THE ANALYSIS OF THE RISK FACTORS INVOLVED IN MELANOCYTIC AND NONMELANOCYTIC SKIN CANCERS

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Abstract: *The continuous growing of the cancers incidence, in generally and the skin cancer, especially was the motivation for studying this theme. I consider that a better understanding of the etiopathogenic factors, which are involved in the onset of the skin tumors, would allow an effective prevention and an early treatment by precocious diagnosis of the tumors, with the cure of the cancer in some cases. Another reason pro-study was the recent data from the literature about the involvement of HPV in cutaneous oncogenesis. The control of these factors will help us to decrease the morbidity and the mortality by skin cancer.*

Cuvinte cheie: *factori de risc, tumori cutanate melanocitare, tumori cutanate nonmelanocitare*

Rezumat: *Incidența în continuă creștere a cancerelor în general, și a celor cutanate în special a constituit motivația studierii acestei teme considerând că o mai bună cunoaștere a factorilor etiopatogenici implicați în apariția și dezvoltarea tumorilor cutanate ar permite o profilaxie eficientă, un tratament mai precoce și implicit vindecarea tumorilor prin diagnostic mai precoce al bolii. Datele recente din literatura de specialitate legate de implicarea virusurilor HPV în oncogeneza cutanată a reprezentat un alt motiv pro-studiu. Controlul acestor factori va permite scăderea morbidității și a mortalității prin tumori cutanate.*

SCIENTIFIC ARTICLE OF BIBLIOGRAPHIC SYNTHESIS

The risk factors involved in the development of skin cancers are well known. The knowledge of the latest data from the literature about the importance of each factor in the appearance of melanocytic (MSC) and nonmelanocytic skin cancers (NMSC) and their control would allow us to decrease the skin cancer morbidity. In this paper work I made an up-date related to this issue.

1. Aggressive and unprotected exposure to UV radiation

It refers to the cumulative effects of UV radiation exposure and to repeated sunburns, especially in childhood. The aggressiveness of UV radiation on the skin is produced by naturally and artificially exposure (sun tanning, phototherapy). Studies published so far have concluded that UVB radiation (length 290-320 nm) plays an important role in the appearance and the development of skin tumors, much higher than UVA radiation (1,2,3). An obvious role in skin carcinogenesis has the combined exposure to UVB and UVA, wich causes more aggressive mutagenic effects and an increasing immunosupressed effects (4).

The photocarcinogenic effect of UVB is due to the suppressing effect of the immune system: the antigen-presenting cell is inhibited by UVB, with secondary release of the immunosuppressive cytokines. This will cause destruction of cellular DNA by generation of pyrimidine dimers in keratinocytes DNA which act as a molecular trigger for the UV-induced immunosuppression (5). The mutations in tumor suppressor genes are cause, also by UV radiation. Thus will be unable to make nuclear repairs and will allow the initiation of further carcinogenesis process.

The outdoor occupations (fishermen, farmers, designers, outdoor athletes) have a higher risk of actinic aggression. The equatorial geographic area, because of intense solar activity have a high risk of developing skin malignancies, but the skin phototype of this population is an important protective factor.

MNSC

The major role of this factor is shown by the frequency of basal cell carcinoma (BCC) appearance in the photoexposed areas, in patients with skin phototype I or II and with a history of sunburns.

A study published by Grossman and Leffell concluded that there was a significant correlation between exposure to UVB and the development of BCC.

Also, the appearance of a significant number of BCC in the cover areas suggests that other risk factors play an important role in the development of BCC.

In 2001, Corona et al. published a study which showed that there was a significant association between the appearance of BCC and the existence of sun exposure during childhood and/or adolescence and also a family history of skin cancer.

The important role of UV radiation in the squamous cell carcinoma (SCC) appearance is highlighted by the most frequent localization of this tumor (in photoexposure areas, especially in the cephalic extremity). The cumulative doses of UV tanning, sun exposure or phototherapy (PUVA, UVB) is the main risk factor involved in the etiopathogenesis of SCC. In patients with SCC, the exposure to UV radiation, even for therapeutic purposes (including PUVA) can cause phototoxic effects with the appearance of mutations in p53 and in the oncogenic Ha-Ras gene (6). There is an increased incidence of SCC in the southern countries, aspect wich is directly correlated

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with a longer time of exposure to UV.

The inactivation of p53 (a tumor suppressor gene) occurs in about 90% of SCC (6). The proteins p16 (INK 4a) and p14 (ARF) are other molecular markers that show mutations in skin cancers (7).

MSC

Intermittent and intense episodes of sun aggression are relevant in this skin cancer. The presence of more than two episodes of severe sunburn, especially before the age of 15 is correlated with the increased risk of malignant melanoma (MM) (8). It was also observed that the patients with MM had used artificial UV radiation more frequently than the general population (9, 10). Another risk factor for developing MM is the history of repeated episodes of exposure to PUVA.

2. Skin photoptype: more sensitive are phototype 1 and 2, with blue or green eyes (11) (table 1).

Table 1. Skin phototypes

Phototype	**The color of the skin**	**Sun burns and tanning status**	**Immediate tanning**	**Late tanning**
I	Very white	It is very easy to burns, never tanning	-	-
II	White	It is easy to burns, less tan	+/-	+/-
III	White	It is moderate to burns and tan	+	+
IV	Light brown	Sometime burns, tan easily	++	++
V	Dark brown	Rarely burns, tan easily	+++	+++
VI	Black	Never burns, tan very easily	+++	+++

The appearance of SCC in black people is rare, but the mortality rate in this category is higher (12). The patients with albinism have a higher risk of developing SCC because of the lack of photoprotection induced by low levels of melanin (13). MM is more common in white people, compared with the Caucasian, Asian / black population (20/1).

3. Presence of precancerous lesions, scars or dysplastic nevi

NMSC

BCC may occur de novo or from the preexisting lesions like: actinic or seborrheic keratoses (14), nevus sebaceous, Gorlin syndrome, epidermodysplasia verruciformis. Other cases of BCC appear in vaccine scars or tattoos.

The SCC may occur on pre-existing lesions like actinic keratosis, chronic radiodermitis, leucoplakia, erosive oral lichen planus, Bowen disease, eritroplasia, chronic discoid lupus, varicose ulcers, lupus vulgaris, necrobiosis lipoidica, lichen sclerosus, chronic deep fungal infections, epidermolysis bullosa, burns, osteomyelitis, acne conglobata, dissecans cellulitis of the scalp, hidradenitis suppurativa, venerian lymphogranulomatosis, etc.

In patients with SCC and dystrophic epidermolysis bullosa were observed mutations in p53 and p16 proteins (15). More recently it was observed that the scars of junctional epidermolysis bullosa have higher risk for SCC (16).

MSC

MM can appears de novo (this form accounts approximately 60% from MM) or from dysplastic nevi or from nevi with changed clinical characters (17). The presence of dysplastic moles may be considered as a marker that identifies the relative risk of developing MM. Congenital giant nevi (over 20 cm) and the presence of large numbers of common nevi are other risk factors in MM appearance.

4. Old age (photoaging)

The NMSC and MSC appear more frequently after 50 years. The possibility of developing skin tumors increases with age. The immunosuppressed patients develop skin cancers in the early ages.

With the exception of basal cell nevomatosis, BCC rarely occurs under the age of 40 years. The most affected age group is 50-80 years (mean age in men is 55 years).

The average age of MM diagnosis is 53 years. It is the most common malignancy in the period of 25-29 years in women and is the 2nd in frequency (after breast cancer) in women with 30-34 years (18). The rates of death in MM in the elderly is higher because of the associated diseases, the inability to tolerate the side effects of certain therapies and to be included in some treatment programs because of the age (19). Lately it is noted that the MM appears increasingly in young people, socially active. This category has a poor prognosis. After the age of 40 the most common MM had a lower Breslow index and a better prognosis (11).

5. Ionizing radiation plays an important role in carcinogenesis of NMSC. The exposure can be accidentally or for therapeutic purposes (physical treatments, medical treatments for cancer).

The risk of BCC can be increased by the prolonged radiological exposures and/or multiple physical therapy with ionization. The existing data in the literature about the effects of PUVA-therapy on the incidence of BCC are inconsistent, so Katz and Lindelof believe that PUVA-therapy used to treat patients with psoriasis increases the risk of BCC. In contradiction, Stern thinks that the risk of inducing a BCC in PUVA treated patients is negligible. In general, any agent that causes DNA alterations predispose furthermore to SCC than BCC. This observation is supported by the spectrum of malignancies that appear in congenital deficiency of DNA repair.

Although the exposure to ionizing radiation for therapeutic purposes is more commonly associated with the development of BCC, but their involvement in the development of SCC is not neglected (20).

6. Personal or family history of skin tumors

The results of some studies showed the existence of DNA alteration in some patients with skin cancer. This observation supports the idea that the genetic factor is determinant. We must also take into consideration the fact that most DNA alterations appear secondary to actinic aggression.

In a patient with a history of skin cancer the risk of a 2nd skin tumor is much increased. The appearance rate of the 2^{nd} skin cancer after 3 years from the first diagnosis is 35% and after 5 years increased to 50% (21). Recent studies had revealed the existence of p53 mutations in patients with skin tumors; mutations that are most likely initiated by UV aggression.

The involvement of the genetic factors has been demonstrated in patients with Gorlin syndrome (where the mutation is in the PTCH gene, a tumor suppressor gene from the 9 chromosome).

A retrospective study reveals that the risk of multiple MM varies between 1,3% and 0,8% (22). The risk of MM appearance in a patient with a family history (first degree relatives) is much higher (17).

The genetic factor is very important; 8-12% of MM appears in families with melanoma. In approximately 25% of MM occur CDKN2A mutations (an inhibitor of cyclin-dependent kinase 2A) and mutations of p16 protein from chromosome 9.

7. Presence of the genetic disorders

The patients with xeroderma pigmentosum have a higher risk of developing NMSC and MSC, because of an enzyme deficiency that doesn't allow DNA repair secondary to

actinic aggression (23).

Other genodermatosis with increased risk of NMSC are epidermodysplasia verruciformis, dystrophic epidermodysplasia bullosa, albinism, congenital dyskeratosis, porokeratosis, nevus sebaceous syndrome, KID syndrome.

The dysplastic nevi syndrome or xeroderma pigmentosum causes a risk to develop a MM of 500-1000 times greater than healthy peoples (24).

8. Chemical carcinogens (arsenic, tar, paraffin, soot) and exposure to **some industrial oils**.

Diepgen and Mahler found that the exposure to carcinogenic chemical factors (especially arsenic, coaltar and psoralen) and ionizing radiation increases the risk of NMSC, especially of SCC. Nowadays the source of arsenic is the contaminated water and the traditional Chinese medicine.

The role of exposure to fiberglass dust and chemical cleaning agents is still under study. Some researchers recognize the involvement of these agents in skin carcinogenesis, a fact that is not confirmed by other studies.

9. Immunosuppressive therapies and the immunocompromise conditions increased the risk of skin tumors of 1.5-100x, depending on the type of tumor (the lowest risk is for MM and the highest is for SCC).

The immunosuppressed transplant patients may develop skin cancers (the risck of BCC in this patients is 10 times higher than in healthy peoples).

Some authors had observed that the risk of SCC is higher in patients with a long period of corticosteroid treatments, emphasizing thus the role of immunosuppression in the development of SCC, but this data were not statistically significant. A history of organ transplantation, hematologic malignancies (especially in chronic lymphocytic leukemia), HIV infection or prolonged immunosuppressive therapy used for autoimmune diseases may increase the incidence of SCC (the risk of SCC is increased by 65-250 times compared with the unaffected population) (25).

The heart transplanted patients have the highest risk. Also pretransplant condition can influence the appearance of the SCC in this group of patients, as follows: the risk of SCC is higher in transplant patients for polycystic kidney and lower in transplant patients for diabetic nephropathy.

In patients with SCC was observe that the tumor suppressor protein p53 may represent a target for CD8+ T cells, suggesting that a functional immune system can target the keratinocytes expressing p53-mutations. The risk of MM in transplant patients is 1.5-2x higher, a much lower risk than SCC (100x higher) (27).

10. Smoking

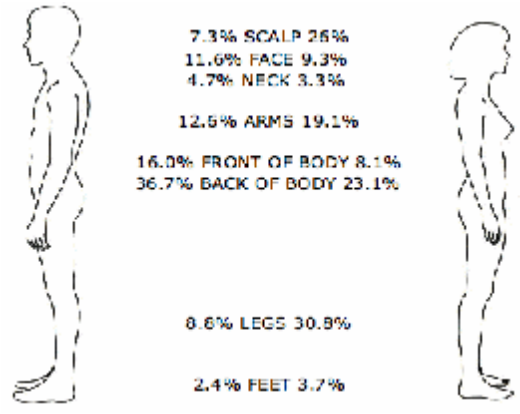
De Hertog et al. found a correlation between smoking and SCC, especially for the lower lips. The importance of smoking in the development of BCC in younger women who smoke was highlighted by Boyd et al in their study.

11. Sex

In BCC the ratio M/F is 2.1/1 (this can be explained by the fact that men had professional activities and hobbies in the outdoors more often than women). In SCC the ratio M/F is 2-3/1, possible due to the cumulative doses of UV exposure.

In the U.S.A the risk of developing MM is higher in women aged 40 (1 in 370 women, compared with 1 in 645 men). After the age of 40, MM is more common in males (one of 39 men compared with 1 of 58 women) (28). In 2002 the ratio M/F of the MM new cases was 0.97/1, but the rate of death was 1.2 men/1 women. The most common location of MM is the thorax (44%), legs and arms (34%), head and neck (10%) and the acral localization (12%) (Figure 1).

Figure no. 1. The localization of MM depending on the sex (28)



12. Pregnancy

Some researchers believe that MM who appears in pregnancy has a more reserved prognosis. Other researchers believe that pregnancy or hormonal therapies are risk factors for the development of MM (29).

13. Chronic trauma injuries

14. Carcinogenic viral factors

NMSC

A correlation between the oncogenic HPV subtypes and BCC was shown by some authors, while Harwood and Proby showed that HPV can inhibit the UV radiation-induced apoptosis. Furthermore, the percentages of HPV DNA detected in patients with BCC was variable, suggesting that the HPV may play an important role in the development of BCC.

The HPV 6 and 11 have been identified in patients with Busche-Lowenstein disease. HPV 16 was found in patients with ano-genital SCC and finger SCC. HPV 5 and 8 have been identified in transplanted or in epidermodysplasia verruciformis patients. International Agency for Research on Cancer (IARC) from France, concluded that HPV 5 and HPV 8 have a recognized carcinogenic role (30).

MSC

The existing data from the literature about the involvement of HPV in the pathogenesis of MM are contradictory. Some authors identified the HPV in MM but the role of HPV in the appearance of this cancer is unknown.

CONCLUSIONS

The incidence of skin tumors is constantly growing. The skin cancer has an increased aggressive behaviour. The early diagnosis of skin tumors and the knowledge of the involved etiopathogenic factors would allow to decrease the morbidity and the mortality in these cancers.

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