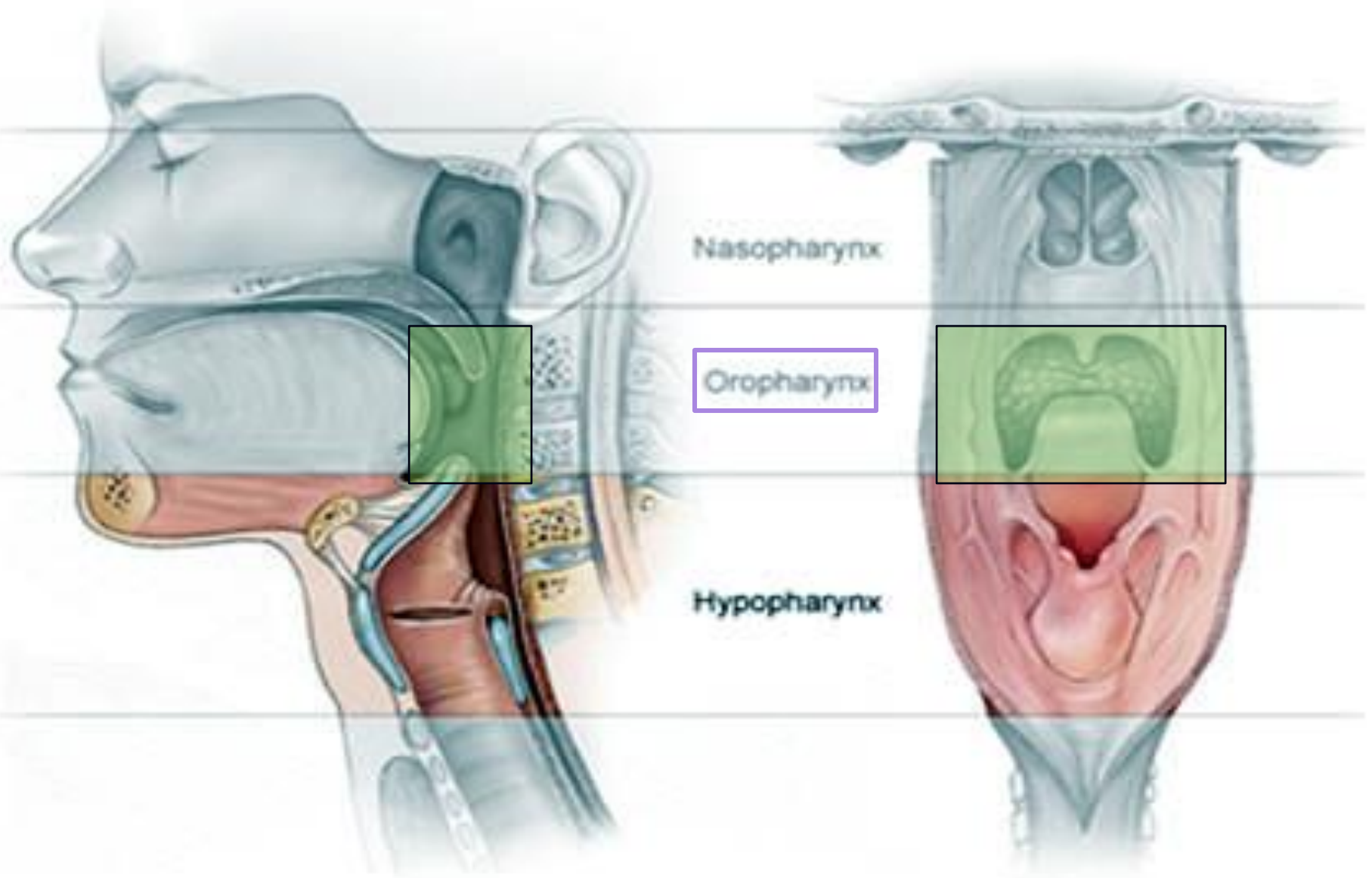
Oral & Oropharyngeal Cancer

■ Since 1973:

- incidence rate (IR) of oral Ca has **gradually declined**
- IR of tongue base and oropharynx (“tonsillar”) Ca has **increased**, with recent rapid growth in case numbers

Tongue





Nasopharynx

Oropharynx

Hypopharynx

Median view of pharynx

Posterior view of pharynx (opened)

Oral Cancer: Risk factors

- Tobacco and alcohol
 - Involved in 80% of oral cancer cases
 - Synergistic effect:
 - RR for smoking (2 ppd) only = 5 X
 - RR smoking/heavy drinking = 15 X
 - Alcohol alone (variable est.) = 0-2 X
- Low socioeconomic status (access to care, nutrient-poor diet [less fruits, vegetables])
- Marijuana: no increased risk by meta-analyses*

*de Carvalho et al, Arch Oral Biol 2015;60:1750-5

Ghasemiesfe M et al, JAMA Netw Open, 2019;2:e1916318

Oral Cancer

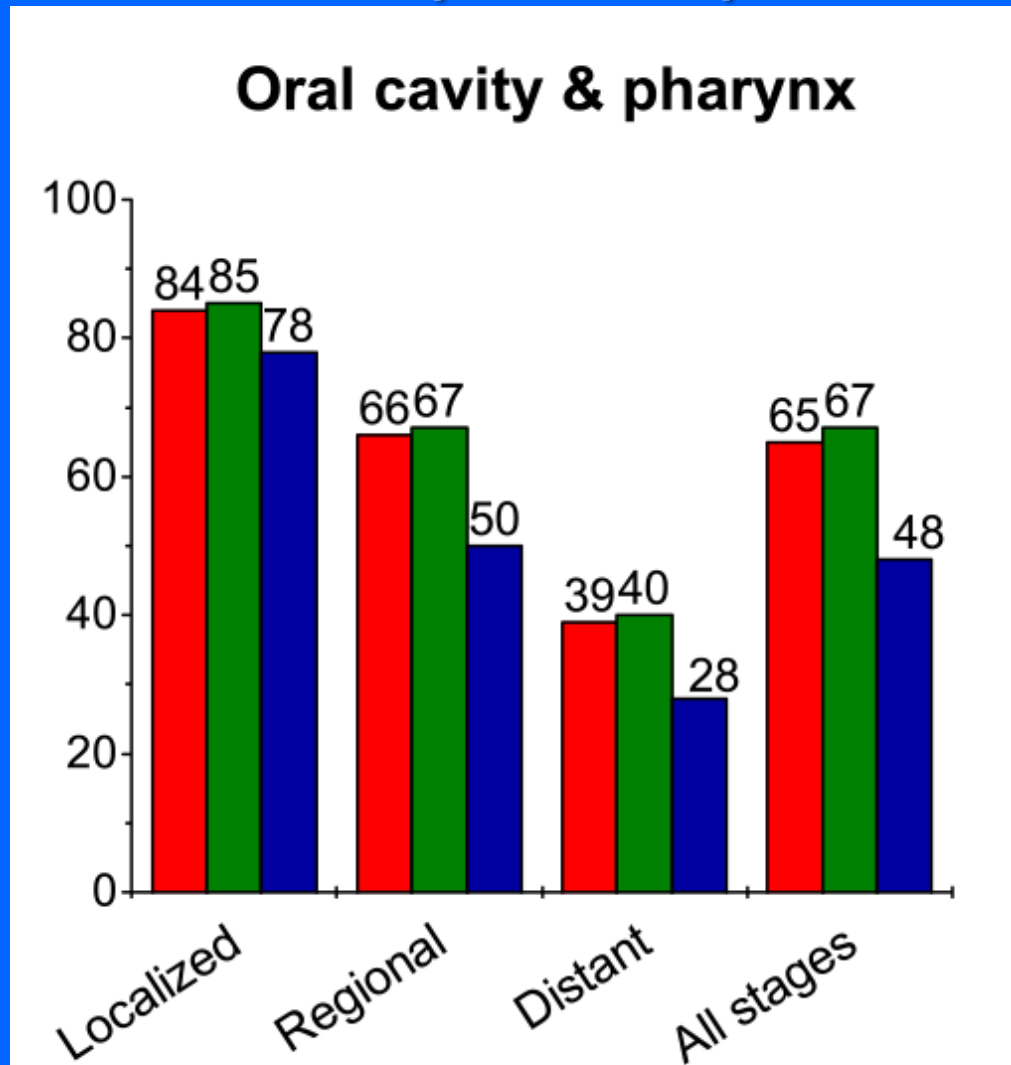
- Age-adjusted IR higher among men (5.8) than women (3.0) (ratio <2:1), with a similar trend in mortality
- 1960s: male/female ratio was 5:1
- African-American men at highest risk (6.4)

Oral Cancer

- Overall 5-yr survival: 65%, but significant racial differences (67% white men, 48% for black men)
- Greater proportion of late (higher stage) diagnoses in black men; access to care?
- Survival has steadily increased since 1975

5-yr relative survival

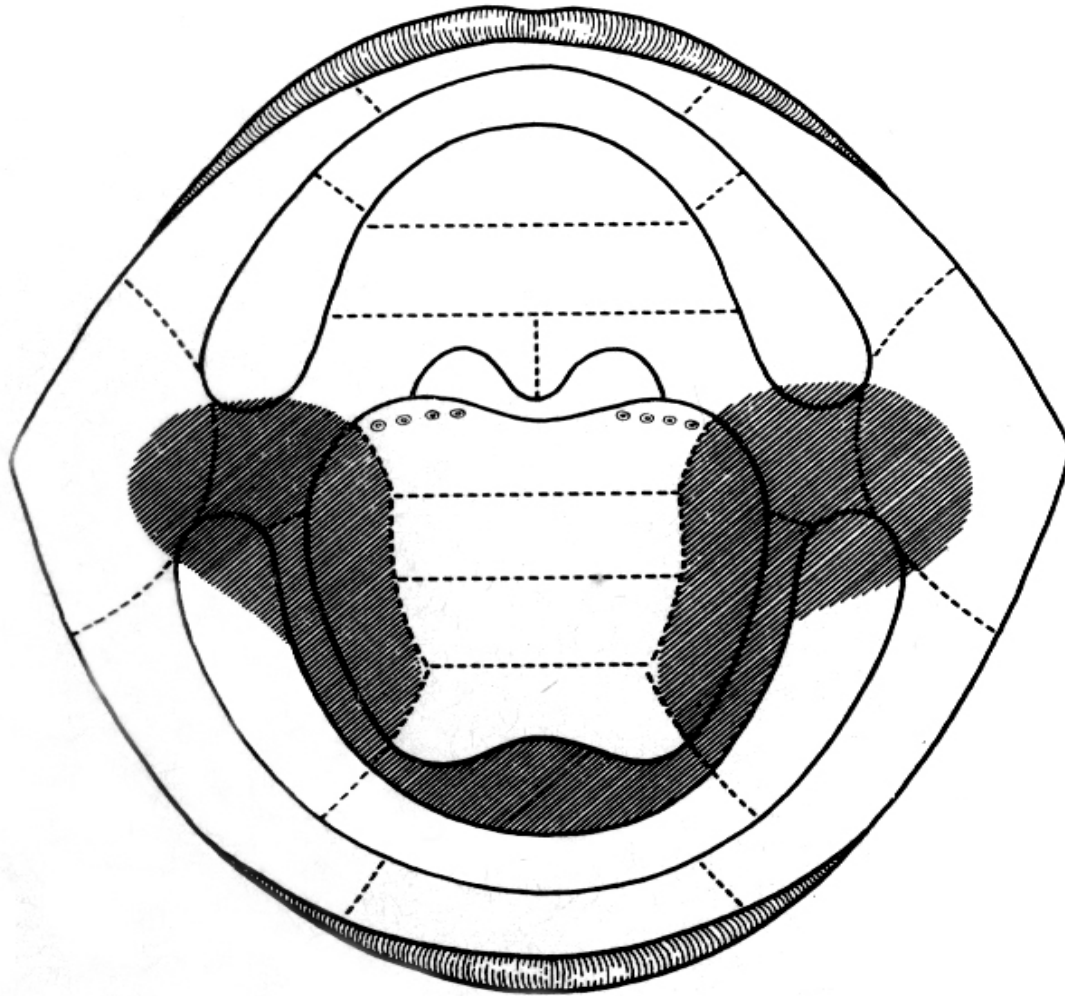
All races, white, black



Where do we look for oral cancer?

- **High-risk sites** for oral squamous cell carcinoma
 - Ventro-lateral tongue
 - Floor of mouth
 - Anterior tonsillar pillars/retromolar area

“High-risk Zone”



What are the clinical features of oral cancerous or precancerous lesions?

- Well-defined white plaques (leukoplakia: more common)
- Well-defined red patches (erythroplakia: uncommon)*
- Suspicious lesional features*
 - Large size (≥ 1 cm diameter)
 - Non-homogenous, irregular surface
 - Reddish (or red-white) surface
 - Progressive enlargement
 - Persistent ulceration, induration

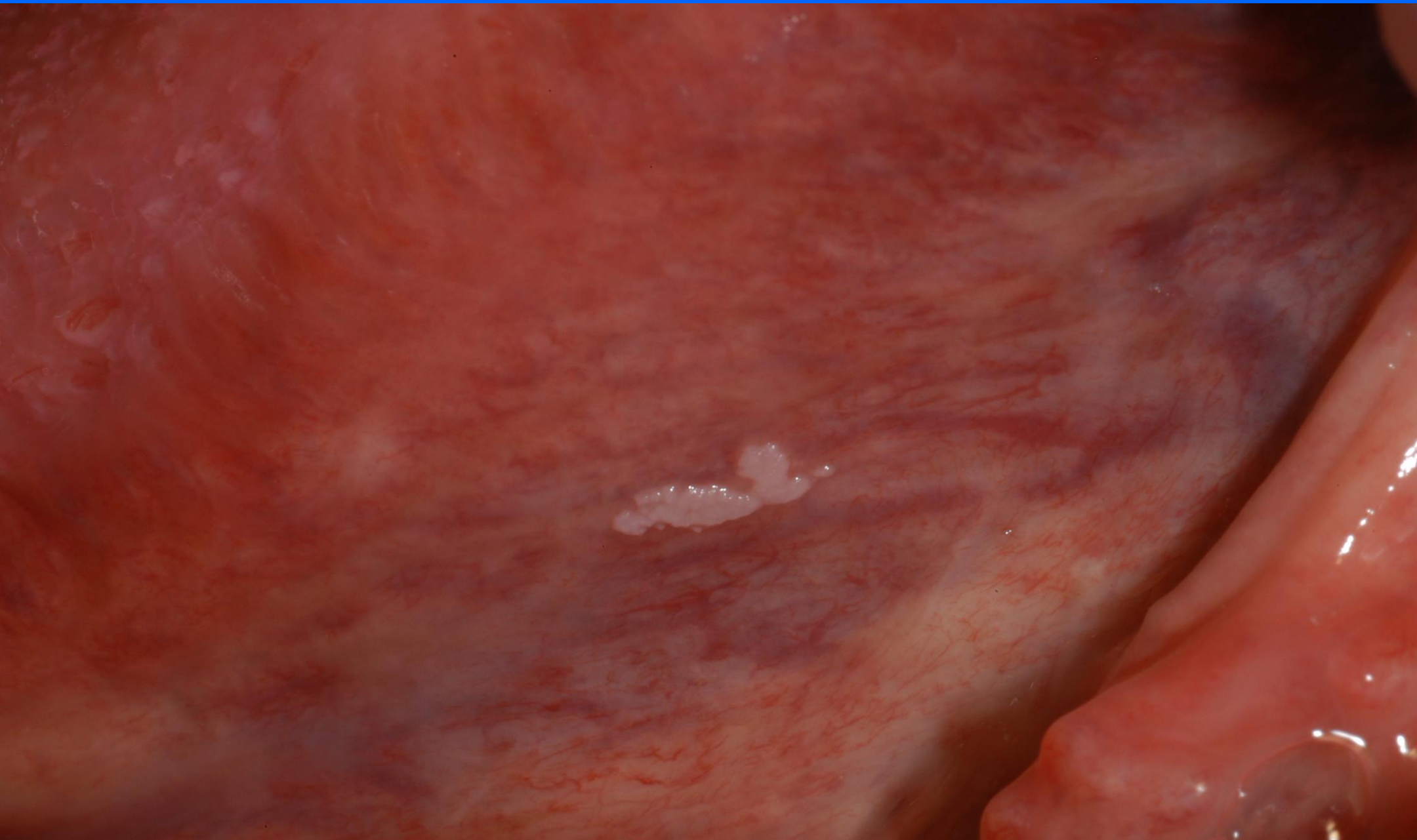
*High risk



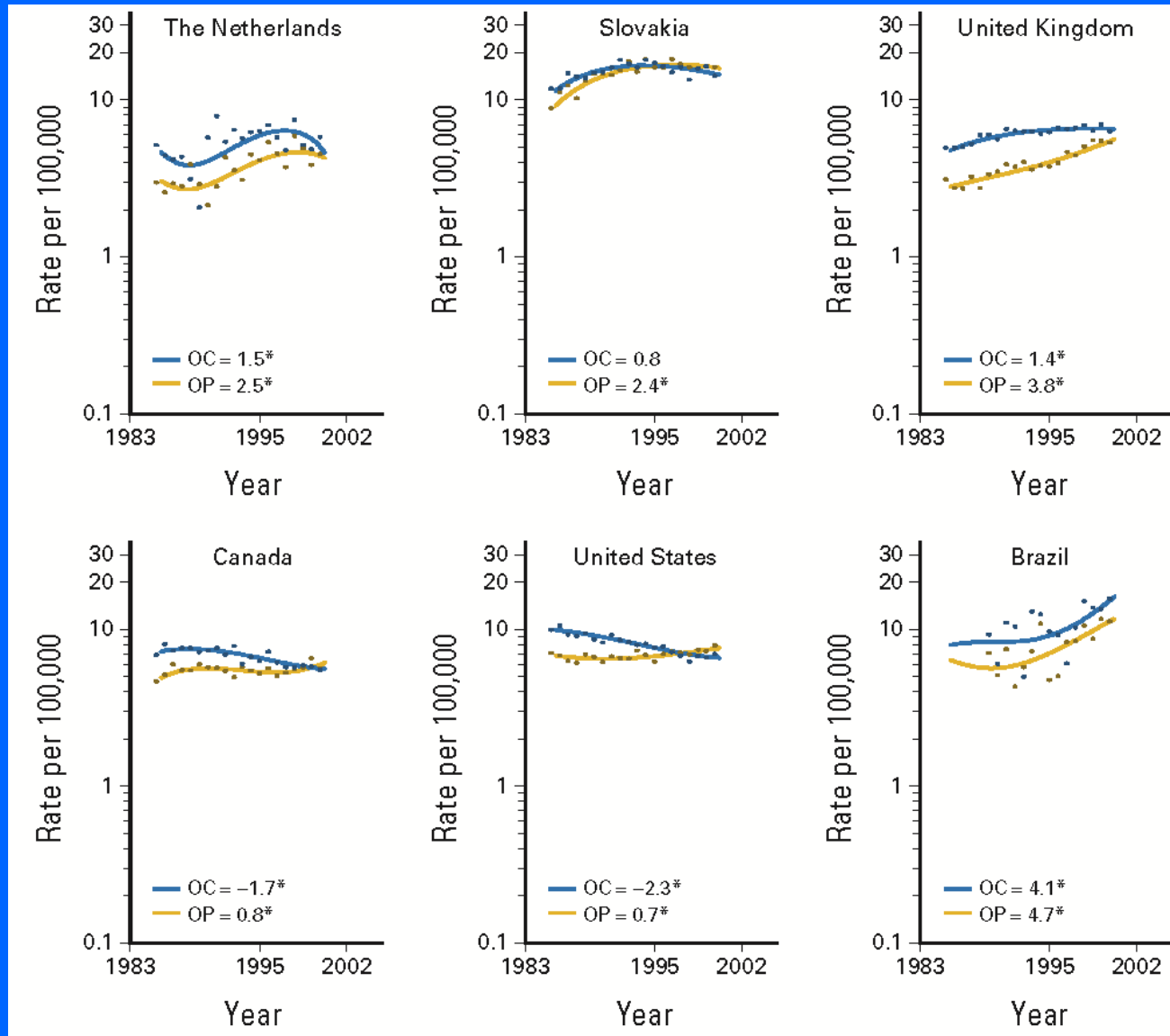




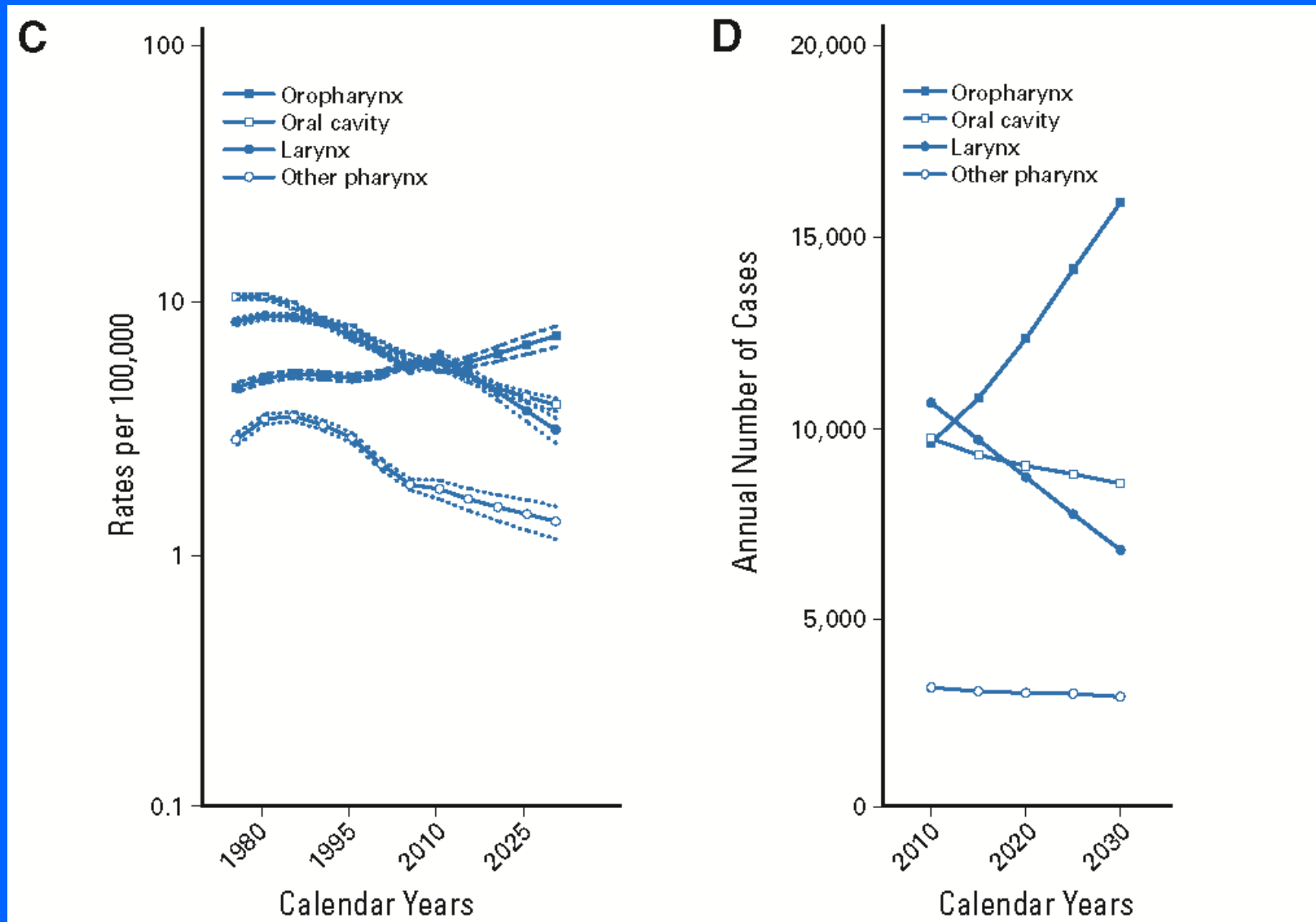




Incidence trends for Oral and OP Ca



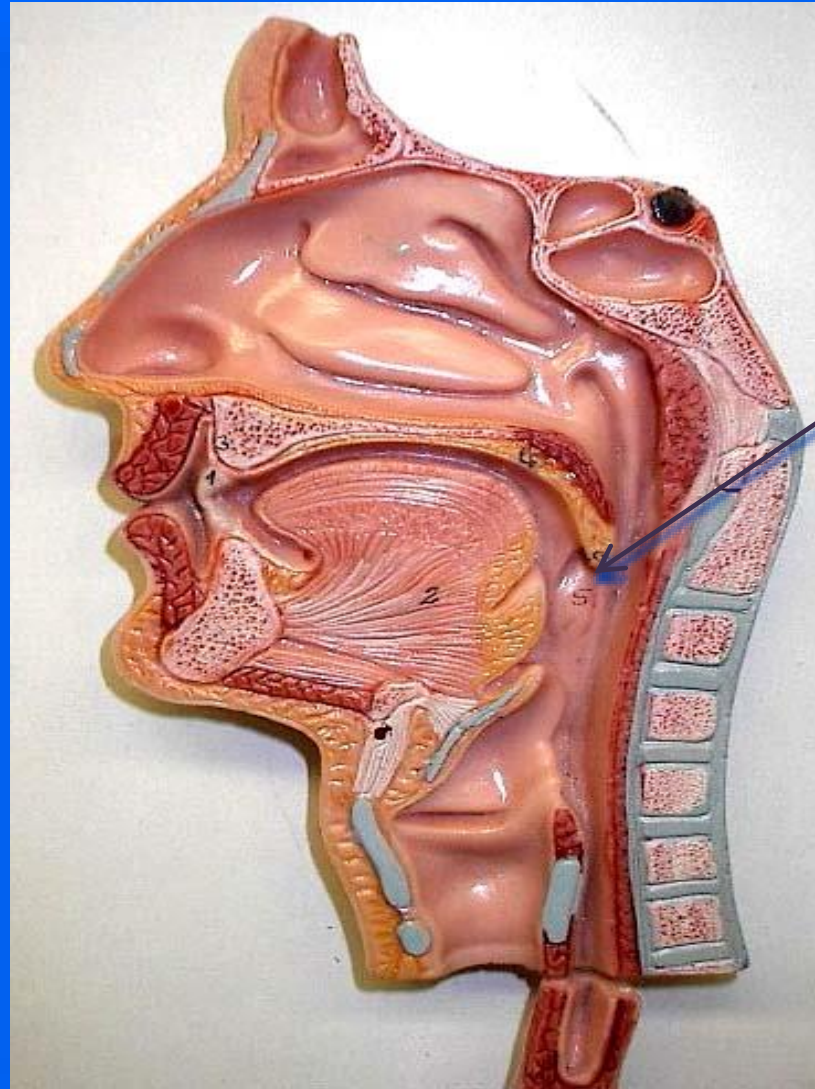
Head & Neck Ca Incidence Projections



Oropharyngeal cancer (OPC) and HPV

- HPV-Ca connection 1st in cervical dysplasia/cancer (2008 Nobel prize: Dr. Harald zur Hausen)
- HPV thought to be **major** risk factor for OPC since early 1980's
- 2007: WHO recognizes HPV 16 as a cause of OPC
- Smoking less frequent factor in OPC compared to oral cancer

HPV in tonsillar cancer



Oropharynx
~80-90%

OPC (tonsillar Ca): A tale of two HPV settings

HPV - negative

- Minority of cases (10%)
- Males (2 to 3:1)
- **Smoking (80-90%)**
- Alcohol synergistic effect
- Unrelated to sexual history
- Incidence: **decreasing**

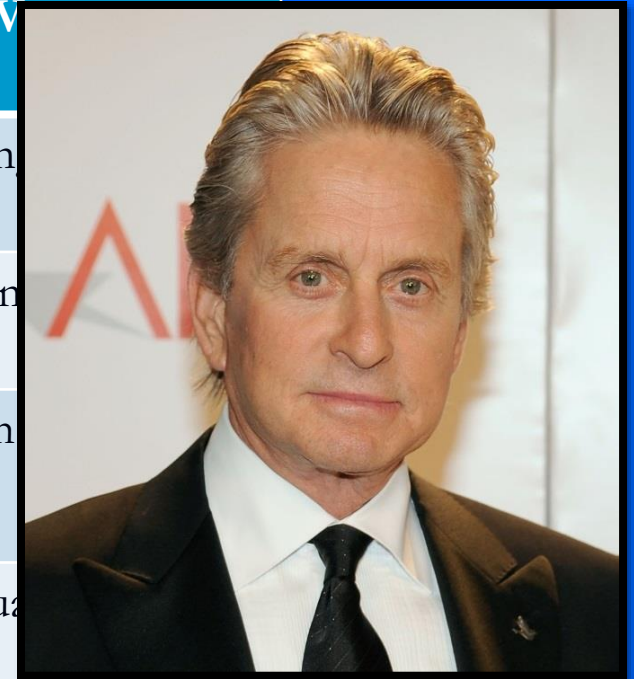
HPV - positive

- Majority of cases (~ 90%)
- Males (4 to 5:1)
- Smoking (50-65%)
- Alcohol not a significant factor
- Related to sexual history
- Incidence: **increasing**

HPV- vs. HPV+ OPSCC



	HPV-	HPV+
	Falling	Rising
	Older	Younger
Immunologic	Low	High
	Tobacco, alcohol	Sexual
Survival	Worse	Better



How is HPV acquired?

- Mode of acquisition:
 - **Sexual (oral-genital) contact** (primary route)
 - Vertical transmission (perinatal): mostly via vaginal delivery
 - Saliva/deep kissing: rare

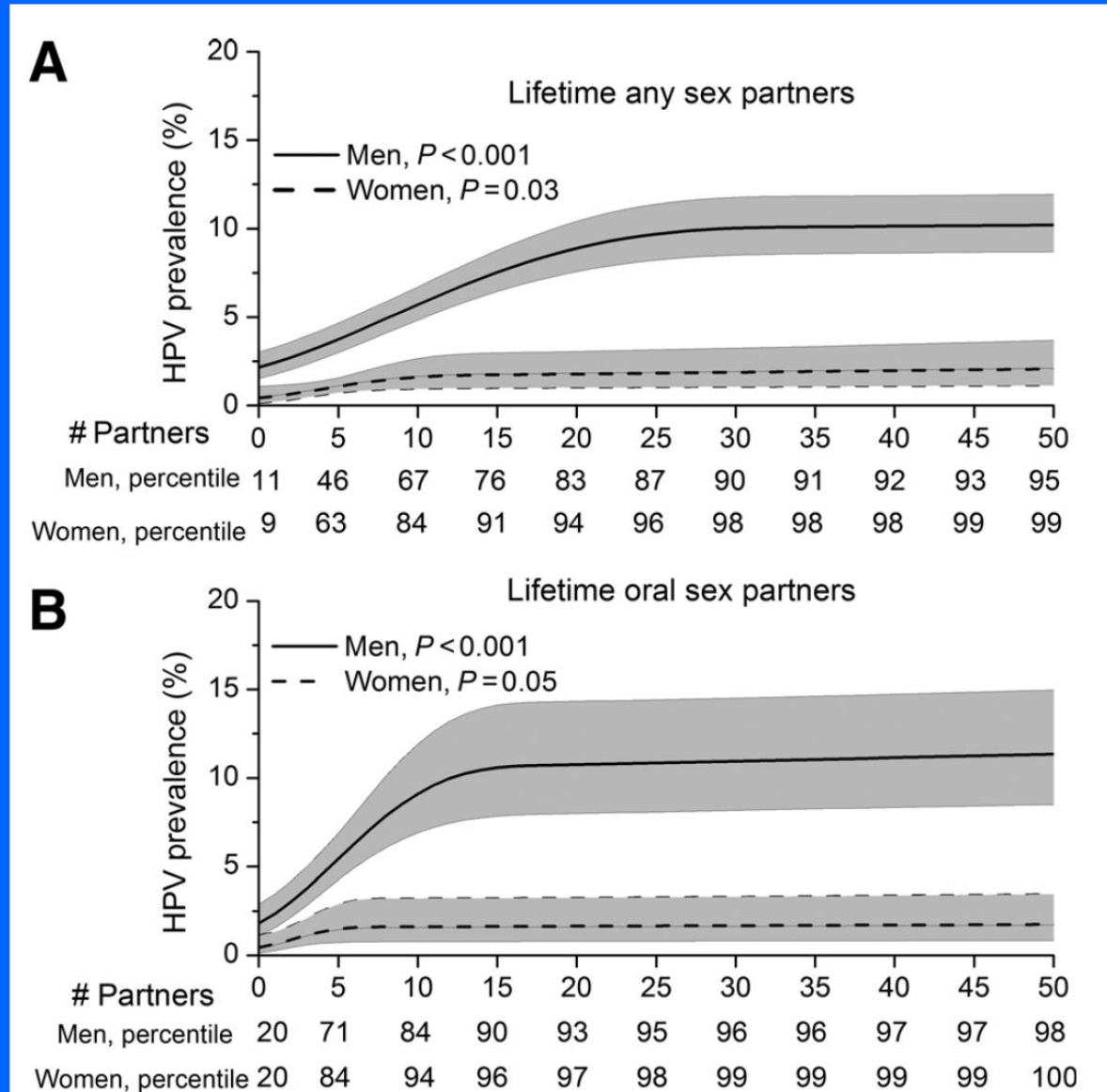
Oral and tonsillar HPV: Prevalence and incidence

- New US infections (2021): ~13 million people/yr
- Oral/tonsillar HPV prevalence in US (2017)*:
 - 11.5% males, 3.2% females
 - 7.3% males, 1.4% females with high-risk HPV
 - 7 million men, 1.4 million women

*Sonawane K *et al.* Ann Intern Med 2017;167:714-724

Oral HPV Prevalence: higher in males

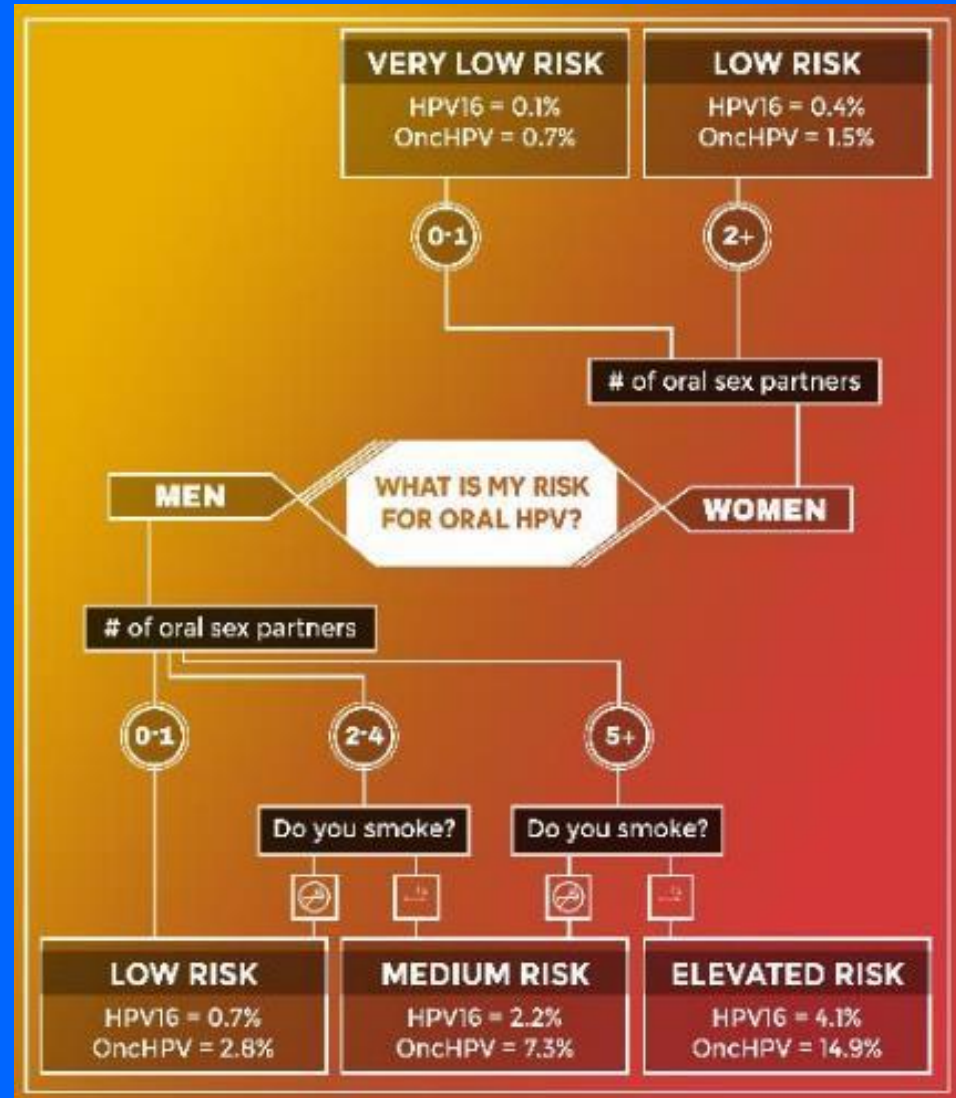
With same # of lifetime sexual partners – **males** have higher oral HPV prevalence.



Risk stratification for oral HPV

Oral HPV prevalence
in U.S. general population

Stratifies into risk groups
by sexual behavior,
tobacco, & sex



Types of HPV infection

- **Transient:** most common, infection often clears with no lesions, both high & low-risk HPV
 - Low-risk HPV types may produce benign lesions: verruca (wart), squamous papilloma, genital wart (condyloma)
- **Chronic:** more frequent with high-risk HPV, in immunosuppressed patients; males slower to clear virus compared to females

Detecting HPV infection

■ Transient carrier (common)

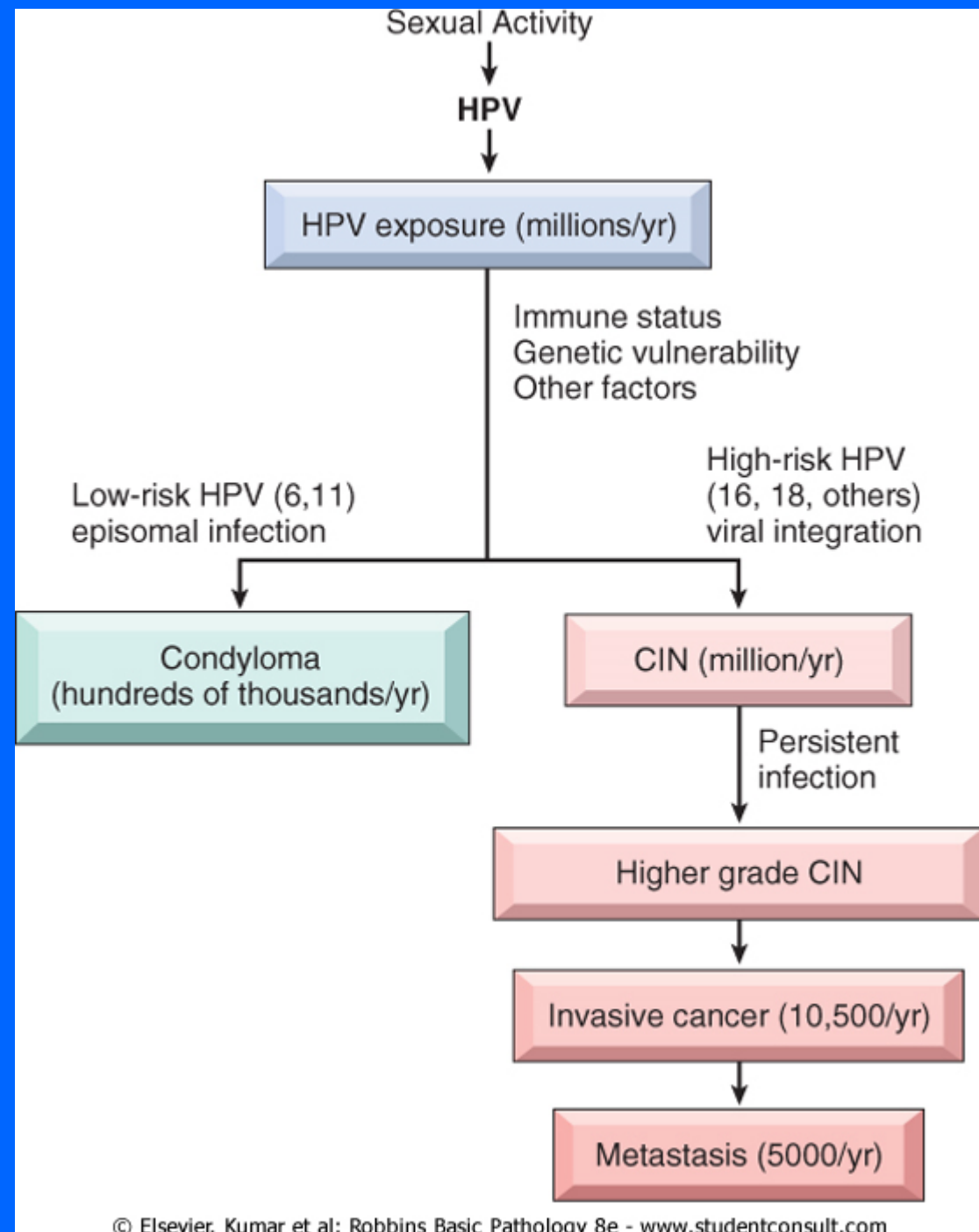
- Antibody status becomes positive
- Presence in mucosa; *in-situ* hybridization or polymerase chain reaction (PCR)
- High-risk HPV is cleared in most patients, gender dependent (females: 6 months; males: up to 3 years)

■ Chronic carrier (uncommon)

- Persistent infection by high-risk HPV strongly associated with both cervical Ca and tonsillar Ca

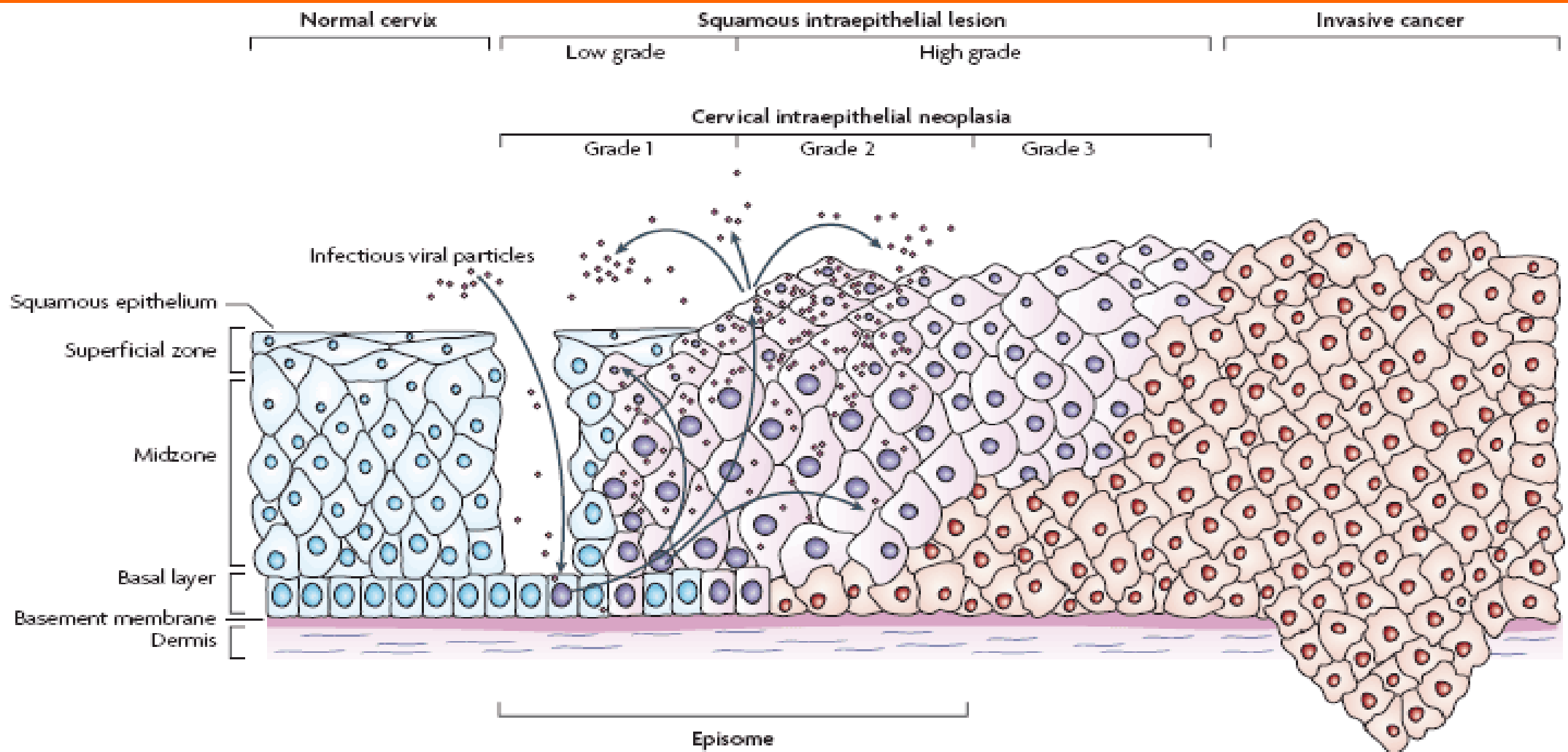
Cervical HPV Infection

- Many ♀ harbor HPV, but only a minority develop cancer

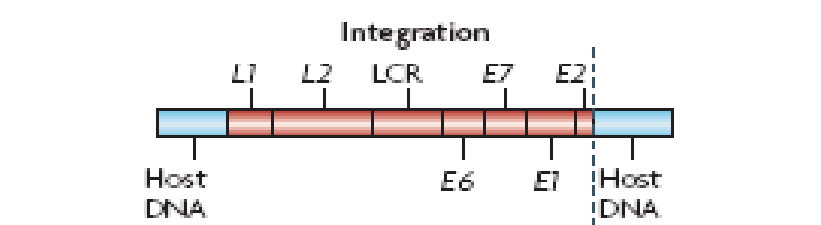
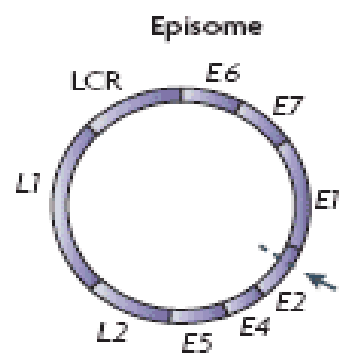


What is high-risk HPV?

- Tonsillar Ca: HPV-16 (~ 90%) and 18
- Also 31, 33, 45, 52, 58; among other subtypes
- HPV DNA becomes integrated into host cell DNA through oncoproteins E6 and E7
- Cells proliferate unchecked and over-express **p16**, a protein readily detected in infected epithelial cells by immunohistochemistry (IHC)

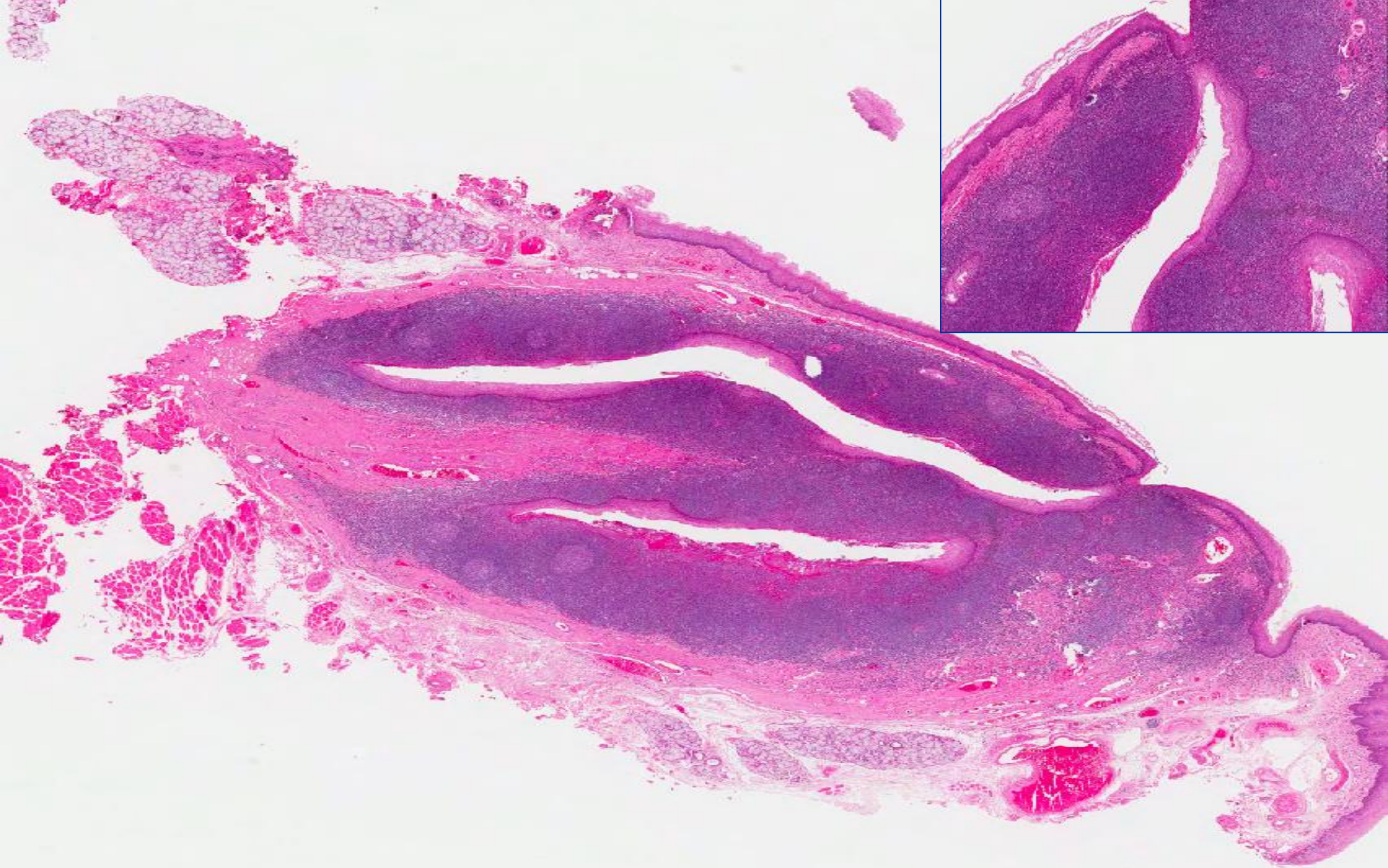


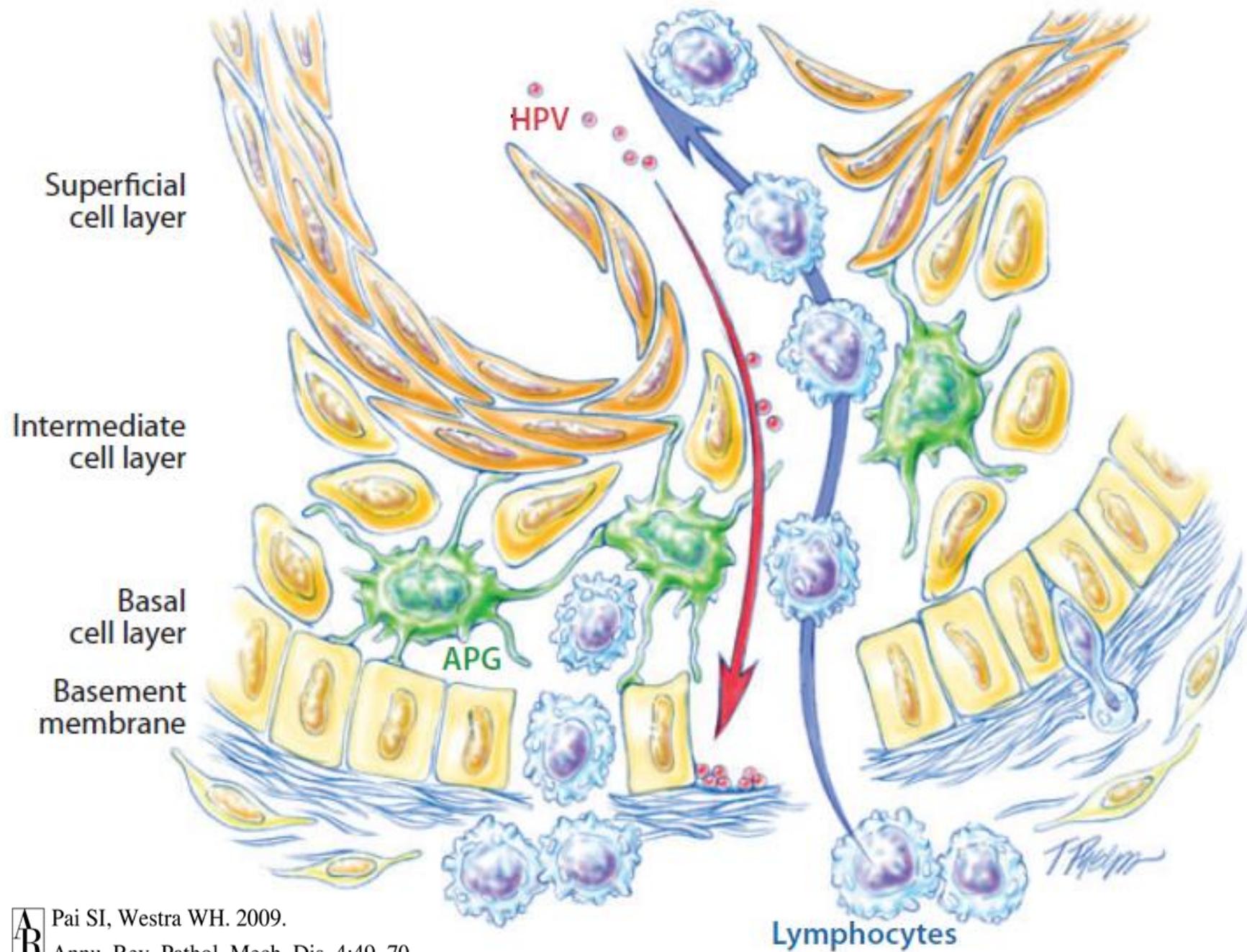
- Nuclei with episomal viral DNA
- Nuclei with integrated viral DNA
- Normal nuclei
- Overexpression of E6 and E7
- Expression of early and late genes



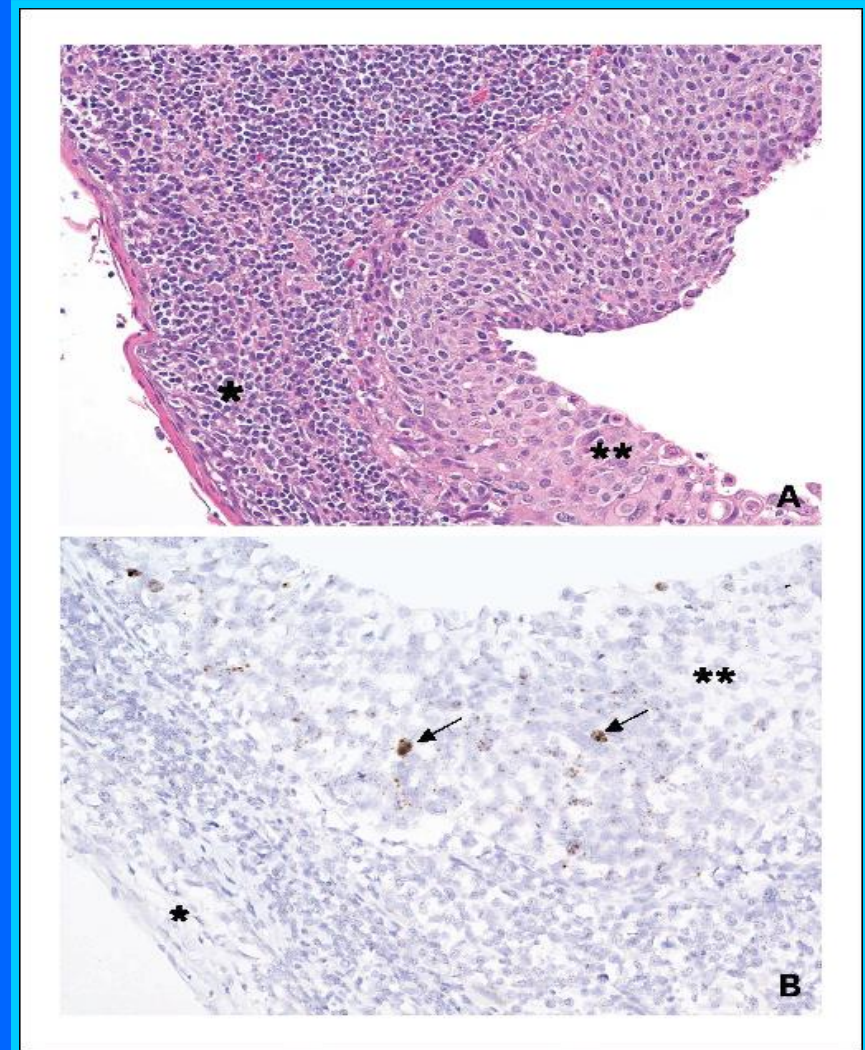
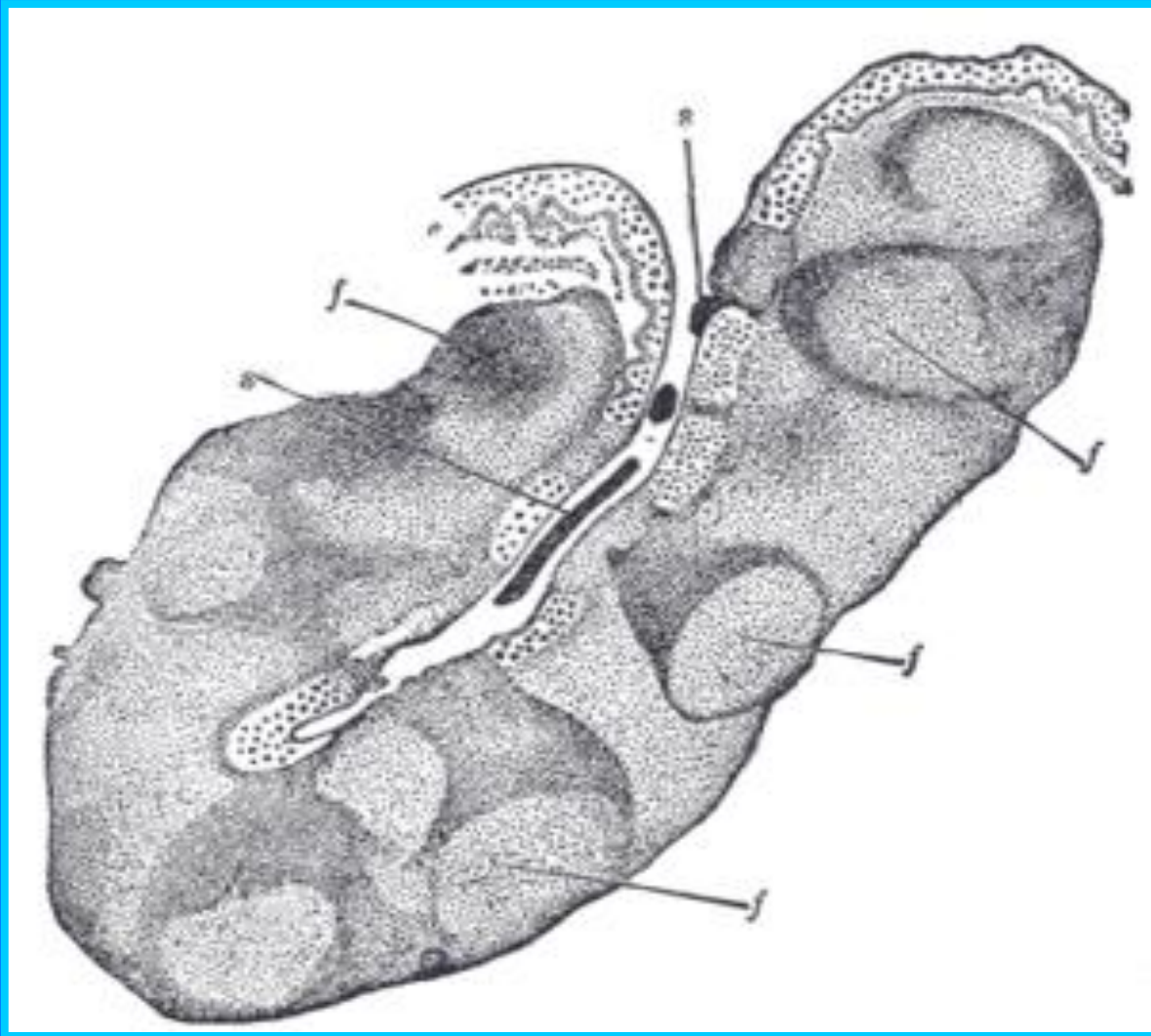
What is a high-risk, HPV-related lesion?

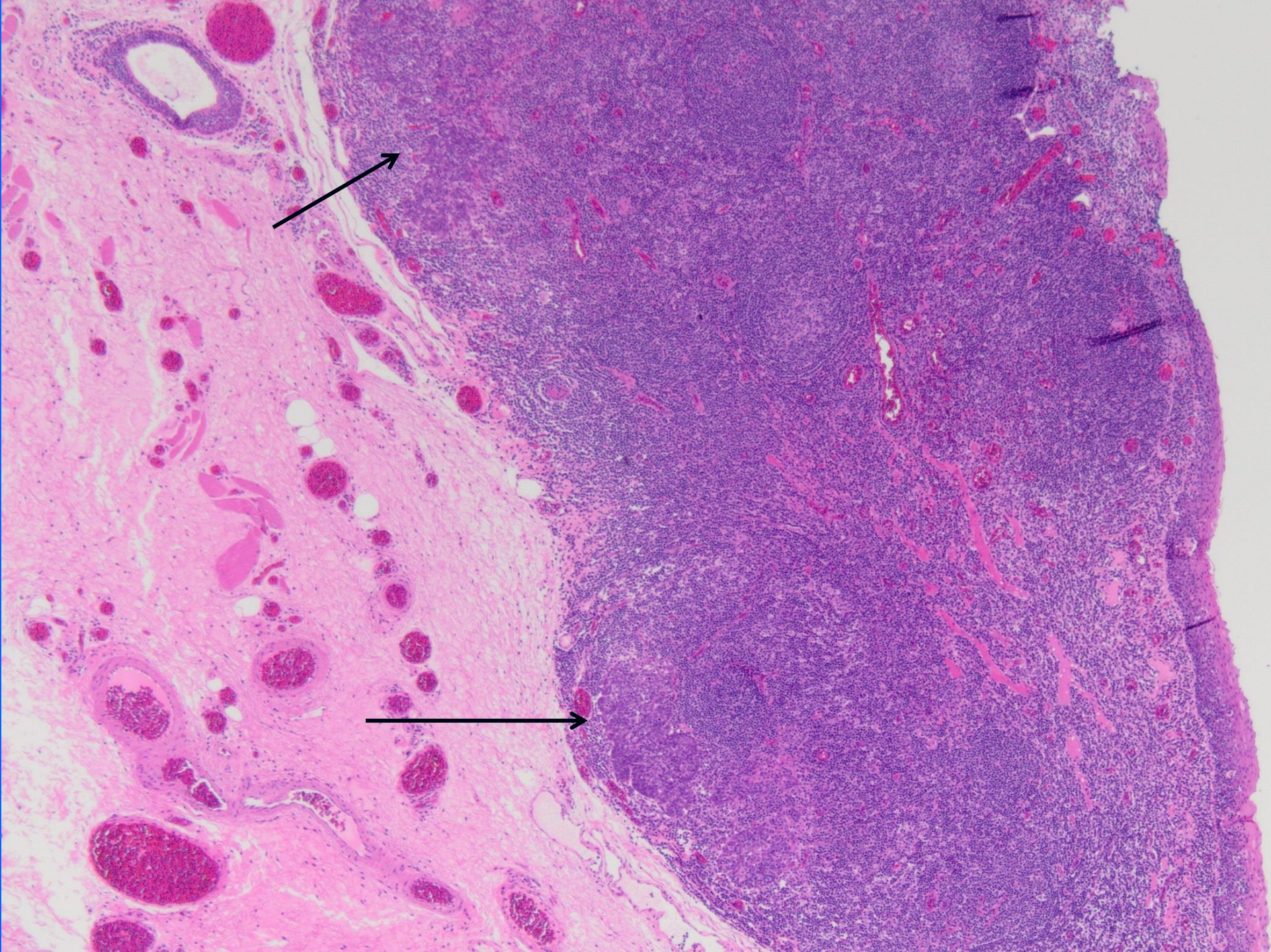
- Immunohistochemistry evidence of p16?
 - p16⁺ not totally specific to HPV integration, may be elevated by other mechanisms
- *In-situ* hybridization?
 - cDNA probe will show both integrated HPV DNA and episomal HPV DNA
- To “prove” HPV-related lesion, need **both**:
 - Evidence of high-risk HPV DNA & evidence of viral DNA integration (p16⁺)

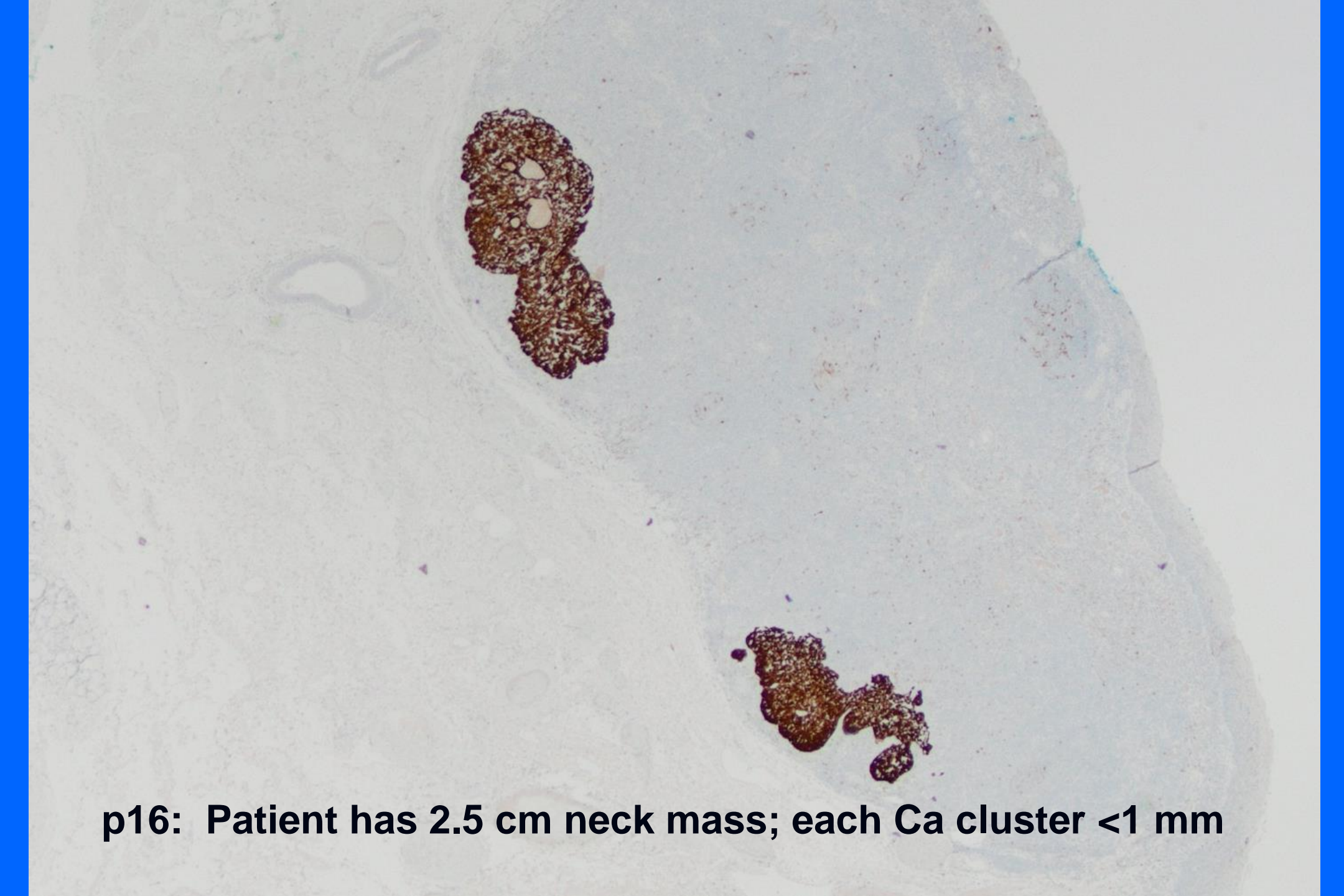




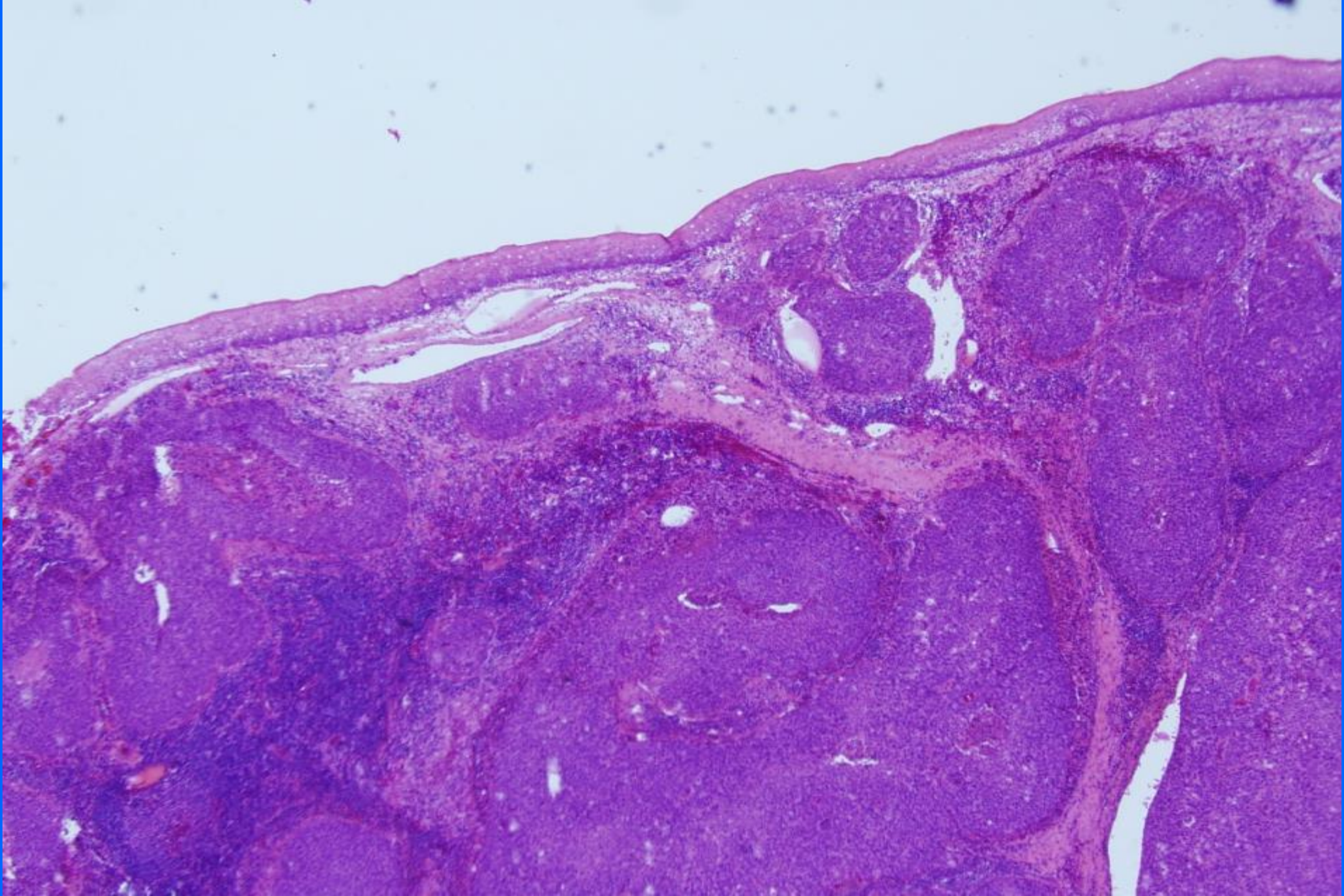
HPV infection deep within tonsillar crypt



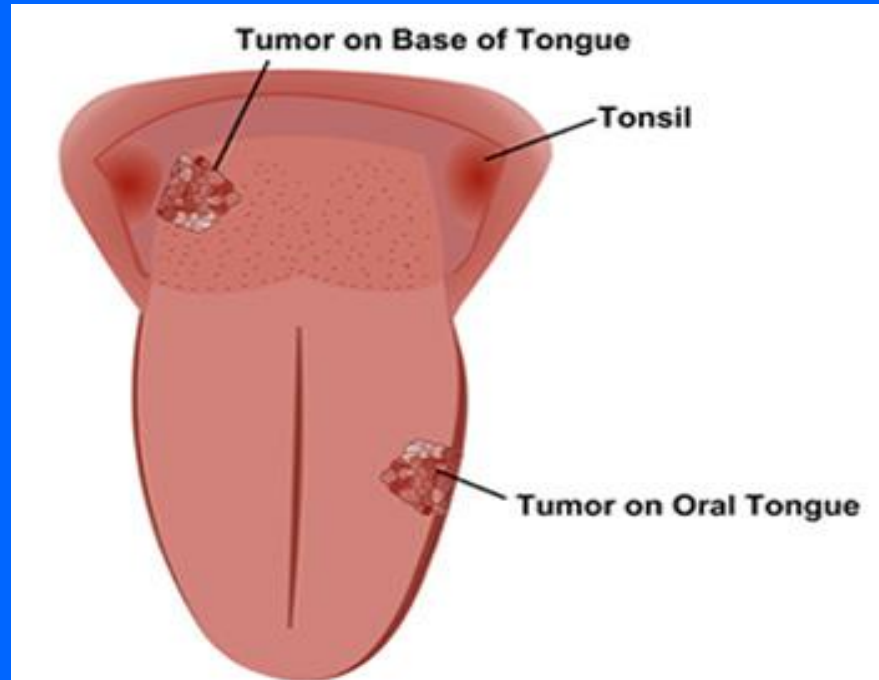
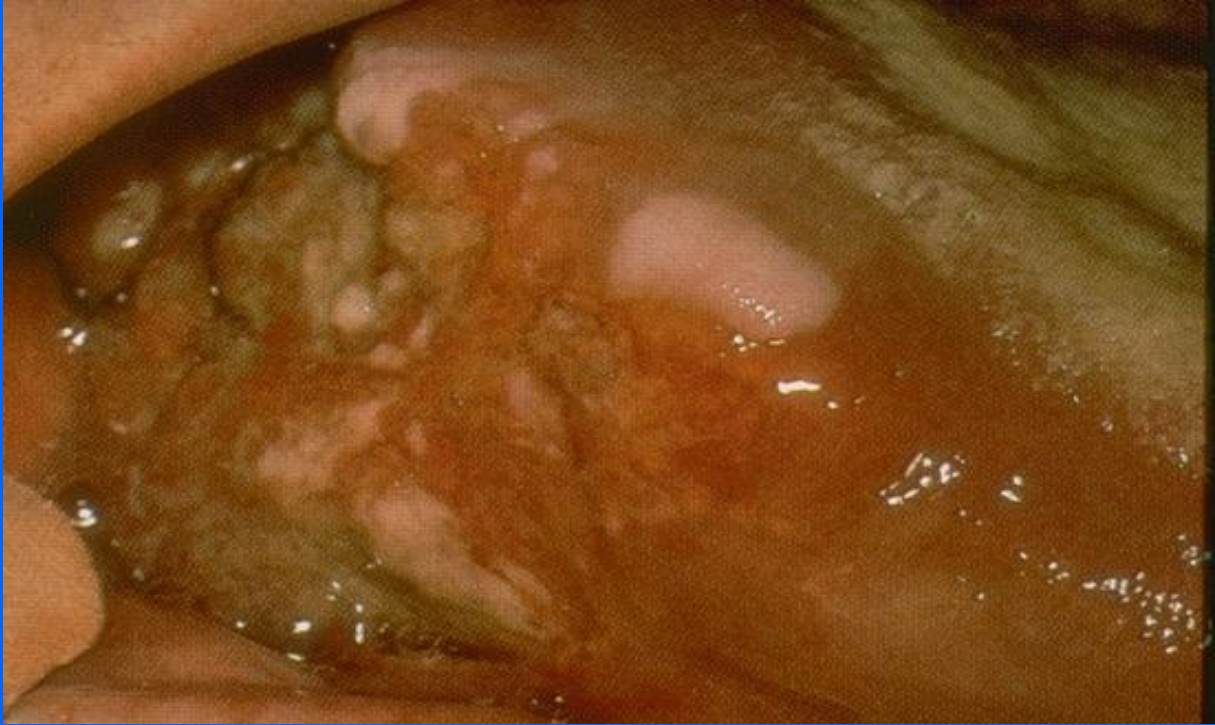
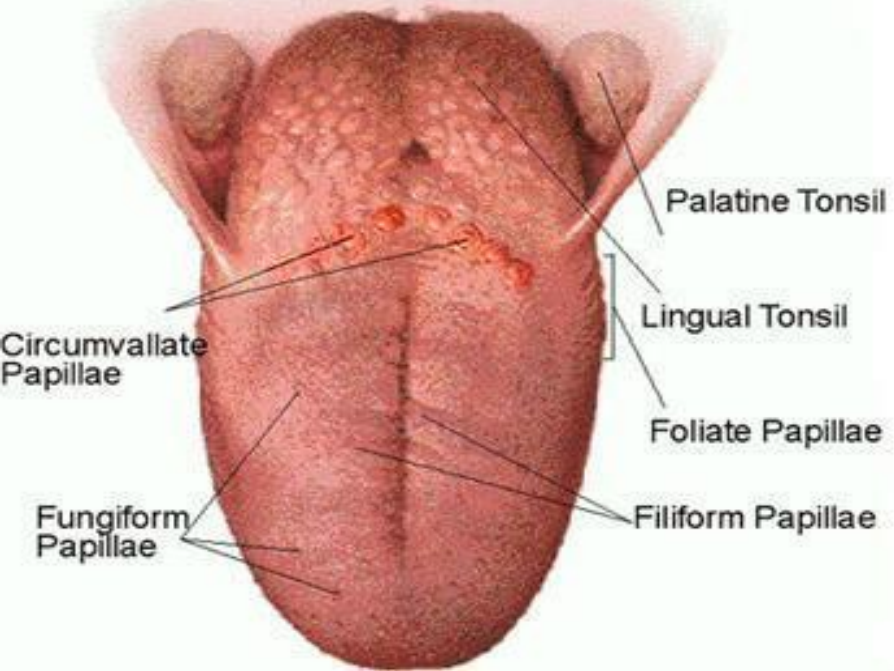




p16: Patient has 2.5 cm neck mass; each Ca cluster <1 mm



Tongue

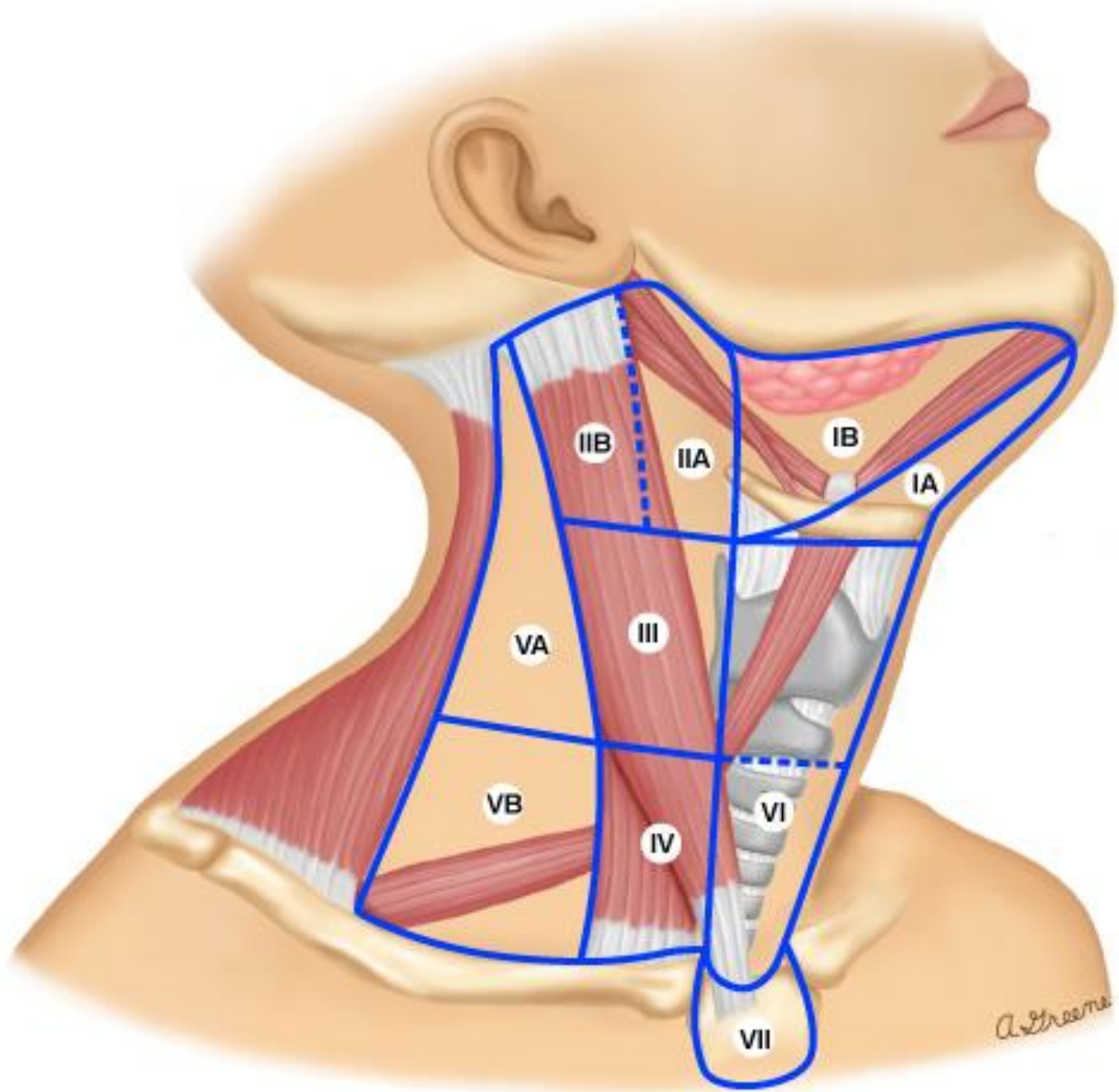


Tonsillar Ca (OPC) vs Oral Cancer

Distinct HPV patterns

HPV and OPC

- ~80-90% are positive for HPV
- Persistent high-risk HPV infection associated with 6-50X increase risk for OPC
- Lymph node metastases at time of presentation:
80-85%



Tonsillar Cancer

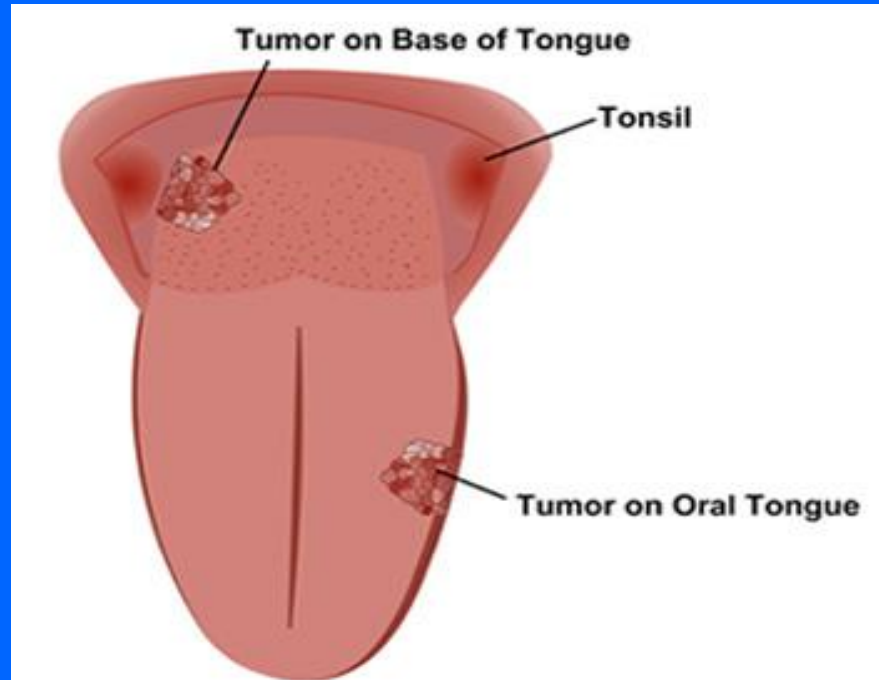
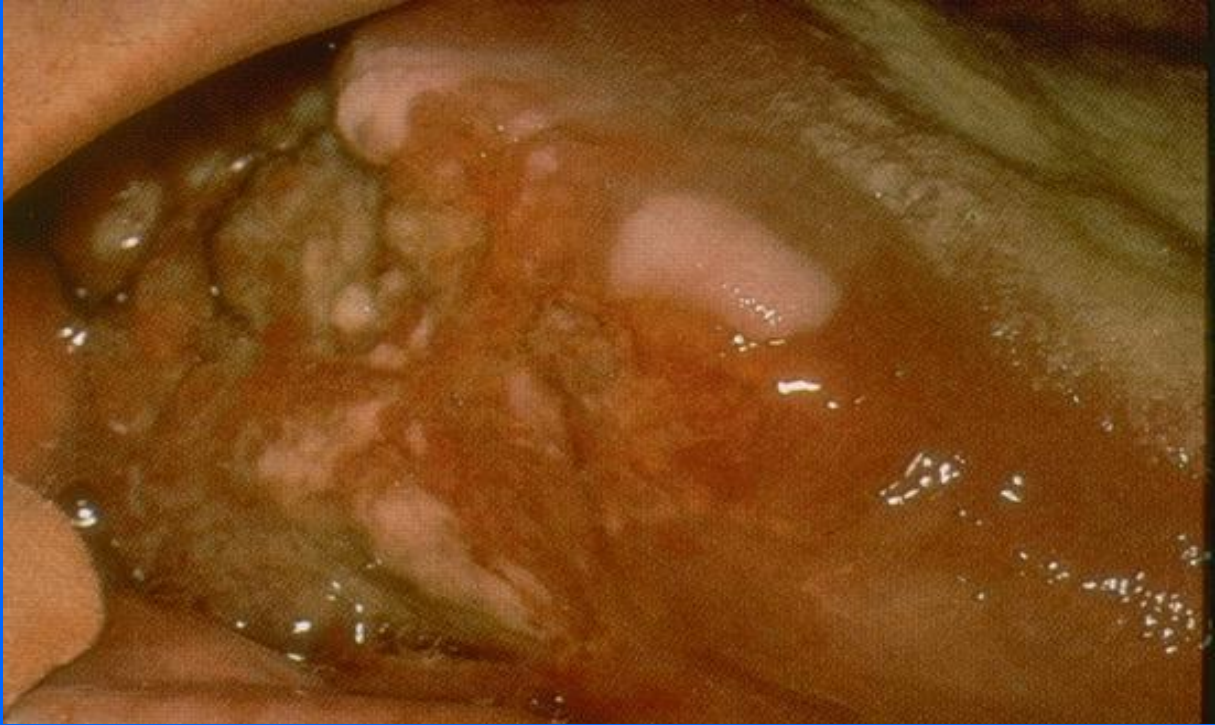
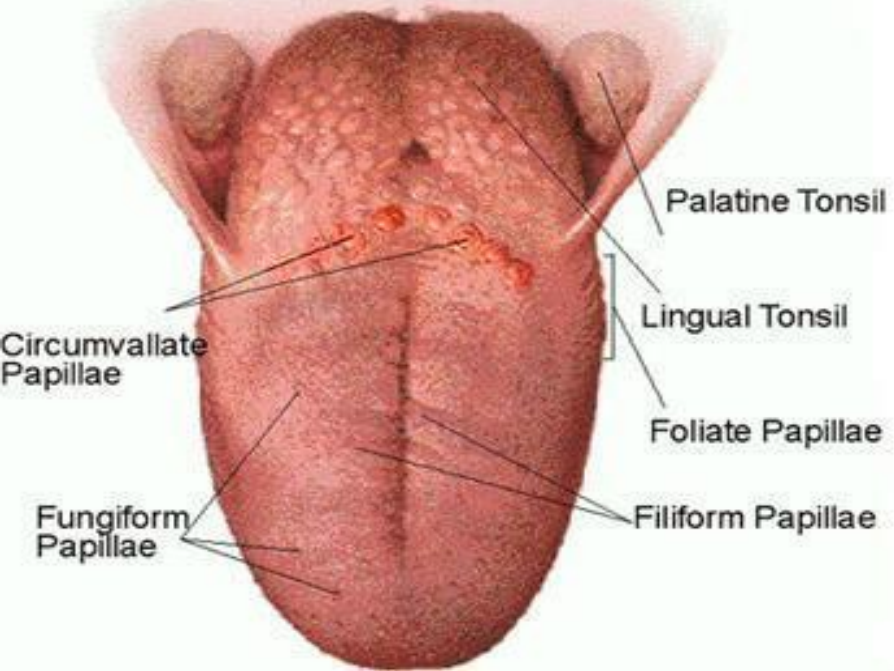
The slightly good news with HPV+ OPC

HPV and Tonsillar Ca (OPC)

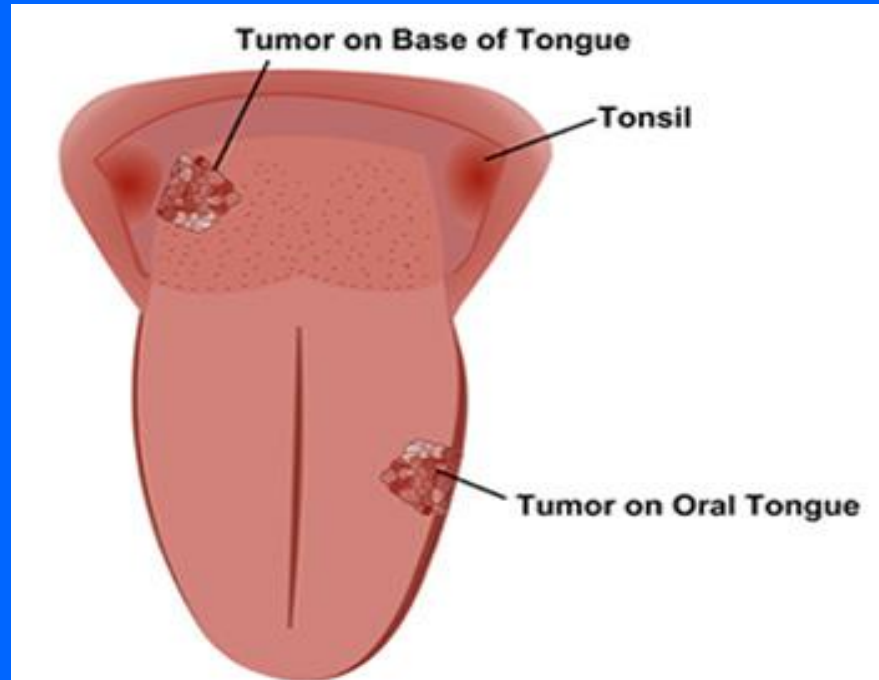
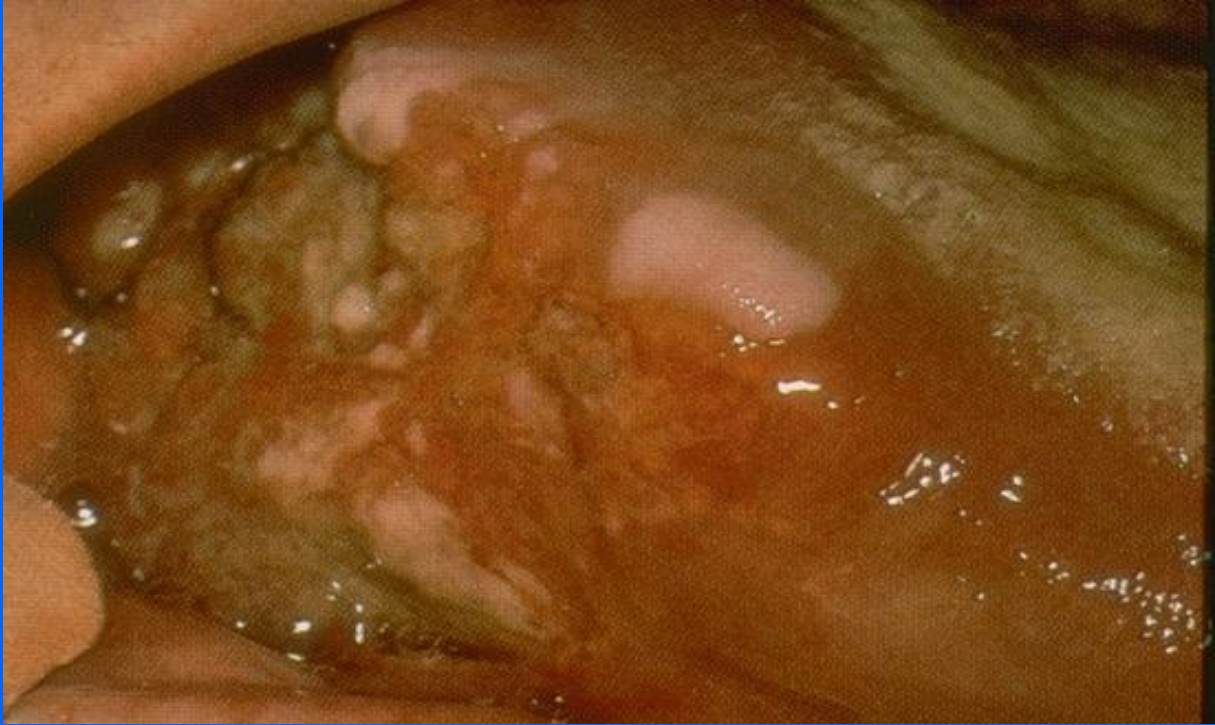
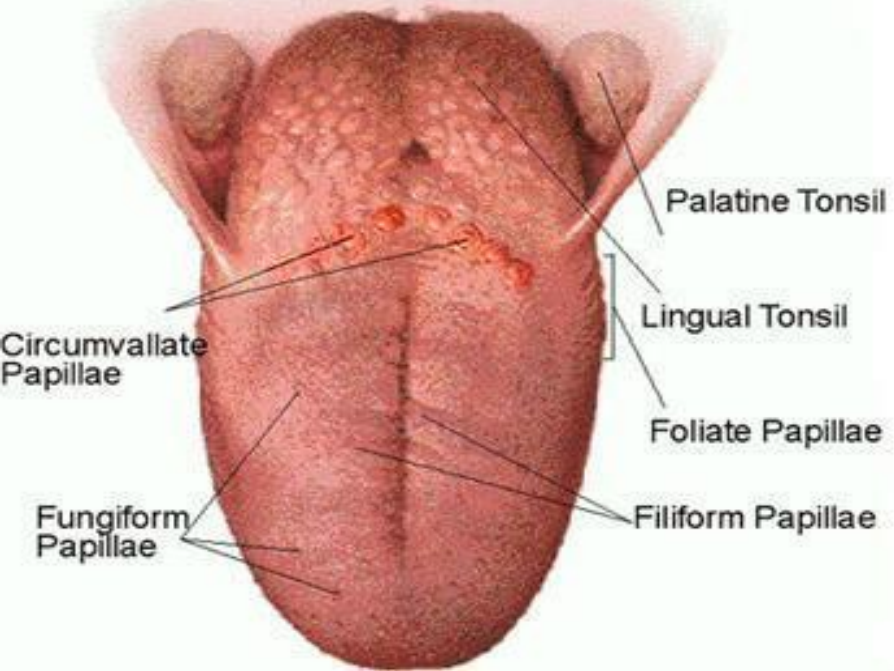
- HPV+ OPC associated with improved 2 yr survival; 92% vs 46% for HPV- OPC*
- 3-5X lower risk overall & disease-specific mortality
- Result: new de-escalated treatment protocols
- However: Smoking negates this improved survival

*Zhu G *et al* JAMA Otolaryngology (2022) 148: 70-9

Tongue



Tongue





What about HPV vaccines?

HPV-related cancers

- Roughly 47,000 HPV-related cancers are diagnosed annually in US
 - 26,000 among women
 - 21,000 among men

<https://www.cdc.gov/cancer/hpv/statistics/cases.htm>

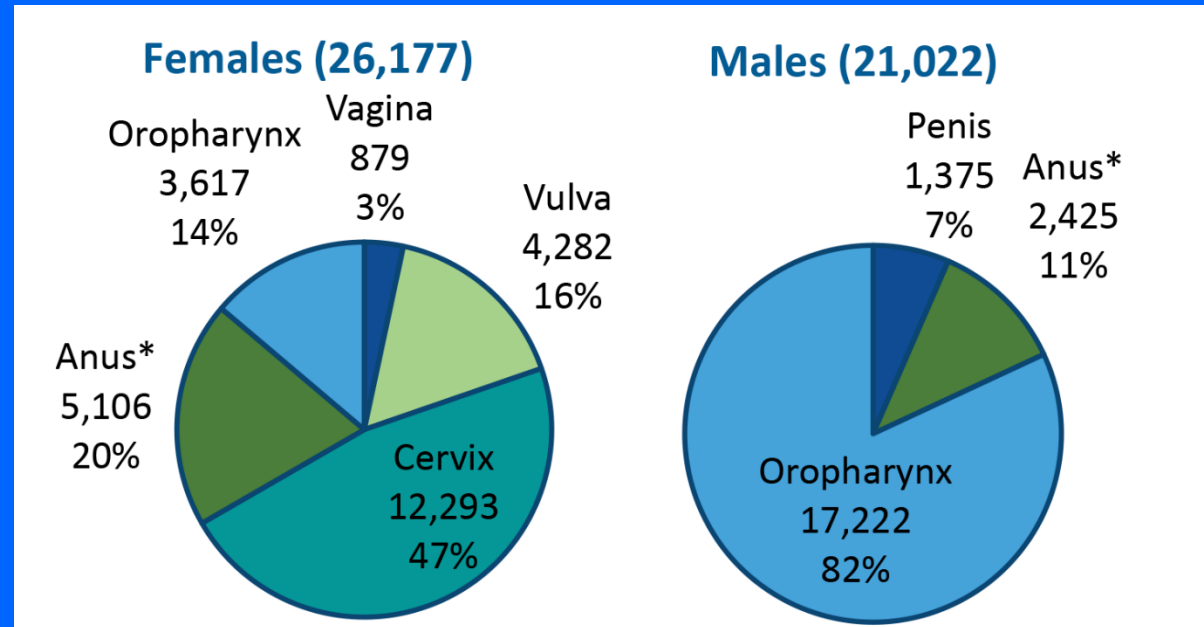
HPV-related cancers in the US

Cancer site	% Associated with HPV
Cervical	>99%
Vaginal	50%
Vulvar	50%
Penile	50%
Anal	>90%
Oropharyngeal	~90%

US HPV-related Cancers, by Sex 2015-2019 data

Most HPV-related cancer is:

- Cervical – in women
- Oropharyngeal – in men



Currently, in US:

Cervical cancers < Oropharyngeal cancers

12,293

20,839

(17,222 in men; 3,617 in women)

HPV Vaccines

- First vaccines developed primarily to prevent cancer:
 - Cervical dysplasia and cervical cancer
 - Oropharyngeal (tonsillar) and other anogenital cancers ???

HPV Vaccines

- Gardasil (Merck): quadrivalent recombinant vaccine against HPV 6, 11, 16, 18 (2006)
- Cervarix (GlaxoSmithKline) bivalent against 16, 18 only (2009), **off US market 2016**
- Gardasil 9 (Merck): Gardasil + 5 additional subtypes (31, 33, 45, 52, 58) (Dec 2014)
 - 9-14 yrs (2 doses)
 - Routinely 11-12 yr olds with Tdap, MenACWY, flu
 - 15-26 yrs (3 doses)

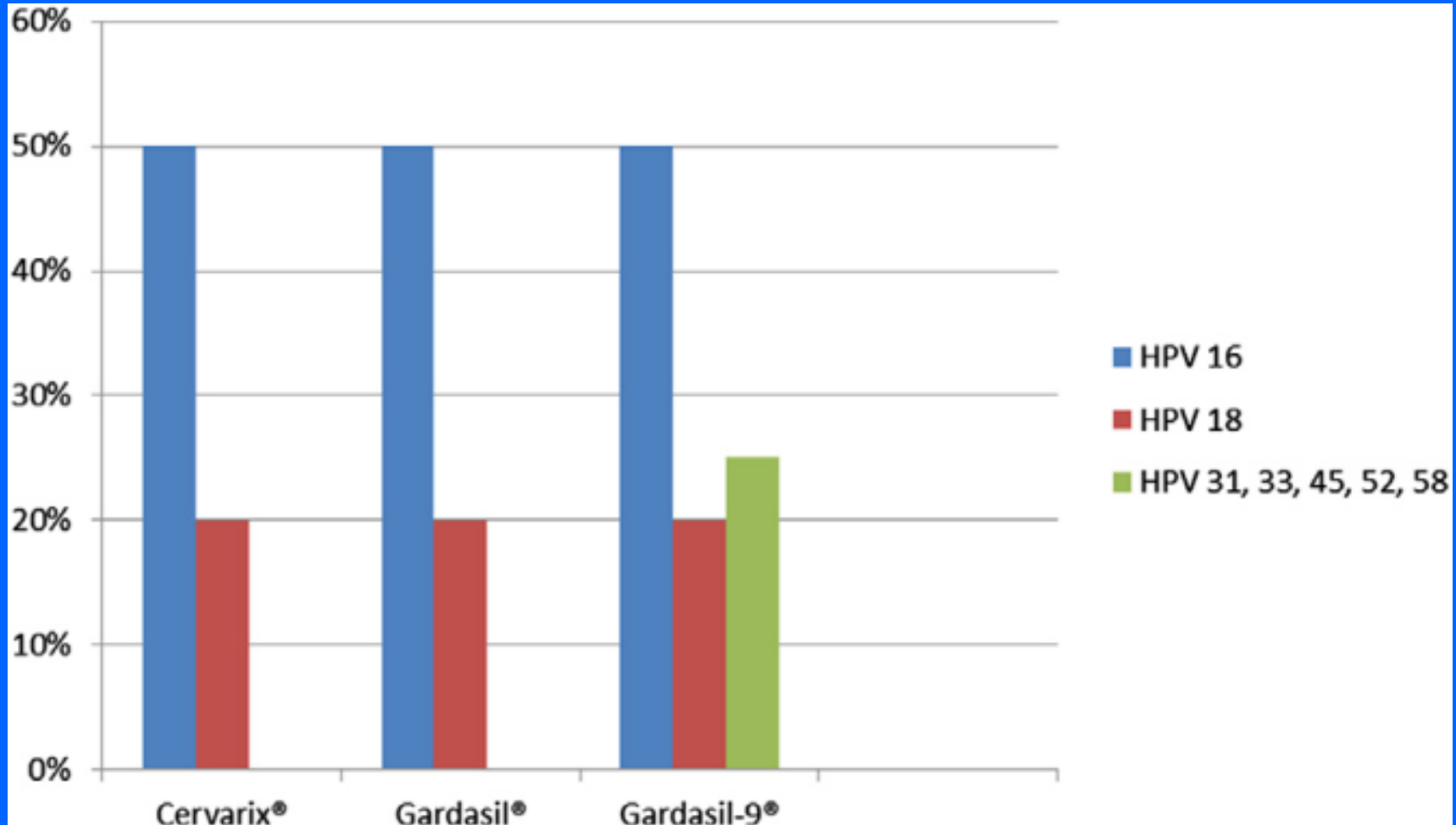
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HPV Vaccines

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 - 9-14 yrs (2 doses)
 - Routinely: 11-12 yr olds with Tdap, MenACWY, flu
 - 15-26 yrs (3 doses)
- October 2018; FDA expanded approval to older adult males and females:
 - 27-46 yrs (3 doses)

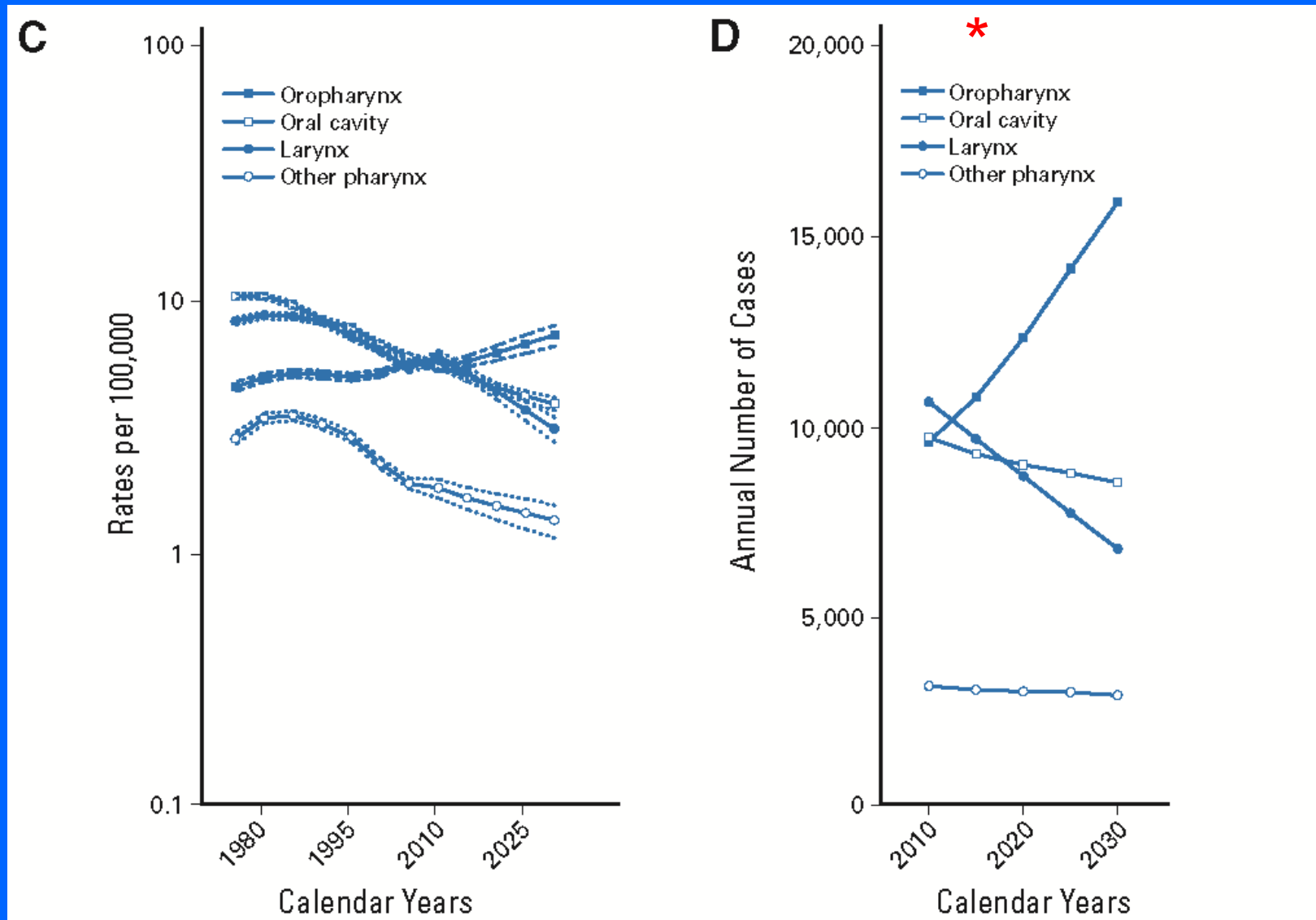
HPV types/vaccine and frequency in cervical cancer worldwide



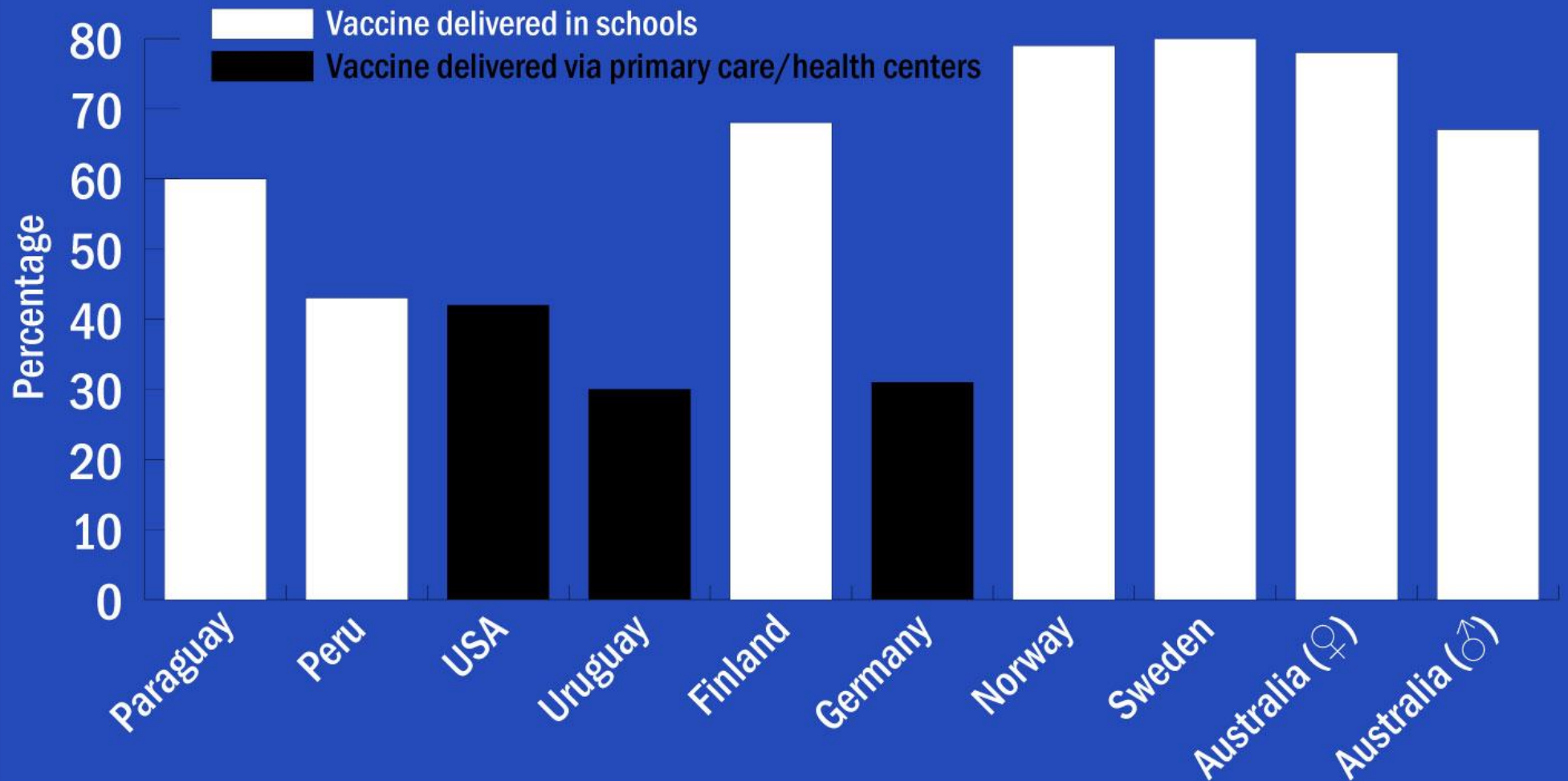
HPV Vaccines

- Both Gardasil and Cervarix have shown:
 - Evidence for prevention of cervical dysplasia
 - Evidence for reduction of cervical cancer
- Broader coverage of Gardasil 9 has shown improved protection
- Impact on oropharyngeal carcinoma: ???

Head & Neck Ca Incidence Projections

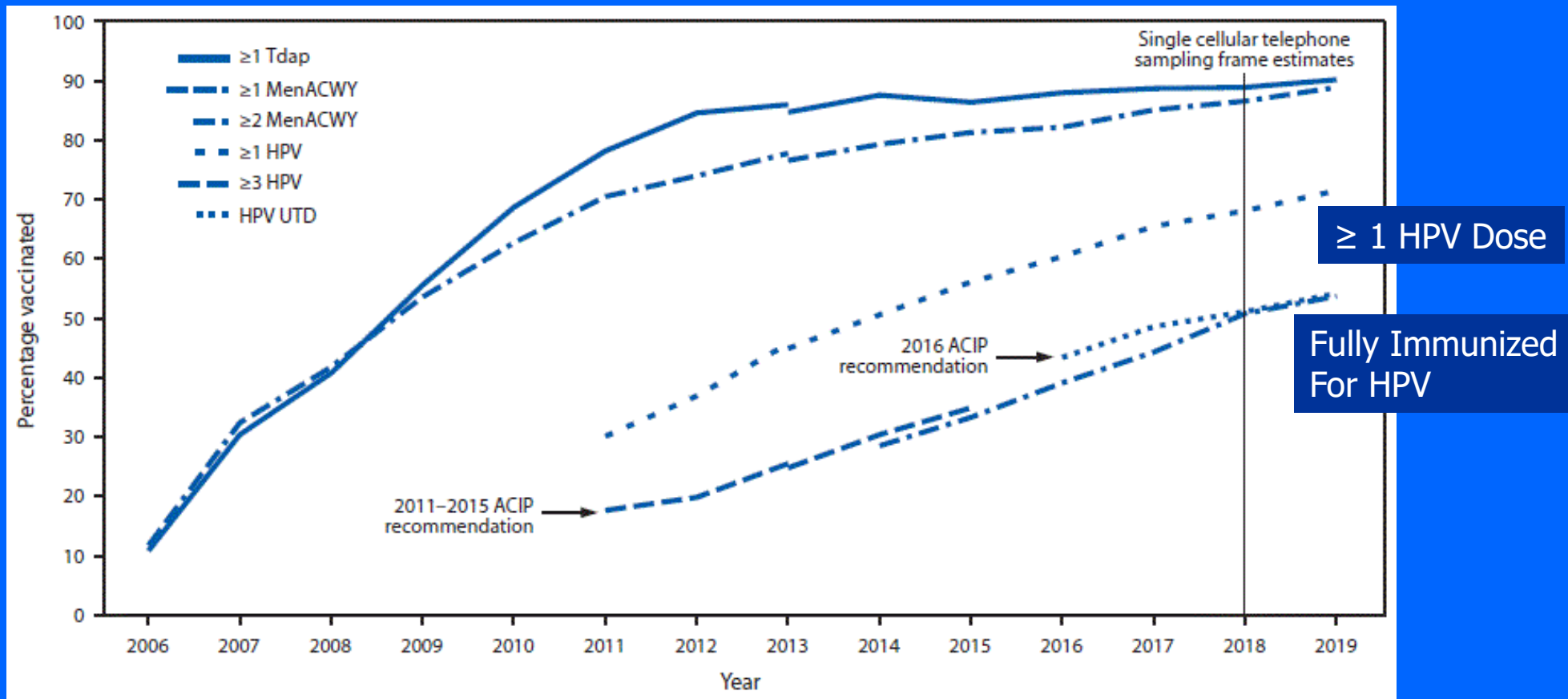


Reported Coverage Among National Immunization Programs, Three-Dose Schedule (2017)



Vaccination coverage with selected vaccines among 13–17 year olds in US 2006–2019 ¹⁰³

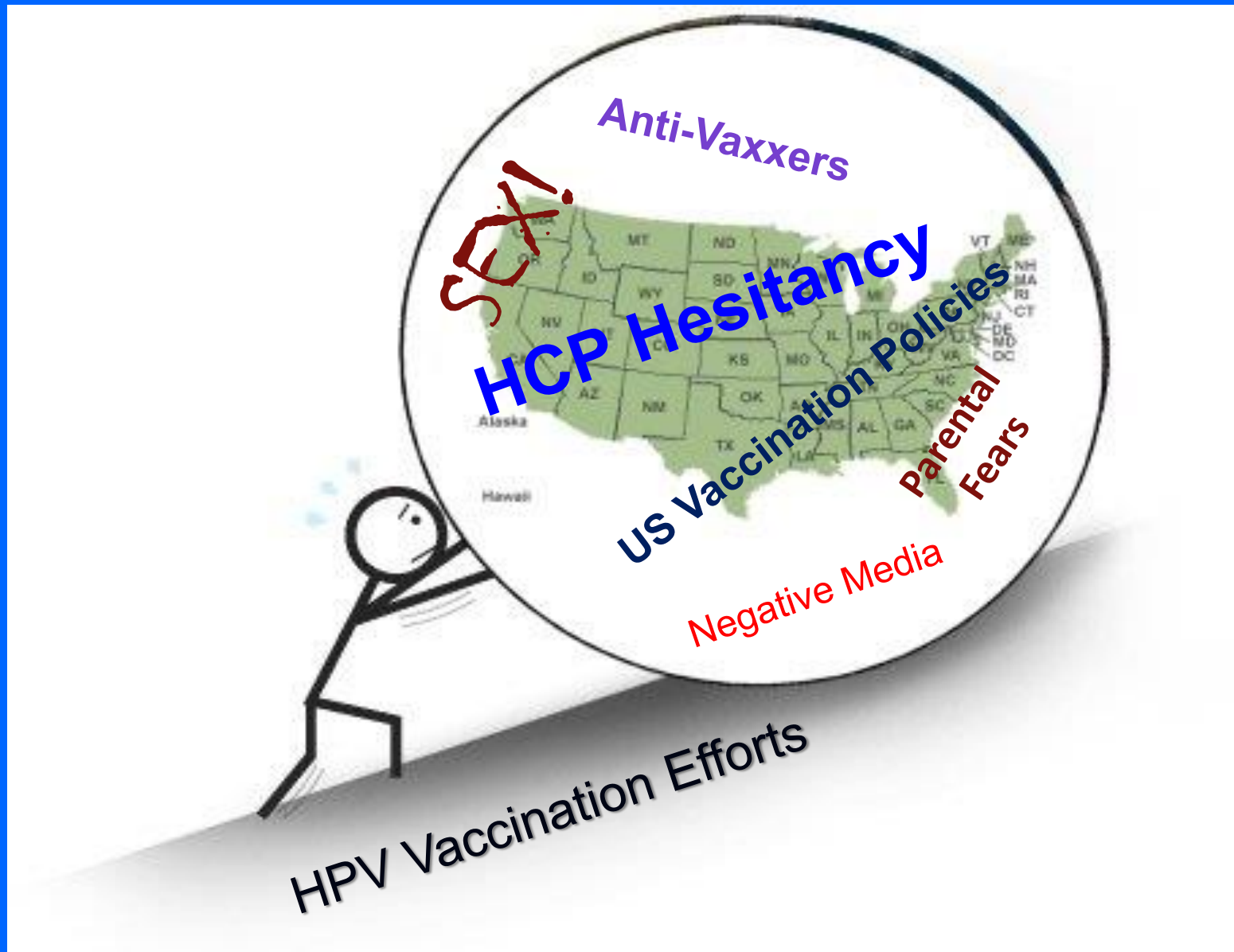
HPV vaccination uptake increasing, but still lags behind other childhood vaccines



Vaccines

- Jan 11, 2017: 69 US Cancer centers issue joint statement of support for HPV vaccination.
 - *“Although many HPV-associated cancers are preventable with the safe and effective vaccine, HPV vaccination rates across the US remain low. Current rates are 41.9% in girls and 28.1% in boys, which is far below the 80% goal set by the US Department of Health and Human Services for 2020.”*

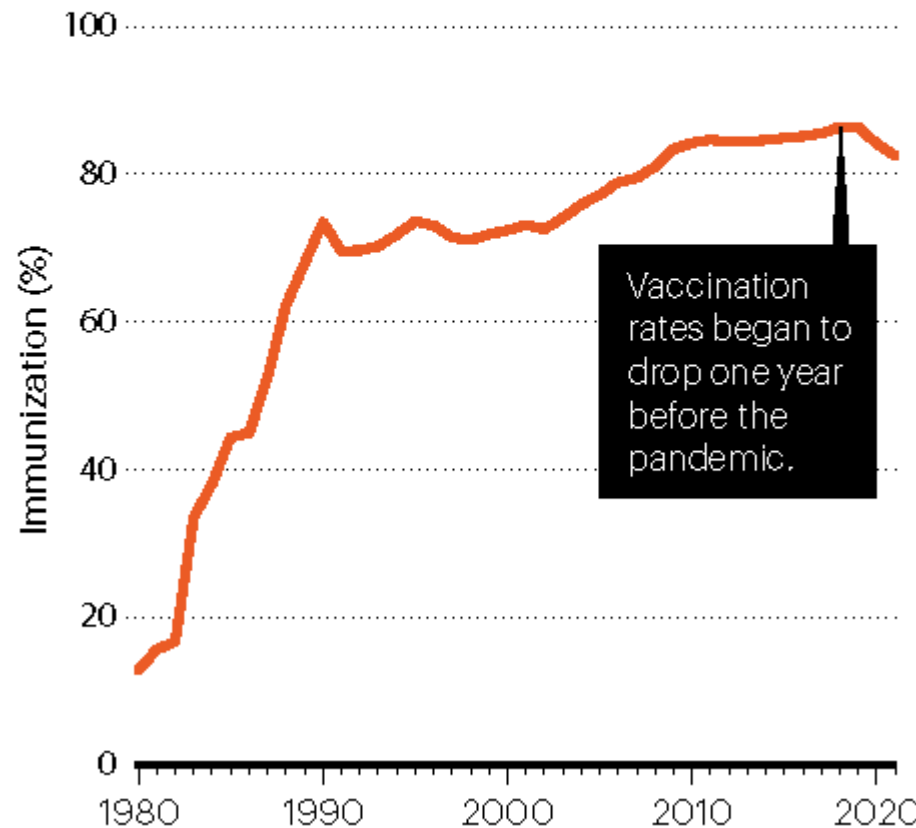
Why such poor HPV vaccination uptake in US?



Measles vax rate; US children 1980-2022

LOST PROGRESS

After years of steady gains, measles vaccination rates in children aged 12 months to 23 months stalled in the years before the COVID-19 pandemic. Since the pandemic, the progress of the past decade has essentially been erased.



HPV Vaccines

Impact on Sexual Behavior

- Not associated with earlier entry into or riskier sexual behavior^{1-5,7}
- Didn't reduce patient concerns about or importance of safe sexual behaviors⁶
- Not associated with markers of sexual behavior⁷

1. Pediatrics 2014;133:404-11

2. J Ped Adolesc Gynecol 2014;27:67-71

3. Am J Prev Med 2012;42:44-52

4. J Community Health 2013;38:1010-4

5. Health Econ Policy Law 2020;15:477-495

6. Arch Ped Adolesc Med 2012;166:82-8

7. Hum Vaccin Immunother 2016 ePub DOI:10.1080/21645515.2016.1141158

HPV Vaccine efficacy

- Confirmed by 2015 report of multinational clinical trial; nearly 20,000 women (15-25 yrs), 4 years follow-up
- Cervarix protection against HPV 16/18 was 90% and against other high-risk strains nearly 50%,
- More effective in younger patients (15-17 yrs vs 18-25 yrs); higher Ab titers, greater protection
- **Vaccine safety confirmed***

HPV Vaccine efficacy

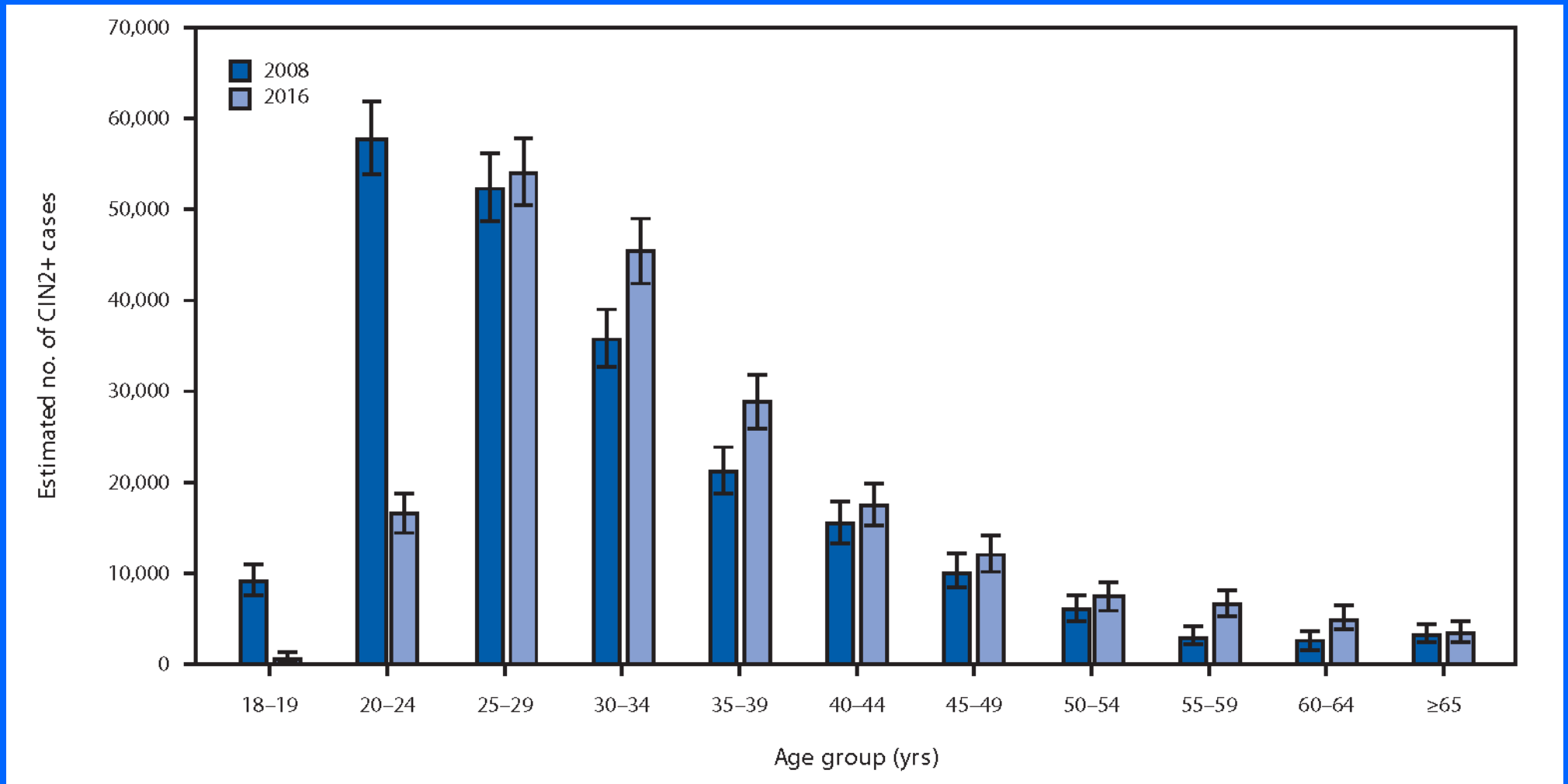
- Nov 2017 multinational Phase 3 study; 14,215 women, 16-26 yrs of age, examining protection from HPV infection and dysplasia with either Gardasil-9 or Gardasil
- Gardasil-9 provided 97.4% improved efficacy compared to Gardasil for HPV 31,33,45,52 & 58 and comparable protection against HPV 6,11,16 and 18
- Sustained protection over the 6 yrs of the study

Huh WK et al, Lancet 2017 390:2143-59

HPV Vaccine efficacy

- Recently, the vaccine impact on high-grade cervical lesions in the US between 2008 and 2016 was estimated by the HPV-IMPACT working group
 - For 2008, there were an est. 216,000 cases
 - For 2016, there were an est. 196,000 cases
- Significant declines in younger age groups attributable to HPV vaccination

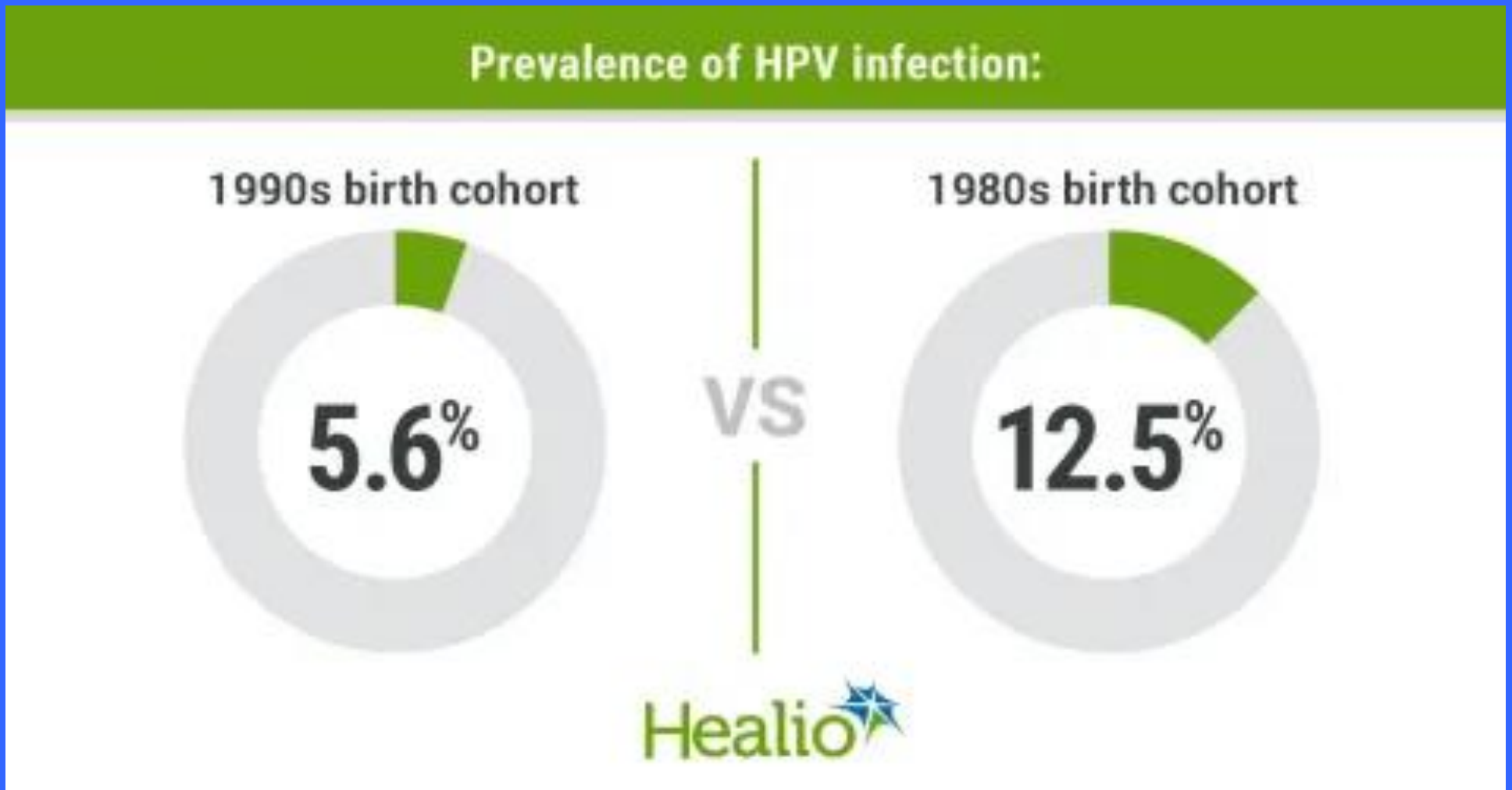
CIN2+ cases by age group: 2008 vs 2016



HPV Vaccine efficacy: latest

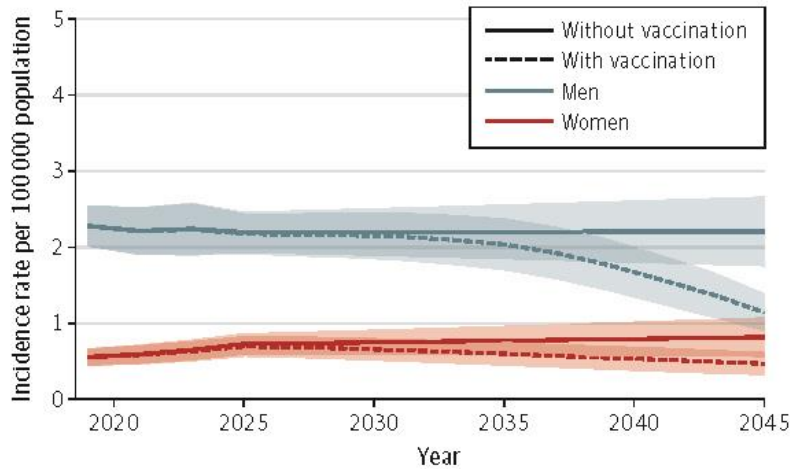
- **August 2022:** comparing vaccine-mediated immunity (born in 1990s) and herd immunity (born in 1980s) on high-risk HPV infection in US women, 18-26 yrs
- Total 2,698 women (1980s: 1,418, 1990s: 1,280)
- Overall: 54% reduction in risk of HPV infection among younger, vaccinated (1990s) cohort
 - Most notable reductions among youngest patients
 - Corresponds to increased vaccine uptake

HPV vaccine reduces cervical infection rate



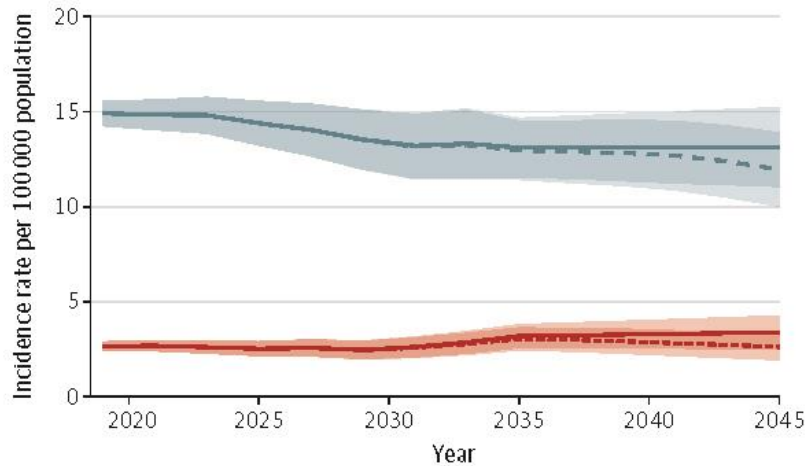
Shahmoradi et al. JAMA Health Forum 2022 3(8):e222706

A Age, 36-45 y



	2018-2019	2024-2025	2034-2035	2044-2045
Men without vaccination	2.3	2.2	2.2	2.2
Men with vaccination	2.3	2.2	2.0	1.1
Women without vaccination	0.6	0.7	0.8	0.8
Women with vaccination	0.6	0.7	0.6	0.5

B Age, 46-55 y



	2018-2019	2024-2025	2034-2035	2044-2045
Men without vaccination	14.9	14.4	13.1	13.1
Men with vaccination	14.9	14.4	13.0	12.0
Women without vaccination	2.7	2.5	3.2	3.4
Women with vaccination	2.7	2.5	3.0	2.6

Tonsillar Ca Incidence Rate Predictions +/- HPV vaccination by sex and cohort age

Zhang et al. JAMA Oncol
doi:10.1001/jamaoncol.2021.2907

JADA

THE JOURNAL OF THE AMERICAN DENTAL ASSOCIATION

GUEST EDITORIAL:
Looking Forward
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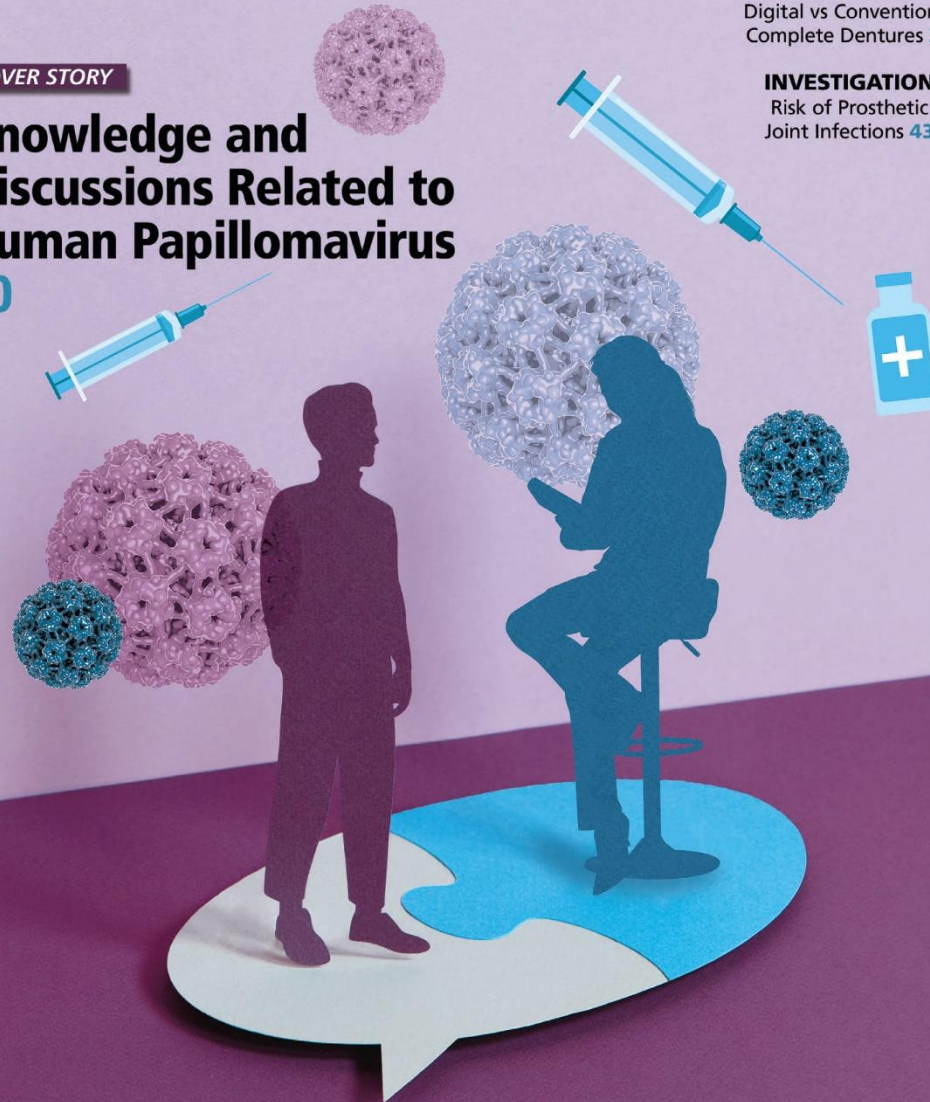
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HPV Vaccine Safety

- Safety of vaccine has been confirmed*
- Confirmed independently by the NIH, CDC and the WHO
- An estimated >300 million doses of HPV vaccine delivered worldwide
- Adverse events have been similar to other vaccines: injection site pain, syncope, nausea, fever, headache and skin rash/hives

HPV Vaccine Safety

- Claims of great harm related to HPV vaccination have included:
 - multiple sclerosis or other demyelinating diseases, premature ovarian failure, complex regional pain syndrome
- To date, the CDC considers Gardasil 9 as a “very safe” vaccine with proven no causality between HPV vaccines and any serious health condition

HPV Vaccine Safety

- Cautionary note:
 - 2017 French study of over 2 million young girls suggested a possible link to Guillain-Barré syndrome
 - Estimated rate: 2 per 100,000 vaccinations (0.002%)
 - Important note: similar linkage has been previously noted with other vaccinations, including seasonal flu

HPV Vaccine Safety

- 2018 Canadian study of 290,939 girls aged 12-17 eligible for vaccination from 2007-2013
- Compared rates of autoimmune disorders diagnosed 7-60 days post-vaccination
- No significantly increased risk for any autoimmune disorder; including Bell palsy, optic neuritis and Guillain-Barré Syndrome

Liu et al. CMAJ 2018 190(21):E648-55

HPV Vaccine Safety

- 2020 meta-analysis of world literature examined risk for 3 autoimmune diseases: autoimmune thyroiditis, Guillain-Barre syndrome and IBD
- Total population: 154,398 exposed and 1,504,322 non-exposed individuals
- No causal association identified



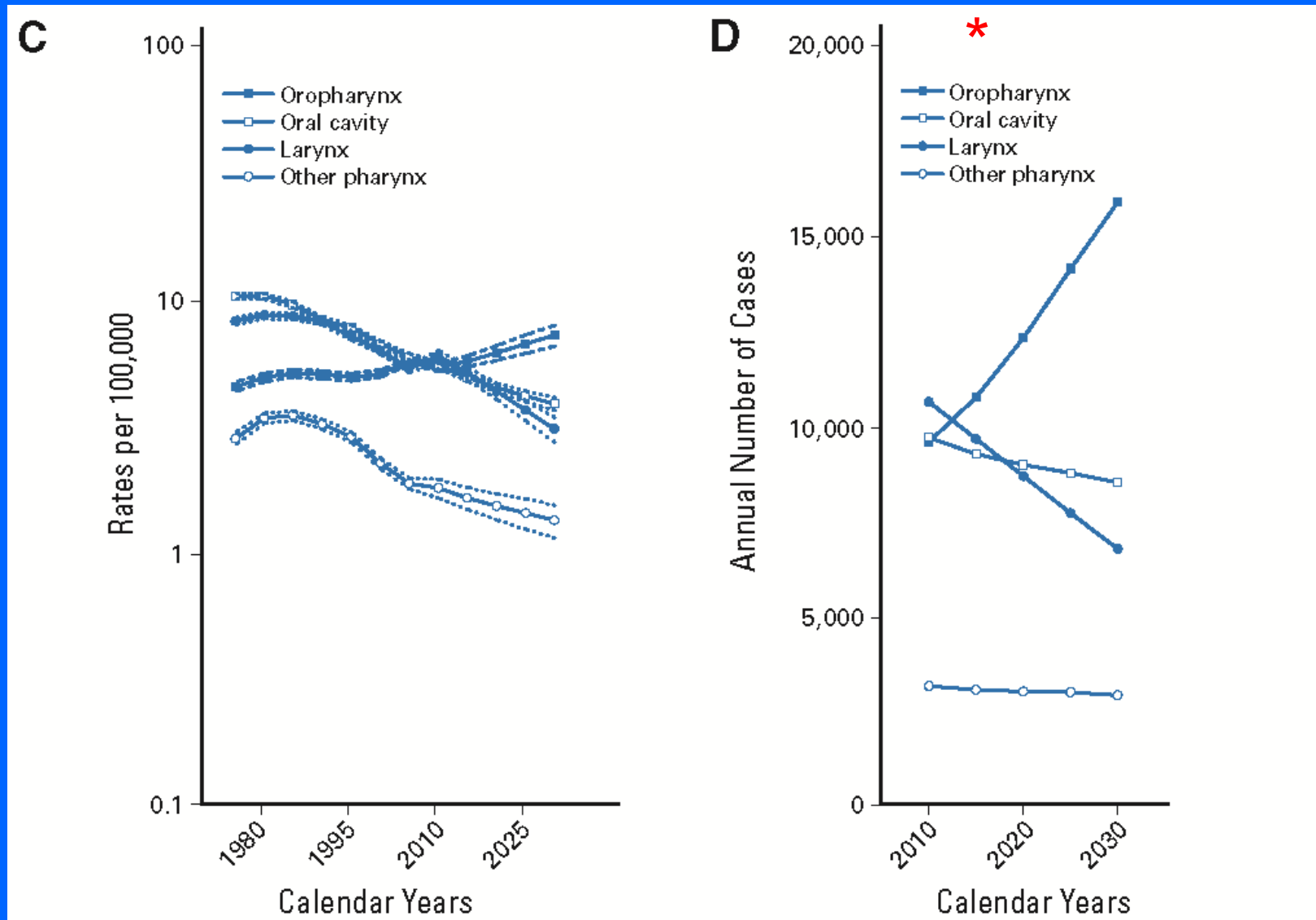
OP/tonsillar Ca Summary

- Most OP HPV infections are transient (0.5-3 yrs)
- Men have:
 - Higher OP HPV acquisition
 - Lower/slower OP HPV clearance
 - Prevalence not fully explained by # oral sex partners
- HPV is associated with most OP/tonsillar Ca
- HPV⁺ OPC has better prognosis than HPV-negative OPC (absent smoking)

HPV Vaccines Summary

- Vaccines are effective and safe in reducing cervical Ca and precancer in women
- HPV vaccines may reduce the risk for tonsillar Ca in both men and women in years to come

Head & Neck Ca Incidence Projections



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