CONTROVERSIES IN MEDICINE

Does the sun play a role in the aetiology of malignant melanoma?

A review

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The role of the sun in the aetiology of malignant melanoma is controversial.

In 1992 Schuster[1] wrote provocatively, 'Despite the lack of evidence of a causal link between sun exposure and melanoma, fear has been used shamelessly to frighten people out of the sun and into pigmented lesion clinics.' He claimed that the main reason for the supposed increase in incidence of melanoma was that many lesions, previously regarded as benign, were being classified as malignant, and that melanomas were being invented not found.

Risk factors

Many publications dealing with the role of the sun accentuate the view that melanocytic naevi are strongly associated with cutaneous melanoma, and that reducing sun exposure in very early life may be effective in reducing naevus prevalence and subsequent melanoma risk.[2-4] Bauer *et al*.[5] claimed that the number of melanocytic naevi is the most important risk factor for melanoma, and that total cumulative sun exposure seems to be the crucial environmental risk factor for the development of naevi. Therefore, reducing sun exposure reduces the number of naevi and consequently reduces melanoma risk. Simplistically: less sun = fewer naevi = less melanoma. This evidence seems to point to the sun as the culprit. However, in total contrast, a compelling study from Iceland of airline personnel showed increased incidence of melanoma but no evidence of excessive sun exposure compared with controls.[6]

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Kennedy *et al*.[7] claimed that painful sunburn before the age of 20 years is associated with an increase in naevi and melanoma. The same authors[7] nevertheless stated that lifetime sun exposure appears to be associated with a lower risk of melanoma, but no reduction in the number of naevi. Rivers[8] stated that outdoor workers have a decreased risk of melanoma compared with indoor workers, leading him to the idea that chronic sun exposure may even have a protective effect. Other authors[9] have found no differences between melanoma cases and controls with regard to sunburn and sun exposure.

Christofers[10] also questioned the role of the sun and suggested that squamous cell carcinoma is due almost entirely to sun exposure, that basal cell carcinoma is partly due to sun exposure, and that melanoma is not due to sun exposure.

Demographic pathology and ethnicity

In the darkly pigmented black people of South Africa, 80% of melanomas occur on the sole of the foot.[11] In other parts of Africa the findings are similar.[12] In populations of intermediate pigmentation, such as China,[13] Japan,[14] Saudi Arabia[15] and India,[16] there is a preponderance of acral lentiginous melanomas, predominantly on the sole of the foot. It is not implied that these population groups have a high incidence of melanoma. In some it is a rare tumour. It is clear that in China and India there is a preponderance of melanoma on the foot. However articles from Japan,[14] Latin America[17] and Saudi Arabia[15] refer to the preponderance of acral lentiginous melanoma but do not specify the site. It is probable that the majority of these tumours occur on the sole of the foot, an area where ultraviolet light is not a factor.

The frequency of melanoma on the sole of the foot varies according to skin pigmentation. The lowest frequency occurs in white-skinned people, an intermediate frequency in subjects with intermediate skin pigmentation, and the highest frequency in black-skinned people.[13] The sun clearly plays no role in melanoma of the sole of the foot or sun-shielded sites such as the vulva.[18]

Sunscreens

There is no definitive evidence that sunscreens protect people from developing melanoma. An analysis of 17 case-controlled studies concluded that the melanoma-protective potential of sunscreens could not be proved using the existing evidence.[19] Other authors[20] have come to the same conclusion.

Among the authors who ascribe a role to the sun in the aetiology of melanoma are those who even suggest that use of sunscreens extends the duration of intentional sun exposure, thereby increasing melanoma risk.[20,21] Other authors[22] have suggested that sunscreens may absorb ultraviolet light and inhibit the skin's inflammatory response, both dynamics promoting instead of protecting against melanoma. Most studies[23,24] have not demonstrated a causative association between sunscreen use and melanoma.

Ultraviolet-A and ultraviolet-B irradiation

It is generally assumed that most of the sun's damage results from UV-B irradiation. However current thought may suggest a major role for UV-A in inducing the genetic changes that ultimately lead to melanoma. No available commercial products adequately shield the skin from UV-A rays.[25] On the basis of animal experiments other authors[26] have maintained that UV-B irradiation is highly mutagenic and carcinogenic compared with UV-A.

Most writers concur that even though sunscreens block the mutagenic UV-B rays, they do not prevent melanoma. This casts doubt on the role of the sun in the aetiology of melanoma.

Eumelanin and phaeomelanin

There are two distinct types of melanin in mammals – eumelanin and phaeomelanin.[27] Eumelanin is brownish-black, and phaeomelanin reddish-yellow. Melanocytes of darker-skinned people show a preference for eumelanin, and melanocytes of light-skinned individuals show a preference for phaeomelanin.[28] Eumelanin protects the skin against UV radiation. In contrast, phaeomelanin does not protect the skin against UV radiation,[27] but actually contributes to UV-induced damage.[28] Eumelanin absorbs UV radiation well. Phaeomelanin has a limited ability to absorb radiation and therefore increases the risk of oxidative stress in the melanocytes. Dysplastic naevi synthesise less eumelanin and more phaeomelanin.[29] The above findings suggest that high phaeomelanin levels in melanocytes may be of significance in the aetiology of melanoma.[30]

Recalling that blacks tend to develop melanoma on the sole of the foot and rarely elsewhere, an obvious question is whether the sole of the foot in black people contains a high phaeomelanin/eumelanin ratio compared with the rest of the body. We do not know the answer. No such study has been performed.

Dysplastic naevi are also related to skin pigmentation. Individuals with red hair and fair skin are more likely to develop dysplastic naevi.[31]

Dysplastic naevi do not occur in black people.[29] Is this because of a high eumelanin-phaeomelanin ratio?

Albinism

Albinism is a condition in which melanogenesis is abnormal. It is divided into two categories, viz. tyrosinase-positive and tyrosinase-negative. Tyrosinase catalyses the formation of dopa (dihydroxyphenylalanine) from tyrosine. Dopa is an intermediary in the formation of melanin. Albinos in South Africa are tyrosinase-positive. Tyrosinase-negative albinos produce no tyrosinase, no dopa and no melanin.

A Japanese study[32] of the hairs of tyrosinase-positive albinos showed phaeomelanin only, unlike the hairs of the single tyrosinase-negative albino which contained neither eumelanin nor phaeomelanin. No studies have been performed on South African tyrosinase-positive albinos. It is, however, likely that they too produce phaeomelanin only. Pavel *et al*.[29] stated that a raised phaeomelanin level increases the risk for melanoma. Is melanoma common in South African albinos who almost certainly produce phaeomelanin only? A study of 111 South African albinos[33] showed that although nearly one-quarter had non-melanoma skin cancers, there was not a single case of melanoma. Other reports[34-36] have confirmed that melanoma is rare in albinos. In other population groups, sun exposure and light colour constitute a major risk for melanoma, whereas in albinos sun exposure and light colour constitute a low risk for melanoma.[37] This is indeed a challenging paradox.

A second paradox relates to the sun. If the sun is a factor in the number of acquired naevi, then albinos who are virtually unprotected from the sun should have large numbers of naevi. However, the number of pigmented naevi in albinos is similar to that found in white subjects.[38] If the number of naevi is a risk factor for melanoma, it becomes difficult to explain the rarity of melanoma in albinos.

A remarkable observation by Wang *et al*.[39] may contribute to understanding some of these paradoxes. They selected an experimental group of 469 patients with skin cancer, of whom 238 had melanoma and 231 had non-melanoma cancers – 88 squamous cell carcinomas and 143 basal cell carcinomas. The control group consisted of 329 cancer-free healthy subjects. Wang *et al*. exposed the white blood cells of the experimental and control groups to UV-B radiation and then analysed DNA repair activity. They assessed mutagen sensitivity by measuring mutagen-induced chromatid breaks per cell in lymphocytes *in vitro*. They discovered that the frequency of UV-B-induced chromatid breaks per cell was significantly higher in the non-melanoma skin cancers (i.e. squamous and basal cell carcinoma) than in control subjects. The striking finding

was that the frequency of UV-B-induced chromatid breaks in melanoma patients was the same as controls. It is clear from their study that an increased number of chromatid breaks indicative of a decreased ability to repair DNA damage caused by UV-B exposure, is a factor in the development of basal cell and squamous cell carcinoma, but not melanoma.

They also state that sensitivity to UV-B radiation may interact with other known risk factors, such as light hair and skin colour, sunburn history, tanning ability and freckling to increase the risk of non-melanoma skin cancer. In contrast, UV-B sensitivity does not increase the risk of melanoma.

Wang *et al.* concluded that non-melanoma skin cancer and cutaneous malignant melanoma have different aetiologies and that UV radiation is not a major factor in the aetiology of malignant melanoma.

However no research has answered the provocative question of why albinos, who are totally unprotected from the sun, develop squamous and basal cell carcinomas but rarely melanomas. Is there a genetic factor protecting them from melanoma?

In summary, with the exception of the above cases, the sun is not a major factor in the aetiology of malignant melanoma and genetic factors may well prove to be of greater significance.

Genetic factors

Melanoma risk is 30 - 70 times higher in individuals with a significant family history compared with the general population.[40,41] Familial melanomas arise through a dominantly inherited susceptibility to melanoma and many are characterised by germ-line mutations in specific genes. The lifetime risk of melanoma in individuals who carry these mutations is very high, but varies among geographical regions. Sporadic melanoma, however, accounts for well over 90% of melanoma cases.

Several of the well-known risk factors for melanoma have a genetic basis. Fair skin, red hair and freckling are genetically determined as complex traits with the input of many gene products in determining the final phenotype. The gene that has been studied most widely in this context is the melanocortin 1 receptor gene (MC1R) which is considered a low-penetrance melanoma-predisposing gene.[42] It is well documented that the presence of specific mutations confers an increased risk of melanoma[42,43] and that MC1R is also a skin colour-independent risk factor for melanoma.[44] In combination with mutations in the high-penetrance melanoma genes, the MC1R genotype can modify the risk of melanoma.[45] It has also been shown that depending on which genotype is present at the albinism locus (OCA2), the risk of melanoma may be higher or lower, but that the effect is less than that of the MC1R locus.[44] It has been suggested that MC1R screening should be included in a clinical assessment of melanoma risk.[46]

Another risk factor for melanoma is mole count.[47] This too has a complex genetic basis and has been calculated to be 42% heritable, with as much as 80% of the heritable component explained by a locus on chromosome 9p21.[48]

Recent molecular investigations have revealed that there are distinct pathways for developing melanomas and that these can be distinguished by the number of chromosomal alterations (duplications and deletions), by the specific regions that are altered and by specific single gene mutations.[49,50]

Genetic factors play a major role in familial melanoma, but a more subtle role in the common sporadic melanomas where an increased risk is present in individuals with combinations of alleles and genotypes that confer susceptibility. Many of the genetic variants that confer susceptibility, for example those in the genes that determine mole count and melanocyte proliferation and differentiation, have not yet been identified. The nature and frequency of these variants are likely to differ between populations, altering their relative genetic risk for melanoma.

Does the sun play a role in malignant melanoma? The jury is still out.

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