Human Papilloma Virus: The new face of head and neck cancer

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Objectives

• Explain the risk between HPV and development of cancer
• Described the changing trends and new risk factors associated with the development of head and neck cancer.
• Explain advances in diagnostic tests utilized to diagnose HPV-associated head and neck cancers
• Discuss treatment strategies which are being developed to target the unique biology of HPV-associated head and neck cancer.
Introduction

• HNSCCs- 6.5% of annual cancer cases worldwide
  – Estimated 38/100,000 new cases/yr (U.S.)
  – Median age = 60 yrs
  – 2/3 Males: 1/3 Females
  – Incidence in Western Europe and U.S increasing over last few decades

• Tobacco and EtOH

Reference: Hafkamp et al., 2004

Introduction

• Approximately 6.2 million new HPV infections occur in the United States each year.
• At any given time, about 26.8% of women 14–59 years old have an HPV infection.
• The lifetime risk of HPV infection is about 75% for sexually active individuals.
• HPV prevalence varies by age and is highest for young women.
• New HPV infection is common in young women.
• In one study of female college students, 39% of those who initially had a negative result for HPV DNA tested positive two years later.
What is HPV?

• Human papillomavirus (HPV) is the broad term for a group of viruses. Certain types of HPV cause warts on the skin and others cause warts in the genital region. Some types of HPV are known to cause cervical cancers, as well as cancers of the anus, penis, vulva, vagina and head and neck.

What is HPV-related Head and Neck Cancer?

• HPV-related head and neck cancers occur primarily in the oropharynx (tonsils and the back of the tongue).
• More common in white men.
• Most caused by tobacco and alcohol use.
• Latest research suggests that up to 80% of oropharyngeal cancers in the U.S. are due to infection with the HPV virus.
• HPV-related head and neck cancer occurs in both people who smoke and those who do not smoke.
A brief history lesson

- **History of Viruses in Oncogenesis**
  - **1933** – Shope and Hurst
    - Identified the first DNA virus causing tumors in mammals
  - **1976** – Zur Hausen
    - Proposed that cervical cancer might be caused by HPV
  - **1983** – Syrjanen et al.
    - Proposed a link between HPV and Head and Neck SCC
Human Papilloma Virus Virology

- *Papovaviridae* family
- small DNA-containing virus
  - double-stranded circular DNA of 7900 base-pairs long
  - 3 segments:
    - Long control
    - Early genes
    - Late genes
- Non-enveloped virus
- Icosahedral Protein Coat (20-sided)
- Epitheliotropic (infects epithelial cells)

Human Papilloma Virus

- >100 types of HPV
- HPV 16, 18, 31, 33 associated with malignancy
Human Papilloma Virus

- Most common sexually transmitted virus
- Wide range of sequelae (mild disease to high-grade squamous lesions)
  - Mild Disease
    - Genital warts
    - Anal warts
    - Cervical dysplasia
  - Severe Disease:
    - Carcinomas of the cervix, vagina, vulva, anus and penis.
- Non-genital types associated with warts on hands, feet etc.

<table>
<thead>
<tr>
<th>HPV-associated diseases</th>
<th>HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin warts</td>
<td>1,2,3,4,7,10,26,27,28,29,31,48,57,60,63,65,75,76,77,78</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis benign</td>
<td>3,5,8,9,12,14,16,17,19,20,21,22,23,24,25,36,38,47,50</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis squamous</td>
<td>5,8,14,17,20,47</td>
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<tr>
<td>cell carcinoma</td>
<td></td>
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<tr>
<td>Periungual squamous cell carcinoma</td>
<td>16,34,35</td>
</tr>
<tr>
<td>Laryngeal papillomas</td>
<td>6,11</td>
</tr>
<tr>
<td>Oral/focal epithelial hyperplasia</td>
<td>13,32</td>
</tr>
<tr>
<td>Squamous cell carcinoma (tongue)</td>
<td>16,33</td>
</tr>
<tr>
<td>Anogenital warts</td>
<td>6,11,40,42,43,44,45,54,55,74</td>
</tr>
<tr>
<td>Low-grade anogenital intraepithelial neoplasia</td>
<td>6,11,16,18,30,31,33,34,35,38,40,45,51,52,56,67,58,59,64,65,66,67,68,70,71,72,73,74</td>
</tr>
<tr>
<td>High-grade anogenital intraepithelial neoplasia</td>
<td>16,18,31,33,34,35,39,45,51,52,56,58,68</td>
</tr>
<tr>
<td>Squamous cell carcinoma (cervix mostly)</td>
<td>16,18,31,33,35,45,51,52,56,58,59,68</td>
</tr>
<tr>
<td>Adenocarcinoma (cervix mostly)</td>
<td>16,18</td>
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</tbody>
</table>
HPV in Recurrent Respiratory Papillomatosis

- HPV- 6, 11
  - Same as in anogenital warts
- 2 main types:
  - Juvenile (aggressive)
  - Adult (non-aggressive)
- Low risk of malignant transformation

Oncogenesis of HPV

- Multistep/Multifactor process
  - Oncogenes
  - Modification of cellular genes
  - Possible genetic susceptibility of host
  - Impaired cell-mediated immunity
- Genome of dsDNA incorporation
  - “Early” Region encodes for “Early Proteins” E1-E7 (important in pathogenesis and transformation)
  - E6, E7 classified as oncogenes
    - E6 binds to p53 and degrades it
    - E7 binds to pRB and causes dysfunction
      - Results in inhibition of the cell cycle control and facilitation of tumor development
Oncogenesis of HPV

• Humoral immunity in HPV not well-understood
  – Incidence of HPV-16 Abs in pts with HNSCC is significantly increased (Mork et al., 2001)
  – Abs to E6 and E7 are more clearly associated with malignant disease (Herrero et al., 2003; Lehtinen and Paavonen, 2001)

HPV in Head and Neck Cancer

Hobbs et al., 2006

• Systematic review & meta-analysis of HPV-16 exposure in H&N cancer
  – Sites: Oral, Oropharynx, Tonsil, Larynx

• Results:
  – 17 studies compared site-specific anatomical sites with a control group
  – 2612 cases
    • 1656 – Oral
    • 383 – Oropharynx
    • 161 – Tonsil (separated from Oropharynx)
    • 412 – Larynx
HPV in Head and Neck Cancer

Hobbs et al., 2006

• **Results:**
  
  – Association b/w HPV and cancer was:
    
    • **Strongest** for **tonsil** (random effects summary OR: 15.1, 95% CI: 6.8-33.7)
    
    • **Intermediate** for **oropharynx** (random effects summary OR: 4.3, 95% CI: 2.1-8.9)
    
    • **Weakest** for **oral** (random-effects summary OR 2.0, 95% CI: 1.0-4.2) and **larynx** (OR = 2.0)
  
  – Some variability in association based on detection method (ELISA or PCR)

HPV in Other Head & Neck Tumors

• Prevalence varies in the literature
  
  – Possibly due to methods of analysis
    
    • 14-35% by PCR
    
    • 25% by Southern Blot
    
    • 18% by FISH
  
  – Most common HPV locations (other than oropharynx) - [Dahlstrand & Dalianis, 2005]
    
    • Tongue Cancer (19-100%)
    
    • Laryngeal Cancer (10-50%)
HPV in Oropharyngeal Cancer

• Tonsillar Cancer most common oropharyngeal malignancy
• >75% are Squamous Cell Carcinoma
• Smoking and EtOH abuse regarded as main etiologic factors in most (80%)
  – Approx 20% of patients do not have these risk factors

HPV in Oropharyngeal Cancer

• HPV DNA present in 45-100% of tonsillar tumors (Mellin & Dalianis, 2005)
  – **HPV-16** predominant type
    • HPV-positive Tonsillar cancer Biopsies
      – 85-100% contain HPV-16
      – 0-7% contain HPV-33
HPV in Oropharyngeal Cancer

Hammarstedt et al., 2006

- 515 pts in Sweden 1970 to 2002
- **Results:**
  - Incidence of **Tonsillar SCC** increased 2.8-fold over time-period
  - Proportion of HPV +ve Tonsillar SCC increased 2.9-fold (p<0.001)
- **Conclusion:**
  - Incidence of tonsillar ca may be associated with increased incidence of HPV

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HPV in Oropharyngeal Cancer

- HPV in lymph nodes?
  - Stroma et al., 2002
    - 94% (15/16) of patients with HPV +ve **Tonsillar SCC** with LN involvement had HPV identified in LNs
    - Pts with HPV +ve Tonsillar ca without metastatic disease had no evidence of HPV in their lymphatic tissue (8 patients)
HPV in Oropharyngeal Cancer

- Significantly higher HPV prevalence found in oropharyngeal SCCs that oral or laryngeal SCCs (Kreimer et al., 2005)
- Proposed that HPV-positive oropharyngeal SCC is a distinct entity, less dependent on smoking and alcohol use (Klussmann et al., 2003)

HPV in Oropharyngeal Cancer

- Pts with HPV-positive **tonsillar tumors** are:
  - Less likely to be heavy smokers & drinkers
  - Synergistic effect possibly with smokers
- Pts with anogenital malignancies have increased risk for a second primary cancer of the tonsils and oral cavity (Boice et al., 1985; Frish & Biggar, 1999; Rabkin et al., 1992)
- Increased incidence of tonsillar cancer in women aged >50 yrs with hx of cervical CIS (Hemminki et al., 2000)
What are signs and symptoms?

- Most are asymptomatic.
- Immune system is able to clear the virus from their body.
- A small percentage of people can’t clear the virus and may develop problems ranging from benign skin warts to abnormal cell growth that could lead to cancer.

Signs and Symptoms

- Otalgia
- Weight loss
- Fever/Chills
- Dysphagia
- Odynophagia
- Hoarseness
- Neck Mass
HPV and Prognosis in Oropharyngeal Cancer

• **HPV may be a favorable prognostic factor**
  (Gillison et al, 2000; Mellin et al., 2000)
  – Mellin et al., 2000
    • 60 pts with tonsillar cancer
      – 52% of pts with HPV +ve tumors were disease free after 3 years
      – 21% of pts with HPV –ve tumors were disease free after 3 years
    • Pts with HPV +ve tumors had significantly increased 5-year survival rates compared to HPV –ve tumors (53% vs. 31%, p=0.047)
    • HPV +ve tumors favorable independent of tumor stage, gender, age or differentiation

Gillison et al., 2000

• 253 head and neck cancer patients
  – 60 oropharyngeal cancers (mostly tonsil)

**Results:**
  – Disease-specific survival significantly higher for HPV +ve tumors
  – No change in disease-specific survival for other head and neck cancers

• Multiples studies have shown **no change** in survival for HPV +ve tumors (except oropharynx) [reviewed by Dahlstrand & Dalia, 2005]
HPV and Prognosis in Oropharyngeal Cancer

Ritchie et al., 2003

- HPV-infected males had better prognosis than HPV-negative males (no difference in females)
- HPV status was identified as an independent prognostic factor in oral and oropharyngeal cancers
- HPV +ve patients had better overall survival

Reimers et al., 2007

- **Purpose**: To assess the prognostic implications of presence of 3 factors: 1. HPV-DNA; 2. EGFR expression; 3. p16 expression
- **Methods**:
  - 106 new diagnosis OPC
  - Analyzed for presence of above 3 factors
  - Reviewed 5-yr survival (Overall and DFS)
- **Results**:
  - 28% HR-HPV
  - 30% p16-positive (highly correlated with presence of DNA)
  - 5-yr DFS significantly better for p16-positive tumors (84% vs. 49%)
  - EGFR-negative tumors **no significant** difference in DFS
HPV and Prognosis in Oropharyngeal Cancer

Reimers et al., 2007

Results:
- Disease-Free Survival:
  - p16 +ve:EGFR –ve → 93% DFS
  - p16 –ve:EGFR +ve → 39% DFS (p=0.003)
  - p16 expression alone – significant prognostic factor for DFS (p=0.031) 7.5 fold increase of relapse in p16 –ve tumors
- Overall Survival:
  - p16 +ve:EGFR –ve → 79% Overall Survival
  - p16 –ve:EGFR +ve → 38% Overall Survival (p=0.010)

Conclusion: p16 and EGFR can be used effectively as prognostic indicators

HPV and Radiosensitivity in Tonsillar Ca.

- Theorized that HPV +ve tumors may have better prognosis b/c they may be more radiosensitive
- Several small studies have shown better response to radiation by HPV +ve tumors → none have shown statistical significance
  - Mellin, 2002; Lindel et al., 2001
HPV & OPC: Genetic Markers

- **EGFR** (Epidermal Growth Factor Receptor) mutations associated with NSCLC in non-smokers
  - No link between EGFR mutations, HPV infection and OPC (Na et al., 2007)
- **Martinez et al., 2007**
  - 397 genes differentially expressed in HPV +ve and HPV –ve OPC tumors → upregulation of:
    - **CDKN2A** (Cell Cycle Regulation)
    - **SFRP4** (Cell Differentiation)
    - **RAD51AP1** (DNA Repair)

HPV Viral Load

**Kreimer et al., 2005**

- **Purpose:** To assess HPV-16 **viral load** and serologic markers in oral/OPC
- **Methods:**
  - Multinational case-control series
    - HPV-16 DNA (PCR)
    - HPV-16 Virus-Like Particles Abs (ELISA)
    - HPV E6 & E7 Abs (ELISA)
  - Compared to 852 controls (HPV –ve)
- **Results/Conclusions:**
  - Viral load was significantly higher among cases or OPC compared to oral cancer
  - Large tumor size was NOT associated with HPV- positivity or viral load
  - High HPV-16 viral load significantly increased the odds of HPV-16 E7 seropositivity by 57-fold.
HPV Viral Load

- Mellin et al., 2002
  - If > **190 copies** of HPV-16 in Tonsillar Ca.
    - longer survival rate than pts with <**60 copies** (p=0.039)
  - Problem: small sample size of 22 cases

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Sexual Transmission of HPV in oral and oropharyngeal cancer

D’Souza et al., 2007

- Methods:
  - Case-control study of 100 pts with new Dx of OPC
  - 200 control patients
  - Used multivariate logistical regression to compare

- Results:
  - High # of vaginal sex partners (>26) associated with OPC
    - Odds Ratio = 3.1
  - High # of oral sex partners (>6) associated with OPC
    - Odds Ratio = 3.4
  - OPC significantly associated with **HPV-16 infection**
    - Odds Ratio = 14.6
Sexual Transmission of HPV in oral and oropharyngeal cancer

D'Souza et al., 2007

• Results (Cont’d):
  – HPV-16 DNA detected in 72% of tumors
  – 64% of pts were were seropositive for E6, E7 or both
  – HPV-16 L1 seropositivity highly asso. with OPC among pts with history of tobacco and EtOH use (OR = 19.4) and those without (OR = 33.6)
  – Tobacco and EtOH use increased the association with OPC primarily among pts w/out HPV-16.

• Conclusion:
  – HPV infection is strongly associated with OPC in pts with or w/out tobacco or EtOH abuse

Sexual Transmission of HPV in oral and oropharyngeal cancer

• Hemminki et al., 2000
  – Husbands of cervical cancer patients developed an excess of both tonsillar cancer and tongue cancer (SIR 2.72)
Sexual Transmission of HPV in oral and oropharyngeal cancer

Smith et al., 2004

• **Purpose:** To determine if HPV +ve and HPV –ve oral/oropharyngeal cancers had different risk factors.

• **Results:**  
  – HR-HPV found in 20% (87% of these HPV-16)  
  – Risk Factors of High-Risk HPV:  
    • Younger age (<55yrs)  
    • Oral-Genital Sex (OR = 4.3)  
    • Oral-Anal Sex (OR = 19.5)

• **Conclusion:**  
  – HR-HPV has higher incidence in those whose sexual practices are associated with transmission of the virus.

Treatment

• Traditionally, OP CA treated with either surgery or XRT for early stage CA, or CRT / Surgery followed by CRT for advanced cancer.

• ? Exists whether or not we can de-escalate therapy given better prognosis for HPV + patients

• Trans Oral Robotic Surgery
Survival Benefits

- **Significantly Better Responses and Survival**
- 96 Patients: Eastern Cooperative Oncology Group (ECOG) 2399 phase 2 trial, and all of them were treated with 2 cycles of induction chemotherapy with intravenous paclitaxel and carboplatin, followed by concomitant weekly intravenous paclitaxel and standard fractionation radiation therapy.
- HPV status was determined by multiplex polymerase chain reaction (PCR) and in situ hybridization. Compared with the remainder of the patients, who were HPV negative, this HPV-positive subgroup showed significantly:
  - higher response rates to chemotherapy (85% vs 55% for HPV negative [a difference of 27%]; *P* = .01);
  - higher response rates to chemoradiation (84% vs 57% in HPV negative [a difference of 27%]; *P* = .007);
  - better overall survival (2-year overall survival, 95% vs 62% [a difference of 33%]; *P* = .005).
There are two vaccines – Cervarix and Gardasil -- commercially available that protect against infection with certain types of HPV. These vaccines prevent only new HPV infections but do not cure HPV infections you already have.

Immunization is recommended for 11 and 12 year-old girls, and the vaccine is approved for girls and women aged 13 – 26. Gardasil is also approved for boys and men aged 9 - 26 and was found to protect against most genital warts and anal cancer.

Vaccine
HPV Vaccines

- **Gardasil**
  - HPV Quadrivalent Recombinant Vaccine
  - HPV 6, 11, 16, 18
  - 3 injections over 6 months
  - Females age 9-26 yrs
  - Possibly pts who are HPV +ve
- CDC in the U.S. voted unanimously to recommend that girls age 11 and 12 yrs receive Gardasil

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HPV Vaccine

  1. Vaccine efficacy 98% in preventing high-grade cervical neoplasia related to HPV-16/18 (Future II Study Group)
  2. Gardasil significantly reduced HPV-associated HPV-anogenital diseases in young females (Garland et al., 2007)
- Recent RCT showed vaccine NOT effective in treating females with HPV-16/18 infection [JAMA. 2007 Aug 15;298(7):743-53]
Conclusions

1. HPV has a strong association with oropharyngeal SCC (particularly tonsil)
2. HPV has weaker associations with oral and laryngeal cancer
3. Pts with HPV +ve oropharynx tumors:
   1. Present at a relatively younger age
   2. Do not have excessive tobacco/EtOH use
   3. Appear to have better survival

4. HPV Vaccine shown to have high efficacy in preventing cervical cancer related to HPV-16 and 18.
5. Screening of patients (esp. tonsillar ca.) for HPV may improve treatment protocols and provide important prognostic information
6. Molecular typing for p16 and EGFR expression may provide important prognostic information
Future Endeavors

• Defining the role of HPV in Laryngeal and Oral Cancers
• Determining the effect of HPV Vaccination on the incidence of head and neck cancers in females
• Determining if vaccines will have a therapeutic effect on already-infected patients

Counseling Patients

• The primary risk factor for HPV infection is sexual activity. Virtually any person who has engaged in sexual activity is likely to have been exposed to HPV.
• HPV is very common. Most people who have been sexually active have had HPV.
• HPV is spread through close contact of genital skin, usually during vaginal or anal intercourse. HPV can be transmitted with non-penetrative sexual activity.
• HPV infection usually causes no symptoms, and most people never know they are infected.
• It may not be possible to know who gave you HPV or when you got it.
• Condom use reduces but does not completely prevent the spread of HPV.
• People who have same-sex partners can be infected by HPV.
• In most cases, the body clears HPV infection on its own.
Thank You
Questions???