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RESEARCH ARTICLE

Advancing New Views on the Causes and Prevention of Skin Cancer and Aging of the Skin

Win L. Chiou, Ph. D.

Independent scholar and former professor at the University of Illinois at Chicago (1971-2005)

*win@chiouconsulting.com

ABSTRACT

The prevailing belief is that sunlight, particularly UV rays, leads to skin damage that accumulates, potentially causing skin cancer and photoaging. Consequently, avoiding or reducing sun exposure is widely advised. This stance, however, challenges the principle of genomic stability, which is essential for the healthy and appearance-preserving progression of generations, potentially except when damage stems from severe sunburn. This leads to the concept of non-cumulative, non-detrimental DNA damage. Such a groundbreaking perspective could profoundly impact research into the causes and prevention of skin cancer and skin aging. Key insights include: the key to prevent skin cancer is to prevent severe sunburn, not chronic moderate sun exposure that could guard against skin cancer; sunscreen is not recommended for intense intermittent sun exposure; long-term regular sun exposure may not lead to wrinkles and sagging; the intrinsic factor dominates skin aging; the UVA blockers in sunscreens might be unnecessary; traditional methods of using bolus UV doses could be problematic; low SPF sunscreens (2-8) might suffice; ultraviolet-protective clothing is advisable; some issues related to tanning salons and tinted glasses are raised; the critical role of water and nutrients is emphasized; effects of wind and heat are considered; and tissue-regenerating moisturizers are recommended for skin protection.

Keywords: skin cancer; skin cancer prevention; skin aging; photoaging; sunscreen; sunburn; stem cells; wrinkles; melanoma; genome homeostasis; DNA lesions and mutation.

Introduction

Over the past century, the prevailing belief[1-3] has been that exposure to non-burning moderate sunlight, particularly its ultraviolet (UV) components, leads to skin damage. This damage is thought to accumulate over time, potentially causing premature skin aging, known as photoaging, and increasing the risk of skin cancer. Consequently, medical professionals and health organizations have recommended that people either reduce or avoid their exposure to sunlight, even on overcast days, or adopt protective measures such as wearing sunscreen, protective clothing, and hats, or seeking shade[1,4]. Despite these widespread advisories, there seems to be a lack of definitive scientific studies that fully endorse this stance. Recently, Chiou[2,3] challenged this traditional view by applying the widely accepted principle of genomic or DNA stability (homeostasis), which is essential for the seamless transfer of health and physical traits through generations[5,6]. Chiou's theoretical analysis suggests that the long-held belief in the harmful effects of non-burning sunlight exposure may indeed be flawed. Building on this foundation, he introduced the concept of "non-cumulative, non-consequential UV-caused DNA damage," and presented new insights into the causes and prevention of skin cancer and skin aging, supported by substantial clinical evidence[2,3]. The primary goal of this article is to offer a brief review of the current understanding in this field, aiming to spark further research and discussion on this topic and its implications for our everyday health.

Genomic Stability Doctrine: Theoretical Considerations

NON-CUMULATIVE, NON-HARMFUL UV DAMAGE: Research indicates that each cell in sunlight-exposed skin can experience up to 70,000 DNA lesions or assaults daily, with 75% originating from internal metabolic reactions and 25% from external sources, predominantly UV radiation[5,6]. To preserve DNA stability, our bodies have developed highly efficient mechanisms to almost immediately repair and eliminate these lesions; in other words, the mutation rate is practically zero[7-9]. The types of damage primarily include cyclobutene pyrimidine dimers (CPDs), pyrimidine (6-4) pyrimidine photoproducts (6-4 PPs), and 8-oxy-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG). The repair mechanisms include the base excision repair pathway, nucleotide excision repair pathway, and apoptosis, and essential all DNA lesions are swiftly repaired or removed leaving little to no trace even after extended daily exposure[2,3,10,11]. This indicates that, in the absence of severe sunburn, exposure to non-burning sunlight or UV rays does not lead to lasting DNA damage. Therefore, these incidents of DNA damage can be described as "non-cumulative, non-harmful UV damages," which are unlikely to cause skin aging or cancer as previously feared in recent decades and over the last century[2,3]. For acral melanoma that is not linked to sunlight exposure and occurs in the nail bed, palms of the hands and soles of the feet, surprisingly, it happens at similar rates in all white and non-white populations and its potential cause remains to be studied[12].

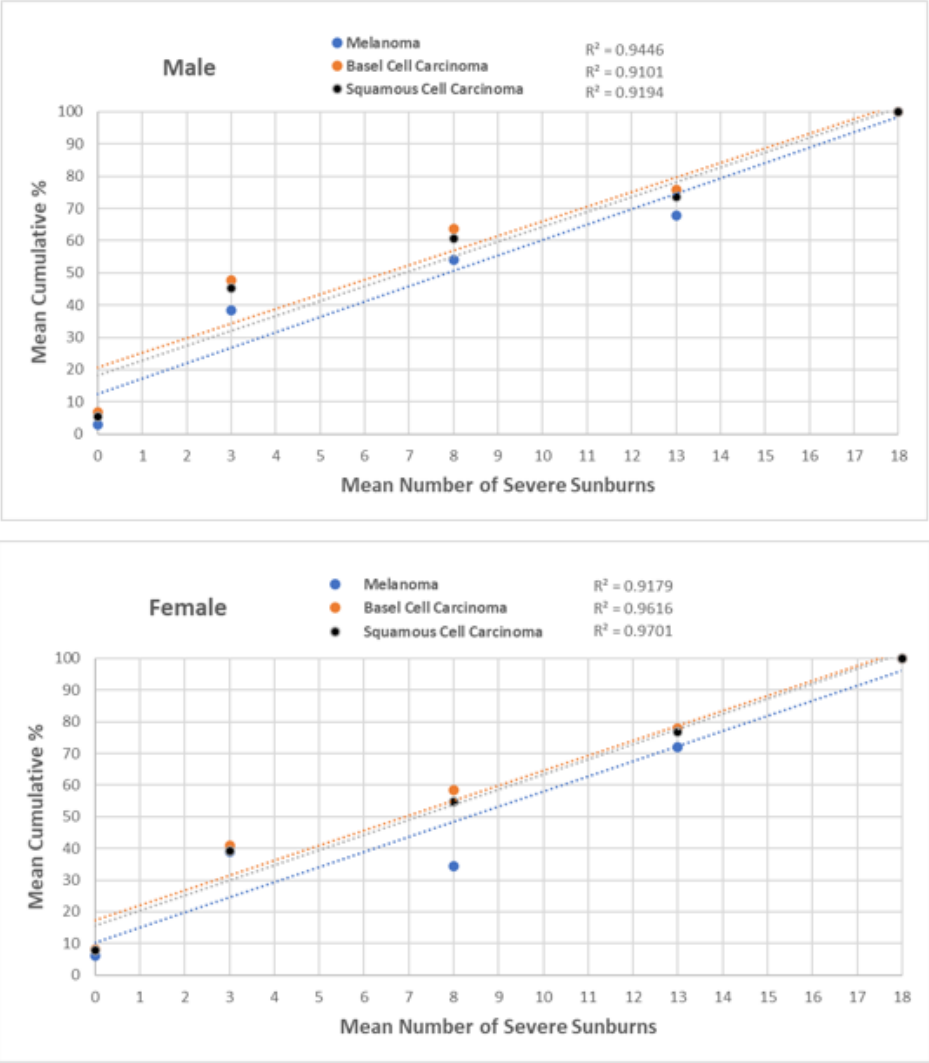
THE LINK BETWEEN STRONG SUNBURN AND SKIN CANCER/AGING: Exposure to intense sunlight or UV rays can inflict a skin cell with up to 100,000 DNA lesions per hour, potentially surpassing the body's repair capabilities[13-15]. Lesions that are not repaired

or eliminated might evolve into precancerous or cancerous tumors after bypassing the body's several defense barriers[13-15]. However, DNA damage from erythema, a mild unburn with skin reddening, is likely to be fully repaired, suggesting that such conditions do not lead to skin cancer or photoaging[2,3]. Intriguingly, erythema often resolves on its own within days, even without intervention[16]. This challenges the traditional view of using erythema as a biomarker of skin cancer[17] and indicates that it likely does not contribute to skin photoaging, with only severe sunburn possibly leading to significant photoaging effects, such as the formation of elastotic materials in the dermis[2,3].

Clinical Evidence Supporting the Genomic Stability Doctrine

THE ROLE OF SEVERE SUNBURN IN SKIN CANCER INITIATION: Reevaluation of data from two extensive prospective cohort studies, involving 120,000 participants with a wide diverse background in skin sensitivity over 28 years in the United States[18], revealed a proportional relationship[2] (Fig. 1) between the occurrence of severe sunburn and the incidence of three major types of skin cancer: cutaneous melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Interestingly, the tree slopes were nearly parallel each other. These findings, suggesting severe sunburn as a common causing factor in these cancers[2], align with a previous meta-analyses linking strong sunlight or severe sunburn to melanoma[19] and eight other studies linking severe sunburn to SCC, alongside Human Papillomavirus infection[2]. Notably, a history of severe sunburn increases cancer risk, yet not all individuals experiencing severe sunburn will develop skin cancer and individuals with 15 or more severe sunburns may not develop any skin cancer indicating the influence of other risk factors in cancer etiology[2,3]. Interestingly, no skin cancer was found in any individuals without severe sunburn[18] further supporting the present genomic stability doctrine. Several other studies linking severe sunburn to SCC or BCC were also reported[2].

Figure 1: Cumulative incidence of cancer as a function of the mean number of severe sunburns for each of 3 cancers in male and female studies (reproduced from Ref 2)



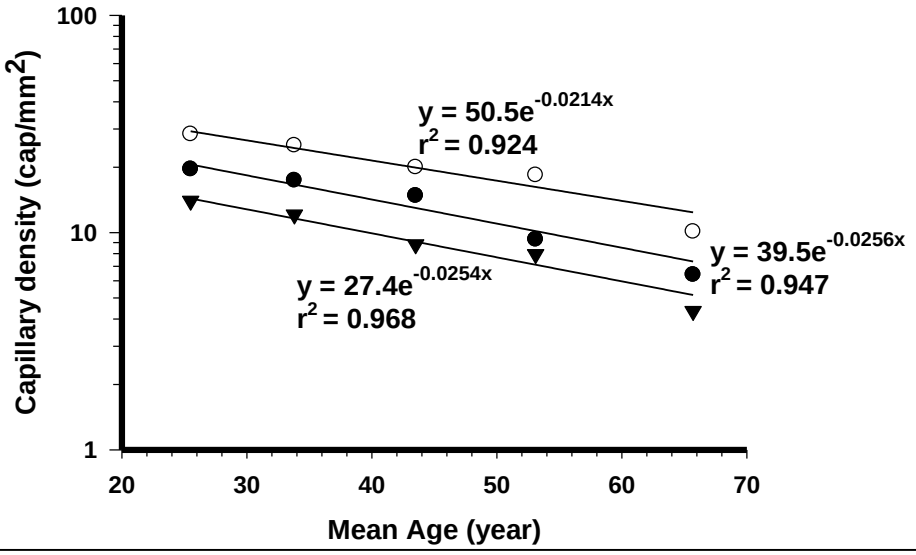
RARE SKIN CANCER IN PEOPLE OF COLOR DESPITE VERY HIGH UV EXPOSURE: Despite residing in tropical or subtropical regions with very intense UV radiation such as UV Index 12 in parts of Africa and Asia, people of color exhibit remarkably low skin cancer rates; indeed skin cancer is regarded as a rare disease[20]. This phenomenon can be partially explained by the natural sun protection afforded by darker and thicker skin, which may act like a sunscreen with an SPF of about 13 for Africans[20], and about 3 to 4 for other populations with darker skin[21]. This means that even under intense UV conditions, the effective UV index experienced by the skin is much lower by about 13- fold for Africans and 3 to 4 times for dark-skinned populations[4], thus reducing their risk of severe sunburn and, consequently, skin cancer. However, their lifetime cumulative UV doses may be tens of thousands of times greater than their minimum erythemal doses[22] defying the classical cumulative-damage concept while being consistent with the present genomic stability doctrine. Interestingly, the sunlight-related skin cancer is also considered as a rare disease for non-white populations in the United States with temperate climate and

similar high lifetime UV fluxes[1] further supporting the genome stability doctrine.

INSIGNIFICANT EFFECT OF NON-BURNING SUNLIGHT ON SKIN AGING AND THE DOMINANT ROLE OF NUTRITION DELIVERY: In a landmark study by Sam Schuster et al. in 1975[23], which involved 154 normal subjects aged between 15 and 93 years, an important finding was observed but has been largely overlooked for decades[1-3,16]. The research showed that the content of collagen in the skin, a crucial protein for skin firmness and texture, was identical in both sun-exposed and sun-protected areas of the studied subjects. This observation[23] suggests that regular exposure to sunlight does not affect the collagen content in the skin of normal individuals, aligning with the genomic stability doctrine's prediction that moderate sunlight exposure does not impact DNA or other skin tissues[2,3]. This finding contrasts with the traditional view that prolonged sunlight exposure accelerates skin aging by promoting collagen degradation and reducing its synthesis, leading to wrinkles and thinner skin[3,16,24,25].

Furthermore, a study[16,26] examining the superficial microcapillary densities in sun-exposed versus sun-protected skin areas in 50 individuals aged 20-74 years supported the lack of significant impact from moderate sun exposure on skin aging as shown by their parallel slopes (Fig. 2). These results, along with other studies reviewed earlier, challenge the conventional belief that extrinsic factors, mainly sunlight exposure, are responsible for 80 to 90% of skin aging in exposed areas[2,16,25]. Instead, these findings suggest that intrinsic factor is the predominant contributor to skin aging[2,16]. It was postulated that reduced cardiac output or reduced delivery of nutrients including water with age is primarily sponsible for the aging of various organs and tissues in the body and the heart serves as the engine of the body with its function decreasing exponentially in normal subjects[16].

Figure 2. Semi-logarithmic plots of mean capillary density versus mean age of five female groups at three sites: volar forearm (✱) representing the non-photo-exposed site; the back of hand (✎) and forehead (▼) representing photo-exposed sites.



Prevention of skin cancer

AVOIDING THE SEVERE SUNBURN: Since severe sunburn may trigger the development of skin cancer, the most important method to prevent skin cancer is obviously to prevent the occurrence of severe sunburn during our life-time[2,3]. Although erythema is only a mild sunburn, it is recommended that consumers should try to avoid getting even erythema from any sun exposure[2,3]. Various risk factors[3] that might affect development of skin cancer and sunburn including genetic traits have been published elsewhere and will not be reviewed here.

ADVOCATING FOR JUDICIOUS SUNLIGHT EXPOSURE: Contrary to the conventional guidance to minimize or avoid sun exposure, Chiou has recently promoted the concept of judicious sunlight exposure as a strategy for skin cancer prevention[2,3]. This stance is supported by evidence suggesting that moderate sun exposure not only lacks direct harmful effects but also confers a variety of health benefits[1-3,27]. For instance, moderate sunlight can enhance skin defenses by thickening the epithelium, boosting melanin production, and strengthening the skin's immunity to DNA damage. This suggests that individuals, particularly those with lighter skin prone to sensitivity, could benefit from controlled, intermittent exposure to sunlight while not incurring severe sunburn such as shown in a British study[28]. Moreover, there is evidence to suggest that sunlight exposure can improve the survival rates for conditions such as melanoma[29] and may reduce the risk of developing other types of cancer, including prostate, colorectal, breast cancer, and non-Hodgkin lymphoma[3,27]. It is emphasized that in the extensive meta-analysis[19] melanoma incidences were found to be inversely proportional to high continuous sun exposure. This may suggest that high continuous sun exposure may be also protective against other types of skin cancer, a new view in cancer prevention.

Beyond cancer prevention, the health advantages of sunlight[27] include the promotion of vitamin D synthesis, reduction in risks of osteoporosis, hypertension, heart attacks, and strokes, as well as the prevention of multiple sclerosis and metabolic syndrome. Sunlight exposure has also been linked to improvements in mood and sleep quality, enhanced immune function and, notably during the Covid-19 pandemic, a potential reduction in infection rates and mortality[1]. Intriguingly, the health risks associated with avoiding sunlight have been compared to the detrimental effects of smoking in terms of their impact on life expectancy[30].

REEVALUATING SUNSCREEN USE DURING INTERMITTENT, INTENSE SUN EXPOSURE: Despite widespread recommendations and increasing use of sunscreen as a protective measure against skin cancer, a paradoxical rise in global skin cancer rates has been observed[1,3]. This trend suggests a critical reassessment of current skin cancer prevention strategies is necessary. Chiou has highlighted a significant issue with sunscreen application, particularly during sporadic, intense sun exposure, where sunscreen may not be applied comprehensively across all exposed skin areas[31]. Studies have found that on average, 20% of exposed skin is left unprotected due to missed applications, especially in hard-to-reach areas such as the

back, neck, and around the eyes and ears[32]. This oversight underscores the need for greater awareness and more effective sun protection measures, as highlighted by studies[33] cautioning that a vacation in the sun often translates to a vacation with sunburn, a warning that seems to have been overlooked by health authorities. Since the missing application can occur with sunscreen having any Sun Protection Factor (SPF) value and with any person, it was proposed that increased use of sunscreen may mainly account for the global increase in skin cancer incidences in recent decades[1-3]. Chiou has recommended not using sunscreen for intense intermittent sun exposure as the most important step for prevention of skin cancer[3].

Considerations Regarding Sunscreen SPF Values and Compositions

SPF VALUES: While current regulations mandate an SPF of 15 or higher, commercially advertised values reaching 100 or beyond have been observed[1]. The designation of SPF 15 was determined without comprehensive modeling studies, either theoretically or experimentally[31], and the original study[34] supporting it was found to have significant experimental flaws[35]. There are suggestions for tailored SPF values based on individual skin sensitivity and usage patterns, with values of 2-4 for non-white individuals and 6-8 for white individuals potentially being adequate[31]. It is noted that a sunscreen with SPF 8 has been found to be effective in preventing melanoma in Australia[36] supporting the pharmacodynamic modelling study[31]. It is of important to note that sunscreen is used regularly in Australia and New Zealand while it is mainly used for intense intermittent sun exposure in countries with temperate climate[1].

SUNSCREEN COMPOSITIONS: Presently, sunscreens must provide protection against both UVA and UVB rays. However, there is a lack of compelling evidence justifying the use of UVA filters in sunscreens[1-3]. Since it is well known that severe sunburn is mainly caused by UVB rays, therefore there seems to have no need to include UVA filters in the sunscreens[1-3].

Ultraviolet Protective Clothing

The use of sun protective clothing has gained popularity as an alternative to sunscreens or physical shelters[37,38]. In theory this approach may be considered as being simple, cost-effective, efficient, and reusable without incurring potential adverse effects of sunscreens to the consumers and the environment.[38] The current regulation requires a Ultraviolet Protection Factor (UPF) of 15 or above for marketing and products with UPF of 50 or higher are available[36,37]. In view of the above discussion this regular standard may need to be modified accordingly. Interestingly, a regular clothing made with natural fabric was found to have a USP of about 4[37] that may be adequate for general use. Theoretically, a clothing with a UPF 2 will reduce a solar UV Index 12 to only 6 on the skin (i.e., Skin UV Index 6[31]) that may be further reduced to 1.5 to 3.0 by the skin of non-white people. Therefore, wearing of most regular clothing may suffice for them[4]. For sunlight with UV Index 6 wearing of such a clothing may also be effective for sun protection in white people since the skin's UV Index is only 3[4]. Wearing clothing may also

minimize water loss from the skin due to sunlight and wind, thereby potentially lessening the skin aging[3]. It should be emphasized that over-protection of the skin from sun exposure may not be always needed as moderate sun exposure may be healthy to the body discussed above. In Singapore where UV Indexes of 10-12 are common in the summer, use of simple inexpensive umbrellas are commonly employed for sun protection.

Tinted Glass Windows

The conventional use of tinted glass to absorb UVA rays for skin protection[39] may need re-evaluation due to the insignificant role of UVA in sunburn and photoaging. Regular glass can absorb most UVB rays, and the need for tinted windows in cars and offices may need to be reconsidered in light of the latest insights.

Tanning Salons

Despite the common use of UVA rays in tanning salons, there is evidence suggesting that UVA could impair the DNA repair capacity for UVB-induced DNA lesions, thus increasing the risk of skin cancer[40]. Also, UVA induced synthesis of the chemical was reported to be ineffective in absorbing UV radiation[41]. Therefore, the preference for simulated sunlight or UVB in tanning salons is recommended over UVA rays[3].

Tissue-Regenerative Moisturizers in Skin Health

Moisturizers containing hyaluronic acid[42], glycerin[43], or propylene glycol[3,43], in addition to moisturizing, offer skin benefits such as increased firmness, smoothness, brightness, and reduced wrinkle depth. Calorie-generating compounds such as propylene glycol[44,45] and glycerin[43] have been shown to promote topical tissue regeneration probably through rejuvenation of their stem/progenitor cells. A 50% aqueous solution of glycerin had an SPF of 2 that protected a non-white person from getting sunburned[31]. Therefore, some moisturizers may also act as sunscreens, helping prevent sunburn and skin cancer, an area deserving further investigation.

Overlooking the Pivotal Role of Water in Molecular Dermatology: Role in stem cell function?

Without a doubt, water ranks as the second most crucial chemical in the body after oxygen, that may influence the rate of body aging[16], life expectancy[16], and probably also the stem cell activity. The emergence of fine lines and wrinkles may be linked to the body's defense mechanism, which aims to reduce the skin's effective surface area and minimize water loss[16]. Age spots may predominantly result from capillary defects, whether congenital or acquired, leading to nutrient or water deficiencies[16]. Interestingly, a striking image featuring unilateral dermatophilosis in a seasoned truck driver (28 years) has been attributed to chronic UVA irradiation through the window[39]. However, the deeply wrinkled skin observed could be primarily caused by the dehydrating effects of sunlight passing through the window, coupled with wind exposure when the window was open for a pleasant breeze[3]. Addressing the issue with an effective moisturizer might suffice for prevention. In this regard, for general daily protection against age spots, dark spots or dyschromia as well as for potential skin-aging reversal, the tissue-regenerative moisturizers may be highly recommended. The common

misconception of hyperallergic property of propylene glycol has been clarified[45].

Given the genomic similarities between plants and humans[46], recent work by Chiou[2] has demonstrated a rapid and complete reversal of withered plants by withholding water and subsequently watering them again (Fig. 3). In this experiment water alone seems to play a decisive role in affecting the texture and function of the leaves. Since stem cell is known to regulate the growth and development of organisms[46], the above experiment may suggest that water could play a vital role in regulating the activity of stem cell and progenitor cell. This line of thinking is consistent with the facts that some moisturizers could have skin-tissue-firming properties discussed above. The potential role of water in the etiology and prevention of skin cancer awaits thorough investigation.

Figure 3. Plant Rejuvenation after water and nutrition

Implications of the Genomic Stability Doctrine in Research Design: Bolus Dose vs. Divided or Constant-Rate Dose

The conventional cumulative-effect concept would assume that a bolus dose, the same divided total dose, or the same total irradiated dose should yield identical biological effects[2,3]. This is, however, inconsistent with the genomic stability doctrine and can lead to misleading results[2,3]. For instance, when a minimum erythemal dose is rapidly applied as a bolus, it might surpass the maximum repair capacity, resulting in observable biological effects, whereas the same bolus dose irradiated over 30-60 minutes may lead to negligible effects[3]. A widely cited study[24] suggesting that exposure to a small bolus dose of UVB rays increases collagen degradation and causes wrinkles may be an artifact due to experimental flaws[3]. This issue is likely quite prevalent in studies on UV or sunlight effects on skin cancer and

photoaging, as briefly summarized earlier[2]. Also, the same total dose administered in 10, 30, 60 or 120 seconds probably as commonly being carried out in laboratories may yield markedly different biological results. This logical question may deserve further experimental validation. In order to simulate the real-world situations, constant irradiation doses used can be calculated based on the simulated intensity of UV Indexes, such as from 1 to 12[4].

Conclusion:

Based on the classical genomic or DNA stability / homeostasis doctrine, Chiou has recently redefined the effect of exposure to sunlight on the health of skin. When sunlight is non-burning, virtually all damages to DNA and other tissue components can be instantly repaired and removed, thus practically resulting in no risks for photoaging and skin cancer in general public. Ironically, such a sun exposure can provide numerous important health benefits including protection against skin cancer. When severe sunburn occurs due to intense sun or UV exposure, the body's defense mechanisms will be overwhelmed that may have a potential to cause skin cancer and photoaging. The above new perspectives may have profound implications in our daily lives as they are drastically different from the current guidelines on how to minimize or avoid sun exposure in order to prevent skin cancer and photoaging. The new perspectives are supported by numerous clinical and epidemiological and molecular studies.

Conflict of Interest:

None

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