# Human Papillomavirus(HPV) Related Head and Neck Cancer: Increasing Incidence and Evolving Treatment

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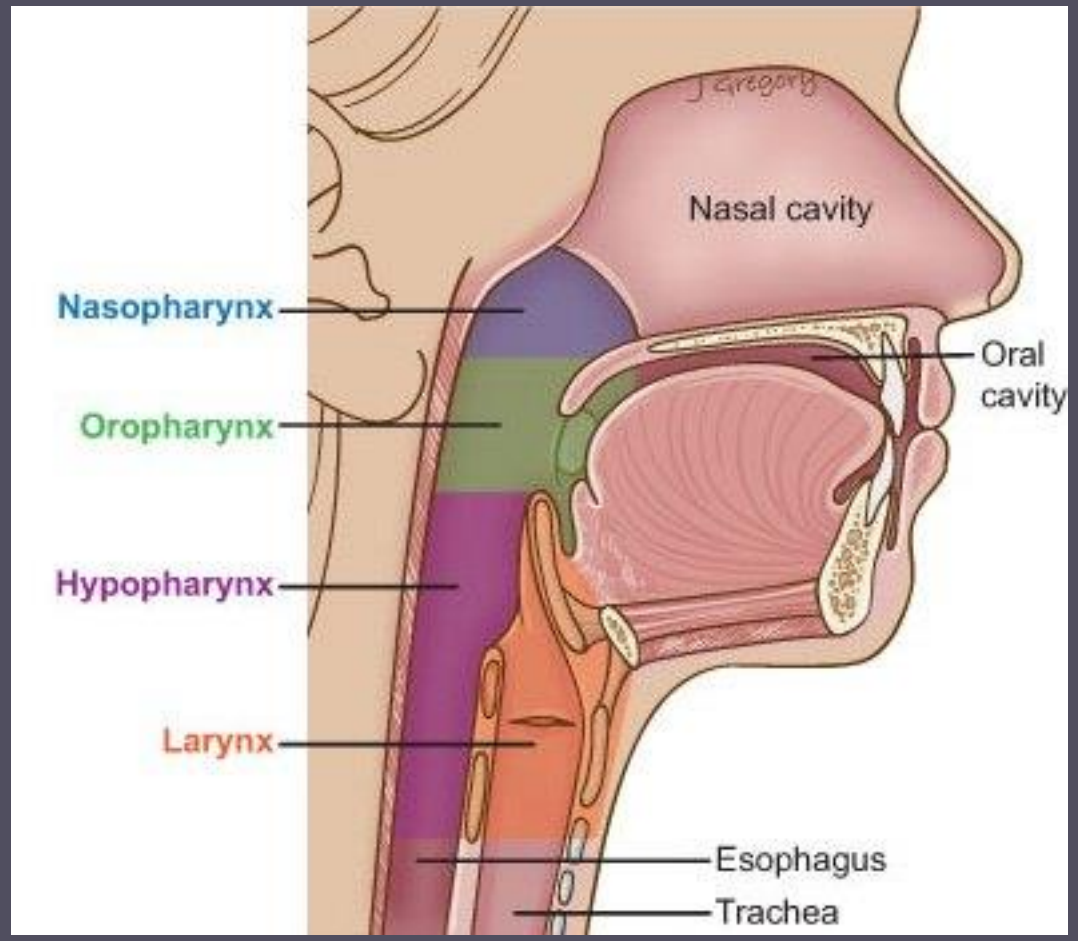
Head and Neck Surgery

February 12th, 2018

# Objectives

- Overview of Head and Neck Cancer (HNC)
- HPV infection and transmission
- Discuss the link between Human Papillomavirus (HPV) and (HNC)
- Trends in HPV related HNC
- Clinical Presentation
- Treatment
- Prevention

# Head and Neck Cancer (HNC)

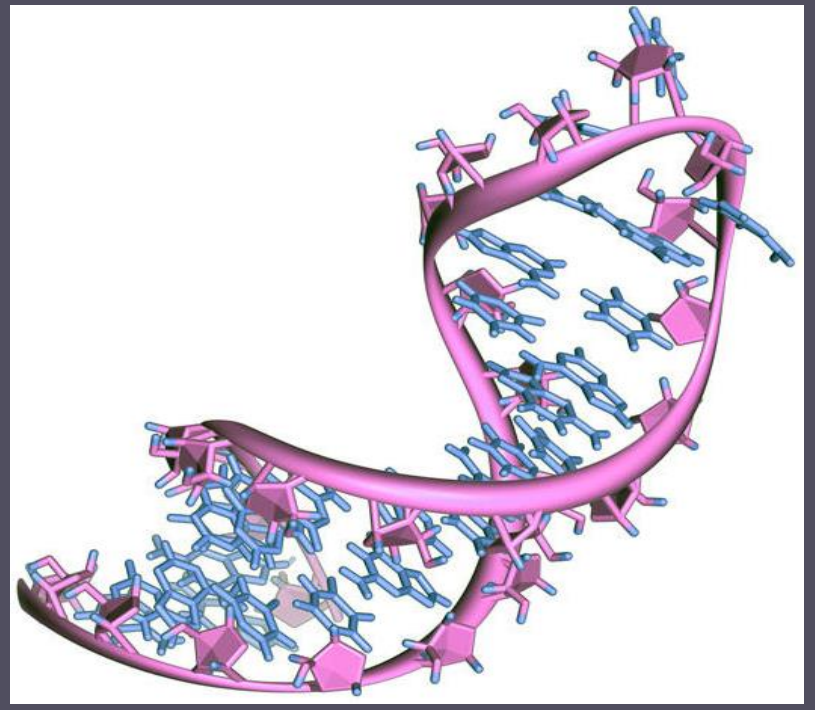



- Arise from the mucosa lining the oral cavity, oropharynx, hypopharynx, larynx, sinonasal tract and nasophaynx.
- Sixth most common cancer worldwide
- The most common pathology is squamous cell carcinoma
- Pathogenesis has historically been associated with tobacco and alcohol

# Human Papillomavirus (HPV)

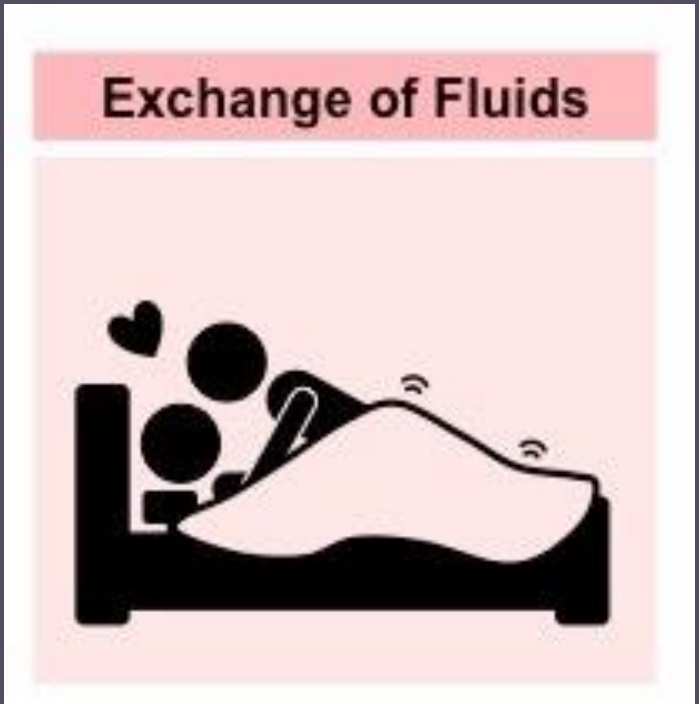
- HPV infections are the most common sexually transmitted infections in the United States.
- About 14 million new genital HPV infections occur each year.
- CDC estimates that more than 90% of sexually active men and 80% of women will be infected with at least one type of HPV at some point in their lives.
- Around one-half of these infections are with a high-risk HPV type

# Human papillomavirus (HPV)



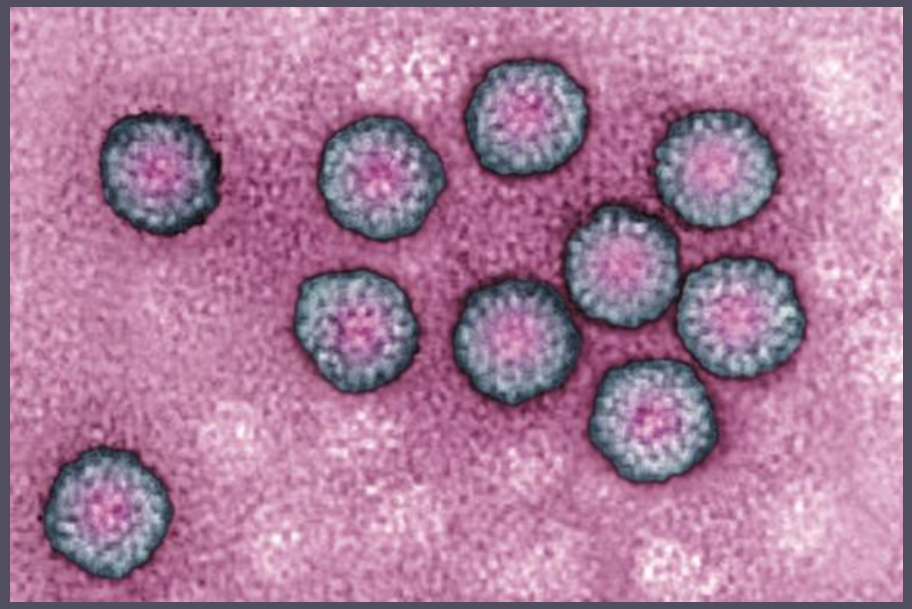
- Double-stranded DNA virus
- 179 distinct HPV genotypes
- Low risk HPV subtypes:
  - skin warts
  - genital warts
  - recurrent respiratory papillomatosis
  - nasal/oral papilloma
- High risk HPV subtypes cause cancers:
  - cervix
  - head and neck
  - anus, vagina, vulva, and penis
- The most commonly implicated subtype in HNC is HPV16
  - Over 80% of HPV+ HNC

# HPV Transmission




- Transmission of HPV is primarily through sexual contact
- A greater number of lifetime sexual partners is associated with a higher likelihood of acquiring HPV
  - even a person with a few or even one lifetime sexual partner can get infected
- Transmission does not require presence of visible lesions
- Transmission of HPV frequently occurs from persons who are asymptomatic or have subclinical infection

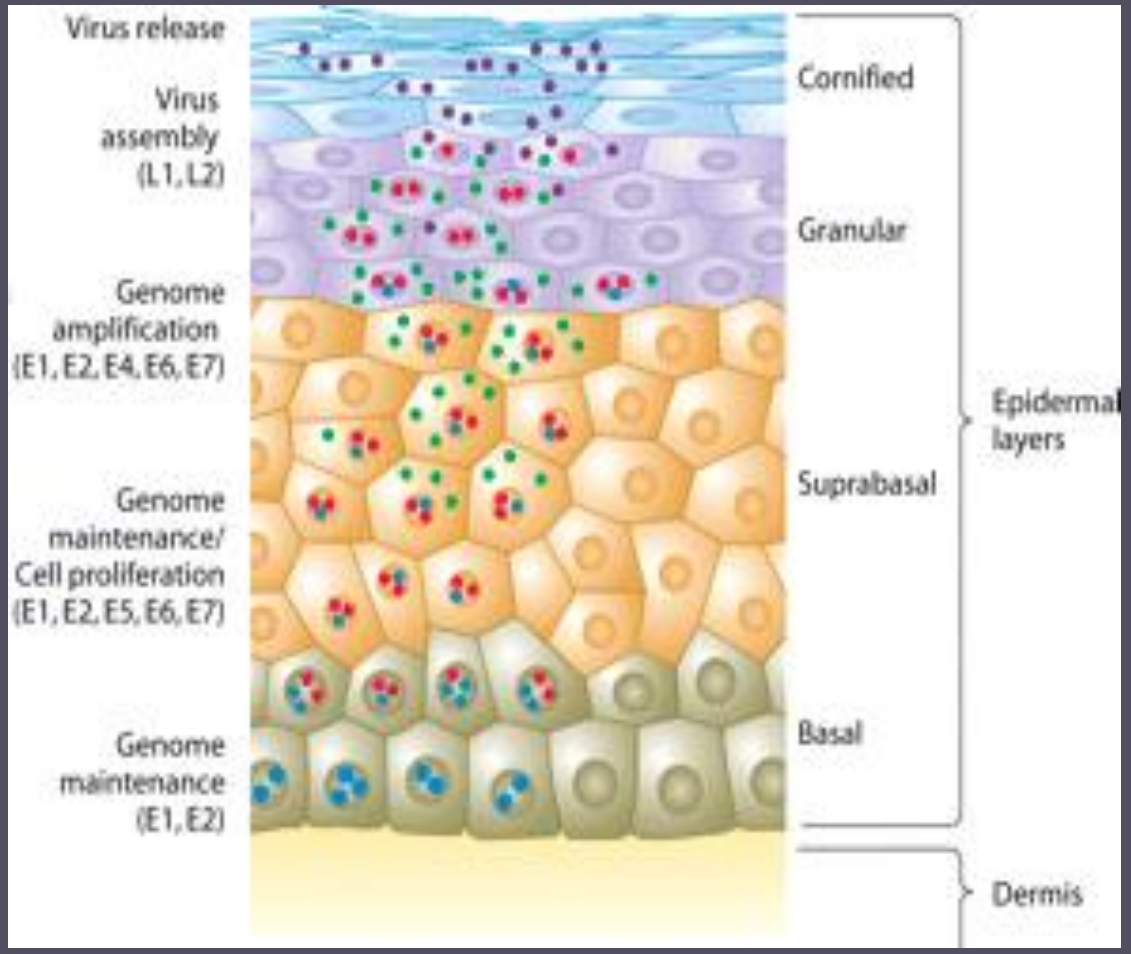
# HPV Infection



- Most individuals will experience transient HPV infection but the immune system will recognizes and clear the virus
- 90% of these infections are clinically silent and resolve spontaneously within 2 years
- Sometimes, the virus is able to integrate and a persistent infection results.
- The incubation period from acquisition to clinical manifestations is variable: months-years
- If cancer develops, it typically occurs decades after the initial infection

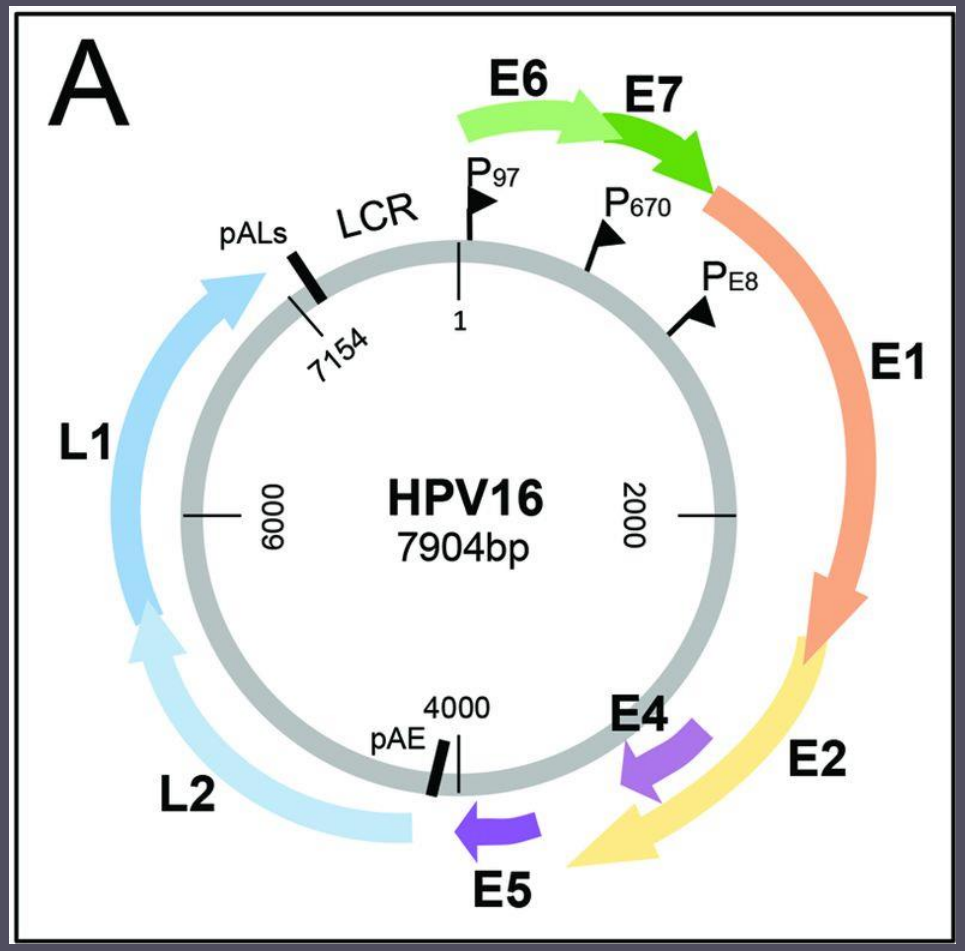
# Human papillomavirus (HPV)

- HPV preferentially targets the reticulated epithelium lining the tonsillar crypts
- HPV infect cells in the basal layer of stratified epithelia and establish their genomes as multicopy nuclear episomes.
- In these cells, viral DNA is replicated along with cellular chromosomes.



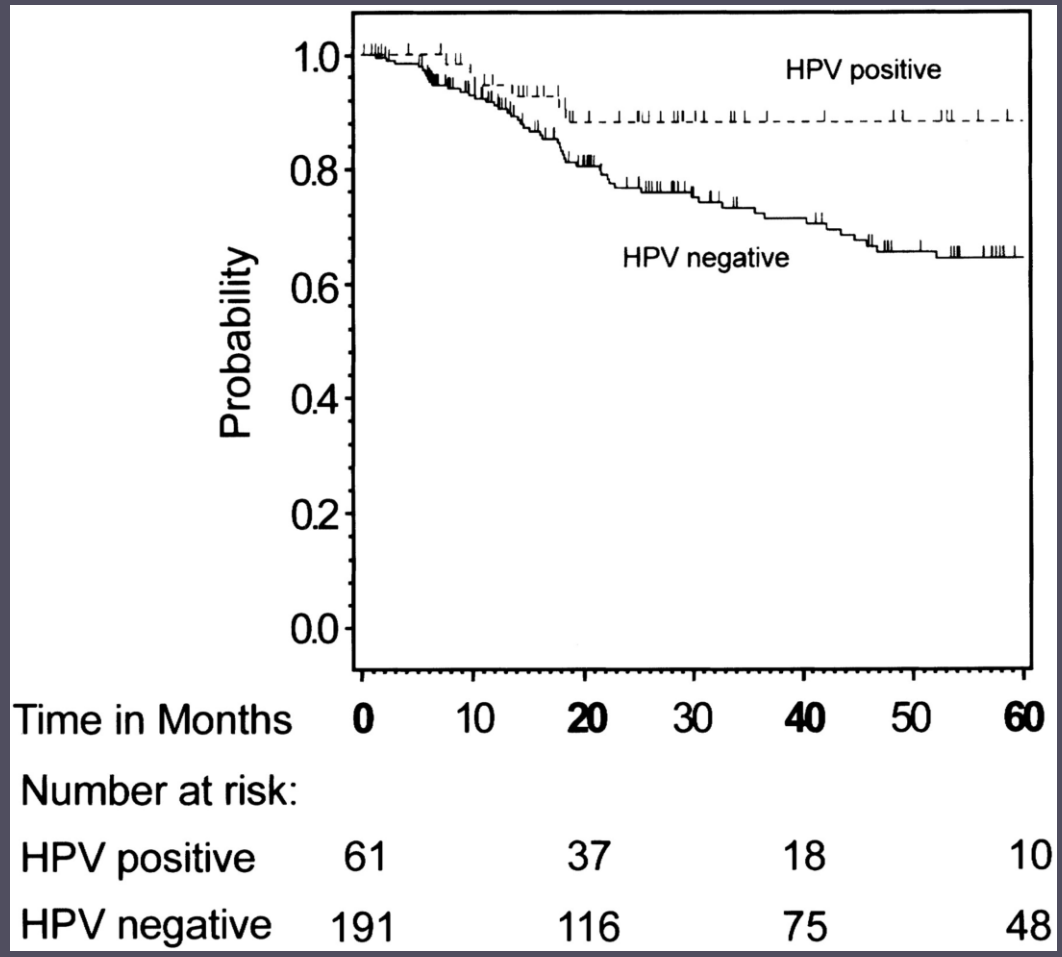
# Human papillomavirus (HPV)

- Integrated virus dysregulates the expression of the oncoproteins E6 and E7
- The E6 protein induces degradation of p53, a tumor suppressor
- The E7 protein binds and inactivates the retinoblastoma(Rb), upregulates p16
  - allowing unchecked cell division, proliferation and malignant transformation



# HPV & HNC

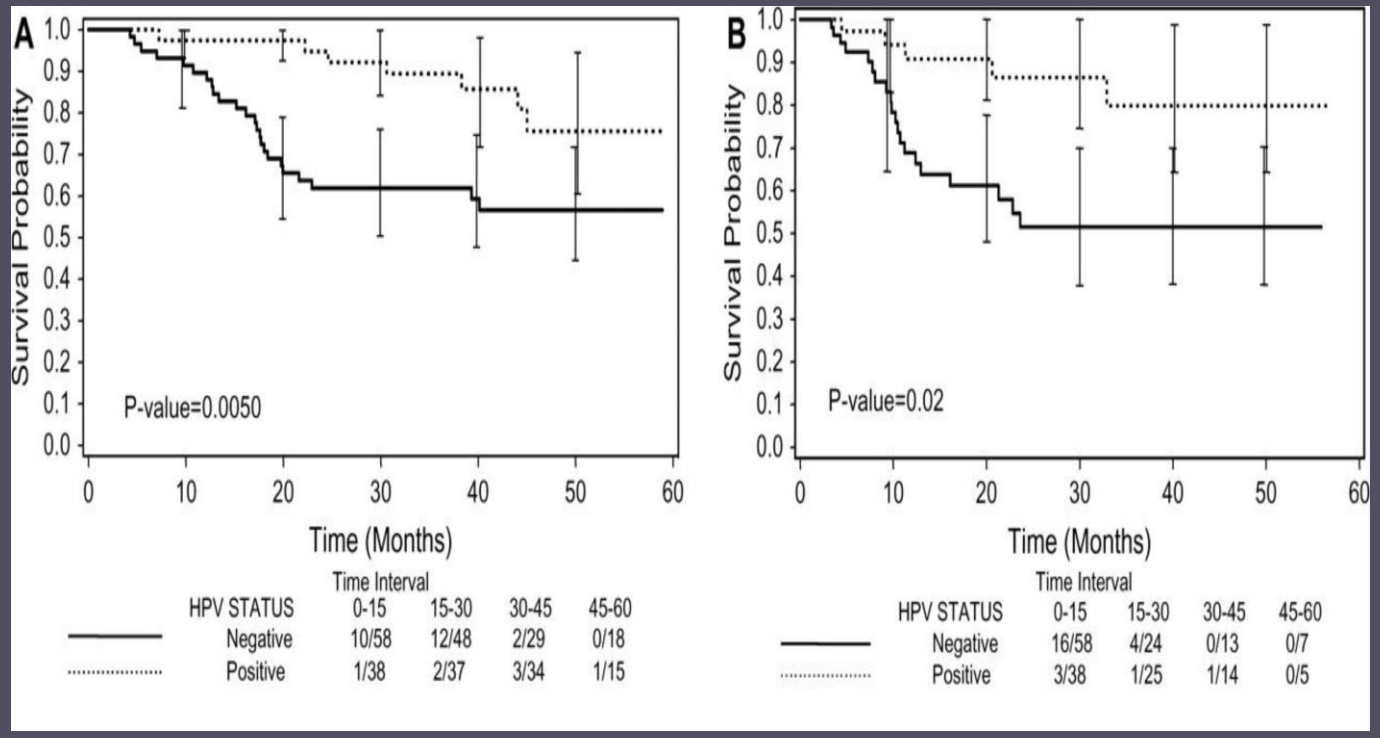
- 1980s and 90s, evidence emerged that an increasing fraction of oropharyngeal cancers was associated with high-risk human papilloma viruses, primarily HPV 16.
- HPV in 25% of patients
- Inverse relationship of HPV detection with alcohol and smoking exposure
- HPV-related patients appeared to have improved disease-specific survival.





- Gillison, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst. 2000 May 3;92(9):709-20.

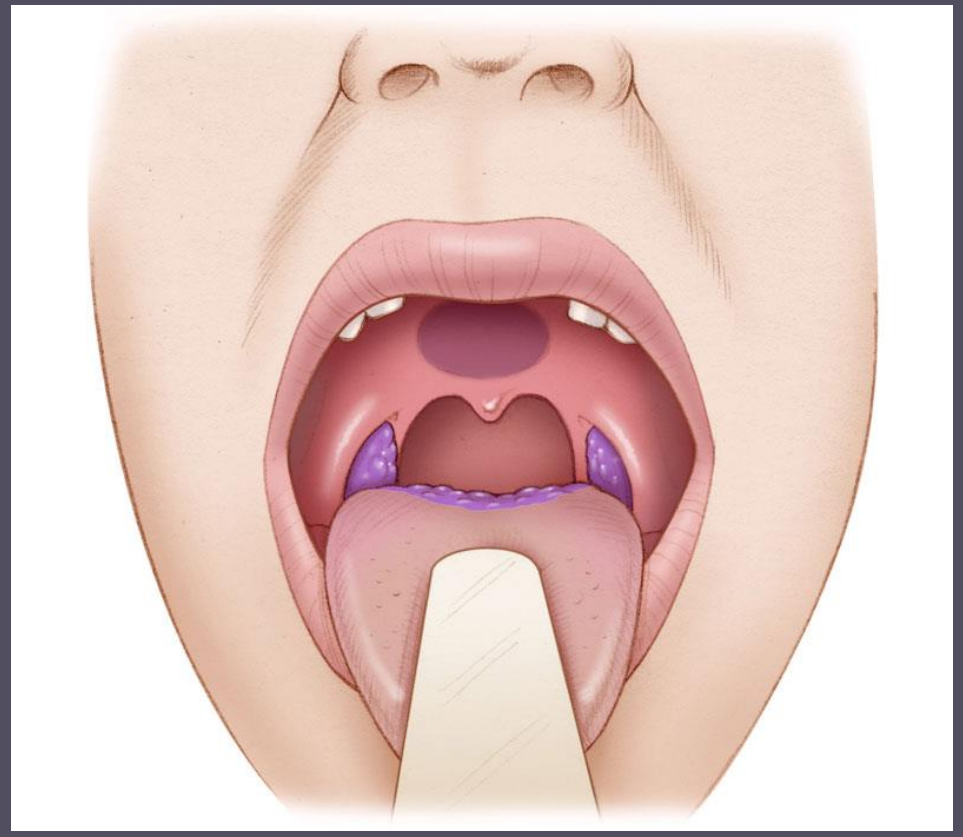
# HPV& HNC



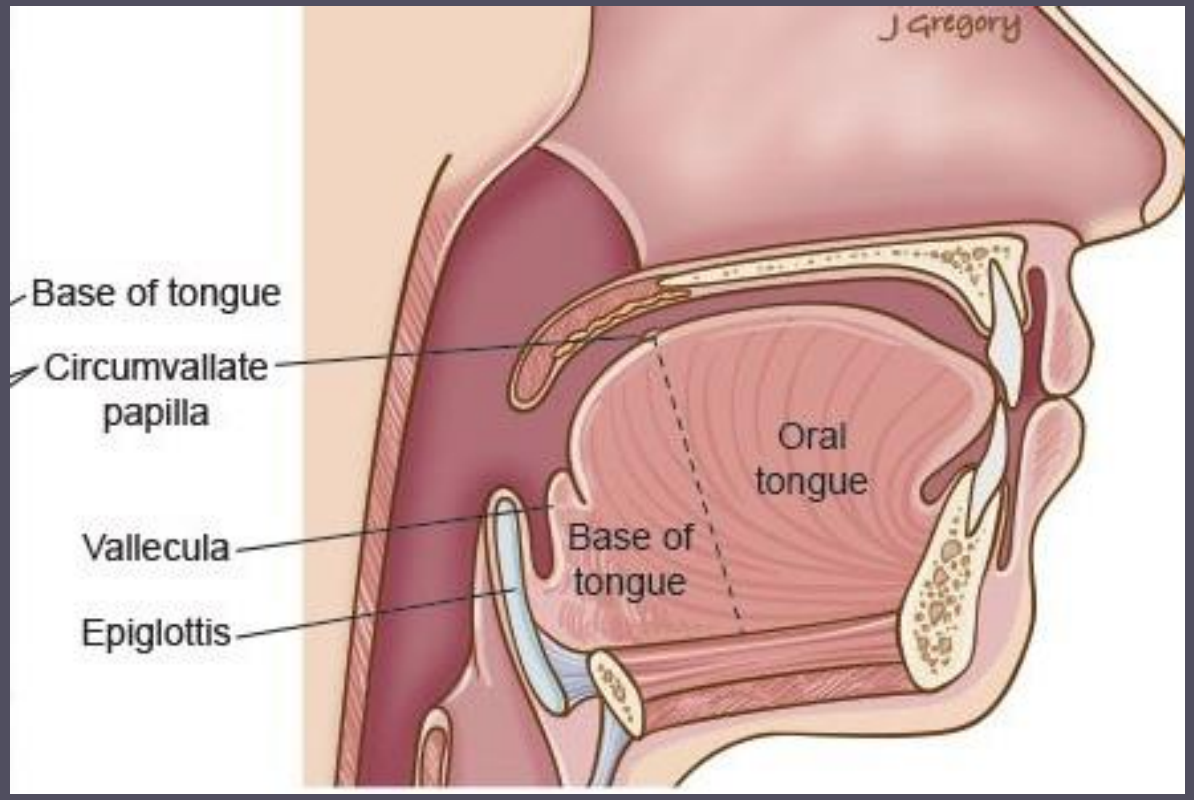

Fakhry, et al;. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008 Feb 20;100(4):261-9.

- Eastern Cooperative Oncology Group (ECOG) 2399
- Patients with oropharyngeal or laryngeal cancer were prospectively treated with two cycles of induction chemotherapy, followed by concomitant chemoradiotherapy
- The patients with HPV-positive tumors had higher response rates and an improved two-year overall survival of 95% compared with 62% of patients with HPV-negative tumors

# Oropharyngeal Carcinoma

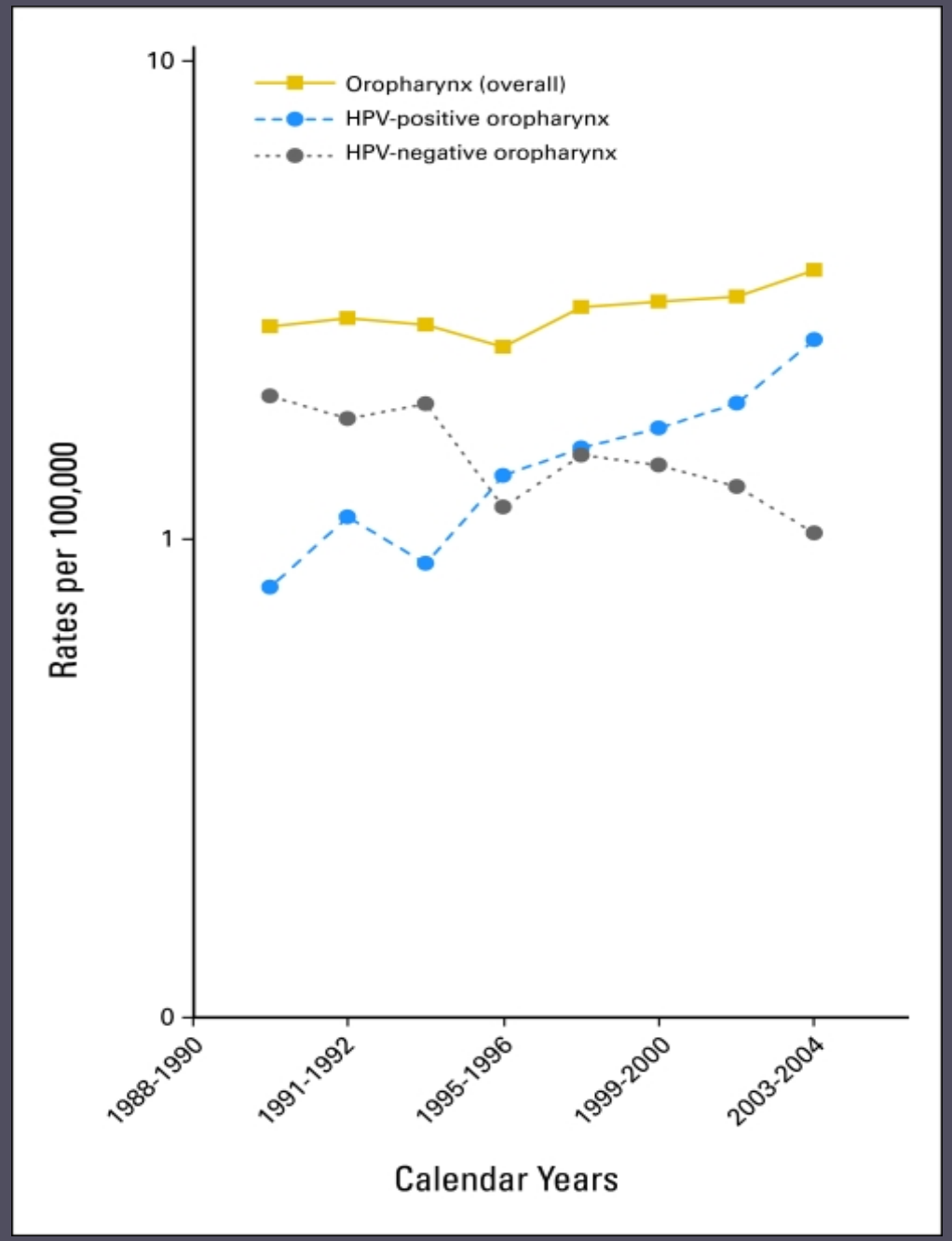


# Oropharyngeal Carcinoma



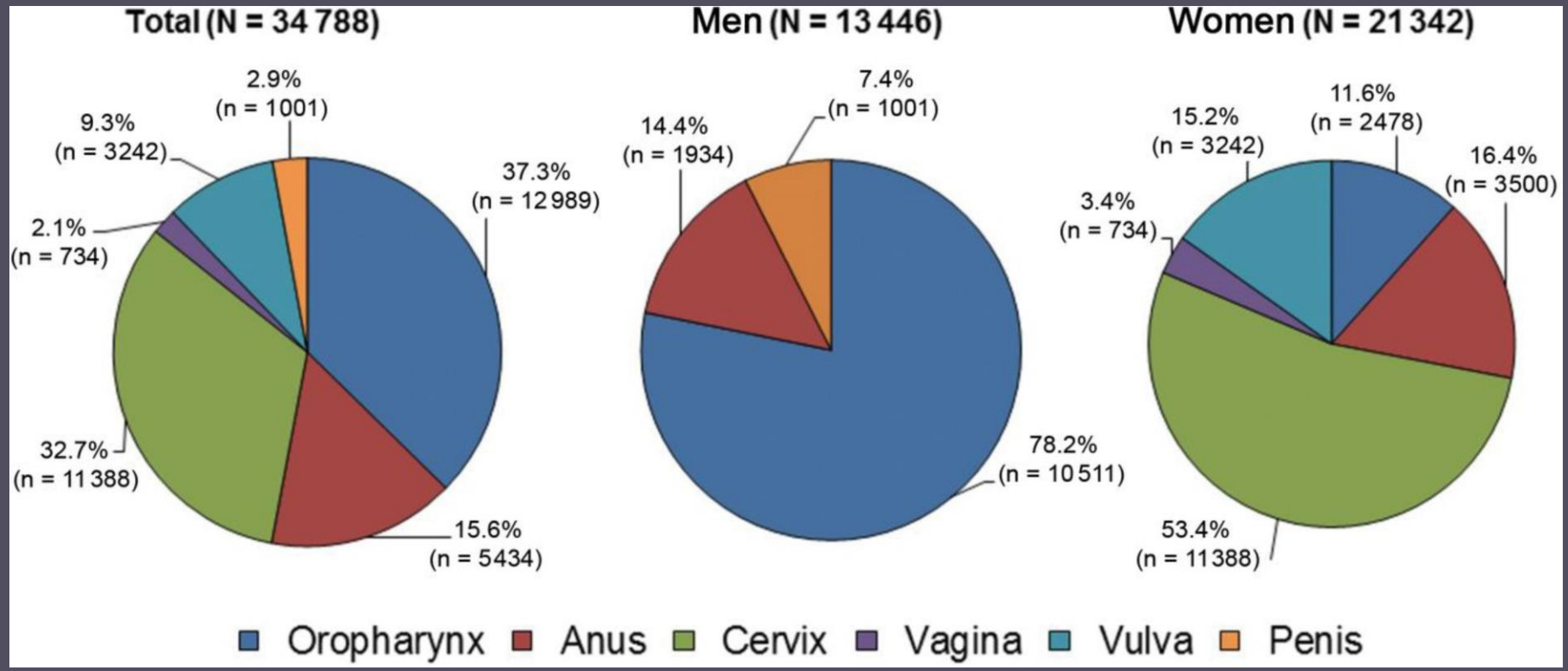

# Increasing Incidence

- Over the past three decades, there has been an increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC).
- From 1988 to 2004, there was a 225% population-level increase in HPV-positive OPSCC in the United States (from 0.8 cases per 100,000 individuals in 1988 to 2.6 per 100,000 in 2004)
- 50% decrease in HPV-negative OPSCC (from 2.0 cases per 100,000 individuals in 1988 to 1.0 per 100,000 in 2004.



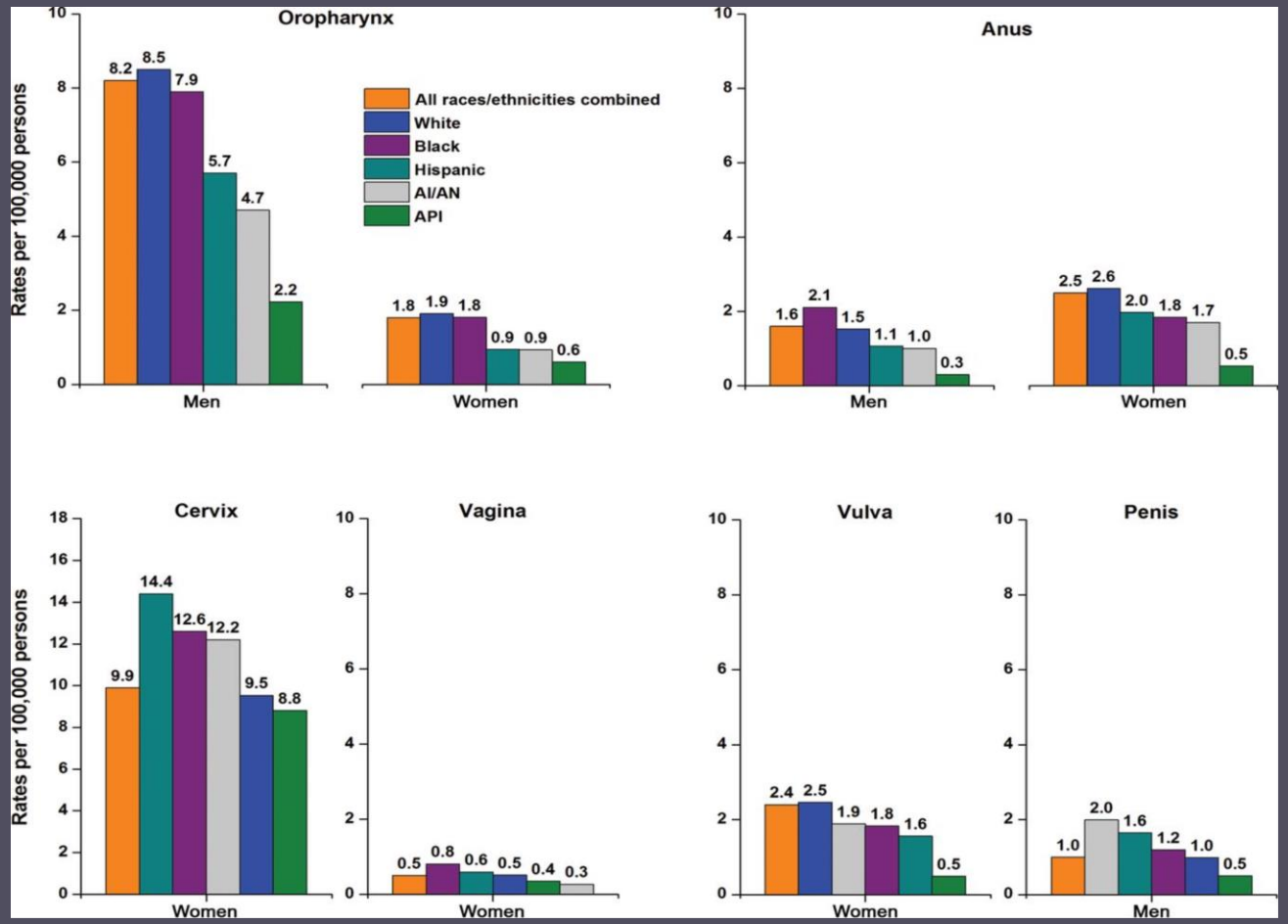

Chaturvedi, et al. Human Papillomavirus and Rising Oropharyngeal Cancer Incidence in the United States. J Clin Oncol. 2011 Nov 10; 29(32): 4294–4301.

# Number of new human papillomavirus (HPV)–associated cancers

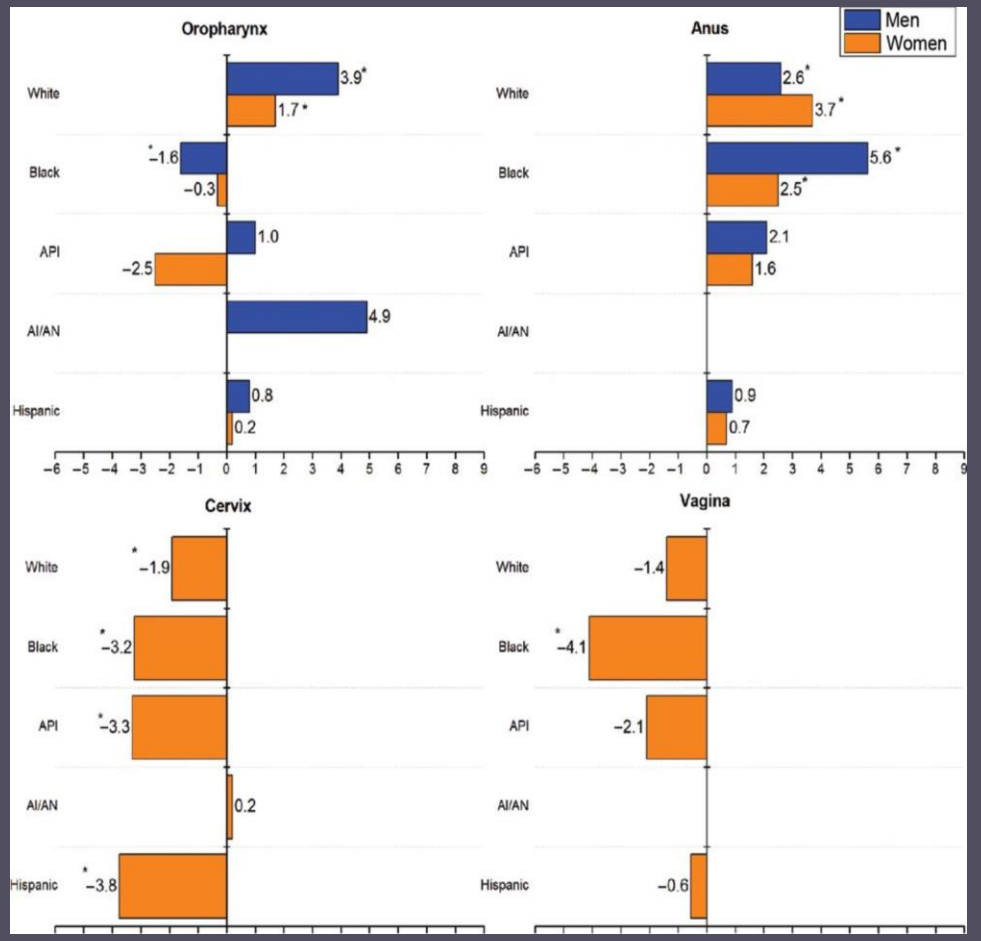



Annual Report to the Nation on the Status of Cancer, 1975-2009, featuring the burden and trends in human papillomavirus(HPV)-associated cancers and HPV vaccination coverage levels. J Natl Cancer Inst. 2013 Feb 6;105(3):175-201.

# HPV OPSCC Incidence



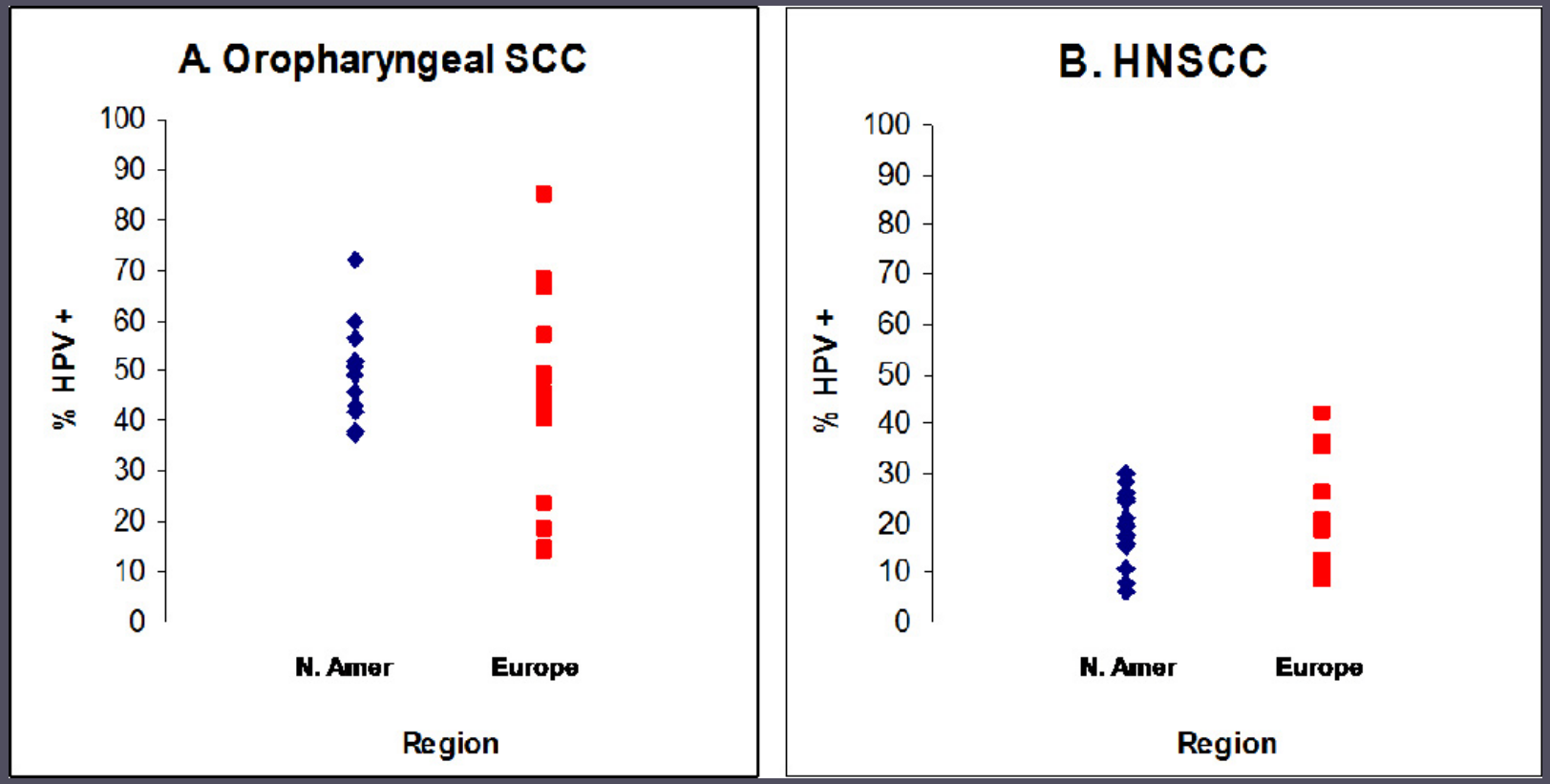

Age-Adjusted incidence rates



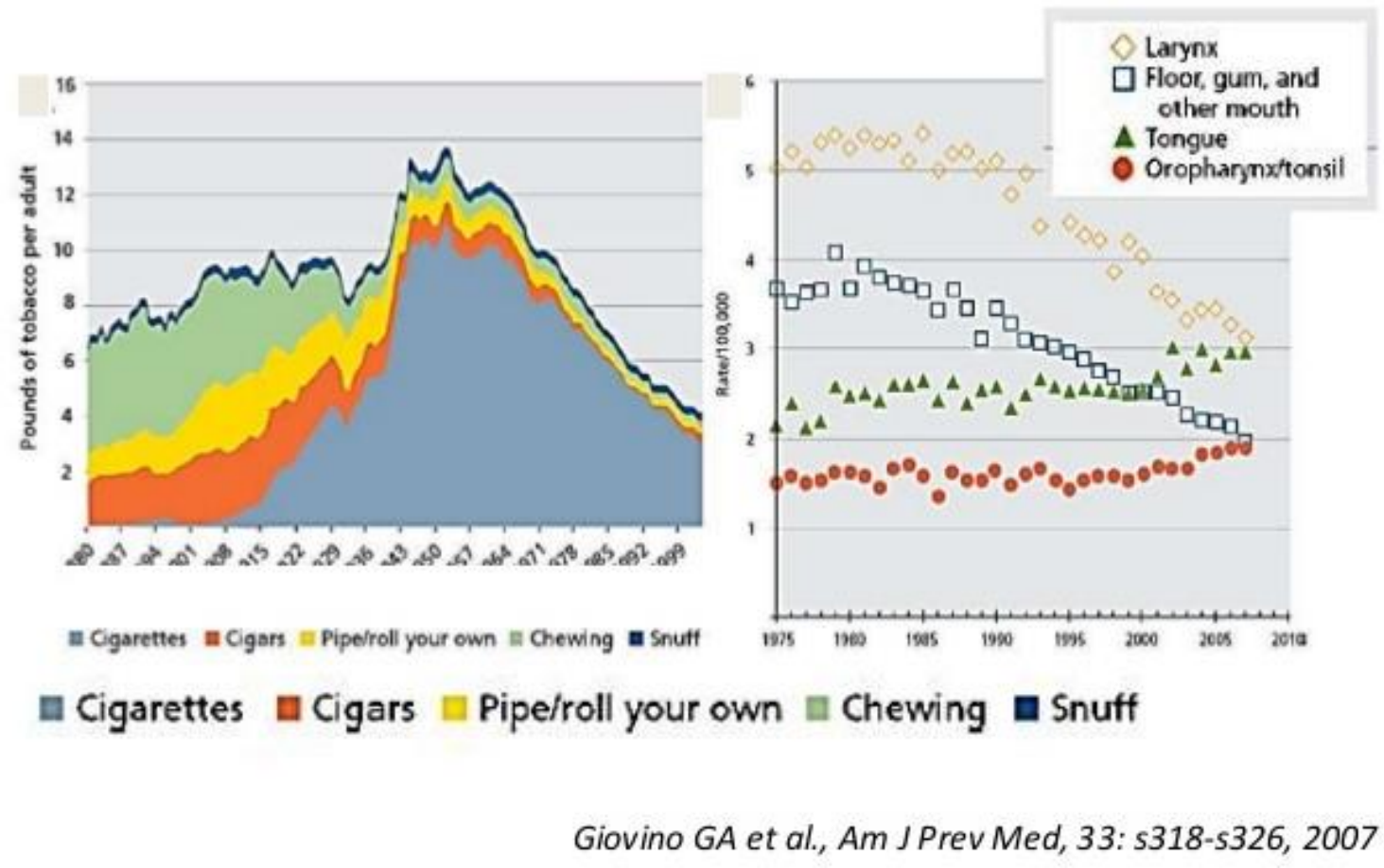

Annual % change in incidence

# Increasing Incidence Worldwide (HPV) & Head and Neck Cancer

- Human papillomavirus (HPV) is involved in up to 25% of HNCs, up to 70-90% of <u>oropharyngeal cancer</u>



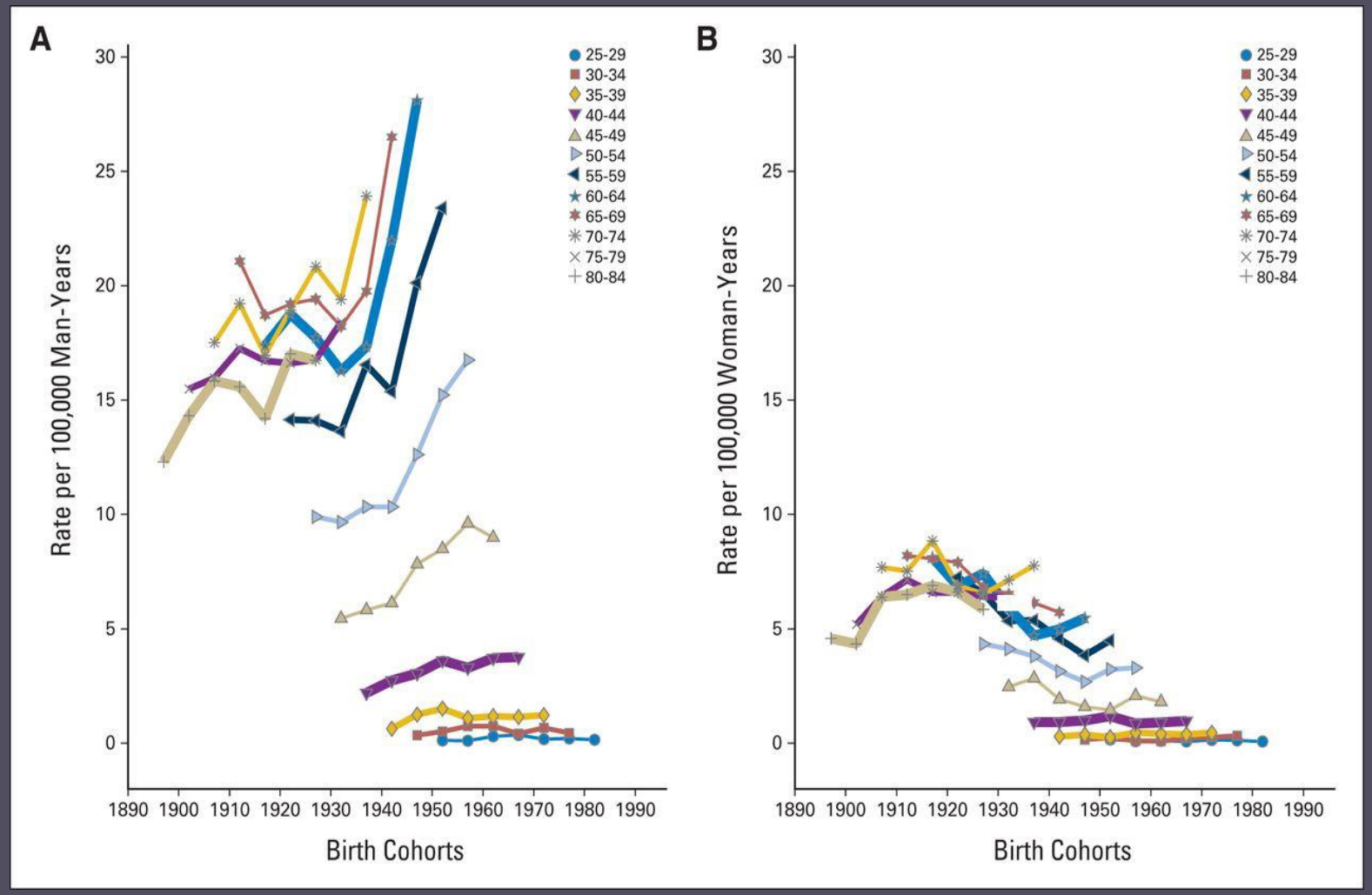
# Increasing Incidence Worldwide




*Giovino GA et al., Am J Prev Med, 33: s318-s326, 2007*

- In the U.S. HPV DNA prevalence of 29% in 1990 to 65% in 2000, to 72% in 2005
- 1995-2010 29% to 63% in Australia
- Swedish Cancer Registry: found tonsillar cancer increased 3.5-fold in women and 2.6-fold in men between 1970–2002
- England incidence increased by 58% from 1995 to 2011

# Future Burden of Disease



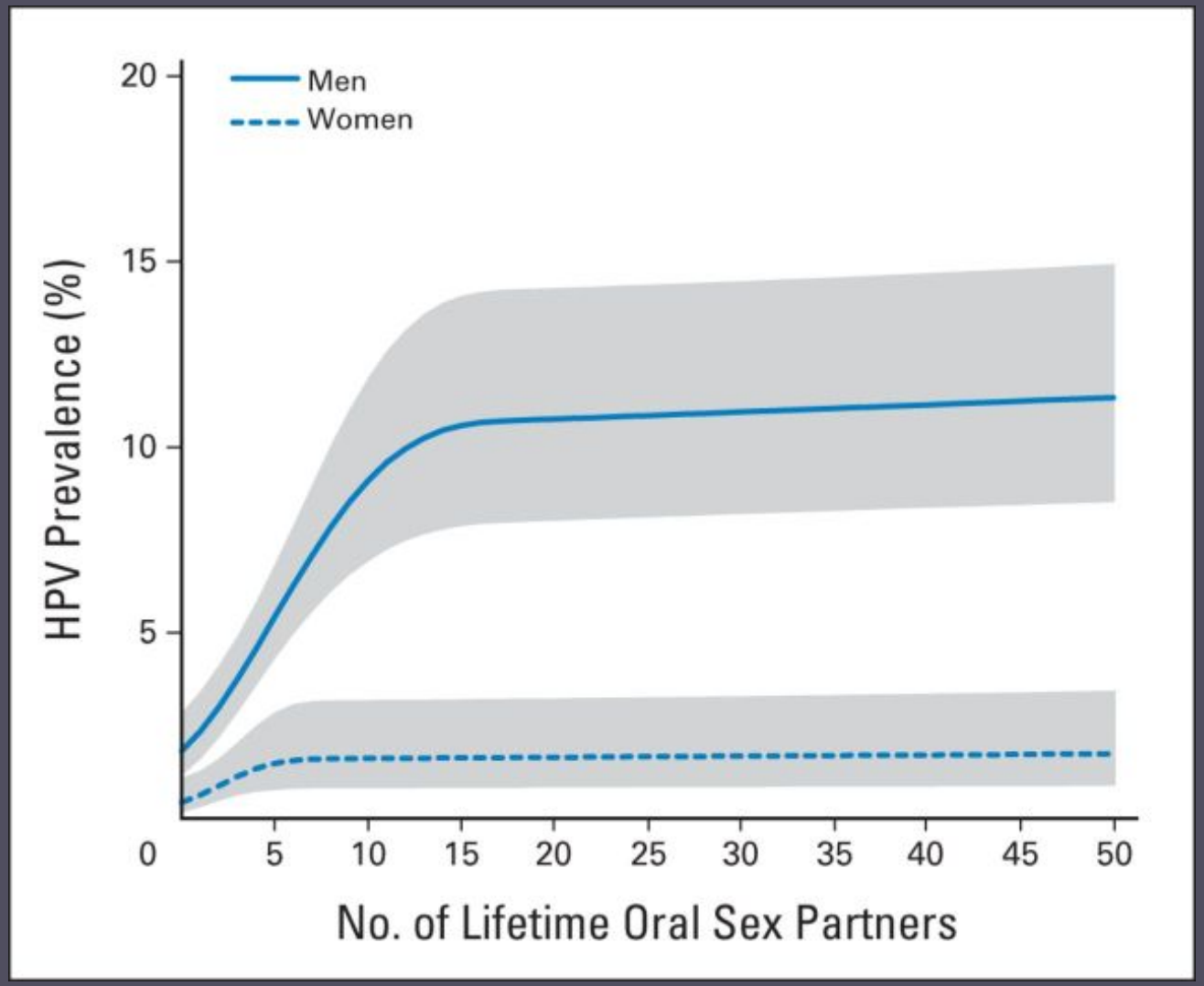

- Oropharyngeal cancers were 1 of 5 cancers to increase in incidence from 1975-2009
- Increased incidence risk for men age 40-70
- Projected to increase in incidence for the next 30 years

# Risk Factors for HPV HNC

- Sexual Behavior is the strongest risk factor for OPC
- Six or more lifetime sexual partners
  - [OR = 1.25, 95% confidence interval (CI) 1.01, 1.54]
- Four or more lifetime oral sex partners
  - (OR = 2.25, 95% CI 1.42, 3.58)
- Ever having oral sex
  - (OR = 1.59, 95% CI 1.09, 2.33)
- Earlier age at sexual debut
  - (OR = 2.36, 95% CI 1.37, 5.05)
- Women: ever having oral sex
  - (OR = 4.32, 95% CI 1.06, 17.6),
- More than one sexual partner
  - (OR = 2.02, 95% CI 1.19, 3.46)
- HPV+ HNC can occur among individuals reporting few sexual partners.

Heck, et al. Sexual behaviours and the risk of head and neck cancers: a pooled analysis in the International Head and Neck Cancer Epidemiology (INHANCE) consortium. Int J Epidemiol. 2010 Feb;39(1):166-81.

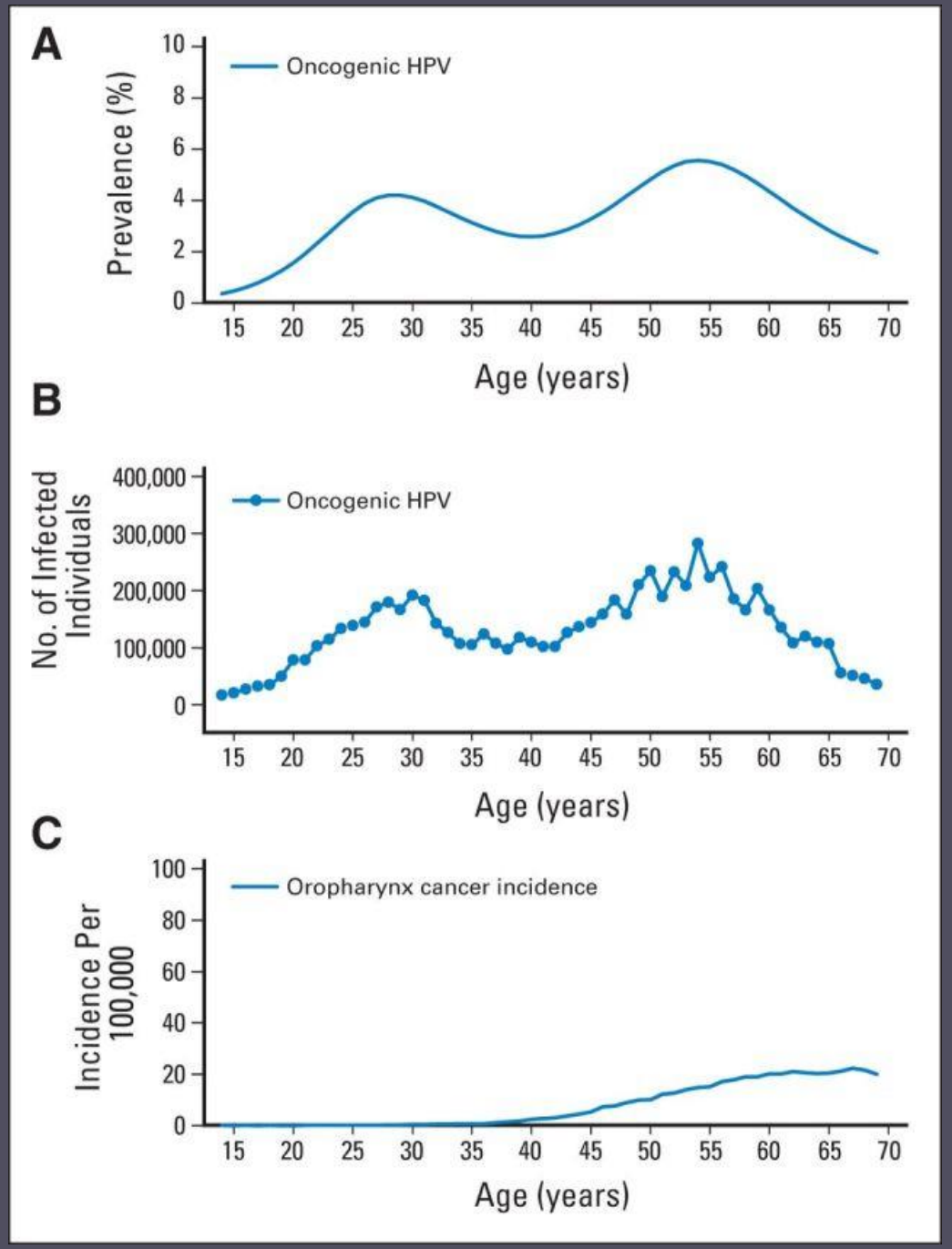
# Risk Factors for HPV HNC




- Prevalence of oral HPV infection is 2-3 times higher in men than women (10% vs. 3.6%)
- NHANES data (2009 to 2012) demonstrated the per sexual partner increase in high-risk oral HPV prevalence to be three-fold greater for men than for women
- This sex difference may reflect reduced seroconversion rates among men versus women after genital HPV infection, resulting in greater protection against subsequent oral infections among women.

# Oral HPV Infection

- Oral HPV infection is the main risk factor for OPC
- 3–5% of adolescents and 5–10% of adults have an oral HPV infection
- Oral oncogenic HPV infection prevalence peaked at ages 25 to 30 years and 55 to 60 years,
- Median age at OPC diagnosis was 63
- Estimate an average latency period for HPV-positive OPC of approximately 10 to 30 years



# Risk Factors for persistent infection

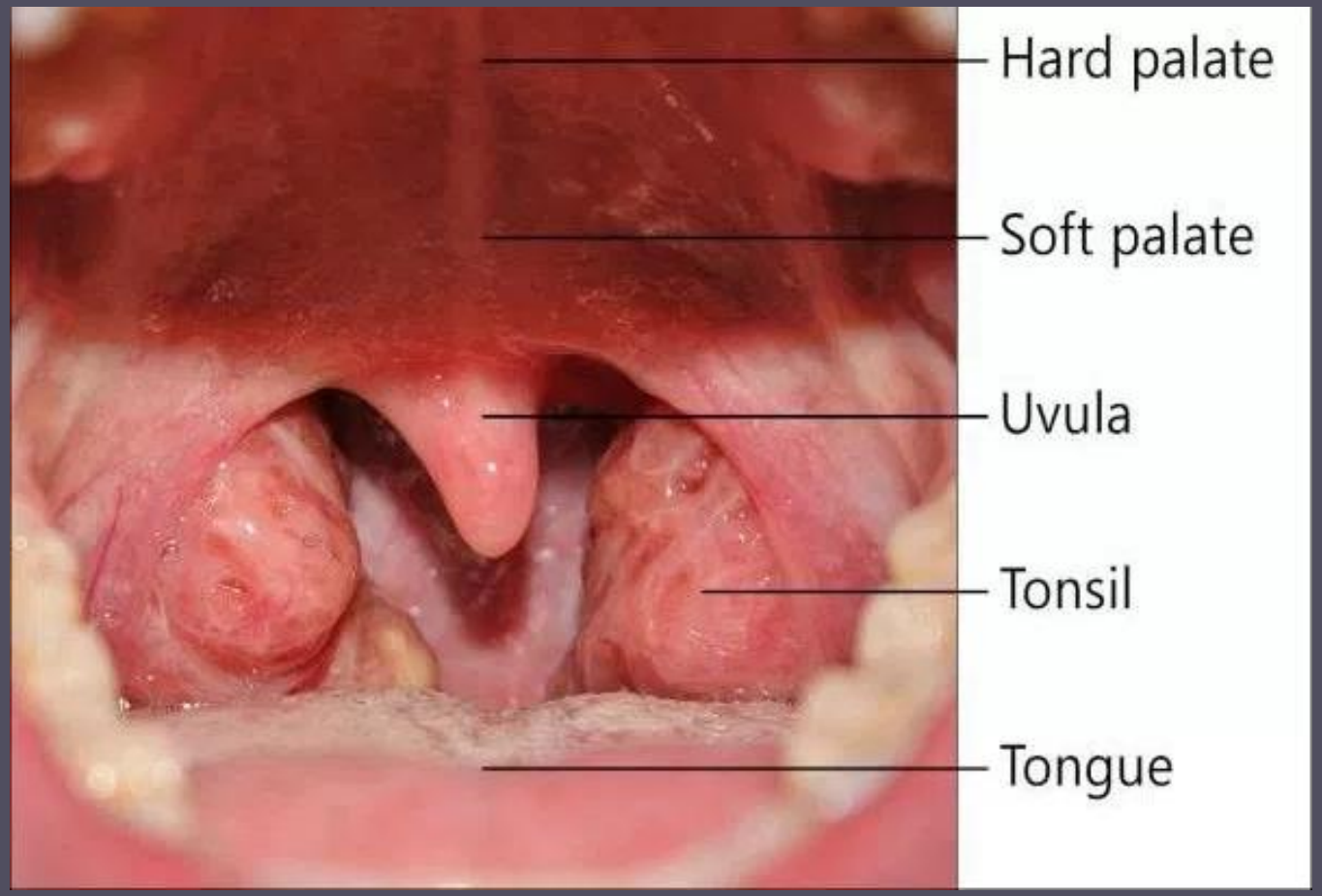
- Older age
- Current smoking
- ever marijuana smokers have an elevated risk of OPC
  - (adjusted odds ratio [aOR]: 1.24; 95% confidence interval [CI]: 1.06, 1.47)
- Most cases of HNC seen among nonsmokers are HPV-related
- 30-60% of HPV-positive HNC in recent studies were heavy tobacco and alcohol users

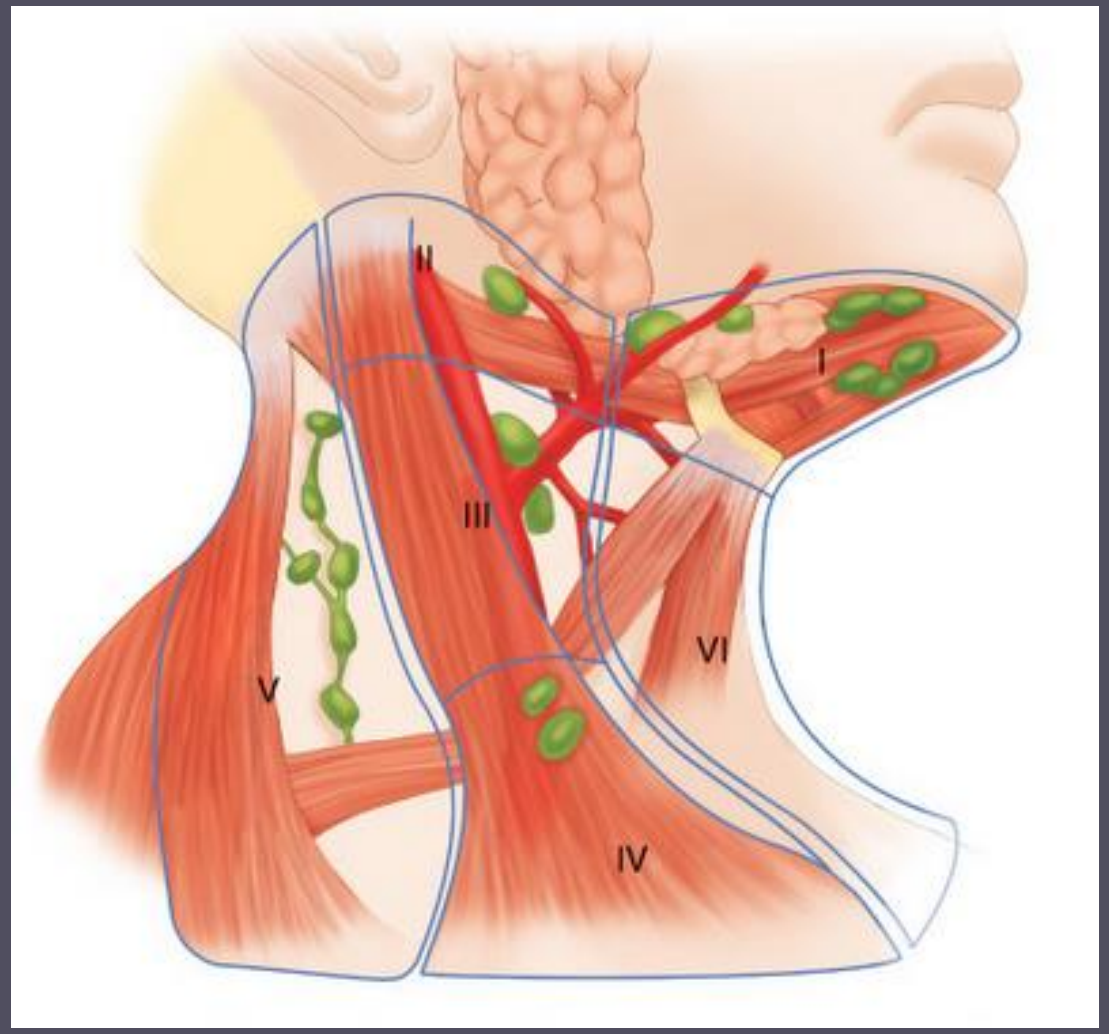
# Clinical Presentation

- 70 year old male with 2 months of throat pain
- 67 year old male with a painless neck mass for a few months
- 63 year old female with throat pain and difficulty swallowing
- 46 year old male with a painless neck mass
- 42 year old female with a sore throat for a few months
- 40 year old male with a painless neck mass
- 47 year old female with a painless neck mass

# Clinical Presentation

- Painless Neck Mass
- Sore throat
- Ear Pain
- Difficulty Swallowing
- Tonsil Asymmetry




II
I
III
VI
V
IV

# Clinical Presentation

- HPV+ HNC patients are younger, median age of 57
- 84% are male
- More likely to present at early stage, small primary tumor
- More likely to present with more neck nodes.
- Less likely to partake in excess alcohol consumption
- Lower rates of smoking are seen. However, many patients with HPV-associated oropharyngeal carcinoma are also current or former smokers (60%-70%)

# Staging & Prognosis

- 5-year overall survival 88-81%
- HPV+ disease shows no differences in overall survival for patients with Stage 1-4.
- HPV- disease 5 year overall survival decreases with increasing stage 76, 68, 53, and 45%

| | N CATEGORY | | |
|---|---|---|---|
| T CATEGORY | N0 | N1 | N2 |
| T0 | NA | I | II |
| T1 | I | I | II |
| T2 | I | I | II |
| T3 | II | II | III |
| T4 | II | II | III |

[a] Any M1 is stage IV.

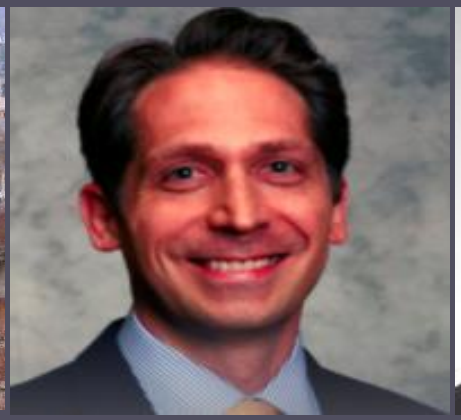
AJCC 8th Edition

# Patient Questions?

- Will I transmit HPV to my partner?
  - Infection is not transmitted through casual contact
  - Infection likely occurred decades previously
- Should I change my sexual behaviour?
  - No, cancer does not = Active infection
- Should I tell my partner?
  - There is no obligation to disclose. 20% report negative impact on their relationship
  - Partners of OPC patients do not have increased risk of oral HPV infection
- Should I get the vaccine?
  - No, the vaccine is prophylactic and does not help clear an infection once present

# Multidisciplinary Treatment

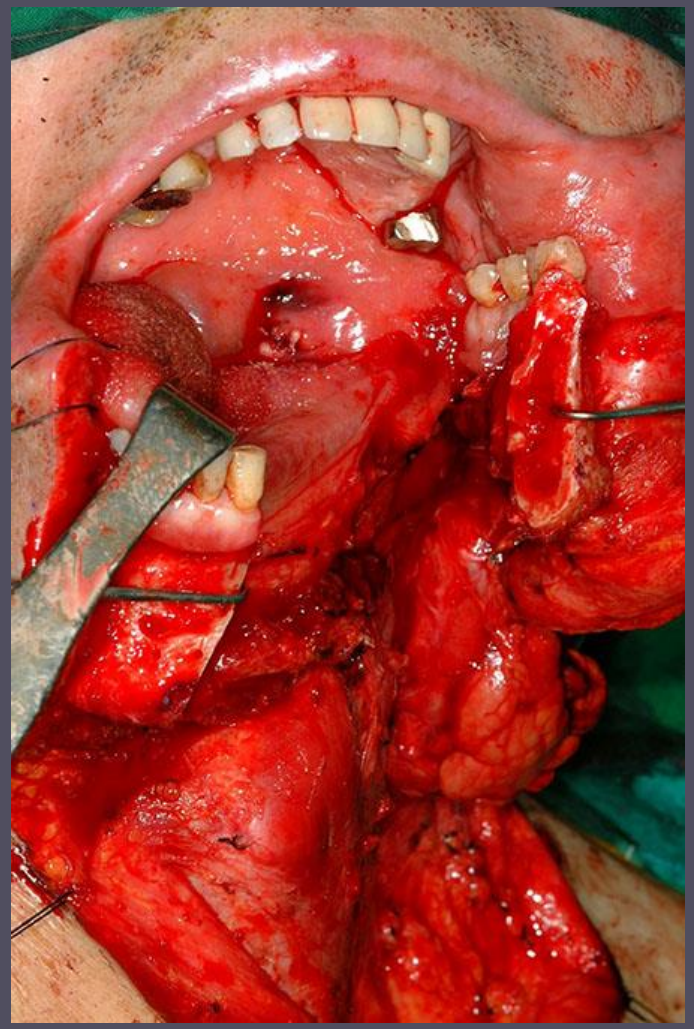
- HPV+ HNC has excellent response to all treatment
  - 3-year overall survival 82%
  - 24% rate of recurrence
- Early Stage tumors can be treated with primary surgery or radiation therapy.
- Later Stage tumors are treated with concurrent chemotherapy and radiation.


- Radiation Oncology
- Medical Oncology
- Head and Neck Surgery
- Speech Pathology
- Nurse Navigation
- Dental
- Physical Therapy
- Palliative Care
- Nutrition
- GI
- Radiology




# Surgical Treatment of OPC



- Historically surgery was through open approaches (mandibulotomy) followed by radiation.
  - Good cancer outcomes, but poor functional outcomes.
  - Trach-G-tube dependent
- Primary chemo-radiotherapy became the treatment of choice 20 years ago
- Toxicities associated with chemoradiation:
  - Dysphagia
  - Xerostomia
  - Fibrosis
  - Osteoradionecrosis
  - Nephrotoxicity
  - Ototoxicity

# Transoral Robotic Surgery

- 2009 TORS was approved for access to the oropharynx
- Allows access to the oropharynx without invasive procedures
- da Vinci Surgical Robot (Intuitive Surgical)
- High magnification and three-dimensional optics allow careful dissection with en bloc resection

# Treatment of early OPC


VISION ELECT HDTV

# Outcomes after TORS for early OPC

- No randomized trials
- Equivalent survival outcomes with RT vs. Surgery
  - 100/92% for T1 lesions vs. 88/100% for RT
  - 87 and 91% for T2 lesions vs. 84/86% for RT
- Trach dependence
  - 0-3.5% vs. 0-4.5%
- Feeding Tube dependence
  - 0-20% (none for TORS alone) vs. 0-18%
- Quality of Life
  - Variable consistency and reporting
  - More dry mouth with RT, dysphagia
  - decrease in speech and aesthetic scores with surgery
  - improved swallowing with TORS
- Complications
  - Mucositis, ORN, xerostomia, death
  - Hemorrhage, hematoma, fistula, death

Yeh, et al. Transoral robotic surgery vs. radiotherapy for management of oropharyngeal squamous cell carcinoma - A systematic review of the literature. Eur J Surg Oncol. 2015 Dec;41(12):1603-14.

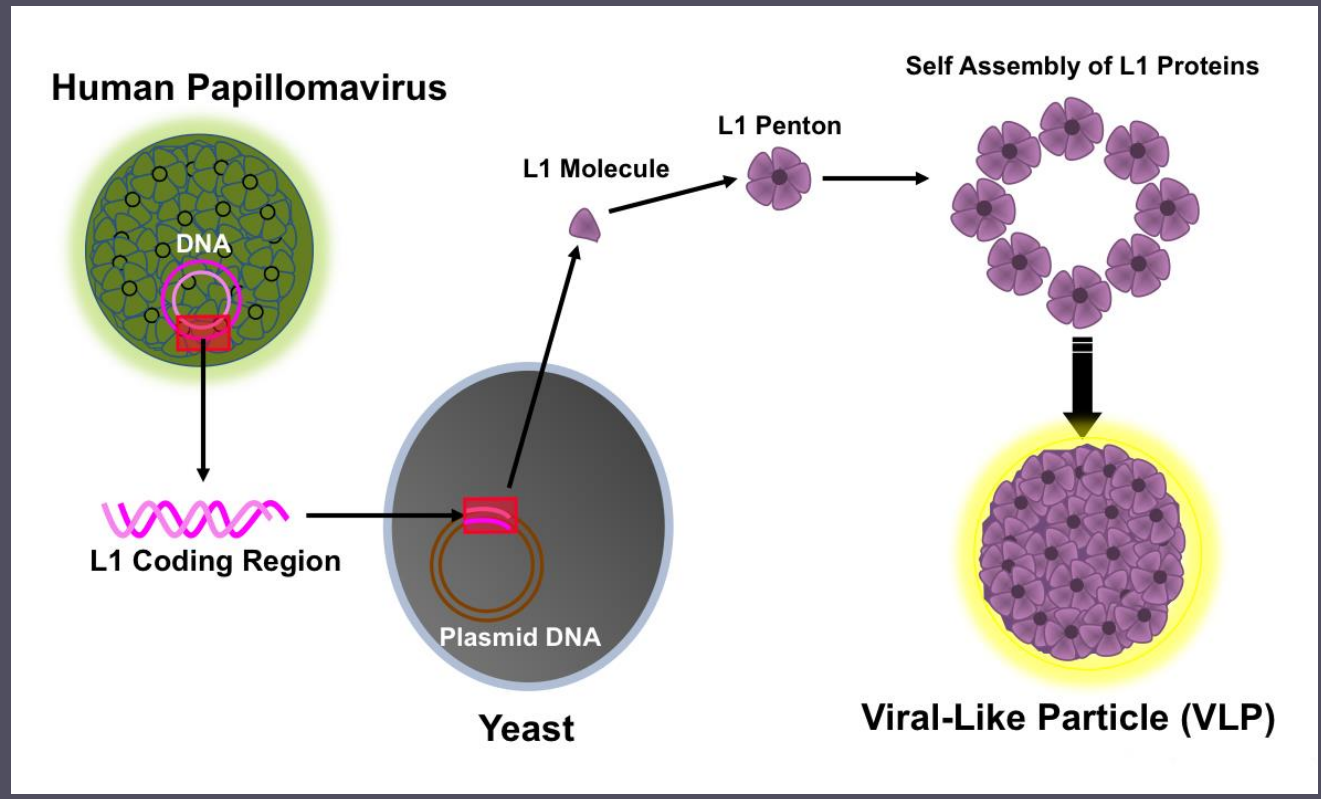
# Frontiers in Treatment of HPV HNC: De-intensification

- ECOG 1308: Neoadjuvant: After induction therapy with cisplatin, paclitaxel, and cetuximab. Lower does RT (54 Gy in 27 fractions) was given to people with a clinical response vs. Conventional (69.3 Gy in 33 fractions).
  - 2-year progression-free survival was 80%
  - 2-year overall survival was 94%
- Phase III comparing 36gy to 60gy with weekly cis. (Mayo Clinic NCT02908477)
- ECOG3311 Phase II randomized trial of transoral resection followed by standard or low-dose IMRT.
- NRG HN-002: phase II RT Stage III/IV HPV OPC randomized to standard RT alone vs. RT with concurrent cisplatin.
- RT to the neck only after TORS resection ( MD Anderson NCT02736786)

# Prevention

Three HPV vaccines licensed in the United States:

- Bivalent vaccine (2vHPV) prevents infection with HPV types 16 and 18
- Quadrivalent vaccine (4vHPV) prevents infection with HPV types 6, 11, 16, and 18, and a
- 9-valent vaccine (9vHPV) Gardasil 9 prevents infection with HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58



# Primary Prevention

- Vaccines are 90-100% effective in preventing HPV infections and associated anogenital precancerous lesions
- Within 6 years of vaccine introduction:
  - 64% decrease in prevalence of the four vaccine-targeted HPV types among females aged 14-19 years
  - 34% decrease among those aged 20 to 24 years.
- Vaccine Efficacy against oral HPV infection and HNC is unknown
- A single study observed a point prevalence for oral HPV 16/18 infection to be lower 4 years after vaccination in women who received the vaccine
- Assuming high efficacy and population coverage, current trends would not be reversed until after 2060


# Secondary Prevention

- Currently unable to detect precursor lesions
- Case-control studies: the presence of oral HPV infection or HPV serum antibodies to L1, E6, E7 was strongly associated with OPC
- Oral HPV 16 infection 3-230 times the risk of OPC
- Current point prevalence for oral HPV 16 infection is low (1.0%)
- Current assays have low sensitivity (50-80%)
- NNT 10,500

# Oral HNC Awareness Week

## Free Screening

**April 9 @ 12:00 pm - 4:00 pm**

Kaiser Permanente Sunnybrook Medical Office
Conference Room A (first floor)
9900 SE Sunnyside Road

ORAL, HEAD & NECK CANCER AWARENESS WEEK®

HEAD AND NECK CANCER ALLIANCE

# Take Home Points

- HPV is the most common sexually transmitted infection
- Most infections are asymptomatic and clear spontaneously within 1-2 years
- Persistent infection with HPV 16 is associated with developing OPC
- HPV-related oropharyngeal cancer is increasing in incidence.
- 70-90% of newly diagnosed OPC in the US are HPV+
- Most people present with neck mass, throat complaints, or are often asymptomatic.
- Any persistent neck mass age 40 or > place ENT referral
- HPV+ OPC has excellent outcomes regardless of treatment type
- Vaccination offers the best opportunity for prevention

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