Head and Neck Cancer: Epidemiology

Professor Kevin Harrington
Joint Head of Division of Radiotherapy and Imaging
The Institute of Cancer Research/The Royal Marsden NIHR Biomedical Research Centre Radiotherapy Theme Lead Team Leader, Targeted Therapy Team
Head and Neck Cancer: Worldwide

- 640,000 cases/year
- 356,000 deaths per annum (55% mortality)
- 5% incidence of all cancers (excl. skin)
- 5% mortality of all cancers
The Royal Marsden

Head and Neck Cancer: UK

- 8600 cases/year
- 2900 deaths per annum (33% mortality)
- 4% incidence of all cancers (excl. skin)
- 2% mortality of all cancers

GLOBOCAN 2008
Head and Neck Cancer: Epidemiology

Geographical distribution - wide variations

- France (supraglottic, oral cancers)
- Hong Kong (nasopharyngeal cancers)
- India (oral cancers)
Head and Neck Cancer: Epidemiology

Data sources:
IARC, GLOBOCAN 2008. Age-specific data from GLOBOCAN 2008 were obtained from IARC, personal communication. For specific estimation methodology refer to http://globocan.iarc.fr/DataSource_and_methods.asp.
Head and Neck Cancer: Aetiology

- >75% overall risk related to tobacco and alcohol
- Betel quid (tobacco, betel leaf, slaked lime, areca nut)
- Mate (yerba mate, Ilex paraguarensis)
- Dental hygiene - questionable
- Occupational exposure - wood dusts (RR-2.4), organic chemicals (RR-1.9), coal products (RR-1.7-2.3), nickel, formaldehyde (RR-1.6), chromium
- Viruses - HPV (25-75%) , EBV (WHO III NPC), HIV (5%).
Head and Neck Cancer: Aetiology

International Head and Neck Cancer Epidemiology Consortium (INHANCE) dataset

- Diet: Fruit (RR 0.52), Vegetables (RR 0.66), Red meat (RR 1.4)
- Coffee: (RR 0.6 > 4 cups/day), Tea – no effect
- Exercise: low (RR 0.78), moderate (RR 0.67) and high (RR 0.53).
THE MORTALITY OF DOCTORS IN RELATION TO THEIR SMOKING HABITS
A PRELIMINARY REPORT

BY
RICHARD DOLL, M.D., M.R.C.P.
Member of the Statistical Research Unit of the Medical Research Council

AND
A. BRADFORD HILL, C.B.E., F.R.S.
Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council
Head and Neck Cancer: Aetiology

Tobacco
- 30 known carcinogens (polycyclic aromatic HCs, nitrosoamines)
- Tar content directly correlates with oral cancer risk
- Unfiltered > filtered cigarettes
- Inhalation > no inhalation
- RR laryngeal cancer = 15.5:1 men, 12.4:1 women
- After stopping smoking, RR reaches control at 15 yrs
- Passive smoking RR 1.6.
Head and Neck Cancer: Aetiology

Tobacco

- Black (air-cured) vs blond (flue-cured)
- Increased alkalinity of air-cured causes more irritation
- Black tobacco associated more with UADT lesions
- Blond tobacco associated more with LADT lesions
- Smokeless tobacco (paan, snuff).
Head and Neck Cancer: Aetiology

Smoking: Issues

• Increased co-morbidity
• Poor treatment tolerance
• Increased mortality

Hazard ratios for mortality from head and neck cancer

<table>
<thead>
<tr>
<th>Smoker</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never smoked</td>
<td>1.00*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.66 (1.32, 2.09)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>1.22 (0.94, 1.58)</td>
</tr>
</tbody>
</table>
Head and Neck Cancer: Aetiology

Alcohol

- Independent activity
- Glottic vs. supraglottic cancers more likely in non-drinkers
- Effect compounded by tobacco consumption
- Synergistic effect
  - ? local solvent
  - cytochrome P450 activation
- decrease activity of DNA repair enzymes.
Interaction between tobacco and smoking
Incidence of tonsillar cancer increased from 28 in 1997 to 703 in 2007

http://info.cancerresearchuk.org/cancerstats/types/oral/incidence/
Incidence of HPV positive oropharyngeal Cancer in Sweden

Age-adjusted Incidence by Calendar Year of Diagnosis for HPV induced cancers

- HPV-R tumours increasing
- HPV-U tumours decreasing

HPV and Head and Neck Cancer

- 40-60% of oropharyngeal cancers HPV+ve
- Sexually Transmitted through oral sex
- Prevalence in UK women with normal cytology 8.9%
- HPV has been detected in the genital tract of 72% of Men in UK
- Patients tend to be younger at diagnosis
- Usually non-smokers.
Risk Factors for HPV-Induced Cancers

- Lifetime partners >5 – OR = 3.0
- Coitarche < 19 yrs – OR = 2.4
- Oral sex before 21 yrs – OR = 2.3
- No condom with oral sex – OR = 3.7
- Infreq condom use – OR = 2.4
- HPV16 L1 sero+ve – OR = 32
- Oral HPV16 – OR = 15
HPV Genome

- Small double-stranded DNA viruses
- Absolute species specificity
- Cutaneous or mucosal predilection
- Low- and high-risk types.
HPV Life Cycle

- Virus particles assembled
- Differentiated cells: E and L viral genes expressed
- Dividing cells: Only E genes expressed, very low levels of protein made
- Viral genomes at 1000's per cell
- Viral DNA amplification in non-dividing cells
- Virus and cell replicate together
- Virus infects a primitive basal keratinocyte at low (<10) copies/cell
- No viraemia, no cytolysis or death, long infectious cycle
Natural History of HPV Infection

- Oropharyngeal mucosa most prone
- Said to infect tonsillar crypt.
- Relatively immune silent
- Immune response against L1 protein
- Sero-positivity indicates previous infection.
Events Leading to Selection of Aggressive Clones

- Primary infection with high-risk genotype
- Viral DNA maintained as low copy-number episomes
- Episomal linearisation and integration
- Complete episomal loss and de-regulation of E6/E7
- Episomal clearance
- Genomic instability
- Cycles of replication and mutation
- CANCER
Molecular Effects of Integration (1)

Loss of E2-mediated repression of E6/E7

Unregulated E6/E7 expression

Linearisation site

De-repressed E6/E7 drive cell division, genomic instability and abrogation of apoptosis
Human Papillomavirus in Head and Neck Cancer: Its Role in Pathogenesis and Clinical Implications

Christine H. Chung¹,² and Maura L. Gillison³

[Diagram of molecular pathways related to human papillomavirus and head and neck cancer]
Molecular Classification Identifies a Subset of Human Papillomavirus—Associated Oropharyngeal Cancers With Favorable Prognosis


Delineation of Prognostic Groups

A

266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors

88 Had HPV-negative tumors

88 Had ≤10 pack-years

90 Had >10 pack-years

23 Had ≤10 pack-years

65 Had >10 pack-years

26 Had N0–N2a cancer

64 Had N2b–N3 cancer

15 Had T2–T3 tumors

8 Had T4 tumors

114 of 266 (42.9%) were at low risk

79 of 266 (29.7%) were at intermediate risk

73 of 266 (27.4%) were at high risk

B

Overall Survival (%)

Years since Randomization

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>114</td>
<td>111</td>
<td>106</td>
<td>102</td>
<td>95</td>
<td>46</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>79</td>
<td>70</td>
<td>64</td>
<td>54</td>
<td>44</td>
<td>24</td>
</tr>
<tr>
<td>High risk</td>
<td>73</td>
<td>52</td>
<td>43</td>
<td>33</td>
<td>28</td>
<td>8</td>
</tr>
</tbody>
</table>
Conclusion

- HNC curable in more than 50%
- Change in the disease paradigm.
- Epidemic of oropharyngeal cancers (HPV related)
- Focus on smoking and alcohol cessation should continue as these are relatively simple targets for primary prevention
- A three pronged strategy of smoking and alcohol cessation and vaccination against HPV will dramatically reduce the incidence of this cancer.