Is sun exposure a major cause of melanoma?

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YES Although various phenotypic characteristics enhance or reduce the risk of developing melanoma, sun exposure is the main cause of the disease. This statement is supported by multiple observations.

Site and sensitivity

Firstly, anatomical site of low and high sun exposure predicts patterns of melanoma. In general, the relative density of melanoma is highest on body sites receiving more sun exposure in both sexes and lowest on sites receiving little (scalp in women and buttocks in both sexes).[1 2] Furthermore, the difference in the patterns of sun exposure between the sexes is consistent with differences in the most common position of melanoma (trunk in men, lower extremities in woman).[3]

The incidence of melanoma is also much higher in people of races who tend to burn rather than tan.[1] The age standardised incidence of melanoma in non-Hispanic white people (populations of mainly European origin) in New Mexico is an order of magnitude greater than that in Hispanic whites, with similar results in non-Hispanic whites versus people of Hispanic, black, and Asian ethnic groups in Los Angeles.[1]

"The relative density of melanoma is highest on body sites receiving more sun exposure"

Within the lightly pigmented populations, studies using skin phototype (colour of non-exposed skin and ability to tan) found a relative risk of melanoma of 3.1 for the lightest quartile and 3.5 for no tanning ability, which is similar to the risk of people with a history of non-melanoma skin cancer.

Association with exposure

Studies looking at melanoma incidence as a function of ambient geographical ultraviolet levels avoid inaccuracies of recall of exposure. When considering race as a variable, ambient ultraviolet index and decreasing latitude were associated with increased incidence of melanoma, but only in non-Hispanic white people in the US and not in other dark skinned races.[4] This is consistent with other studies showing incidence of melanoma increasing with decreasing latitude where racial differences (other than populations of mainly European origin) are less observed.[5] Such racial differences explain the general increasing incidence of melanoma with decreasing latitudes within countries but not necessarily within continents.[6]

The increased incidence of melanoma in mid-European countries in people residing in sunny areas, particularly before 10 years of age,[7] is consistent with previous migration and geographical residence studies showing that either early exposure or longer exposure in an environment with high ambient solar radiation leads to an increased risk of melanoma.[8] Finally, increasing evidence suggests that the incidence of many cancers is inversely related to ambient solar ultraviolet B radiation exposure. However, the pattern for melanoma is reversed, with a positive association between solar ultraviolet B exposure and incidence.[9]

Case-control studies confirm intermittent sun exposure and sunburn as risk factors for melanoma. Two meta-analyses of case-control studies found that chronic exposure was either negatively associated (odds ratio=0.86)[10] or not associated.[11] In contrast, there were positive associations with intermittent exposure, lifetime sunburn, and childhood sunburn.[10 11] Although studies in children are unclear whether total or intermittent exposure conveys risk of melanoma,[8] all studies published since the last meta-analysis support the positive association of sun exposure and melanoma risk.[12-15] These studies lack objective measures of exposure, which may reduce the association between personal exposure and melanoma.[16] In contrast, studies attempting to measure total sun exposure by cutaneous microtopography show a significant association with melanoma for high grade solar damage, freckling as a child, and history of solar keratoses.[1]

Epidemiological and mutational analyses strongly support at least two divergent pathways to induce melanoma: those induced by chronic exposure (preferential head and neck site, associated with a history of non-melanoma skin cancer, no mutation in the BRAF gene (which controls the proliferation of melanocytes) and fewer naevus counts) and those induced by intermittent exposure (related to naevus density, BRAF mutation, and a preferential trunk site).[17 18] Epidemiological studies may produce confusing results if these divergent pathways are not taken into account.

Genetic evidence

In young adults with xeroderma pigmentosum, who have a defect in the repair mechanism of ultraviolet radiation induced thymidine dimers, the incidence of melanoma is 1000 times higher than in controls, although the anatomical distribution is the same.[19]

Analysis of melanoma mutations found in the suppressor oncogene CDKN2A (P16/INK4a) and ras oncogene family is consistent with induction by ultraviolet radiation.[20] Evidence suggests that although ultraviolet radiation is required to induce BRAF mutations found in melanoma and acquired naevi, other factors are also necessary.[21 22]

Protection

Overall, case-control studies have not shown a reduction in the incidence of melanoma with sunscreen use.[23 24] However, sunscreens are used to prolong intentional sun exposure,[25] they tend to be used by people at higher risk of melanoma, and the studies did not assess the sun protection factor or correct application of sunscreens. Nevertheless, the incidence of melanoma among young adults in Australia fell from 1983 to 1996, coinciding with strong public health messages to use protection.[1]

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Every summer we are reminded about the dangers of the sun. **Scott Menzies** argues that the risks of malignant melanoma are real, but **Sam Shuster** is unconvinced

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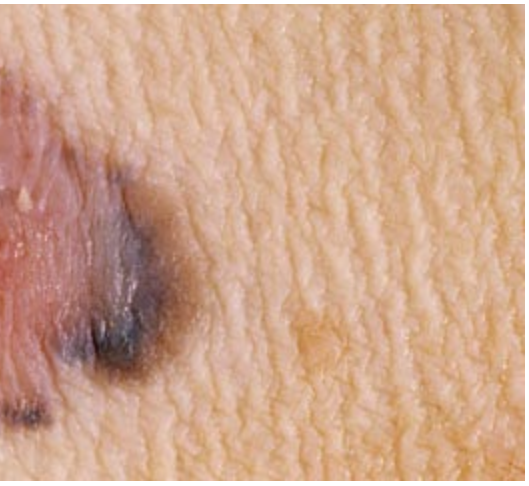
NO The list of harmful things grows daily, freshly mined by descriptive epidemiology, a substitute for research that confuses association with cause. Although most disappear under the weight of their own inconsequence, the alleged increase in melanoma from ultraviolet radiation has survived on the life support of regular promotion. I am therefore setting out what is known, which is rather different from what is believed.

Does ultraviolet light cause melanoma?

There is solid descriptive, quantitative, and mechanistic proof that ultraviolet rays cause the main skin cancers (basal and squamous). They develop in pale, sun exposed skin,[1] are related to degree of exposure and latitude,[2] are fewer with avoidance and protection,[3 4] are readily produced experimentally,[4] and are the overwhelmingly predominant tumour in xeroderma pigmentosum, where DNA repair of ultraviolet light damage is impaired.

None of these is found with melanoma. Variation is more ethnic[5-7] than pigmentary,[8] and 75% occur on relatively unexposed sites,[9] especially the feet of dark skinned Africans.[6 7] The relation to latitude is small and inconsistent in, for example, Europe[10] and the United States[11]; incidence and mortality fall with greater exposure[7-17]; incidence is unaffected or increased by use of sunscreens[18]; and the effect of sun bed exposure is small and inconsistent.[19] In addition, melanomas are difficult to produce experimentally with ultraviolet[20] light and are far less common than non-melanoma cancers in xeroderma pigmentosum.



Therefore, the effect of ultraviolet light can only be minimal, and the case against a major role is clear. Attempts to relate light exposure to surface area and site are irrelevant, since the cell of origin of melanoma and its distribution are unknown. The suggestion that the poor correlation of melanoma to ultraviolet light is because the causal event is sunburn from intermittent exposure in early life[13-17 21] is easily excluded, because the melanomas would then occur at the burn sites; there is no evidence for this, and it is unlikely that any will be found, because sunburn occurs in sun exposed sites, and these are not the sites at which melanomas occur.[7 8]

"The reported increase in melanoma is probably an erroneous reclassification of benign naevi"

There is an association between melanoma and number of naevi,[13 22] and naevi increase after exposure to ultraviolet light[22 23]; but this does not implicate ultraviolet light in the aetiology of melanoma, for the same reasons related to site. The likely explanation of the association is that stimulation of naevus growth by ultraviolet light simply increases the number of visible (and therefore countable) lesions. The associated histological changes can be indistinguishable from melanoma, as is the case with the benign lesions of lentigo maligna in elderly people, sun bed users, and psoriasis patients treated with psoralen and ultraviolet A; benign naevi stimulated by shave excision; and juvenile melanoma. Thus, unlike for squamous and basal cell cancers, there is no proof that ultraviolet light exposure is a significant cause of melanoma.

Is the reported increase in melanoma real?

In the past, naevi were left untreated and usually caused no harm. Then, fear of litigation and the search for early lesions led to removal of benign lesions; this introduced an ambiguity into histological classification, which eventually changed the definition of malignancy. Those who observed the process believe misdiagnosis of benign naevi explains the melanoma epidemic.[24] This view is supported by the findings of the Eastern region of England that the increase in new "melanomas" during 1991-2004 was entirely due to benign naevi (Levell et al, personal communication); a melanoma mountain in Australia has also been attributed to confusion with a benign disease.[25] The relation between incidence of new melanomas and higher social class[26] is best explained by removal of benign naevi after health warnings and encouragement to attend "pigmented lesion clinics"—the middle classes are always first on the scene.[27]

The subjective histopathological criteria used to diagnose melanoma have become too vague for use and are commonly found in benign disease. This problem can be resolved only by research, including a blind re-examination of histological slides used for past and present diagnoses, and a better distinction between benign and malignant changes in naevi.[24 27] Meanwhile, it can only be concluded that the reported increase in melanoma is probably an erroneous reclassification of benign naevi. Thus the question of whether ultraviolet light causes melanoma becomes irrelevant, because there is no case to answer.

Balancing the effects of ultraviolet light

Of course we know that ultraviolet light causes the common, virtually benign, and mostly trivial skin cancers and that, like smoking, it makes the skin look as if it has been well lived in. But is this enough to justify blanketing the sun when balanced against the possible advantages? We know the sun makes us feel better, although not how[28]; we need skin synthesis of vitamin D for our bones; ultraviolet light may protect against some forms of cancer[29] including melanoma[14]; and it has important, unexplained immunological effects.[30] We need to know much more before we can balance the biological books on ultraviolet radiation, even if we can now close the chapter on melanoma.[24]

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