Human Papilloma Virus in Oropharyngeal Malignancies

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First Annual Oncology Symposium 2018

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- **NO DISCLOSURES.**

Human Papilloma Virus (HPV)

- **History**

  1842: Rigoni noted association of cervical cancer in married women, widows and prostitutes, but rare occurrence in virgins and nuns

  1970s: plurality of HPV became apparent

  1976: koilocytotic cells represent hpv changes

  1978: presence of HPV viral particles seen in koilocytotic cells

  1983-4: HPV demonstrated in precursor lesions of cervical neoplasia (southern blot hybridizations)

  1985: first unequivocal report of HPV 16 in tongue and other oropharyngeal cancer (OPC).

  ****One of the most significant infectious carcinogens in humans

HPV

- **Definition**

  HPVs are DNA viruses with specific tropism for squamous epithelia

  *more than 120 subtypes

  low risk = HPV 6 and 11

  High risk = 16, 18, 31, 33, 35.

  *HPV 16 and 18 capable of transforming cells from genital and upper respiratory tract.

  * High-risk HPV 16 accounts for vast majority of HPV+ oropharyngeal tumors.

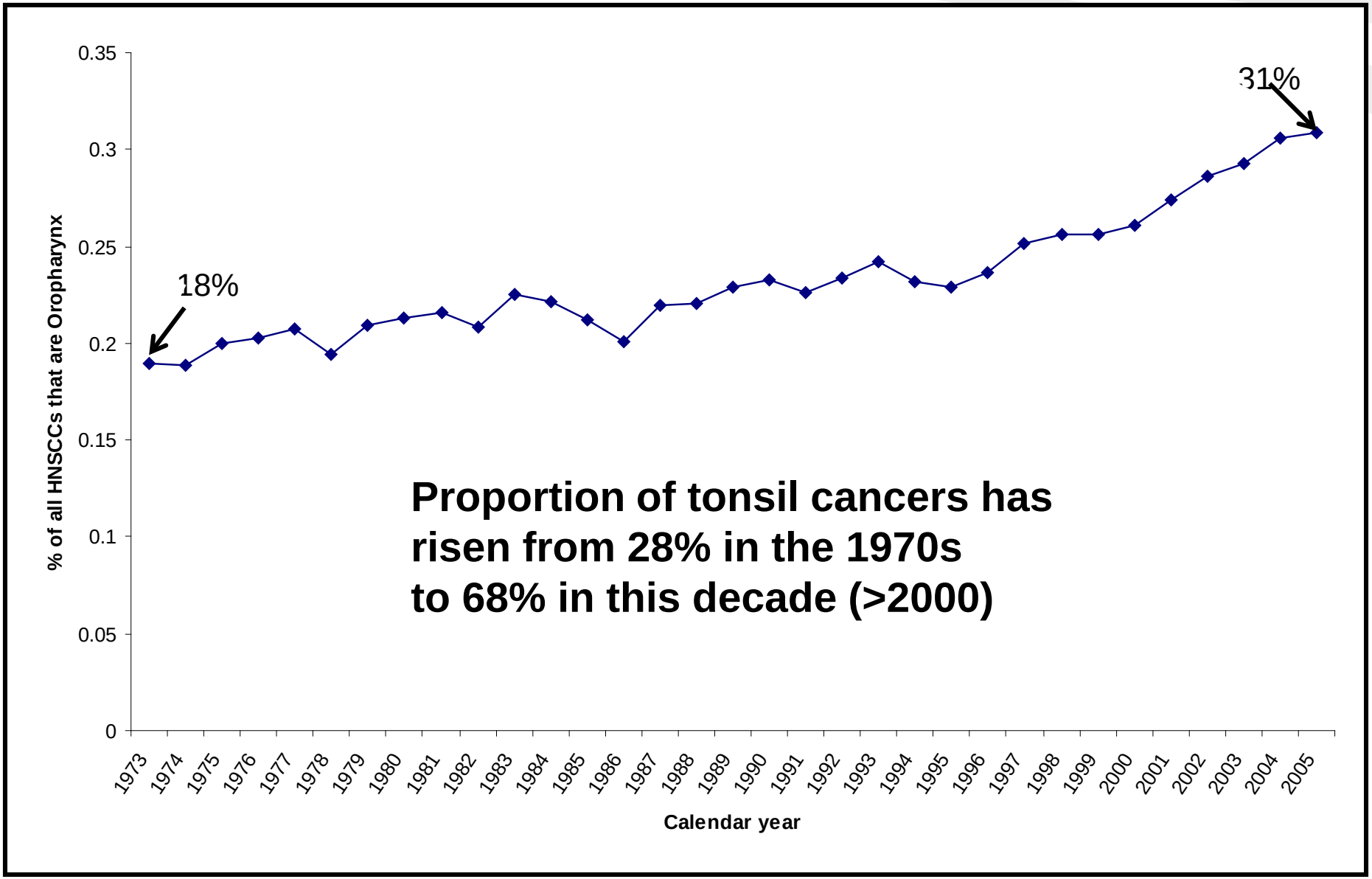
HPV

- **Summary of Molecular Biology**
  - *HPV infection is specific to tumor cell nuclei; infection precedes histopathologic progression to tumor
  - *Epithelium-transforming potential of high-risk HPVs results from viral oncoproteins E6 and E7
    - *these inactivate p53 and pRb (tumor suppressor genes)
    - **low pRb levels lead to p16 upregulation and levels; overexpression of p16 is surrogate marker for oropharyngeal primary site and HPV association; in contrast, loss of p16 expression is common and early event in smoking-related cancers.
    - *expression of high-risk HPV E6/E7 results in cellular proliferation, cell cycle dysregulation, increased mutations and chromosome instability

HPV

- **Epidemiology**
  - 1973-2001 Surveillance, Epidemiology and End Results (SEER) database evidence show that there is increasing incidence of both oral tongue and tonsil/base of tongue cancer.
  - HPV-unrelated cancers stable through 1983, then declined significantly from 1983-1984.
  - HPV-related cancers increased significantly from 1973-2004

    Resulting from changing sexual behaviors?

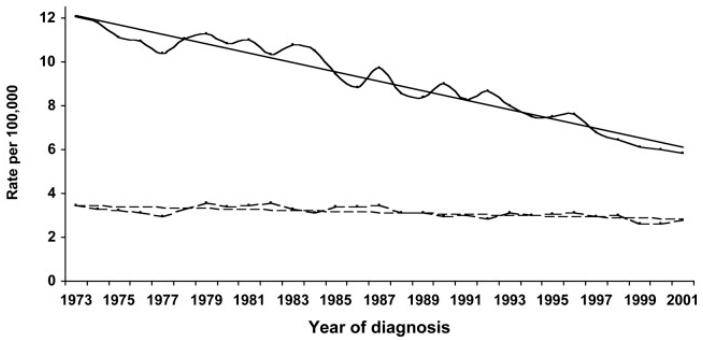


Chaturvedi A. J Clin Oncol 2008

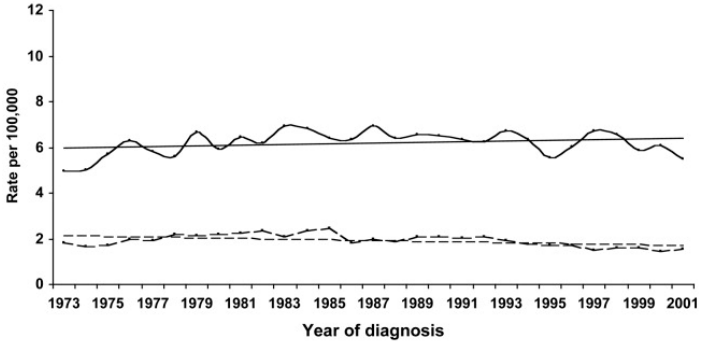
New Facts: Disease Causation and HPV

(A) Oral Cavity & (B) Oropharynx

Figure 1

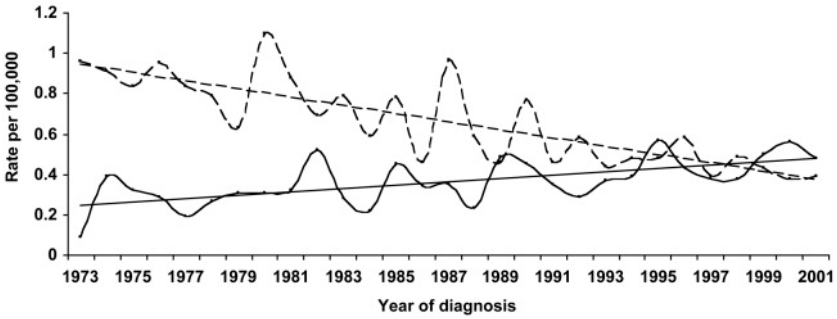


A —— Men: PC = -52; APC = -2.4; $P < 0.001$
– – –Women: PC = -20; APC = -0.7; $P < 0.001$

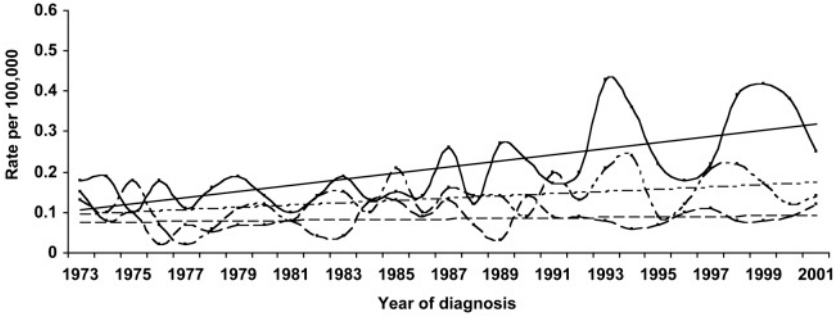


B —— Men: PC = 11; APC = 0.1; $P = 0.5$
– – –Women: PC = -15; APC = -1.0; $P < 0.001$

Figure 2



A —— Oral tongue: PC = +465; APC = +2.1; $P < 0.001$
– – –Other oral cavity sites: PC = -59; APC = -3.13; $P < 0.001$



B ——Tonsil: PC = +41; APC = +3.9; $P < 0.001$
– - - –Base of tongue: PC = +8.6; APC = +1.73; $P = 0.04$
– – – Other pharynx: PC = -21; APC = 0.24; $P = 0.7$

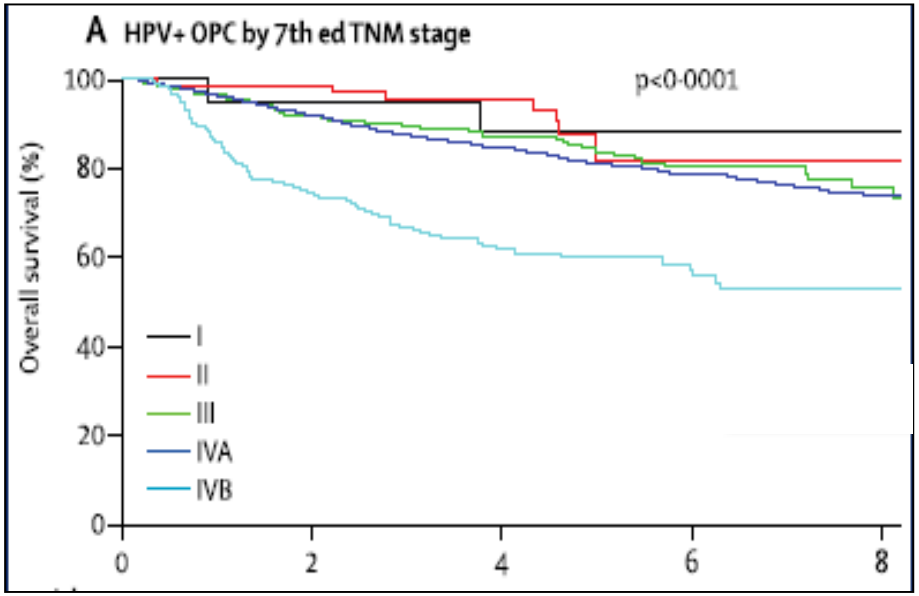
Cancer 2005 Shiboski et al.

Separation of Oropharynx Cancer (OPC) Staging by HPV Status

- Since 1990, the incidence of HPV associated cancers of the tonsil and tongue base has increased by 5% per year
- HPV–associated tumors occur in younger, healthier individuals, many with little or no tobacco exposure.
- It is highly responsive to treatment and has an excellent prognosis.
  - **Higher response rates after induction chemotherapy/chemoradiation treatment (J Natl Ca Inst 2008; 100:261)**

Separation of Oropharynx Cancer (OPC) Staging by HPV Status

- Reflects behavior of tobacco-related SCC, *not HPV+ disease*.
- The 7th edition lost the ability to differentiate between stages, HPV (+)
  - Hazard discrimination
- The numerical balance shifted toward stage III & IV
  - Loss of predictive ability



New AJCC Staging for OPC 2018

Separate staging for HPV(+) OP cancer

- Largely unchanged except:
  - Carcinoma in situ (Tis) removed
  - T4b removed
- N Classification:
  - Difference between clinical and pathologic staging
  - Clinical staging based on laterality and size of nodes
  - Pathologic staging based on number of nodes
- Obviously for surgical patients only
  - ENE not included
- M Classification: Unchanged
- Overall Stage: Drastic Change
- Stage IV reserved for M1 disease

OPC Clinical and Pathological Staging

T CATEGORY	T CRITERIA
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond[b]

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

N CATEGORY	N CRITERIA
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

New AJCC Staging for OPC 2018

	N CATEGORY			
T CATEGORY	N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

- Stage IV reserved for M1 disease

HPV Negative OPC Staging

- **T Classification:**
  - Unchanged except T0 removed
  - Non-viral T0 tumors can be from any site and thus cannot localize to oropharynx
- **N Classification:**
  - Unchanged with the exception of Extra Nodal Extension (ENE)
  - N3 divided into N3a and N3b
  - N3a, lymph node >6cm in dimension, no ENE
  - N3b, any ENE
- **M Classification: Unchanged**
  - Overall Stage: Unchanged

- **ENE now N3b so higher proportion of patients in stage IVb group**

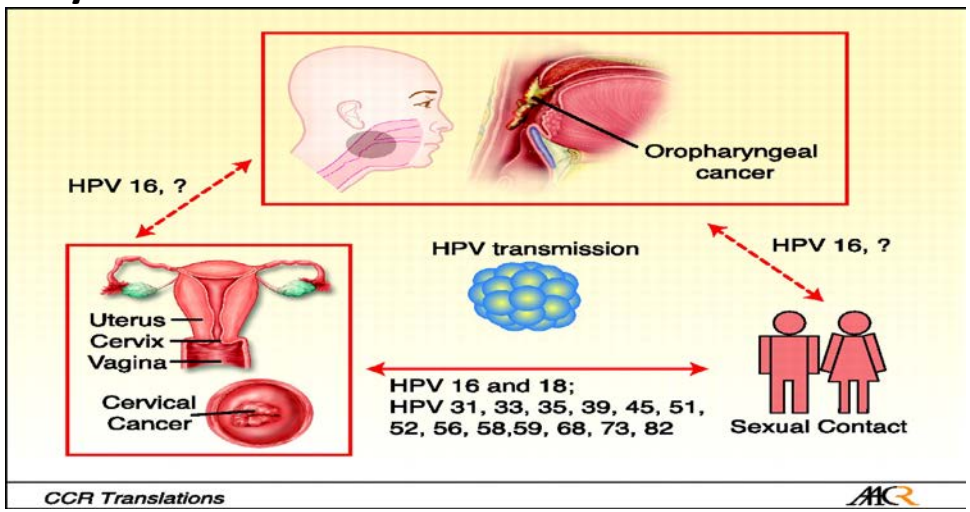
HPV- Mode of Transmission

- **HPV is the most common sexually transmitted infection in the United States**
- **>50% of people who are sexually active will have acquired genital HPV over their lifetime**
- **>80% of women over the age of 50 will have contracted at least one strain of HPV**

****One of the most significant infectious carcinogens in humans

HPV- Mode of Transmission

- **More than 40 subtypes of HPV can infect both males and females through sexual contact**
- **HPV can be passed through genital contact and oral sex**
  - **10% general population orally infected with HPV at any given time**
  - **3% of 16 - 20 year-olds are infected**



**** Cancer occurs when infection persists & immune surveillance fails

Sok, J. C. et al. Clin Cancer Res 2008;14:6723-6724

Clinical Cancer Research

Table 1. Characteristics of HPV-Related and HPV-Unrelated Oral Squamous Cell Carcinomas From 1973 to 2004

Characteristic	HPV-Related (n = 17,625)*		HPV-Unrelated (n = 28,144)†		
	No.	%	No.	%	P‡
Age at diagnosis, years					
Mean	61.0		63.9		< .001§
Standard deviation	11.3		12.9		
Sex					< .001
Male	12,794	72.6	17,416	61.9	
Female	4831	27.4	10,728	38.1	
Race/ethnicity					< .001
White	14,642	83.1	24,030	85.4	
Black	2,404	13.6	2,673	9.5	
Other	552	3.1	1,338	4.7	
Unknown	27	0.2	103	0.4	
Marital status at diagnosis					< .001
Never married	2,491	14.1	3,457	12.3	
Ever married	14,299	81.1	22,857	81.2	
Unknown	835	4.7	1,830	6.5	
Stage at diagnosis					< .001
Localized	3,054	17.3	12,291	43.7	
Regional	10,880	61.7	11,611	41.2	
Distant	2,734	15.5	1,973	7.0	
Unstaged	957	5.4	2,269	8.1	
Radiotherapy					< .001
No	3,714	21.1	14,813	52.6	
Yes	13,316	75.5	12,552	44.6	
Unknown	595	3.4	779	2.8	

Two Different Kinds of HNC?

	HPV-positive	HPV-negative
Anatomic site	Tonsil / BOT	All sites
Histology	PD, Basaloid	Keratinized
Age	Younger	Older
Gender	3:1 men	3:1 men
Stage	Tx, T1-2	variable
Risk factors	Sexual behavior	Alcohol / tobacco
Cofactors	Marijuana immunosuppression?	Oral hygiene
Incidence	Increasing	Decreasing
Survival	Improved	Unchanging

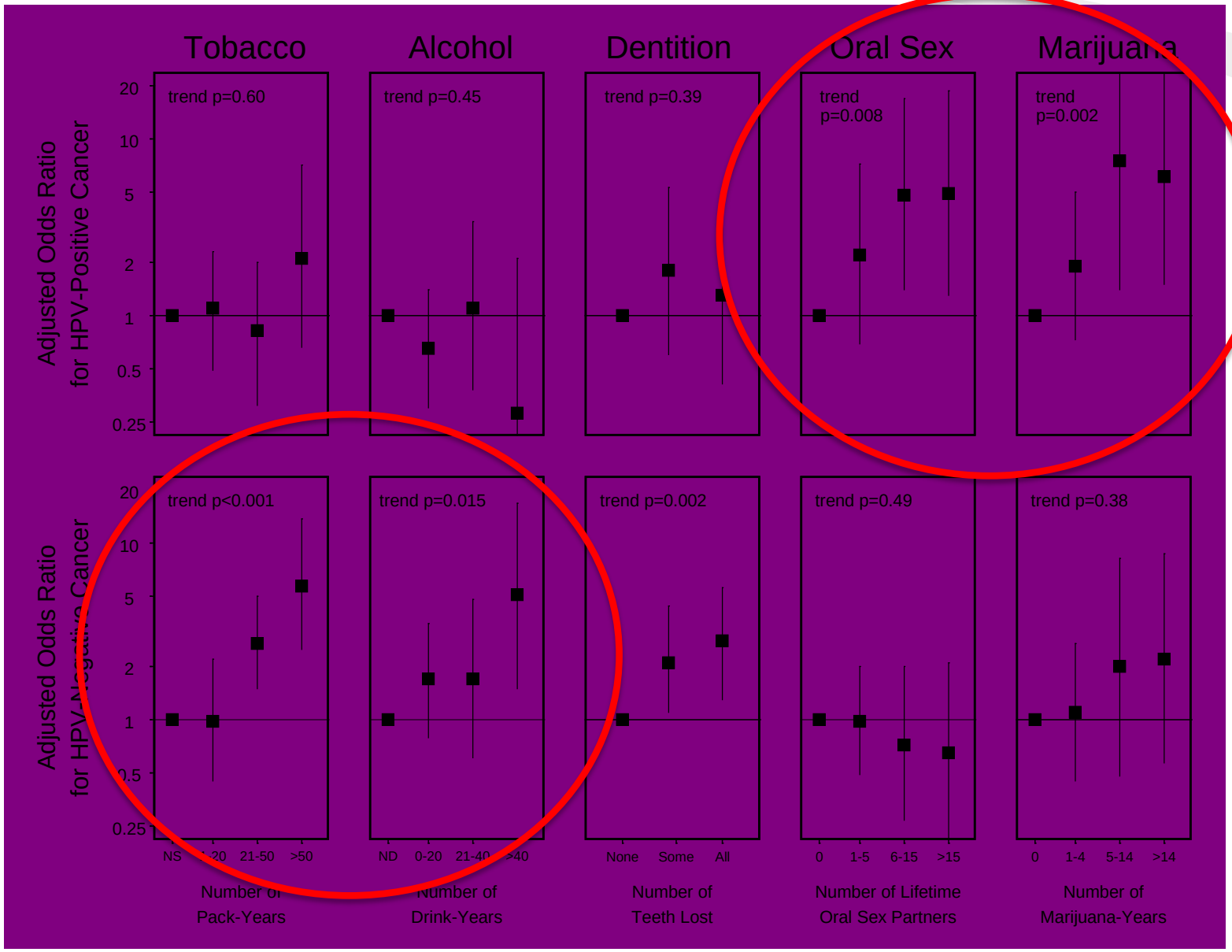
HPV – Potential Risk factors

- **Men > Women**
- **History of HPV associated anogenital cancers**
- **husbands of women with cervical cancer**
- **High lifetime number (≥ 26) of vaginal sex partners**
- **≥ 6 lifetime oral-sex partners**
- **Immunocompromised individuals**
  - **Transplant**
  - **HIV, STDs**
- **Exposure to marijuana (increasing association with intensity and duration of marijuana use)**

Gillison M, D'Souza G, Westra W, et al; Distinct Risk Factors for Human Papillomavirus Type 16-Positive for Human Papillomavirus Type 16-Negative Head and Neck Cancers. J Natl Cancer Inst. 2008; 100: 407-420.

D'Souza G, Kreimer A, Viscidi R, et al; Case-Control Study of Human Papillomavirus and Oropharyngeal Cancer. N Engl J Med. 2007; 356: 1944-1956.

Risk Factors for HPV+ Head and Neck Cancer



Odds ratios adjusted for age, gender, race, tobacco, alcohol, oral hygiene, marijuana and oral sex, as appropriate

Gillison M et al, JNCI. 2008

HPV – Signs/Symptoms

- **In >90% of cases the body's immune system will clear the HPV (usually within 9 months to 2 years)**
- **Majority of patients develop no signs or symptoms of infection and thus infected individuals can remain oblivious**
- **In some instances patients will develop signs of infection in the genital areas or in the oropharynx (includes the tonsils, base of tongue, soft palate, and pharyngeal walls)**
  - Normal cells begin to behave in an abnormal fashion
  - These signs/symptoms can take years/decades to develop

HPV – Oropharynx Cancer Signs/Symptoms

- Persistent sore throat
- Ear pain
- Swallowing difficulty
- Lump in the neck
- Weight loss
- Bleeding from throat
- Often relatively advanced by the time symptoms occur

HPV - Clinical Significance/Relevance

Diagnosis

*p16 immunohistochemistry is surrogate marker for HPV transcriptional activity

*HPV status can be determined (via in-situ hybridization) in tumor cells aspirated from necks of patients with metastatic HNSCC; reliable indicator of oropharyngeal primary

* detection of plasma HPV 16 DNA or HPV E6 and E7 antibodies in serum may be useful in the future

Prognosis

*60-80% reduction of risk in dying form HNSCC compared to HPV negative pt; may be due to:

*lack of field cancerization

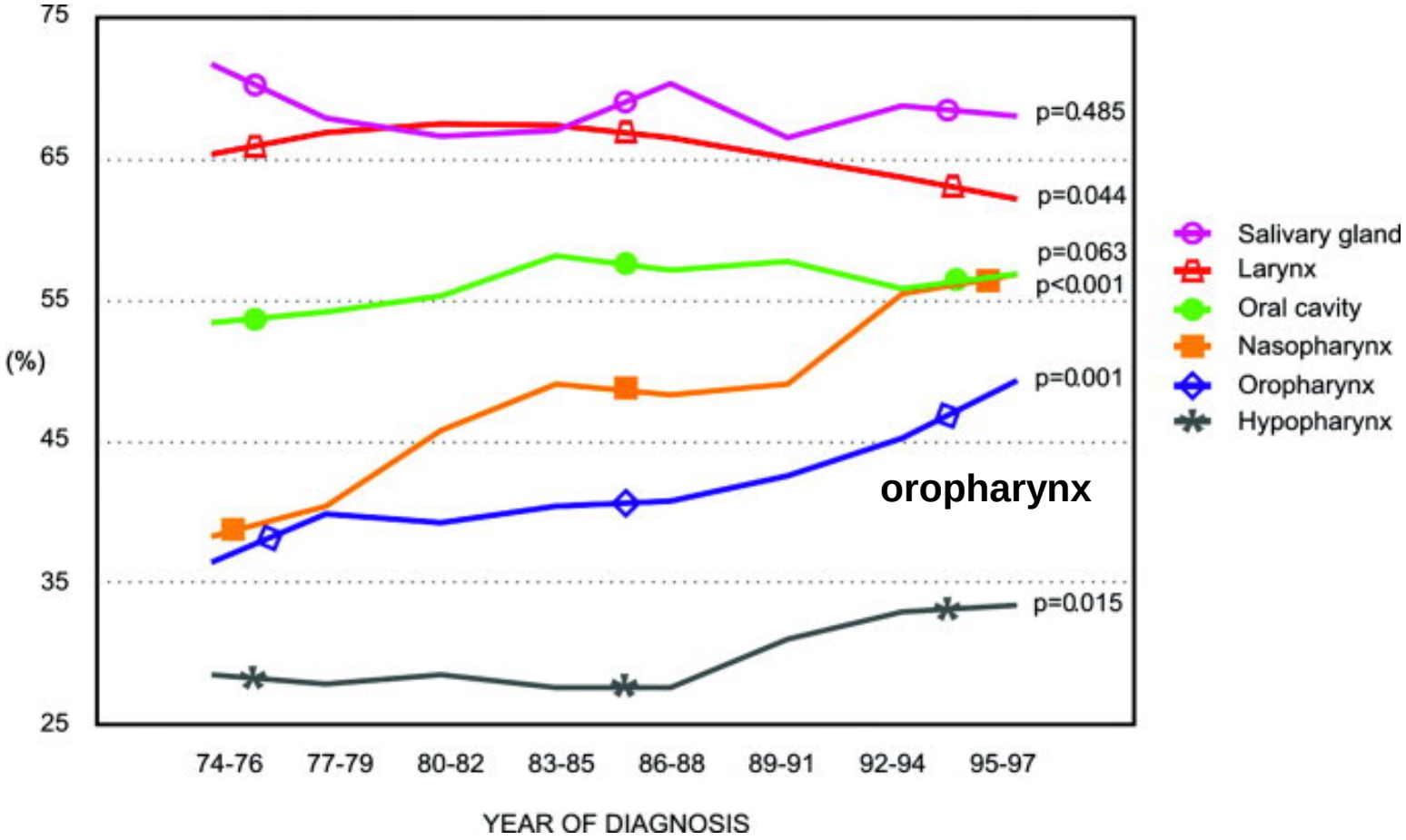
*Sensitivity to radiation

* Intact apoptotic response (wild-type p 53)

HPV – Diagnosis in the Oropharynx

- Clinical examination by inspection, palpation, and fiberoptic scope examination
- Biopsy of suspected area and testing for HPV status
- Imaging for staging purposes
- Multidisciplinary planning

Trends in Survival According to Tumor Site and Year of Diagnosis



Carvalho et al. Int J Cancer 2005 (SEER Database)

HPV - Clinical Significance/Relevance

Treatment

*Trials may stratify more/less intensive tx based on HPV status

superior response rates to induction and chemoradiation

*HPV 16 specific therapeutic vaccine (enhances cytotoxic T-cell response to HPV 16 oncoproteins) in trial phases

HPV - Clinical Significance/Relevance

Prevention

*Screening not recommended in general population

*Prevention may include:

- Abstinence
- Condoms – this may reduce the risk however any exposure to affected areas can transmit virus
- Limiting Number of Partners – again may reduce the risk however even one infected partner can pose the risk
- Routine screenings in the case of cervical and anal cancers – this includes those who are vaccinated
- Vaccination – can protect against most but not all subtypes

HPV - Clinical Significance/Relevance

Prevention

Natural history of HPV infection is unknown; routine screening for HPV-associated HNSCC not recommended.

- **Current Centers for Disease Control and Prevention (CDC) vaccination recommendations**

  *The HPV vaccine is routinely recommended for 11 and 12 year-old girls. The vaccine series can be started at 9 years of age. Catch-up vaccination is recommended for 13 through 26 year-old females who have not yet received or completed the vaccine series.

  ***Cervarix FDA approved for girls 10 to 25 years**

  - (targets 16 and 18)

  ***Gardasil approved for girls and boys 9 to 26 years**

  - (targets HPV 6, 11, 16 and 18)

  - Reports on adverse events after immunization (**JAMA2009:302; 750)** noted a disproportionate reporting of syncope and venous thromboembolism

    Impact of the vaccines on incidence of persistent oral HPV infection not investigated (yet!)

HPV - Vaccination

- The vaccines provide little benefit to those already infected with HPV
- There are no therapeutic effects on existing HPV infections or disease
- The vaccine is not mandated and <50% of teenage girls in the last year have received the vaccination
- Duration of how long the vaccine stays effective is not yet established

HPV – Testing

- Currently there are no FDA approved tests for “HPV status”
- Tests on the market are only to screen patients for cervical or anal cancer (ie. Pap smear)
- The FDA approved the HPV DNA test as an adjunct to Pap smear to determine HPV cervical infection
- There are no tests approved to screen for early signs of HPV (+) oropharyngeal cancer

HPV – Testing

- **Testing for HPV Status . . . p16**
- Must be simple, inexpensive, and reproducible
- Needs to be available worldwide
- Immunohistochemistry for overexpression of the tumor suppressor protein p16
  - Established, reliable surrogate biomarker
  - Independent positive prognosticator for OPC
  - Inexpensive, widely availability, easy to interpret
- OPC will now be staged according to 2 distinct systems, depending on whether or not they overexpress p16
  - p16 overexpression = diffuse >/=75% tumor expression, with at least moderate (+2/3) staining intensity

HPV - Treatment

- **There is currently no specific treatment to clear the HPV once infected**
- **According to the CDC the HPV clears naturally in >90% cases**
- **The available treatments target the diseases caused by the HPV**

HPV – Treatment of Oropharyngeal Cancers

- **Treatment regimens may include:**
  - Radiation +/- Chemotherapy
  - Surgery +/- Radiation
    - Including Transoral robotic surgery (TORS)
    - Possible addition of chemotherapy
- **Modality depends on staging and possible stratification by HPV status**
- **Improved prognosis regardless of treatment strategy compared to HPV (-) oropharyngeal cancers**

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THANK YOU