Diversity of Oral Cancer

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Lecture Goals

- Understand the role of gender, race, age, and habits in oral cancer
- What is the etiology of oral cancer in non smokers?
- How is HPV implicated in oral and oropharyngeal cancer
- Role of HPV vaccine
University of Maryland OMS Oncology

► Total Patients 3,291

► Cancer Patients 2,032 (61.4%)

► Oral/Jaw Cancer 1,842 (89% of cancers)
Pathologic Variants

**Cancer Oral Cavity/Jaws**
- Epidermoid carcinoma  79.6%
- Salivary (intra-oral)  11.7%
- Sarcomas  2.8%
- Lymphomas  2.6%
- Metastatic  2.3%
- Others  1.0%
• Oral cancer is a disease of elderly men who abuse tobacco and alcohol and usually present with advanced disease
Demographic Changes

- Gender
- Habits
- Race
- Age
Gender
Sex Ratio for Oral Cancer

- Male : Female
- 1930 : 10 : 1
- 1950 : 6 : 1
- 2000 : 3 : 2
• “For almost every smoking/alcohol category the risks are higher for women then men.”

• “Among women increased risks were observed for all levels of smoking and alcohol intake.”

Gender differences in smoking and risk for Oral Cancer

- There is a significantly higher trend in the ORs for women than men for both the cumulative tar measure and pack year measure (adjusted for alcohol and other variables). >40 pack-years smoking increases risk of oral cancer 2-fold in men and 5-fold in women.

- Muscat et al 1996
• “Women may be more vulnerable than men to alcohol-induced carcinogenesis.”


• Drinkers > than 35 drinks/week compared
to nondrinkers showed OR of 2.4 in men and
OR 14.4 in women, CI 95%. These risk
estimates were not statistically heterogenous.
Alcohol and Tobacco consumption in cancer of the mouth, pharynx and larynx: A study of 316 female patients

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
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<th>Females</th>
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<td>n</td>
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<td>11</td>
<td>3.5</td>
</tr>
</tbody>
</table>

- Controlled for age, alcohol, tobacco

- Luce et al, Laryngoscope 1988
Habits
Patients without risk factors for oral cancer

Non-smokers
Non-drinkers
Non-Smokers

- Disproportionate number of women, oral cavity (especially tongue), and very young or old individuals (46 patients)

Non-Smokers

- The proportion of female patients amongst nonsmokers with HNSCC is significantly higher than among smokers.

  - Hodge et al. Cancer 1985
  - Wynder et al. Cancer 1957
Non-Smokers

► Male Smokers
  – Tongue Ca 57%
  – Floor of Mouth 74%

► Female Smokers
  – Tongue Ca 53%
  – Floor of Mouth 75%

► Prevalence of smoking was lowest for tongue and highest for floor of mouth.

* Muscat et al Cancer Res 1996
Non-Smokers

- Nonsmokers
  - 54% tongue
  - 3.7% Floor of mouth.

Koch et al Laryngoscope 1999

- Floor of mouth cancer
  - in smokers 37.8% and
  - in non smokers 6.6%.

Schmidt et al J Oral Maxillo Fac Surg 2004
Non-Smokers
What is the etiology?

- Cancer of the Oral Cavity and Pharynx in non-smokers who drink alcohol and in non-drinkers who smoke tobacco.

- In nonsmokers:
  - OR not > by 35 drinks or less/week,
  - OR 5.0 for 35-55 dpw and
  - 5.3 > 56 dpw.
  - Confirmed statistically significant risk of O/PSCC with heavy alcohol intake in never smokers.
Non-Smokers
What is the etiology?

• Is alcohol responsible for more intra-oral cancer?

  Hindle et al. Oral Oncology 36:2000

• Population based study (OPCS mortality data) Lung cancer and liver cirrhosis used as surrogate markers for smoking and drinking.
Non-Smokers
What is the etiology?

- The strongest associations were in males aged 35-64 years.

- **Negative** correlation lung/OSCC  -0.98  p0.01
- **Positive** correlation cirrhosis/OSCC  0.71  p0.01

- Suggests rising alcohol consumption since the 1950s more closely related to > incidence OSCC than smoking most notably amongst young males since the 1970s

  Hindle et al.  Oral Oncology  36:2000
Non-Smokers

What is the etiology?

- OR for OED in smokers 4.1 (adjusted for alcohol). Risk increased with > levels of smoking.
- Patients drinking >7 drinks/week OR 2.4 for OED (controlled for smoking).
- Both smoking and alcohol risk factors for OED

• Morse et al Cancer Epi Bio Prev 1996
Non-Smokers
What is the etiology?

– Many non-smokers are non-drinkers or drink little alcohol.

•

• 84% non-smokers also non-drinkers.

•

• 54% non-smokers also non-drinkers and 33% drank < 1 drink a day

•

Koch et al

Ord RA
Non-Smokers

What is the etiology?

- Review of 7 case-control studies regarding mouthwash use and oral cancer.

- “Neither the data for the overall association nor the analysis in patients without other clinical risk factors support a link between mouthwash use and oral cancer.”

  Elmore and Horwitz OtoHNS 113:1995
Non-Smokers
What is the etiology?

► Review of 10 Case Controlled Studies on Mouthwash use and Oral Cancer.

► No epidemiological evidence to support a link between oral cancer and mouthwash.

• La Vecchia C. Oral Oncology 2009
Non-Smokers
What is the etiology?

• Studies of young patients (under 40) who are non-smokers showed over expression of p53 despite a lack of mutations.
  Sorenson et al. 1997; Lingen et al. 2000

• Young non-smokers with SCCHN show increased sensitivity to chromosomal damage upon exposure to mutagens.
  Schantz et al. JAMA 262:1989
Non-Smokers
What is the etiology?

Tumors of nonsmokers harbor a lower frequency of common genetic changes than those of smokers. Fewer genetic alterations may be involved in malignant transformation in at least some of these tumors. Increased LOH at 6p in nonsmokers in this study did not reach statistical significance.

Koch et al. Laryngoscope 109:1999
Non-Smokers
What is the etiology?

• **Oral Cancer the evidence for sexual transmission.**

• Recent studies indicate HPV may be etiologically important in some OPC.

• Studies of OSCC have suggested possible sexual transmission of HPV.

  
  Scully C. Brit Dent J. 2005
Non-Smokers
What is the etiology?

• **HPV Prevalence (5,046 cases)**
  - OSCC 23.5% HPV16 68.2%
  - HPV18 34.1%
  - OPSCC 35.6% HPV16 86.7%
  - HPV18 2.8%
  - Larynx 24.0% HPV16 69.2%
  - HPV18 17.0%

• Kreimer et al Cancer Epidemiol Biomarkers Prev 2005
Age
Age in Oral Cancer

• Median Age for Oral Cancer     60-65 years

• Patients less than 40 Years     0-3%
Increase in Tongue Cancer in Young Adults

• Finland – 4% 1960’s
  7% 1980’s
  Atula et al Arch OtoHNS 122:1996

• USA – 4% 1971
  18% 1993
  Myers et al OtoHNS 122:2000
Review of NCI SEER Data 1973-1997

- 63,409 H+N Cancer Patient
- 3,339 less than 40 years.

- 1973-1984 compared to 1985-1997,
  - showed 60% increase in tongue cancer in patients under 40 years.

- Change affected birth cohorts between 1938-1948.

- Distinct disease process apparent in white not blacks.

- Schantz and Yu  Arch OtoHNS 128:2002
Oral Cancer in Young Patients

1. What is the Etiology?

2. How does this cancer behave?
Etiology of Oral Cancer in Young Patients

- Initial studies focused on the percentage of non-smokers, non-drinkers, or that the duration of exposure may be too short in this population to induce tumorigenesis.
Etiology of Oral Cancer in Young Patients

1. Conflicting evidence regarding tobacco/alcohol
2. Meager information regarding occupation, familial risk, immune deficits, and virus infection
3. Predisposition to genetic instability?

• Llewellyn et al. Oral Oncology 37:2001
Etiology of Oral Cancer in Young Patients

- “Most are exposed to traditional risk factors of tobacco smoking, alcohol, and low consumption of fruit and vegetables.”

- 109 patients 1981-1995 Scotland
- 38 returned questionnaires

Mackenzie et al Oral Oncology 36:2000
Etiology of Oral Cancer in Young Patients

137 cases. <46 years from 2 case controlled studies in Italy and Switzerland

- OR 20.77 >25 cigarettes/day,
- OR 4.9 >10 drinks/day,
- combination of tobacco+alcohol OR >48.
- High coffee OR 0.25,
- fresh vegetables OR 0.39,
- fruit OR 0.73,
- β-carotene OR 0.48

Rodriguez et al Oral Oncology 2004
Etiology of Oral Cancer in Young Patients

• Tobacco accounted for 77% of all cancer cases in this population, alcohol for 52%, low vegetable consumption for 52% and the combination of all three for 85%.

• Rodriguez et al Oral Oncology 2004
Etiology of Oral Cancer in Young Patients

- 6 cases aged 19-38 years H+N cancer in marijuana smokers.

  Donald, PJ. Otolaryngol Head Neck Surg 1986

- Marijuana smoking as a possible cause of tongue cancer in young patients.

  Almadori et al J Laryngology Otol 1990
Etiology of Oral Cancer in Young Patients

• Lifetime prevalence of marijuana use was 49.9% among full-time college students, and 54.5% among young adults 19-28 years in 1998.
Etiology of Oral Cancer in Young Patients

• OR for marijuana smokers for head and neck cancer was 2.6 (173 cases) case controlled

• “Further epidemiological studies are necessary to confirm the association of marijuana with head and neck cancers.”
• Mathematical models estimate 7-10 individual genetic alterations must occur for the development of cancer.

• This can involve activation of oncogenes and inactivation of tumor suppressor genes.
• Inactivation of p53 tumor suppressor gene common in SCCHN with approximately 50% of cancers having a mutant p53 protein.

Field  Eur J Cancer  28B:1992
• A strong correlation between mutation of p53 and chronic tobacco and alcohol use is documented.

• In non-smokers only 14-17% incidence of p53 mutations.

• Lingen et al. Curr Opin Oncol 13:2001
• Absence of p53 mutation in SCC of the tongue in non-smoking and non-drinking patients younger than 40 years
  
  Sorensen et al  Arch OtoHNS  123:1997

• Over expression of p53 in SCC of the tongue in young patients with no known risk factors is not associated with mutations in Exons 5-9.
  
  Lingen et al  Head and Neck  22:2000
Etiology of Oral Cancer in Young Patients

- LOH at 3, 9, and 17p chromosomes in young adults no different to those found in older patients.
  - Jin, Y-T Oral Oncology 35:1999

- No significant differences in the expression of p53, p21, Rb, and MDM2 proteins from tongue SCC in patients <35 years compared to patients >75 years.
  - Regezi, JA Oral Oncology 35:1999
Etiology of Oral Cancer in Young Patients

- Genetic Predisposition
  - Young adults with H+N Ca. > susceptibility to mutagen-induced chromosome damage.
    - Schantz et al JAMA 1989
  - Increased frequency of carcinogen-metabolising polymorphisms.
    - Cheng et al Int J Cancer 1999
  - Increased frequency of DNA repair gene polymorphisms.
    - Sturgis et al Carcinogenesis 1999
Etiology of Oral Cancer in Young Patients

Correlation of HPV and Oral Ca.

Gillison et al. Curr Opin Oncol 1999

5x higher expression HPV in OSCC than normal oral mucosa.


HPV 16 + 18 carcinogenic correlate with p53 mutation.

Etiology of Oral Cancer in Young Patients

► HPV integration into oral epithelium cell genome leads to cellular immortalization and enhances chemical carcinogenesis.

- Li et al Carcinogenesis 1992

- It is not proven that HPV infection increases over time in young patients and that this increase is a responsible factor for increase in tongue cancer in young patients.

- Schantz SP, and Yu G-P Arch Otolaryngol HNS 2002
Behavior of Oral Cancer in Young Patients

- **Increased mortality in young patients in:**
  - **Europe:** Levi et al, Eur J Cancer 1999
  - Franchesci et al, Eur J Cancer 1994
  - **USA:** Schantz and Yu, Arch Otolaryngol HNS 2002
  - **India:** Gupta, PC. J Indian Med Assoc 1999
Behavior of Oral Cancer in Young Patients

• 27 patients
  – <40 Yale-New Haven MC
  – 1958-80 with oral/oropharyngeal CA.

• 3 year survival rate was 17%.

• Loco-regional recurrence was 91%.

Son Y and Kapp D, Cancer 1985
Behavior of Oral Cancer in Young Patients

  - 64% Stage I and II
  - 57% Locoregional Failure
  - 47% Died of Disease
Behavior of Oral Cancer in Young Patients

• Oral Tongue Cancer in Young Adults Less Than 40 Years of Age: Rationale for Aggressive Therapy.

• Sarkaria JN, Harari PM. Head and Neck 16:1994
Behavior of Oral Cancer in Young Patients

- Squamous Cell Carcinoma of the Tongue in Young Patients: A Matched-Pair Analysis.

- 36 patients under 40 matched to older population. There was no significant difference in disease free survival, local, regional or distant recurrence.
- There was a significant increase in loco-regional recurrence in the younger patients which did not translate into a survival difference.
Behavior of Oral Cancer in Young Patients

• A Matched Control Study of Treatment Outcome in Young Patients with SCC of the Head and Neck.
  Verschuur et al Laryngoscope 109:1999

• 185 cases HNSCC
  – <40 compared to control group
  – >40 selected randomly.

• 5 year cause specific survival no difference.
• Younger cases significantly better overall survival.
Behavior of Oral Cancer in Young Patients

• Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes.

  Myers et al Otolaryngol HNS 2000

• T stage, N stage, perineural and lymphatic invasion were all associated with decreased survival. Patients who received a neck dissection as part of primary treatment had better chance of survival.
Behavior of Oral Cancer in Young Patients

• 5 year survival 1985-97 (SEER)
  – 70.6% <40yr
  – 49.8% 40-64 yr,
  – 45.8% >65yr.

• 1973-97: 5 year survival increased in all age groups.
  – Absolute increase largest in <40yr 11.7%, p=.009.
  – Increase of 20% in young patients with regional or distant disease,
  – only 3% in localized disease.

• Schantz and Yu Arch Otolaryngol HNS 2002
Human Papilloma Virus
Human Papilloma Viruses
risk stratification

• LOW RISK TYPES
  • Associated with benign proliferative growths
  • (HPV 1, 2, 6, 11)

• HIGH RISK TYPES
  • Infection with high risk types is associated with both pre-malignant and malignant lesions
  • (HPV 16, 18, 31, 33, 35, 39, 45)
Cervical Cancer and HPV

- HPV 16/18
  - 99.7% of cases of cervical cancer
- Increase risk 200X to develop cervical cancer
- 20,000,000 currently infected
Histologic Progression of Cervical Cancer

- **Squamous Intraepithelial Lesion (SIL)**
  - **Low Grade**
    - Condyloma
    - Cervical Intraepithelial Neoplasia (CIN)
      - Grade 1
      - Grade 2
      - Grade 3
  - **High Grade**
    - Normal
    - Very Mild-Mild Dysplasia
    - Moderate Dysplasia
    - Severe Dysplasia
    - In situ Carcinoma

- **Microinvasive Carcinoma**

*Fields Virology, 4th ed, Knipe & Howley, eds,*
Histologic Progression of Cervical Cancer

HPV Infection

- 10,000,000 - 20,000,000

Low-grade Dysplasia

- 1,000,000

High-grade Dysplasia

- 300,000

Cervical Cancer

- 12-14,000 - 4,000 deaths/year

HPV Infection

- 10,000,000-20,000,000
HPV Natural History

- Nearly ubiquitous
  - >90% sexually active adults have antibodies to L1 protein

- Transient
  - >90% of infections are cleared
  - No sequelae

- Dysplasia
  - May develop in low risk types/carriers
  - Persistent infection with high risk HPV
    - may lead to dysplasia [CIN 2,3] and cancer
HPV and Cervical Cancer

• CDC estimates of HPV infection
  – Lifetime risk ≥50% of sexually active females
  – 80% infected by age 50
  – 10% of population has active HPV infection

• WHO estimates of Cervical Cancer
  – 12,200 cases in 2003 in US
    • 4100 deaths in 2003 in US
  – 500,000 cases worldwide
    • 250,000 deaths each year worldwide
  – Second most common cancer in the world for women
Head and Neck Cancer

- 4% of all cancers
- 34,000 new cases each year in US
- 7,000 deaths each year
- 271,000 deaths annually worldwide
- Roughly 15-20% associated with HPV infection

Jemal, 2004; Mork, 2001
Cervical cancer data

Isolation of HPV from HNSCCa

HPV-HNSCCa case control studies

Syrjanen K, et al
“Morphological and immunohistochemical evidence suggesting human papillomavirus (HPV) involvement in oral squamous cell carcinogenesis

Park NH, Min BM, Li SL
“Immortalization of normal oral human keratinocytes with type 16 human papillomavirus”
Trends in Head and Neck Cancer

rise in oropharyngeal cancer

Carvalho A.  Int J Cancer 2005
HPV and HNSCCa

- **SEER Database**
  - Increased incidence of oropharynx cancer
    - 2.1% increase of base of tongue cancer
    - 3.9% increase of tonsil cancer
  - Different demographic
    - increased among white men and women
    - increased for ages 20-44
    - 2-3% per year increase in tonsil cancer among men younger than 60 1975-1998
  - More than doubled from 1975-2005
Head and Neck Cancer Trends

- US
  - BOT 1.27%/year
  - Tonsil 0.6%/year
Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer

- 1.3/100,000 $\rightarrow$ 3.6/100,000

Hammarstedt, Int J cancer, 2006
Estimates
HPV related Oropharyngeal Cancer

- World wide
  6000-33000/year
  US 800-4600/year
- HPV Oropharyngeal related cancers (%)
  North America 47%
  Asia 46%
  South/Central America 36%
  Europe 26%
What did the initial studies show?

- High risk type HPV (16) is a cause of oropharyngeal cancer
- HPV related HNSCCa is a distinct disease from traditional HNSCCa
## Risk Factors

### HPV and Head and Neck Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>HPV-16-positive case subjects, % (n = 92)</th>
<th>Control subjects, % (n = 184)</th>
<th>Adjusted OR (95% CI)</th>
<th>( P_{\text{trend}} )</th>
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<td>Total lifetime number of vaginal sex partners</td>
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<td>Total lifetime number of oral sex partners</td>
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<td>0</td>
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<td>1.0 (referent)</td>
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<td>History of casual sex</td>
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<tr>
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<td>40</td>
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<td>Yes</td>
<td>60</td>
<td>39</td>
<td>2.9 (1.5 to 5.6)</td>
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<td>Age at first sexual intercourse, y</td>
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<td>≥19</td>
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<td>&lt;19</td>
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<td>&lt;21</td>
<td>52</td>
<td>36</td>
<td>1.7 (0.90 to 3.1)</td>
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</table>
Risk Factors
HPV and Head and Neck Cancer

► Is Oropharyngeal cancer an STD?
  – Increased number of vaginal-sex partners
  – Increased number of oral-sex partners
  – Early age 1st intercourse
  – Anal sex
  – “One-night stands”
  – Rare condom use
  – History of STDs
Epidemiology of HPV+ HNSCCa

- Never smokers
- Mild alcohol use
- Intact dentition
- High oral sex exposure
- Age <45
Tonsillar Cancer
Outcomes
HPV+ versus HPV -

- Improved responses to induction chemotherapy
- Improved response to chemoradiotherapy
- Improved 2 year survival
- Improved performance status
- Lower risk of disease progression
Outcomes HPV+ versus HPV -

- Phase II ECOG trial
- Stage III/IV HPV +/-
- Induction chemo + concomitant chemo + standard regime XRT

Overall survival

Fakhry et al. Journal National Cancer Inst, 2008
Outcomes HPV+ versus HPV -

- HPV +
  - Improved DSS
  - ↑ p16 levels
  - ↑ HPV integration
  - ↓ tobacco/etoh use
  - ↓ Cellular differentiation
  - ↓ Regional metastasis
  - ↓ LR recurrence
Outcomes HPV+ versus HPV -

Links between cervical cancer and HNSCC

- Lifetime risk of second HNSCC in patients with cervical cancer SIR 1.7 (standardized incidence ratio) Rose et al Head Neck 2008

- Female patients with cervical CIS had SIR 1.68, and invasive cervical cancer SIR 2.45 and husbands also had an elevated SIR for HNSCC.

  Hemminiki et al Eur J cancer Prev 2000
HPV vaccine
Common Infection

Infected with HPV
Infection Is Sexually Transmitted
Virus Uncoats

Nucleus

Viral DNA enters nucleus

mRNAs for viral proteins E6 and E7

Epithelial cell interior

Virus "uncoats"
Virus Disables Suppressors

- E6 viral protein
- E7 viral protein
- Suppressor protein 1
- Suppressor protein 2
- Degraded suppressors

Mucus
Healthy cells
Cancerous epithelial cells
Virus-Like Particles
Antibodies Prevent Infection

Papillomavirus

\[ \gamma = \text{Antibodies} \]

No DNA strands can escape the capsid
Prophylactic HPV Vaccine

- FDA approved
  - Cervarix
    - HPV 16, 18, 31, 33, 45
  - Gardasil
    - HPV 16, 18, 31
    - HPV 6, 11 (venereal warts, papillomatosis)

Neither has been shown to prevent cancer
Incidence and persistence of infection ↓90%
Decrease CIN2/3 97.1%

Villa et al, Lancet Oncology, 2005
## Vaccine Recommendations

### Table 2. Current Guidelines and Recommendations for HPV Vaccine Use

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Centers for Disease Control Advisory Committee on Immunization Practices⁵³</td>
<td>Routine vaccination 11-12 years old; can start as young as 9 years old; catch-up vaccination at 13-26 years old</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists⁵⁴</td>
<td>Routine vaccination of females aged 9-26 years old</td>
</tr>
<tr>
<td>American Cancer Society⁵⁵</td>
<td>Routine vaccination of girls aged 11-12 years old; girls as young as 9 years old may get vaccinated; catch-up vaccination at 13-18 years old; inadequate information for vaccinating women 19-26 years old</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus.
Vaccine for men

• 2009 approved for the prevention of genital warts in men 9-26 years.
THANK YOU!