Head and neck cancer and Fanconi anemia

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Factors promoting cancer development

Inherited Factors

Environmental Factors

Carcinogen Exposure

Host Defenses

Cancer Development
Genetics - An overview

DNA -> Protein -> Cell

[Diagram showing DNA, protein, and cell structures]
Head and neck cancer pathogenesis

Genomic instability

0 - >10,000 mutations

Normal mucosa → Benign hyperplasia → Dysplasia → Carcinoma in situ → Invasive Cancer
Factors predisposing to the accumulation of genetic events

• Carcinogen exposure
  – Tobacco
  – Alcohol
• Inherited factors
Familial HNSCC

• Susceptibility to carcinogens modified by many factors
  – First degree family members w/ 2-14 fold increase HNSCC risk—related to tobacco use
    • Non-smokers who get head and neck cancer
      – Issues of second hand smoke

• Activating carcinogens
  – Cytochrome p450 (CYP1- meta analysis)

• Clearing carcinogens (detoxifying enzymes)
  – GSTM1

• Repairing tobacco induced damage
  – XRCC1
Rising prevalence of HPV+ oropharyngeal cancer

Ernster et al, Laryngoscope 2007
Nasman et al, Int J Cancer 2009
Maxwell et al, ClinCancer Res 2010
Ang et al, NEJM 2010
Emerging role of HPV

• Meta analysis-- 26% of HNSCC with HPV
  – >40-50% of oropharyngeal cancers (exp. tonsillar cancers)
• Related to sexual history
• Predilection for non-smokers
• Basaloid histology

Gillison. JNCI 2000
Weinberg. JCO 2006
Kutler...Singh JNCI 2004
Natural course of HPV infection

1 year

<5 years

Up to decades

Initial HPV infection → Persistent infection → Pre-cancer → Invasive cancer

Cleared (immunologically)
Mechanism of HPV induced oncogenesis

- E7 rescues E6 from INK4A inhibition
- E6 prevents apoptosis caused by high expression of E7
- INK4A becomes functionally inactive
- Release of phosphorylated RB results in upregulation of INK4A

**E6 activities**
- Cooperative functions
  - Essential functions for immortalization
    - Prevention of p53 and BAK-mediated apoptosis
    - Blockade of IRF3 function
  - Activation of telomerase
  - Activation of SRC kinases
- Induction of chromosomal instability by inhibition of p53-mediated DNA repair

**E7 activities**
- Cooperative functions
  - Essential functions for immortalization
    - E2F release, bypass of cyclin-D-CDK4 regulation
  - Stimulation of S-phase genes cyclins A and E
  - Functional inactivation of WAF1+KIP1
  - Centriole amplification, induction of aneuploidy

**Synergistic effect in cell immortalization**
HPV

• More than 100 types
• 40 types infect mucosal tissues
  – High risk “oncogenic types”
    • 16, 18, 31, 33, 35, 45, 52,…
  – Low risk types
    • 6, 11, 42, 43, 44, …

HPV associated cancer distribution

- Cervix
- Anus
- Vagina/Vulva
- Penis
- Oral
- Tonsil

Annual number of cases worldwide

HPV-Induced
Total
Distribution of HPV types in HNSCC

Increased prevalence in oropharynx

Kreimer. Cancer Epidemiol Biomarkers Prev 2005
Different paths -- same cancer?

Tobacco

HPV
Survival in HPV-HNSCC

Gillison. JNCI 2000
## Clinical trials analysis

<table>
<thead>
<tr>
<th>Trial</th>
<th>HPV +</th>
<th>HPV -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tax 324</td>
<td>79%</td>
<td>31%</td>
</tr>
<tr>
<td>ECOG 2399</td>
<td>95%</td>
<td>62%</td>
</tr>
<tr>
<td>RTOG 0129</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>RTOG 9003</td>
<td>60%</td>
<td>29%</td>
</tr>
</tbody>
</table>
Different path to HNSCC in FA?

- Instability
- Genetic aberrations
- Progression
- Head and neck cancer

Fanconi anemia
Effect of genetic factors

Genomic instability

0  

Normal mucosa  Benign hyperplasia  Dysplasia  Carcinoma in situ  Invasive Cancer

>10,000 mutations

Effect of genetic factors

Genomic instability

0  

Normal mucosa  Benign hyperplasia  Dysplasia  Carcinoma in situ  Invasive Cancer

>10,000 mutations
## Genetic syndromes associated with HNSCC

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Other cancers</th>
<th>H &amp; N Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi</td>
<td>FANC family</td>
<td>Hematological</td>
<td>&gt;500 fold</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>DKC1, hTR/TERC or TERC</td>
<td>AML, leukoplakia</td>
<td>Significant increase</td>
</tr>
<tr>
<td>Bloom</td>
<td>BLM (RecQ like helicase)</td>
<td>Hematological, Wilms tumor</td>
<td>Significant increase</td>
</tr>
<tr>
<td>Rothmund-Thompson</td>
<td>RECQL4 (RecQ like helicase)</td>
<td>Skin cancer</td>
<td>Oral tongue</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>XP-A to XP-G</td>
<td>UV induced skin cancer</td>
<td>Rare</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
<td>Leukemia, lymphoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Li Fraumeni</td>
<td>p53</td>
<td>Lymphoma, sarcoma</td>
<td>Rare</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Rb</td>
<td>Rb, sarcomas</td>
<td>NC (32 fold)</td>
</tr>
<tr>
<td>N/A</td>
<td>p16</td>
<td>Melanoma</td>
<td>Rare</td>
</tr>
<tr>
<td>N/A</td>
<td>RNASEL</td>
<td>Prostate, cervix, breast</td>
<td>1.5 fold risk</td>
</tr>
</tbody>
</table>
## Supporting events in progression to HNSCC

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Association</th>
</tr>
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<tr>
<td>Fanconi</td>
<td>FANC family</td>
<td>HPV?</td>
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<tr>
<td>N/A</td>
<td>RNASEL</td>
<td>HPV?</td>
</tr>
<tr>
<td>Bloom</td>
<td>Helicase</td>
<td>??</td>
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<td>RNASEL</td>
<td>HPV</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB</td>
<td>Radiation</td>
</tr>
<tr>
<td>XP</td>
<td>XP Family</td>
<td>UV</td>
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</table>
HNSCC in FA: Increased frequency

- Shorter latency

Cumulative Incidence

Time to Squamous Cell Carcinoma (in years)

Cumulative Incidence

21% incidence by age 40

Standardized Incidence Ratio (SIR) = 500 (95% CI: 300-781, p<0.0001).

SEER population
Expected incidence: 0.038%

FA population
Cumulative incidence: 19%

21% incidence by age 40
HPV positivity: Supporting events

FA associated SCC vs. control SCC

FA-associated SCC

HPV -
HPV +

83% HPV Positive
N=25

Normal control SCC

HPV -
HPV +

36% HPV Positive
N=50

P<0.001
HPV Types in FA-associated HNSCC

FA-Associated

- HPV type 16
- HPV type 18
- HPV type 52

Normal control SCC

- HPV type 67
- HPV type 33
- HPV type 16
Is HPV a cause of HNSCC?

FA population
Cumulative incidence: 19%

SEER population
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HPV positivity
FA associated SCC vs. control SCC

FA-associated SCC

- HPV -
- HPV +

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N=25

Normal control SCC

- HPV -
- HPV +

36% HPV Positive
N=50

P<0.001
• Controversial
  – US vs. European data
• Factors in support
  – Ano-genital association
  – Anatomic distribution
  – Laboratory data
  – Human tumor analysis
  – “Hit and run” theory
TNM staging

Percent

Stage 1 | Stage 2 | Stage 3 | Stage 4
---|---|---|---
FA | Gen. Pop

Hoffmann et al. Arch Oto. 1998
Overall survival

2-year OS: 49% vs. 70%

Hoffmann et al. Arch Oto. 1998
Reasons for worse outcome

• Tumor biology
• Advanced stage at presentation
• Inadequate treatments
• Limitations in adjuvant treatment
  – 100% have adverse effects with Rtx
  – ~50% with severe toxicity
  – <50% can finish radiation
Treatment approach

- EARLY DETECTION
- Surgery is the preferred treatment
- Use radiation and chemotherapy with caution and in limited circumstances
- ? Need for modification of treatment (use non-DNA damaging chemotherapy modalities)
- Very close surveillance
How can we prevent head and neck cancer?
• Abstinence from tobacco and alcohol use
  – Avoidance of second hand smoke exposure
• Maintenance of oral hygiene
  – Avoid alcohol containing mouthwashes
• Aggressive monitoring and routine screening
Tobacco cessation and cancer risk

Alcohol cessation and cancer risk

Vaccine targeting

• HPV L1 capsid protein assembles into Viral like particles and provokes immune response

• Two types of vaccines available:
  – Quadravalent (Gardasil)—6/11/16/18
    • Reduction in CIN reported (Future II. NEJM 2007)
    • Reduction of anogenital disease (Garland. NEJM 2007)
  – Bivalent (Cervarix)-16/18
    • Reduction in CIN (Harper. Lancet 2006)

• Effects though to be optimal before HPV infection (prevention NOT therapy)
Routine screening

Start evaluation of head and neck at age 10 years
1. Head and neck exam by experienced professional
2. Flexible fiberoptic examination

Normal exam
Evaluate patient on a semi-annual basis

Lichen planus
Leukoplakia
Erythroplakia

Excisional biopsy
Increase surveillance timing to once every 2-3 months

Lesion suspicious for squamous cell carcinoma

Biopsy of lesion
Appropriate treatment, if positive
Close follow-up every 2-3 months
Who should do the screening?

• What should I do
• Type of health care professional
• What should be done
What should I do if I’m diagnosed with head and neck cancer?

• Treatment at major center with experienced treatment team
• Surgery is the main stay of treatment as much as possible
• Role of radiation and chemotherapy
Post-treatment surveillance after treatment for cancer

• Routine follow-up is mandatory (every 3 months or better)
  – Complete examination of upper aerodigestive tract mucosa
  – Chest X-ray annually
  – ? Use PET scan ?

• Screening to include gynecological exam in women
New Cancer Appearance after Treatment of H&N Primary

![Graph showing new cancer appearance over time](image)

- **Year**: 0, 1, 2, 3, 4, 5
- **%/Yr**: 0, 1, 2, 3, 4, 5, 10, 15

- **Local Recurr**
- **Neck Recurr**
- **Distant Mets**
- **2nd Primary**
Second primary malignancies: Screening/prevention

- 12 of 19 (63%) developed multiple malignancies during their lifetime.
- 5 patients had >2 malignancies

Surveillance recommendations for SCC in FA patients

• Routine head and neck screening
  – Role of qualified examiner
  – Age of onset (12-14 years)
  – Frequency- Biannual

• HPV vaccination
Vaccine targeting

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Effect of vaccination on HPV prevalence

Brisson M et al. Sex Transm Infect 2011;87:41-43
Effect of vaccination on HPV-diseases

Number of Cases

Cases Without Vaccination

After Vaccination With HPV 16/18

After Vaccination With HPV 6/11/16/18

Genital warts
CIN 1
CIN 2/3
Cervical Cancer

HPV 16, 18
-70%
-50%
-25%

HPV 6, 11
-10%
-90%
# Vaccine specific recommendations

<table>
<thead>
<tr>
<th></th>
<th>Quadrivalent HPV L1 VLP Vaccine (MSD)</th>
<th>Bivalent HPV L1 VLP Vaccine (GSK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV VLPs</td>
<td>HPV types 6, 11, 16, 18</td>
<td>HPV Types 16, 18</td>
</tr>
</tbody>
</table>
| Schedule | 0, 2, 6 months  
Flexibility up to 12 months | 0, 1, 6 Months |
| Indication | 9 - 26 years  
*(Boys 9 – 15 yrs (some countries)*  
In US: Prevention of cervical, vulval, and vaginal cancers caused by HPV types 16/18; genital warts caused by HPV types 6/11; and CIN 1, CIN 2/3, AIS, VIN 2 and 3, or VaIN2 and 3 caused by HPV types 6/11/16/18 | 10 – 25 years  
Prevention of premalignant cervical lesions and cervical cancer causally related to HPV types 16/18 |
Questions--Contact

singhb@mskcc.org
Tobacco use and cancer rates in California

California as a model. Bal. JCO. 2001
Changing management

1930-90’s  Surgery mainstay of Rx
2000-pres  Non-surgical Rx
Future  Changing epidemiology

Incidence of oropharyngeal cancer in white males under 60

Incidence of head and neck cancer

Relative cigarette consumption

Year

1900  1970  2000
Rising prevalence of HPV+ oropharyngeal cancer
HPV

- More than 100 types
- 40 types infect mucosal tissues
  - High risk “oncogenic types”
    - 16, 18, 31, 33, 35, 45, 52,…
  - Low risk types
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Mechanisms of HPV associated carcinogenesis
Natural course of HPV infection

1 year

<5 years

Up to decades

Initial HPV infection → Persistent infection → Pre-cancer → Invasive cancer

Cleared (immunologically)
HPV related diseases

Cervical cancer: 325 cases/80 deaths
High-grade precancerous lesions: 1600
Low-grade cervical lesions: 2400
Genital warts: 2400
HPV infection without detectable abnormalities: 30,000
Mechanism of HPV induced oncogenesis

- E7 rescues E6 from INK4A inhibition
- E6 prevents apoptosis caused by a high expression of E7
- Release of phosphorylated RB results in upregulation of INK4A

**E6 activities**
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**Proliferation**

**Progression**

**Synergistic effect in cell immortalization**

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  - Centriole amplification, induction of aneuploidy

**INK4A becomes functionally inactive**

**Cell death**

Nature Reviews | Cancer
HPV associated cancer distribution

![Graph showing the annual number of cases worldwide for different HPV associated cancers. Cervix has the highest number, followed by Oral and Oropharynx. Other locations have significantly fewer cases.]
Distribution of HPV types in HNSCC

Increased prevalence in oropharynx

Kreimer. Cancer Epidemiol Biomarkers Prev 2005
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Kutler…Singh. JNCI 2004

P<0.001
Implications of HPV on HNSCC
HPV related cancers

\(~32,000\) cases/yr

- Cervix (95%)
- Anal (90%)
- Oropharynx (60%+)
- Vulvar (50%)
- Penile (35%)

*Vaccine 2006;24(suppl 3):S11–S25.*
Projected cases of cervical cancer

Projected cases in Developed Regions. 2002-2050
Projected cases in Developing Regions. 2002-2050