Oral HPV infection and the changing epidemiology in head and neck cancer

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Disclosures

- None
Intro: Head and Neck Cancer in the U.S.

- 52,610 new HNC cases each year
  - 8\textsuperscript{th} among males
  - 14\textsuperscript{th} among females
- 5-year survival: 61%

- Traditional risk factors:
  - Tobacco and alcohol

- Newly defined risk factor:
  - HPV infection
Topics for today

• HPV & role in cancer
• Burden and trends of HNC
• Patient characteristics of HPV+ and HPV- HNC
• Oral HPV infection – acquisition and persistence
• Prevention
  – Vaccination and Screening
Human Papillomavirus

- Small, circular DNA virus
- Infects basal cells in squamous epithelium
- >100 different types
  - Cutaneous or mucosal
  - High-risk and low-risk types
- Commonly found in the anogenital region
  - Necessary cause of cervical cancer
“High-risk” HPV types have established carcinogenicity

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV types</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha HPV types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>Most potent HPV type, known to cause cancer at several sites</td>
</tr>
<tr>
<td>1</td>
<td>18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59</td>
<td>Sufficient evidence for cervical cancer</td>
</tr>
<tr>
<td>2A</td>
<td>68</td>
<td>Limited evidence in humans and strong mechanistic evidence for cervical cancer</td>
</tr>
<tr>
<td>2B</td>
<td>26, 53, 66, 67, 70, 73, 82</td>
<td>Limited evidence in humans for cervical cancer</td>
</tr>
<tr>
<td>2B</td>
<td>30, 34, 69, 85, 97</td>
<td>Classified by phylogenetic analogy to HPV types with sufficient or limited evidence in humans</td>
</tr>
<tr>
<td>3</td>
<td>6, 11</td>
<td></td>
</tr>
<tr>
<td>Beta HPV types</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2B</td>
<td>5 and 8</td>
<td>Limited evidence for skin cancer in patients with epidermodyplasia verruciformis</td>
</tr>
<tr>
<td>3</td>
<td>Other beta and gamma types</td>
<td>...</td>
</tr>
</tbody>
</table>
HOW DO WE KNOW HPV CAUSES SOME HNC?
HPV and HNSCC
Molecular evidence

- localized to nuclei in tumor cells
- transcriptionally active
- integrated
- found in high copy number (clonal)
- oncoprotein (E6/E7) expression
- not found in surrounding tissue
- HPV16 DNA localized in tumor of 50-80% of OPSCC

Gillison et al. JNCI 2000; D'Souza et al. NEJM 2008
Epidemiologic Evidence: HPV Biomarkers and OP cancer

<table>
<thead>
<tr>
<th>Measure of HPV Exposure or Disease</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted*</td>
</tr>
<tr>
<td>HPV-16 L1 serologic status</td>
<td></td>
</tr>
<tr>
<td>Seronegative</td>
<td>1.00</td>
</tr>
<tr>
<td>Seropositive</td>
<td>32.2 (14.6–71.3)</td>
</tr>
<tr>
<td>Oral HPV-16 infection†</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive</td>
<td>14.6 (6.3–36.6)</td>
</tr>
<tr>
<td>Any oral HPV infection‡</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.00</td>
</tr>
<tr>
<td>Positive</td>
<td>12.3 (5.4–26.4)</td>
</tr>
<tr>
<td>HPV-16 E6 or E7 serologic status</td>
<td></td>
</tr>
<tr>
<td>Seronegative for E6 and E7</td>
<td>1.00</td>
</tr>
<tr>
<td>Seropositive for E6 or E7</td>
<td>58.4 (24.2–138.3)</td>
</tr>
</tbody>
</table>

# Epidemiologic Evidence:
## Sexual Behavior and OP Cancer

<table>
<thead>
<tr>
<th>Sexual Behavior</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
</tr>
<tr>
<td>Lifetime no. of oral-sex partners</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–5</td>
<td>1.9 (0.8–4.5)</td>
</tr>
<tr>
<td>≥6</td>
<td>3.4 (1.3–8.8)</td>
</tr>
</tbody>
</table>

Prospective evaluation of HPV and head and neck cancer

292 HNC incident & 1568 controls nested in Nordic cohort, tested for HPV antibodies at baseline

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>% cases HPV Ab+</th>
<th>% controls HPV Ab+</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>26</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>Tongue</td>
<td>57</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>19</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>23</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>Larynx</td>
<td>76</td>
<td>12%</td>
<td>5%</td>
</tr>
<tr>
<td>ALL HNC sites</td>
<td>292</td>
<td>12%</td>
<td>7%</td>
</tr>
</tbody>
</table>
Etiologic role of HPV in OP cancer clear

- Conclusive evidence showing
  - Consistency
  - Temporal relationship
  - Dose-response (with increasing # sex partners)
  - Biological rationale
  - Molecular evidence

- “There is sufficient evidence in humans for the carcinogenicity of HPV16 in the oropharynx”
BURDEN AND THE CHANGING TRENDS OF HNC
Worldwide Incidence of HPV-associated cancers

![Bar chart showing the annual number of HPV-associated cancer cases for different body parts: Cervix, Anus, Vulva/vagina, Penis, Mouth, Oropharynx. The chart indicates a significant number of cases for the Cervix, with smaller numbers for other locations.]

Number of cases per year

Cancer Site

Modified from: CDC, SEER, Parkin 2006, Chaturvedi 2011
Incidence of HPV-Associated Cancer in US

Number of new HPV-associated cancers in US in 2009 by gender & site

Men (N = 13,446)

- OP: 78.2% (n = 10,511)
- Anal: 14.4% (n = 1,934)
- Penis: 7.4% (n = 1,001)

Women (N = 21,342)

- OP: 11.6% (n = 2,478)
- Anal: 16.4% (n = 3,500)
- Cervix: 53.4% (n = 11,388)
- Vagina: 3.4% (n = 734)

Increasing OPC incidence is caused by HPV:

U.S (SEER, Chaturvedi, JCO 2011)

Sweden; Nasman Int J Cancer. 2009
Increasing % of OPC with HPV DNA: Summary of literature
HNC cancer incidence by tumor site

Will OPC incidence continue to increase?
HNC Cancer Trends 1973-2006, men increase only among younger men in US

A) Oropharyngeal Cancer increasing in < 55 yr olds

B) Other HNC sites decreasing

HPV-POSITIVE AND HPV-NEGATIVE HNC

different etiologies,
different patient populations,
different survival
Who is at increased risk of HPV+OPC?

1. Men
2. Risk increases with age
3. HIV-infected
4. Husbands of women with cervical cancer
   - ~3-fold increased risk of tonsillar cancer
   - Unclear in spouse of HPV+ OPSCC at increased risk
5. Individuals with hx of anogenital SCC
   - 4-6 fold increase risk of tonsillar cancer

Patient Characteristics Differ
HNC Case Series

- Different HPV+ and HPV- Patient Populations

- HPV+ cases more likely to be:
  - nonsmokers, nondrinkers
  - younger age
  - White
  - higher SES
  - palatine and lingual tonsils
  - poorly differentiated (basaloid)
Risk Factors for HPV-negative HNC Case-Control

Gillison et al. JNCI 2008: 407
Risk Factors for HPV-positive HNC
Case-Control

Gillison et al. JNCI 2008: 407
Warning: association does not imply prediction

- >50% of HPV+ OP cases have ≤ 5 lifetime oral sex partners
  - Oral HPV is a fairly common infection
- HPV+ OP cases can also commonly occur among smokers
  - ~20% of HPV+ OP cancers are nonsmokers/nondrinkers
- Demographics, tobacco, alcohol & sexual behavior had only moderate predictive ability for HPV status
  - OP: PPV=55%, NPV=65%
  → Many false positive and negative predictions
- Tumor testing is necessary to identify HPV status of cancer
Survival Differs by Tumor HPV Status

- Eastern Cooperative Onc. Group (ECOG) - 96 stage III or IV oropharynx or larynx cancers

<table>
<thead>
<tr>
<th></th>
<th>HPV+</th>
<th>HPV-</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Responsive to treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>induction chemotherapy</td>
<td>82%</td>
<td>55%</td>
<td>0.01</td>
</tr>
<tr>
<td>chemo-radiation treatment</td>
<td>84%</td>
<td>57%</td>
<td>0.007</td>
</tr>
<tr>
<td>2 year survival</td>
<td>87%</td>
<td>62%</td>
<td>0.008</td>
</tr>
<tr>
<td>Disease progression</td>
<td>13%</td>
<td>34%</td>
<td>0.02</td>
</tr>
<tr>
<td>Death</td>
<td>18%</td>
<td>41%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Fakhry, C. et al. JNCI 2008:261-269
Survival Differs: Tobacco & HPV

HPV and tobacco predict survival

Ang et al. NEJM 2010

- HPV+ <10pkyr: 93%
- HPV+ ≥10pkyr & HPV- <10pkyr: 71%
- HPV- ≥10pkyr: 46%

3 yr survival
HNC Treatment Complications

- HNC treatments are *currently* similar to HPV+ and HPV- HNC: surgery, chemotherapy, radiation therapy
- Complications are common:
  - Difficulty swallowing/speaking
  - Change in taste
  - Decreased saliva production
  - Osteoradionecrosis (ORN)
  - Thyroid problems
  - Infection
  - Decreased neck mobility
  - Concerns regarding cognitive function
ORAL HPV INFECTION-PREVALENCE, ACQUISITION & PERSISTENCE
Natural history of HPV: Cervical cancer model of progression

Co-factors:
• Smoking
• Immunosuppression
• Long term oral contraceptive use
Oral HPV prevalence among the US general population:

- Any type = 6.9%
- High risk = 3.7%
- HPV16 = 1.0%
Oral HPV Prevalence by NHANES: Men

Men, any HPV infection

HPV Prevalence, %

Age, y

Unadjusted
--- 95% CI

Adjusted

Gillison, Chaturvedi. JAMA 2012
Oral HPV Prevalence by age
NHANES: Women

Women, any HPV infection

- Unadjusted
- 95% CI
- Adjusted

Gillison, Chaturvedi. JAMA 2012
Oral HPV Acquisition

- Incidence approximately 5-10x lower than genital HPV infection in females and males\textsuperscript{1-5}

<table>
<thead>
<tr>
<th>Study population</th>
<th>Country</th>
<th>N</th>
<th>Incidence rate/1000 person-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>College students (Gillison\textsuperscript{1})</td>
<td>US</td>
<td>1000</td>
<td>5.7</td>
</tr>
<tr>
<td>Adult men (Kreimer\textsuperscript{2})</td>
<td>3 countries</td>
<td>1626</td>
<td>5.7</td>
</tr>
<tr>
<td>Young adults in STD Clinic (D’Souza\textsuperscript{3})</td>
<td>US</td>
<td>550</td>
<td>26</td>
</tr>
<tr>
<td>HIV+ adults (Beachler\textsuperscript{4})</td>
<td>US</td>
<td>404</td>
<td>31</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Pickard Gillison et al. STD 2012: 559-66. \textsuperscript{2}Kreimer et al. Lancet 2013. \textsuperscript{3}DSouza unpublished \textsuperscript{4}Beachler et al. JID 2013; 121:143 \textsuperscript{5}Giuliano, Lancet 2011
Cumulative Oral HPV Incidence in a high risk population

p-trend < 0.001

Percentage of participants

Months since study entry

HIV-uninfected
HIV-infected CD4 >= 500
HIV-infected CD4: 200-499
HIV-infected CD4 < 200

Beachler et al, Submitted for Publication
Factors associated with increased oral incidence

Potential Transmitters:
- Performing oral sex\textsuperscript{1,2}, particularly on a woman\textsuperscript{1,3}
- Autoinoculation\textsuperscript{4}
- Deep (French) kissing\textsuperscript{2}
- Some infections may be latent and re-activated\textsuperscript{1,3}

Other potential risk factors:
- HIV-infection and recent immunosuppression\textsuperscript{1}
- Smoking\textsuperscript{5}
- Single status\textsuperscript{5}
- No history of tonsillectomy\textsuperscript{1}

Persistence of incident oral HPV infections in middle age men

Any HPV (Clearance)

Cumulative Probability of Infection

Number at Risk

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
</tr>
<tr>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
<td>3</td>
</tr>
</tbody>
</table>

Kreimer/Pierce-Campbell et al, Lancet 2013
Persistence of Oral HPV in high risk HIV+ and HIV- individuals

Incident Oral HPV, One Negative

HR=0.96 (0.70-1.3)
p=0.80
Oral HPV Persistence

– Oral HPV is most often transient
  • The rate of oral HPV clearance may be similar\(^1\) or even higher\(^2\) compared to anogenital HPV clearance

Factors associated with increased oral persistence
– Cigarette smoking\(^3,4\)
– Older age\(^3,5\)
– Male gender\(^3\)
HPV-ASSOCIATED HNC PREVENTION
HNC Prevention Options

– Primary Prevention – Behavior Change
  • Limiting number of sexual partners
  • Smoking cessation
– Prophylactic HPV vaccination
– Screening

¹Fakhry CPR, 2011, ²Denny Vaccine 2012
Prophylactic HPV vaccination

- Two prophylactic vaccines on market – Gardasil (6/11/16/18) and Cervarix (16/18)
  - Likely to protect against oral HPV acquisition\(^1\)

- Currently recommended for both boys and girls aged 9-26 by the CDC’s Advisory Committee on Immunization Practices (ACIP)
  - Recommended age: 11-12
  - 33% of girls and 7% of boys followed current recommendations (3 doses) in 2012\(^2\)

- Current trials exploring long-term immunogenicity and efficacy against oral HPV in various groups
  - Older individuals - likely less benefit considering previous exposure
    - Evidence of oral HPV acquisition at older ages suggests potential for a small benefit in older populations

\(^1\) Herrero, Plos One 2013, \(^2\) CDC MMWR 2013
Screening – Can we replicate the success seen with Cervical Cancer?

Wright TC NEJM 2003
Clinical, Pathological, and Molecular Progression of Oral Cavity Cancer

A

Benign squamous hyperplasia
Dysplasia
Carcinoma in situ
Dysplasia
Carcinoma
Dysplasia

B

Normal mucosa
Hyperplasia
Dysplasia
Carcinoma in situ
Carcinoma

C

9p21 LOH
p16 inactivation
3p21, 17p13 LOH
p53 mutation
13q21, 14q32 LOH
Cyclin D1 amplification
6p, 8, 4q27, 10q23 LOH
pTEN inactivation
Difficulties in Screening – Oropharyngeal Cancer

• Difficulty identifying precancerous lesion
  – Cancer often originates in the base of tongue or in the tonsillar crypt
  – Anatomic differences in cervical and tonsillar mucosa affect the ability of the cytobrush to collect premalignant or malignant epithelial cells\(^1\)

• Relatively modest burden of disease
  – Very high specificity need for reasonable PPV\(^2\)
  – Randomized trial would be difficult to conduct
  – Limit to higher risk groups? – harder to identify

1Lingen M W Cancer Prev Res 2011, 2 Castle PE JCO 2014
Screening possibilities for HPV-related HNC

Options:

• Visual detection
  – Difficult due to location/size of oropharyngeal cancer

• Oral Pap smear
  – HPV detection was not associated with cytological abnormalities among a high risk population in recent study
  – Limitation in sampling the relevant tonsillar crypt epithelium (brush biopsy not sufficient)

• Oral HPV (16) DNA
  – Low specificity
  – Not recommended by medical and dental organizations

• Other possibilities
  – HPV16 viral load, antibodies to HPV16 E6/E7 oncoproteins potential candidates, advanced imaging/ultrasound – need further research (PBRN collaboration)

Oral Cancer Screening Study w. the PBRN

iPad for informed consent and oral HPV risk factors survey

Not selected by web-app
- Lower deciles of risk
- 641 (64.1%) subjects

End of Study

Selected by web-app
- Top deciles of risk
- 359 (35.9%) subjects

Oral rinse sample

High-risk HPV negative
- 334 (33.4%) subjects

Notification of results

End of Study

High-risk HPV positive
- 25 (2.5%) subjects

Notification of high risk

Telephone informed consent

- Blood Sample
- Oral Cancer Screening
- Demographic-Behavioral Survey
- Repeat Oral Rinse Sample

Courtesy of Maura Gillison
Conclusion

• HPV is an a distinct etiologic factor of head and neck cancer

• The incidence of HPV-positive HNC is rapidly increasing in the high income countries whereas HPV-negative HNC is declining

• Oral HPV infection is fairly commonly acquired, but usually these infections clear or are controlled within 1-2 years

• New potential avenues for primary and secondary prevention of HNC
Acknowledgments

• Gypsyamber D’Souza, Carole Fakhry – Hopkins

• Maura Gillison – Ohio State
  – Working with PBRN in developing a oral cancer screening study - “HPV Screening in Dental Offices and Oral Cancer Prevention”
Thank you

Questions?