Primary and secondary prevention opportunities for HPV-driven head and neck cancer

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Overview

1. Should we even consider preventing this cancer?
   - Trends in incidence over time

2. How can we prevent this cancer?
   - Primary prevention via prophylactic HPV vaccination?
   - Secondary prevention via screening?

3. Areas for future research
Incidence of OP cancer in the US

Data from SEER9
1988-2004

Rising OP incidence in the US

Similar trends:
– Canada¹
– Netherlands²
– Sweden³
– United Kingdom⁴
– Australia⁵

References:
¹ Auluck A. Cancer 2010; 116:2635
² Braakhuis BJ. Oral Oncol 2009; 45:e85
³ Hammarstedt L. Acta Otolaryng 2007; 127:988
⁴ Conway DL. Oral Oncol 2006; 42:586
⁵ Hong AM. Vaccine 2010; 28:3269
HPV explains rising OP incidence

Observed and projected incidence rates of OP and cervical cancers (US)

Incidence of HPV-associated cancers - USA

Rising OPC incidence occurs at younger ages in the U.S.

Slide courtesy of Anil Chaturvedi
U.S. incidence rates: summary

• Increasing oropharyngeal cancer incidence
  – Men
  – Younger ages

• Decreasing incidence for oral cavity cancers
  – Men and women
  – Younger ages

• Oropharyngeal cancer incidence rates inconsistent with trends in smoking
  – Supports the role of HPV infection
International trends among men 1983-2002

- Rising oropharyngeal cancer incidence in developed countries

- Decreasing incidence for oral cavity cancers and lung cancers

- Oropharynx cancer incidence inconsistent with trends in smoking

International trends among men 1983-2002

• Rising oropharyngeal cancer incidence in developed countries

• Decreasing incidence for oral cavity cancers and lung cancers

• Oropharynx cancer incidence inconsistent with trends in smoking

International trends among women 1983-2002

• Rising oropharyngeal cancer generally accompanied by rising incidence for oral cavity and lung cancers

• Oropharynx cancer incidence consistent with trends in smoking

OPC trends by age in men

Rising OPC incidence predominantly at younger ages

Worldwide incidence trends: summary

• Increasing oropharynx cancer incidence during the past 20-30 years in the U.S. and other developed countries
  – Predominantly in men
  – Younger ages

• Oropharynx cancer incidence rates not consistent with incidence for other smoking-associated cancers (oral cavity and lung)

• Rising incidence because of HPV?
Prevention methods for HPV-associated cancers

1. Primary- prophylactic HPV vaccination

2. Secondary- viral DNA or other viral determinants
   - HPV16 E6 serum antibodies
Primary prevention
Prophylactic HPV vaccination

# FDA-approved HPV vaccines

<table>
<thead>
<tr>
<th>Manufacturer (Trade name)</th>
<th>Vaccine types</th>
<th>Cervical vaccine efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck (Gardasil)</td>
<td>HPV16 and 18 HPV6 and 11 ‘quadrivalent’</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>GlaxoSmithKline (Cervarix)</td>
<td>HPV16 and 18 ‘bivalent’</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

Both vaccines were tested and approved using a 3-dose regimen.
# Efficacy at non-cervical sites

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Published vaccine efficacy against HPV16/18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Merck</td>
</tr>
<tr>
<td>Anus</td>
<td>High</td>
</tr>
<tr>
<td>Vagina/Vulva</td>
<td>High</td>
</tr>
<tr>
<td>Penis</td>
<td>High</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Not evaluated</td>
</tr>
</tbody>
</table>
Costa Rica Vaccine Trial

7,466 Women
18-25 years old
2004-2005

Control vaccine
Hepatitis A Vaccine

Cervarix
HPV-16/18 Vaccine

Herrero R et al/ Cancer Discovery 2011;1:408
Herrero R et al/ Vaccine 2008;26:4795
Costa Rica Vaccine Trial

- 7,466 Women
- 18-25 years old
- 2004-2005

- Control vaccine
  - Hepatitis A Vaccine
- Cervarix
  - HPV-16/18 Vaccine

- Annual follow-up for 4 years
- Cervical samples collected at all visits
- Oral specimens collected at 4 year visit
Vaccine efficacy against oral HPV 16/18 infections - 4 years of protection

<table>
<thead>
<tr>
<th>Arm</th>
<th># Women</th>
<th># HPV16/18 Infections</th>
<th>HPV16/18 VE (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV</td>
<td>2910</td>
<td>1</td>
<td>93% (63% to 100%)</td>
</tr>
<tr>
<td>Control</td>
<td>2924</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

Herrero R et al *PLOS ONE* 2013
Current vaccine implementation

• Does the natural history of oral HPV infection differ from that of cervical?
  – Relevant for vaccine administration
  – Prophylactic vaccine- needs to protect against bolus of incident infection
How long does the vaccine need to work?

Cervical HPV infection

HSIL

Cancer

Schiffman M et al. CEBP 2013.
How long does the vaccine need to work?

Oral HPV infection - carcinogenic types

Gillison ML et al. JAMA 2012.
Age-specific prevalence of oral HPV infection

\[
\text{Prevalence} = \text{Incidence} \times \text{Duration}
\]

Gillison ML et al. JAMA 2012.
Incidence of oncogenic oral HPV infections: the *HIM* Study

Duration of vaccine protection at different anatomic sites

<table>
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<tr>
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<th>Non-cervical sites</th>
<th>Cervix</th>
</tr>
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<tbody>
<tr>
<td>Years of follow-up</td>
<td>4</td>
<td>&gt;8</td>
</tr>
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Long-term follow-up studies are required
CVT Long-term follow-up

7,466 Women
18-25 years old
2004-2005

Control vaccine
Hepatitis A Vaccine

Cervarix
HPV-16/18 Vaccine

10 total years of follow-up

Pls: Kreimer AR and Hildesheim A
Population-level impact on cervical precancer

Australia: uptake ~80% for all 3 doses

HPV-vaccine uptake among females (1st dose), USA

Website: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-jun-2012/02-HPV-Cullen.pdf
HPV-vaccine uptake among females (1st dose), USA

Website: http://www.cdc.gov/vaccines/acip/meetings/downloads/slides-jun-2012/02-HPV-Cullen.pdf
Secondary prevention will remain necessary

1. Inadequate rates of vaccine uptake
   • USA: females (20 to 40%) and males (<5%)

2. Current generations at risk for cancer will not be protected by vaccination
   • at least the next several decades
Potential for screening HPV-driven oropharyngeal cancer?

- Case-control studies: HPV16 E6 antibody positivity associated with current diagnosis of HPV16-positive oropharyngeal cancer
- L1 antibodies- markers of exposure
- E6 antibodies- more likely to mark disease
Potential for screening HPV-driven oropharyngeal cancer?

- Case-control studies: HPV16 E6 antibody positivity associated with current diagnosis of HPV16-positive oropharyngeal cancer
  - L1 antibodies - markers of exposure
  - E6 antibodies - more likely to mark disease
- Can HPV16 E6 serum antibodies predict risk of HPV-driven oropharynx cancer?
European Prospective Investigation into Cancer and Nutrition (EPIC)

- 400,000 participants gave a blood sample
- Evaluated HPV serologic biomarkers in head and neck cancer cases and controls
- Blood draw to cancer diagnosis: 6.5 years (0.1 to 14 years)

## HPV16 E6: OPC marker?

<table>
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<tr>
<th></th>
<th>Controls (n= 1599)</th>
<th>Oral cavity (n= 180)</th>
<th>Larynx (n= 247)</th>
<th>Oropharynx (n= 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>9 (0.6%)</td>
<td>2 (1.1%)</td>
<td>3 (1.2%)</td>
<td>47 (34.8%)</td>
</tr>
<tr>
<td>adjOR</td>
<td>1.3 (0.3-6.9)</td>
<td>3.8 (0.8-18)</td>
<td>274 (110-681)</td>
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HPV16 E6 seropositivity among oropharyngeal cancer cases

Years between blood draw and cancer diagnosis

HPV 16 E6 Seropositive (%)
Current investigations

1. Will our findings replicate in other cohorts?

2. What is the sensitivity of this marker?

3. HPV-driven oropharyngeal cancer, or anogenital cancers as well?

4. How long does an oral HPV16 infection need to persist before HPV16 E6 antibodies are made?
Checklist: Oropharyngeal Cancer Screening

- Test that detects cancer before symptoms
- Identifiable precancerous state
- Effective treatment
- Evidence of reduced incidence/mortality
- Benefits outweigh risks and costs
What would screening for OP cancer look like in the US?

<table>
<thead>
<tr>
<th>Cancer Outcome</th>
<th>5yr cancer risk per 100K</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th># needed to screen per cancer case detected</th>
<th># needed to screen positive per case detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td>32.6</td>
<td>63%</td>
<td>99.8%</td>
<td>4862</td>
<td>11</td>
</tr>
<tr>
<td>Cervix</td>
<td>68.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytology</td>
<td>58%</td>
<td>92%</td>
<td></td>
<td>2519</td>
<td>202</td>
</tr>
<tr>
<td>HPV</td>
<td>98%</td>
<td>91%</td>
<td></td>
<td>1491</td>
<td>135</td>
</tr>
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Primary Prevention

1. Demonstrated high vaccine efficacy against oral HPV infections
   - Potential to prevent all HPV-driven cancers

2. Wide coverage required
   - Remains inadequate in most regions

3. Additional data needed
   - Duration of protection, efficacy of fewer doses, L2 vaccine, etc.
Secondary Prevention

• Additional data are needed
  • What is the sensitivity of HPV16 E6 marker?
  • Will it predict HPV-driven cancers at other anatomic sites?
  • Is there a precursor lesion?
  • What diagnostics should be used to identify precancer?
  • How should a precancer be treated?
  • Will treatment work to reduce incidence of cancer?
  • Who should be screened?
Collaborators

NCI
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– Hormuzd Katki (BB) – John Schiller (CCR)
– Doug Lowy (CCR) – Mark Sherman (DCP)
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– Michael Pawlita (DKFZ, Germany)

Moffitt Cancer Center
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– Christine Pierce Campbell