



Open Access

Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models

Win L Chiou^{1*}

¹Chiou Consulting Inc, 8552 Johnston Road, Burr Ridge, Illinois, 60527, USA

***Corresponding Author:** Win L Chiou, PhD, Chiou Consulting Inc, 8552 Johnston Road, Burr Ridge, Illinois, 60527, USA; E-mail: win@chiouconsulting.com

Received Date: 12-04-2022; **Accepted Date:** 24-04-2022; **Published Date:** 02-05-2022

Copyright © 2022 by Chiou WL. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Based on analysis of published data of incidence of melanoma, basal cell carcinoma and squamous cell carcinoma from 2 large prospective cohort studies involving about 120,000 health workers in USA, excellent linear relationships between skin cancer incidence and Severe Sunburn (SS) incidence suggesting their causal association were found. It is postulated that the SS-caused UV radiation overwhelms the skin cell's capacity to repair/remove DNA lesions (about 70,000 non-cumulative lesions per day) and any of these un-repaired/un-removed lesions can eventually become a pre-cancerous tumor or cancer after overcoming numerous barriers of body's repair/defense mechanisms. The above rationale for cancer etiology seems consistent with the classical wound-to-tumor doctrine. Infection with Human Papillomavirus will reduce the threshold for non-cumulative DNA lesions thereby facilitating cancer initiation. The proposed SS theory may be generally applicable to people with different races, skin types, hair colors and sunlight exposures. The proposed non-cumulative UV damage concept is supported by published data showing parallel first-order aging kinetics of human skin being exposed and un-exposed to sunlight in ordinary people. Solar UVA only plays a minor or insignificant role in skin cancer and premature aging. Prevalence of SS is reviewed. Controversies on skin cancer risks for indoor and outdoor workers such as airplane pilots and crew, health workers, gardeners and truck drivers are discussed. Potential shortcomings of a common practice of using highly unphysiological UV, UVA or UVB doses in animal, cell

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

culture or human skin studies are discussed. Demonstration resembling the reversibility of intrinsic skin aging using a plant deprived of and then replenished with water is presented. It is hoped that this apparently provocative work may stimulate further discussions in the literature.

Keywords

Sunburn; Skin Cancer Etiology; Melanoma: Ultraviolet Rays; Human Papillomavirus: Risk Factors for Skin Cancer; Sunlight Benefits; Sunscreen: Food and Drug Administration; Aging /Antiaging Theories

Introduction

It was recently reported by Chiou that Severe Sunburn (SS) might be an overwhelming risk factor for the three most common skin cancers, namely, melanoma, Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) in both males and females with predominantly fair skin in two well-executed large prospective cohort studies involving about 120,000 subjects in the United States [1,2]. This is because virtually all of their occurrences (1065 cases for melanoma, 16,546 cases for BCC and 2,164 cases for SCC) were associated with their prior SS incidences during childhood and adolescence [1]. It was postulated that SS might even serve as a general prerequisite for these cancers to develop [1]. The above suggestions/hypotheses are different from a recent study, suggesting that there is no role of sunburn in skin cancer, no role of ultraviolet (UV) B rays in the melanoma development and melanoma is mainly caused by Human Papillomavirus (HPV)-mediated UVA radiation and BCC and SCC are caused mainly by HPV-mediated (non-burning) UV radiation [3]. They are also different from the main-stream views in the last one or two decades that chronic or cumulative sun exposure is generally more important for incidences of BCC and SCC [1,3-6]. Also, compared with UVB, the weaker UVA has been commonly considered to play a much more dominant role in cancer development. This is because the solar UVA is much more abundant (95% or more) and can penetrate more deeply into the skin tissue, namely, dermis, while UVB can only penetrate the top epithelium [7,8]. The main purposes of this work are to expand on the last study to provide additional evidence to support the hypothesis that SS is the trigger initiating cancer development, to provide a new molecular insight on the SS theory and to comment on some issues related to skin cancer incidence and etiology [1]. These issues include additional skin cancer studies involving or not involving Human Papillomavirus (HPV), prevalence of SS, animal and cell models used to support the human studies, cancer risks of indoor and outdoor workers, as well as the role of UVA and HPV. Application of the present non-cumulative DNA

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

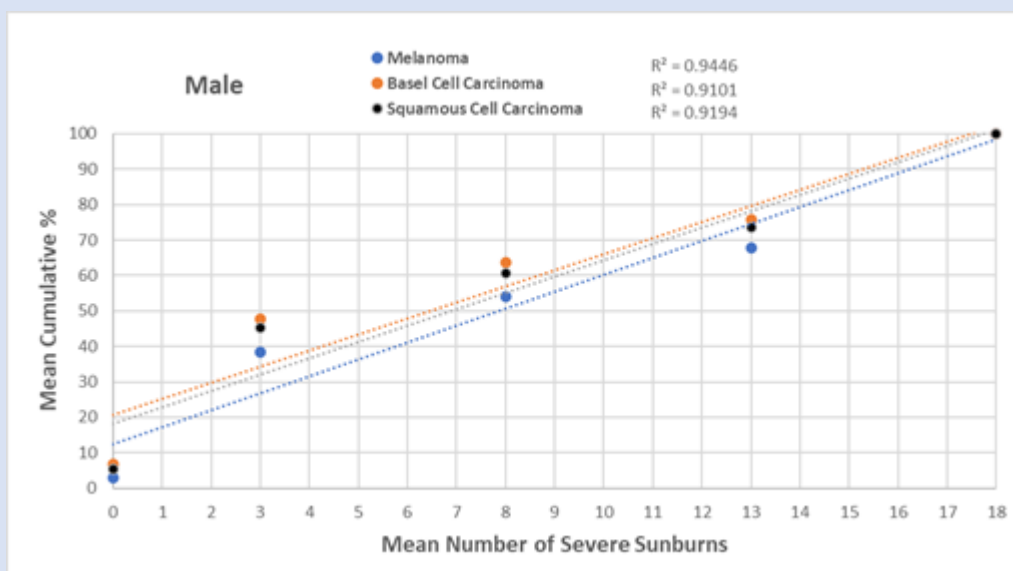
Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

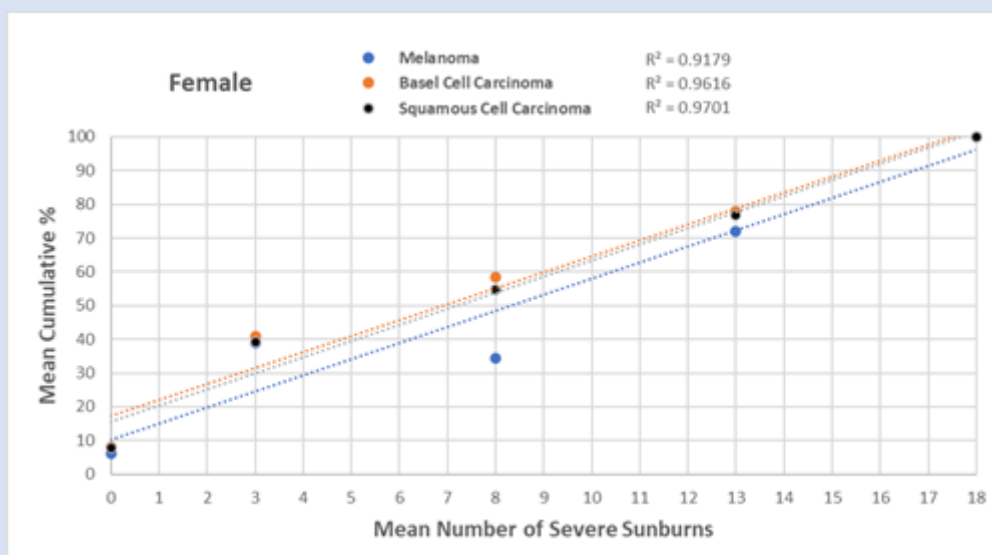
lesion concept to skin aging theory and a demonstration resembling reversibility of intrinsic skin aging using a plant deprived of and then replenished with water are presented.

Linear relationship between skin cancer incidence and SS incidence

Based on the reported data, the relationship between percent of cumulative incidence of each cancer in both men and women and the number of mean SS incurred is shown in Fig. 1 [1,2]. The correlations are all very strong with correlation coefficients being all > 0.95 . Statistically speaking, this kind of relationship indicates a causative relationship, i.e., SS is the common cause for all 3 cancers [3,9]. Furthermore, their 3 regression lines are virtually all parallel each other and this may further suggest that their underlining key-step etiologies may be virtually identical except occurring at different depths from the skin surface. In the present analysis the number of mean SS incurred for SSs = or > 16 is assumed to be 18. This is justified because use of 17 or 19 all results in similar correlations.



	Mean # of Severe Sunburns				
Cancer (Male)	0	3	8	13	18
Melanoma	2.8	38.3	54.2	67.8	100
Basal Cell Carcinoma	6.9	47.7	63.6	75.8	100
Squamous Cell Carcinoma	5.3	45.4	60.7	73.6	100

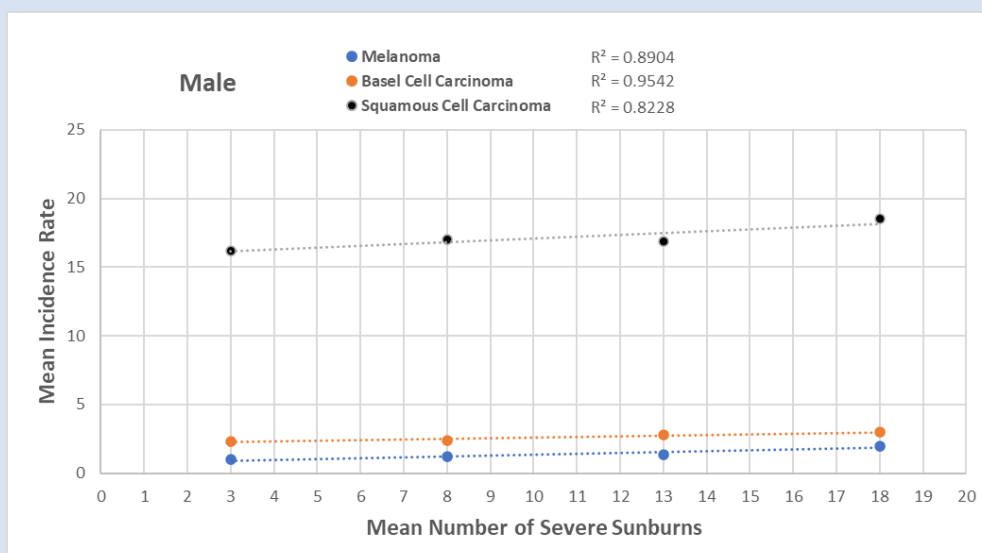


	Mean # of Severe Sunburns				
Cancer (Female)	0	3	8	13	18
Melanoma	6.1	38.8	34.3	72.1	100
Basal Cell Carcinoma	8.1	40.9	58.3	78	100
Squamous Cell Carcinoma	7.8	39.1	54.8	76.9	100

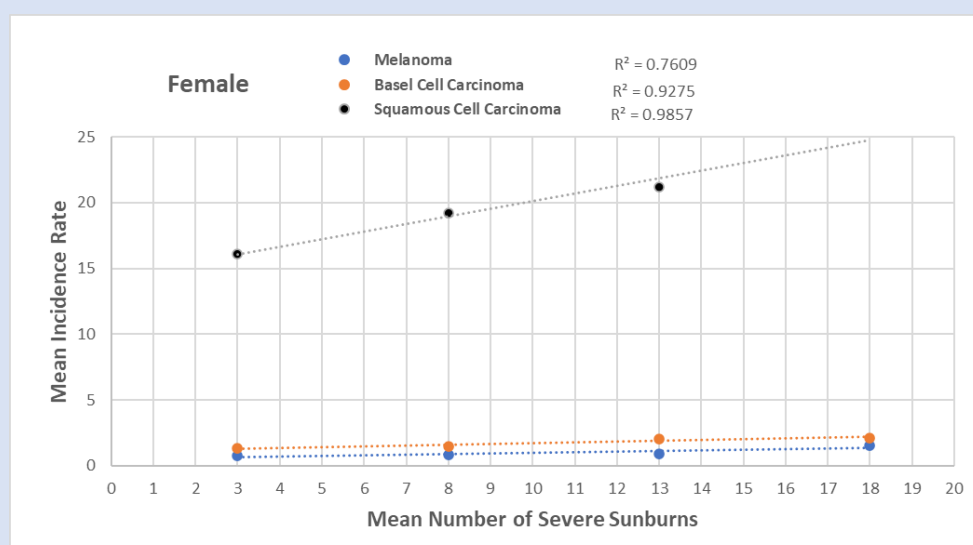
Figure 1: Male and Female Cumulative incidence of cancer as a function of the mean number of severe sunburns for each of 3 cancers in male and female studies based on data reported in ref. 1 and ref. 2.

Linear relationship between mean cancer incidence rate and mean SS number

Based on the reported data, the relationships between mean incidence rate of each cancer and mean number of SS incurred for both men and women are shown in Fig. 2 [1,2]. Again, the correlation coefficients are generally very high also indicating a causative relationship.



	Mean # of Severe Sunburns			
Cancer (Male)	3	8	13	18
Melanoma	1	1.2	1.35	1.97
Basal Cell Carcinoma	2.3	2.4	2.8	3
Squamous Cell Carcinoma	16.2	17	16.9	18.5



Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

	Mean # of Severe Sunburns			
Cancer (Female)	3	8	13	18
Melanoma	0.77	0.82	0.92	1.53
Basal Cell Carcinoma	1.31	1.46	2.02	2.14
Squamous Cell Carcinoma	16.1	19.2	21.2	25.1

Figure 2: Male and Female Mean incidence rate in % of 3 skin cancers with different mean number of severe sunburns in male and female studies based on data reported in ref. 2.

Support of the SS theory from other human studies: HPV-mediated skin cancers

The present SS theory for melanoma is consistent with results from previous extensive meta-analyses showing a proportional relationship between incidences of intensive intermittent sun exposure or sunburn and the incidence of melanoma [9,10]. It is consistent with studies showing positive association (not linear association) of blistering or painful sunburn with melanoma, BCC and SCC [4,11]. Positive associations of SS with BCC and/or SCC have also been reported [12-15].

It is now well recognized that HPVs may be involved in skin cancer initiation by reducing the host's repair mechanisms and act as a facilitator or cofactor with UV irradiation in a hit-and-run manner [3,16-18]. A review of the literature clearly indicates that sunburn or perhaps SS was predominantly associated with the HPV-mediated SCC [19-27]. These studies are consistent with the classical wound-related tumor theory that tumor is a wound that does not heal [16,28]. Although the nature of UV irradiation was not explicitly mentioned in an extensive review, it apparently referred to wounds like blistering or swollen sunburn that is consistent with the present SS theory [16]. It is to be noted that to date case reports regarding HPV-mediated melanoma or BCC incidents appear very limited and its potential clinical significance may remain to be explored [29]. The above UV-wound concept has been proven in mouse models and use of UVA rays alone could not induce papillomatosis in mice [16,30]. Although the participants in these 2 nation-wide cohort studies were largely fair-skinned whites, there were also some non-white participants (probably about 20%) [2]. Thus, the proposed SS theory may be applicable to general populations with different skin types, races, latitudes, hair colors, eye colors, health status, social behaviors and UV fluxes. Obviously, it cannot be applied to acral melanoma. It is well known that Caucasian whites living in Australia with UV Index of 10-14 in the summer and in Norway with UV Index of only up to 5 in their summer (per Google search) have very high incidences of skin cancers. Asians living in Singapore where UV Index peak is about 11 in summer have very low incidence of skin cancers. The above cancer data may be simply related to their SS data.

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

Prevalence of SS

Studies on the prevalence of SS in the general population appear quite limited. A very preliminary literature search revealed 4 interesting reports. It was reported that in Western Australia there were 321 kids admitted to hospitals for serious sunburn treatment in 2021 and this number was almost double than that 6 years ago [31]. A 2003 survey of 56 sunburned beachgoers in Galveston, Texas, USA showed that 68% of respondents had painful or blistering sunburn and the resulting loss of work and treatment might cost more than \$10 million [32]. A 2017 report showed that in Florida, USA 37% of its population had red or painful sunburn in the last 12 months [33]. In a national survey in USA, incidences of sunburns and sunscreen use were found to increase by 30.5% and 51% between 1986 and 1996, respectively [34]. As discussed above, numerous studies related to HPV-mediated SCC incidences were also associated with SS or sunburn injury.

Use of sunscreen during intense intermittent sun exposure has been postulated as a major reason for causing exponential increase of sunburn (including SS) and skin cancer in the last few decades worldwide [6]. Virtually unavoidable missing application of sunscreen has been postulated as the major culprit [35]. In this regard there were 2 studies showing all vacationers at subtropical beaches in Spain developed sunburn although they all used broad-spectrum sunscreens [36,37]. In an elegant study a mean 20% of simulated sun-exposed skin from subjects wearing a sunbathing suit was found to have missed the application [38]. Until recently, it has been commonly accepted that “sunburn is a “sunburn” no matter whether it is very mild or very severe and they are all regarded as a biomarker for skin cancer (per DM Holman) [1,6,39]. Because of this, it is not surprising to have large discrepancy on sunburn data reported from different studies for the same population. Such a view may need to be modified in future studies.

Non-cumulative, non-burning solar-light damage vs overwhelming solar-light damage: Role of SS as a cancer trigger

It has been estimated that each person has about 13 trillion cells in the body and each sun-exposed cell is subjected to 70,000 DNA lesions or damages per day and about 75% of the lesions are caused by the intrinsic metabolic factor and about 25% by extrinsic (mainly solar rays) factor [41,42]. Interestingly, strong sunlight can induce about 100,000 DNA lesions per exposed cell per hour [41]. The lesion products include cyclobutene pyrimidine-dimer (CPD), pyrimidine (6-4) pyrimidine photoproducts (6-4 PPs) and 8-oxy-7,8-dihydro-2-deoxyguanosine (8-oxo-dG). Most of the DNA lesions are rapidly repaired or removed in hours or few days by our body's extremely efficient repair mechanisms such as base excision pathway, nucleotide excision pathway and apoptosis, it seems unimaginable how these instantaneous reactions proceed molecularly! [5,40-44]. However, when the repair capacity is

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

overwhelmed, each un-repaired lesion has a potential to become a mutagen that has a potential to eventually develop into a pre-cancerous tumor or a cancer after overcoming many other hurdles [40-42]. Since most people do not develop skin tumor or cancer in their lifetime, one may then conclude that these virtually unlimited number of non-cumulative lesions or damages are eventually all completely repaired or removed and practically cause no special harm to the body. Hence, it seems reasonable to hypothesize that probably only the SS, not mild erythema (mild skin reddening) and chronic non-burning sun exposure, can overwhelm the repair/removal capacity and cause subsequent DNA mutation that may have the potential to eventually become a pre-cancerous tumor (e.g., actinic keratosis being a known precancerous tumor for SCC) or cancer. Conversely, one may also reason that practically all DNA damages caused by non-burning sunlight that includes UVA, UVB and visible rays are non-cumulative and not particularly harmful as commonly assumed (i.e., solar radiation damage is cumulative) in the last century. In this regard, it seems that one may need caution in jumping into a definitive conclusion on clinical implications simply based on results obtained from a short-term study of non-cumulative UV/solar-ray damages. It should be noted that a person with a strong immune system could have 16 or more SS and the chance of successfully developing a melanoma, BCC and SCC could be only about 2%, 25% and 5%, respectively, clearly demonstrating our body's extremely efficient defense/repair capability [1]. On the other hand, a person with a weak immune system such as one with organ transplant may easily develop a skin cancer after only one SS episode. Obviously, one eventually needs to develop the first cancerous stem cell in order to multiply into a cancer and the process for such development is extremely complicated involving numerous hurdles or barriers and remains to be explored [5,45]. Regarding the role of HPV in cancer initiation, one may have two hypotheses:

1. It can decrease the threshold for non-cumulative UV DNA lesions thereby making it easier to incur SS
2. Sunburn, not necessary SS, is sufficient to facilitate cancer initiation. However, a mild erythema is probably not enough to help initiate the process. The above non-cumulative damage assumption cannot be applied to the eyes due to its known high sensitivity to UV rays

Apparent misconceptions of UVB rays in skin penetration and UVA rays in cancer development

For decades UVA has been commonly accepted as the main cause for skin cancer and premature skin aging. This notion is apparently partly prompted by a notion that the weaker but more abundant (up to 95%) UVA can penetrate deeper into the dermis layer of skin to inflict more damage, while the more damaging UVB can only penetrate into epidermis layer [6,7]. However, this statement is not entirely correct. For example, when erythema or severe

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

sunburn (painful, peeling, swollen or blistering) occurs, the damage caused mainly by UVB is clearly in the dermis [46]. Another example is that a melanoma fish model for UVA reported earlier in 1989 that was found later in 2010 to be non-reproducible has been often mistakenly cited to this date as a key reference in highly cited articles to support the involvement of UVA in cancer etiology in the last 3 decades [47-49]. As to be discussed later, apparently the use of extremely physiologically unrealistic doses of UVA to show its ability to cause skin cancer has also greatly contributed to the formation of current consensus. Interestingly, contrary to our common belief, radiation by UVA and visible light (320-500 nm) has been shown to decrease the formation of melanotic tumors from UVB radiation in opossums, this is however, consistent with the view that chronic exposure to solar light is protective against melanoma in humans [9,50]. It is also consistent with that exposure to non-burning sunlight could increase survival rate of melanoma patients [51].

Evidence showing non-cumulative damage in aging due to oxidative stress in general public

Oxidative stress, a sign of cellular lesions or damages that involve DNA, has been commonly accepted as the major reason for causing aging in our body [53,54]. This would then lead to a conclusion that body aging is an accelerating process [52-54]. This is, however, inconsistent with data that the aging kinetics of human hearts represented by the cardiac index, a proposed aging marker for the whole body, did not show an accelerating pattern during several decades of life span [54]. Instead, it followed a first order kinetics as reproduced in Fig. 3 [54]. Also, contrary to the expectation, the aging kinetics of superficial microcapillary densities in humans over several decades of life span were found to follow the first order kinetics indicating a lack of accelerating process as reproduced in Fig. 4 [54]. Furthermore, plots of aging kinetics from superficial capillaries exposed or unexposed to sunlight were virtually parallel each other (Fig. 4) also clearly indicating a lack of any significant photoaging effect [54]. It is well accepted that exposure to UV light and visible light will result in increased degradation of skin collagen and decreased synthesis of collagen in the skin and this should theoretically result in an accelerated aging [52-55]. This apparently also did not happen as shown in Fig. 5 [54]. Furthermore, total collagen contents of skin exposed or not exposed to sunlight from different parts of the body of the same person were practically the same suggesting insignificant or minor effect from sun exposure [54]. The above phenomena may be rationalized by the fact that invisible non-burning solar ray damage at the molecular level in the skin may be eventually completely repaired by our body and is practically non-cumulative and non-harmful to skin aging as discussed above in skin cancer etiology. For visible solar ray damages such as erythema or even SS, they could be visibly healed in days or in weeks with no or only minimum intervention due to our body's extremely sophisticated healing power [54]. One simple convincing example to counter the current photoaging theory that sunlight may account for up

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

to 80% to 90% of total skin aging may be the following [52,54]: Old Muslim women who wear clothing to cover the whole body except the eyes when staying outdoors during daytime can also develop deep wrinkles, age spots and sagging skin. Other shortcomings of the conventional aging theories and new proposed aging theories have been discussed in detail [6,54]. It may be of interest to note that contrary to the classical concept, aging of skin and stem cells may be quite reversible depending mainly on the availability of nutrients [54,56,57]. Fig. 6 illustrates how a plant's "health" is rapidly reversible simply by hydration and dehydration. In this study a small plant was first deprived of water in a room at about 25°C with a LED grow light. After 68 hours the plant totally withered ('simulating' deep wrinkle formation in humans due to lack of adequate hydration or nutrients). After adding water, the plant fully recovered 8 hours later. In the above study no UV radiation was involved. It is hypothesized that chronic wind blowing or heat application from any source can cause severe dehydration of skin that may also result in deep wrinkle formation. Wrinkle is formed due to a body's defense mechanism in order to reduce the effective surface area to minimize water loss [54]. It is known that a person with severe malnutrition could have sagging skin and deep wrinkles without any prolonged exposure to UV rays.

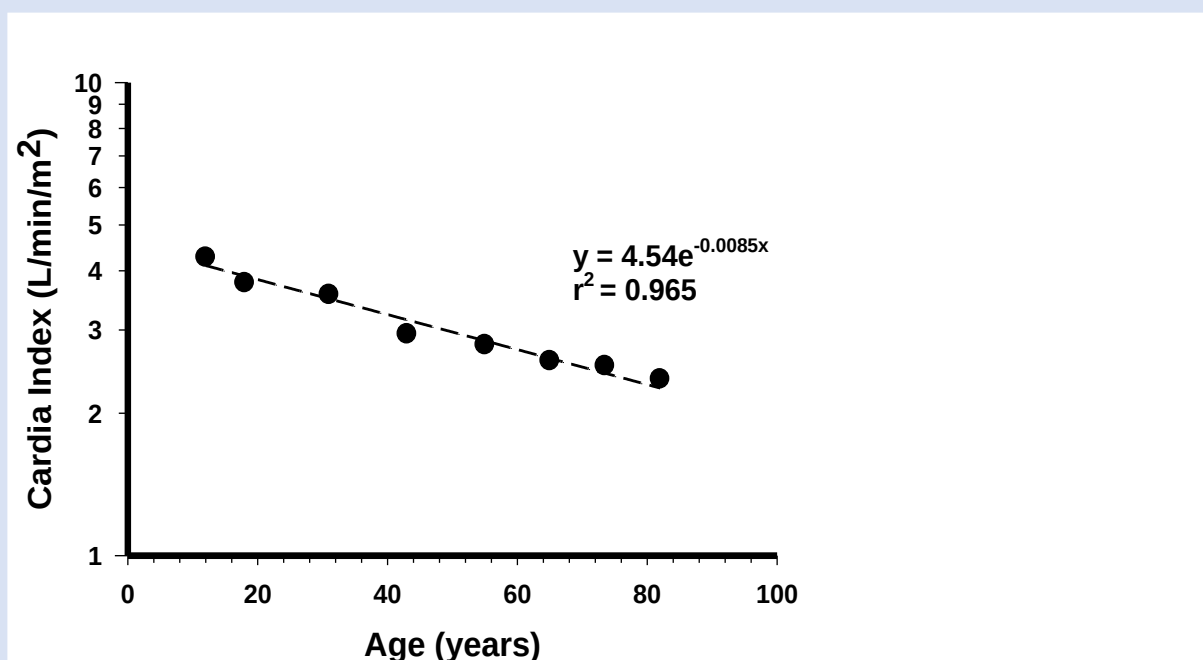


Figure 3: Cardiac index in humans as a function of age plotted on a semi-logarithmic scale. Reproduced from referenc54.

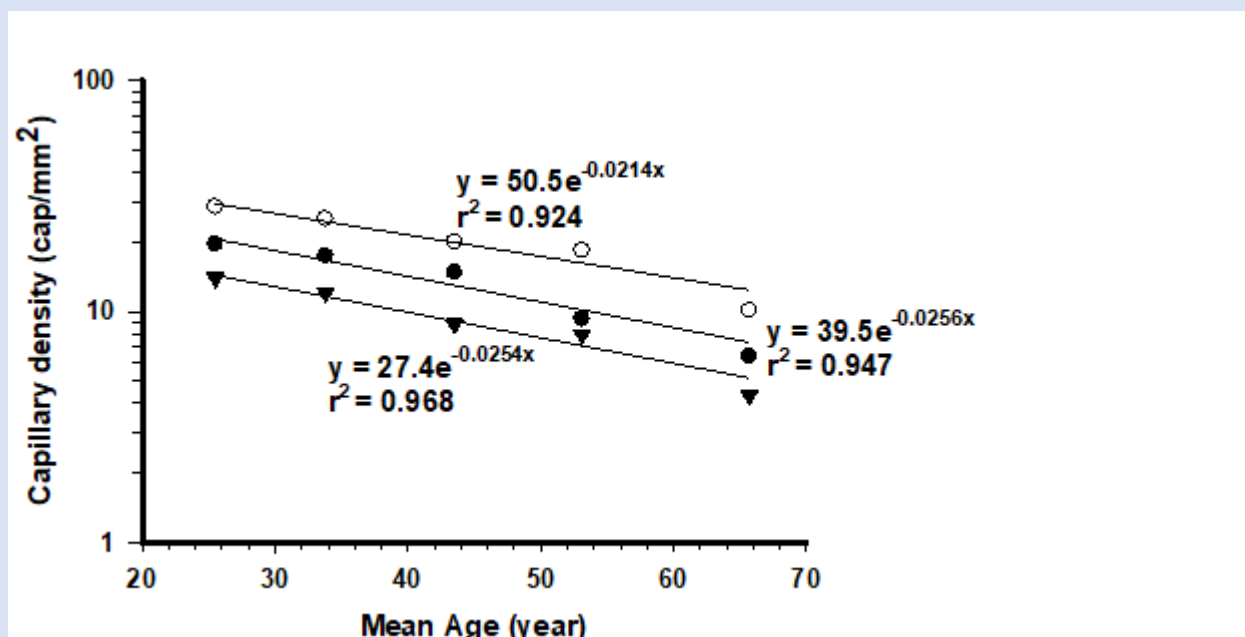


Figure 4: Semi-logarithmic plots of mean capillary density versus mean age of five female groups at three sites: volar forearm (●) representing the non-photo-exposed site; the back of hand (○) and forehead (▼) representing photo-exposed sites. Reproduced from reference 54.

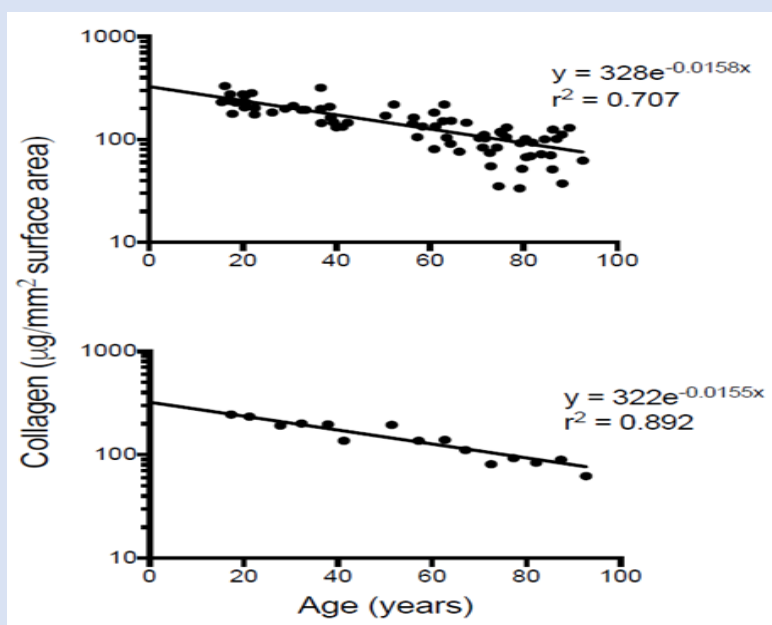


Figure 5: Relationship between mean skin collagen content per unit skin surface area and mean age in 70 males. Top graph based on individual data. Bottom graph based on mean data for every 5 years in age. Reproduced from reference 54.



Figure 6: Plant Rejuvenation after water and nutrition.

Controversies on risks of different professions in skin cancers

In recent decades there have been numerous often controversial reports on risks of cancer in different professions. Some of them will be briefly reviewed below. Airplane pilots and crews are often reported to have more incidences of melanoma than the general public and this has been mainly attributed to their exposure to more damaging UVA rays through windows that can block most UVB but not UVA [3,58]. However, such notion has been questioned as it could not rule out other social/economic factors [59]. Indeed, these more affluent pilots and crews might have better opportunities to fly (probably at no cost to them as part of their employment benefits) to more sunny places to enjoy sunbathing and incur sunburn after work hours [60,61]. Such a likely scenario is consistent with the present SS theory. Also, in a complete reversal, outdoor workers such as fishermen and gardeners in Sweden were recently found to have had less BCC incidences than indoor workers such as physicians and lawyers [62]. This finding clearly contradicts the current consensus that BCC is mainly caused by cumulative UV exposure. Since the outdoor workers spent 3 to 10 times longer times than the indoor workers, it seems impossible for them to spend more times in the sun during the non-office hours and weekends to offset their indoor work hours [3]. The most likely reason for this phenomenon to occur is that these more affluent indoor workers could spend more times for intermittent sun exposure resulting in more SS as being postulated in melanoma examples above. Also, there were many studies reporting potential asymmetric distribution of skin cancer

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

of car or truck drivers with sun-faced side developing more incidences of cancer [63-66]. This phenomenon has been mainly attributed to chronic exposure to UVA rays. However, it is quite possible that drivers might open the side window to enjoy the sunlight and breezy wind while driving in the hot summer; obviously this kind of driving habit may result in sunburn on that side of face and neck. The above brief review may suggest that for any person or profession incurrence of SS is probably the most impotent factor to influence the chance of getting a skin cancer and efforts to avoid or minimize SS should be the key to prevent skin cancer [1].

Potential shortcomings of extremely high UV doses used in animal and culture cell studies

Body surface area concept has been successfully employed in the past many decades to determine interspecies dosage used in pharmacokinetic and pharmacodynamic studies [67,68]. In studying the effect of sunlight on skin cancer development, one could use dosage range (joule/m²) encountered in the real world during chronic sunlight exposure or acute intermittent exposure. A limited review of the literature reveals that extremely high UV doses have been commonly employed in studies in humans, animals and cell cultures. In humans one Standard Erythral Dose (SED) for UVB is 100 J/m² and one minimum UVA erythral dose (MED) for skin type 1 is 20 J/cm² [69,70]. Since UVA in solar light is weak the actual dose received is known to be only a small fraction of the MED; for the present discussion it is assumed to be 5-fold less. Based on the above doses one can estimate the following number of folds used in reported studies: 50-fold of UVA in human skin, 162-fold of UVA and 76-fold of UVB in human cells, 45-fold of UVB in mice, 6-fold of UVA in opossums about 5-fold of UVA in mice [71-75]. Thus, one may need caution in extrapolating the results to human use especially for etiological studies. For the last two studies, the UVA doses used were similar to the one that will cause sunburn or SS in humans [74,75]. Therefore, these studies support the observation that tanning from tanning salons may increase melanoma incidence due to their use of very high doses of UVA causing sunburn or perhaps SS in earlier years [76]. Since no UVA in our solar light can cause sunburn, this study may not support the hypothesis that UVA causes skin cancers in general public as commonly assumed [3,5,74,75]. Use of burning erythral UVB doses to promote melanoma development in animal models has been reviewed [6,49]. It was stated that prolonged UV was not a factor in melanoma genesis [49].

Conflict of Interest

The authors declare that they have no conflict of interest.

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. J Dermatol Res. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

References

1. Chiou WL. Severe sunburn as the overwhelming risk factor for 3 common skin cancers: new prevention strategy. *J Dermatol Res*. 2021;2:1-9.
2. Wu S, Cho E, Li WQ. History of severe sunburn and risk of skin cancer among women and men in 2 prospective cohort studies. *Amer J Epidemiol*. 2016;183:824-33.
3. Godar DE. UV and reactive oxygen species activate Human Papillomaviruses causing skin cancers. *Curr Probl Dermatol*. 2021;55:339-53.
4. Wu S, Han J, Laden F. Long-term ultraviolet flux, other potential risk factors and skin cancer risk: A cohort study. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1080-9.
5. Pfeifer GP. Mechanisms of UV-induce mutations and skin cancer. *Genome Instab Dis*. 2020;1(3):99-113.
6. Chiou WL. Perspectives on the FDA's sunscreen policy: new aging theory, sunlight benefits, enhanced immunity, Covid-19 mortality, modelling analyses, melanoma risks and etiology. *J Dermatol Res*. 2021;2(1):1-13.
7. What's the Difference Between UVA and UVB Rays? [Last accessed on April 27, 2022]. <https://www.webmd.com/melanoma-skin-cancer/difference-between-uva-rays-and-uvb-rays#091e9c5e821f3cf1-1-2>
8. Khan AQ, Travers B, Kemp MG. Roles of UVA radiation and DNA damage responses. *Environ Mol Mutag*. 2018;59:438-60.
9. Gandini S, Sera F, Cattaruzza MS. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. *Eur J Cancer*. 2005;41:45-60.
10. Dennis LK, Vanbeek MJ, Beane Freeman LE. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. *Ann Epidemiol*. 2008;18:614-27.
11. Kennedy C, Bajdik CD, Willemze R. Skin cancer study: The influence of painful sunburns and lifetime sun exposure on the risk of actinic keratoses, seborrheic warts, melanocytic nevi, atypical nevi, and skin cancer. *J Invest Dermatol*. 2003;120:1087-93.
12. Iannaccone MR, Wang W, Stockwell HG. Patterns and timing of sunlight exposure and risk of basal cell and squamous cell carcinomas of the skin-a case-control study. *BMC Cancer*. 2012;12:417.
13. Zanetti R, Rosso S, Martinez C. The multicentre south European study 'Helios'. I: skin characteristics and sunburns in basal cell and squamous cell carcinomas of the skin. *Br J Cancer*. 1996;73:1440-6.
14. English DR, Armstrong BK, Krickler A. Case-control study of sun exposure and squamous cell carcinoma of the skin. *Int J Cancer*. 1998;77(3):347-53.
15. Krickler A, Armstrong BK, English DR. Does intermittent sun exposure cause basal cell carcinoma? A case-control study in Western Australia. *Int J Cancer*. 1995;60(4):489-94.
16. Hufbauer M, Akgul B. Molecular mechanisms of Human Papillomavirus induced skin carcinogenesis. *Viruses*. 2017;9(7):187.
17. Gheit T. Mucosal and cutaneous human Papillomavirus infections and cancer biology. *Front Oncol*. 2019;9:355.
18. Beceeril S, Corchado-Cobos R, García-Sancha N. Viruses and skin cancer. *Int J Mol Sci*. 2021;22(10):5399.
19. Bavinck JNB, Feltkamp M, Struijk L. Human Papillomavirus infection and skin cancer risk in organ transplant recipients. *J Invest Dermatol Symp Proc*. 2001;6(3):207-11.
20. Termorshuizen F, Feltkamp MCW, Struijk L. Sunlight exposure and (sero) prevalence of epidermodysplasia verruciformis-associated human papillomavirus. *J Invest Dermatol*. 2004;122:1456-62.
21. Struijk L, Bavinck JNB, Wanningen P. Presence of human papillomavirus DNA in plucked eyebrow hairs is associated with a history of cutaneous squamous cell carcinoma. *J Invest Dermatol*. 2003;121(6):1531-5.
22. Karagas MR, Nelson HH, Sehr P. Human papillomavirus infection and incidence of squamous cell and basal cell carcinomas of the skin. *Natl Cancer Inst*. 2006;98(6):389-95.
23. Feltkamp MCW, de Koning MNC, Bavinck JNB. Betapapillomaviruses: Innocent bystanders or causes of skin cancer. *J Clin Virol*. 2008;43:353-60.

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. *J Dermatol Res*. 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

24. Iannacone MR, Wang W, Stockwell HG. Sunlight exposure and cutaneous human papillomavirus seroreactivity in basal cell and squamous cell carcinomas of the skin. *J Infect Dis.* 2012;206(3):399-406.
25. Viariso D, Müller-Decker K, Accardi R. Beta HPV38 oncoproteins act with a hit-and-run mechanism in ultraviolet radiation-induced skin carcinogenesis in mice. *PLoS Pathog.* 2018;14(1):e1006783.
26. Smola S. Human Papillomaviruses and Skin Cancer. *Adv Exp Med Biol.* 2020;1268:195-209.
27. Rollison DE, Viariso D, Amorrortu RP. An emerging issue in oncogenic virology: the role of beta human papillomavirus types in the development of cutaneous squamous cell carcinoma. *J Virol.* 2019;93(7):e01003-18.
28. Dvorak HF. Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. *N Engl J Med.* 1986;315(26):1650-9.
29. Chen ML, Wang SH, Wei JCC. The impact of Human Papillomavirus infection on skin cancer: a population-based cohort study. *Oncologist.* 2021;26(3):e473-83.
30. Marcuzzi GP, Hufbauer M, Kasper HU. Spontaneous tumour development in human papillomavirus type 8 E6 transgenic mice and rapid induction by UV-light exposure and wounding. *J Gen Virol.* 2009;90(12):2855-64.
31. Sunburn statistics from Australia. [Last accessed on April 27, 2022]. <https://www.abc.net.au/btn/classroom/sunburn-statistics/13235190>
32. Warthan MM, Sewell DS, Marlow RA. The economic impact of acute sunburn. *Arch Dermatol.* 2003;139:1003-6.
33. Arutyunyan S, Alfonso SV, Hernández N. Predictors of sunburn risk among Florida residents. *J Am Osteopath Assoc.* 2017;117(3):150-7.
34. Robonson JK, Riel DS, Amonnette RA. Trends in sun exposure knowledge, attitudes and behaviors: 1986 to 1996. *J Am Acad Dermatol.* 1997;37:179-86.
35. Chiou WL. Pharmacodynamic modeling of sunscreens: new efficacy evaluation, risks of sunburn and melanoma and very low to very high sun protection factor. *J Dermatol Res Ther.* 2020;1:20-9.
36. Narbutt J, Philipsen PA, Harrison GI. Sunscreen applied at $\geq 2 \text{ mg cm}^2$ during a sunny holiday prevents erythema, a biomarker of ultraviolet radiation-induced DNA damage and suppression of acquired immunity. *Br Med J.* 2018;180:604-14.
37. Petersen B, Thieden E, Philipsen PA, Heydenreich J. A sun holiday is a sunburn holiday. *Photodermatol Photoimmunol Photomed.* 2013;29:221-4.
38. Heerfordt IM, Torsness LR, Philipsen PA. Sunscreen use optimized by two consecutive applications. *PLoS One.* 2018;13(3).
39. Holman DM, Ding H, Guy GP, Watson M, Hartman AM, Perna FM. Prevalence of sun protection use and sunburn and association of demographic and behavioral characteristics with sunburn among US adults. *JAMA Dermatol.* 2018;154(5):561-8.
40. Jackson SP, Jiri Bartek J. The DNA-damage response in human biology and disease. *Nature.* 2009;461(7267):1071-8.
41. Saini N, Giacobone CK, Klimczak LJ. UV-exposure, endogenous DNA damage and DNA replication errors shape the spectra of genome changes in human skin. *PLOS Genetics.* 2021.
42. Schuch AP, Moreno NC, Schuch NJ. Sunlight damage to cellular DNA: Focus on oxidatively generated lesions. *Free Radic Bio Med.* 2017;107:110-24.
43. Ahmed NU, Ueda M, Nikaido O. High levels of 8-hydroxy-2'-deoxyguanosine appear in normal human epidermis after a single dose of ultraviolet radiation. *Br J Derma.* 1999;140:226-31.
44. Qing X, Shi D, Lv X. Prognostic significance of 8-hydroxy-2'-deoxyguanosine in solid tumors: a meta-analysis. *BMC Cancer.* 2019;19(1):997.
45. Sun Q, Lee W, Mohri Y. A novel mouse model demonstrates that oncogenic melanocyte stem cells engender melanoma resembling human disease. *Nature Commun.* 2019;10(1):5023.
46. Gilchrist BA, Soter NA, Stoff JS. The human sunburn reaction: histologic and biochemical studies. *J Am Acad Dermatol.* 1981;5(4):411-22.

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. *J Dermatol Res.* 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

47. Setlow RB, Woodhead AD, Grist E. Animal model for ultraviolet radiation-induced melanoma: playfish-swordtail hybrid. *Pro Natl Acad Sci.* 1989;86:8922-6.
48. Mitchell DL, Fernandez AA, Nairn RS. Ultraviolet A does not induce melanomas in a Xiphophorus hybrid fish model. *Pro Natl Acad Sci.* 2010;107:9329-34.
49. Fernandez AA, Paniker L, Garcia R. Recent advances in sunlight-induced carcinogenesis using the Xiphophorus melanoma model. *Compar Biochem Physiol.* 2012;155:64-70.
50. Ley RD, Applegate LA, Padilla RS. Ultraviolet radiation-induced malignant melanoma in *Monodelphis domestica*. *Photochem Photobiol.* 1989;50(1):1-5.
51. Alfredsson L, Armstrong BK, Butterfield DA. Insufficient sun exposure has become a real public health problem. *Int J Environ Res Public Health.* 2020;17(14):5014.
52. Fisher GJ, Datta SC, Talwar HS. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. *Nature.* 1996;379:335-9.
53. Panich U, Sittthumcharee G, Rathviboon N. Ultraviolet radiation-induced skin aging: the role of DNA damage and oxidative stress in epidermal stem cell damage mediated aging. *Stem Cells Int.* 2016.
54. Chiou WL. Aging kinetics of human hearts and skin: New aging theories and implications in the use of sunscreens. *Dermatol Arch.* 2017;1:1-5.
55. Zastrow L, Lademann J. Light - instead of UV protection: New requirements for skin cancer Prevention. *Anticancer Res.* 2016;36:1389-93.
56. Grignorian-Sharmagian L, Liu W, Fereydooni S. Cardiac and systemic rejuvenation after cardiosphere-derived cell therapy in senescent rats. *Eur Heart.* 2017;38(39):2957-67.
57. Chiou WL. Compositions and methods for tissue regeneration. United States Patent No. 10456366. 2019.
58. Sanlorenzo M, Wehner MR, Linos E. The risk of melanoma in airline pilots and cabin crew: a meta-analysis. *JAMA Dermatol.* 2015;151(1):51-8.
59. Jiang AJ, Rambhatla PV, Eide MJ. Socioeconomic and lifestyle factors and melanoma: a systematic review. *Br J Dermatol.* 2015;172(4):885-915.
60. Rafnsson V, Hrafnkelsson J, Tulinius H. Risk factors for cutaneous malignant melanoma among aircrews and a random sample of the population. *Occup Environ Med.* 2003;60(11):815-20.
61. Dos Santos Silva I, De Stavola B, Pizzi C. Cancer incidence in professional flight crew and air traffic control officers: disentangling the effect of occupational versus lifestyle exposures. *Int J Cancer.* 2013;132(2):374-84.
62. Lindelöf B, Lapins J, Dal H. Shift in occupational risk for basal cell carcinoma from outdoor to indoor workers: a large population-based case-control register study from Sweden. *Acta Derm Venereol.* 2017;97(7):830-3.
63. Paulson KG, Iyer JG, Nghiem P. Asymmetric lateral distribution of melanoma and Merkel cell carcinoma in the United States. *J Am Acad Dermatol.* 2011;65(1):35-9.
64. Elwood JM, Gallagher RP. Body site distribution of cutaneous malignant melanoma in relationship to patterns of sun exposure. *Int J Cancer.* 1999;78(3):276-80.
65. Butler ST, Fosko SW. Increased prevalence of left-sided skin cancers. *J Am Acad Dermatol.* 2010;63(6):1006-10.
66. Lee E, Kang MY, Kim J. Cancer risk in road transportation workers: a national representative cohort study with 600,000 person-years of follow-up. *Sci Rep.* 2020;10:11331.
67. Chiou WL, Hsu FH. Correlation of unbound plasma clearances of fifteen extensively metabolized drugs between humans and rats. *Pharm Res.* 1988;5:668-72.
68. Chiou WL, Ma C, Chung SM. Similarity in the linear and nonlinear oral drug absorption of drugs between human and rat. *Int J Clin Pharmacol Ther.* 2000;38:532-9.
69. Diffey BL, Jansén CT, Urbach F. The standard erythema dose: a new photobiological concept. *Photodermatol Photoimmunol Photomed.* 1997;13(1-2):64-6.
70. Beattie PE, Dawe RS, Ferguson J. Dose-response and time-course characteristics of UV-A1 erythema. *Arch Dermatol.* 2005;141(12):1549-55.

Chiou WL | Volume 3; Issue 2 (2022) | JDR-3(2)-039 | Commentary Article

Citation: Chiou WL, et al. Severe Sunburn Triggers the Development of Skin Cancers: Non-cumulative/Overwhelming UV Damages, UVA Rays, Human Papillomavirus, Indoor/Outdoor Workers and Animal Models. *J Dermatol Res.* 2022;3(2):1-17.

DOI: <https://doi.org/10.46889/JDR.2022.3208>

71. Mouret S, Baudouin C, Charveron M. Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. *Proc Natl Acad Sci.* 2006;103:13765-70.
72. Besaratinia A, Synold TW, Chen HH. DNA lesions induced by UV A1 and B radiation in human cells: Comparative analyses in the overall genome and in the p53 tumor suppressor gene. *Proc Natl Acad Sci.* 2005;102(29):10058-63.
73. Viarisis D, Mueller-Decker K, Klotz U. E6 and E7 from beta Hpv38 cooperate with ultraviolet light in the development of actinic keratosis-like lesions and squamous cell carcinoma in mice. *PLoS Pathog.* 2011;7(7): e1002125.
74. Ley RD. Dose response for ultraviolet radiation A-induced focal melanocytic hyperplasia and nonmelanoma skin tumors in *Monodelphis domestica*. *Photochem Photobiol.* 2001;73(1):20-3.
75. Noonan FP, Zaidi MR. Melanoma induction by ultraviolet A but not ultraviolet B radiation requires melanin pigment. *Nat Commun.* 2012;3:884.
76. Le Clair, McCookburn MG. Tanning bed use and melanoma: establishing risk and improving prevention interventions. *Prev Med Rep.* 2016:139-44.