Dermato-Endocrinology 1:6, 294-299; 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

William B. Grant

Sunlight, Nutrition and Health Research Center (SUNARC); San Francisco, CA USA

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.

Correspondence to: William B. Grant; Email: wbgrant@infionline.net
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

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.

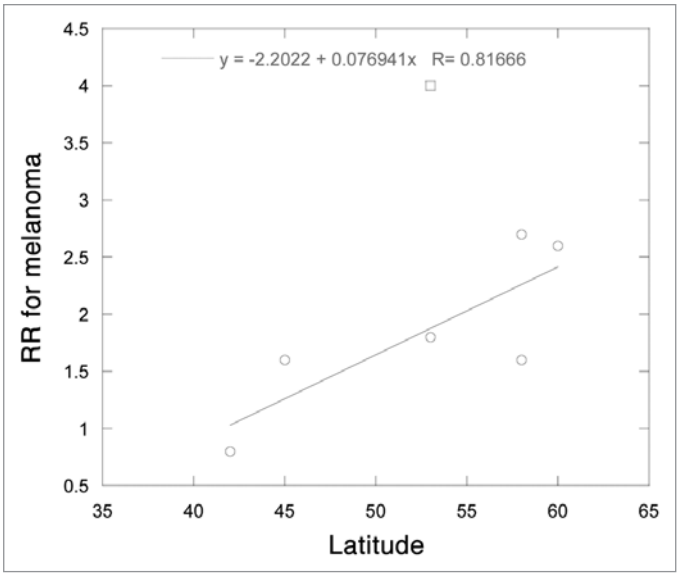

Figure 1. Plot of the relative risk for cutaneous melanoma versus mean latitude of those who first used sunbeds when younger than 35 years on the basis of data in Figure 2 of ref. 1. Data from the UK were not used in the regression analysis.

for the 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 US 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 US, from Connecticut,[16] the authors studied home and commercial sunlamp use occurring between 1987 and 1989. Because concern in the US is with commercial units, not home units—which have different spectral outputs—only the finding for every 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 US 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 US prior to age 35 years would be about 0.75. As seen in **Table 2**, CMM incidence rates in the US are comparable to the highest rates in Europe, which is likely due to the facts that those living in the US 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 US increase with decreasing latitude except near the US-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 US, 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 US 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 US, 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 US[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 US 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, US 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 US, 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 US RRs.

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).

References

1. International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer 2007; 120:1116-22.
2. El Ghissassi F, Baan R, Straif K, Grosse Y, Secretan B, Bouvard V, et al. WHO International Agency for Research on Cancer Monograph Working Group. A review of human carcinogens—part D: radiation. Lancet Oncol 2009; 10:751-2.
3. Bataille V, Winnett A, Sasieni P, Newton Bishop JA, Cuzick J. Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. Eur J Cancer 2004; 40:429-35.
4. Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP. A case-control study of the possible association between oral contraceptives and malignant melanoma. Br J Cancer 1981; 44:45-50.
5. Swerdlow AJ, English JS, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, et al. Fluorescent lights, ultraviolet lamps and risk of cutaneous melanoma. BMJ 1988; 297:647-50.
6. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet 1989; 2:487-90.
7. Dunn-Lane J, Herity B, Moriarty MJ, Conroy R. A case control study of malignant melanoma. Ir Med J 1993; 86:57-9.
8. Holman CD, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, et al. The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. Recent Results Cancer Res 1986; 102:18-37.
9. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma II. Importance of UV-light exposure. Int J Cancer 1988; 42:319-24.
10. Zanetti R, Rosso S, Faggiano F, Roffino R, Colonna S, Martina G. A case-control study of melanoma of the skin in the province of Torino, Italy. Rev Epidemiol Sante Publique 1988; 36:309-17.
11. Walter SD, King WD, Marrett LD. Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. Int J Epidemiol 1999; 28:418-27.
12. Garbe C, Weiss J, Kruger S, Buttner P, Bertz J, Hoffmeister H, et al. The German melanoma registry and environmental risk factors implied. Recent Results Cancer Res 1993; 128:69-89.
13. Autier P, Doré JF, Lejeune F, Koelmel KF, Geffeler O, Hille P, et al. Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. EORTC Melanoma Cooperative Group. Int J Cancer 1994; 58:809-13.
14. Westerdahl J, Olsson H, Måsbäck A, Ingvar C, Jonsson N, Brandt L, et al. Use of sunbeds or sunlamps and malignant melanoma in Southern Sweden. Am J Epidemiol 1994; 140:691-9.
15. Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. Am J Epidemiol 1995; 141:923-33.
16. Chen YT, Dubrow R, Zheng T, Barnhill RL, Fine J, Berwick M. Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut USA. Int J Epidemiol 1998; 27:758-65.
17. Westerdahl J, Ingvar C, Måsbäck A, Jonsson N, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 2000; 82:1593-9.
18. Naldi L, Gallus S, Imberti GL, Cainelli T, Negri E, La Vecchia C. Sunlamps and sunbeds and the risk of cutaneous melanoma. Italian Group for Epidemiological Research in Dermatology. Eur J Cancer Prev 2000; 9:133-4.
19. Kaskel P, Sander S, Kron M, Kind P, Peter RU, Krähn G. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. Br J Dermatol 2001; 145:602-9.
20. Veierød MB, Weiderpass E, Thörn M, Hansson J, Lund E, Armstrong B, et al. A prospective study of pigmentation, sun exposure and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003; 95:1530-8.
21. Bataille V, Boniol M, De Vries E, Severi G, Brandberg Y, Sasieni P, et al. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer 2005; 41:2141-9.
22. Han J, Colditz GA, Hunter DJ. Risk factors for skin cancers: a nested case-control study within the Nurses' Health Study. Int J Epidemiol 2006; 35:1514-21.
23. Review Manager (RevMan) [Computer program]. Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2003.
24. Jablonski NG, Chaplin G. The evolution of human skin coloration. J Hum Evol 2000; 39:57-106.
25. Boniol M, Doré JF, Autier P, Smans M, Boyle P. Ch. 10 in Ringborg U, Brandberg Y, Breitbart EW, Greinert R. Skin Cancer Prevention. Informa Healthcare. New York 2007; 203-23.
26. Moan J, Dahlback A, Setlow RB. Epidemiological support for an hypothesis for melanoma induction indicating a role for UVA radiation. Photochem Photobiol 1999; 70:243-7.
27. Moan J, Porojnicu AC, Dahlback A. Ultraviolet radiation and malignant melanoma. Adv Exp Med Biol 2008; 624:104-16.
28. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide IARC CancerBase No. 5. version 2.0, IARC*Press*, Lyon, 2004. http://www-dep.iarc.fr/ (accessed 2010).
29. Sunderland E. Hair-colour variation in the United Kingdom. Annls Hum Genet 1956; 20:312-30.
30. Scherer D, Nagore E, Bermejo JL, Figl A, Botella-Estrada R, Thirumaran RK, et al. Melanocortin receptor 1 variants and melanoma risk: a study of 2 European populations. Int J Cancer 2009; 125:1868-75.
31. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. Adv Exp Med Biol 2008; 624:162-78.
32. Garland CF, Garland FC, Gorham ED. Epidemiologic evidence for different roles of ultraviolet A and B radiation in melanoma mortality rates. Ann Epidemiol 2003; 13:395-404.
33. Bentham G, Aase A. Incidence of malignant melanoma of the skin in Norway, 1955–1989: associations with solar ultraviolet radiation, income and holidays abroad. Int J Epidemiol 1996; 25:1132-8.
34. Agredano YZ, Chan JL, Kimball RC, Kimball AB. Accessibility to air travel correlates strongly with increasing melanoma incidence. Melanoma Res 2006; 16:77-81.
35. Devesa SS, Grauman DJ, Blot WJ, Pennello GA, Hoover RN, Fraumeni JF Jr. Atlas of Cancer Mortality in the United States, 1950–1994. NIH Publication No. 99-4564: National Institute of Health; 1999. http://www3.cancer.gov/atlasplus/ (accessed 2009).
36. Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? Br J Dermatol 2002; 147:197-213.
37. Millen AE, Tucker MA, Hartge P, Halpern A, Elder DE, Guerry D, 4th, et al. Diet and melanoma in a case-control study. Cancer Epidemiol Biomarkers Prev 2004; 13:1042-51.
38. Gandini S, Raimondi S, Gnagnarella P, Doré JF, Maisonneuve P, Testori A. Vitamin D and skin cancer: A meta-analysis. Eur J Cancer 2009; 45:634-41.
39. Kennedy C, Bajdik CD, Willemze R, De Gruijl FR, Bouwes Bavinck JN, et al. The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi and skin cancer. J Invest Dermatol 2003; 120:1087-93.
40. Agar N, Young AR. Melanogenesis: a photoprotective response to DNA damage? Mutat Res 2005; 571:121-32.
41. Lang J, Hayward N, Goldgar D, Tsao H, Hogg D, Palmer J, et al. The M53I mutation in CDKN2A is a founder mutation that predominates in melanoma patients with Scottish ancestry. Genes Chromosomes Cancer 2007; 46:277-87.
42. Garland FC, White MR, Garland CF, Shaw E, Gorham ED. Occupational sunlight exposure and melanoma in the U.S. Navy. Arch Environ Health 1990; 45:261-7.
43. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 2005; 41:45-60.
44. Gorham ED, Mohr SB, Garland CF, Chaplin G, Garland FC. Do sunscreens increase risk of melanoma in populations residing at higher latitudes? Ann Epidemiol 2007; 17:956-63.
45. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005; 97:195-9.
46. Freedman DM, Sigurdson A, Doody MM, Rao RS, Linet MS. Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. Cancer Causes Control 2003; 14:847-57.
47. Odenbro A, Gillgren P, Bellocco R, Boffetta P, Håkansson N, Adami J. The risk for cutaneous malignant melanoma, melanoma in situ and intraocular malignant melanoma in relation to tobacco use and body mass index. Br J Dermatol 2007; 156:99-105.
48. Grant WB. Skin aging from ultraviolet irradiance and smoking reduces risk of melanoma: epidemiological evidence. Anticancer Res 2008; 28:4003-8.
49. Veierød MB, Adami HO, Lund E, Armstrong BK, Weiderpass E. Sun and solarium exposure and melanoma risk: effects of age, pigmentary characteristics, and nevi. Cancer Epidemiol Biomarkers Prev 2010; 19:111-20.
50. English DR, Armstrong BK, Kricker A, Fleming C. Sunlight and cancer. Cancer Causes Control 1997; 8:271-83.

51. Chang YM, Barrett JH, Bishop DT, Armstrong BK, Bataille V, Bergman W, et al. Sun exposure and melanoma risk at different latitudes: a pooled analysis of 5,700 cases and 7,216 controls. Int J Epidemiol 2009; 38:814-30.
52. Sheehan JM, Cragg N, Chadwick CA, Potten CS, Young AR. Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. J Invest Dermatol 2002; 118:825-9.
53. Hoffmann K, Kaspar K, von Kobyletzki G, Stücker M, Altmeyer P. UV transmission and UV protection factor (UPF) measured on split skin following exposure to UVB radiation—correlation with the minimal erythema dose (MED). Photodermatol Photoimmunol Photomed 1999; 15:133-9.
54. Wulf HC, Sandby-Møller J, Kobayasi T, Gniadecki R. Skin aging and natural photoprotection. Micron 2004; 35:185-91.
55. Dal H, Boldemann C, Lindelöf B. Does relative melanoma distribution by body site 1960–2004 reflect changes in intermittent exposure and intentional tanning in the Swedish population? Eur J Dermatol 2007; 17:428-34.
56. Grant WB, Garland CF, Holick MF. Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. Photochem Photobiol 2005; 81:1276-86.
57. Randerson-Moor JA, Taylor JC, Elliott F, Chang YM, Beswick S, Kukalizch K, et al. Vitamin D receptor gene polymorphisms, serum 25-hydroxyvitamin D levels, and melanoma: UK case-control comparisons and a meta-analysis of published VDR data. Eur J Cancer 2009; 45:3271-81.
58. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004. Am J Clin Nutr 2008; 88:1519-27.
59. Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. Arch Intern Med 2009; 169:626-32.
60. Glass D, Lens M, Swaminathan R, Spector TD, Bataille V. Pigmentation and vitamin D metabolism in Caucasians: low vitamin D serum levels in fair skin types in the UK. PLoS One 2009; 4:6477.
61. van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, Eyles DW, et al. The high prevalence of vitamin D insufficiency across Australian populations is only partly explained by season and latitude. Environ Health Perspect 2007; 115:1132-9.
62. Albert MR, Ostheimer KG. The evolution of current medical and popular attitudes toward ultraviolet light exposure: part 3. J Am Acad Dermatol 2003; 49:1096-106.
63. Weinstock MA, Moses AM. Skin cancer meets vitamin D: the way forward for dermatology and public health. J Am Acad Dermatol 2009; 61:720-4.
64. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, et al. The role of vitamin D in cancer prevention. Am J Public Health 2006; 96:252-61.
65. Garland CF, Gorham ED, Mohr SB, Garland FC. Vitamin D for Cancer Prevention: Global Perspective. Ann Epi 2009; 19:463-8.
66. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: Systematic review and meta-analysis. Maturitas, epub, doi:10.1016/j.maturitas.2009.12.013.
67. Bikle DD. Vitamin D and the immune system: role in protection against bacterial infection. Curr Opin Nephrol Hypertens 2008; 17:348-52.
68. Cannell JJ, Zasloff M, Garland CF, Scragg R, Giovannucci E. On the epidemiology of influenza. Virol J 2008; 5:29.
69. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266-81.
70. Grant WB. In defense of the sun: An estimate of changes in mortality rates in the United States if mean serum 25-hydroxyvitamin D levels were raised to 45 ng/mL by solar ultraviolet-B irradiance. Dermato-Endocrinology 2009; 1:207-14.
71. Grant WB, Cross HS, Garland CF, Gorham ED, Moan J, Peterlik M, et al. Estimated benefit of increased vitamin D status in reducing the economic burden of disease in western Europe. Prog Biophys Mol Biol 2009; 99:104-13.
72. Grant WB, Schwalfenberg GK, Genuis SJ, Whiting SJ. An estimate of the economic burden and premature deaths due to vitamin D deficiency in Canada, Molec Nutr Food Res. In press.
73. Godar DE, Landry RJ, Lucas AD. Increased UVA exposures and decreased cutaneous Vitamin D(3) levels may be responsible for the increasing incidence of melanoma. Med Hypotheses 2009; 72:434-43.
74. Tangpricha V, Turner A, Spina C, Decastro S, Chen TC, Holick MF. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am J Clin Nutr 2004; 80:1645-9.
75. Porojnicu AC, Bruland OS, Aksnes L, Grant WB, Moan J. Sun beds and cod liver oil as vitamin D sources. J Photochem Photobiol B 2008; 91:125-31.
76. Moan J, Lagunova Z, Cicarma E, Aksnes L, Dahlback A, Grant WB, et al. Sunbeds as vitamin D sources. Photochem Photobiol 2009; 85:1474-9.
77. Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab 1989; 68:882-7.
78. Epstein E, Lindqvist PG, Geppert B, Olsson H. A population-based cohort study on sun habits and endometrial cancer. Br J Cancer 2009; 101:537-40.
79. Lindqvist PG, Epstein E, Olsson H. Does an active sun exposure habit lower the risk of venous thrombotic events? A D-lightful hypothesis. J Thromb Haemost 2009; 7:605-10.
80. Autier P. Perspectives in melanoma prevention: the case of sunbeds. Eur J Cancer 2004; 40:2367-76.
81. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. Prev Med 1991; 20:47-63.
82. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A prospective, observational study of postmenopausal hormone therapy and primary prevention of cardiovascular disease. Ann Intern Med 2000; 133:933-41.
83. Lawlor DA, Smith GD. Cardiovascular risk and hormone replacement therapy. Curr Opin Obstet Gynecol 2006; 18:658-65.
84. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002; 288:872-81.
85. Mohr SB. A brief history of vitamin D and cancer prevention. Ann Epidemiol 2009; 19:79-83.
86. Grant WB, Mohr SB. Ecological studies of ultraviolet B, vitamin D and cancer since 2000. Ann Epidemiol 2009; 19:446-54.
87. IARC. Vitamin D and Cancer. IARC Working Group Reports Vol.5, International Agency for research on Cancer, Lyon 2008.
88. Grant WB. A critical review of Vitamin D and cancer: A report of the IARC Working Group on vitamin D. Dermato-Endocrinology 2009; 1:25-33.
89. Hill AB. The environment and disease: Association or causation? Proc R Soc Med 1965; 58:295-300.
90. Grant WB. How strong is the evidence that solar ultraviolet B and vitamin D reduce the risk of cancer? An examination using Hill's criteria for causality. Dermato-Endocrinology 2009; 1:17-24.