– SCENIHR –

Preliminary Opinion on

„Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes“

Critical Review

SCENIHR – Public hearing

Luxembourg, April 12, 2016

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The SCENIHR report:
an alarming tendency for an unbalanced view

- Main conclusions not supported by our present scientific knowledge
- Ignors body of evidence from epidemiological and animal studies demonstrating no increase in melanoma risk following chronic UV exposure
- Ignors body of evidence demonstrating beneficial health effects of UV radiation
- Ignors consequences of vitamin D deficiency

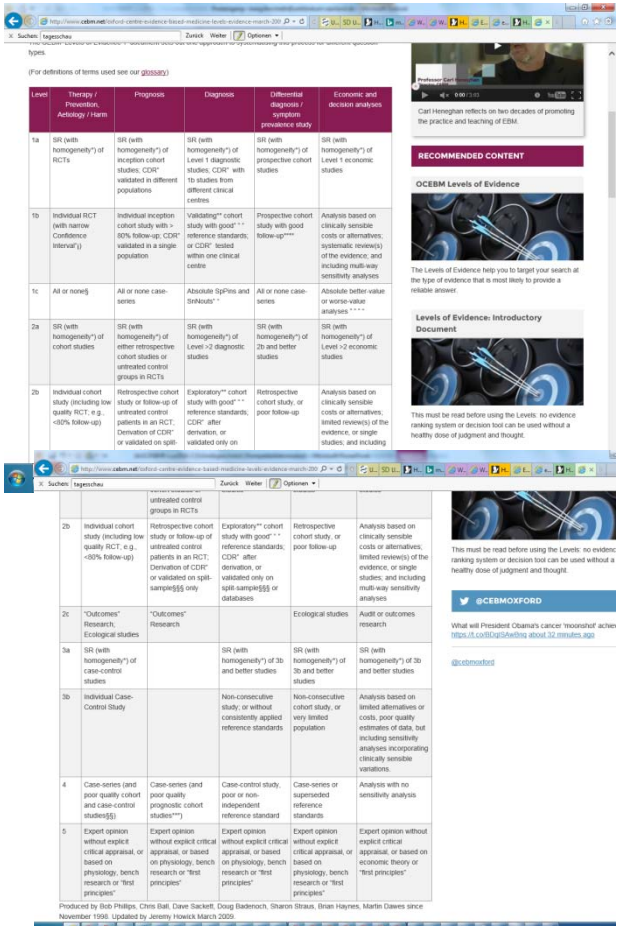
No scientific evidence that solarium use increases melanoma risk

- Present scientific knowledge based on observational studies with poor quality, which report associations but do not prove causality.
- 30 case-control (cc) and 2 cohort (co) studies; several meta-analyses, e.g. Boniol et al. 2012: summary relative risk of 1·20 (95% CI 1·08-1·34) for the association of ever exposure to UV radiation from sunbeds with melanoma risk (based on 27 studies).
- Overall study quality poor, due to lack of interventional studies and severe limitations of cc and co studies that include unobserved or unreported confounding.
- Subgroup analysis of studies performed in Europe does not show association of ever exposure to UV radiation from sunbeds with melanoma risk.

Study-limitations cause overestimation of the association of solarium use with melanoma risk

- Recall bias.
- Dermatologic phototherapy often included (e.g. PUVA – Landi et al.)
- Control selection bias (e.g. non-melanoma skin cancer excluded in controls but not in cases).
- Difficulties in adjusting for confounding factors, including solar UV and life style: only a minority of studies report ORs adjusted for the same confounding factors, 12 studies not for a single confounder. 20 studies adjusted for age (n=15), sex (n=11), and skin color (n=11), hair color (n=10), sun exposure (n=8), sunburns (n=8), family history of melanoma (n=7), naevi (n=7), freckles (n=5) and education (n=5). Individual confounders assessed differently, only partly comparable.

Association of solarium use with melanoma risk: resulting levels of evidence (3a-) and grades of recommendation (D) low due to lack of interventional studies and severe limitations including unobserved or unrecorded confounding



Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR* validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR* with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR* validated in a single population	Validating** cohort study with good* † reference standards; or CDR* tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts* †	All or none case-series	Absolute better-value or worse-value analyses * † ‡
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR* or validated on split-sample§§§ only	Exploratory** cohort study with good* † reference standards; CDR* after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§);	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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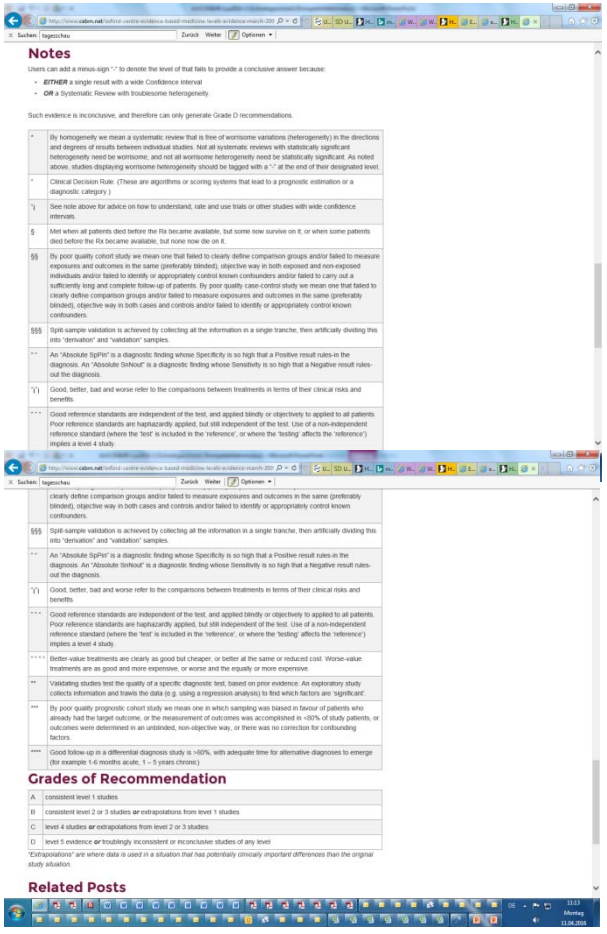

Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because:

- *EITHER* a single result with a wide Confidence Interval
- *OR* a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	level 4 studies *or* extrapolations from level 2 or 3 studies
D	level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation that has potentially clinically important differences than the original study situation.

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Conclusions:

Present scientific knowledge based on observational studies with poor quality, that report associations but do not prove causality.

At present no convincing evidence that moderate/responsible solarium use may increase melanoma risk !

SCENIHR - Ignors body of evidence from studies demonstrating no increase in melanoma risk following chronic UV exposure

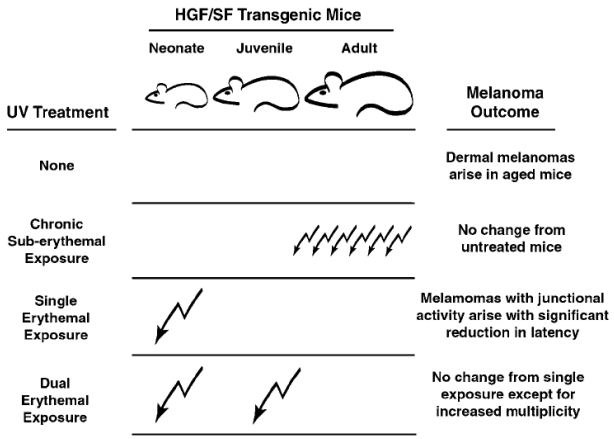

Figure 2 UV-inducible melanomagenesis in the HGF/SF transgenic mouse. Dermal melanomas arise in untreated HGF/SF transgenic mice with a mean onset age of approximately 21 months, a latency that was not overtly altered in response to chronic adult suberythemal, or nonskin reddening, UV irradiation (UV doses from an FS40 sunlamp graded from 2.3 to 6.0 kJ/m^2 three times weekly) (Noonan *et al*., 2000). In contrast, a single erythemal dose (9.6 kJ/m^2) from the same sunlamp to 3.5-day-old neonatal HGF/SF transgenic mice induced cutaneous melanoma with significantly reduced latency (Noonan *et al*., 2001). Moreover, the UV-induced murine melanomas frequently resembled their human counterpart with respect to histopathological appearance and graded progression. Exposure of HGF/SF transgenic neonates to a second erythemal dose of UV irradiation did not accelerate melanomagenesis; however, the dual exposure did significantly increase the number of melanocytic lesions arising per mouse (Noonan *et al*., 2001)

ORIGINAL ARTICLE

The Influence of Painful Sunburns and Lifetime Sun Exposure on the Risk of Actinic Keratoses, Seborrheic Warts, Melanocytic Nevi, Atypical Nevi, and Skin Cancer

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Painful sunburns are implicated in the pathogenesis of squamous cell carcinoma, basal cell carcinoma, and malignant melanoma. Chronic exposure to ultraviolet radiation is known as the most important risk factor for the development of actinic keratoses and squamous cell carcinoma. The purpose of the study was to assess the effect of painful sunburns and lifetime sun exposure on the development of actinic keratoses and seborrheic warts in relation to the development of squamous cell carcinoma and basal cell carcinoma, and on the development of melanocytic nevi and atypical nevi in relation to the development of malignant melanoma. We made use of a cohort of 966 individuals who participated in a case-control study to investigate environmental and genetic risk factors for skin cancer. Exposure measurements for sunlight were collected and actinic keratoses, seborrheic warts, melanocytic nevi, and atypical nevi were counted. Relative risks were estimated using exposure odds ratios from cross-tabulation. Multivariate logistic regression was used to adjust for potential confounders. The recall of painful sunburns before the age of 20 y was associated with an increased risk of squamous cell carcinoma, nodular basal cell carcinoma, and multifocal superficial basal cell carcinoma as well as actinic keratoses. Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type were 1.5 (0.97; 2.3); 1.6 (1.1; 2.2); 2.6 (1.7; 3.8); and 1.9 (1.4; 2.6) for the three types of nonmelanoma skin cancer and actinic keratoses, respectively. Painful sunburns before the age of 20 y were also associated with an increased risk of malignant melanoma and the development of its precursors, melanocytic nevi and atypical nevi. Odds ratios with 95% confidence intervals adjusted for age, sex, and skin type were 1.4 (0.86; 2.1); 1.5 (1.1; 2.0); and 1.4 (0.88; 2.3) for malignant melanoma and the two types of precursors, respectively. Lifetime sun exposure was predominantly associated with an increased risk of squamous cell carcinoma (p-value for trend = 0.03) and actinic keratoses (p-value for trend < 0.0001) and to a lesser degree with the two types of basal cell carcinoma. By contrast, lifetime sun exposure appeared to be associated with a lower risk of malignant melanoma, despite the fact that lifetime sun exposure did not diminish the number of melanocytic nevi or atypical nevi. Neither painful sunburns nor lifetime sun exposure were associated with an increased risk of seborrheic warts. *Key words: actinic keratoses/atypical nevi/melanocytic nevi/seborrheic warts/skin cancer/ultraviolet light. J Invest Dermatol 120:1087–1093, 2003*

SCENIHR - Ignors body of evidence demonstrating beneficial health effects of UV radiation

Original Article · Journal of INTERNAL MEDICINE

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Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort

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Abstract. Lindqvist PG, Epstein E, Nielsen K, Landin-Olsson M, Ingvar C, Olsson H (Karolinska University Hospital, Lund University, Lund, Sweden). Avoidance of sun exposure as a risk factor for major causes of death: a competing risk analysis of the Melanoma in Southern Sweden cohort. *J Intern Med* 2016; doi: 10.1111/joim.12496.

Objective. Women with active sunlight exposure habits experience a lower mortality rate than women who avoid sun exposure; however, they are at an increased risk of skin cancer. We aimed to explore the differences in main causes of death according to sun exposure.

Methods. We assessed the differences in sun exposure as a risk factor for all-cause mortality in a competing risk scenario for 29 518 Swedish women in a prospective 20-year follow-up of the Melanoma in Southern Sweden (MISS) cohort. Women were recruited from 1990 to 1992 (aged 25–64 years at the start of the study). We obtained detailed information at baseline on sun exposure habits and potential confounders. The data were analysed using modern survival statistics.

Results. Women with active sun exposure habits were mainly at a lower risk of cardiovascular disease (CVD) and noncancer/non-CVD death as compared to those who avoided sun exposure. As a result of their increased survival, the relative contribution of cancer death increased in these women. Nonsmokers who avoided sun exposure had a life expectancy similar to smokers in the highest sun exposure group, indicating that avoidance of sun exposure is a risk factor for death of a similar magnitude as smoking. Compared to the highest sun exposure group, life expectancy of avoiders of sun exposure was reduced by 0.6–2.1 years.

Conclusion. The longer life expectancy amongst women with active sun exposure habits was related to a decrease in CVD and noncancer/non-CVD mortality, causing the relative contribution of death due to cancer to increase.

Keywords: cigarette smoke, cohort study, CVD, melanoma, mortality, public health.

Introduction

There is ongoing debate about whether avoidance of sunlight or vitamin D deficiency is a major risk factor for health. The findings of two recent reviews on the impact of vitamin D were completely different, with one showing that no firm conclusions could be drawn [1] and the other demonstrating a population attributable risk of death in the same range as smoking, inactivity or obesity [2]. Studies regarding sun exposure are rare, but recently, we reported that the mortality rate was doubled in women in the Melanoma in Southern Sweden (MISS) cohort who avoided active sun exposure, compared to those with the highest sun exposure [3]. In addition, we found no differences in all-cause or cutaneous malignant melanoma (MM) mortality between those who expose themselves to and those who avoid the sun.

Most studies have analysed the relationship between the upper extreme of sun exposure and skin cancer and have showed an increased incidence. Therefore, it is difficult to investigate sun

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Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort

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Abstract. Lindqvist PG, Epstein E, Landin-Olsson M, Ingvar C, Nielsen K, Stenbeck M, Olsson H (Clintec, Karolinska University Hospital, Stockholm; Karolinska University Hospital, Stockholm; Lund University Hospital, Lund; Lund University Hospital, Lund; Lund University, Lund; Karolinska Institutet, Stockholm; Lund University Hospital, Lund). Avoidance of sun exposure is a risk factor for all-cause mortality: results from the MISS cohort. *J Intern Med* 2014; **276**: 77–86.

Background. Sunlight exposure and fair skin are major determinants of human vitamin D production, but they are also risk factors for cutaneous malignant melanoma (MM). There is epidemiological evidence that all-cause mortality is related to low vitamin D levels.

Methods. We assessed the avoidance of sun exposure as a risk factor for all-cause mortality for 29 518 Swedish women in a prospective 20-year follow-up of the Melanoma in Southern Sweden (MISS) cohort. Women were recruited from 1990 to 1992 and were aged 25 to 64 years at the start of the study. We obtained detailed information at baseline on their sun exposure habits and potential confounders. Multivariable flexible parametric survival analysis was applied to the data.

Results. There were 2545 deaths amongst the 29 518 women who responded to the initial questionnaire. We found that all-cause mortality was inversely related to sun exposure habits. The mortality rate amongst avoiders of sun exposure was approximately twofold higher compared with the highest sun exposure group, resulting in excess mortality with a population attributable risk of 3%.

Conclusion. The results of this study provide observational evidence that avoiding sun exposure is a risk factor for all-cause mortality. Following sun exposure advice that is very restrictive in countries with low solar intensity might in fact be harmful to women's health.

Keywords: evolution, longevity, melanoma, population attributable risk, UV radiation, vitamin D.

Introduction

Ultraviolet (UV) radiation from the sun is known to heighten the risk of developing malignant melanoma (MM) of the skin. This condition is primarily responsible for increased mortality due to UV radiation exposure. The risk of MM varies widely amongst people of different skin colour, depending on the type of melanin in their skin. MM is most common amongst Northern Europeans with pale skin and is rare amongst Africans with very dark skin [1]. Individuals with red hair or a tendency to develop freckles are at increased risk of developing MM. The highest risk has been found amongst those of European ancestry living in Northern Australia [1]. This has been the basis for considering UV radiation as the major cause of MM. Programmes for avoiding UV radiation are widely implemented in societies in which a large proportion of the population is descended from Europeans [2].

Nevertheless, exposure to sunlight remains the main source of vitamin D. Sunlight UVB radiation with a wavelength between 290 and 315 nm penetrates the skin and converts 7-dehydrocholesterol to 25-hydroxycholecalciferol vitamin D_3 via previtamin D [3]. Low vitamin D levels have been

SCENIHR - Ignors consequences of vitamin D deficiency

Overall conclusion

The SCENIHR report shows an alarming tendency for an unbalanced view and is scientifically highly questionable.

At present, there is no convincing evidence that moderate/responsible solarium use increases melanoma risk.