PREVENTION & RESEARCH
Freely available online
ISSN:2240-2594

SUN: FRIEND OR ENEMY?

SOLE: AMICO O NEMICO?

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Citation: Miraglia E, Persechino F, Visconti B, et al. Sun: friend or enemy? Prevent Res 2013; 3 (2): 152-162. Available from: http://www.preventionandresearch.com/

Key words: ultraviolet radiation, photoaging, photoprotection and sunscreens

Parole chiave: radiazione ultravioletta, fotoinvecchiamento, fotoprotezione e filtri solari

Abstract

Exposure to ultraviolet radiation (UVR) is the most significant environmental risk factor for all types of skin cancer.

UVR is defined as the radiation with wavelengths between 100 and 400 nanometers (nm) and is further subdivided into UV-A (315–400nm), UV-B (280–315 nm) and UV-C (100–280nm). The stratospheric ozone layer totally blocks UV-C and UV-B rays with wavelengths below 295nm, whereas 90–95% of the UV-A reach the Earth surface.

A wide variety of skin diseases may arise in UVR-exposed areas and they can be either induced or exacerbated by irradiation from the sun.

Well-known acute clinical effects of UVR in the skin are inflammation (sunburn) and reactive epidermal hyperplasia thickening of stratum corneum and tanning. Chronic changes include photoaging immunosuppression and skin cancer.

Skin tumours are mainly divided into melanoma and non-melanoma skin cancers (NMSCs), the latter including basal cell carcinomas (BCC) and squamous cell carcinomas (SCC). Melanoma is responsible for most of the cancer-related mortalities, and NMSCs are typically described as having a more benign course with locally aggressive features.

Photoprotection is the primary strategy against photoaging, photodermatoses and photocarcinogenesis. Recommended measures include avoiding sun exposure during peak UV periods, wearing sunglasses and protective clothing against ultraviolet radiation penetration and applying appropriate topical sunscreens prior and during exposure.

Today topical sunscreens are divided into two broad categories: organic (formerly designated as chemical) and inorganic (formerly designated as physical) agents. Organic sunscreens act by absorbing the ultraviolet radiation that excites the agent’s electrons from the ground to the excited state.

When returning to a steady state, energy is emitted as warmth or fluorescent radiation. Physical agents are composed of sizable particles (titanium dioxide and zinc oxide) that reflect and scatter ultraviolet and visible radiation from a film of inert metal particles which forms an opaque barrier. The disadvantage of physical sunscreens is that they give the skin a white tinge, which is scarcely accepted cosmetically even because of the irregular tan it can produce. This effect can be avoided with the use of nanoparticles (single particles with a <100nm diameter), which prevent the skin from getting white and pasty upon topical application, while at the same time maintaining the reflective effect and reducing the visibility of the cream.

These measures are necessary in case of a prolonged outdoor activity and particularly important for individuals with light skin phototypes, multiple or atypical nevi or a history of skin cancer. To minimize the deleterious effects of ultraviolet radiation while at the same time obtaining all the beneficial effects that sunlight provides, public education on photoprotective measures should be continually encouraged and developed.

Abstract

L'esposizione ai raggi ultravioletti (UVR) è il principale fattore di rischio ambientale per i tumori della cute.

Gli UVR sono radiazioni con una lunghezza d'onda compresa tra i 100 e i 400 nanometri (nm) e si suddividono in ultravioletti di tipo A (315-400nm), di tipo B (280-315 nm) e di tipo C (100-280nm).

Gli UVC e gli UVB con una lunghezze d'onda inferiore a 295nm vengono bloccati completamente a livello dello strato di ozono mentre il 90-95% degli UVA raggiunge la superficie terrestre.

Gli UVR possono essere la causa di molte alterazioni cutanee a livello delle zone foto-esposte o aggravare patologie già esistenti.

Tali effetti a livello della cute possono essere definiti acuti come l'eritema solare e l'abbronzatura o cronici come il fotoinvecchiamento, l'immunosoppressione e le neoplasie cutanee.

I tumori della cute sono classificati in melanoma e tumori non-melanoma che a loro volta sono suddivisi in carcinomi basocellulari e carcinomi spinocellulari.

Il melanoma è responsabile della maggior parte dei decessi mentre i carcinomi hanno una prognosi migliore perchè caratterizzati da un'aggressività prevalentemente locale.

La fotoprotezione è la strategia principale contro il fotoinvecchiamento, le fotodermatosi e l'insorgenza di neoplasie cutanee.

Le principali raccomandazioni sono evitare l'esposizione solare durante le ore più calde della giornata, indossare indumenti protettivi e occhiali da sole e l'applicazione di filtri solari adeguati prima e durante l'esposizione.

Attualmente i filtri solari per uso topico sono divisi in due grandi categorie: biologici (precedentemente indicati come chimici) ed inorganici (definiti precedentemente come fisici).

I filtri solari biologici agiscono assorbendo i raggi ultravioletti che attivano gli elettroni dallo stato di riposo alla fase di eccitamento. Quando si ritorna alla condizione di stabilità, l'energia viene emessa sotto forma di calore o radiazione fluorescente.

I filtri inorganici, composti da particelle di considerevoli dimensioni quali biossido di titanio e ossido di zinco, costituiscono un film di particelle metalliche inerti che forma una barriera opaca a livello della cute in grado di riflettere e disperdere le radiazioni ultraviolette e visibili. I filtri solari fisici hanno lo svantaggio di essere visibili poiché conferiscono alla cute un colorito biancastro, non sempre accettato dal punto di vista estetico anche a causa di un'abbronzatura non sempre uniforme. Questo fenomeno può essere evitato introducendo delle nanoparticelle (singole particelle con un diametro inferiore a 100 nm) che rendono i filtri trasparenti e la cute non più bianca pur mantenendo l'effetto riflettente.

Queste misure protettive sono necessarie per una prolungata attività all'aperto ed in modo particolare sono importanti per persone con fototipo chiaro, con nevi multipli o atipici o che riferiscano una storia personale e/o familiare di tumori cutanei. Per ridurre al minimo il danno indotto dalle radiazioni ultraviolette ed ottenere tutti i vantaggi possibili dall'esposizione ai raggi solari è opportuno educare la popolazione e promuovere continuamente le principali misure di prevenzione ed in particolare la fotoprotezione.

Ultraviolet Radiation

Exposure to ultraviolet (UV) radiation is the most significant environmental risk factor for all types of skin cancer. Therefore, prevention of skin cancer focuses on limiting UV exposure through sunprotective behaviors.

The action of UV radiation on the skin follows direct absorption of energy by the molecules, in particular nucleic acids and proteins (direct effects) and it is amplified by the presence of fluorescent substances of endogenous (porphyrins) or exogenous (quinine, hydrocarbons) kind, responsible for the so-called photodynamic action (indirect effects). In this case we are in the presence of photosensitizing substances, which absorb radiations with a specific wavelength and re-emit them with a longer wavelength together with the free radicals formed during the reaction.

At a molecular level the absorption of UV radiation is conditioned by the absorption spectrum of the molecules targeted, which depends on their structural characteristics. Therefore, the longer the wavelength the greater the absorption resulting from the compound targeted. Photoreceptors being present on the cell surface transduce the signal through the activation of a transcription factor called NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells) which determines the release of various cytokines.

A prolonged exposure may trigger phenomena leading to benign keratoses and to an increase of melanogenesis in melanocytes. Cells exposure to UV rays with a wavelength between 250 and 300 nm has as its main target nucleic acids and proteins. Living organisms are sensitive to UV radiation because they are devoid of molecules absorbing UV rays (1).

UVR is defined as the radiation with wavelengths between 100 and 400 nanometers (nm) and is further subdivided into UV-A (315–400nm), UV-B (280–315 nm) and UV-C (100–280nm). The stratospheric ozone layer totally blocks UV-C and UV-B rays with wavelengths below 295nm, whereas 90–95% of the UV-A reach the Earth surface.

Depending on wavelength, UV radiation has diverse effects on the skin, and these effects can be immediate (e.g. tanning, sunburn, indoor tanning) or long-term (e.g. photoaging, immunosuppression, photocarcinogenicity).

Radiation is absorbed by melanin that exerts a protective action, as demonstrated by the fact that sunlight sensitivity is increased in case of fairer skin tones.

UVA are divided into short-wave (320–340nm) and long-wave UVA (340–400nm), which are the most important. While exposure to UVA usually remains constant, UVB exposure is more frequent in the summer. UVA effects usually manifest themselves after a long sun exposure, even in small doses. UVA activate enzymes called metalloproteases, which have the function of degrading elastin and collagene, hence resulting into reduced skin elasticity and increased wrinkling.

UVA radiation penetrates skin layers and produces reactive oxygen species resulting in acute and chronic changes. UVA radiation can cause nuclear and mitochondrial DNA damage, gene mutations and skin cancer, dysregulation of enzymatic chain reactions, immunosuppression, lipid peroxidation (membrane damage), and photoallergic and phototoxic effects. Furthermore, UVA rays are responsible for skin aging. Today, the use of UV-A lamps in sun tanning beds is raising growing concern because of the body exposure to artificial sources (2).

Ultraviolet B (UV-B) can also cause erythema (sunburn),changes of pigmentation, skin cancer, and immunosuppression.

Both UVA and UVB radiation can cause sunburn, photoaging reactions, erythema, and inflammation. However, solar UV-B radiation is crucial for vitamin D synthesis because it triggers the transformation of ergosterol in vitamin D, which allows a regular deposition of calcium in the bones. A few studies suggest that vitamin D could reduce the risk of breast, prostate and colorectal cancer (2).

Ultraviolet C (UV-C) is virtually completely screened out by the Earth atmosphere thus representing a negligible source of adverse human health effects.

Immunosuppression

Sun exposure can also cause both local and systemic immunosuppression depending on the area exposed and UV radiation dose. Systemic immunosuppression, such as in organ transplant patients, can lead to an increased risk of skin cancer, as evidenced by the frequent development of non-melanoma skin cancers in patients who have undergone organ transplantation, with reported incidence rates of 21% to 50% (3, 4).

The immunosuppressive and carcinogenic effects of UV light on the skin are complex, involving a variety of cell types, including antigen-presenting cells, lymphocytes, and cytokines. UV radiation can cause dysregulation of antigen-

presenting cells such as Langerhans cells and dermal dendritic cells, which in turn can activate regulatory T cells that suppress the immune system.

UV radiation can also induce keratinocytes to produce immunosuppressive cytokines which inhibit the production of a number of “repair cytokines” that fix UV-induced DNA damage. The repair cytokines can mitigate UV-induced immunosuppression (3, 5). Both UV-A and UV-B interact to enhance UV-induced immunosuppression, and this can occur even at the Minimum Erythematous Dose (6).

Skin Disorders

A wide variety of dermatoses may arise in exposed areas which can be either induced or exacerbated by irradiation from the sun.

Well-known acute clinical effects of UVR on the skin are inflammation (sunburn) and reactive epidermal hyperplasia thickening of stratum corneum and tanning. Chronic changes include photoaging immunosuppression and skin cancer.

The skin has some repair capacity of UVR-induced damage provided UVR exposure is avoided. According to some authors acute effects are reversible, whereas chronic degenerative changes tend to accumulate in the tissue over time.

Tanning

UV exposure can lead in a matter of just a few seconds to the formation of reactive oxygen species which determine photo-oxidation of preexisting melanin thus resulting in immediate pigment darkening which resolves after a few hours, whereas more persistent pigment darkening occurs 2–24 h after UV exposure after redistribution of the photooxidized pre-existing melanin. Skin photoprotection gained from the adaptive formation of new melanin in response to UVB takes place until 3 days after UV exposure.

Sunburns

Excessive exposure to UV radiation leads to sunburn, which is mainly due to UVB. Sunburns are the most common damage to the skin and cause redness and intense burning sensation and sometimes pain, 4-6 h after exposure to the sun. Intense exposure to UV light, intermittent during childhood and adolescence leads to the formation of blisters and burns, increasing the risk for basal cell carcinoma, malignant melanoma, actinic keratosis and squamous cell carcinoma.

Indoor Tanning

In Europe, the sunbed fashion follows a clear South-to-North gradient. The sunbed fashion started in the 1980s in the Nordic countries and extended to Southern countries in the 1990s. Surveys in Europe and North America indicate that between 15% and 35% of women and between 5% and 10% of men - aged 15 to 30 - have used sunbeds (7, 8).

In Sweden, after 1995, 70% of females and 50% of males - aged 18 to 50 - reported sunbed use (9, 10). In the late 1990s, the indoor tanning fashion rapidly extended to Mediterranean areas like the north of Italy (11, 12).

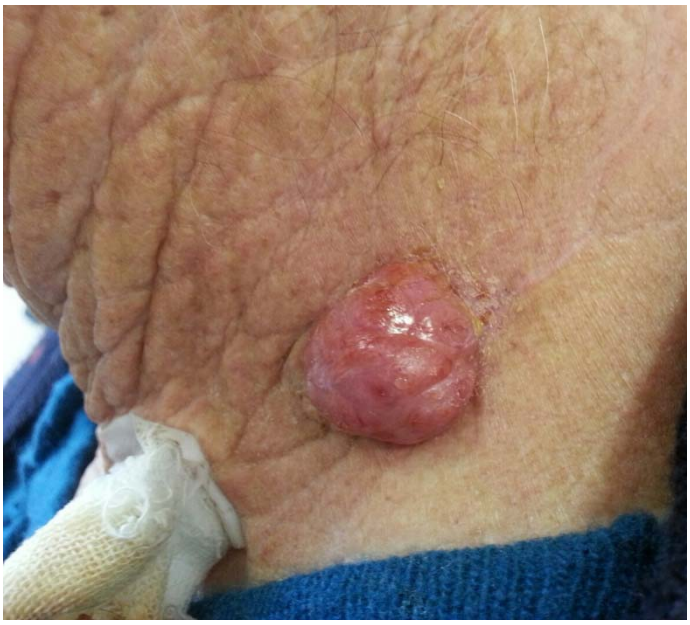
The National Institute of Environmental Health Sciences (NIEHS) warns that solar UVR and exposure to sunlamps and tanning beds are carcinogenic. It has been suggested that artificial UVR may be linked to melanoma development (13). The effects of natural and artificial UV exposure may take 20 or more years to produce skin cancer. In a study, it was estimated that people using artificial UV tanning have a 2–3 fold increased risk of NMSCs (14). A recent study showed that tanning-bed bulbs emit mostly UVA radiation and 5% UVB. In general, young women were more frequent users of tanning beds than men. In addition, there is a positive correlation between tanning bed usage and melanoma.

Actinic Elastosis and Cutis Rhomboidalis Nuchae

Any sunlight-exposed skin shows elastosis histologically. Often there are no distinct clues, but in other cases there may be a yellow tint. Perioral and periorbital wrinkles are early accompanying signs.

The clinical picture of deep furrows in rhomboid pattern on the nape associated with thickened skin and yellow plaques is known also as farmer's neck or sailor's neck (Figure 1). It is less common in women , whose nape is commonly protected by hair.

Figure 1 - *Cutis rhomboidalis nuchae with nodular basal cell carcinoma.*



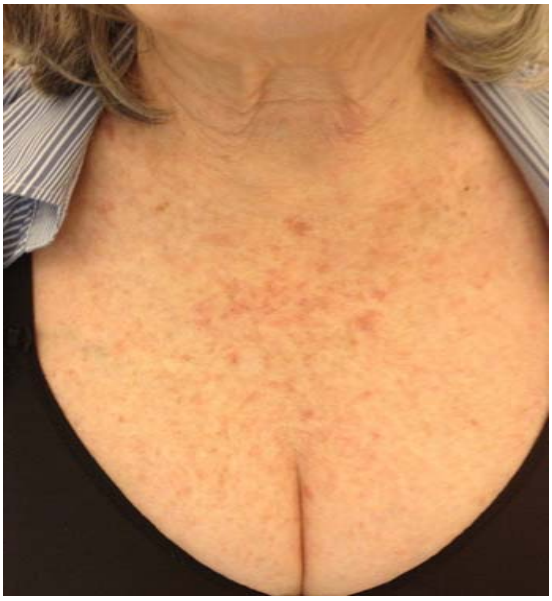
Photoaging

Aging is a continuous mechanism, much less striking in its appearance than photoaging (Figure 2).

Photoaging is a long-term effect of UV exposure and refers to the cumulative, degenerative process of external or premature aging of the skin caused primarily by UVA radiation.

Aged skin shows a slight atrophy of the epidermis, Langerhans cells tend to decrease whereas skin dryness tends to ncrease, resulting in a skin xerosis condition. Elastic fibers tend to decrease in the dermis of aging skin, the capillaries become fragile, collagen metabolism is slower, and there is a progressive lowering in concentration of glycosaminoglycans. Radiations produce the formation of pirimydine dimers. UVB affects mainly cells until the epidermal basal cell layer, whereas UVA penetrates into the dermis. Aging alters gene expression of keratinocytes, whereas photoaging increases inducibility of photooncogenes by ultraviolet light. Damage induced directly by radiation or else by means of free radicals liberates cytokine (15).

Figure 2 – *Photoaging*



Actinic Keratoses (AK)

Actinic keratoses or solar keratoses are intraepithelial skin neoplasms constituted by atypical proliferation of keratinocytes. AKs were previously considered precancerous or premalignant lesions with a potential for evolving into SCCs. In recent years, they have been redefined as malignant neoplasms, since they are squamous cell carcinomas in situ, and thus precursors of invasive squamous cell carcinoma.

They are located on sun-exposed sites, typically the dorsal areas of the hands, the forearms, the face and the scalp. They may be associated with other stigmata of sun-damaged skin, such as telangiectasia, irregular pigmentation, solar elastosis or skin atrophy. There are several clinical subtypes of actinic keratoses, including the erythematous and the hypertrophic one.

The cutaneous horn or cornu cutaneum is considered by some authors a type of hypertrophic AK. They are often asymptomatic, but common signs and symptoms include pruritus, burning or stinging pain, bleeding and crusting (16).

Their presence indicates longterm sun damage and identifies a group of individuals at high risk for developing SCC, BCC and to a lesser extent melanoma (17). Several studies have shown that pain and inflammation are signs of AK progression to SCC. The risk of progression is difficult to assess and varies in the literature from less than 1 to 20% (18). The inability to predict which AKs will persist, regress or proceed to SCCs makes treatment of all AKs indispensable.

Treatment aims to clinically evident lesions but also non-apparent lesions in the cancerization field.

Tumour

Solar radiation is the main risk factor for the major forms of skin cancer. They are mainly divided into melanoma and nonmelanoma skin cancers (NMSCs), the latter including basal and squamous cell carcinomas (BCC and SCC, respectively). Melanoma is responsible for most of the cancer related mortalities, and NMSCs are typically described as having a more benign course with locally aggressive features. Nevertheless, they represent “the most common type” of cancer in humans and they can result in significant disfigurement, leading to adverse physical and psychological consequences for the affected patients. Basal cell carcinoma occurs about four times more frequently than SCC (19, 20).

BCC

Basal cell carcinoma is the most common malignant neoplasm in humans; it accounts for 75% of NMSC cases , whereas squamous cell carcinoma accounts for the remaining majority of NMSC cases. BCC is extremely locally invasive and destructive but only rarely metastasizes (21).

Different types of BCC can be distinguished clinically: nodular (Figure 1), cystic, pigmented, superficial, morphea-like and ulcerative. The nodular and cystic variants are usually found on the face, and are up to 10 mm or more in diameter (22).

The morphoeic type shows scarring and a diffuse edge and is also often found on the face, whereas multicentric superficial tumours, which can extend to several centimetres in diameter, typically occur on the trunk.

Diagnosis is primarily clinical and is completed with histological confirmation. Punch biopsy is the preferred biopsy method; sometimes a shave biopsy is, however, also adequate.

Dermoscopy is used as an aid for diagnosis of BCC, with maple leaf-like structures, blue-ovoid nests, blue-gray globules, spoke-wheel structures, and arborizing blood vessels seen upon examination (23).

Squamous Cell Carcinoma (SCC)

Squamous cell carcinoma has a destructive pattern of growth and it metastasizes. While sporadic BCC develops de novo, SCC arises from precursor lesions of actinic keratosis and Bowen’s disease, and represents a multistep accumulation of genetic damage. Like BCC, it is more commonly found in men than in women.

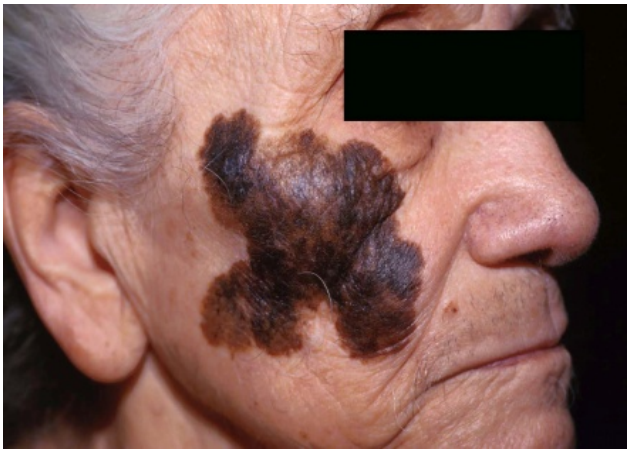
Sex-related differences in exposure to the sun during occupational and leisure activities, in the use of sun protection, and scalp hair are probably reasons for the higher prevalence of NMSC in men (19). Typically, SCC is found in sun-exposed skin such as the head, neck, and back of the hands of elderly individuals. SCC tends to present as a rapidly growing pink or red nodule or plaque, which may be hyperkeratotic or ulcerated. It may also be pigmented, verrucous or appear as a thick cutaneous horn. Progressive tumor invasion results in tenderness and fixation to underlying tissues. Especially in the head and neck region, an enlarged lymph node may indicate tumor metastasis.

Any persistent, enlarging, or non-healing lesion, particularly on a sun-exposed site, must be evaluated histologically.
At an early stage, it is easily cured, usually by surgical removal, but if untreated it may cause local destruction of underlying structures or spread to regional lymph nodes (23).

Lentigo Maligna and Lentigo Maligna Melanoma

Lentigo maligna (LM) is a subtype of melanoma in situ with a prolonged radial growth phase.
If left untreated, LM may evolve into the invasive form of lentigo maligna melanoma (LMM).
LMM is the most common subtype of melanoma on the face; its presentation may be quite subtle, particularly in early stages and delayed diagnosis is common (24).
The most common location is on the chronically sun-exposed face, most commonly cheeks and nose, then neck, scalp and ears.
LM pathogenesis is thought to be associated with cumulative, and not intermittent, sun exposure (25). It presents as a flat, slowly enlarging macular lesion with poorly defined irregular borders, asymmetry and pigment variation, persisting for years on chronically sun-exposed skin of elderly individuals.
LMM is frequently larger than LM and may continue to be macular, although a nodular portion is often seen within the macule as the lesion progresses (Figure 3).

Figure 3 - *Lentigo maligna melanoma of the cheek*

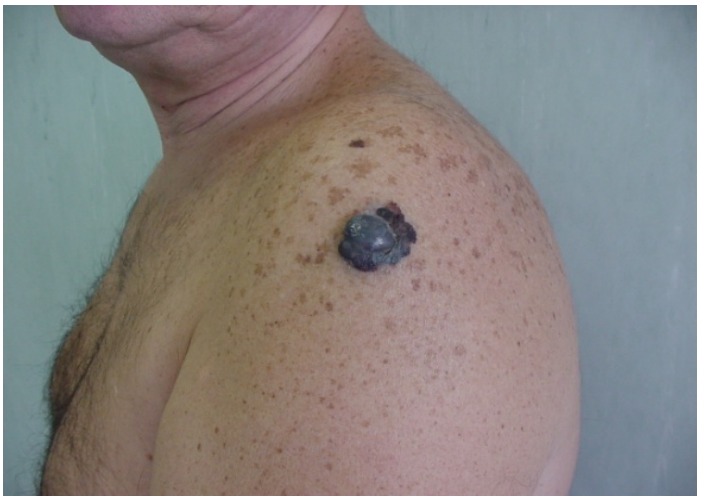


Early clinical detection of LM is imperative, though often very difficult. Differential diagnoses include solar lentigo, early lesions of seborrheic keratosis, lentigo maligna melanoma, lichen planus-like keratosis, pigmented actinic keratosis and melanocytic naevus (26).

Melanoma

While the relationship between UV exposure and basal cell and squamous cell carcinoma is very clear and well documented, the role of UVR in the induction and progression of melanoma remains unclear. The likelihood of an individual developing melanoma is the result of a combination of inherited or predisposition and exposure to environmental factors relevant to tumorigenesis.
It is a malignant skin tumour and appears as a pigmented atypical lesion or with nodular (Figure 4) or ulcerated aspect.

Figure 4 - *Nodular melanoma of the arm*



Melanocytic lesions do not necessarily appear on the most heavily sun-exposed parts of the body, nor do they correlate with occupational or cumulative exposure to sunlight. Nonetheless, it is believed that the major risk for melanoma is skin color and skin reaction to sunlight. It has been shown that fair-skinned people who burn only and never tan after sunlight exposure have a relatively higher incidence of melanoma as pigmentation is inversely correlated with the incidence of cutaneous melanoma (27). A history of childhood sunburn may be sufficient to result in the formation of melanoma in later years (28), while some studies suggest that recreational activity resulting in adult sunburn is associated with melanoma risk (29).

Photoprotection

Photoprotection is the primary strategy against photoaging, photocarcinogenesis and photodermatoses. Recommended measures include avoiding exposure to the sun during hours of peek UV irradiation, wearing protective clothing against ultraviolet radiation penetration and sunglasses and applying an appropriate topical sunscreens prior and during exposure (30). These measures are necessary for prolonged outdoor activity and particularly important for individuals with light skin phototypes, multiple or atypical nevi or a history of skin cancer. In fact UV radiation has been included in the Tenth Report on Carcinogenesis published by the National Institute of Environmental Health Sciences.

Sunlight is vital for us, conferring important health benefits, many of which are mediated by the synthesis of vitamin D however in a skin cancer prevention strategy, behavioral measures (wearing protective clothes and reducing sun exposure to a minimum) play a key role (31).

The best technique for reducing ultraviolet exposure is to avoid sun in the middle of the day, because at the solar zenith the sun's rays have less atmosphere to pass through so less ultraviolet radiation is absorbed (32).

There is evidence that topical sunscreens are able to prevent UV –induced skin damage, reduce the incidence of some skin cancers such as squamous cell carcinoma and attenuate new nevus development (33, 34). Obviously these products must be safe and stable not only for humans but also for the environment. The protective effects of novel sunscreens include direct absorption of photons from both UVA and UVB, inhibition of chronic inflammation, modulation of immunosuppression, induction of apoptosis and antioxidant activity (35).

Today topical sunscreens are divided into two broad categories: organic (formerly designated chemical) and inorganic (formerly designated physical) agents. Organic sunscreens act by absorbing ultraviolet radiation that excites the agent's electrons from the ground to the excited state. When returning to a steady condition, energy is emitted as warmth or fluorescent radiation. The most recently introduced chemical agents in our sunscreens are MEROXYL and TINOSORB filters. Terephthalydene dicamphor sulfonic and drometrizole trisiloxane (Meroxyl SX and XL) absorb UVB and UVA radiation, Tinosorb M and S both absorb and reflect photons (35,36)

Physical agents are composed of sizable particles (titanium dioxide and zinc oxide) that reflect and scatter ultraviolet and visible radiation from a film of inert metal particles which forms an opaque barrier. The disadvantage of physical

sunscreens is that they give the skin a white tinge, which is scarcely accepted cosmetically even because of the irregular tan it can produce. This is avoided by introducing nanoparticles (single particles with a <100nm diameter) which prevent the skin from getting white and pasty upon topical application, while at the same time maintaining the reflective effect and reducing the visibility of the cream (35).

The sun protector factor (SPF) is a widely accepted method of measuring sunscreen efficacy and is defined as the sun radiation dose (mainly UVB) required to induce the minimum erythematous dose (MED; the threshold dose that can produce sunburn) after application of 2 mg/ cm2 of sunscreen divided by the dose producing 1 MED on unprotected skin. An SPF of 2 absorbs 50% of UVB, SPF of 8 can filter out 87.5%, SPF16 93.6%, SPF 32 96.9% and SPF 64 98.4% (30).

The most important factors for effectiveness of the sunscreens are the application of a liberal quantity of sunscreen, followed by the uniformity of application, the SPF and the specific absorption spectrum of the agent used. Application of sunscreens to exposed sites should be done 15–30 minutes before going out into the sun and repeated after swimming followed by toweling, friction with clothing or sand, and sweating. In these cases water resistant or waterproof sunscreens are preferred. Broad-spectrum sunscreens with adequate UVA protection should be used and sunscreens should not be abused in an attempt to increase time in the sun to a maximum.

To reduce the deleterious of ultraviolet radiation to a minimum but at the same time to obtain all the beneficial effects that sunlight provides, public education on photoprotective measures should be promoted continually.

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