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SOLAR RADIATION AS A RISK FACTOR FOR CUTANEOUS MELANOMA: REVIEW

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SUMMARY

Melanoma is a particularly aggressive type of skin cancer, and its incidence has been increasing steadily since the 1970s.
In this article we have reviewed the main risk factors for this disease in particular: sun exposure, the use of tanning beds or sunlamps and skin phototype.
We also mention the importance of primary prevention in subjects at risk to reduce the onset of cutaneous melanoma.

Introduction

Malignant melanoma is the most aggressive form of skin cancer. Its incidence has been increasing faster than any other cancer in the United States. Overall, melanoma incidence has increased 3.1% annually during the last 20 years. In 2007 the incidence rate in the United States was 27.5/100.000 in whites and 1.1/100.000 in blacks (1). Over the last 25 years, cutaneous melanoma has become an increasingly common cause of cancer morbidity and mortality in the Caucasian population worldwide (2) .
The etiology of melanoma is multifactorial with environmental, host, and genetic factors contributing to its development. In this paper we have reviewed the evidence regarding all known risk factors for melanoma, looking in particular at sun exposure, use of tanning beds and sunlamps and the phenotypic characteristics of the subject at risk.

Sun exposure and sunburns

Since the early 1980s, sun exposure has emerged as the main environmental cause of melanoma, but despite this its association with the disease, the relationship between sun exposure and melanoma is still understood to be complex and is discussed widely. (3,4)
Indeed, Gandini et al (5) analyzed the results of 57 international research works published during the period 1969-2002 (50 case-control studies, 5 cohort studies and 2 *nested* case-control studies). The authors calculated a pooled relative risks ratios (RR) for melanoma of 1,34 (95% CI: 1,02-1,77), in subjects exposed to UV radiation compared to those unexposed to UV radiation. Furthermore, the authors identified different types of the sun exposure: intermittent (as in open air sports, water sports, holidays in sunny

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places), continuous (only occupational exposure) and total (both intermittent and continuous). The risk, compared to unexposed subjects, is significantly more elevated in those with intermittent exposure (RR=1,61; 95% CI: 1,31-1,99) than those with continuous exposure. (RR: 0,98).

Subjects with a history of sunburn have a risk of about two times higher (RR=2,03; 95%CI: 1,73-2,37) than those with a negative history of sunburn. Furthermore, risk is greater when episodes of sunburn occurred in childhood compared to adulthood. (5)

Dennis et al (6) analyzed the results of 51 international studies, published in the period 1985-2002, assessing the risk of melanoma compared to the history of sunburn and sun exposure throughout the life of the subjects. The authors showed that the risk of melanoma as a result of sunburn in a specific period of life is slightly higher if the sunburn occurred in childhood (OR: 1,9; 95% CI:1,6-2,3) and in adolescence (OR=1,6; 95% CI: 1,4-1,9) compared to adulthood (OR=1,4; 95% CI: 1,3-1,6).

The calculated risk over the whole period of life is 1,6, which is coherent with the risk observed in the single period of life. In 26 works it was possible to calculate the risk of melanoma by number of sunburns (clinically relevant) occurring during the subject's life . The authors calculated that for increments of five sunburns occurring in different periods of life; the risks are 1,4 in childhood, 1,4 in adolescence and 1,5 in adulthood, confirming that sunburn and number of sunburns are an important risk factor of for the onset of melanoma. (6)

In conclusion, the literature shows that there is a positive association between sun exposure and risk of melanoma and that the risk is high for all ages. Risk increases with the number of sunburns occurring during life, especially during childhood.

These aspects are represented in **table 1**.

Artificial UVR exposure

For most individuals, the main source of exposure to ultraviolet radiation is the sun. Nevertheless, some individuals are exposed to substantially high doses of UV through artificial sources. Tanning beds and sunlamps used for tanning purposes are the major source of deliberate exposure to UV radiation. (7)

UV radiation has a wavelength of between 100 nm e 400 nm and is classified into UVA (400-315nm), UVB (315-280nm) and UVC (280-100nm). Modern equipment for tanning emits primarily UVA radiation, but a fraction <5% of this spectrum is in the UVB range. Before 1992, UVB radiation was considered the only carcinogenic part of the solar spectrum, but since then UVA radiation has also been suspected as being a potential carcinogen. Therefore, in 1992, the IARC classified UVA and UVB radiation, and "the use of tanning beds and sunlamps" as a probable human carcinogenic agents. (Group 2a IARC classification) (8).

In 2010, Lazovich et al (9) confirmed this association in a population-based case-control study in Minnesota, demonstrating that melanoma risk significantly increased among those using either UVB- or UVA-emitting devices. Risk also significantly increased with frequency of use, measured in years of tanning (multivariate odds ratio [OR] 1.47; confidence interval [CI] 1.06-

	OR/RR	References
Intermittent exposure	**RR1.61; 95% CI1.31-1.99**	**(6)**
Sunburn in childwood	**OR1.9; 95% CI: 1.6-2.3**	**(6)**
Sunburn in adolescence	**OR1.6; 95% CI: 1.4-1.9**	**(6)**
Sunburn in adults	**OR1.4; 95% CI: 1.3-1.6**	**(6)**
Exposure during leisure time and trunk melanoma	**OR1.7; 95% CI: 1.4-2.2**	**(26)**
Exposure during leisure time and limbs melanoma	**OR1.4; 95% CI: 1.1-1.7**	**(26)**
Occupational exposure and head-neck melanoma (in low latitude)	**OR1.7; 95% CI: 1.0-3.0**	**(26)**

Table 1: Sunlight exposure and sunburn as melanoma risk factor

2.02) for 1 year vs OR 2.45 [CI 1.83-3.28] for 10 years; *P* for trend 0.006); hours of tanning (OR 1.46 [CI 1.15-1.85] for 1-9 hours vs OR 3.18 [CI 2.28-4.43] for 50 hours; *P* for trend 0.0001); and number of tanning sessions (OR 1.34 [CI1.00-1.81] for 10 sessions vs OR 2.72 [CI 2.04-3.63] for 100 sessions; *P* for trend 0.0002). Furthermore, the increased melanoma risk was present irrespective of the age at which indoor tanning commenced. (9)
In conclusion, as shown in **table 2**, the results of the scientific literature, indicate that there is a significantly increased risk of melanoma in subjects that make use of sunlamps or tanning beds and that the risk is greater if the sun-exposure occurs at younger age. Furthermore, the data support the statements of the IARC: the tanning obtained with artificial radiation is carcinogenic to humans and should be avoided to reduce the risk of melanoma. (10) In Italy a decree was promulgated by the Ministry of Economic Development (num. 110 , 12 May 2011), which prohibits the use of this equipment for subject under 18 years, pregnant women, people who suffer or have suffered from skin cancer and those who tan with difficulty or who burn easily.

Phenotipic characteristics
Phenotipic characteristics such as hair, eye and skin color, sensitivity to sunburn (determined through the Fitzpatrick classification) as well as the ability to tan can determine melanoma susceptibility (refers to **table 3**). (5)
One factor that plays an important role in protecting against the effects of UVR exposure is melanin. It is produced by melanocytes, the cells of origin for melanoma, and plays a critical role in protecting keratinocytes from the damaging effects of UVR. Exposure to UVR stimulates melanin synthesis in melanocytes through the action of "melanocyte-stimulating hormone" on its receptor; the melanocortin 1 receptor (*MC1R*).
Melanin forms supranuclear caps in keratinocytes and functions as a chromophore, absorbing UVR photons and scavenging reactive oxygen species, thereby protecting DNA from pyrimidine base formation and oxidative damage. (11-12)
The *MC1R* gene is responsible for determining the type of melanin produced and thus accounts for variation in human pigmentation, with wild-type *MC1R* associated with high ratios of eumelanin (brown-black color) to pheomelanin (redyellow color), and *MC1R* polymorphisms associated with low ratios of eumelanin to pheomelanin. Although eumelanin can absorb UVR and transform the energy into heat, preventing it from damaging DNA, pheomelanin is unable to function in this way. (13) Therefore, individuals with wild-type *MC1R*, who predominantly produce eumelanin, have better photoprotection from UVR compared with those with *MC1R* variants, who often have red hair, fair skin, and freckling and predominantly produce pheomelanin (14)

	OR/RR	References
Artificial UVR exposure	**OR1.74; 95% CI: 1.42-2.14**	(9)
Artificial UVA exposure	**OR4.44; 95% CI: 2.45-8.02**	(9)
1 year of tanning	**OR1.47; 95% CI: 1.06-2.02**	(9)
10 year of tanning	**OR2.45 95% CI: 1.83-3.28**	(9)
1-9 hours of tanning	**OR1.46 95% CI: 1.15-1.85**	(9)
50 hours of tanning	**OR3.18 95% CI: 2.28-4.43**	(9)
10 tanning sessions	**OR 1.34 95% CI:1.00-1.81**	(9)
100 tanning sessions	**OR 2.72 95% CI: 2.04-3.63**	(9)

Table 2: Artificial UVR exposure as melanoma risk factor

The low incidence of melanoma in populations with darker skin attests to the photoprotective role of eumelanin. (15)
Many epidemiological studies (1984-2004) have assessed the association between melanoma risk and certain features in a phenotypic population. The majority of these studies showed an increased risk of melanoma in individuals with high density freckles (risk between 1,7 and 6,9) to low density; (light risk between 1,1and 3,8) and blue eyes (risk between 1 and 4,5) to black eyes; red (risk between 1,2 and 3,8) and blond (risk between 1,1 and 4,9) hair to black hair; light skin (risks between 1,6 and 9) to dark skin.
Two meta-analysis studies have also been published recently. (16-17).
Firstly, Gandini et al (16) analyzed the data from 60 international works published during the period 1969-2002. The authors showed that subjects with a high density of freckles have a risk of melanoma two times higher than those without freckles (RR=2,10 95% CI 1,80 – 2,45). The subjects with Fitzpatrick skin phototype 1 to those with phototype IV have a risk of melanoma of 2,0. Finally, the risk of melanoma in subjects with light skin is greater than those with dark skin (RR=20,6; 95 % CI= 1,68-2,52).
Secondly, Olsen et al's meta-analysis (17) reviewed the data of 66 international works published during the period 1979-2008 (42 hospital case-control studies, 3 case-control studies of population, 3 cohort studies and 1 *nested* study). The authors calculated the pooled risk ratios as; 2,64 for subjects with red/blond hair, 2 and 1,46 respectively for those with blond and light brown hair to subject with black hair. Furthermore, the risks are: 2,27, 1,99 and 1,35 for subjects with skin phototype I, II, III respectively to those with skin phototype IV.
In conclusion, there is reasonable scientific evidence that subjects with light skin, eye and hair and with skin phototype I\II have a risk of melanoma which is twice as high as those with black hair, dark eyes and skin phototype IV.

Use of sunscreens

Sunscreens are designed to protect the skin from the damaging effects of sunlight. Some studies suggest that limiting exposure to UV radiation by using sunscreen can reduce the risk of non melanoma skin cancer by up to 78 %. Conversely, other studies suggest that sunscreen does not protect against the risk of melanoma. However, individual susceptibility to the sun has probably produced a misleading association between the use of sunscreens and risk of melanoma. In fact, people who are more sensitive to solar radiation are also those more inclined to use sunscreens. (18, 19)
Therefore, the possible increased risk of melanoma among users of sunscreen could be a result of the sensitivity to the sun of the subjects, the false security that can induce the users to be exposed to solar radiation for long periods and the fact that many are unaware that the application needs to be repeated regularly over the course of the day. (20)
A strong risk factor for the development of cutaneous malignant melanoma in white populations is the presence of acquired melanocytic nevi. (21) There is a consistent rise in risk of melanoma with increasing

	OR/RR	References
Family history of melanoma	**RR1.74; 95% CI: 1.41-2.14**	**(16)**
>100 common nevi/ versus <15	**RR6.89; 95% CI: 4.63-10.25**	**(5)**
>5 dysplastic nevi /versus 0	**RR6.36; 95% CI: 3.80-10.33**	**(5)**
High density of frechles	**RR2.10; 95% CI: 1.80-2.45**	**(16)**
Clear eyes/ vs dark eyes	**RR1.62; 95% CI: 1.44-1.81**	**(16)**
Clear skin	**RR2.06; 95% CI: 1.68-2.52**	**(16)**

Table 3: Other Risk factors melanoma associated

numbers of nevi in virtually every study that has assessed this relationship. (22) The presence of remnants of preexisting nevi in about 50% of melanoma (23) indicates that acquired nevi are precursor lesions for many, although not all, melanomas. (24)

In recent years, several randomized trials have evaluated education intervention to increase the use of sunscreen and other photoprotective measures especially in school age children and adults.

The most important published study is a randomized controlled trial by Richard et al.(25)

A total of 458 schoolchildren in grades 1 and 4 in Vancouver, British Columbia, were randomized in 1993. After exclusion of nonwhite children and those lost to follow-up or with missing data, 309 children remained for analysis. Each child's nevi were enumerated at the start and end of the study in 1996. Parents of children randomly assigned to the treatment group (n=222) received a supply of SPF 30 broad-spectrum sunscreen with directions to apply it to exposed sites when the child was expected to be in the sun for 30 minutes or more. Children randomly assigned to the control group (n=236) received no sunscreen and were given no advice about sunscreen use. Children in the sunscreen group developed fewer nevi than did children in the control group (median counts, 24 vs 28; *P*=.048). A significant interaction was detected between freckling and study group, indicating that sunscreen use was much more important for children with freckles than for children without. Modeling of the data suggests that freckled children assigned to a broad-spectrum sunscreen intervention develop 30% to 40% fewer new nevi than freckled children assigned to the control group. This data indicate that broad-spectrum sunscreens may attenuate the number of nevi in white children, especially if they have freckles. (25)

Conclusion

In general melanoma may be largely preventable, but it is difficult to understand how changes in the behavior of subjects at risk can reduce the incidence and the mortality of this disease.

The recommendations for primary prevention should include minimizing sun exposure, avoiding sunburns and the use of tanning beds or sunlamps to acquire or maintain a tan.

The use of water resistant sunscreen is strongly recommended, particularly in patients at risk such as: children, patients with a positive history of skin cancer, pregnant women and those with skin phototype 1-2. Sun screen itself must offer high protection and contain filters for both UVA and UVB; however, it must also be applied in appropriate doses several times a day. Despite the correct use of sunscreen, we always recommend avoiding exposure during the hours when the sun is at its strongest (from 11a.m. to 4 p.m) and continuous exposure.

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