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Opinion Article

Perspectives on the FDA's Sunscreen Policy: New Aging Theory, Sunlight Benefits, Enhanced Immunity, COVID-19 Mortality, Modelling Analyses, Melanoma Risks and Etiology

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Abstract

Currently, the U.S. Food and Drug Administration's policy on sunscreens assumes that exposure to sunlight, mainly ultraviolet (UV) rays, damages the skin, the damage is cumulative and any sun exposure should be avoided or minimized. Sunscreens are approved to help prevent early skin aging, sunburn and skin cancer. This work presents provocative perspectives on some issues related to use of sunscreens shown below. Skin aging is predominantly caused by the intrinsic nutritional factor. Sunlight damage is unlikely cumulative due to extremely efficient self-repair/self-defense mechanisms of the body. Regular exposure to moderate non-burning sunlight increases immunity and protects against sunburn, melanoma, COVID-19 mortality, high blood pressure, etc. White and non-white populations may need sun protection only when the UV Index is $\geq$ 5-6 and $\geq$ 7-8, respectively. Modelling analyses suggest that sunscreens with SPF 8 and 2-6 may be adequate for whites and non-whites, respectively. There are inherent risks of sunburn and melanoma when sunscreen is used intermittently mainly due to unavoidable SPF-independent missing applications and may serve as a false security; this may mainly account for exponential increases in melanoma incidences in recent decades; thus, the more intermittent use of sunscreen, the more incidence of sunburn and skin cancer. 10am-2pm sunlight avoidance guidelines may need modification. Extensive human studies suggest that intense UVB from sunburn, not UVA or sub-erythemal UVB, may cause melanoma; this hypothesis is supported by mouse and fish models. Without exposure to burning sunlight, we

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may not need to use broad-spectrum sunscreens or UVB-based sunscreens in our daily lives. Potential implications of this work may be immense in terms of saving lives and improving health of consumers, reducing costs associated with marketing and use of sunscreens, as well as reducing environmental pollution.

Keywords

Food and Drug Administration; Sunscreen Policy; Sunlight Benefits; Aging/Anti-Aging Theory; Enhanced Immunity; Melanoma Incidence/Etiology; COVID-19 Mortality; Sunscreen Modelling; UV Index

Introduction

In the United States broad-spectrum sunscreens with a Sun Protection Factor (SPF) equal to or greater than 15 or 30 are currently marketed as over-the-counter drugs to help prevent early skin aging, sunburn and skin cancer. Their efficacy and safety have been generally regarded as facts [1-3]. It is commonly accepted that exposure to sunlight which has been regarded as a carcinogen damages the skin and the damage is cumulative [1,2,4,5]. Hence, the current FDA's policy recommends zero tolerance toward sunlight exposure. In fact, infants under six months are advised to avoid sun exposure even on cloudy days [1,5]. It also adopts a one-size-fits-all product for every user in terms of SPF [5]. However, it appears that no theoretical or clinical rationale for this policy has been published to date. This is relevant in view of well-known marked differences in skin sensitivity toward sunlight exposure between whites and non-whites [6-8]. In the U.S., the non-whites presently account for about 40% of the population and may become the majority in 2050 [9,10]. Also, until recently no pharmacodynamic modelling studies regarding dosing evaluation have ever been published, although this kind of study has been generally required for new drug development and approval [11]. In this regard, some organic sunscreens were unexpectedly found to be significantly absorbed into the body, triggering the requirement for safety studies [12].

The main goal of this article is to present provocative perspectives on some issues related to the use of sunscreens based on an updated review of the literature with the hope that it may stimulate further discussions and studies. The major topics to be covered are described below under each heading.

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New Alternative Skin Aging/Anti-Aging Theory

Skin aging is caused by the intrinsic chronological factor and the extrinsic factor due to exposure to sunlight and environmental pollutants and possibly smoking [13,14]. Aging due to sunlight exposure, i.e., photo aging, may account for up to 80% or 90% of total skin aging [13,14].

Numerous studies have elegantly demonstrated that UV radiation can simultaneously reduce collagen synthesis and increase collagen degradation thereby resulting in a reduction of skin collagen with age in an accelerated manner [1,2,15-19]. However, this concept seems inconsistent with a widely cited pioneering study in 1975 demonstrating that total collagen contents from skin exposed or not exposed to sunlight in Caucasian whites over a wide range of age were practically the same [20]. Furthermore, the aging kinetics of collagen surprisingly followed a first- order kinetics, i.e., logarithmic linear decline, without showing the expected accelerated aging [21]. Results were similar for the parallel exponential aging kinetics of superficial microvascular density data from sites exposed or not exposed to sunlight in humans [21,22]. These findings suggest that skin aging in ordinary people is predominantly due to the intrinsic factor [21,23].

A new cardiac index/nutrition aging theory was recently proposed to explain the aging kinetics of the whole body and its various organs or tissues [21]. The cardiac index, postulated as a whole body's aging marker, was found unexpectedly for the first time to decrease exponentially with a mean half-life of 82 years based on a re-analysis of previously reported data [21,24]. Obviously, a decreasing cardiac index can result in reduced delivery of nutrients to various organs and tissues including skin through vascular capillaries that are required to maintain their normal function and vitality [25]. Interestingly, this theory is consistent with two recent reports on anti-aging and tissue regeneration:

1. The topical use of propylene glycol, an FDA-approved calorie-generating nutrient, could quickly promote growth of tissues such as hair, nail, skin and gums apparently through the rejuvenation of each tissue's stem/progenitor cells [26]
2. The rejuvenation of hearts in old rodents could quickly produce unexpected systemic effects, reverse the aging process of hearts (including removal of scar tissue and repair of congestion), skin, hair, kidney and muscle and potentially increase the life span of rodents or humans [11,21,27]

Exposure to excessive (UV Index, skin-sensitivity and time-length dependent) sunlight can obviously accelerate intrinsically induced aging symptoms such as age spots, wrinkles and sagging. In this new aging theory, formation of age or dark spots is attributed to born or acquired deficiencies in superficial microcirculation and formation of fine lines and wrinkles may result from a defense mechanism that could reduce the effective skin surface area to

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minimize its water loss [21]. As expected, age spots can also occur in areas usually not exposed to sunlight such as thighs and trunks and increase in number and size with age [21]. Based on the conventional aging theory, facial wrinkles and age spots are formed from exposure to sunlight. However, this theory does not seem statistically reasonable because the whole face, not an isolated area, is virtually uniformly exposed to sunlight all the time [21].

Benefits of Non-Burning Sunlight: Enhanced Immunity and Reduction of Sunburn, Melanoma and Mortality from COVID-19

This subject has been well reviewed and only a few points will be highlighted. Although exposure to intense or burning sunlight is well known to be immunosuppressive, moderate sunlight may increase immune function and this may be partly related to enhanced synthesis of vitamin D, which has numerous potential health benefits [28-36]. Sunlight can increase production or release of nitric oxide that may dilate blood vessels, increase blood flow to tissues and enhance immunity, as well as to reduce blood pressure, heart attack and stroke; nitric oxide can be induced by solar UVA and UVB rays [29-32,37,38]. It was stated that the risk of sunlight avoidance is equivalent to smoking in reducing life expectancy [39]. Obviously, chronic exposure to wind or heat of any sources which can increase loss of water from the skin may also enhance the aging process.

Instead of causing sunburn and skin cancer as expected from the current policy, regular exposure to non-burning sunlight may ironically be protective against sunburn and melanoma. For example, outdoor professional workers had less incidences of melanoma than indoor workers in countries with a temperate climate [29-32,40]. In the state of Washington, regular exposure to sunlight was protective against melanoma in children with sun-tanned skin [41]. In Germany, outdoor activities in the absence of sunburn during childhood were protective against melanoma [42]. In a British study, spending weekends sunbathing at a beach (UV Index < 6 or 7) without wearing sunscreen was protective against melanoma [43]. Surprisingly, melanoma incidences were inversely proportional to a high continuous pattern of sun exposure from a meta-analysis [44]. The protection of non-burning sunlight against sunburn may be primarily attributed to increased melanin secretion that serves as a natural sunscreen; protection against melanoma may be attributed to reduced sunburn incidence and enhanced immunity or repair mechanism against DNA mutation. Interestingly, sunlight exposure could also increase the survival rate in melanoma patients [29,31,45].

Apparently after realizing the potential benefits of sunlight, Australia in 2014 and New Zealand in 2019 started adopting the World Health Organization guidance recommending their residents to enjoy sunshine when the UV Index is below 3 and to seek sun protection only when the UV Index is ≥ 3 [5,46-48]. These two countries are known to have the highest melanoma

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incidences in the world. In view of the above, in the U. S. we may need sun protection only when the UV Index is ≥ 5 or 6 for whites and ≥ 7 or 8 (even 9 for short periods) for non-whites [5].

During the current COVID-19 pandemic, the potential role of sun exposure has received much attention. For example, in a study involving 88 countries their mortality rates were positively correlated with their distance from the equator [49]. In Iceland (mean peak UV Index being about 1.5) and Singapore (mean peak UV Index being about 11.8) where both countries had similar populations with similar GDPs per person in 2019 (about 67,000 vs 66,000 USD) and similar infected cases as of May 1, 2020, the mortality rate in Iceland was, however, surprisingly 79 times higher compared to Singapore [49]. In another study, the COVID-19 mortality rates in continental metropolitan France were negatively correlated with their average annual sunlight hours [50]. In the U.S., the mortality rates of various states were also generally higher with higher latitudes [51]. Despite the limitation of potential numerous confounding factors, the above examples, especially between Singapore and Iceland, seem to strongly support the role of sunlight in increasing the immunity which can suppress and kill the COVID-19 virus. Furthermore, a preliminary review showed that globally COVID-19 fatality rates paralleled vitamin D deficiency rates which may also be related to sun exposure [52]. Hence, non-burning sunlight exposure and blood measurements and oral supplements of vitamin D may be considered as part of a defence strategy against COVID-19.

In various states in the U.S., COVID-19 mortality rates were zero or negligible in young people under age 16-20 [53]. This interesting phenomenon is generally consistent with their highest cardiac indexes and highest immune function compared to other age groups [21,54].

Skin Cancer: A Rare Disease in Non-Whites

Skin cancer has been conveyed to the public as the most commonly occurring cancer in the U.S. However, this can only be applied to light-skinned Caucasians [6,7]. For non-whites such as blacks, Hispanics and Asians in the U.S. and many other countries, skin cancer is a rare disease and generally has no correlation with sun exposure [6,7,55,56]. Interestingly, their melanomas often occur at sites usually not exposed to sunlight such as the soles of feet, palms of hands, beneath toenails, groin areas and oral gums [6,7,55,56]. Early detection is emphasized for successful treatment whereas late detection is often associated with higher morbidity and mortality (6,7,55,56). Therefore, one may need to have a different health message for different constituents.

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Cumulative Damage vs Extremely Efficient Self-Repair and Self-Defence Mechanisms: Implications

Skin damage due to sunlight may not cumulate [5,21]. For example, erythema may heal itself in days and a more serious blistering sunburn may be healed with minimum intervention within weeks [5,21,57]. Generally, mutation damage to DNA can be virtually completely repaired or removed through apoptosis within weeks or months and normal cells and mutated cells in our body are constantly maintained in a homeostatic state [5,32,58,59]. Therefore, our body has extremely efficient self-defense and self-repair mechanisms that may account for insignificant adverse effects of sunlight exposure on skin aging as discussed above and for the age-independent incidences of sunburn, basal cell carcinoma, squamous cell carcinoma and melanoma [5,21,29].

Interestingly, it has been stated that melanoma is a rare disease because only a very tiny fraction of mutant DNAs could escape the repair mechanism and develop into melanoma [44]. This tiny fraction may represent some of those mutant DNAs induced probably only by the intense UVB from sunburn, not from the non-burning UVA or UVB as commonly assumed (more discussion below). Thus, there may exist a critical level of DNA damage that is needed for developing into melanoma.

Peak Noon Hours Concept and UV Index Monitoring

Presently, the public is advised to avoid sun exposure between 10 am and 2 pm due to peak sunlight intensity (1, 2). Such a recommendation may need to be revised. This is because the peak UV Index may vary greatly with the location and time of year. For example, in winter and early spring most of the U.S. has a UV Index below 3 to 5, thus there may be no need to seek sun protection for most of us. In fall and late spring most UV Indexes are probably below 6 to 7, thus there may be no need to exercise this precaution for non-whites. It seems that the importance and regular monitoring of UV Index should be properly conveyed to our general public.

Pharmacodynamics modelling: New Efficacy Evaluation and SPF Recommendations

A new Skin UV Index (SUI) was introduced recently [11]. It refers to sunlight heat intensity on the skin in terms of UV Index after sunscreen application. It was estimated that SUIs were all below 3 when sunscreens with an SPF ranging from 4 to 100 were applied according to the

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label instruction. i.e., 2 mg/cm^2 and the UV Index was 10 [11]. This suggests that for Caucasian white's use of these sunscreens may be effective against sunburn and melanoma and any reported inefficacies of sunscreens may be mainly attributed to various degrees of non-compliance with the label instruction [11]. SUIs were also estimated when only 50% and 25% of labelled amounts were applied as they may often occur in the real world [11]. The present modelling analysis may thus provide a novel rationale as to why regular use of an SPF 8 sunscreen was effective against melanoma in Australia [60]. It was suggested that in the U.S., SPF 8 sunscreen may be adequate for whites and SPF 2-6 sunscreens may be sufficient for non-whites [11]. The above findings seem important in view of recent discussions on the use of sunscreens with SPFs higher than 50 or 100 for achieving greater efficacy [1,11,61-64].

It is noteworthy that the well-known pivotal study of AC Green, et al., in 2011 that has been universally used as a gold standard for setting the current minimum SPF 15 requirement has been reported to have serious shortcomings in the study design, data interpretation and application [3,11]. Therefore, the justification of its use as a regulatory supporting evidence is now in doubt [3,11].

Risks of Sunburn and Melanoma from Sunscreen

In recent decades, there has been an exponential increase in melanoma incidences in many countries [65]. An intriguing question arises as to whether increased use of sunscreen has played a role and this issue has been extensively reviewed [11]. Because in the U.S., sunscreens have been primarily used intermittently for sunbathing at beaches or vacation at high-altitude snow resorts under intense sunlight, an unavoidable, SPF-independent missing application of sunscreen on the body may result in sunburn on these areas that may later develop into melanoma [11]. Conceivably, missing application may most often occur on the trunk of the body or lower legs. Therefore, it is not surprising that melanoma has been indeed found to occur most often in these two areas [57,66]. It is noteworthy that after one week of sun vacation and wearing a broad-spectrum SPF 30 sunscreen at a beach in Spain, all 25 Danish vacationers were found to experience sunburn [67]. The author of this study referred to such a sun vacation as a sunburn vacation. It is important to emphasize that even 1% or 0.1 % of missing application may result in that missed area to develop into sunburn. The missed areas may also include face, neck, eyelids, ears and lips. It was hypothesized that the increasing use of sunscreen may primarily account for the reported exponential increase in melanoma in many Western countries over the last few decades mainly due to their intermittent use [11,65]. Thus, the use of sunscreen can protect or harm the skin. The potential risks of sunburn and melanoma or perhaps other skin cancers from use of sunscreen during intermittent exposure may probably need to be reflected on product labels [11].

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Alternative Hypothesis on Etiology of Melanoma in Caucasian Whites: Implications

Solar UV rays reaching the Earth's surface contain UVA and UVB [1,2]. The UVA is much more abundant and can penetrate deeper into the skin than UVB to cause more damage to DNA, collagen, etc. [1,2,32,66,68,69]. In the last two decades, the major cause of skin aging and melanoma has been largely or predominantly attributed to UVA radiation [1,2,32,66,68,69]. As discussed above, regular exposure to non-burning sunlight may not have a significant adverse effect on skin aging. Could this kind of phenomenon also occur in the etiology of skin cancers, especially melanoma? A review of literature suggests that this may also occur as discussed below.

Since chronic exposure to non-burning sunlight has been repeatedly shown to be protective against melanoma, therefore, it seems unlikely that the non-burning solar UVA or UVB may cause melanoma [5,29-31,40-44]. Because sunburn is a biomarker for melanoma (70) and five or more serious sunburns in a lifetime could double the melanoma risk and an increased risk of melanoma with increasing number of sunburns was observed during all life periods, hence, the UVB-dominated burning solar ray may be hypothesized to predominantly cause the melanoma in humans [71,72]. This is consistent with the above discussion that use of sunscreens may account for increasing incidences of melanoma in recent decades due to intermittent exposure [11]. Also, melanoma incidences were reported to be proportional to incidences of intermittent high-UV-intensity sun exposures [44]. Thus, the above discussion suggests that there may exist a critical level of DNA damage that is needed for it to develop into melanoma. Obviously damage from severe sunburn may be more critical than the simple superficial erythema [66]. The present hypothesis seems to be supported by animal studies. For example, only the erythemal dose of UVB, not UVA or repeated sub-erythemal UVB doses, could induce melanoma in mice and only the erythemal dose of UVB could induce melanoma development in neonatal mice [73,74]. Results from two other mouse studies also seem to support the present theory [75,76]. Furthermore, only UVB, not UVA, could induce melanoma in a fish model [66,75-77].

The above discussion suggests that for the general public we may need to reconsider the need of using broad-spectrum sunscreens or even traditional UVB-based sunscreens for protecting us from photo aging and melanoma or perhaps also other types of skin cancers in our daily lives. We may need to emphasize that the best way to prevent skin cancer is to prevent sunburn by avoiding exposure to excessive burning sunlight, by seeking shade or by wearing protective clothing and hats [1,2,5,40]. Although visible and infrared light wavelengths can generate 50% of all free radicals in the skin and cause similar collagen damage, there may be no need to protect against them [78]. Interestingly, moisturizers containing hyaluronic acid, glycerin or

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propylene glycol have unique anti-skin-aging properties, a 50% glycerin solution was tested to have an SPF 2 and used to protect against sunburn [11,79-81-83].

Concluding Statements: Implications

Obviously, the potential implications of the above perspectives, if implemented, may be quite immense in terms of saving lives and treatment costs of patients suffering from skin cancer due to their intermittent use of sunscreens, savings of costs associated with the use and marketing of sunscreens, reduction of environmental pollutions from sunscreens and improvements in mental and physical health, as well as in life expectancy of people from regular exposure to moderate non-burning sunlight [32]. Clearly, unnecessary use of sunscreen in our daily lives may deprive us from the potential benefits of sunlight [21]. It is my view that if needed, inorganic sunscreens such as zinc oxide and titanium dioxide should be our preferred choices because of their non-absorbability and inertness and use of organic sunscreens should be strongly discouraged mainly because of their potential long-term adverse effects on users and the environment [1,12,82,83].

Conflict of Interest

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