UVB - susceptibility in malignant melanoma *

UVB: suscetibilidade no melanoma maligno

Nilton Nasser [1]

Abstract: BACKGROUND: It is well established that UV radiation provokes an immunological depletion in the skin, enabling the development of malignant cutaneous tumors. Most nonmelanoma skin cancer patients are considered to be UVB-susceptible.
OBJECTIVE: To study the behavior of UVB- susceptibility in malignant melanoma (MM) patients and whether this is a risk factor to the development of MM.
METHODS- Eighty-eight volunteers were selected and divided into two groups: healthy control group (n = 61) and MM group (n = 27), which were identified according to the following clinical criteria: histopathological type, level of invasion, skin phototype, sex and age. Susceptibility to ultraviolet B (UVB) radiation was measured by the onset of a contact hypersensitivity reaction to diphenylcyclopropenone among individuals sensitized in previously irradiated areas.
RESULTS - Susceptibility to UVB radiation was 81.5 in the MM group and 31.2% in the control group. The risk of an UVB-susceptible individual to develop MM was 9.7 times higher than when UVB resistant.
CONCLUSION - UVB susceptibility should be considered an important risk factor to the development of this type of cancer.
Keywords: Melanoma; Photobiology; Ultraviolet rays

Resumo: FUNDAMENTOS: Está bem definido que a radiação ultravioleta provoca depleção imunológica na pele, permitindo o desenvolvimento de tumores cutâneos malignos. A maioria dos pacientes de cânceres da pele não melanomas são considerados UVB-suscetíveis.
OBJETIVOS: Estudar a UVB-suscetibilidade nos pacientes com melanoma maligno e se este é um fator de risco para o desenvolvimento desse câncer.
MÉTODOS: Foram selecionados 88 voluntários divididos em dois grupos: grupo-controle saudável (n=61) e grupo de portadores de melanoma (n=27), todos identificados de acordo com os critérios: tipo histológico, nível de invasão, fotótipos de pele, sexo e idade. A suscetibilidade à radiação ultravioleta B (UVB) foi medida pela reação de hipersensibilidade ao contato com o difenciprone nos voluntários sensibilizados em áreas previamente irradiadas.
RESULTADOS: A suscetibilidade à radiação UVB foi de 81,5% nos pacientes com melanoma maligno e de 31,2% no grupo-controle. O risco de um indivíduo desenvolver o melanoma maligno foi 9,7 vezes maior do que nos indivíduos UVB-resistentes.
CONCLUSÕES: A UVB-suscetibilidade pode ser considerada um fator de risco importante para o desenvolvimento do melanoma maligno.
Palavras-chave: Fotobiologia; Melanoma; Raios ultravioleta

Received on 01.09.2009.
Approved by the Advisory Board and accepted for publication on 22.10.2010.
* Work conducted at the Regional University of Blumenau – Blumenau (SC), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

[1] PhD in Dermatology - Professor – Universidade Regional de Blumenau – Blumenau (SC), Brasil.

INTRODUCTION

Malignant melanoma (MM) is the most frequent cause of death among skin diseases. The American Cancer Society estimates that there were 68,720 new cases of melanoma in the United States of America in 2009. [1]

The incidence and mortality of malignant skin melanoma have increased dramatically over the last 25 years, especially in Caucasians.

The highest incidence of MM occurs in Queensland (Australia) with 56 new cases per 100,000 inhabitants per year in men and 43 in women. Mortality rates appear to have stabilized in the United States, Australia and Europe. [1,2,3,4,5]

Epidemiological studies on MM over the last decades have indicated as main risk factors those associated with the environment (sun exposure and geographic zone) and those associated with the individual (skin, eyes, and hair color), [4,5,6,7] and, among these, photoimmunologic behavior and more recently genetic tests. [8,9]

It is known that the capacity that ultraviolet B radiation (UVB) has to alter the skin's immune system has been widely documented and is an important risk factor to the development of sun-induced skin cancer. [4-5-6]

Strong epidemiologic and molecular evidence relate sun exposure to the development of malignant melanoma. In fact, sun exposure is the most important risk factor to the development of this type of skin cancer. [7,10,11,12]

Schwarz A. *et al.* demonstrated the importance of T regulatory cells in the inhibition of the induction and in the suppression of the effector phase of contact hypersensitivity in ultraviolet light-exposed skin. [13]

The immune response of the skin to haptens, called contact hypersensitivity, is a standard model that has been developed in rats and humans to study the effects of ultraviolet B radiation (UVB) on local and systemic immunity. [14]

The application of haptens to UV-irradiated skin may depress the immune response of UVB-susceptible individuals and induce a contact hypersensitivity reaction in UVB-resistant subjects. [15]

Most non-melanoma skin cancers are considered UVB-susceptible. [15]

The study of susceptibility in MM patients is very important to establish this factor as an important risk for the development of this cancer.

Therefore, our objective in this study will be to determine the UVB-susceptibility of MM patients and the importance of this risk factor for UVB-susceptible individuals to develop melanoma.

MATERIAL AND METHODS

Participants

Inclusion criteria: both men and women of at least 18 years old, previously informed about the nature of the procedures, with formal approval, with no history of photosensitivity, immunosuppression, use of corticosteroids or other drugs.

Exclusion criteria: pregnancy or breastfeeding, previous history of allergy, immunosuppressive disorders, relatives of MM patients in the control group, use of corticosteroids and/or other immunosuppressive drugs, history of photosensitivity.

All participants followed a specific protocol and all of them signed an informed consent.

The study, the protocols and consent forms were approved by the Ethics Committee of the Regional University of Blumenau, process number 008/04.

This is a case-control study with healthy and MM groups, of both sexes, aged between 18 and 78 years.

Eighty-eight volunteers were included in the study and divided into a control group with 61 healthy individuals and an MM group with 27 patients.

The MM group was identified based on sex, age, skin phototypes I, II and III (Fitzpatrick classification), [16] histological type, and degree of invasion according to Clark's level and Breslow's depth.

The control group was identified based on sex, age, and skin phototypes, all skin phototypes I, II, and III.

Tests were performed between 2004 and 2008, and the groups were standardized based on sex and minimum age due to the test reactions. Age equalization was not considered because UVB-susceptibility is due to a genetic factor present at birth and that continues until death, thus suffering no influence of this factor. [15,17]

Determination of the Minimal Erythema Dose (MED)

Once the phototype was defined, the skin was exposed to UVR to determine the minimal erythema dose (MED).

The minimal erythema dose (MED) is defined as the time needed for the formation of a discrete erythema with well-demarcated borders and without blisters, after a single UVR exposure, expressed in energy by surface unit (KJ/m^2).

The area chosen was the medium or low untanned portion of the dorsum, that is, a skin area unexposed to the sun. Psora-Comb Dermalight 80 (Dr K. Hönle Gmb, Munich, Germany) was used as an UVR emitting source. It emits ultraviolet radiation with a continuous spectrum with peaks of 313 nm, placed at a distance of 2.5 cm.

The test area was covered with an opaque film,

with 4 (four) 2 cm^2 openings through which irradiation was performed for 15, 30, 45, and 60 seconds, corresponding to doses of 0.375, 0.75; 1.125 and 1.5 KJ/m2 UVB at a distance of 2.5 cm.

The squared openings were progressively closed in the corresponding times.

Patients were oriented to avoid sun exposure during the observation period.

MED results were read 24 hours after irradiation.

Susceptibility to Ultraviolet B radiation

All the volunteers received the equivalent of 4 MED in a 4 cm^2 area unexposed to the sun. This dose is considered sufficient for the depletion of antigen-presenting skin cells and nearly capable of causing a burn similar to sunburn.

Immediately after irradiation, 0.1 ml of 2% diphencyprone in acetone in Finn Chambers was applied to the irradiated skin and fixated with hypoallergenic adhesive. It was then removed after 48 hours. Diphencyprone is considered a potent contact sensitizer hapten.

21 to 28 days after sensitization, a hypersensitivity contact test was performed using a chamber with 0.025% diphencyprone placed in a non-irradiated area of the dorsum or arm.

Results were read 48 hours after application, always by the same observer and at least 30 minutes after the removal of the adhesive, complying with the following criteria: (-) negative reaction; (+) weak reaction = discrete erythema, little infiltration, no vesiculation; (++) strong reaction = moderate erythema, occasional papules, few vesicles; (+++) very strong reaction= strong erythema, edema and many vesicles; (++++) extreme reaction = blistering and ulceration.

Interpretation of the results of the 0.025% DPCP test

- Negative = Non-reactive: considered UVB-susceptible (UVB-S)
- Positive = reactive: UVB-resistant (UVB-R)

Statistical Analyses

The odds ratio (OR) was calculated with confidence intervals (95%) for the association of UVB-susceptibility in the two groups. Significance was determined by the Chi-square test and the Mantel-Haenzel test was used to determine OR.

RESULTS

Eighty-eight individuals completed the study: 27 malignant melanoma patients (12 men and 15 women) and 61 control subjects (30 men and 31 women).

Table 1 shows the main result of this study, that is, the UVB-susceptibility found in MM patients and in the control group.

MM patients were considered UVB-susceptible in 81.5% of the cases and UVB-resistant in 18.5%. In the control group 32.2% of the individuals were UVB-susceptible and 68.8%, UVB resistant.

The odds ratio was 9.73 with a confidence interval (95%) ranging from 2.89 to 34.8 (p=0.0000127)

These results show that the risk of UVB-susceptible individuals to develop malignant melanoma is 9.7 times higher than for UVB-resistant individuals.

Table 2 shows the histological types of malignant skin melanoma found in our study in relation to UVB-susceptible individuals. We observed that the group with nodular melanoma includes 80% of UVB-susceptible individuals and the group with the superficial spreading type includes 82.3% of UVB-susceptible individuals, showing high susceptibility and similar susceptibility rates for the two histological types.

Table 3 shows the histological types and the degree of invasion based on Breslow's depth.

Table 4 shows the participants, their skin phototypes and irradiation doses needed to reach the minimal erythema dose. We observed that phototype I individuals need a lower dose of UVB radiation than phototype II individuals to obtain the minimal erythema dose. The latter need less radiation than phototype III individuals.

According to the primary localization (table 5), 45% of the melanomas were found in exposed areas and 55% in unexposed areas of UVB-susceptible patients. UVB-resistant patients had 60% of their primary lesions in exposed areas and 40% in unexposed ones.

Table 1: UVB-susceptibility in malignant melanoma (MM) patients and in the control group

	Malignant Melanoma		Control Group		Total	
UVB-susceptible	22	81,5 %	19	31,2 %	41	46,5 %
UVB-resistant	5	18,5 %	42	68,8 %	47	53,5 %
Total	27	100 %	61	100 %	88	100 %

OR = 9,73; intervalo de confiança = 2,89-34,8; p = 0,0000127

Table 2: UVB-susceptibility in melanoma patients according to histological type

	Superfial Spreading Melanoma		Nodular Melanoma		Total
UVB-susceptible	14	82,3 %	8	80 %	22
UVB-resistant	3	17,7 %	2	20 %	5
Total	17	100 %	10	100 %	27

Table 3: Percentage of the degree of invasion based on Breslow's depth in the histological types shown by the malignant melanoma group

Histological type	Breslow < 1MM	Breslow > 1MM	Total
Superficial spreading	13 (75,5%)	4 (24,5%)	17(100%)
Nodular	4 (40%)	6 (60%)	10(100%)
Total	17 (63%)	10 (37%)	27(100%)

DISCUSSION

Exposure of untanned Caucasians to acute and low UVB radiation doses allows us to classify individuals into two groups denominated UVB-resistant and UVB-susceptible. [15]

Groups are defined when a sensitizing hapten (diphencyprone) is applied to a previously irradiated area. Individuals who do not react to hapten exposure after previous sensitization are denominated UVB susceptible and those who respond with a vigorous reaction to the contact hypersensitivity test are called UVB-resistant. The phenotype of UVB susceptibility/resistance in humans is genetically determined and, as previously seen, is an epidermal phenomenon associated with contact sensitivity (CHS). [15,17]

UVB susceptibility is found in 40% of humans and is a better indicator than sun exposure to determine the risk for developing skin cancer. [4,5,6,15,17]

In this study the control group with healthy volunteers had a 31.2% incidence of UVB susceptibility. This number contrasts with the high frequency of 81.5% of UVB susceptibility found in the MM group.

The odds ratio was 9.73, which indicates that the risk of UVB susceptible individuals to develop MM is 9.7 times higher than for UVB resistant individuals. This strongly suggests that UVB-susceptibility in humans may be considered a risk factor for the development of malignant melanoma.

The study showed that individuals with nodular melanoma were UVB-susceptible in 80% of the cases and those with superficial spreading melanoma were UVB-susceptible in 82.3% of the cases.

The incidence of malignant melanoma is increasing worldwide, particularly in the white population. [1-2-3-4-5-6-7]

Early histological diagnosis identifies a high proportion of melanomas denominated thin tumors with a better prognosis, and this indicates that prevention is the best way to reduce mortality. [4-10]

Many characteristics have been recognized as risk factors for the development of malignant melanoma, such as fair skin, light hair, blue eyes, ephelides, great number of melanocytic nevi, family incidence and tendency to sunburn. [4-5-7-10-12]

In view of the results of this study, we suggest that the determination of UVB-susceptibility can contribute to the evaluation of the risk of malignant melanoma development when associated with clinical

Table 4: Minimal erythema dose (MED) calculated for the participants (malignant melanoma (MM) and control groups) based on their phototypes

Phototype	Mm	Med kj/m^2	Control	Med kj/m^2	Total	Med kj/m^2
I	4	0,375	3	0,375	7	0,375
II	19	0,414	40	0,480	59	0,464
III	4	0,562	18	0,729	22	0,656
Total	27		61		88	

Table 5: UVB-susceptibility in melanoma patients based on the primary localization (exposed and unexposed areas)

Area of localization	UVB-susceptible	UVB-resistant	Total
Exposed	10 (45%)	3 (60%)	13 (48%)
Unexposed	12 (55%)	2 (40%)	14 (52%)

Exposed areas – face, head, back of the neck, hands, forearms and feet
Unexposed areas – torso, thighs and arms

and epidemiological markers and, whenever possible, with genetic tests.

CONCLUSION

The rapid increase of the incidence of malignant melanoma worldwide in the white population shows the need for prevention and determination of the risk factors for the development of this type of skin cancer.

This study shows the presence of UVB-susceptibility in 81.5% of the individuals with malignant melanoma. It also shows that UVB-susceptible individuals are 9.7 times more likely to develop melanoma as compared with the general population.

Therefore, we can state that UVB-susceptibility is an important risk factor to the development of malignant melanoma. The identification of UVB susceptible individuals offers another parameter for early diagnosis and primary prevention.

UVB-susceptible individuals should receive instruction on photoprotection, on how to recognize the early signs of melanoma (ABCD rule) and to self-examine. They should also visit their dermatologist regularly. ❑

REFERENCES

1. American Cancer Society [internet]. Cancer facts and figures 2009. [cited 2009 Mar 26]. Available from: www.cancer.org/downloads/STT/CAFF2009PWSecured.pdf.
2. Giblin AV, Thomas JM. Incidence, mortality and survival in cutaneous melanoma. J Plast Reconstr Aesthet Surg. 2007;60:32-40.
3. Staples MP, Elwood M, Burton RC, Williams JL, Marks R, Giles GG. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. Med J Aust. 2006;184:6-10.
4. Markovic SN, Erickson LA, Rao RD, Weenig RH, Pockaj BA, Bardia A, et al. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. Mayo Clin Proc. 2007;82:364-80.
5. Leiter U, Garbe C. Epidemiology of melanoma and nonmelanoma skin cancer--the role of sunlight. Adv Exp Med Biol. 2008;624:89-103.
6. Moan J, Porojnicu AC, Dahlback A. Ultraviolet radiation and malignant melanoma. Adv Exp Med Biol. 2008;624:104-16.
7. 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.
8. Schwarz T, Halliday GM. Photoimmunology. In: Lim HW, Honigsmann H, Hawk JLM, eds. Photodermatology. New York: Informa Healthcare USA Inc; 2007. p.55-74.
9. Gerstenblith MR, Goldstein AM, Tucker MA, Fraser MC. Genetic testing for melanoma predisposition: current challenges. Cancer Nurs. 2007;30:452-459.
10. Bordeaux JS, Lu KQ, Cooper KD. Melanoma: prevention and early detection. Semin Oncol. 2007;34:460-6.
11. 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.
12. Lea CS, Scotto JA, Buffler PA, Fine J, Barnhill RL, Berwick M. Ambient UVB and melanoma risk in the United States: a case-control analysis. Ann Epidemiol. 2007;17:447-53.
13. Schwarz A, Maeda A, Wild MK, Kernebeck K, Gross N, Aragane Y, et al. Ultraviolet radiation-induced regulatory T cells not only inhibit the induction but can suppress the effector phase of contact hypersensitivity. J Immunol. 2004;172:1036-1043.
14. Streilein JW, Taylor JR, Vincek V, Kurimoto I, Shimizu T, Tie C, Colomb C. Immune surveillance and sunlight-induced skin cancer. Immunol Today. 1994;15:174-9.
15. Yoshikawa T, Rae V, Bruins-Slot W, Van Den Berg JW, Taylor JR, Streilein JW. Susceptibility to effects of UVB radiation on induction of contact hypersensitivity as a risk factor for skin cancer in humans. J Invest Dermatol. 1990;95:530-6.
16. Fritzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol. 1988;124:869-71.
17. Yoshikawa T, Streilein JW. Genetic basis of the effects of ultraviolet light B on cutaneous immunity. Evidence that polymorphism at the Tnfa and Lps loci governs susceptibility. Immunogenetics. 1990;32:398-405.

MAILING ADDRESS / ENDEREÇO PARA CORRESPONDÊNCIA:
Nilton Nasser
Rua Curt Hering, 20 – 3º andar – Centro
89010-030 Blumenau – SC, Brazil
Phone.: 47 8408 0453
E-mail: ninasser.bnu@terra.com.br

How to cite this article/*Como citar este artigo*: Nasser N. UVB - susceptibility in malignant melanoma . An Bras Dermatol. 2010;85(6):843-8.