Head and Neck Cancers and HPV

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Disclosures

No Commercial COI (both speakers)

Objectives - Head and Neck Cancers and HPV

By the end of session, participants should be able to:

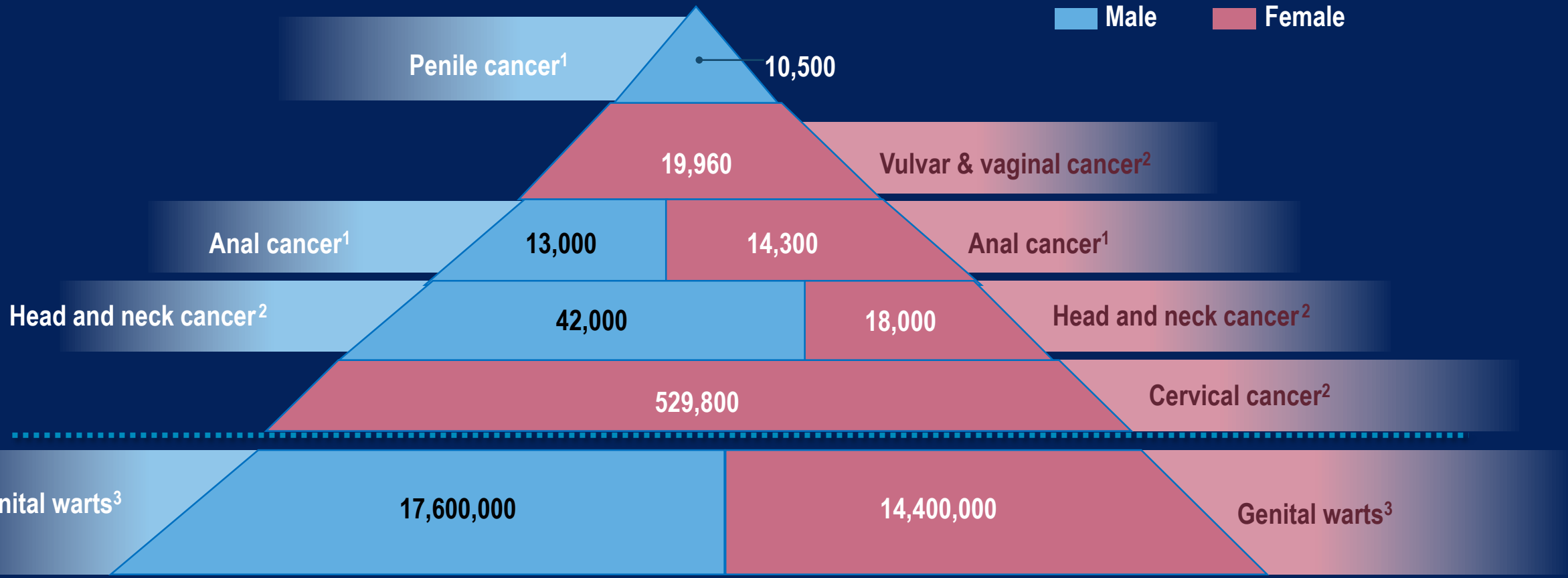
Advise patients about the epidemiology of HPV related disease

Discuss the probable mechanism of HPV malignant transformation

Formulate strategies to treat HPV related head and neck cancers

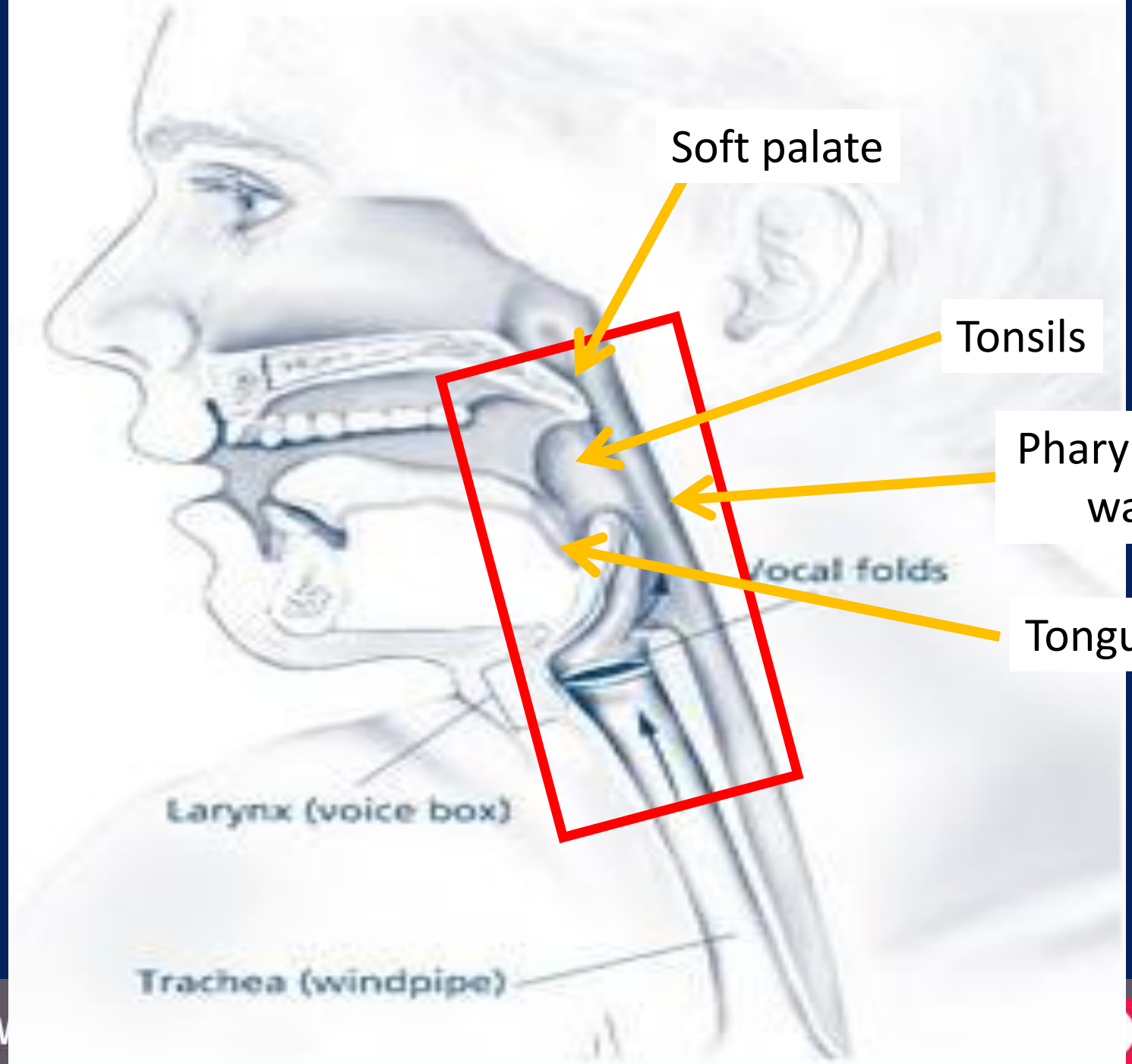
HPV Causes More Cancers and Diseases in Men & Women Globally

Estimated annual new HPV-related disease cases in males and females globally



1. Parkin DM et al. *Vaccine*. 2006;24(Suppl 3):S3/11–S3/25. **2.** WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre). Human Papillomavirus and Related Cancers in World. Summary Report 2010. http://www.who.int/hpvcentre/en/. Accessed June 21, 2012. **3**. World Health Organization (WHO). Executive summary: the state of world health. 1995. http://www.who.int/whr/1995/media_centre/executive_summary1/en/index3.html#. Accessed June 7, 2012.

Not Mouth
Not Larynx



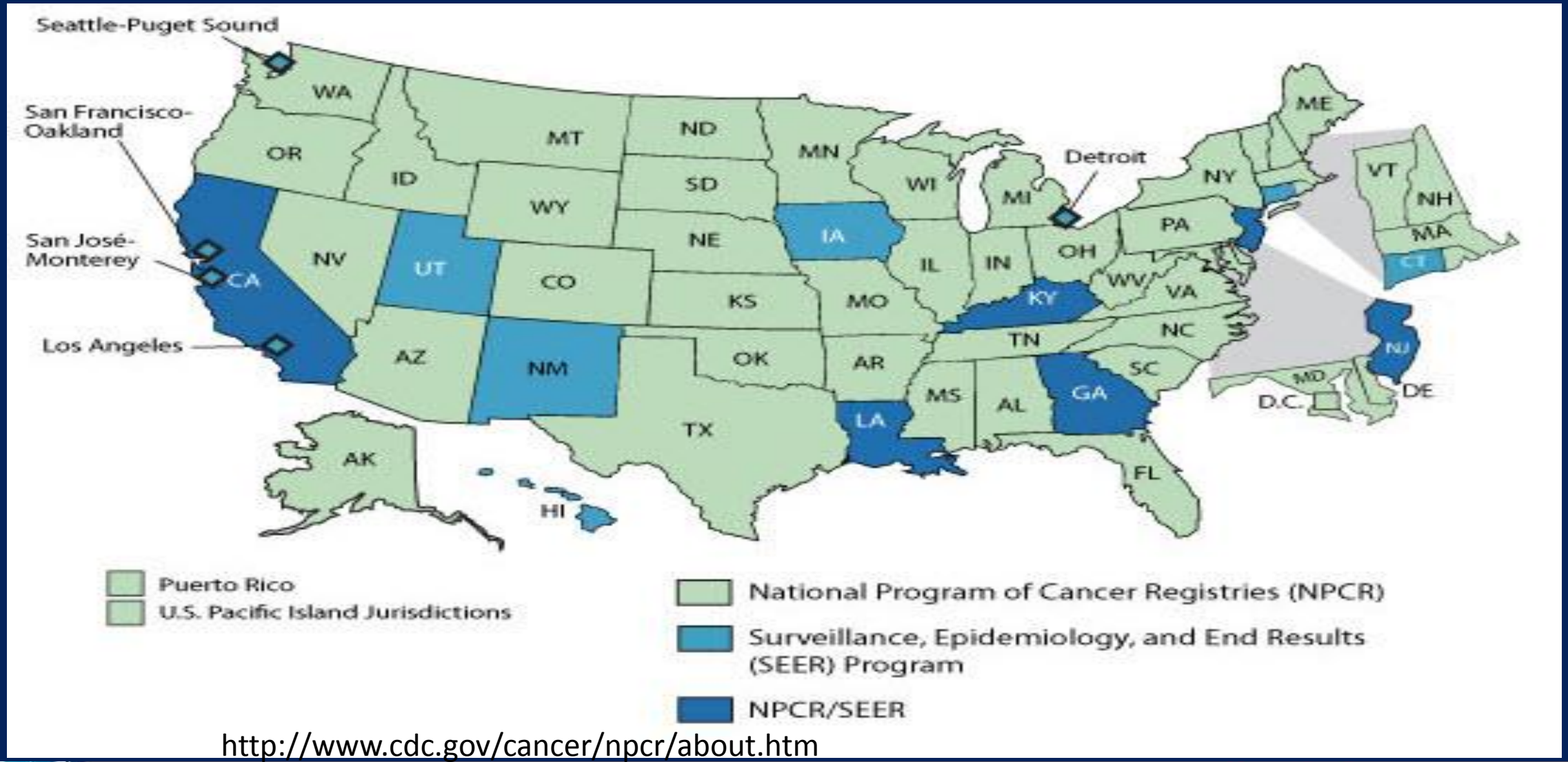
US Cancer Data where do we get #s from

Number of new cases (numerator) -from cancer registries

Denominator-from US census

Percentage of cancers attributable to HPV—from special studies, not routinely done in surveillance or by cancer registries (JNCI study)

Federally Funded Cancer Registries



http://www.cdc.gov/cancer/npcr/about.htm

Number of HPV-Associated Cancer Cases Probably Caused by HPV per Year in the United States, 2008–2012

Cancer site	Average number of cancers per year in sites where HPV is often found (HPV-associated cancers)	Percentage probably caused by all HPV types combined	Number probably caused by all HPV types combined	Percentage probably caused by HPV types 16/18[1]	Number probably caused by HPV types 16/18[1]	Percentage probably caused by HPV types 31/33/45/52/58[2]	Number probably caused by HPV types 31/33/45/52/58[2]
Cervix	11,771	91%	10,700	66%	7,800	15%	1,700
Vagina	802	75%	600	55%	400	18%	100
Vulva	3,554	69%	2,400	49%	1,700	14%	500
Penis	1,168	63%	700	48%	600	9%	100
Anus	5,010	91%	4,600	79%	4,000	8%	400
Female	3,260	93%	3,000	80%	2,600	11%	400
Male	1,750	89%	1,600	79%	1,400	4%	100
Rectum	750	91%	700	79%	600	8%	100
Female	513	93%	500	80%	400	11%	100
Male	237	89%	200	79%	200	4%	0
Oropharynx	15,738	70%	11,000	60%	9,500	6%	900
Female	3,100	63%	2,000	51%	1,600	10%	300
Male	12,638	72%	9,100	63%	8,000	4%	600
TOTAL	**38,793**		**30,700**		**24,600**		**3,800**

[1]HPV types 16/18 can be prevented by the bivalent, quadrivalent, and 9-valent HPV vaccines.

[2]HPV types 31/33/45/52/58 can be prevented by the bivalent, quadrivalent, and 9-valent HPV vaccines.

Data are from population-based registries participating in CDC's National Program of Cancer Registries or NCI's Surveillance, Epidemiology, and End Results Program, meeting USCS publication criteria quality for all years 2008–2012, and cover about 99% of the US population. HPV-associated cancers were defined as cancers at specific anatomic sites with specific cellular types in which HPV DNA frequently is found. All cancers were confirmed histologically. Cervical cancers (ICD-O-3 site codes C53.0–C53.9) were limited to carcinomas (ICD-O-3 histology codes 8010–8671, 8940–8941). Vaginal (ICD-O-3 site code C52.9), vulvar (ICD-O-3 site codes C51.0–C51.9), penile (ICD-O-3 site codes C60.0–60.9), anal (ICD-O-3 site code C21.0–C21.9), rectal (ICD-O-3 site code C20.9) and oropharyngeal (ICD-O-3 site codes C01.9, C02.4, C02.8, C05.0, C05.1, C05.2, C05.8, C05.9, C09.0, C09.1, C09.8, C09.9, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C14.0, C14.2 and C14.8) cancers were limited to squamous cell carcinomas (ICD-O-3 histology codes 8050–8084, 8120–8131).

Adapted from: Viens et al. Human Papillomavirus- Associated Cancers—United States, 2008–2012. MMWR 2016;65(26):661-666.

Burden of Disease Attributable to HPV Types

- Understanding HPV-associated disease attributable to HPV types important to assessing potential impact of vaccines
- HPV-associated cancers include: cervical, vaginal, vulvar, anal, penile and oropharyngeal cancers
- Data on laryngeal cancers is not currently accepted as HPV-associated
- Determining types responsible for HPV-associated disease depends on a variety of factors, including population sampled, quality of specimen, assay used to detect HPV, algorithm to assign type attributable if multiple types
- Studies have evaluated HPV-associated disease using different assays and methodologies

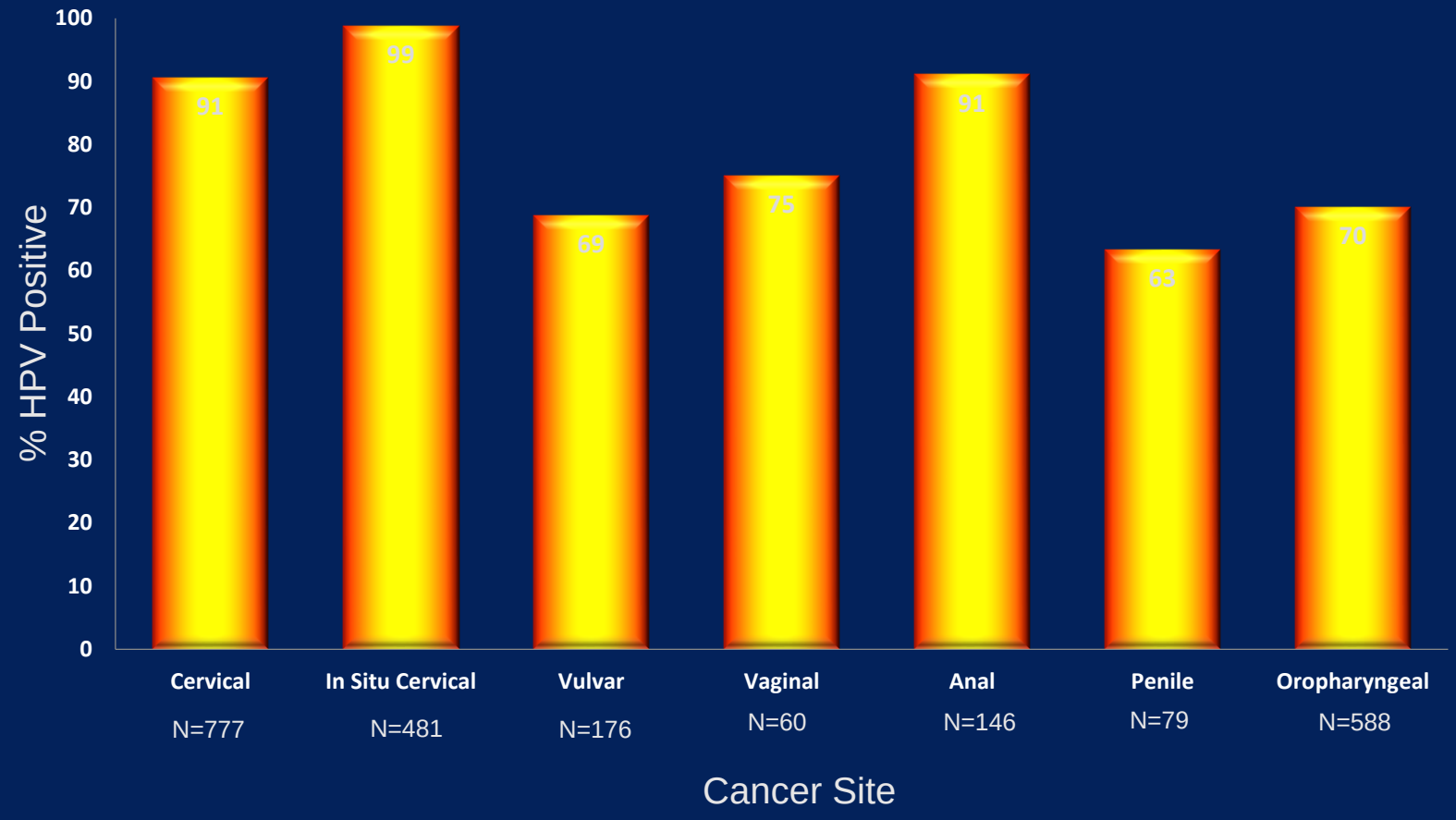
CDC Initiatives

- HPV Impact Study—HPV typing of CIN2/3
  - 2008, population based
  - Five sites: California, Connecticut, New York, Oregon and Tennessee
  - Histopathology laboratories serving catchment areas:
    - Report histologically confirmed CIN2+ diagnoses in adult residents of catchment (18 and older)
    - Submit and succesfully archived diagnostic tissue from women aged 18-39 years for HPV DNA typing (n=5498)
- HPV typing of cancers study
  - Cancer-registry based for invasive cancers (cervix, anal, vaginal, vulvar, anal, oropharyngeal, larynx, oral cavity) and select CIN3, VIN3
  - Seven sites – Michigan, Lousiana, Florida (3 counties), Hawaii, Los Angeles, Kentucky, Iowa
  - Submit and successfully archived diagnostic tissue for HPV DNA typing for cancers (n=2670) diagnosed from 2004-2005 (some older)

HPV Type Attribution PreCancers: General Findings

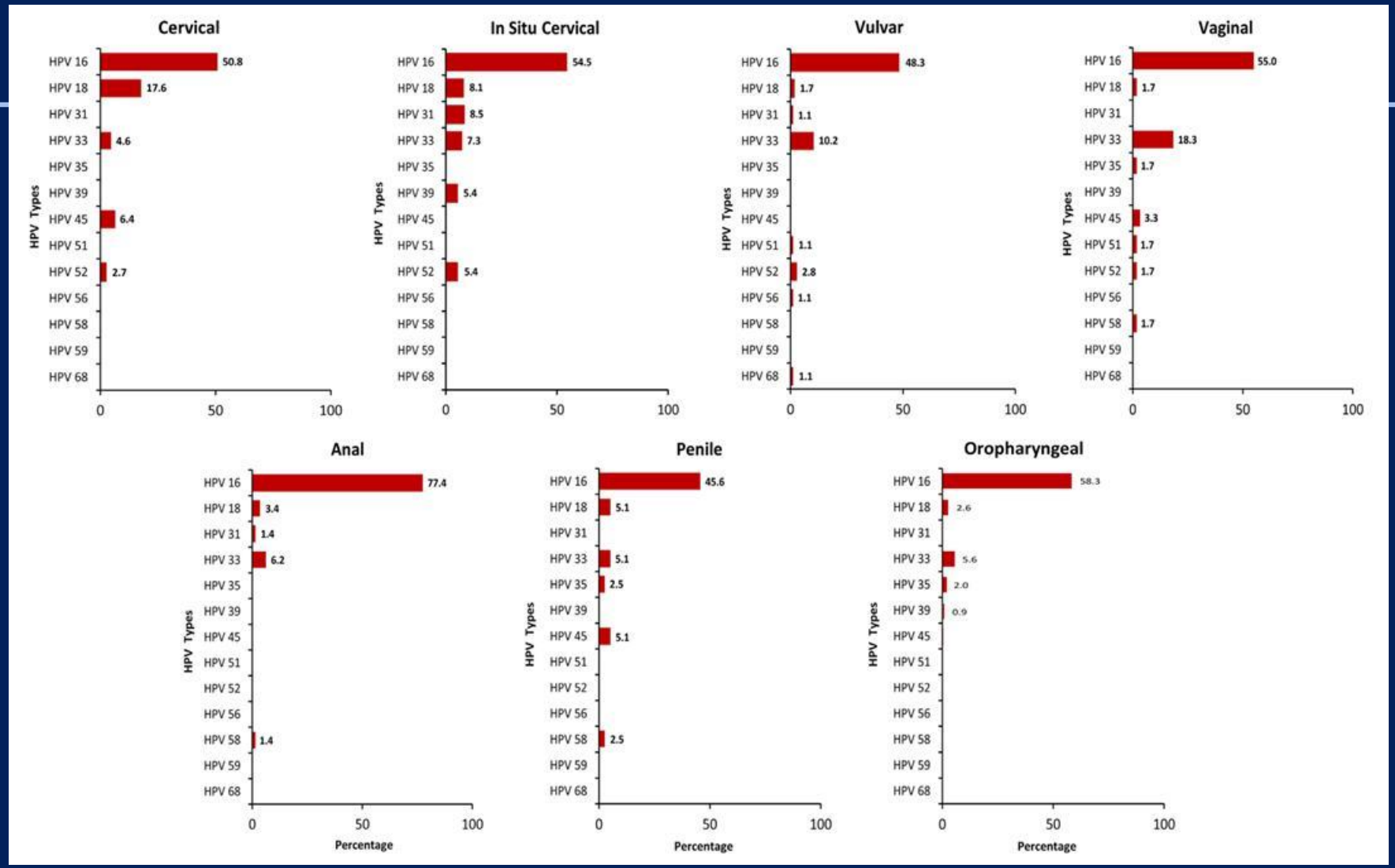
- Overall
  - 50% CIN2+ lesions attributable to HPV16 and HPV18
  - Additional 25% of CIN2+ lesions attributable to HPV31/33/45/52/58
- By Age: Higher proportion of lesions due to HPV16 and HPV18 in women under 35 years
  - Stronger carcinogens
  - Faster progression to disease
- By Race:
  - Largest proportion of CIN2+ lesions across all racial/ethnic groups attributable to HPV16/18
  - Higher proportion of CIN2+ lesions attributable to HPV16/18 in non-Hispanic white women compared to other racial/ethnic groups
  - May be due to differences in underlying prevalence of HPV type or screening and treatment

HPV Detection by Cancer Site



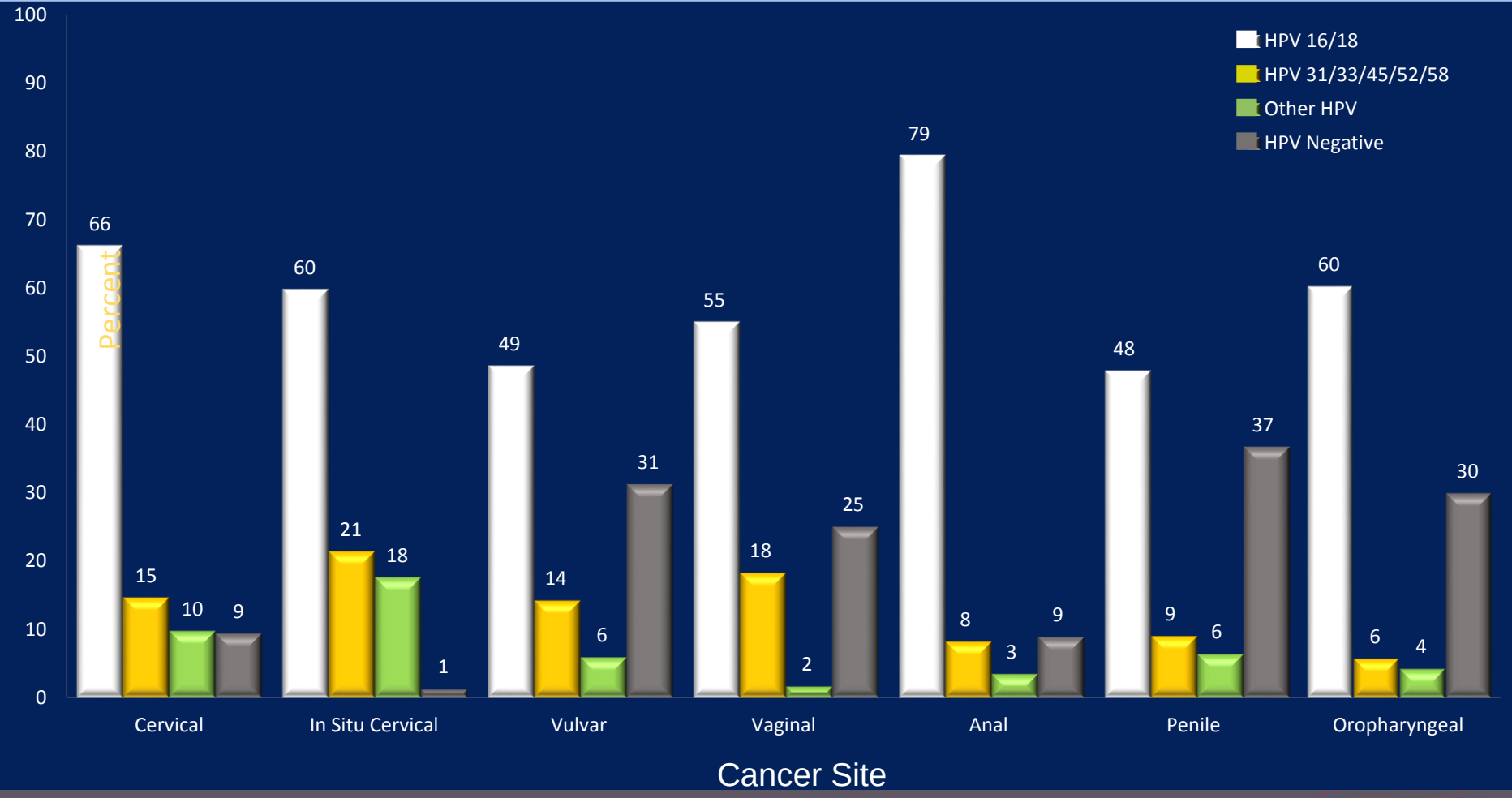
Saraiya et al. JNCI 2015

Top 5 Oncogenic Types in Select Cancers



Saraiya et al, presented at AACR Health Disparities in Cancer, 2013

Type Attribution by Cancer Site



Saraiya et al, presented at AACR Health Disparities in Cancer, 2013

HPV Type Attribution Invasive Cancers: General Findings

By age

- Higher proportion of cancers in younger age groups attributable to HPV 16/18

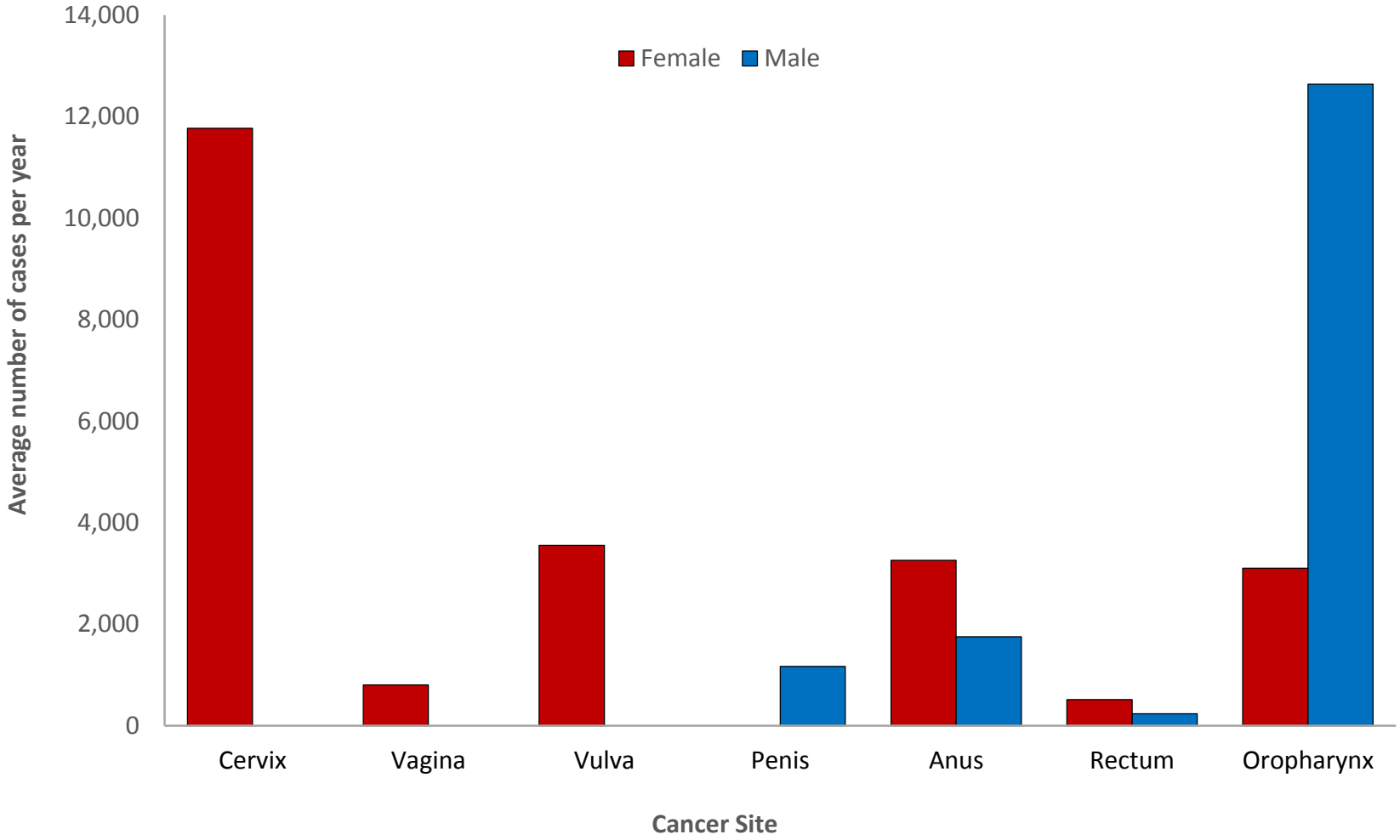
By race/ethnicity

- No differences for cancers except
  - *In situ* cervical cancer (lower 16/18 among blacks)
  - Oropharyngeal cancers-lower percentage attributable to HPV positive (or HPV 16/18) among blacks

By gender, no differences for cancers except

- Oropharyngeal cancers-lower percentage attributable to HPV (or HPV16/18) among females

Average Number of HPV-Associated Cancers Per Year in the United States, 2008–2012



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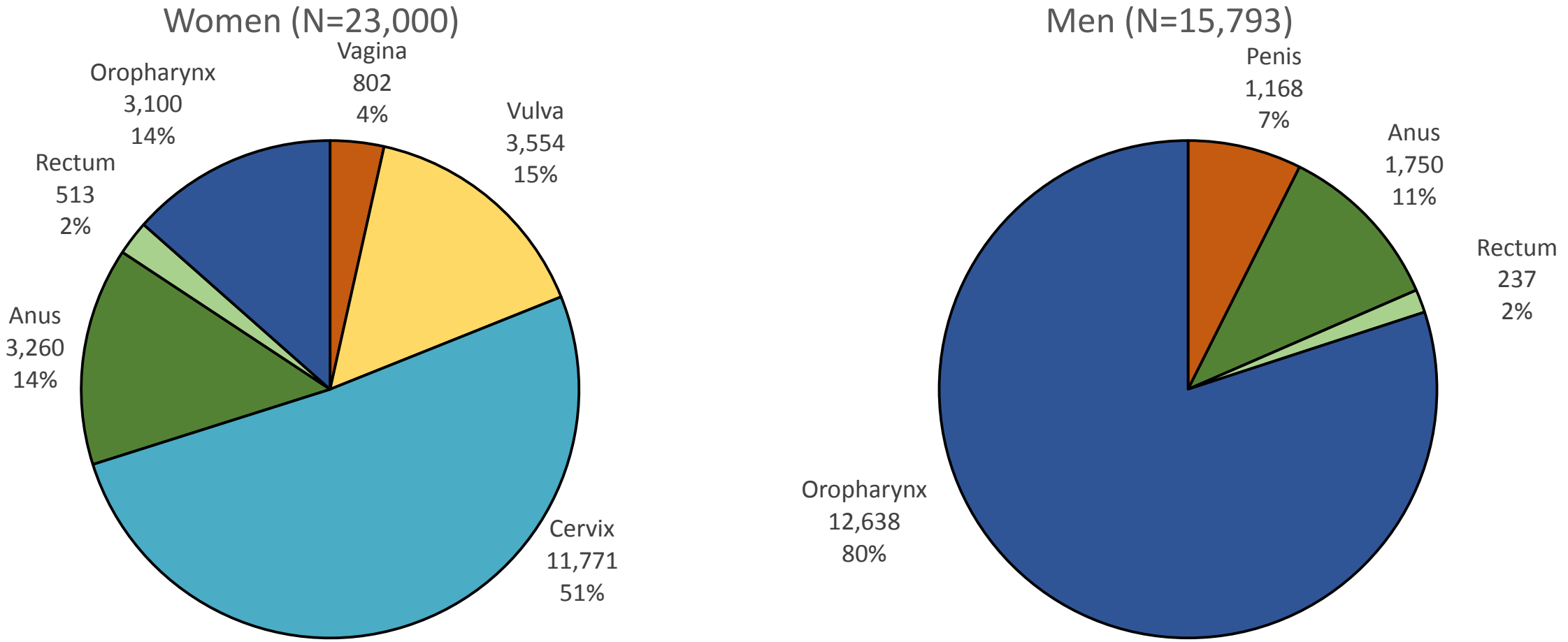

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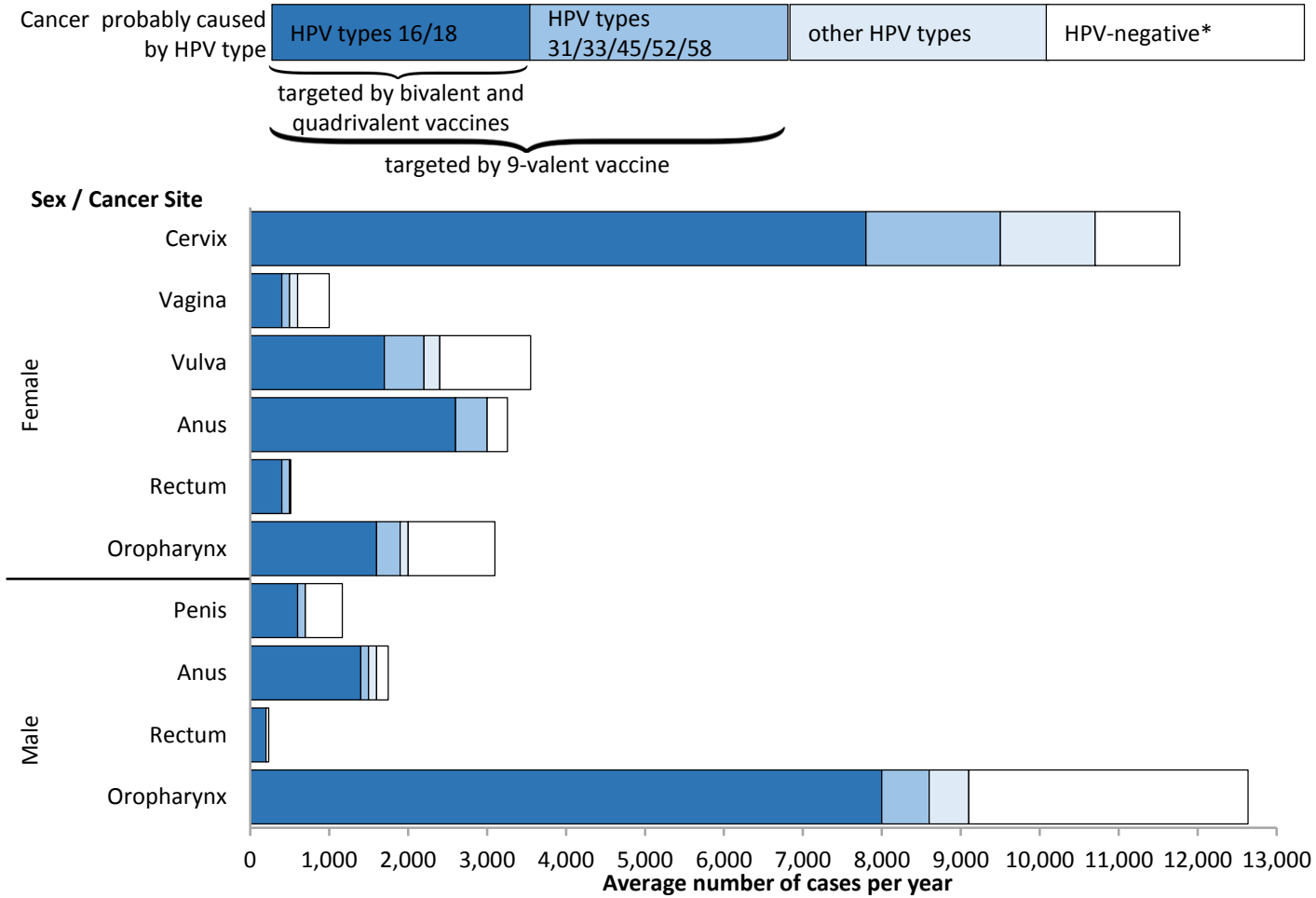
Number of HPV-Associated Cancer Cases Probably Caused by HPV per Year in the United States, 2008–2012



*HPV DNA was not detected in a percentage of cancers (Saraiya M et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst. 2015;107:djv086).

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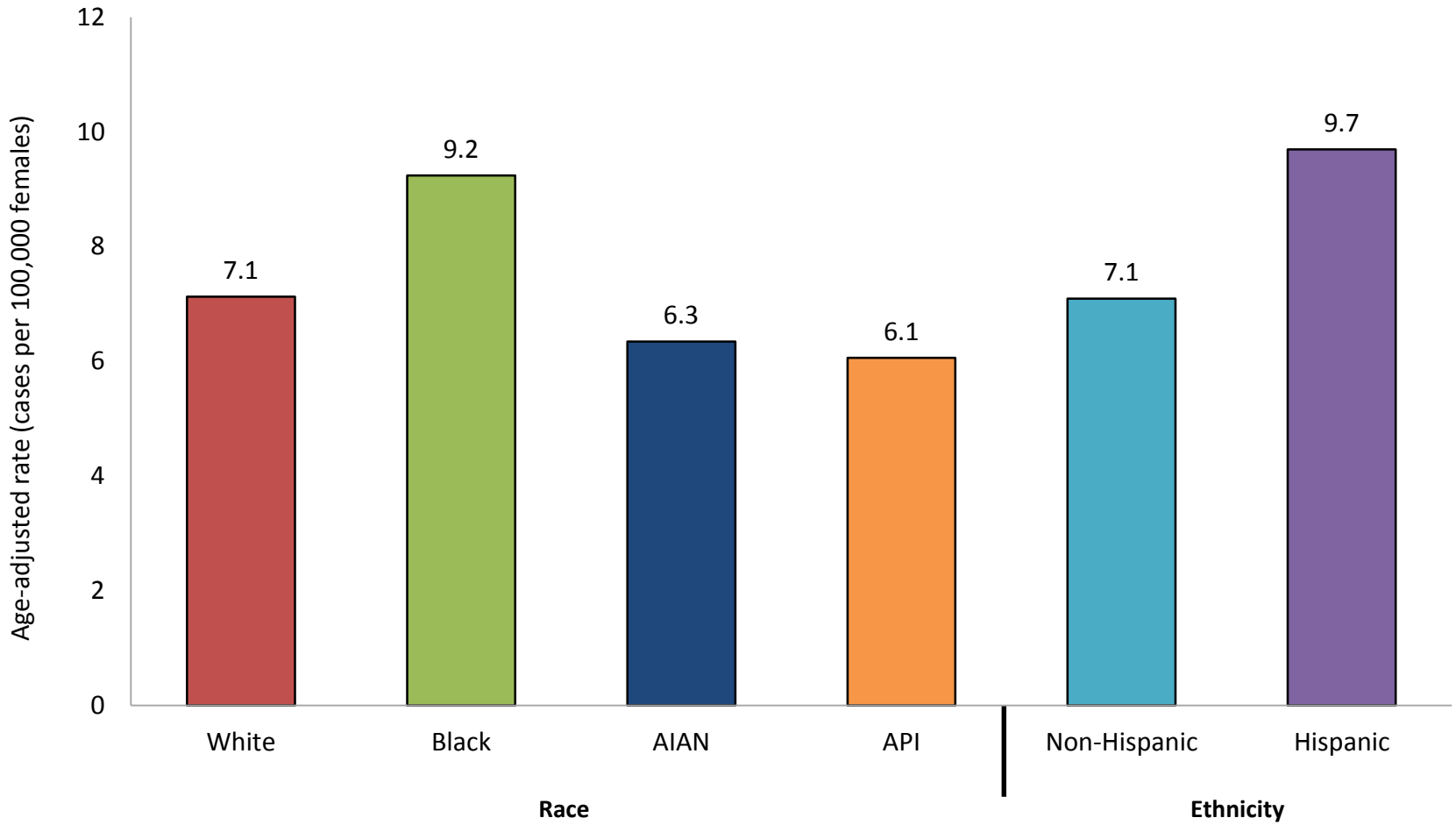
HPV-Associated Cervical Carcinoma Rates by Race and Ethnicity, United States, 2008–2012



Rates are per 100,000 persons and age-adjusted to the 2000 US standard population.
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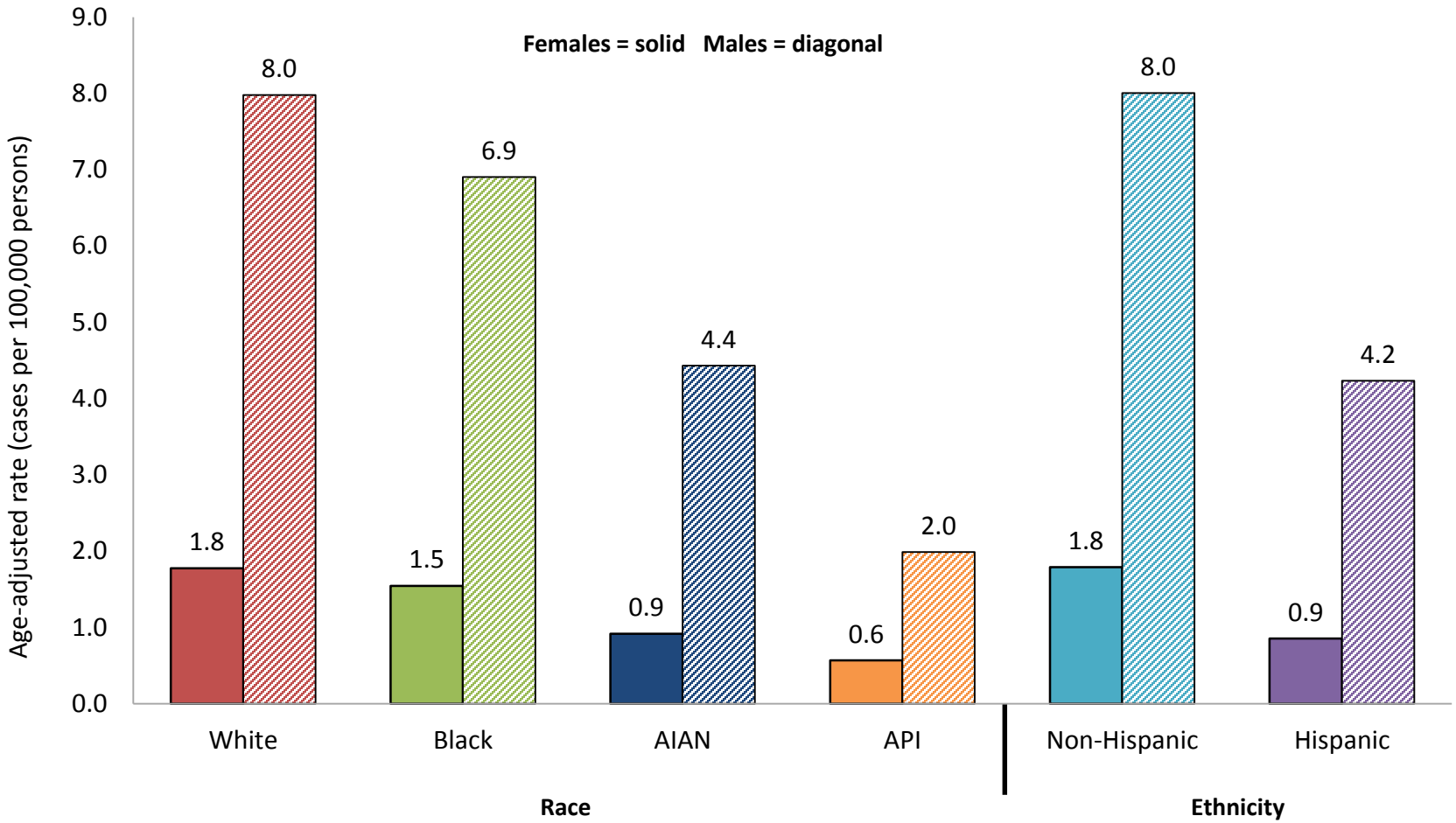
HPV-Associated Oropharyngeal Squamous Cell Carcinoma Rates by Race and Ethnicity, United States, 2008–2012



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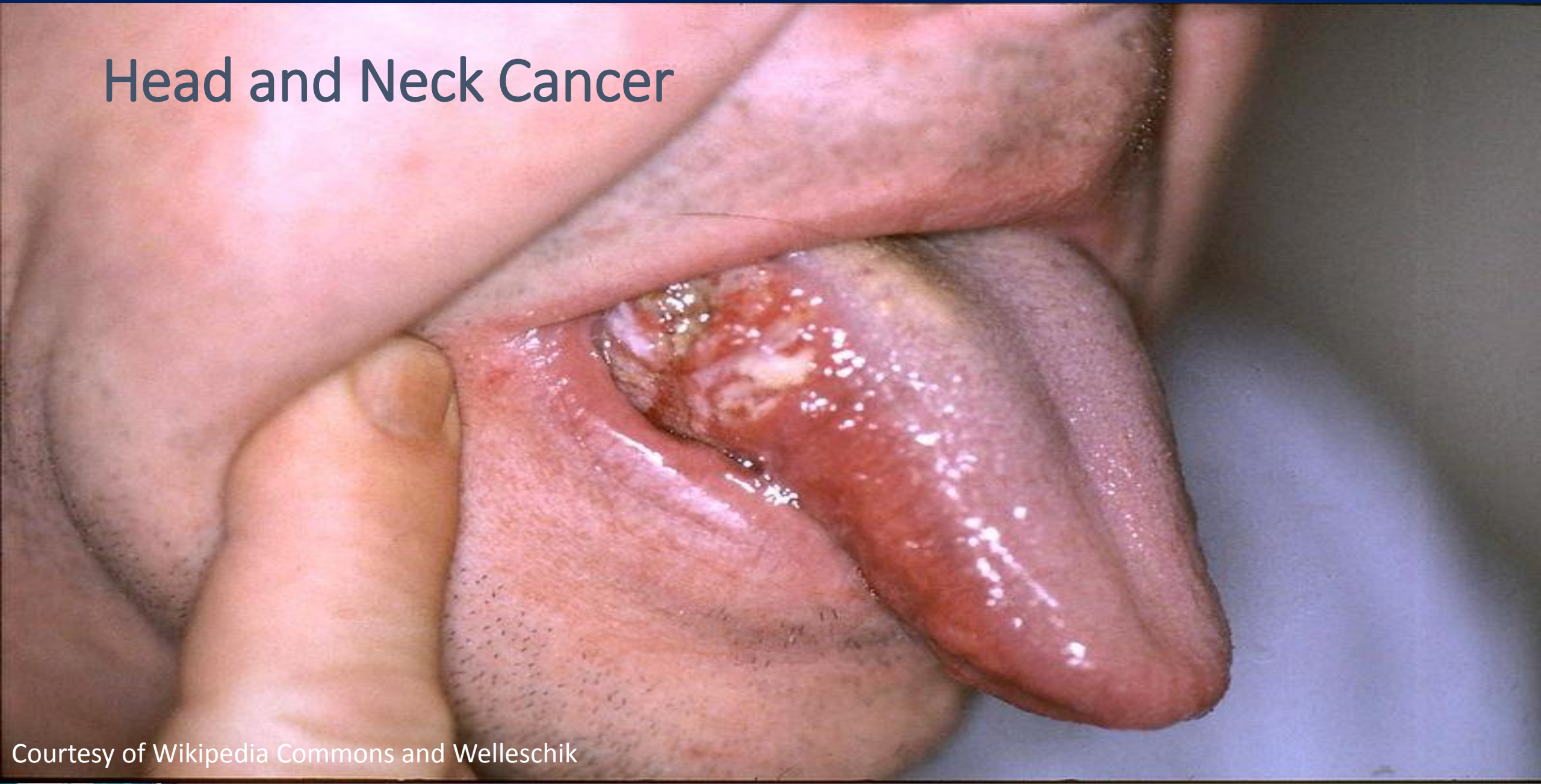
Head and Neck Cancer



Courtesy of Wikipedia Commons and Welleschik

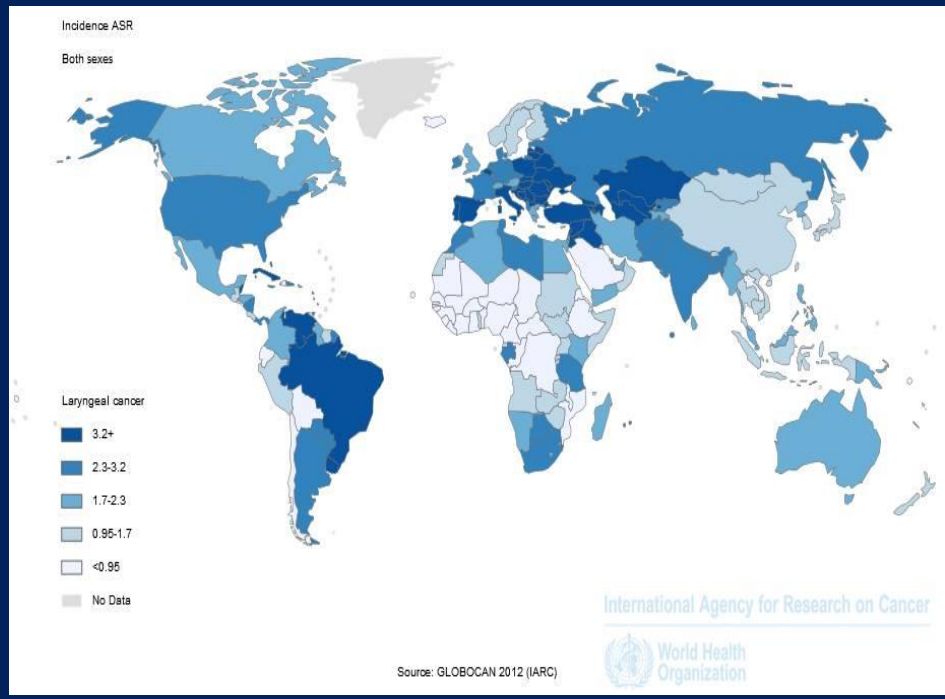
HNC Incidence

840,000 cases worldwide (IARC-2008)

- 68% in men
- 510,000 deaths worldwide (2008)

~50,000 cases U.S. (mostly SCC)

- ~13,000 deaths (2012)
- 8th in incidence among men
- 14th among women



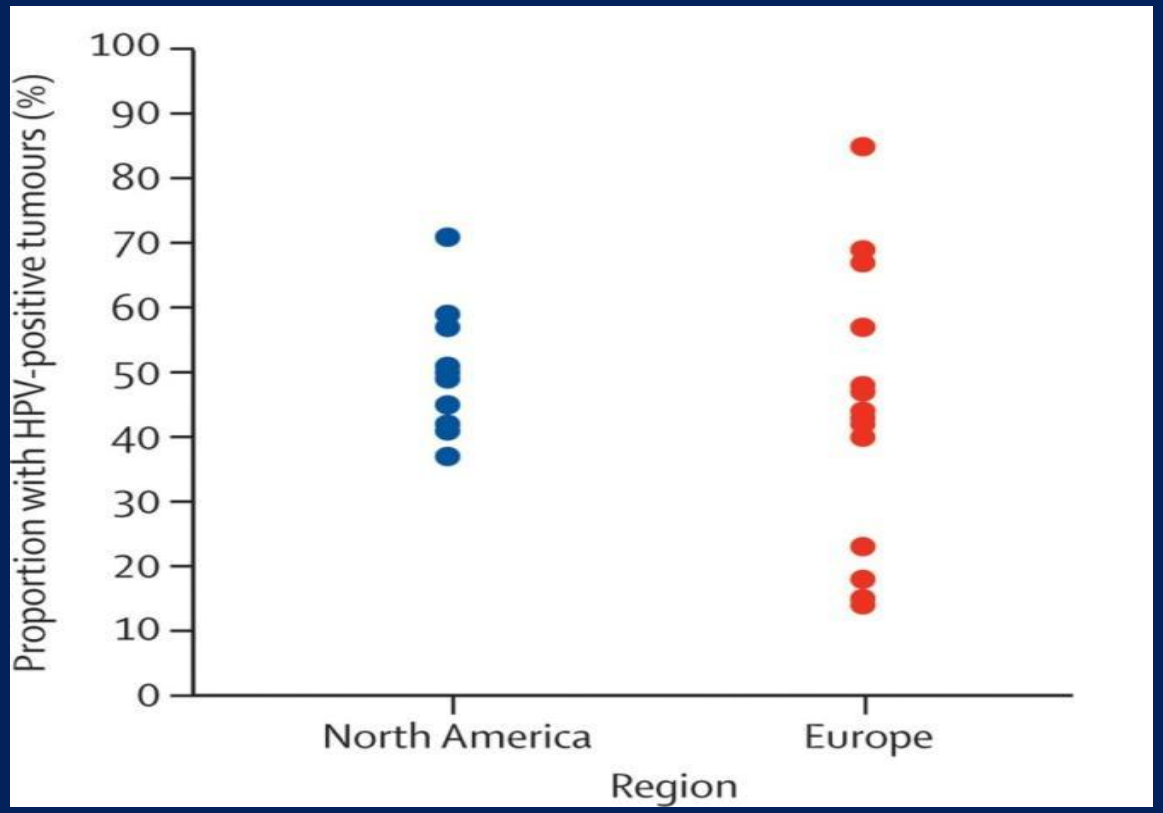
1. Ferlay J, et al. GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–2917.
2. Siegel R, et al. Cancer statistics, 2012. CA Cancer J Clin 2012;62:10-29.

Parkin DM, et al. Int J Cancer J Int Du Cancer 1993;54:594–606.

Epidemiology

~60% of OPSCC positive for HPV16 in North America

In Europe, proportion varies widely based on proportion of smokers



Marur, S. HPV-associated head and neck cancer: a virus related cancer epidemic. Lancet Oncology 2010; 11:781-789.

Incidence of HPV Associated OPC

Prevalence of HPV infection in OPC varies widely but increasing

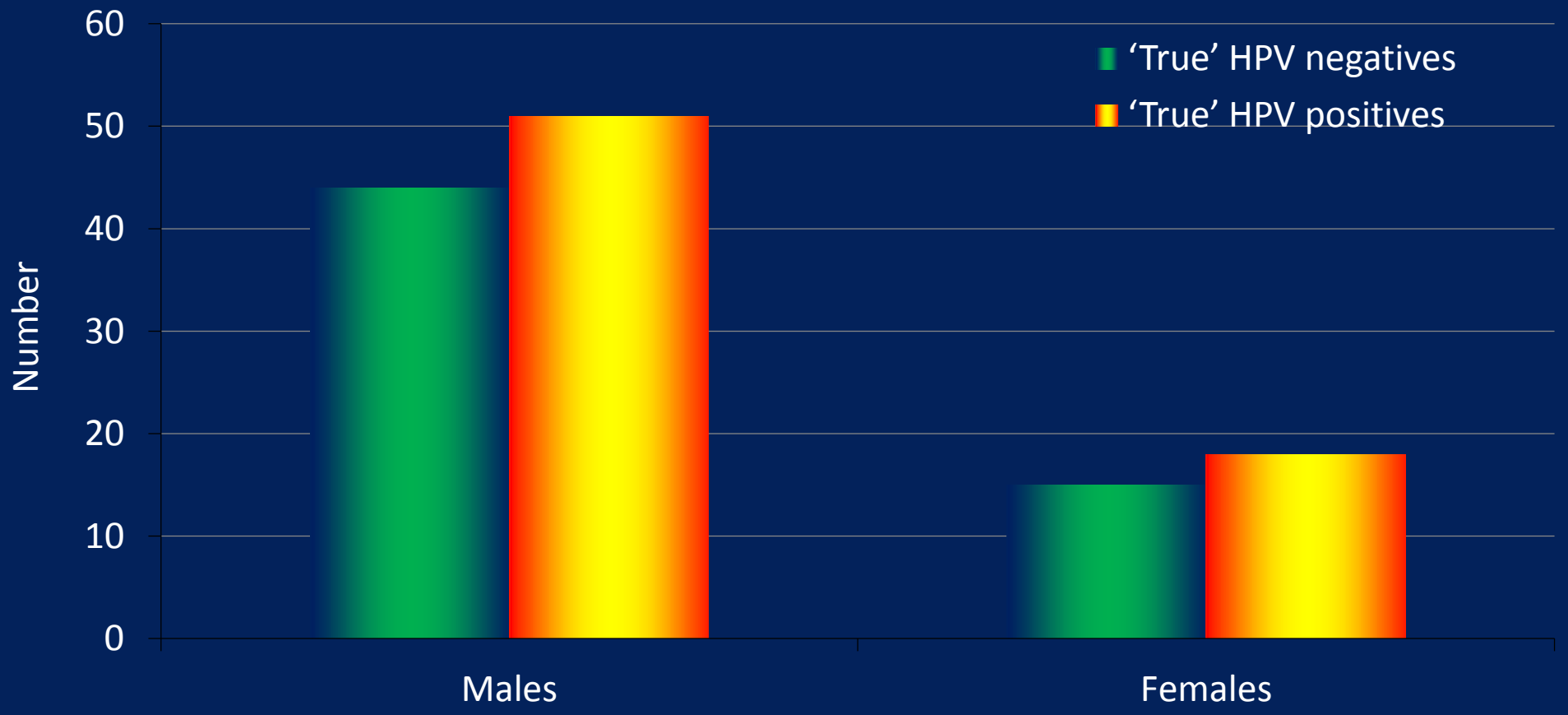
- IARC 2003 = 18% [1]
- USA 2005 = 82% [2]
- IARC 2013 = 39% [3]

OPCs 1 of only 5 cancer types increased in incidence from 1975 to 2009 [4]

Most cases (90-95%) HPV 16 associated

1. Herrero R, et al. J Natl Cancer Inst 2003;95:1772-83. 2. Begum S, et al. Clin Cancer Res 2005;11:5694-9. 3. Anantharaman D, et al. J Natl Cancer Inst. 2013 7;105(8):536-45. 4. Jemal A, et al.. J Natl Cancer Inst 105:175-201, 2013

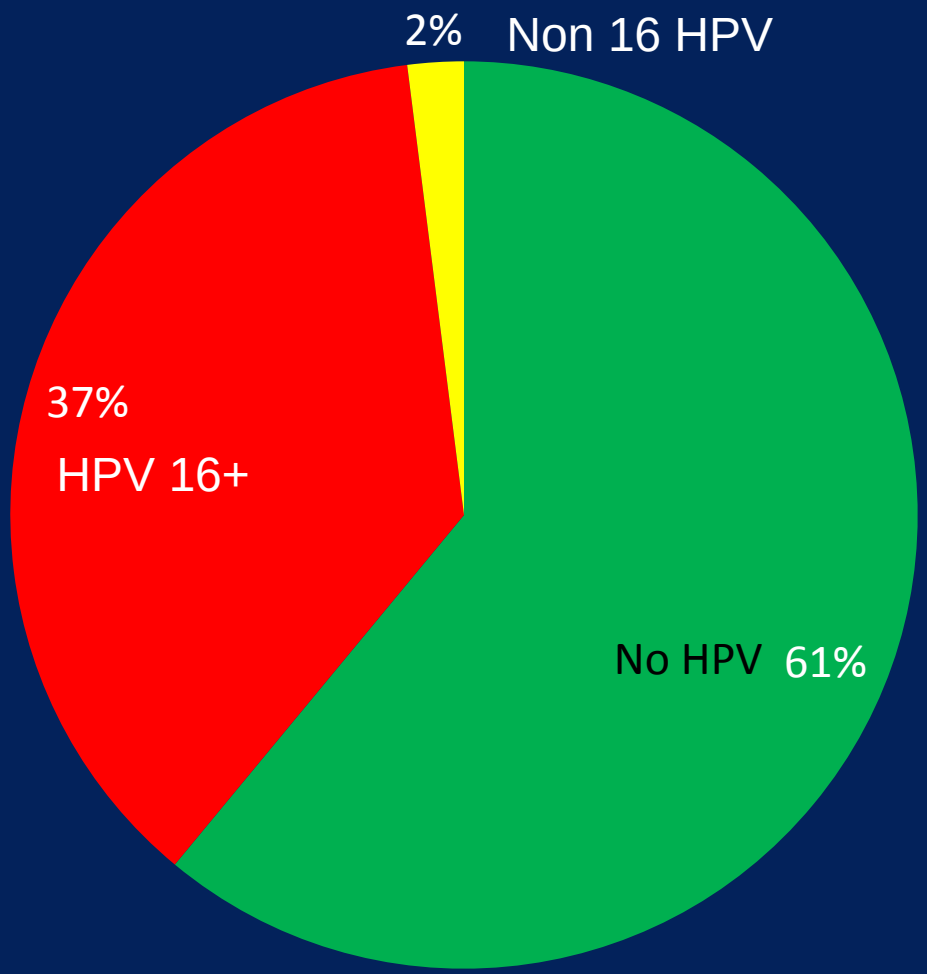
UK HPV vs nonHPV-Associated OPSCC



United Kingdom: 54% of males and 55% of females HPV+

Evans M, et al. BMC Cancer. 2013 May 1;13:220. doi: 10.1186/1471-2407-13-220.

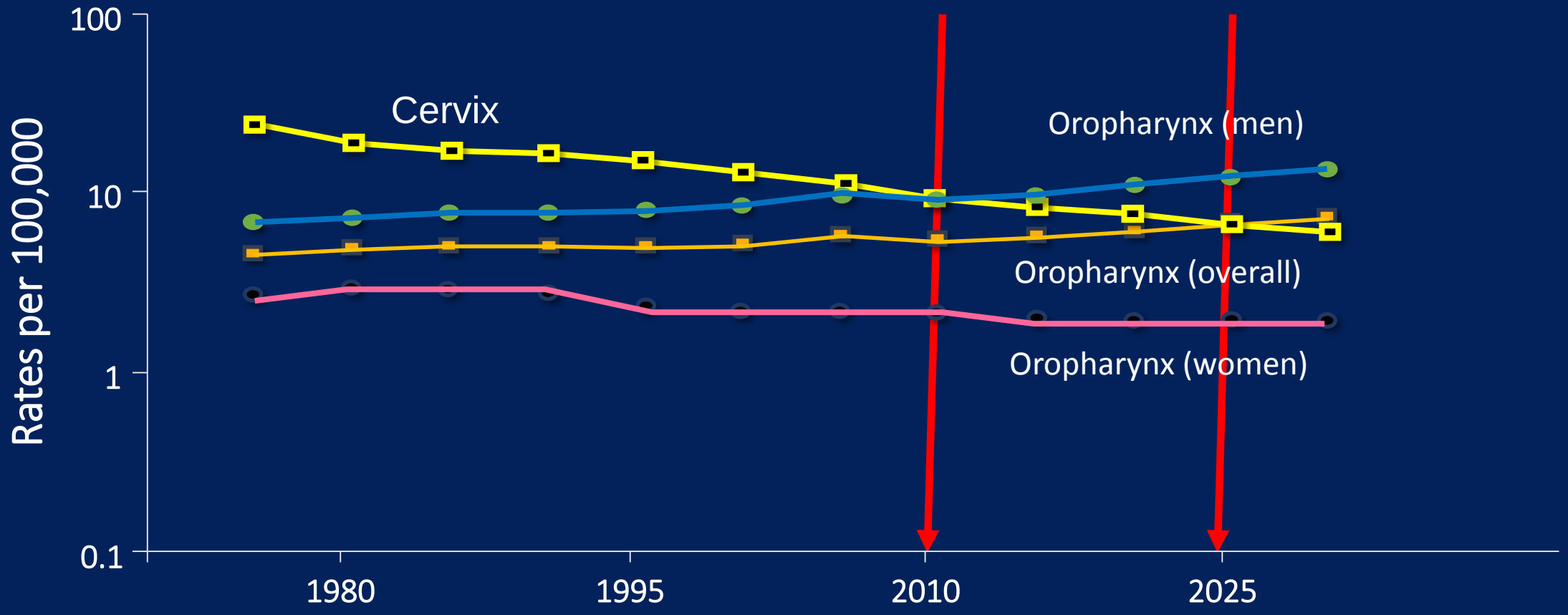
HPV DNA Presence in OPSCCs



1496 patients from 10 European countries (Alcohol-Related Cancers and Genetic Susceptibility in Europe (ARCAGE) Study)

Anantharaman D, et al. J Natl Cancer Inst. 2013 Apr 17;105(8):536-45. doi: 10.1093/jnci/djt053. Epub 2013 Mar 16.

Observed and Projected U.S. Incidence Rates for Oropharyngeal Cancers and Cervical Cancer

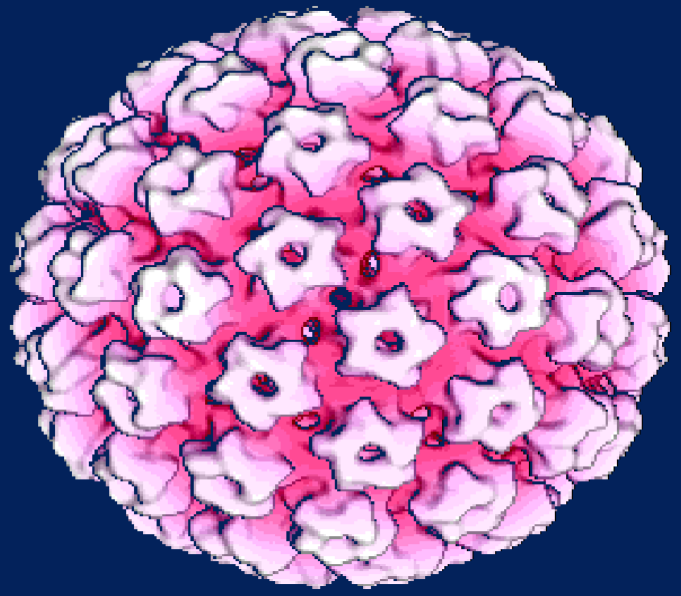


Chaturvedi AK et al. *J Clin Oncol*. 2011;29:4294–4301.

HPV and Cancer

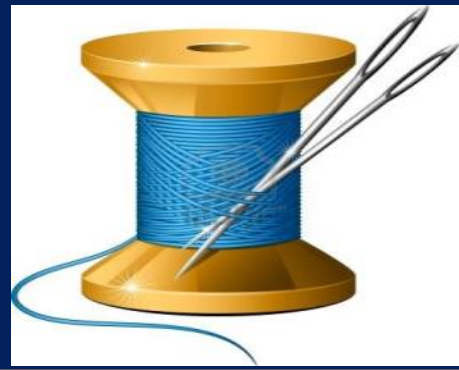
Cervical

Anal

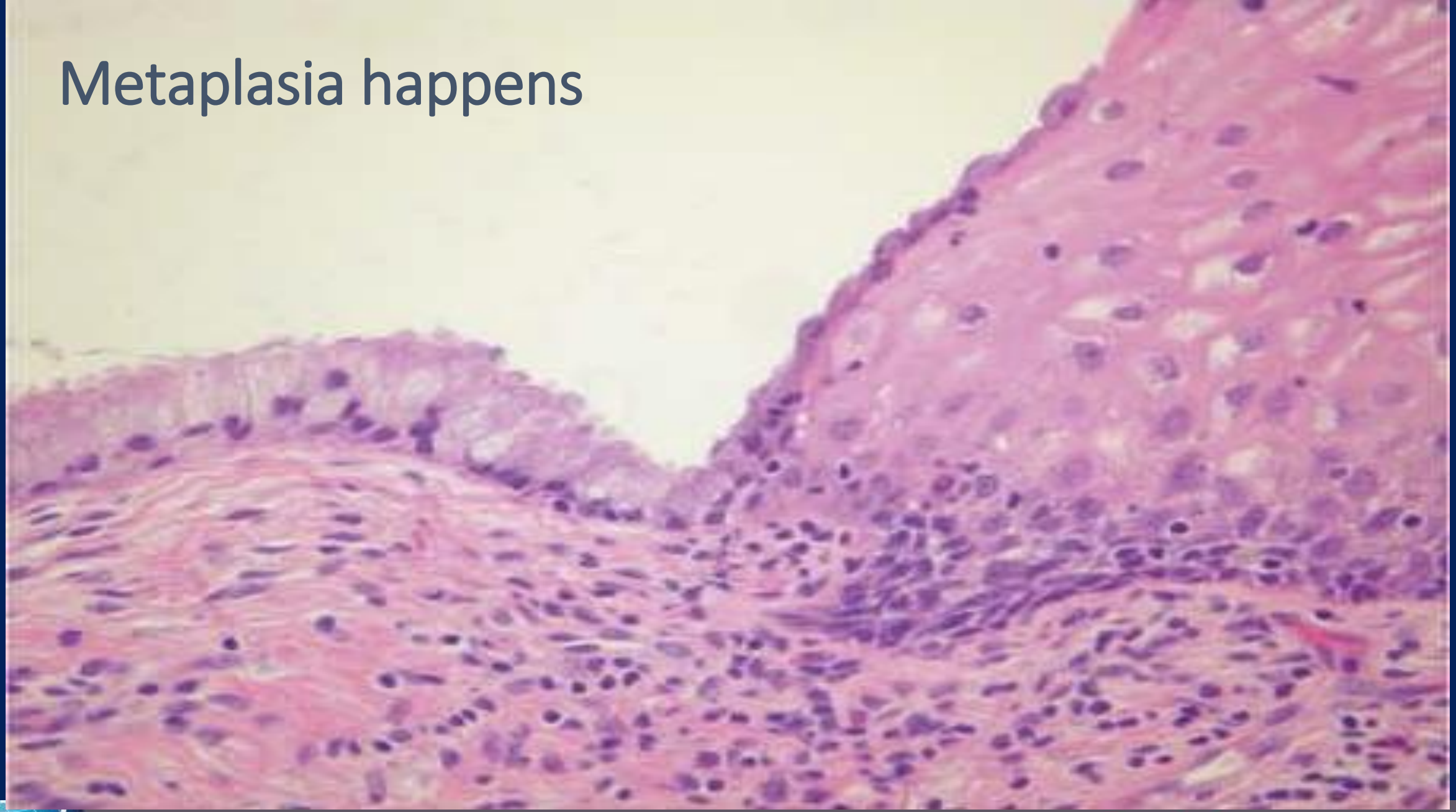


Head & Neck?

What is the common thread?



Metaplasia happens



Epithelia Transition

Epithelia of body openings have stratified squamous epithelium

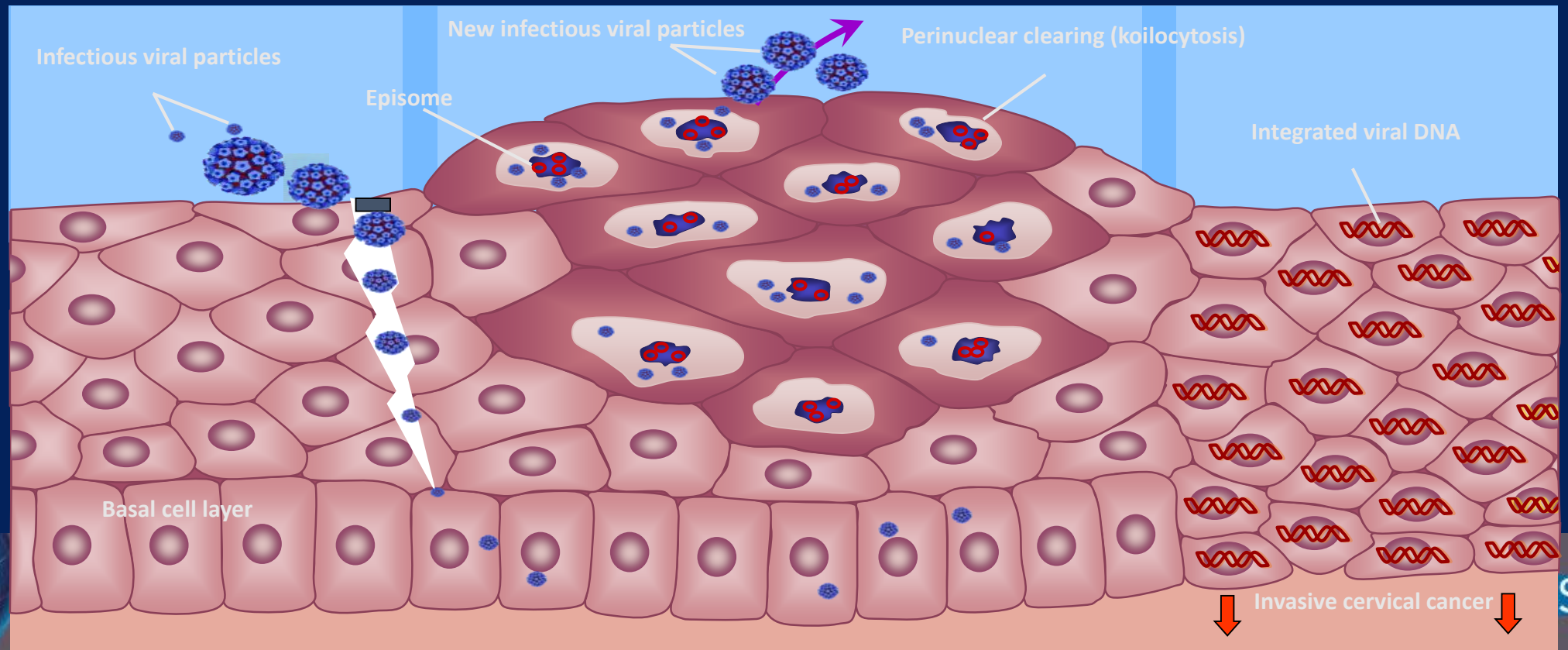
- More internal areas have columnar epithelia

A band of rapidly dividing metaplastic cells (transformation zone) establishes a squamo-columnar junction somewhere near each body opening

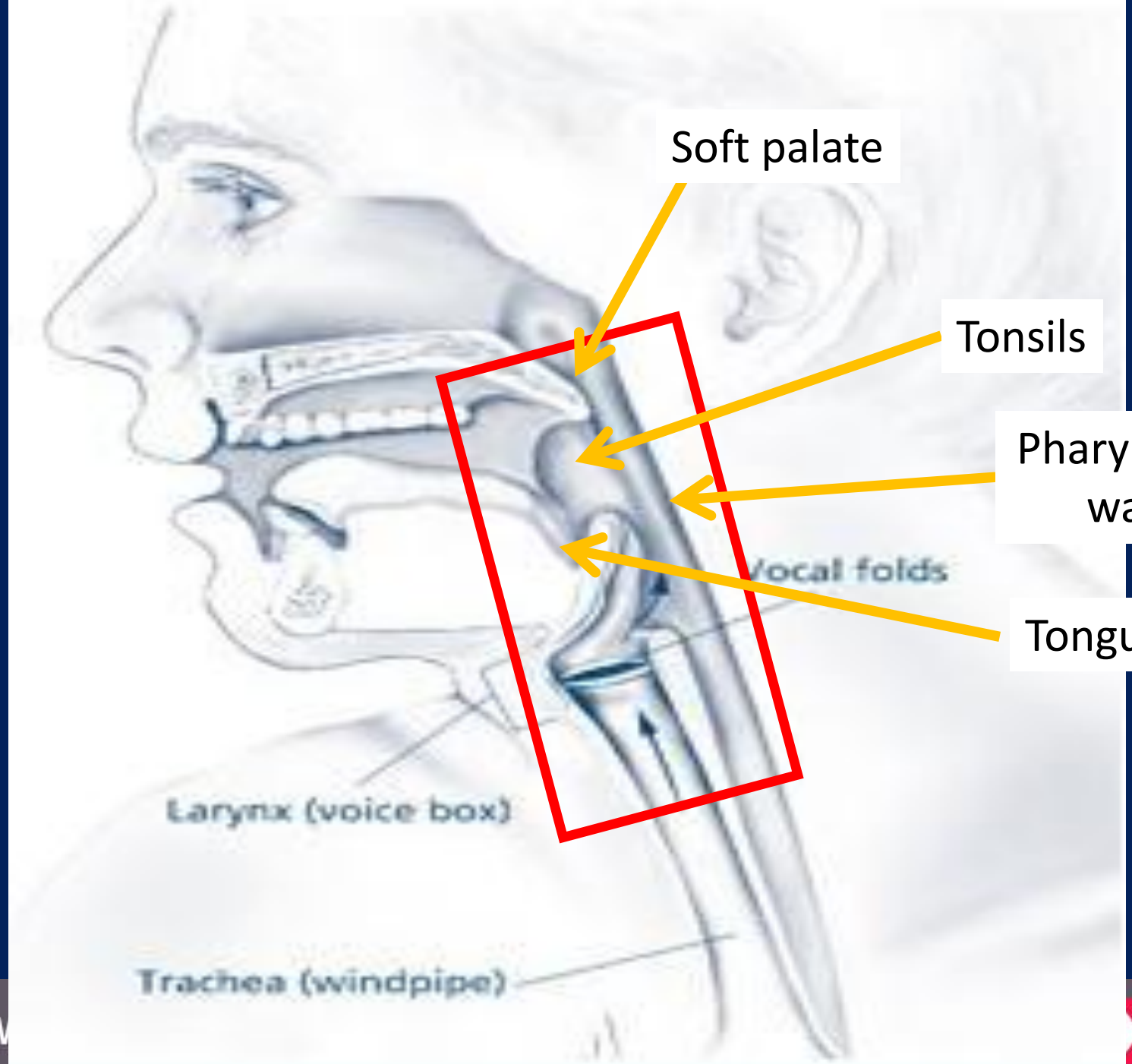
Also occurs with lymphoid crypts

HPV Biology

- HPV Infection
  - Breaks in epithelium expose basal cells
  - Endocytosed into basal cells
  - Mitosis of basal cells gives HPV access to nucleus
  - DNA episomes establish infection in nucleus



Not Mouth
Not Larynx



HPV Oncogenesis

Experimental data supports a causal association between HPV and a subset of oropharyngeal cancers

Repression of viral oncogene expression in HPV+ OPSCCs induces

- Massive apoptosis
- Restoration of p53 and pRb tumor suppressor pathways

Rampias T, et al. J Natl Cancer Inst 2009;101:412–23.

HPV OP Natural History

Currently poorly defined

Believed to be sexually acquired

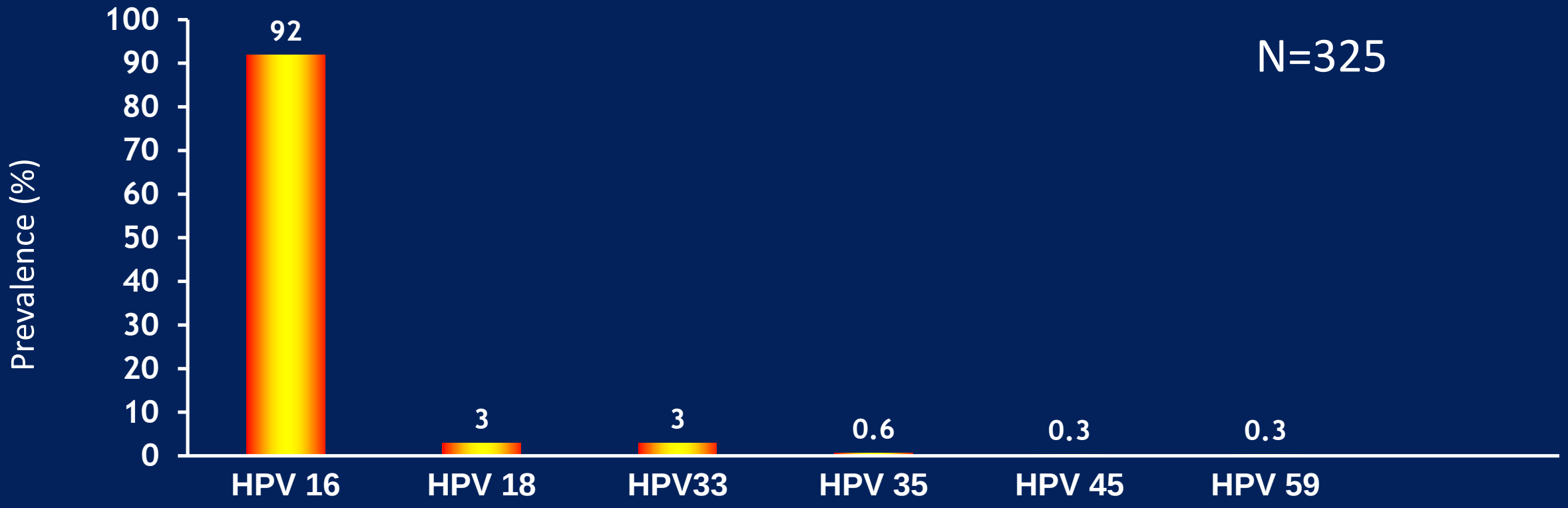
- Associated with sexual behavior 1,2

Questions largely unknown:

- Duration of infection
- Degree of oral transmission
- Whether productive viral infections are established in the oropharynx

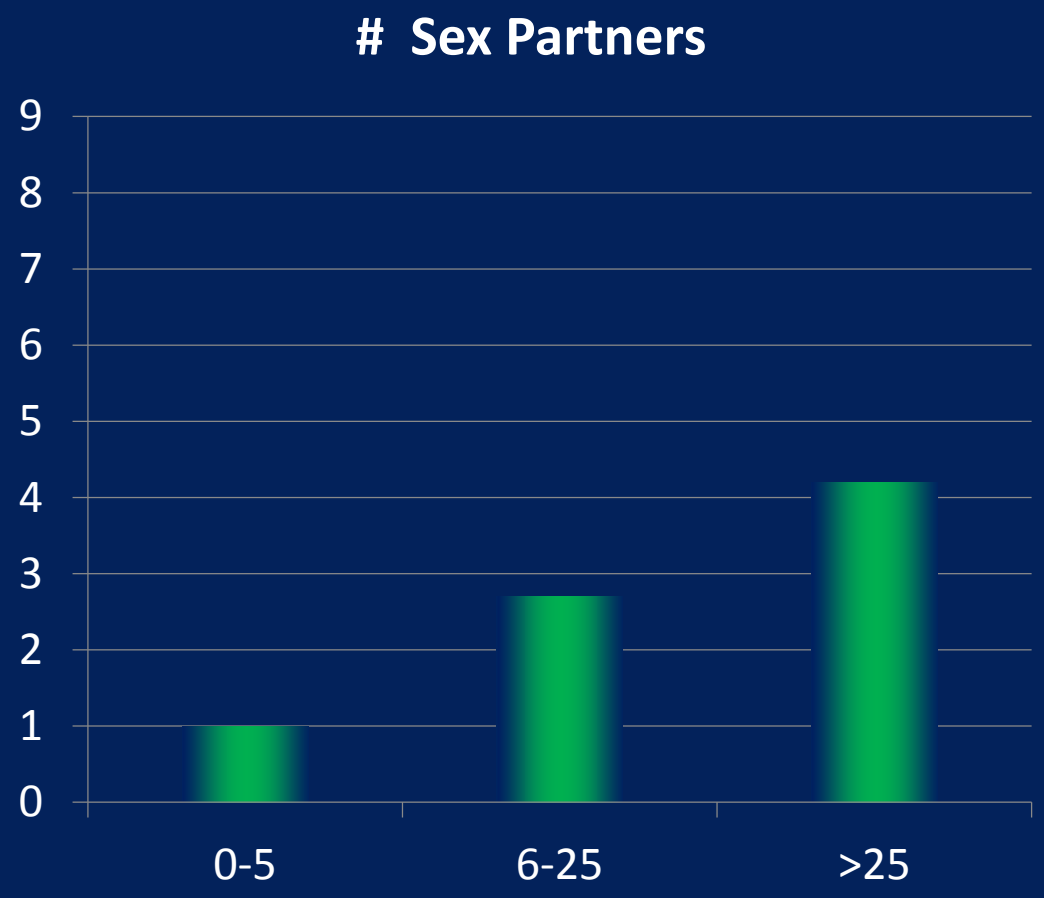
1. D'Souza G. N Engl J Med 2007;356:1944-1956.
2. Kreimer AR. J Infect Dis 2004;189:686-698.

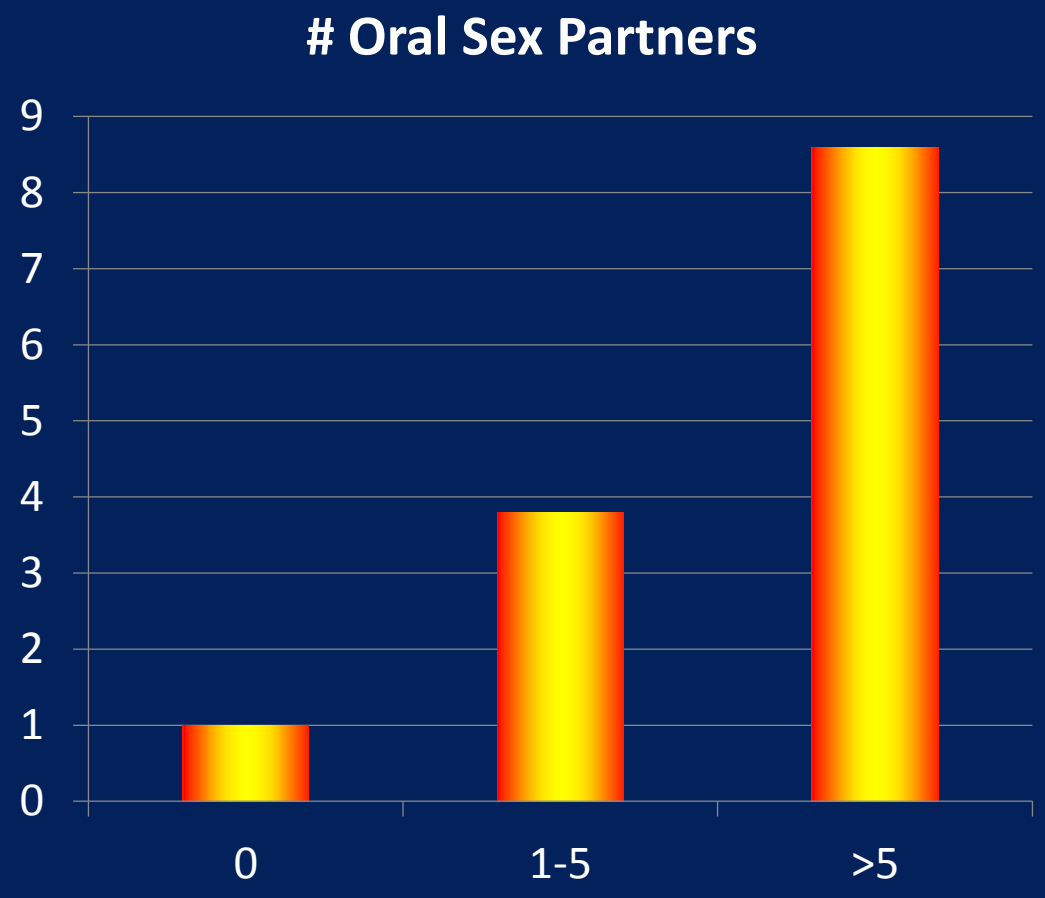
HPV Type distribution in HPV DNA- positive Oropharynx Cases



Kreimer AR CEBP 2005

HPV+ and Sexual Behavior





OR - Adjusted for age, gender, tobacco, alcohol, family Hx, and dental hygiene

D'Souza G. N Engl J Med 2007;356:1944-1956.

Risk Factors for HPV+ OPC

Case-control studies show association between HPV-positive OPC and certain sexual behaviors

- High lifetime number of oral sex or vaginal sex partners
- Early age at first intercourse
- Infrequent use of condoms
- Mirror cervical cancer risks

D'Souza G, et al. N Engl J Med 2007;356:1944-1956.

Risk Factors for HPV+ OPC

History of CIS or cancer = increased risk of HPV-positive OPC [1]

Associated with oral HPV infection (OR 14.6 (6.3-36.6) [2,3]

Associated with HPV16 L1 sero-positivity (OR 32.2 (14.6-71.3) [4]

1. Hemminki K. Eur J Cancer Prev 2000;9:433-437.
2. Mork J. N Engl J Med 2001;344:1125-1131.
3. Hansson BG. Acta Otolaryngol 2005;125:1337-1344.
4. D'Souza G. N Engl J Med 2007;356:1944-1956.

HPV Causing OPC

All HPV+ HNSCCs and most anogenital SCCs share highly similar

- Gene expression
- DNA methylation profiles
- Keratinizing, basaloid histopathological features
- Lack of TP53 or CDKN2A alterations

1. Chakravarthy A, et al. J Clin Oncol. 2016 Dec;34(34):4132-4141.

HPV Causing OPC

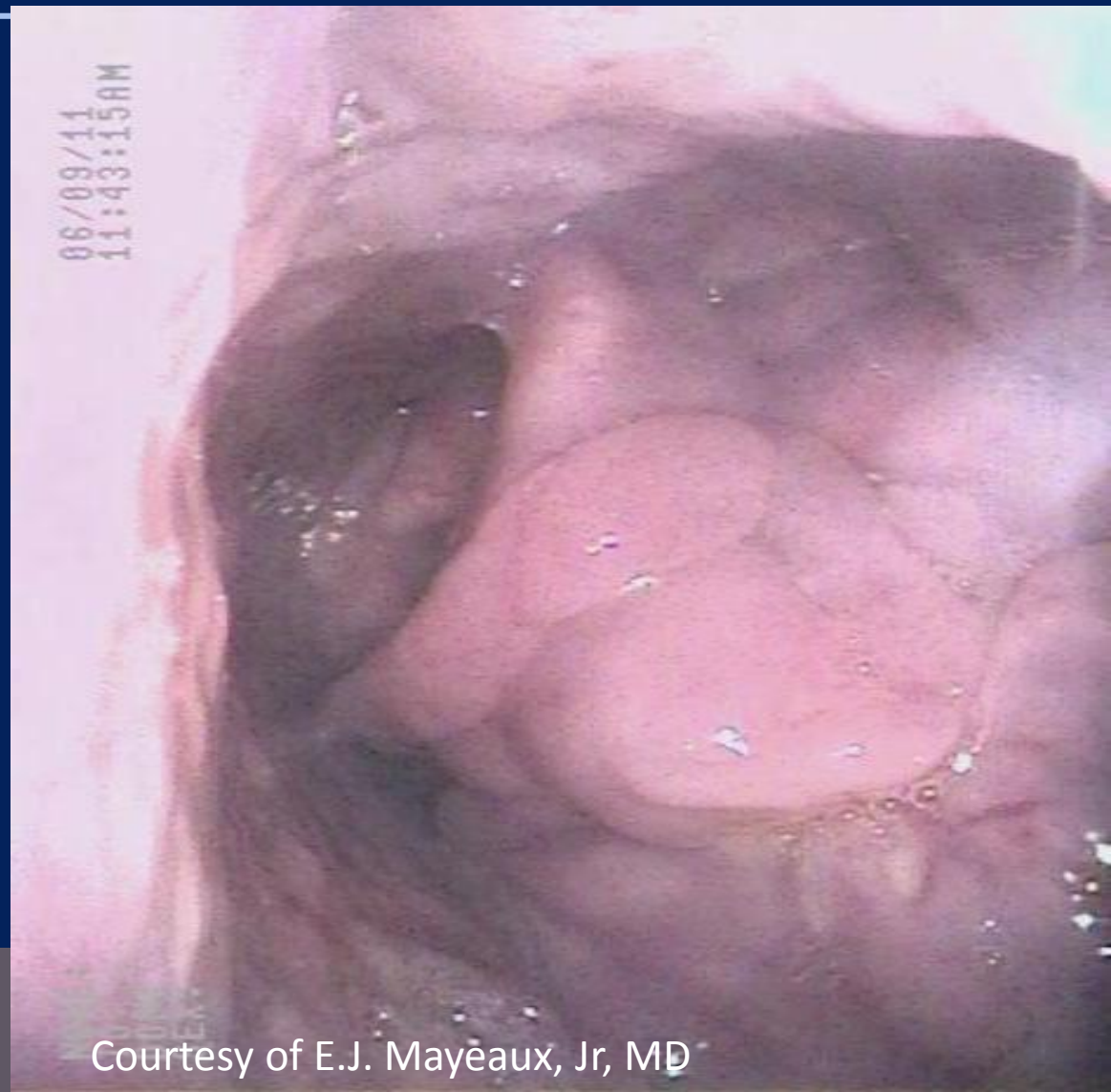
In 2012, the International Agency for Research on Cancer (IARC) stated that human papillomavirus (HPV) type 16 causes cancer of the oropharynx

World Health Organization. IARC monographs on the evaluation of carcinogenic risks to humans: volume 100B-Biological Agents. A review of human carcinogens. Lyon: International Agency for Research on Cancer 2012.

Risk Factors for HPV+ OPC

Probably 2 distinct pathways for OPC

- Carcinogenic effects of tobacco or alcohol
- HPV-induced



Courtesy of E.J. Mayeaux, Jr, MD

Parameter	HPV-Negative	HPV-Positive
Gender	2–3x men > women	4–5x men > women
Age	Median age late 50s and 60s	Median age early-mid 50s, with ↑ incidence in younger cohorts
Race	Worse prognosis in blacks	Higher incidence in whites
Smoking	>90% have smoking history; ↑ Risk with ↑ tobacco use	50%–65% have smoking history
Alcohol use	Synergistic with tobacco	Not a risk factor
Sexual hx	Not a significant risk factor	↑ oral sex partners ↑ risk
Site	Larynx and oral cavity mainly	Oropharynx, specifically tonsils and tongue base
Presentation	Varies	Enlarged Cx lymph nodes; OP pain, dysphagia, otalgia
Incidence	Decreasing	Increasing
Prognosis	Oropharynx: 5-year survival 20%–25%, 5-year rec. 50%	Oropharynx: 5-year survival 60%–90%, 5-year rec.10–15%

Rettig EM. Surg Oncol Clin N Am. 2015 Jul;24(3):379-396.

HPV+ OPC Characteristics

Patients with HPV-positive OPC [1]

- Younger by 5-10 years
- More likely to be non-smokers/drinkers
- Men and women seem to be at unequal risk
- Present with more advanced stage
- Cystic lymph node metastases common [2]
- Worse histology - poorly differentiated, basaloid histology [3]

1. Fakhry C. J Clin Oncol 2006;24: 2606-2611. 2. Goldenberg D. Head Neck 2008;30:898-903. 3. Adelstein DJ. Head Neck 2009;31:1393e1422.

Why is OPC 4x More Common in Men?

Three- to five-fold higher prevalence of oral high-risk and HPV 16 infections

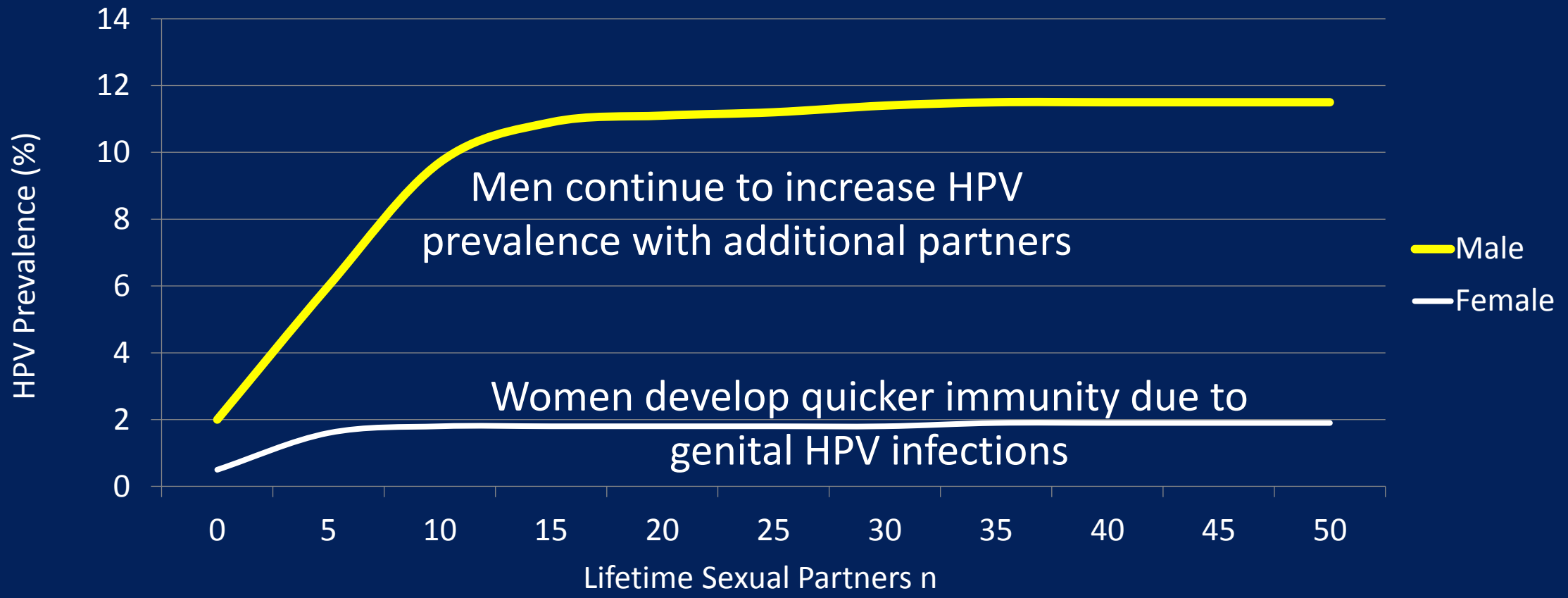
US men have a higher average number of lifetime oral sexual partners

3x higher transmission rates for HPV from female to male

Plateau in male prevalence at ~15 oral sexual partners in contrast to ~5 partners among women

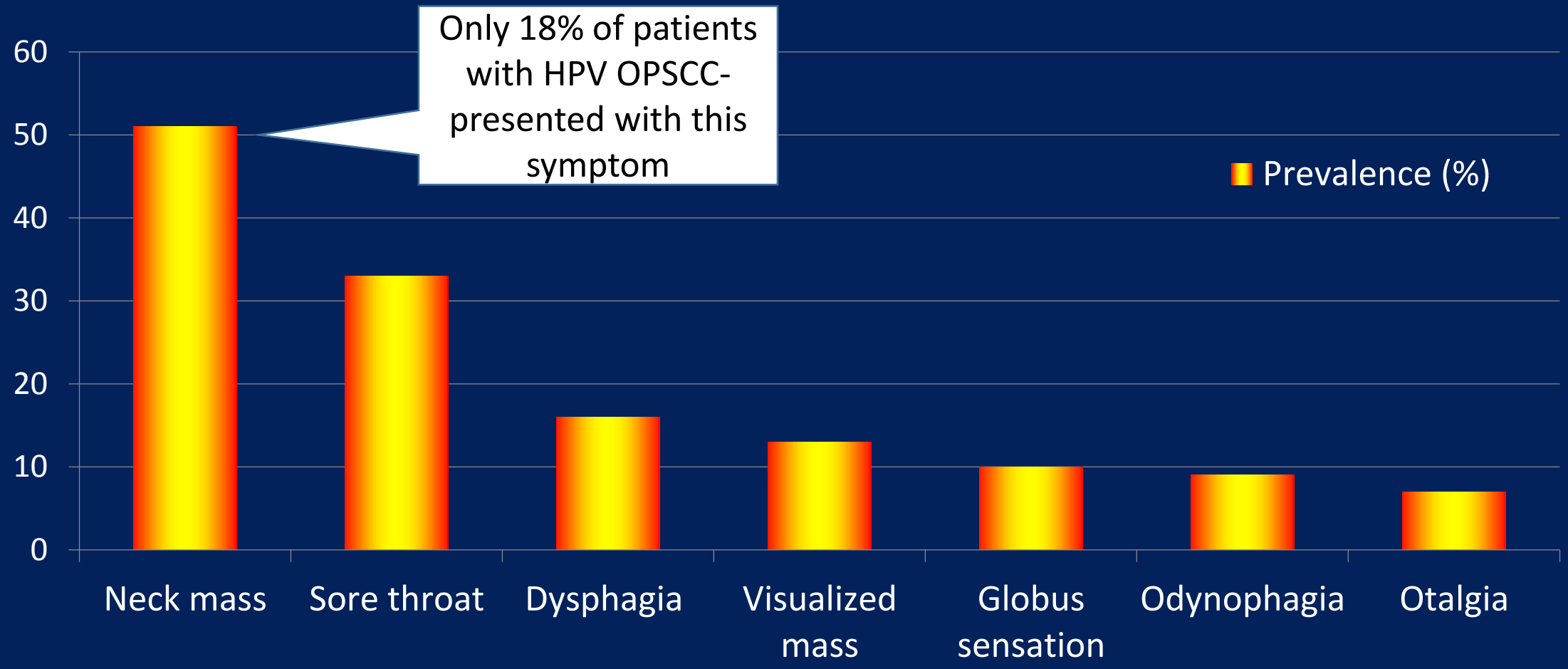
50% less seroconversion rates among men versus women after genital HPV infection (>protection against subsequent oral infections)

Lifetime number of oral sex partners and oral HPV prevalence – US ages 14 to 69 years (NHANES)



Modified from: McIlwain WR, et al. JAMA Otolaryngol Head Neck Surg 2014;140:441–7.

HPC+ OPC Presenting Symptoms



McIlwain WR, et al. JAMA Otolaryngol Head Neck Surg 2014;140:441–7.

Diagnosis of HNSCC

There are no validated or FDA approved tests to evaluate for precancerous OPSCC lesions (such as the Papanicolaou test and HPV DNA testing for cervical cancer)

A detailed review of systems and physical examination remain the most important method for early detection

Moore KA 2nd, Mehta V. J Am Board Fam Med. 2015 Jul-Aug;28(4):498-503.

NonFDA-approved Tests

- Visual examination
- Blue ligh tissue autofluorescence
- OraRisk®HPV test - Salivary DNA genotyping

- No FDA-approved test to diagnose HPV in mouth or throat
- Medical and dental organizations do not recommend screening for oral HPV
- More research is needed to find out if screening for these cancers will have health benefits

1. https://www.cdc.gov/std/hpv/stdfact-hpvandoropharyngealcancer.htm 2. http://www.oraldna.com/oral-hpv-testing.html
3. https://www.questdiagnostics.com/testcenter/testguide.action?dc=WP_Oral_HPV

Diagnosis of HNSCC

A unilateral neck mass who does not respond to antibiotics or has a history that is suspicious for HNC should receive an FNA and a CT scan in a timely manner

Suspicious lesions require timely workup and referral to an otolaryngologist

FNA is associated with minimal discomfort and can be performed in the office

- FNA of lymph node metastases had sensitivity & specificity of 88.2% and 100%
- Cells obtained by FNA can also be examined for HPV biomarkers

CT can provide information related to primary tumor size and location as well as metastatic spread

Moore KA 2nd, Mehta V. J Am Board Fam Med. 2015 Jul-Aug;28(4):498-503.

Prognosis of HPV+ HNSCC

HPV status important prognostic factor

- 50-80% reduction in risk of cancer-related death for HPV+ OPC [1-4]

HPV-positive OPC seems to have a better response to treatment with

- Induction chemotherapy [5,6,7]
- Radiotherapy [8]
- Combination Chemoradiotherapy [5,7]

1. Weinberger 2006. 2. Gillison ML 2000 3. Mellin 2000
4. Ritta 2009 5. Fakhry 2008 6. Kumar 2008 7. Worden 2008 8. Lassen 2009

Treatment of Oropharynx SCC

Treatment deintensification for OPSCC (only) being evaluated [1]

Clinical and radiographic delineation of tumors and staging are paramount to determining patients' eligibility

Ultrasound is not currently used in clinical evaluation [2]

- Promising imaging modality for evaluating the base of the tongue and the palatine tonsils

Ultrasound is comparable and complementary to CT and MRI, which have recognized limitations [2]

Coquia SF, et al. AJR Am J Roentgenol. 2015;205(6):1288-94.

Future Directions: Treatment

Higher survival rates seen in HPV+ OPC

HPV status becoming a routine molecular test for patients with OPSCC

Tx protocols being modified according to HPV status

De-escalation of treatment intensity for patients with HPV-positive OPC but not other HNSCC

Chakravarthy A, et al. J Clin Oncol. 2016 Dec;34(34):4132-4141.

Fakhry C, et al. J Natl Cancer Inst 2008; 100:261–269.

Treatment of HNSCC

Earlier stages treated with surgical excision or radiation alone [1]

Later stages treated with chemoradiation and surgical modalities a

More conservative treatment [2]

- Decreases morbidity from xerostomia and dysphagia from radiation therapy or side effects from chemotherapy
- Decreased likelihood of functional impairment related to resection

1. Broglie MA, et al. Laryngoscope 2013;123:164 –70.
2. Moore KA 2nd, Mehta V. J Am Board Fam Med. 2015;28(4):498-503.

Future Directions: Screening

Do paradigms for prevention of cervical cancer apply to OPC?

Will require :

- Premalignant phase
- A screening test (not necessarily cytology)
- Treatment to prevent progression

Future Directions: Screening

Most likely candidate for a screening test is HPV testing

- Odds ratios for oral HPV16 infection and OPC are less than for cervical cancer
- May be limitation of sampling technique
- Research vs clinical tools

Tonsillectomy or destruction for tx

Munoz N. N Engl J Med 2003;348:518-527.

Future Directions: Prevention

Prophylactic HPV vaccination

Both of the commercially available vaccines target HPV types 16 and 18

- Up to 95% of HPV+ OPC associated with HPV16 infection
- Vaccination may reduce prevalence of HPV16 and reduce HPV+ OPC
- Very long-term prospect

Need data on outcomes

Future Directions: Vaccination

Vaccine efficacy against OP HPV infection unknown

Regulatory agencies have required a clinical disease end point for trials

- No such lesions for HPV-positive OPC

In 2014, WHO rec. efficacy against incident and persistent HPV infection

- No study meets this yet

Gillison ML, et al. J Clin Oncol. 2015 Oct 10;33(29):3235-42.

Oral HPV Patient Ed Points

Initial studies suggest that most people clear oral HPV infections within 1-2 years

- Some oral HPV infections persist [1]

More common in individuals with higher number of lifetime and recent vaginal and oral sexual partners [2]

- Rarely detected with no oral sex [2]

Not a marker of promiscuity [2]

1. D'Souza G, et al. In: 28th IPV conference, Puerto Rico; 2012. p. 215.
2. Gillison ML, et al. JAMA J Am Med Assoc 2012;307:693–703.

Oral HPV Patient Ed Points

Unknown whether open-mouth kissing can transmit HPV

Three studies reported an association [1-3]

- Limited by small sample sizes and confounding variables

Other studies have not found an association [4,5]

1. Gillison ML, 2012; 2. D'Souza G, 2009; 3. Pickard RK, 2012. 4. Beachler DC, 2012; 5. Edelstein ZR, 2012

Partners Patient Ed Points

May have slightly higher rates of other HPV-associated cancers

- Cancers rare and absolute risk is low [1]
- Women should follow cervical cancer screening guidelines [2]

No screening guidelines for OP

OP ‘‘Pap-test equivalent’’ studied

- May not be useful for early detection of Ca [3]

1. Capone RB, et al. Am Assoc Cancer Res 2000;6:4171–5.
2. ASCCP Guidelines. 3. Fakhry C, et al. Cancer Prev Res (Phila) 2011;4:1378–84.

Safer Sex

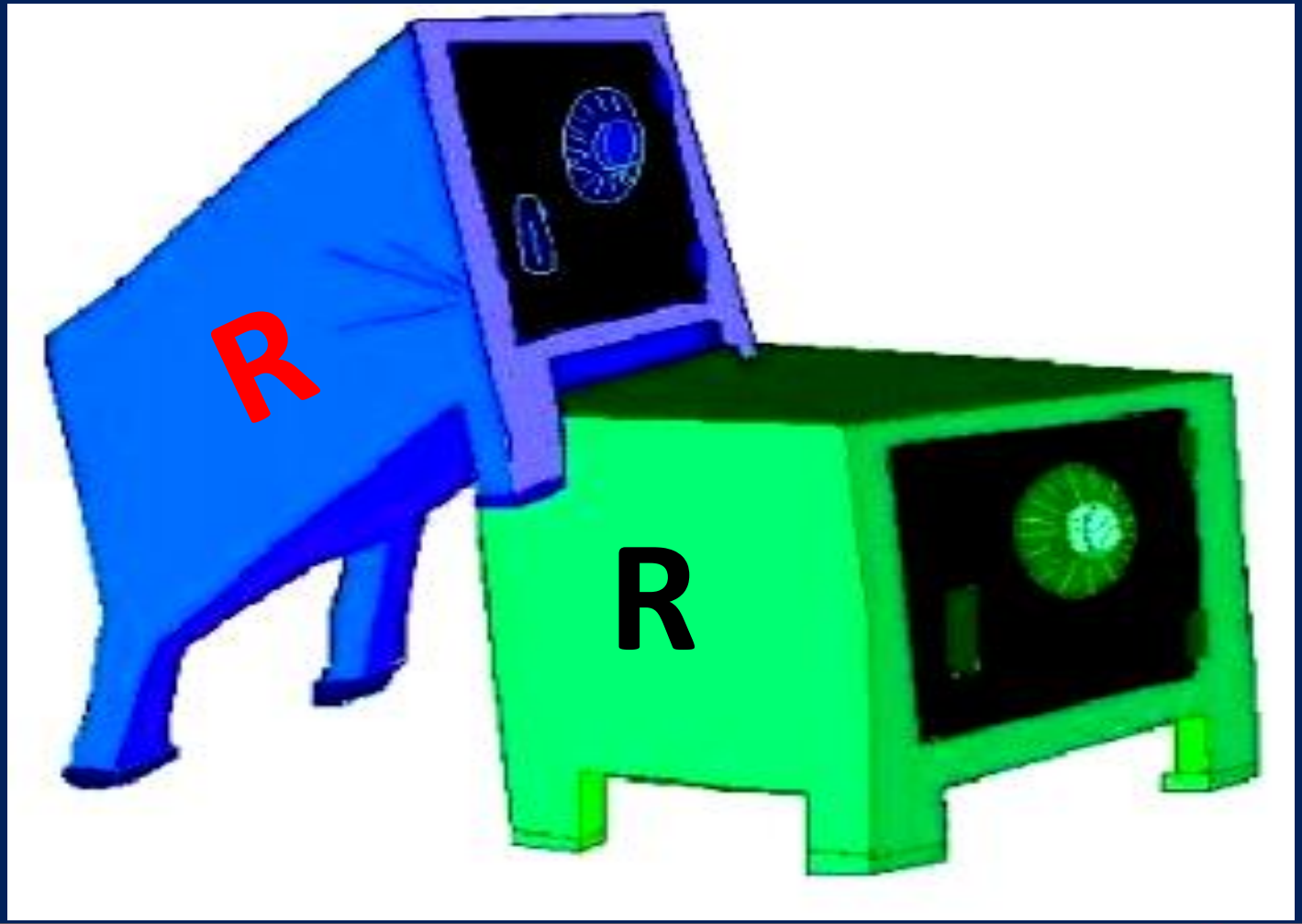


Photo by Alan Waxman, MD