

SCENIHR

Public hearing on the Preliminary Opinion:

'Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes'.

Luxembourg, April 12th, 2016

Malignant Melanoma of The Skin -
Still A Medical Conundrum?

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Key Message

- Epidemiologic studies cited in the SCENIHR Opinion were not adjusted for some relevant host factors and confounding factors

Outline

- Estrogen as a confounding factor
- Other confounding factors
- Heterogeneity of melanoma as a host factor

CMM is influenced by estrogenic stimulation

Oral contraceptive preparations (OCP)

Hormone replacement therapies (HRT)

Estrogens, oral contraceptives and hormonal replacement therapy increase the incidence of cutaneous melanoma: a population-based case-control study

Koomen E. R., Joosse A., Herings R. M., Casparie M. K., Guchelaar H. J. and Nijsten T.
Ann Oncol 20(2):358-64 (2009)

RESULTS: In total, 778 cases and 4072 controls were included. CM risk was significantly associated with estrogen use (≥ 0.5 year; adjusted OR = 1.42, 95% CI 1.19-1.69). This effect was cumulative dose dependent (P trend < 0.001). CM risk was also significantly associated with the use of HRT (≥ 0.5 year: OR = 2.08; 95% CI 1.37-3.14) and OC (≥ 0.5 year: OR = 1.28; 95% CI 1.06-1.54).

CONCLUSION: Our study suggests a cumulative dose-dependent increased risk of CM with the use of estrogens

Estrogen Receptor β Agonists Differentially Affect the Growth of Human Melanoma Cell Lines

Marzagalli M., Casati L., Moretti R. M., Montagnani Marelli M. and Limonta P.
PLoS One 10(7):e0134396 (2015)

CONCLUSIONS: Our results demonstrate that ER β is expressed in melanoma cell lines and that ER β agonists differentially regulate the proliferation of these cells. These data confirm the notion that **melanoma is a heterogeneous tumor and that genetic profiling is mandatory** for the development of effective personalized therapeutic approaches for melanoma patients.

7.2.1.3 Cohort Studies

„Cohort studies are known to be less susceptible to biases than case-control studies and bring higher level of evidence.“

None of the cohort studies cited in the Opinion is adjusted for estrogen as a risk factor due to the study population:

- Veierod et al. 2003, 2010:
106,379 Norwegian and Swedish **women**
- Zhang et al. 2012:
Nurses Health Study II, 73,494 **female** nurses
- Nielsen et al. 2012:
40,000 Swedish **women**

Other Confounding Factors not Assessed

Role of melatonin

Endocrine disruption

Parabens in cosmetic products

Role of human papilloma virus (HPV)

Human Papilloma Virus Found in 50% of Melanoma Biopsies

REPORT

Dermato-Endocrinology 7:1, e1004018; January-December 2015; Published with license by Taylor & Francis Group, LLC

Exponentially increasing incidences of cutaneous malignant melanoma in Europe correlate with low personal annual UV doses and suggests 2 major risk factors

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Keywords: environment, HERV, HPV, latitude, melanoma, skin cancer, sunlight, ultraviolet, vitamin D₃

Abbreviations: CMM, Cutaneous Malignant Melanoma; HERV, Human endogenous retrovirus; HPV, Human Papilloma Virus; OR, odds ratio; IARC, International Agency for Research on Cancer; UVA, 316–400 nm; UVB, 290–315 nm; UV, Ultraviolet, 290–400 nm

Important Host Factors, not Assessed

Hormone receptor distribution / Gender

MC1R receptor variants

BRAF or N-RAS mutations

TP53 protein expression level

other oncogenes (e.g. CDK4, CCND1)

CMM: Various Histologic Growth Patterns

Four “histogenetic” types of melanoma: superficial spreading, lentigo maligna, nodular, and acral lentiginous melanoma.

Some MC1R Variants are Independent of UV Exposure

Melanocortin 1 receptor (*MC1R*) gene variants may increase the risk of melanoma in France independently of clinical risk factors and UV exposure

E Matichard, P Verpillat, R Meziani, B Gérard, V Descamps, E Legroux, M Burnouf, G Bertrand, F Bouscarat, A Archimbaud, C Picard, L Ollivaud, N Basset-Seguain, D Kerob, G Lanternier, C Lebbe, B Crickx, B Grandchamp, N Soufir

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J Med Genet 2004;**41**:e13 (<http://www.jmedgenet.com/cgi/content/full/41/2/e13>). doi: 10.1136/jmg.2003.011536

Melanocortin 1 receptor variants and skin cancer risk

Han J., Kraft P., Colditz G. A., Wong J. and Hunter D. J.
International Journal of Cancer 119(8):1976-84 (2006)

„These findings indicated that the effects of the MC1R variants on skin cancer risk were independent from self-reported phenotypic pigmentation.“

Study population: Nurses Health Study, **FEMALE**

BRAF Mutations

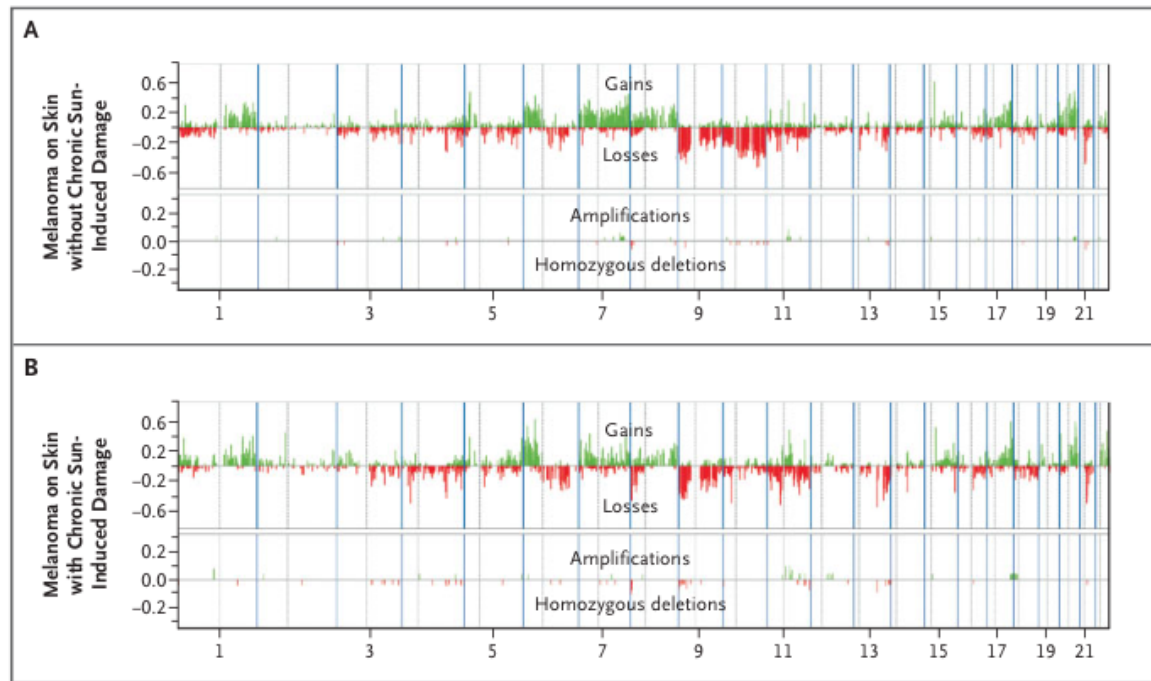
BRAF mutations are **common** only in melanomas arising in areas **intermittently exposed** to the sun

BRAF mutations are **rare** in melanomas on skin that is **chronically exposed** to the sun

Distinct Sets of Genetic Alterations in Melanoma

Curtin J. A., Fridlyand J., Kageshita T., Patel H. N., Busam K. J., Kutzner H., Cho K. -H., Aiba S., Bröcker E. -B., LeBoit P. E., Pinkel D. and Bastian B. C.

New England Journal of Medicine 353(20):2135-47 (2005)



The genetic alterations identified in melanomas at **different sites and with different levels of sun exposure** indicate that there are distinct genetic pathways in the development of melanoma and implicate CDK4 and CCND1 as independent oncogenes in melanomas without mutations in BRAF or N-RAS.

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„Understanding whether the **heterogeneity of melanoma** with respect to the site, degree of exposure to the sun, and histologic characteristics is caused by biologically distinct types of melanoma is of great clinical importance, because it is likely to **result in separate targeted therapeutic approaches and prevention strategies.**“

Open Questions

- Why do many melanomas appear in body sites without UV exposure?
- How can gender differences in body sites be explained?
- Why is low sun exposure a risk factor for melanoma?
- Which role plays the hormone receptor expression (e.g. estrogen) for the development of melanoma?
- Which roles play other confounding factors (e.g. for the development of melanoma)?
- How can uveal melanoma develop in a region with no UV?

Key Message, Part 2

- Epidemiologic studies cited in the SCENIHR Opinion were not adjusted for some relevant host factors and confounding factors
- Therefore, conclusions drawn from these studies might be incorrect or misleading
- More studies are needed acknowledging the recent findings

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