



ICNIRP 7th International NIR Workshop
Edinburgh, United Kingdom, 9-11 May 2012



UV AND SKIN CANCER CAUSATION, AND SOME UNANSWERED QUESTIONS

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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 (*in whites*)
- Incidence in Australia ~330 / 100,000
- Incidence in UK ~33/ 100,000
- Occur: Head & neck+ Arms+hands



Actinic keratoses (AKs)

- *Prevalence >40years*
40-60% Australia 10% UK
- *Natural history*: High turnover (... rarely -> 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





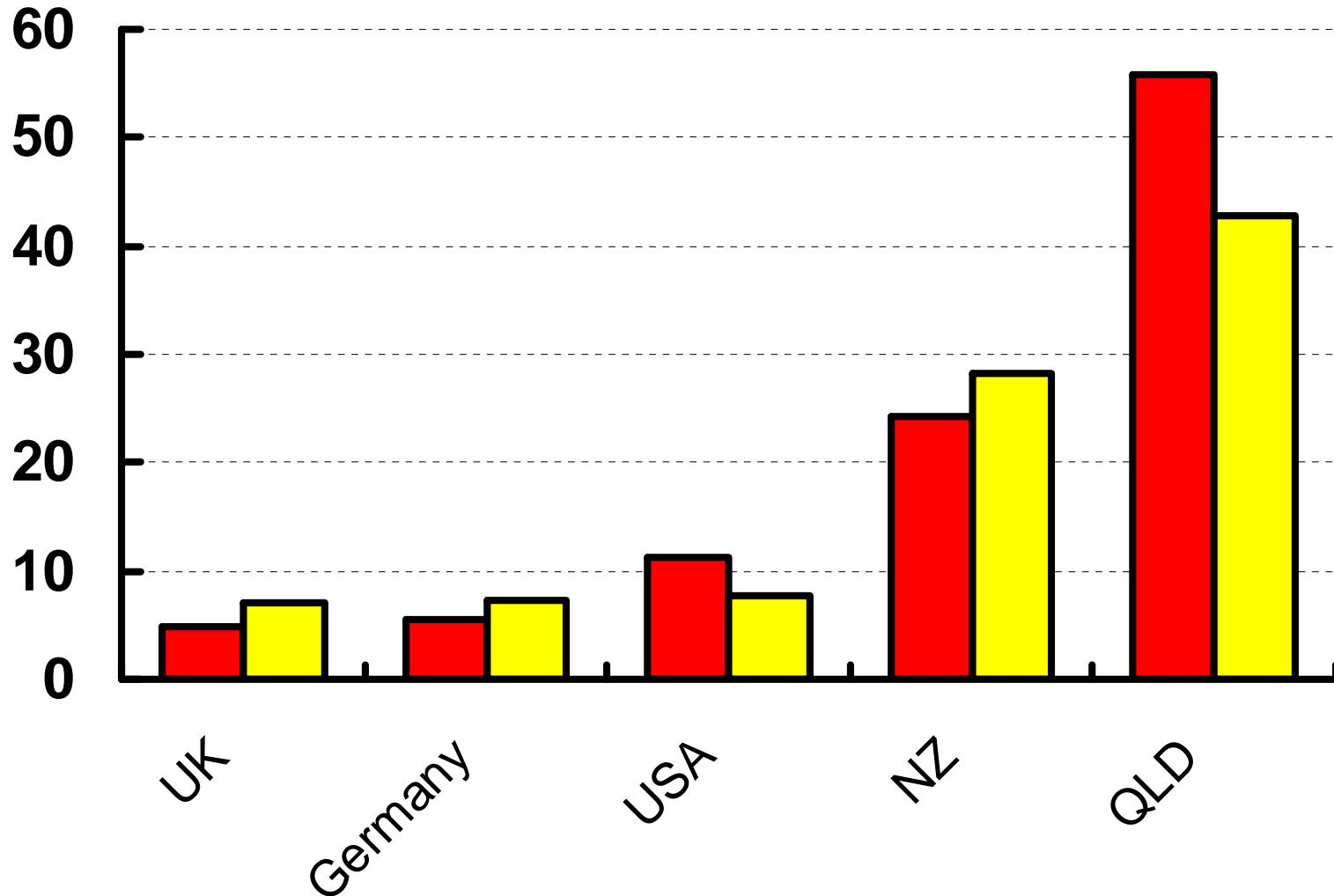
Causes of skin cancer

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

All are Class 1 carcinogens (IARC 2009)



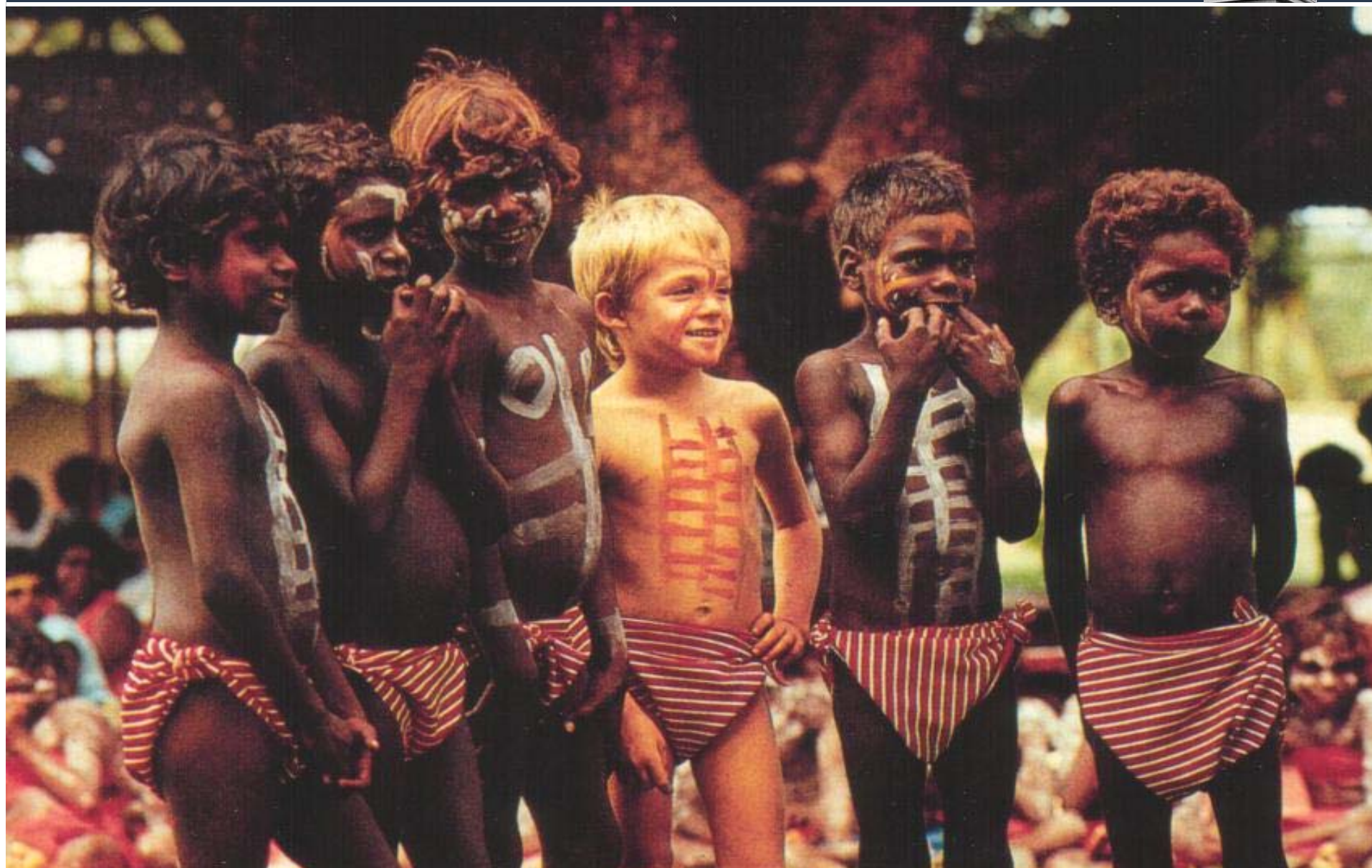
Latitude gradient for *melanoma* incidence





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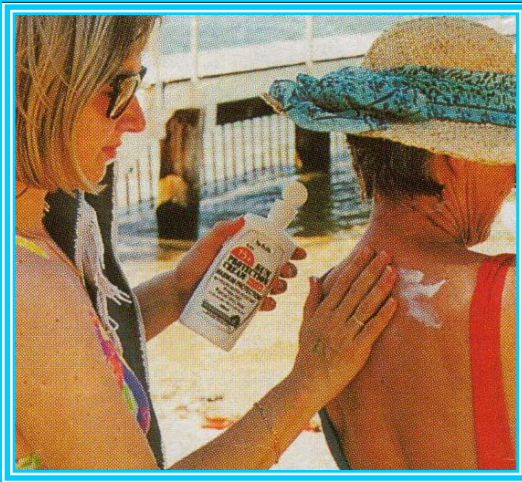




	BCC	SCC	Melanoma	
			Face	Back
Age	++	+++	+++	+
Sex	M/F	M	M/F	M/F
Skin burns easily	++	+++	+++	++
Many freckles	++	++	+	+++
Many naevi	+	-	+	+++



	BCC	SCC	Melanoma	
			Face	Back
Childhood sun exposure	+	+	(+)	(++)
Recreational	++	+	-	+
Occupational	+	++	+++	-
<i>Ambient UV</i>	++	++	++	++
<i>Many Sunburns</i>	+	++	++	++
<i>Actinic Keratoses</i>	++	+++	+++	+



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

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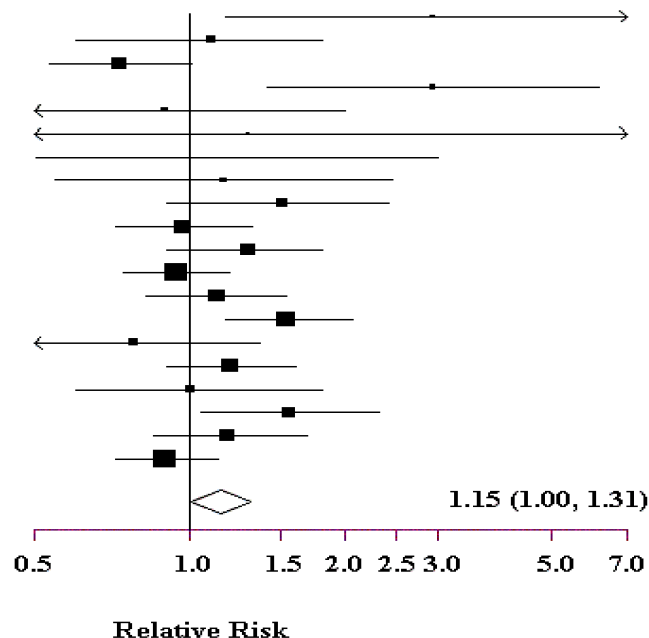
Melanoma : ever use of indoor tanning facilities

19 studies+ summary estimate

IARC, Int J Cancer 2007

Studies

- Adam et al., 1981
- Holman et al., 1986
- Osterlind et al., 1988
- Swerdlow et al., 1988
- Zanetti et al., 1988
- MacKie et al., 1989 (Men)
- MacKie et al., 1989 (Women)
- Dunn-Lane et al., 1993
- Garbe et al., 1993
- Autier et al., 1994
- Westerdahl et al., 1994
- Holly et al., 1995
- Chen et al., 1998
- Walter et al., 1999
- Naldi et al., 2000
- Westerdahl et al., 2000
- Kaskel et al., 2001
- Veierod et al., 2003
- Bataille et al., 2004
- Bataille et al., 2005



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

Hirst et al, Health Policy 2009

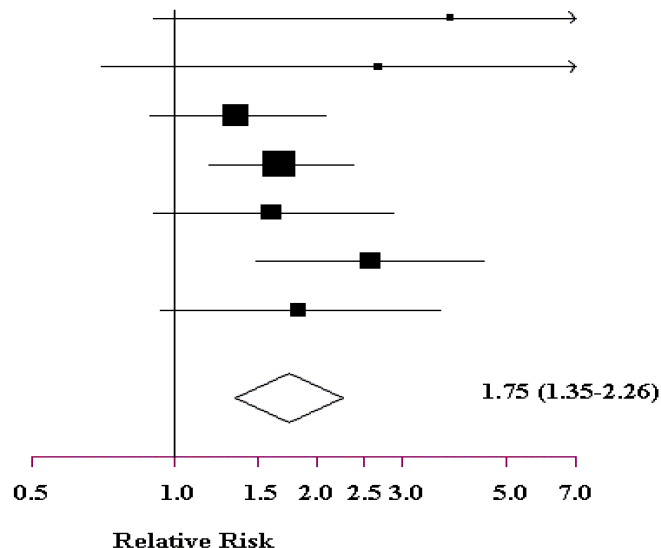


Melanoma associated with first use of indoor tanning facilities in youth

Estimates of 7 studies and summary estimate

Studies

Swerdlow et al, 1988
Westerdahl et al., 1994
Chen et al., 1998
Walter et al., 1999
Westerdahl et al., 2000
Veierod et al., 2003
Bataille et al., 2005



IARC, Int J Cancer 2007



Indoor tanning and risk of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC)

Exposure	Number of studies	Summary relative risk (95% CI)	Heterogeneity P-value χ^2
Squamous cell carcinoma			
Ever use of indoor tanning equipment	3	2.25 (1.08–4.70)	0.10
Basal cell carcinoma			
Ever use of indoor tanning equipment	4	1.03 (0.56–1.90)	0.06



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? ...



	BCC	SCC	Melanoma	
			Face	Back
Age of onset	++	+++	+++	+
Sex	M/F	M	M/F	M/F
Skin burns easily	++	+++	+++	++
Many freckles	++	++	+	+++
Many naevi	+	-	+	+++



	BCC	SCC	Melanoma Face	Melanoma Back
Childhood sun exposure	+	+	(+)	(++)
Recreational	++	+	-	+
Occupational	+	++	+++	-
<i>Ambient UV</i>	++	++	++	++
<i>Many Sunburns</i>	+	++	++	++
<i>Actinic Keratoses</i>	++	+++	+++	+



How / why *three* faces of UV carcinogenesis?

Questions	BCC	SCC *	Melanoma
Cell of origin?	<i>Epithelial stem cell</i> (hair /inter follicular)	<i>Epithelial stem cell</i> (interfollicular)	<i>Melanocyte</i>
Early UV exposure?	No	No	Yes
UV Dose-response?	<i>Yes and no</i>	Yes	<i>Yes and no</i>
Precursor?	No	<i>Actinic keratoses**</i>	<i>Melanocytic naevi</i> (moles)
Genetic susceptibility?	(MC1R) Patched	(MC1R) (XP)	(MC1R) CDKN2A



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

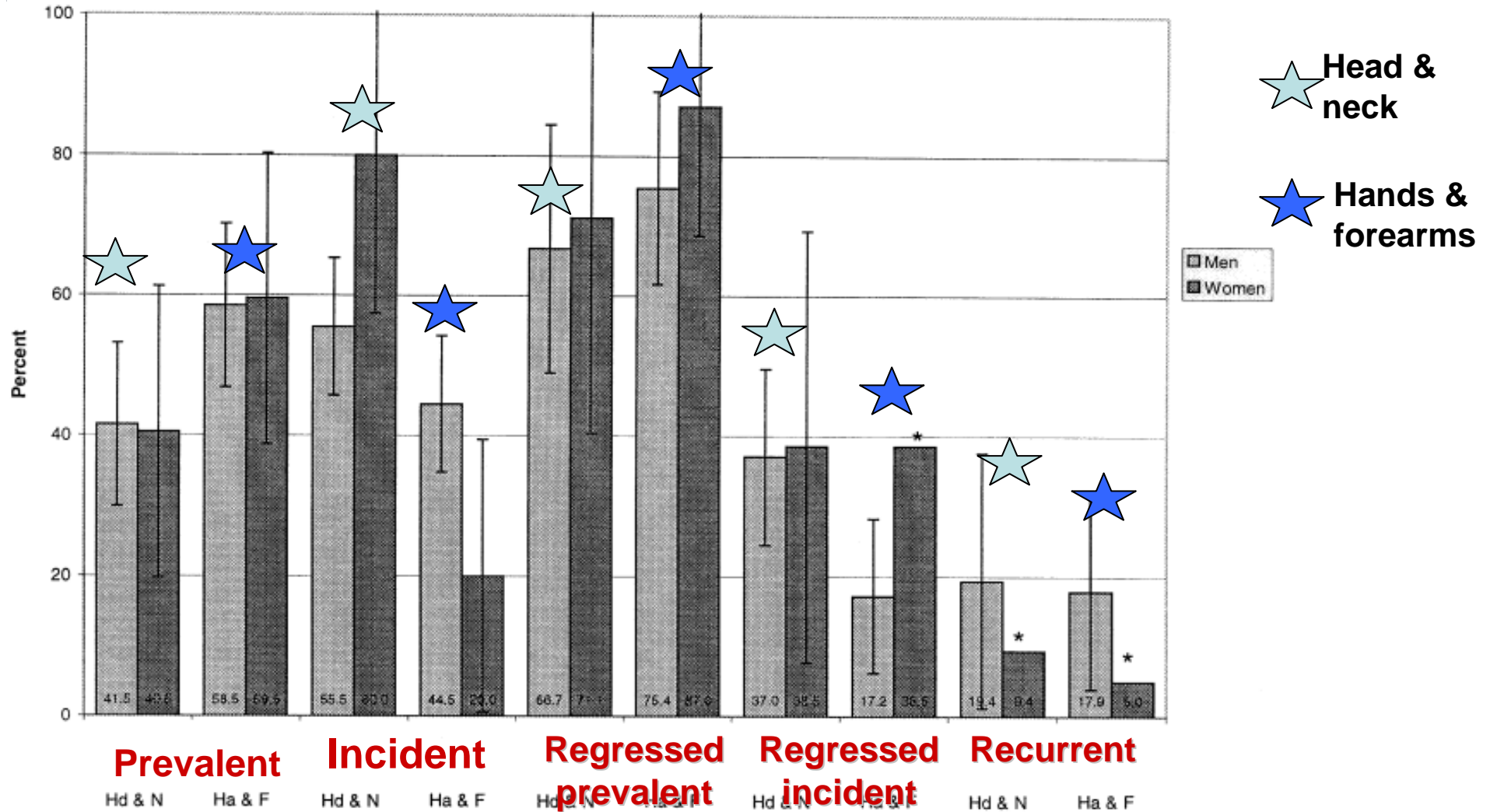
Quaedvlieg et al.2006

- **Natural History of AKs??**



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AKs as SCC precursors?

Frost *et al.*, J Invest Dermatol 2000



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!

