Update of the role of Human Papillomavirus in Head and Neck Cancer

2013 International & 12th National Head and Neck Tumour Conference
Shanghai, 11-13 Oct 2013

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Department of Microbiology
550,300  head & neck cancer / yr

Head & neck cancer ranks:
7th in men
13th in women
Human Papillomaviruses HPV

Oropharyngeal cancer

Vaginal cancer
Vulval cancer
Anal cancer
Penile cancer

Non-enveloped Papillomavirus

Enveloped Herpesvirus
Transmission

Cutaneous HPV:
- Direct skin contact
- Fomite / environment

Mucosal (Anogenital / oral) HPV:

Sexual:
- Through sexual intercourse
- Genital–genital, manual–genital, oral–genital
- Condom use reduce the risk, but it is not fully protective

Nonsexual:
- Mother to newborn (vertical transmission)
- Fomites / environment
Previous HPV infection does not result in long-term protection

- Poor immune stimulator
- Only ~60% seroconvert
- Low level of serum antibody

*CIN = cervical intraepithelial neoplasia
Normal Cervix  
HPV Infection/ CIN* 1  
CIN 2 / CIN 3 / Cervical Cancer

*CIN = cervical intraepithelial neoplasia
Normal Cell Cycle Control

Chromosome segregation (Mitosis)

G2/M checkpoint

M PHASE

G2 PHASE

G1 PHASE

S PHASE

DNA replication

p53

pRb

E6

E6

E6

E6

E7

E7

E7

E7
Viral integration → Lost of negative control on E6 & E7 → ↑ E6 & E7 → X p53 & pRb
Human papillomavirus

Oropharyngeal cancer

How common is oral HPV infection?
HPV Infection in Men (HIM) study
Brazil, Mexico, USA
1626 men, age 18-73 yr, healthy, HIV-negative
HPV test every 6 month

4.4% acquired oral HPV (all types)
1.7% acquired oral oncogenic HPV

Acquisition rate of oncogenic HPV
/ 1000 person-months

Oral: 2.5
Genital: 22.2
Anal: 3.7

Lancet 2013; 382: 877
HPV Infection in Men (HIM) study
Brazil, Mexico, USA
1626 men, age 18-73 yr, healthy, HIV-negative
HPV test every 6 month

Clearance:
Most cleared < 1 yr
Similar across HPV groups

any HPV  oncogenic HPV  HPV 16
Any preferred anatomical sites within H & N region?
## Association of head & neck squamous cell cancer with HPV16

### Oral Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandtsma 1989</td>
<td>4.7 (0.2, 105.5)</td>
</tr>
<tr>
<td>Dillner 1995</td>
<td>0.6 (0.1, 6.2)</td>
</tr>
<tr>
<td>Monk 2001</td>
<td>2.5 (1.2, 5.2)</td>
</tr>
<tr>
<td>Chan 2002</td>
<td>12.8 (3.3, 48.9)</td>
</tr>
<tr>
<td>Van Doornum 2003</td>
<td>1.2 (0.6, 2.8)</td>
</tr>
<tr>
<td>Dahlinstrom 2003</td>
<td>0.5 (0.1, 2.0)</td>
</tr>
<tr>
<td>Herrera 2003</td>
<td>1.5 (1.2, 2.0)</td>
</tr>
<tr>
<td>Zheng 2004</td>
<td>3.6 (1.6, 8.1)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>2.0 (1.2, 3.4)</td>
</tr>
</tbody>
</table>

### Larynx cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandtsma 1989</td>
<td>1.3 (0.2, 8.4)</td>
</tr>
<tr>
<td>Dillner 1995</td>
<td>0.2 (0.03, 1.5)</td>
</tr>
<tr>
<td>Garcia-Milian 1998</td>
<td>18.5 (2.2, 154.8)</td>
</tr>
<tr>
<td>Nishikawa 1999</td>
<td>3.8 (0.7, 21.1)</td>
</tr>
<tr>
<td>Smith 2000</td>
<td>2.9 (0.2, 58.4)</td>
</tr>
<tr>
<td>Monk 2001</td>
<td>2.5 (1.1, 5.7)</td>
</tr>
<tr>
<td>Van Doornum 2003</td>
<td>5.0 (0.6, 43.0)</td>
</tr>
<tr>
<td>Dahlinstrom 2003</td>
<td>1.1 (0.6, 2.2)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>2.0 (1.2, 4.2)</td>
</tr>
</tbody>
</table>

### Oropharynx cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klussmann 2001</td>
<td>21.6 (1.2, 391.9)</td>
</tr>
<tr>
<td>Monk 2001</td>
<td>8.6 (2.6, 28.5)</td>
</tr>
<tr>
<td>Van Doornum 2003</td>
<td>2.3 (1.0, 5.0)</td>
</tr>
<tr>
<td>Dahlinstrom 2003</td>
<td>19.0 (2.5, 142.0)</td>
</tr>
<tr>
<td>Herrera 2003</td>
<td>2.5 (1.6, 3.9)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>4.3 (2.1, 8.9)</td>
</tr>
</tbody>
</table>

### Tonsil cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandtsma 1989</td>
<td>18.8 (0.8, 447.7)</td>
</tr>
<tr>
<td>Niedobitek 1990</td>
<td>17.6 (0.9, 329.2)</td>
</tr>
<tr>
<td>Snijders 1992</td>
<td>15.0 (0.7, 332.0)</td>
</tr>
<tr>
<td>Lewensohn 1994</td>
<td>5.0 (0.2, 166.6)</td>
</tr>
<tr>
<td>Mallin 2000</td>
<td>16.1 (0.9, 287.9)</td>
</tr>
<tr>
<td>Klussmann 2001</td>
<td>34.0 (1.8, 635.6)</td>
</tr>
<tr>
<td>Stromme 2002</td>
<td>10.2 (2.8, 37.0)</td>
</tr>
<tr>
<td>Dahlinstrom 2003</td>
<td>26.9 (4.7, 155.1)</td>
</tr>
<tr>
<td>Combined estimate</td>
<td>15.1 (6.8, 33.7)</td>
</tr>
</tbody>
</table>
Cervical cancer develops from transformation zone
Tonsillar cancer develops from crypts

http://all-about-health.blogspot.hk/2013/05/tonsil.html
Which HPV type?
HPV type distribution in head and neck cancer

- **Oral cavity SCC**: 2642 cases
- **Oropharyngeal SCC**: 969 cases
- **Laryngeal SCC**: 1435 cases

**HPV16 among HPV-positive SCC**
- Oropharyngeal: 86.7%
- Oral cavity: 68.2%
- Laryngeal: 69.2%

**HPV18 among HPV-positive SCC**
- Oropharyngeal: 1.0%
- Oral cavity: 8.0%
- Laryngeal: 3.9%

Cancer Epidemiol Biomarkers Prev 2005; 14: 467
Role of HPV in oral precancerous lesions ?
Natural History of cervical HPV Infection

- Transient Infection (1-2 Year)
- Normal cervix
- Persistent Infection (2–5 Years)
- Low-Grade Dysplasia CIN 1 (4–5 Years)
- High-Grade Dysplasia CIN 2/3 (9–15 Years)
- Invasive Cancer

HPV Infection:
- Over 2 Years

Persistent Infection:
- Transient Infection
- Normal cervix

Low-Grade Dysplasia CIN 1:
- Transient Infection
- Normal cervix
- Persistent Infection

High-Grade Dysplasia CIN 2/3:
- Persistent Infection
- Invasive Cancer
HPV prevalence in oral potentially malignant disorder (OPMD)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OPMD Events</th>
<th>Normal tissue Events</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.1 OPMD not specified</td>
<td>16</td>
<td>5</td>
<td>4.48 [0.97, 20.59]</td>
<td>1987</td>
</tr>
<tr>
<td>Giovannelli 2002</td>
<td>90</td>
<td>35</td>
<td>4.82 [1.72, 13.54]</td>
<td>2009</td>
</tr>
<tr>
<td>Luo 2007</td>
<td>90</td>
<td>35</td>
<td>2.84 [1.19, 6.81]</td>
<td>2007</td>
</tr>
<tr>
<td>Debanth 2009</td>
<td>41</td>
<td>35</td>
<td>4.44 [2.64, 7.49]</td>
<td>2009</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>267</td>
<td>247</td>
<td>4.44 [2.64, 7.49]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>104</td>
<td>27</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.76, df = 4 (P = 0.60); I² = 0%

Test for overall effect: Z = 5.60 (P < 0.00001)
### Lichen planus

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OPMD Events</th>
<th>Normal tissue Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.2 Lichen planus</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6.6%</td>
<td>2.00 [0.11, 35.81] 1993</td>
</tr>
<tr>
<td>Cox 1993</td>
<td>6</td>
<td>22</td>
<td>12</td>
<td>6.2%</td>
<td>9.85 [0.51, 191.74] 2000</td>
</tr>
<tr>
<td>Sand 2000</td>
<td>10</td>
<td>38</td>
<td>20</td>
<td>6.5%</td>
<td>15.11 [0.84, 272.68] 2003</td>
</tr>
<tr>
<td>OFlatharta 2003</td>
<td>14</td>
<td>71</td>
<td>90</td>
<td>37.0%</td>
<td>4.18 [1.43, 12.23] 2004</td>
</tr>
<tr>
<td>Campisi 2004</td>
<td>3</td>
<td>15</td>
<td>2</td>
<td>10</td>
<td>1.00 [0.14, 7.39] 2006</td>
</tr>
<tr>
<td>Cianfriglia 2006</td>
<td>39</td>
<td>119</td>
<td>72</td>
<td>30.6%</td>
<td>5.12 [2.46, 10.93] 2009</td>
</tr>
<tr>
<td>Szarka 2009</td>
<td>269</td>
<td>209</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>75</td>
<td>13</td>
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</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 5.61$, df = 5 ($P = 0.35$); $I^2 = 11$
Test for overall effect: $Z = 4.23$ ($P < 0.0001$)

### Leukoplakia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OPMD Events</th>
<th>Normal tissue Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.3 Leukoplakia</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>2.5%</td>
<td>6.43 [0.23, 181.82] 1993</td>
</tr>
<tr>
<td>Cox 1993</td>
<td>2</td>
<td>7</td>
<td>12</td>
<td>2.8%</td>
<td>11.36 [0.46, 278.14] 2000</td>
</tr>
<tr>
<td>Sand 2000</td>
<td>12</td>
<td>68</td>
<td>90</td>
<td>18.1%</td>
<td>3.64 [1.22, 10.90] 2004</td>
</tr>
<tr>
<td>Campisi 2004</td>
<td>12</td>
<td>20</td>
<td>10</td>
<td>8.1%</td>
<td>6.00 [1.00, 35.91] 2006</td>
</tr>
<tr>
<td>Cianfriglia 2006</td>
<td>16</td>
<td>35</td>
<td>30</td>
<td>18.6%</td>
<td>2.77 [0.94, 8.12] 2008</td>
</tr>
<tr>
<td>Szarka 2009</td>
<td>37</td>
<td>87</td>
<td>100</td>
<td>36.0%</td>
<td>4.48 [1.32, 4.65] 2009</td>
</tr>
<tr>
<td>Majumder 2009</td>
<td>285</td>
<td>319</td>
<td>100.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>101</td>
<td>43</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 7.56$, df = 6 ($P = 0.27$); $I^2 = 21$
Test for overall effect: $Z = 5.04$ ($P < 0.00001$)

Oral Diseases 2011; 17: 51: 58
Dysplasia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>OPMD Events</th>
<th>Normal tissue Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4.6 Dysplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holliday 1993</td>
<td>6</td>
<td>27</td>
<td>1</td>
<td>6</td>
<td>1.43 [0.14, 14.70] 1993</td>
</tr>
<tr>
<td>Mao 1996</td>
<td>5</td>
<td>13</td>
<td>0</td>
<td>6</td>
<td>7.6% [0.39, 181.19] 1996</td>
</tr>
<tr>
<td>Bouda 2000</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>6</td>
<td>4.7% 363.00 [6.41, 20565.48] 2000</td>
</tr>
<tr>
<td>Patiman, 2001</td>
<td>20</td>
<td>30</td>
<td>1</td>
<td>7</td>
<td>12.5% 12.00 [1.27, 113.74] 2001</td>
</tr>
<tr>
<td>Sugiyama 2003</td>
<td>31</td>
<td>51</td>
<td>16</td>
<td>44</td>
<td>35.4% 2.71 [1.18, 6.24] 2003</td>
</tr>
<tr>
<td>Debanth 2009</td>
<td>17</td>
<td>35</td>
<td>5</td>
<td>35</td>
<td>27.9% 5.67 [1.78, 18.00] 2009</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>161</td>
<td>23</td>
<td></td>
<td></td>
<td>5.10 [2.03, 12.80]</td>
</tr>
</tbody>
</table>

Total events: 84, 23

Heterogeneity: Tau² = 0.44; Chi² = 7.95, df = 5 (P = 0.16); I² = 37%
Test for overall effect: Z = 3.47 (P = 0.0005)
Oral proliferative verrucous leukoplakia

Carcinoma in-situ
A distinct entity?
Unique characteristics of HPV-positive oropharyngeal cancer

**Demographic & risk factors:**
- Male
- White
- Younger
- Non-smoker
- Non-drinker
- Higher socioeconomic status
- Sexual behavior

**Clinical characteristics:**
- Early T stage, advanced nodal stage
- Better response to treatment

**Pathological features:**
- Arise from tonsillar crypts
- Without significant keratinization
- Basaloid morphology
- Lymphocyte infiltration
- ↑ p16
- Wild type p53
Trend of disease burden?
Changes in incidence of head & neck cancer 1973-2006, USA

NOT HPV-related sites, men

HPV-related sites, Men

NOT HPV-related sites, women

HPV-related sites, Women
Tonsillar SCC
Stockholm 1970-2006,

Oropharyngeal SCC
Hawaii, Iowa, Los Angeles 1988-2004
No. of new cancers at anatomical sites and cellular types in which HPV is frequently found
USA, 2009

Total (N = 34,788)

- **Cervix**
  - 32.7% (n = 11,388)
- **Vagina**
  - 2.1% (n = 734)
- **Vulva**
  - 9.3% (n = 3,242)
- **Penis**
  - 2.9% (n = 1,001)
- **Oropharynx**
  - 37.3% (n = 12,989)
- **Anus**
  - 15.6% (n = 5,434)

**Estimated contribution of HPV:**
- Cervical cancer: ~100%
- Anal cancer: 90%
- Oropharyngeal cancer: >60%
- Vagina, vulva, penile ~40%
Prevent by screening & vaccination?
Quadrivalent HPV Vaccine QARDASIL®
HPV 6,11, 16,18 + Aluminium

Bivalent HPV vaccine CERVARIX®
HPV 16,18 + Al + AS04

High-risk HPVs
We are just at the beginning of a cancer epidemic!