

HPV-associated oropharyngeal cancer *ACIP*

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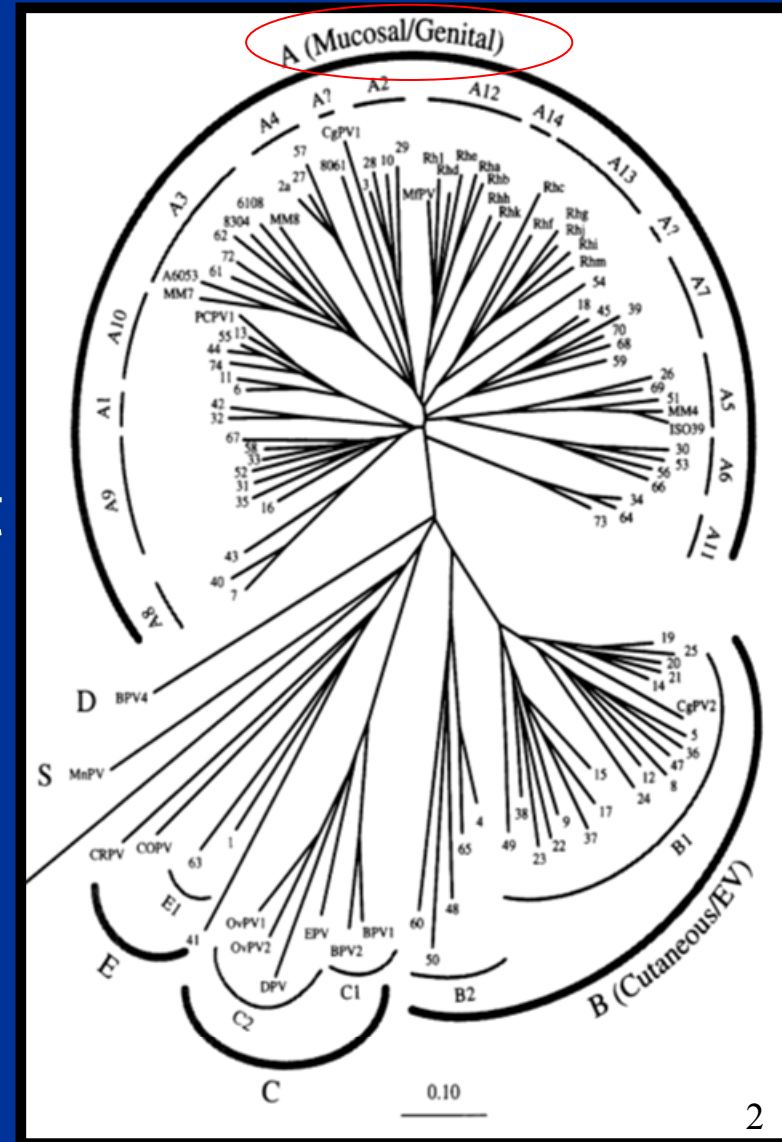
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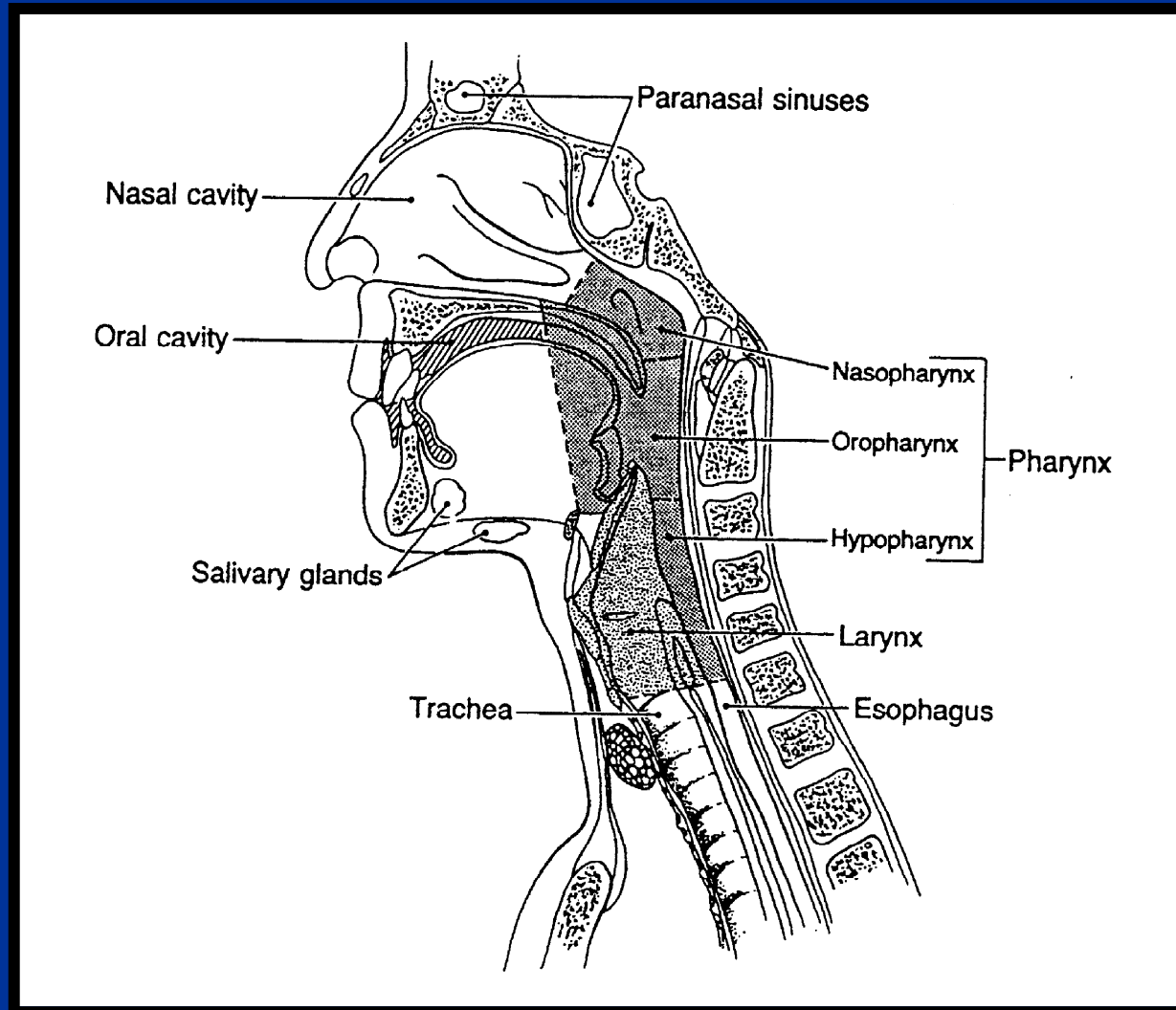
Human Papillomavirus (HPV)

>120 HPV types, about 40 of which infect anogenital region

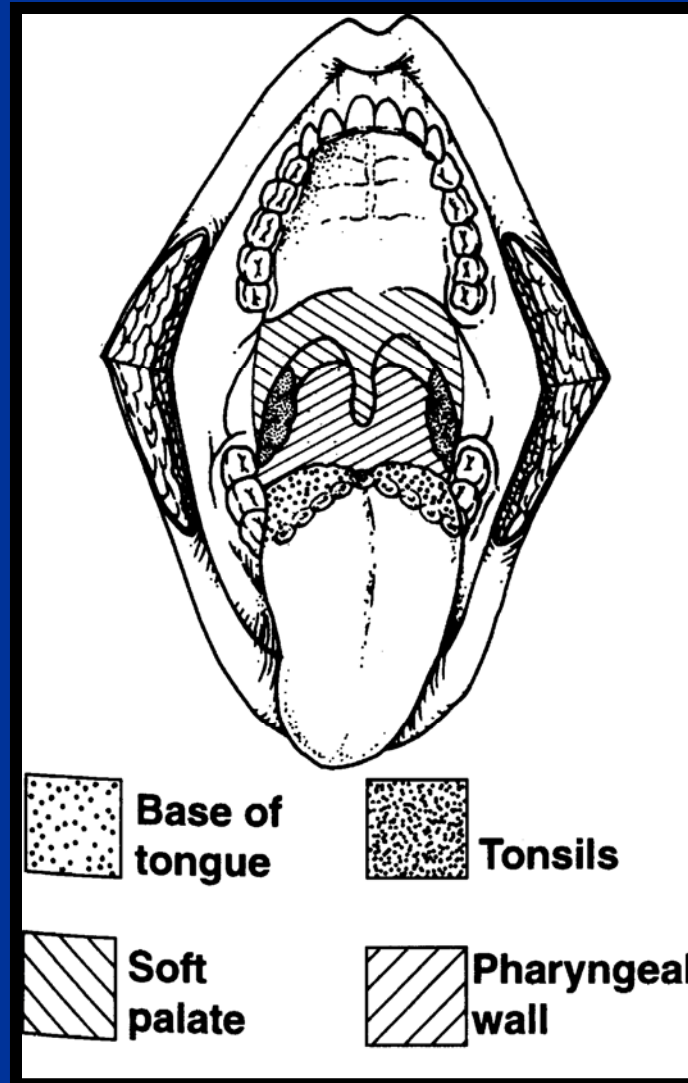
- Non-carcinogenic HPV
- Carcinogenic HPV (N= \sim 15)
- HPV16 is the most prevalent and carcinogenic



Anatomy of the head and neck



Oropharynx (OP): the HPV-related subsite of the head and neck



IARC: Carcinogenicity of HPV

| Group 1 agent | Cancers for which there is sufficient evidence in humans | Other sites with limited evidence in humans |
|--|---|---|
| Epstein-Barr virus (EBV) | Nasopharyngeal carcinoma, Burkitt's lymphoma, immune-suppression-related non-Hodgkin lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin's lymphoma | Gastric carcinoma,* lympho-epithelioma-like carcinoma* |
| Hepatitis B virus (HBV) | Hepatocellular carcinoma | Cholangiocarcinoma,* non-Hodgkin lymphoma† |
| Hepatitis C virus (HCV) | Hepatocellular carcinoma, non-Hodgkin lymphoma* | Cholangiocarcinoma* |
| Kaposi's sarcoma herpes virus (KSHV) | Kaposi's sarcoma,* primary effusion lymphoma* | multicentric Castleman's disease* |
| Human immunodeficiency virus, type 1 (HIV-1) | Kaposi's sarcoma, non-Hodgkin lymphoma, Hodgkin's lymphoma,* cancer of the cervix,* anus,* conjunctiva* | Cancer of the vulva,* vagina,* penis,* non-melanoma skin cancer,* hepatocellular carcinoma* |
| Human papillomavirus type 16 (HPV-16)† | Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and tonsil | Cancer of the larynx |

IARC: Carcinogenicity of HPV

| Group | HPV types | Comments |
|------------------------|--|---|
| Alpha HPV types | | |
| 1 | 16 | Most potent HPV type, known to cause cancer at several sites |
| 1 | 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 | Sufficient evidence for cervical cancer |
| 2A | 68 | Limited evidence in humans and strong mechanistic evidence for cervical cancer |
| 2B | 26, 53, 66, 67, 70, 73, 82 | Limited evidence in humans for cervical cancer |
| 2B | 30, 34, 69, 85, 97 | Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans |
| 3 | 6, 11 | .. |
| Beta HPV types | | |
| 2B | 5 and 8 | Limited evidence for skin cancer in patients with epidermodysplasia verruciformis |
| 3 | Other beta and gamma types | .. |

Association between HPV and OP cancer

Prospective evaluation of HPV and head and neck cancer

| SITE† | SEROPOSITIVE PATIENTS | SEROPOSITIVE CONTROLS | CRUDE ODDS RATIO (95% CI) | ADJUSTED ODDS RATIO (95% CI)‡ | PATIENTS POSITIVE FOR HPV-16 DNA§ |
|---|-----------------------|-----------------------|---------------------------|-------------------------------|-----------------------------------|
| | no./total no. (%) | | | | no./total no. (%) |
| Lips (code 140) | 2/57 (4) | 21/307 (7) | 0.5 (0.1–2.4) | 0.5 (0.1–2.1) | 0/32 (0) |
| Tongue (code 141) | 9/57 (16) | 22/302 (7) | 2.7 (1.2–6.4) | 2.8 (1.2–6.6) | 4/29 (14) |
| Floor of mouth (code 143) | 0/23 (0) | 15/125 (12) | — | — | 0/15 (0) |
| Oral cavity, not otherwise specified (code 144) | 2/19 (11) | 2/104 (2) | 5.4 (0.8–38.8) | 3.6 (0.5–26.3) | 0/15 (0) |
| Oropharynx (code 145) | 10/26 (38) | 14/137 (10) | 8.6 (2.6–28.5) | 14.4 (3.6–58.1) | 9/18 (50) |
| Nasopharynx (code 146) | 0/10 (0) | 2/60 (3) | — | — | 1/7 (14) |
| Hypopharynx (code 147) | 0/16 (0) | 3/81 (4) | — | — | 0/8 (0) |
| Nose and paranasal sinuses (code 160) | 2/7 (29) | 3/36 (8) | 3.5 (0.6–20.7) | 3.4 (0.6–20.8) | 0/4 (0) |
| Larynx (code 161) | 9/76 (12) | 20/411 (5) | 2.5 (1.1–5.8) | 2.4 (1.0–5.6) | 1/32 (3) |
| All sites | 35/292 (12) | 102/1568 (7) | 2.1 (1.4–3.2) | 2.1 (1.4–3.2)¶ | 15/160 (9) |

Prospective evaluation of HPV and head and neck cancer

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Case-control study: HPV Biomarkers and OP cancer

| Measure of HPV Exposure or Disease | Prevalence | | Odds Ratio (95% CI) | |
|------------------------------------|--|---|---------------------|-------------------|
| | Case Patients (N= 100) <i>number (percent)</i> | Control Patients (N= 200) <i>number (percent)</i> | Unadjusted | Adjusted* |
| HPV-16 L1 serologic status | | | | |
| Seronegative | 43 (43) | 186 (93) | 1.00 | 1.00 |
| Seropositive | 57 (57) | 14 (7) | 17.6 (8.8–34.5) | 32.2 (14.6–71.3) |
| Oral HPV-16 infection† | | | | |
| Negative | 68 (68) | 192 (96) | 1.00 | 1.00 |
| Positive | 32 (32) | 8 (4) | 11.3 (5.0–25.7) | 14.6 (6.3–36.6) |
| Any oral HPV infection‡ | | | | |
| Negative | 63 (63) | 189 (94) | 1.00 | 1.00 |
| Positive | 37 (37) | 11 (6) | 10.0 (4.8–20.7) | 12.3 (5.4–26.4) |
| HPV-16 E6 or E7 serologic status | | | | |
| Seronegative for E6 and E7 | 36 (36) | 192 (96) | 1.00 | 1.00 |
| Seropositive for E6 or E7 | 64 (64) | 8 (4) | 33.3 (16.2–68.6) | 58.4 (24.2–138.3) |

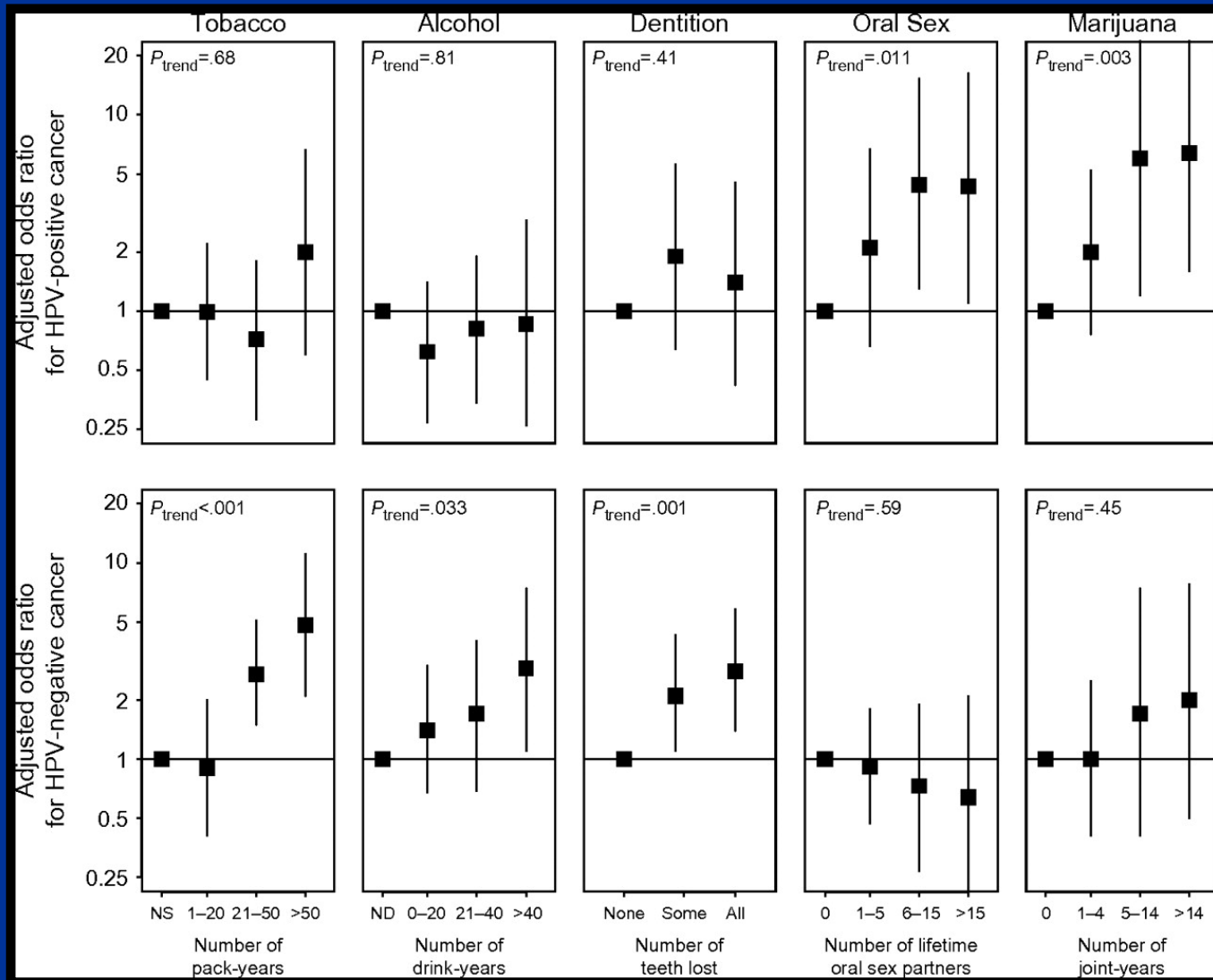
Case-control study: Sexual behavior and OP Cancer

| Sexual Behavior | Patients with Oropharyngeal Cancer (N=100) | Control Patients (N=200) | Adjusted Odds Ratio (95% CI) [†] | |
|--------------------------------------|---|-----------------------------|---|-------------------------------|
| | | | All Patients | HPV-16+ Patients [‡] |
| <i>number (percent)</i> | | | | |
| Lifetime no. of vaginal-sex partners | | | | |
| 0–5 | 31 (31) | 108 (54) | 1.0 | 1.0 |
| 6–25 | 41 (41) | 63 (32) | 2.2 (1.2–4.0) | 2.7 (1.4–5.5) |
| ≥26 | 28 (28) | 29 (14) | 3.1 (1.5–6.5) [§] | 4.2 (1.8–9.4) [¶] |
| Lifetime no. of oral-sex partners | | | | |
| 0 | 12 (12) | 38 (19) | 1.0 | 1.0 |
| 1–5 | 46 (46) | 110 (55) | 1.9 (0.8–4.5) | 3.8 (1.0–14.0) |
| ≥6 | 42 (42) | 52 (26) | 3.4 (1.3–8.8) | 8.6 (2.2–34.0) ^{**} |
| Anal sex | | | | |
| No | 55 (55) | 129 (64) | 1.0 | 1.0 |
| Yes | 45 (45) | 71 (36) | 1.3 (0.8–2.2) | 1.6 (0.9–2.8) |
| Casual-sex partner ^{††} | | | | |
| No | 42 (42) | 120 (60) | 1.0 | 1.0 |
| Yes | 58 (58) | 80 (40) | 1.7 (1.0–3.0) | 2.4 (1.2–4.7) |
| Age at first intercourse | | | | |
| 18 yr or older | 30 (30) | 87 (44) | 1.0 | 1.0 |
| 17 yr or younger | 70 (70) | 113 (56) | 1.3 (0.7–2.3) | 2.1 (1.1–3.6) |

Case-control study: Tobacco, alcohol, HPV and OP cancer

| Variable | Odds Ratio (95% CI) | | Synergy Index (95% CI) |
|---|------------------------|------------------------|------------------------|
| | HPV-16 L1 Seronegative | HPV-16 L1 Seropositive | |
| Unstratified risk of oropharyngeal cancer | | | |
| Tobacco use | | | |
| <20 pack-yr | 1.0 | 37.1 (15.6–88.4) | |
| ≥20 pack-yr | 2.8 (1.2–6.4) | 27.8 (6.7–114.6)† | 0.7 (0.5–1.1) |
| Alcohol use | | | |
| <15 drink-yr | 1.0 | 36.2 (15.1–86.5) | |
| ≥15 drink-yr | 2.5 (1.1–5.5) | 29.1 (7.4–115.3)§ | 0.8 (0.5–1.2) |
| Tobacco and alcohol use | | | |
| <20 pack-yr and <15 drink-yr | 1.0 | 33.6 (13.3–84.8) | |
| ≥20 pack-yr and ≥15 drink-yr | 7.7 (2.7–22) | 19.4 (3.3–113.9) | 0.5 (0.4–0.6) |
| Risk of oropharyngeal cancer stratified by measures of HPV-16 exposure | | | |
| Tobacco use | | | |
| <20 pack-yr | 1.0 | 1.0 | |
| ≥20 pack-yr | 2.8 (1.2–6.7) | 0.8 (0.2–4.0) | |
| Alcohol use | | | |
| <15 drink-yr | 1.0 | 1.0 | |
| ≥15 drink-yr | 2.6 (1.1–5.9) | 0.9 (0.2–4.3) | |
| Tobacco and alcohol use | | | |
| <20 pack-yr and <15 drink-yr | 1.0 | 1.0 | |
| ≥20 pack-yr and ≥15 drink-yr | 8.9 (3.0–27)** | 0.46 (0.07–3.0)†† | |

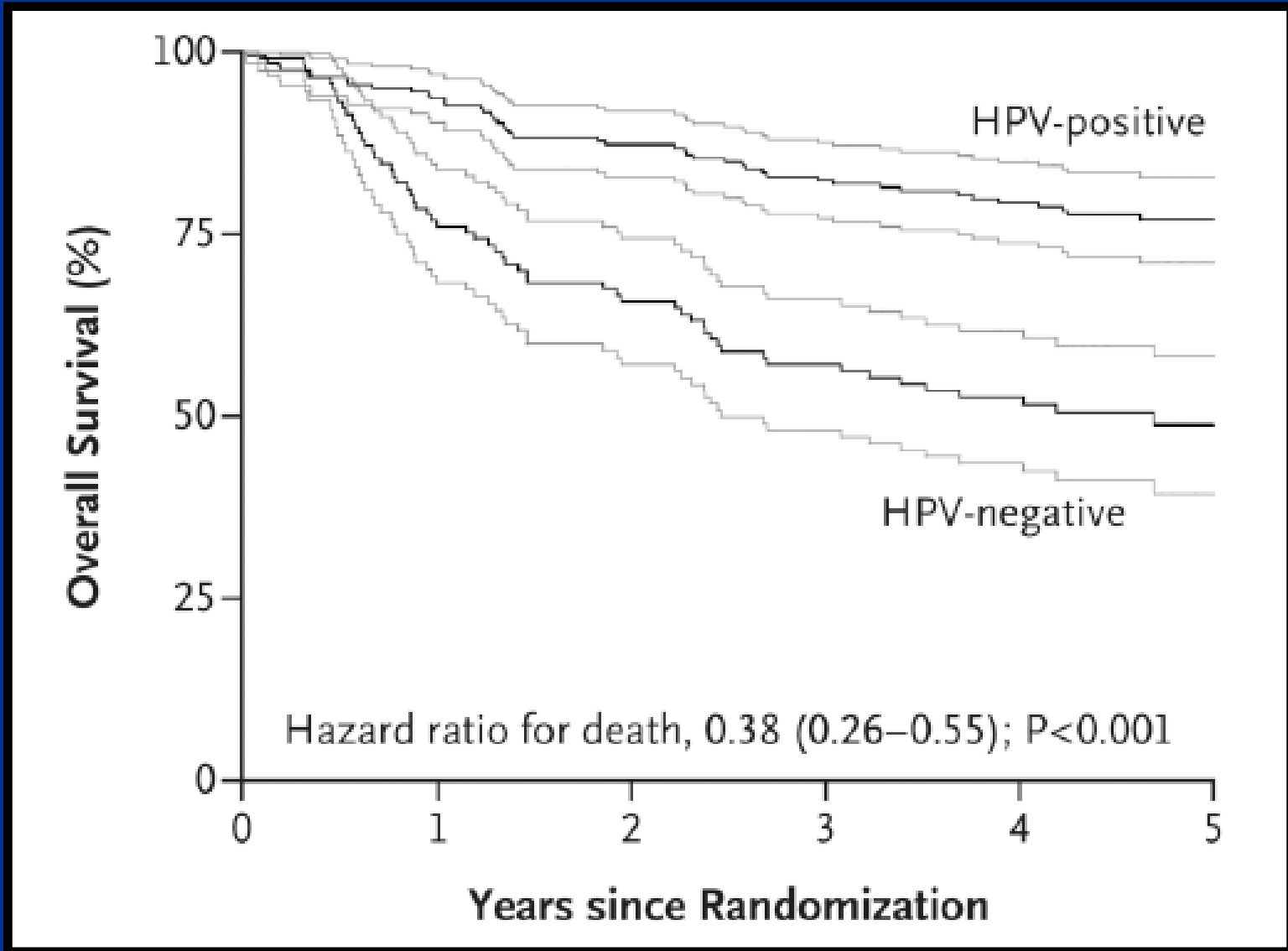
HPV-positive and -negative HNSCCs have distinct risk factor profiles



HPV-positive OP cancers have distinct pathologic, molecular, and clinical features

- Pathologic
 - Basaloid histopathology
 - Poorly differentiated
- Molecular
 - Viral integration and expression of viral oncogenes (E6 and E7)
 - Fewer TP53 mutations
 - p16 over expression
- Clinical
 - Diagnosed at later stage
 - Commonly have nodal metastases

Survival differs by tumor HPV status



Individuals at increased risk of OP

1. Persons with AIDS¹
 - SIR for OP: 1.6 (95%CI = 1.2 to 2.1)
2. Husbands of women with cervical cancer²
 - ~3-fold increased risk of tonsillar cancer
 - Concurrent HPV-positive tonsillar carcinomas in couples (n=3)³
3. Individuals who had anogenital SCC⁴
 - RR for tonsillar cancer ranged from 4 to 6 based on anogenital anatomic site of primary cancer— cervical, vulvar/vaginal, anal

¹Chaturvedi A JNCI 2010; ²Hemminki K Eur J Cancer Prevention 2001; ³Andrews E J Infect Dis 2009; ⁴ Frisch M Lancet 1999

Oral HPV Epidemiology

Oral HPV in healthy individuals: systematic review of the literature

| | # of studies | # of individuals | HPV Prevalence (95%CI) |
|---------------------|---------------------|-------------------------|-------------------------------|
| HPV16 | 13 | 3977 | 1.3% (1.0%-1.7%) |
| Carcinogenic | 17 | 4441 | 3.5% (3.0%-4.1%) |
| Overall | 16 | 4070 | 4.5% (3.9%-5.1%) |

Oral HPV Incidence at 6-months

| Study population | Country | N | Incidence rate |
|------------------------------------|----------------|----------|-----------------------|
| Healthy men and women ¹ | Finland | 462 | <3% |
| High-risk HIV- women ² | US | 59 | 10% |
| HIV+ women ² | US | 123 | 20% |

¹Rintala M et al. J Clin Virol 2006; 35:89.

²D'Souza A et al. Int J Cancer 2007; 121:143.

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| HIV+ women ² | US | 123 | 20% |
| CERVIX³ | | | ~20% |

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²D'Souza A et al. Int J Cancer 2007; 121:143

³Winer RL et al. Am J Epidemiol 2003; 157:218.

Oral HPV Persistence at 6-months

| Study population | Outcome | N | # of baseline infections | % persisted |
|----------------------------|---------|------|--------------------------|-------------|
| Healthy men ¹ | Any HPV | 1680 | 56 | 61% |
| Men and women ² | HR-HPV | 462 | 59 | 100% |

¹Kreimer AR. 2010 International IPV Meeting, July 2010

²Rintala M et al. J Clin Virol 2006; 35:89.

Oral HPV Persistence at 6-months

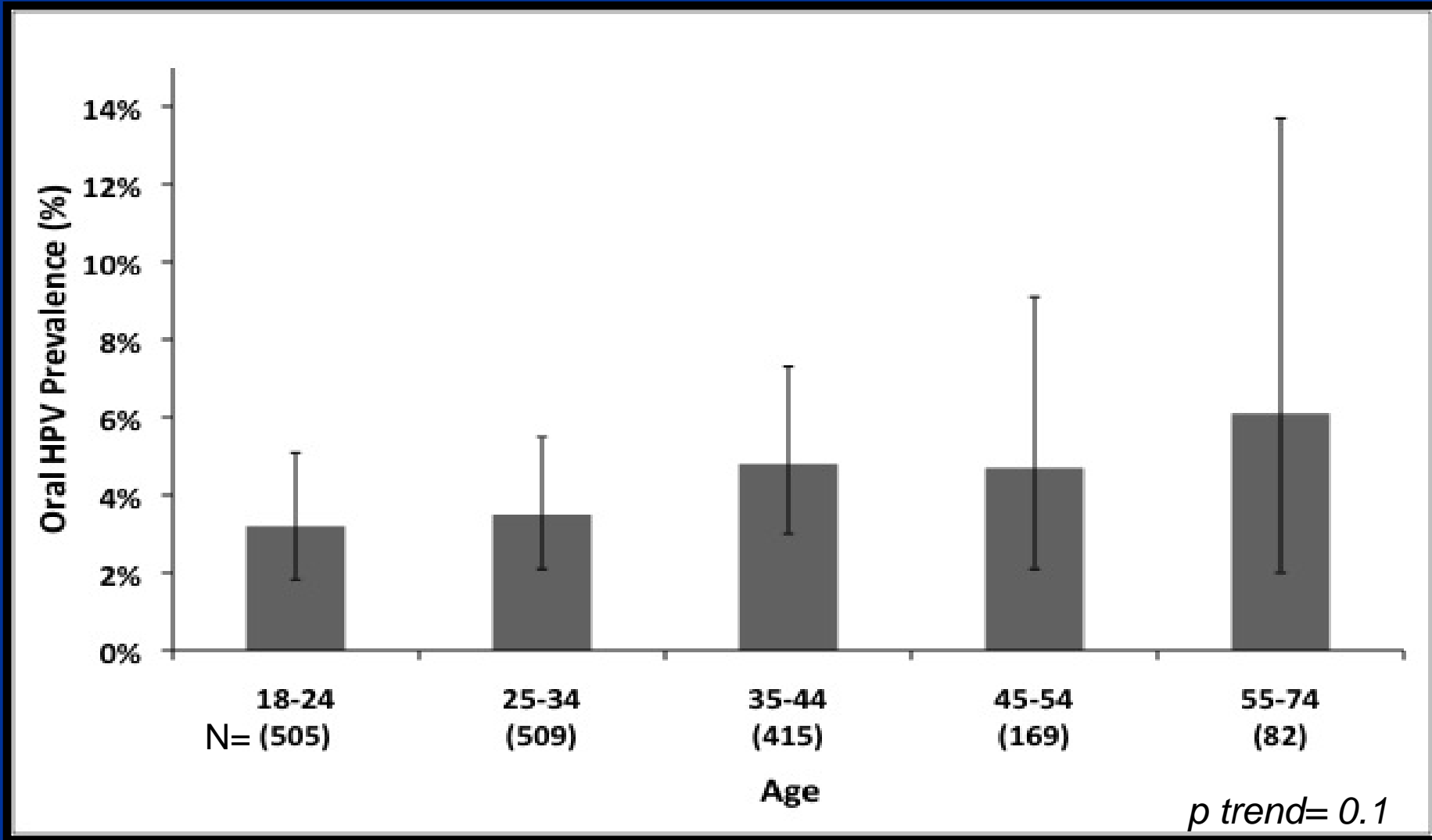
| Study population | Outcome | N | # of baseline infections | % persisted |
|----------------------------|---------|------|--------------------------|-------------|
| Healthy men ¹ | Any HPV | 1680 | 56 | 61% |
| Men and women ² | HR-HPV | 462 | 59 | 100% |
| CERVIX³ | | | | 70% |

¹Kreimer AR. 2010 International IPV Meeting, July 2010

²Rintala M et al. J Clin Virol 2006; 35:89.

³Winer RL Cancer Epidemiol Biomarkers Prev 2011; 20:699.

Age-specific oral HPV in 3 countries



Risk factors for oral HPV infection

- Sexual behavior
 - lifetime and recent numbers of sexual partners
 - oral sexual behaviors
 - kissing
- Current tobacco use
- HIV infection

Important research questions

1. Is persistent oral HPV infection a risk factor for OP cancer and, if so, what is the time between persistent oral HPV infection and OP cancer?
2. Does a precancerous state exist for OP cancer?
3. Does HPV cause cancers in the head and neck beyond the OP?
4. Will prophylactic HPV vaccines protect against HPV in the oral region, and thereby protect against a subset of these cancers?

SUMMARY

- HPV16 causes a subset of head and neck cancers, predominantly in the OP
 - Molecular, epidemiological, and clinical evidence suggest these tumors are distinct from HPV-negative head and neck cancers
- Oral HPV16 is rare in healthy people, although the natural history of the infection is not well-studied
- OP cancer is increasing in the US and other countries
 - Due to HPV infection
- Direct evidence showing the HPV vaccine protects against oral HPV infection is lacking