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Do Sunscreens Increase Risk of Melanoma in Populations Residing at Higher Latitudes?

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BACKGROUND: Sunscreens may allow overexposure to ultraviolet A (UVA) in fair-skinned persons and prevent symptoms of sunburn, but their benefits for the prevention of melanoma are uncertain.
METHODS: A PubMed search was performed that identified all known studies of the association of sunscreen use with melanoma risk during 1966-2007. A total of 18 studies were identified, of which 17 met criteria for inclusion in the analysis. Of these, 10 were conducted at latitudes $>40°$ from the equator and 7 at $\leqslant 40°$. Data were pooled for all latitudes combined and also according to these latitude strata. The association of skin pigmentation and latitude with odds ratios was estimated using linear regression.
RESULTS: Overall, there was no statistically significant effect of use of sunscreens on risk of melanoma (odds ratio 1.2, 95% confidence interval [95% CI] 0.9–1.6; p for heterogeneity < 0.0001). However, there was an interaction with latitude. At $>40°$ from the equator, the odds ratio was 1.6 (95% C.I. 1.3–1.9; p for heterogeneity $= 0.006$), whereas it was 0.7 at $\leqslant 40°$ (95% C.I. 0.4–1.0; p for heterogeneity $= 0.0002$).
CONCLUSIONS: Use of common sunscreen formulations that absorb UVB almost completely, but transmit large quantities of UVA, may contribute to risk of melanoma in populations at latitudes $>40°$.
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KEY WORDS: Melanoma, Ultraviolet A, Ultraviolet B, Sunscreens, Meta-analysis.

Melanoma is a public health problem of growing concern. In 2007, approximately 60,000 cases and 8,000 deaths are expected to occur in the United States (1). The global melanoma burden as of 2002 was 160,000 cases and 41,000 deaths annually (2). Annual age-standardized melanoma incidence rates in the United States (Connecticut) increased from 7.5 per 100,000 population in 1973 to 23.5 per 100,000 in 2003, the latest year for which age-standardized rates are available (3). Incidence rates also have increased during the past 25 to 30 years in the United Kingdom (4), Norway (5), Australia (6, 7), and several other countries (8). However, there has been a plateau in mortality rates of melanoma in young adults (ages 35 years and younger) in Australia, which began in approximately 1985 (9). The flattening in mortality rates may be the result of reduction of the rate of increase in incidence rates in younger adults (6, 7), improvements in melanoma diagnosis and treatment (7), or both. The apparent leveling off of incidence rates of melanoma in Australia may be the result of an influx of immigrants from Southeast Asia (10) to New South Wales, where one-third of the population resides (11).

It has been hypothesized that solar ultraviolet A (UVA) is an important risk factor for the development of melanoma (12–15). Solar ultraviolet radiation (UVR) is mainly (97.5%) UVA (16–17). UVA induces major mutations in the DNA of melanocytes as the result of oxidative stress, due to UVA penetration to the melanocyte and irradiation of intracellular chromophores that release mutagenic reactive oxygen species that cause mutations in the DNA (18).

Ultraviolet B (UVB) instead typically induces distinct signature mutations in keratinocytes, including cyclobutane dipyrimidine dimers (CDD), that are usually readily repaired by DNA repair enzymes present in keratinocytes (19, 20). Generation of CDD triggers the human photoprotective response, including upregulation of DNA repair enzymes via increased expression of p53 gene products (19, 21). Common sunscreens substantially reduce UVB transmission to the skin, but absorb far less UVA (22), with attenuation factors ranging from 2 to 5 across the UVA spectrum, with poorest absorption in the long UVA region (360–400 nm) (22). Most contemporary popular sunscreens have usually included only oxybenzone as the partial UVA absorber since 1989 (23, 24), although a few expensive products are available, mainly through pharmacies, that contain more efficient UVA absorbers, such as Avobenzone and Mexoryl SX (23, 24).

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Selected Abbreviations and Acronyms

UVB = ultraviolet B
UVA = ultraviolet A
UVR = ultraviolet radiation
GLOBOCAN = Global cancer database of the International Agency for Research on Cancer

Previous meta-analyses (25, 26) have not found a statistically significant overall association between use of sunscreens and risk of melanoma. However, no previous study has examined this association by latitude of residence of the cases and controls. This meta-analysis examined the effect of latitude on the strength and direction of the association between sunscreen use and risk of melanoma.

METHODS

The National Library of Medicine PUBMED database was searched for epidemiological studies of sunscreen use and melanoma risk for the period from January 1966 to January 2007 by using the terms ("melanoma," and "sunscreen"), and ("cohort" or "case-control" or "case-cohort" or "incidence" or "occurrence" or "epidemiology") and "human" as medical subject heading (MeSH) terms and words in the abstract.

Two investigators independently reviewed each study. The most thoroughly adjusted odds ratios were obtained from each. The log odds ratio and its variance from each study were pooled to calculate the summary log odds ratio. DerSimonian and Laird random effects models were also used to calculate the summary odds ratio and to assess heterogeneity (27). All calculations were performed using Review Manager (Copenhagen, Denmark: The Nordic Cochrane Center).

The latitude and Jablonski–Chaplin pigmentation score (28) for each study site was determined. The Jablonski–Chaplin score is a measure of skin pigmentation obtained from a meta-analysis of anthropological data collected worldwide on skin reflectance (28, 29). Skin reflectance is a measure of the concentration of melanin in solar-unexposed skin, specifically, the cutaneous optical depth. A red light source is placed on into the skin, and the reflectance is measured by a photocell and displayed in microvolts. Strong reflection indicates a low amount of absorbance of light by melanin, whereas weak reflection indicates a high amount of absorption. Because the measurement is made under the arm, which is mainly shaded from the sun, it is considered a measure of constitutive pigmentation, or the amount of melanin in the skin in the absence of substantial solar ultraviolet exposure (29).

Linear regression using a random effects model was used to assess the relationship between the natural log of the odds ratio from each of the 17 studies and the pigmentation score and absolute value of the distance of each study site from the equator in degrees. Regression analysis was performed using JMP 5.1.2 (SAS Institute, Cary, NC).

Eighteen studies (30–46) (M. Berwick, personal communication, 2006) were identified. One was excluded because the authors reported on use of suntan lotion or sun lotion instead of sunscreen specifically (30). Of the remaining 17 (31–46) (M. Berwick, personal communication, 2006), 10 (31, 33–35, 37, 40, 41, 43, 44) (M. Berwick, personal communication, 2006) were conducted in regions with latitudes $>40°$, and these were pooled for analysis. Separate pooled analyses were performed of the seven studies conducted at latitudes $\leq 40°$ (32, 36, 38, 39, 42, 45, 46). Finally, an analysis was performed of all 17 studies at all latitudes combined (31–46) (M. Berwick, personal communication, 2006).

The cutpoint of 40° was chosen based on predicted skin pigmentation according to latitude (28) (Figure 1). The cutpoint of 40° is a natural dividing point for difference in skin pigmentation of the earth's population, according to a pooled analysis of anthropological data collected worldwide on skin reflectance, a marker of constitutive baseline cutaneous optical column melanin pigment absorption of light, which correlates well and inversely with penetration of UV radiation into the epidermis (28).

RESULTS

All 17 studies were of case-control design (Table 1). The overall pooled odds ratio associated with sunscreen use was 1.2 (95% CI 0.9–1.6; p for heterogeneity < 0.0001). Of the 10 (31, 33–35, 37, 40, 41, 43, 44) (M. Berwick, personal communication, 2006) studies conducted at latitudes $>40°$ from the equator, seven (31, 34, 35, 37, 40, 41, 44) detected significantly high odds ratios associated with sunscreen use and three (33, 43) (M. Berwick, personal communication, 2006) found slightly increased odds ratios that did not achieve statistical significance. The pooled odds ratio associated with sunscreen use in these 10 studies was 1.6 (95% CI 1.3–1.9; p for heterogeneity $= 0.006$; Table 1 and Figure 1). In an analysis of the seven studies (32, 36, 38, 39, 42, 45, 46) that were performed at latitudes $\leq 40°$ from the equator, the overall pooled odds ratio associated with sunscreen use was 0.7 (95% CI 0.4–1.0; p for heterogeneity $=$ 0.0002).

A linear regression model was calculated using Jablonksi–Chaplin skin pigmentation scores (28) and latitude as the independent variables and the log odds ratio as the dependent variable. Because studies were the units of the analysis, the error term in the regression equation represents variability among studies. The proportion of the variance in the log odds ratios accounted for by latitude was 61% ($p = 0.01$; Table 2). The proportion of the variance