UV AND SKIN CANCER CAUSATION, 
AND SOME UNANSWERED QUESTIONS

ADELE GREEN
ICNIRP MEMBER
+ ICNIRP STANDING COMMITTEE I, EPIDEMIOLOGY

Queensland Institute of Medical Research, Australia
and
University of Manchester, UK
Basal-cell carcinomas (BCCs)

- The most common cancer
  (in white populations)

- Incidence in Australia
  \(~800/100,000\)

- Incidence in UK
  \(~60/100,000\)

- Occur: Head & Neck + Trunk
Squamous-cell carcinomas (SCCs)

- Second most common cancer  \textit{(in whites)}

- Incidence in Australia  \textasciitilde 330 / 100,000

- Incidence in UK  \textasciitilde 33 / 100,000

- Occur: Head \& neck + Arms + hands

Actinic keratoses (AKs)

- \textit{Prevalence} >40 years
  - 40-60\% Australia  10\% UK

- \textit{Natural history}: High turnover (\ldots rarely \rightarrow SCC)
Melanoma

- Third most common skin cancer

- Incidence in Australia
  ~50/ 100,000

- Incidence in UK
  ~10/ 100,000

- Occurs:  Head & Neck + Trunk
  +Limbs of women
Causes of skin cancer

• Sun exposure
• Artificial tanning devices
• Ultraviolet radiation (UVA+UVB+UVC)

All are Class 1 carcinogens (IARC 2009)
Latitude gradient for melanoma incidence

Incidence of melanoma cases/100,000 per year

UV and Skin Cancer Causation and Questions
Adele Green ICNIRP
UV and Skin Cancer Causation and Questions

Adele Green ICNIRP
<table>
<thead>
<tr>
<th></th>
<th>BCC</th>
<th>SCC</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Face</strong></td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Back</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>M/F</td>
<td>M</td>
<td>M/F</td>
</tr>
<tr>
<td><strong>Skin burns easily</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Many freckles</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Many naevi</strong></td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>BCC</td>
<td>SCC</td>
<td>Melanoma</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td></td>
<td>Face</td>
<td>Back</td>
<td></td>
</tr>
<tr>
<td><strong>Childhood sun exposure</strong></td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Recreational</strong></td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Ambient UV</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Many Sunburns</strong></td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Actinic Keratoses</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Long-term Sunscreen intervention in adults

- 40% reduction in **SCC incidence** with 5 yrs use, seen after 8 more yrs
  
  van der Pols et al, Cancer Epi Biomark Prev 2006

- 50% reduction of **melanoma incidence**, seen after 10 more years
  
  Green et al, J Clin Oncol 2011
Causes of skin cancer

• Sun exposure
• Artificial tanning devices
• Ultraviolet radiation (UVA+UVB+UVC)
Melanoma: ever use of indoor tanning facilities

19 studies+ summary estimate

IARC, Int J Cancer 2007

Updated (+extra cohort study USA) -> Pooled Relative Risk: 1.2 (1.1 - 1.4)

Hirst et al, Health Policy 2009
Melanoma associated with first use of indoor tanning facilities in youth  Estimates of 7 studies and summary estimate

IARC, Int J Cancer 2007
Indoor tanning and risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Number of studies</th>
<th>Summary relative risk (95% CI)</th>
<th>Heterogeneity P-value $\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use of indoor tanning equipment</td>
<td>3</td>
<td>2.25 (1.08–4.70)</td>
<td>0.10</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use of indoor tanning equipment</td>
<td>4</td>
<td>1.03 (0.56–1.90)</td>
<td>0.06</td>
</tr>
</tbody>
</table>
Causes of skin cancer

• Sun exposure
• Artificial tanning devices
• Ultraviolet radiation
  (UVA+UVB+UVC)
Ultraviolet Radiation: mechanisms of action

- Photoproduct formation
  - DNA photoproducts: direct and indirect formation

- UV-induced mutation profiles (genes targeted eg p53)

- UV-induced genomic instability

- UV-induced cell killing

- Immunologic effects (systemic, local)

  ▶ UVA+UVB+UVC
Some Unanswered Questions

Carcinogenesis of one body site: skin
Caused by one agent: UV radiation

three very different skin cancers

How / why? … When? …
<table>
<thead>
<tr>
<th></th>
<th>BCC</th>
<th>SCC</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Sex</td>
<td>M/F</td>
<td>M</td>
<td>M/F</td>
</tr>
<tr>
<td>Skin burns easily</td>
<td>++</td>
<td>+++</td>
<td>++++</td>
</tr>
<tr>
<td>Many freckles</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Many naevi</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>BCC</td>
<td>SCC</td>
<td>Melanoma</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----</td>
<td>-----</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Childhood sun exposure</strong></td>
<td>+</td>
<td>+</td>
<td>(+)</td>
</tr>
<tr>
<td><strong>Recreational</strong></td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Occupational</strong></td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Ambient UV</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Many Sunburns</strong></td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Actinic Keratoses</strong></td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

*UV and Skin Cancer Causation and Questions*
### Questions

<table>
<thead>
<tr>
<th></th>
<th>BCC</th>
<th>SCC *</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell of origin?</strong></td>
<td><em>Epithelial stem cell (hair / inter follicular)</em></td>
<td><em>Epithelial stem cell (interfollicular)</em></td>
<td><em>Melanocyte</em></td>
</tr>
<tr>
<td><strong>Early UV exposure?</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>UV Dose-response?</strong></td>
<td>Yes and no</td>
<td>Yes</td>
<td>Yes and no</td>
</tr>
<tr>
<td><strong>Precursor?</strong></td>
<td>No</td>
<td><em>Actinic keratoses</em>*</td>
<td><em>Melanocytic naevi</em> (moles)</td>
</tr>
<tr>
<td><strong>Genetic susceptibility?</strong></td>
<td><em>(MC1R) Patched ....</em></td>
<td><em>(MC1R) (XP) ....</em></td>
<td><em>(MC1R) CDKN2A ....</em></td>
</tr>
</tbody>
</table>

- BCC: Basal Cell Carcinoma
- SCC: Squamous Cell Carcinoma
- *: Includes SCC and other SCC-like lesions
- UV: Ultraviolet

#### Three faces of UV carcinogenesis:

1. **Cell of origin**: Differentiation and stem cell theory.
2. **Early UV exposure**: Developmental and early exposure.
3. **UV Dose-response**: Dose-dependent relationship.
4. **Precursor**: Pre-cancerous lesions.
5. **Genetic susceptibility**: Genetic predispositions.

---

*Elucidating the multifaceted mechanisms of UV carcinogenesis: Integrating stem cell biology, genetic susceptibility, and dose-response.*
Malignant transformation of AK to SCC

- Promoted by UV radiation
  AK and SCC reduced by sunscreen application
  Thomson et al, 1993; Darlington et al, 2003

- Systematic review of 15 studies:
  Estimated risk of AK progression to SCC =
  From 0.025% to 20% per year/per lesion
  Quaedvlieg et al. 2006

- Natural History of AKs??
AKs as SCC precursors?  
Frost et al., J Invest Dermatol 2000  
UV and Skin Cancer Causation and Questions  
Adele Green ICNIRP
Transformation of Actinic Keratoses to SCC: a contentious, under-studied issue

- AKs highly labile: more volatility with more frequent monitoring
- Misdiagnosis of AKs/BCC/SCC common
- Need mapping/tracking over time with biologic/tissue markers for range of AK lesions
- Holy Grail: Ability to predict which AK will transform to SCC
Summary

re Causation of BCC, SCC, melanoma

• Sun exposure
• Artificial tanning devices
• Ultraviolet radiation (UVA+UVB+UVC)

Target-Cells of Origin for UV?
Timing of causal UV?
Roles of precursors, genetic susceptibility?

.....awaiting answers!
Thank you!