Dermato-Endocrinology

ISSN: (Print) 1938-1980 (Online) Journal homepage: http://www.tandfonline.com/loi/kder20

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To cite this article: William B. Grant (2009) Critique of the International Agency for Research on Cancer meta-analyses of the association of sunbed use with risk of cutaneous malignant melanoma, Dermato-Endocrinology, 1:6, 294-300, DOI: 10.4161/derm.1.6.11461

To link to this article: http://dx.doi.org/10.4161/derm.1.6.11461

Dermato-Endocrinology 1:6, 1-7; November/December 2009; © 2009 Landes Bioscience

Critique of the International Agency for Research on Cancer's meta-analyses of the association of sunbed use with risk of cutaneous malignant melanoma

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Key words: IARC, melanoma, meta-analysis, skin cancer, skin phenotype, sunbeds, ultraviolet-A, ultraviolet-B, vitamin D

The International Agency for Research on Cancer (IARC) reported meta-analyses of the association of cutaneous malignant melanoma (CMM), finding significant correlations with ever use of sunbeds and first use of sunbeds prior to age 35 years; it did not claim that the associations showed causal links. However, some observational studies in the meta-analysis included individuals in the UK with skin phenotype at increased genetic risk of CMM without adjustment for skin phenotype. Treating the five UK studies separately from the other 14 corrected this oversight. In the original study, the summary relative risk (RR) of CMM with respect to sunbed use was 1.15 (95% confidence interval [CI], 1.00–1.31). In this study, the similar RR was 1.20 (95% CI, 1.03–1.38). The RR for the five UK studies was 2.09 (95% CI, 1.14–3.84), whereas the RR for the other 14 studies was 1.09 (95% CI, 0.96–1.24). For first use of sunbeds prior to age 35 years, the IARC found a summary RR of 1.75 (95% CI, 1.35–2.36). This study plotted the RRs versus latitude of each study population, with a linear regression analysis carried out for all but the one UK study. The RR increased at 0.077 per degree of latitude and the regression explained 67% of the variance. It is also argued that factors other than sunbed use explain the increasing worldwide trends in CMM. Because solar-UV-simulating sunbeds induce production of vitamin D, the health benefits of their use greatly outweigh any possible risks.

Introduction

In 2007, the International Agency for Research on Cancer (IARC) reviewed the association of sunbed use with risk of melanoma through meta-analyses of observational studies.[1] There were two important findings: (1) ever use of sunbeds was positively associated with melanoma (summary relative risk [RR], 1.15; 95% confidence interval [CI], 1.00–1.31, although there was no consistent evidence of a dose-response relationship; and (2) first exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on seven informative studies (summary RR, 1.75; 95% CI, 1.35–2.26). These findings led to the World Health Organization classification of ultraviolet (UV)-emitting tanning devices emitting radiation between 100 and 400 nm as Group 1 human carcinogens,[2] joining solar radiation, tobacco and ethanol.

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Submitted: 01/22/10; Accepted: 02/10/10
Previously published online:
www.landesbioscience.com/journals/dermatoendocrinology/article/11461

The questions addressed in this review include whether the evidence presented in the IARC review supports a role of sunbed use as a risk factor for cutaneous malignant melanoma (CMM) for the general public and that first use of sunbeds prior to age 35 years is associated with increased risk of CMM. In health studies, the evidence considered strongest in making causal inferences is the randomized, controlled trial. Unfortunately, such studies do not exist for risk of CMM with respect to sunbed use because such studies would both be unethical to conduct and take too long to be useful. The next best approach is meta-analyses of observational studies, which the IARC used. However, in conducting such studies, it is important to ensure proper accounting of confounding factors. Related studies can also be used in the evaluation—here, studies of risk of CMM from solar UV irradiance.

This review will examine the data used in the meta-analyses, seeing whether the data used accurately reflect the data published in the studies reviewed by the IARC, the handling or not of confounding factors, and what is known about risk of CMM from solar UV irradiance. This analysis will also discuss factors that might be responsible for CMM trends, as well as the health benefits of vitamin D production from natural and artificial UVB irradiance.

Results

Table 1 presents the results of several meta-analyses of CMM with respect to sunbed use. Omitting any adjustments for confounders increases the RR of the original 19 studies by 0.05, to 1.20 (95% CI, 1.03–1.38). However, omitting two or five UK studies decreased the odds ratio (OR) by 0.07 or 0.11, respectively. The RR for the five UK studies was 2.09 (95% CI, 1.14–3.84). Thus, the UK studies were apparently responsible for the

Table 1. Results of meta-analyses' calculations performed using various studies

Conditions	Ref. 1	OR, starting with original set in ref. 1	OR, starting with original set in ref. 1 plus ref. 22
Original set (refs. 2–21)	1.15 (95% CI, 1.00–1.30)	1.20 (95% CI, 1.03–1.38)	1.21 (95% CI, 1.05–1.39)
Original set less 2 UK studies (refs. 5, 14)		1.13 (95% CI, 0.99–1.29)	1.14 (95% CI, 1.00–1.30)
Original set less 5 UK (refs. 3, 5–7, 21)		1.09 (95% CI, 0.96–1.24)	1.10 (95% CI, 0.98–1.25)
Five UK studies (refs. 3, 5–7, 21)		2.09 (95% CI, 1.14–3.84)	

Table 2. Melanoma incidence and mortality rates in the countries for which data were available for first use of sunbeds prior to age 35 years[28]

Country	Latitude (°N)	Males-I*	Males-M**	Females-I*	Females-M**	M Mo/I	F Mo/I
United States	39	17.2	2.6	12.1	1.3	0.15	0.11
Canada	46	9.1	2.1	8.2	1.2	0.23	0.15
France	48	6.6	1.6	11.2	1.3	0.24	0.12
Belgium	52	3.6	1.4	6.2	1.3	0.39	0.21
Netherlands	52.5	3.6	1.4	12.1	1.8	0.39	0.15
United Kingdom	53	7.5	2.0	9.3	1.5	0.27	0.16
Sweden	58	12.5	2.9	12.8	1.6	0.23	0.13
Norway	60	16.0	3.8	15.7	2.0	0.24	0.13

*cases/100,000/year; **deaths/100,000/year; F, female; I, incidence; M, male; Mo, mortality.

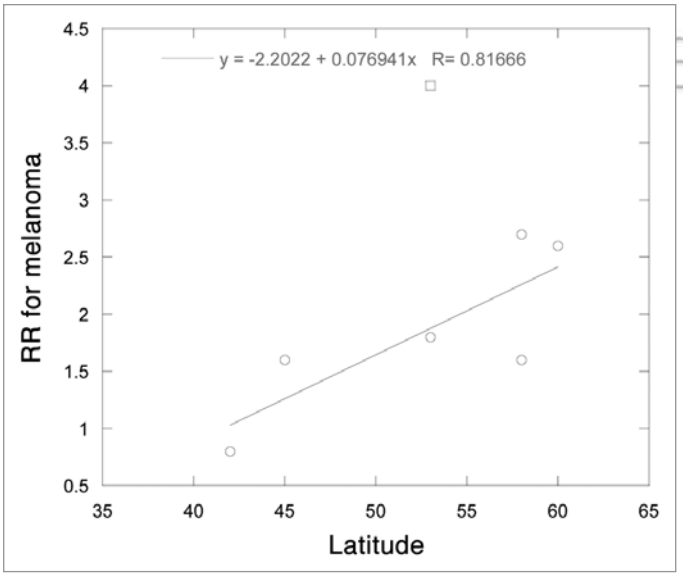

Figure 1. Plot of the relative risk for cutaneous melanoma versus mean latitude of those who first used sunbeds when younger than 35 years on the basis of data in Figure 2 of ref. 1. Data from the UK were not used in the regression analysis.

RR of CMM risk, with respect to sunbed use apparently being statistically significant. With them removed, the statistical significance disappears.

Incidence and mortality rates for CMM for the countries included in the seven studies addressing the association of CMM with respect to first use of sunbeds prior to age 35 years are given in **Table 2**. Incidence and mortality rates generally increase with latitude in the European countries. Incidence rates in the United States are comparable to the highest rates in the European countries but the mortality rates for females are near the lowest and those for males are near the highest.

For first use of sunbeds prior to age 35 years, this analysis used a graphical approach. The study with the highest RR, 4.0, was again from the UK.[5] Thus, the higher genetic risk of CMM there probably affected this value, and it was treated as an outlier. In the only study from the United States, from Connecticut,[16] the authors studied home and commercial sunlamp use occurring between 1987 and 1989. Because concern in the United States is with commercial units, not home units—which have different spectral outputs—only the finding for ever use of commercial sunlamps prior to age 35 is appropriate. The adjusted OR given for age at first use of commercial sunlamps prior to age 25 years was 0.63 (95% CI, 0.29–1.36) for 14 users. The adjusted OR for first use between the age of 25 and 45 years was 1.07 (95% CI, 0.53–2.17) for 18 users. Assuming that half of the 25- to 45-year-old users were younger than 35 years, then combining the two ORs, the value is 0.80 (95% CI, 0.47–1.13), i.e., a lower risk than that in the general population.

Figure 1 shows the relative risk of CMM vs. latitude of the study for the data from ref. 1 those younger than 35 years. For the six countries other than the UK, the linear fit to the data has a slope of 0.08 per degree of latitude and explains 67% of the variance. The UK study is clearly a several-sigma outlier.

Discussion

These results indicate no statistically significant relation between sunbed use and risk of CMM when studies largely influenced by inclusion of people with skin phenotype I, without adjustment for skin phenotype, are removed from the meta-analysis. The reported frequency of red hair in the UK in 1956 was between 5.3% and 7.7%.[29] Such people cannot tan and have an increased

risk factor for melanoma associated with a variant of the melanocortin receptor 1 gene.[30] This result is consistent with the recent large-scale European study that also made a similar finding.[31]

Several factors contribute to the interesting finding that the RR for melanoma associated with first use of sunbeds prior to age 35 years depends strongly on latitude. One is that darker pigmentation is protective against melanoma. This factor is important for two reasons. First, darker pigmentation reduces penetration of UV radiation to the lower epidermis, where melanin is located;[24] melanin repairs the damage from UV irradiance.[31] In Europe, skin pigmentation gradually becomes lighter at higher latitudes in the absence of UV irradiance or tanning. Second, UVB levels decrease at higher latitudes, so the ratio of UVA to UVB increases with increasing latitude.[32] Combined, these two factors diminish tanning to protect against UV at higher latitudes. Also, the sun shines longer in the summer at high latitudes than at lower latitudes. Those at higher latitudes frequently travel to the Mediterranean area, which has also been associated with increased risk of CMM.[33,34] Thus, risk of melanoma increases with latitude in European countries.[24,32] That the RR for sunbed use and incidence of CMM increases with increasing latitude is probably also attributable to lower solar UV irradiance for those who do not use sunbeds.

The mean center of U.S. population in 2000 was in Phelps County, Missouri (37.7° N). According to the latitudinal regression line in **Figure 1**, the RR of melanoma from first use of sunbeds in the United States prior to age 35 years would be about 0.75. As seen in **Table 2**, CMM incidence rates in the United States are comparable to the highest rates in Europe, which is likely due to the facts that those living in the United States have lightly-pigmented skin but much higher solar UV doses than in Europe. Thus, indoor tanning represents a smaller contribution to total UV irradiance than might be the case in European countries. CMM mortality rates for white people in the United States increase with decreasing latitude except near the U.S.-Mexico border,[35] reflecting that the similarity of skin pigmentation of white Americans across most parts of the country. The category "white American" includes persons of Hispanic heritage, which explains the effect near the border.

However, even if the meta-analyses' RR showed a significant risk, they were based on observational studies. The primary problem in observational studies is not accounting for confounding factors. Those who use sunbeds probably also often tan in solar UV radiation, and separating the effects of natural and artificial UV irradiance is difficult.

Risk-modifying factors for CMM. Table 3 lists the most important risk-modifying factors identified for CMM. Many have been identified only recently; thus, they would not have been included in the data acquisition and analysis of CMM associated with sunbed use. Separating the effect of solar UV irradiance and sunbed use for risk of CMM is also difficult.

Risk of CMM from solar UV irradiance. A much larger body of literature examines the risk of CMM from solar UV irradiance, and such research has yielded several important findings. One is that UVA is the more important spectral region of risk in the absence of sunburning. The evidence for this finding includes ecological studies of CMM rates with respect to latitude for those with northern European ancestry living in Europe, Canada, the United States, Australia and New Zealand.[26,27] The latitudinal dependence for CMM is weaker than that for squamous cell carcinoma and basal cell carcinoma. Solar UVA has a weaker latitudinal dependence than solar UVB. Integrated lifetime UVB irradiance is a strong risk factor for squamous cell carcinoma.[50] Additional evidence is that for those living poleward of 40°, sunscreen use is a risk factor for CMM.[44] Sunscreen generally sold in the United States did not until recently block much in the UVA spectral region. Equatorward of 40°, sunscreen use was associated with reduced risk of CMM, probably through protecting against severe sunburn, an important risk factor for CMM.[49]

Table 3. Risk-modifying factors for CMM

Risk	Risk reduction	Reference
Skin type I	Skin type III, IV	3
UVA		26, 27, 32
Travel to sunny locations		33, 34
	UVB	36
	Vitamin D	37
High-fat diet	Fruits, vegetables	37
VDR	VDR	38
Sunburning		3, 39
	Melanogenesis	40
Gene present among Scots		29, 41
	Chronic solar UV irradiance	39, 42, 43
Sunscreen use		44
Skin aging, elastosis		45
	Smoking	46–48
Nevi		49

VDR, vitamin D receptor.

Although solar UV irradiance is an important risk factor for CMM, occupational UV irradiance is generally not associated with increased risk of CMM; however, recreational UV irradiance is.[51] Humans have lived in harmony with the sun throughout our history, nature having devised ways to protect us from the adverse effects of sun exposure. One such adaptation is skin pigmentation, dark enough for protection against UV, light enough to permit sufficient UVB penetration to generate vitamin D for its many health benefits.[24] Tanning is also protective against CMM.[6,8] Tanning reportedly induced a sun protection factor of 2 after 2 weeks of daily suberythemal UV doses in skin types II and III.[52] Another study reported induced sun protection factor values of 3.[53] The benefits of the induced tan or melanogenesis include both protection against penetration of UVA and increased ability to repair DNA damage.[40] The stratum corneum also thickens with UV irradiance,[54] providing additional protection.

The other adaptation is skin aging, which evidently makes it more difficult for melanoma to develop.[48] This finding appears to explain why melanoma develops later in life on the face and hands rather than on rarely exposed body surfaces such as the trunk and legs.[55] To the extent that sunbed lamps mimic midday

solar UV (3%–5% UVB) at midlatitude, using sunbeds is similar to sunbathing. In the United States, about 90% of vitamin D results from solar UVB irradiance.[56]

Benefits of UVB irradiance. Although the authors of ref. 1 discussed the adverse roles of both UVB (280–315 nm) and UVA (315–400 nm) with respect to risk of CMM, they omitted any discussion of the beneficial roles of UVB in reducing the risk of CMM. A growing body of literature indicates that vitamin D reduces the risk of CMM. Recent work outlined the case for a beneficial role of vitamin D.[34] Dietary vitamin D correlated inversely with incidence of CMM.[37] Some recent evidence indicates a reduced risk of CMM with respect to vitamin D.[57]

Levels of 25(OH)D in the blood serum have decreased in the United States[58,59] and the UK,[60] and levels in Australia are lower than expected for such a sunny country.[61] The most likely explanation for these trends is people having heeded the messages from dermatologists for sun avoidance and sunscreen use.[62] However, spending more time indoors for other reasons cannot be ruled out. It is encouraging that the head of the American Cancer Society's Skin Cancer Advisory Committee recently acknowledged the need for vitamin D for optimal health.[63]

A recent study estimated the changes in U.S. mortality rates if everyone would increase serum 25(OH)D levels to near 45 ng/mL through doubling of solar UVB irradiance. Given all the benefits of vitamin D for cancer,[64,65] cardiovascular disease,[66] infectious diseases,[67,68] and many other diseases,[69] as well as preliminary serum 25(OH)D dose-disease outcome relations, I estimated a 15% mortality rate reduction, or 400,000 deaths/year, whereas an additional 11,000 deaths/year from CMM and other skin cancer might occur.[70] Two other recent studies also estimated the health benefits of increased serum 25(OH)D levels at the population level, one for western Europe,[71] the other for Canada.[72]

CMM trends. If the interest in regulating use of indoor tanning facilities is to try to stem the rising trends of melanoma worldwide, it is important to examine all factors that may be causing the trends. Some identified as such include increased travel to sunny locations,[33,34] use of sunscreen that blocks UVB but does not block UVA well,[44] and increased UVA irradiance due to increased window area in home and office buildings.[73] For example, U.S. nonmelanoma skin cancer mortality rates decreased between 1950–1954 and 1970–1974, whereas CMM rates increased during that time and have continued rising.[35] These opposite trends are consistent with both increased use of sunscreen and sun avoidance.

Sunbed use can confer health benefits. Vitamin D production in sunbeds with 1.5%–5% of the UV spectral output in the UVB region has been well documented.[74-76] Spending a few minutes in a sunbed can produce more than 10,000 IU of vitamin D. However, advocating sunbed use for vitamin D production would be premature without careful studies. Such studies should include time in sunbeds for maximum vitamin D production, which peaks after a few minutes because of photogradation at wavelengths out to 330 nm.[77] A study in Boston found higher bone mass density among sunbed users.[74] Two recent studies from Sweden found reduced risk of disease associated with use of sunbeds more than three times a year for endometrial cancer[78] and thrombotic events.[79]

Examining the policy issues related to sunbed use in light of the foregoing discussion is useful. European countries limit UVB to 1.5% of total UV radiation.[80] In the United States, lamps may have up to 5% UVB, which is similar to midlatitude, midday solar UV radiation. It is not clear whether the difference in fraction of UV as UVB explains any of the difference between European and United States RRs.

The health literature has many examples in which relying on observational studies led to flawed health policy decisions. Use of hormone replacement therapy (HRT) for postmenopausal women is a well-known example of confounding factors that colored findings based on observational studies. In 1991, a meta-analysis of 16 observational studies reported that 15 found a reduction in risk of coronary heart disease for use of HRT.[81] A quantitative overview of all studies taken together yielded an RR of 0.56 (95% CI, 0.50–0.61), and with only the internally controlled prospective and angiographic studies, the RR was 0.50 (95% CI, 0.43–0.56). By 2000, a prospective study found that coronary heart disease risk was lower, but risk of stroke was much higher, thereby canceling the beneficial effect for cardiovascular disease.[82] This finding was recently confirmed.[83] Eventually, Nelson et al.[84] determined that HRT has many adverse effects, and its use then declined dramatically.

On the other hand, most evidence for a beneficial role of UVB irradiance and vitamin D in reducing the risk of many types of cancer is based on ecological and observational studies.[64,65,85,86] It is interesting that the IARC reviewed the literature on vitamin D and cancer and concluded that strong support for a protective role exists only for colorectal cancer.[87] A critical review of the IARC report found that it embodied many errors and omissions that led to the conclusion that the evidence for several other types of cancer was not strong.[88]

The IARC meta-analyses show association but do not demonstrate causality. The criteria for causality in a biological system as laid down by Hill[89] include: strength of association, consistency in repeated observations, biological gradient, preferably linear dose-response, plausibility (supported by mechanisms), coherence (not in conflict with known facts of the natural history and biology of the disease), experiment (e.g., randomized controlled trial), and analogy with related studies. A recent review found that the evidence for a beneficial role of vitamin D in reducing the risk of cancer largely satisfied Hill's criteria for causality in a biological system for breast and colorectal cancer and reasonably well for ten other types of cancer.[90] As for causality for risk of CMM with respect to sunbed use, there are three major problems: one, that the findings are not consistent e.g., a major study in Europe found a reduced risk of CMM with respect to sunbed use [overall adjusted OR associated with ever sunbed use was 0.90 (95% CI: 0.71–1.14)];[21] two, confounding factors have not been carefully accounted for; and three, the UV dose-CMM risk does not have a linear dose-response relation as chronic UV irradiance such as through occupational exposure does not increase risk of CMM.[51]

Data and Methods

Ever use of sunbeds. To examine the role of skin phenotype in the meta-analysis of CMM related to ever use of sunbeds, I incorporated the studies used in ref. 1 (reviewed in refs. 3–21), along with an additional recent study,[22] into a new meta-analysis. This new analysis segregated the studies according to some information on skin phenotype and whether the data used in ref. 1 had been corrected for the known confounders. The two earliest UK studies[4,5] used data that were not adjusted for confounders.

Statistical analysis. Meta-analyses were performed using a random-effects model. RRs with 95% confidence intervals (CIs) were calculated to estimate pooled exposure effects. All statistical tests were two-sided, and $p < 0.05$ was the cutoff for statistical significance. Weights used represent individual estimates of exposure effect (weighted averages) weighted by assessment of precision of the estimates. Statistical analyses were performed using RevMan software.[23] This work used the unadjusted data because obtaining all the information required to use adjusted data was not practical. Eleven of the original studies did not adjust for confounders.

The data were used in the meta-analyses as follows: all 19 original studies; those plus ref. 22; the original 19 studies less the five UK studies (reviewed in refs. 3–7); those plus ref. 22; the original 19 studies less the two earliest UK studies; and those plus ref. 39. Thus, even though this analysis uses unadjusted data, comparison with the results in ref. 1 will be possible.

First use of sunbeds prior to age 35 years. This analysis first examined the data for the seven studies[5,11,14,16,17,20,21] used in ref. 1 for accuracy. Considerable difference existed in the RRs by country. Risk of CMM varies with respect to skin pigmentation and geographical location. Skin pigmentation decreases with latitude in Europe.[24] Risk of CMM increases with increasing latitude in Europe[25] but increases with decreasing latitude for those of northern European ancestry living around the world.[26,27] Data on CMM incidence and mortality rates for the countries included in the seven studies for 2002 were obtained from the IARC.[28] To see the effect of geographical location, this report plots the RRs versus the mean latitude of each population studied.

Summary and Conclusion

This meta-analysis of the association of CMM risk with respect to sunbed use by the IARC does not support the evidence that sunbed use is a risk factor for CMM when the confounding factors of skin phenotype and latitude are considered. The IARC study only claims association, not causality, and the criteria for causality do not appear to be satisfied. In addition, sunbed use produces vitamin D, which has many health benefits. Thus, prohibiting sunbed use other than to those with skin type I based on the IARC study[1] seems ill advised.

Acknowledgements

I receive funding from the UV Foundation (McLean, VA), the Sunlight Research Forum (Veldhoven), and Bio-Tech-Pharmacal (Fayetteville, AR), and have received funding from the Vitamin D Society (Canada).

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