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Exploring the Role of Artificial Light and Tanning for Skin Cancer

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ABSTRACT

Skin cancer is a complex health condition with a high mortality rate all over the world. The present review article examines the relationship between artificial light exposure, tanning practices, and skin cancer. Artificial light exposure and tanning practices have been linked to various health concerns, particularly skin cancer. Artificial light sources that initiate and progress skin cancers are blue light, laptops, smartphones, and personal computers, leading to significant impacts on the human body. Artificial light exposure and tanning practices have been linked to various health concerns, particularly skin cancer. Both artificial light sources, such as tanning beds) and natural sunlight emit UVA and UVB rays, which can damage DNA in skin cells, leading to mutations that can develop into skin cancer. Tanning beds, in particular, pose a significant risk due to their high levels of UVA radiation. In addition, skin cancer was induced only in the mice exposed to blue light. Long-term blue light irradiation also increased the migration of neutrophils and macrophages involved in carcinogenesis in the skin. The review article also summarized the mechanisms of action of these factors in the progression and development of skin cancer as well.

INTRODUCTION

Skin cancer exhibit serious health concerns and fatal cancer types globally. In the United States, skin cancer is the most prevalent type of cancer to afflict a body organ, and throughout the past few years, its frequency has kept steadily increasing, mostly among young people. Although many contributing factors contribute to this trend, UV exposure patterns are widely acknowledged as one of them since they are consistent with the mounting proof that UV radiation damages DNA in the skin, which may start the carcinogenic process [1]. Specifically, DNA's aromatic heterocyclic bases capture UVB light significantly, which results in the formation of cyclobutane pyrimidine dimer chains that induce CTT and CCTT mutations. According to the latest studies, UVA radiation may also cause DNA mutations by forming cyclobutane pyrimidine dimers. Although p53 itself is susceptible to dipyrimidine mutagenesis in the layer of skin, systems comprising the tumour suppressor p53 may fix this DNA damage from sunlight [2]. Alternatively, in instances that involve more substantial damage, p53 modulates apoptosis. Therefore, UV-mediated DNA damage can cause

cancer by causing p53 malfunction as well as starting mutations across the whole genome [3, 4].

Within the spectrum of light that is observable through the naked eye, the blue spectrum which has a wavelength between 380 and 500 nm, possesses the smallest wavelength and the most intensity. Blue light is abundant in LED bulbs and is seen in computers and cell phones. The biological clock is likewise influenced by blue light. Circadian rhythms are regulated by photoreceptor cells found in the retina [5]. Cells of this kind can only react with radiation that has a wavelength of 460 nm, or blue light. Over the daytime, being exposed to blue light from the sun tends to maintain the internal clock. Insomnia can arise as the body clock is thrown off, which has an impact on a person's wellness. Thus, it can be concluded that exposure to blue light during the whole day is necessary for the survival of humans [6]. On the other hand, continuous usage of a smartphone or computer at any time of day, is common in modern culture, which could lead to illnesses. Moreover, prolonged exposure to blue light from computers, cellphones, and televisions strains the eyes more. This leads to the appearance of symptoms like dry eyes, impaired vision, and lack of focus. As it worsens, headaches, tight shoulders, as well as blurred vision also happen [7].

UV rays are generally the most energetic type of light in sunshine and have been associated with damage to skin and eyes. UV radiation, although scarcely enters the retina because it gets captured by the lens and aqueous body of the eyeball. Furthermore, blue light is the visible spectrum type having the highest energy level and the shortest wavelength [8]. Along with additional light in the long wavelength range, it may penetrate the retina without being taken up by the lens or vitreous body. As a result, prolonged interaction with blue light can harm the retina and result in macular degeneration, which is age-related. Moreover, blue light has an impact on every part of the human anatomy, not only the eyes. As previously indicated, extended night-time exposure to blue light can skew the biological clock's ability to distinguish between day and night, leading to irregularities in the circadian cycle [9]. This leads to anomalies in neurological function, which in turn induces the internal organs and blood vessels to circulate more vigorously during the day and at night. This accelerates the ageing process, aggravates ailments associated with decisions about lifestyle, and results in inadequate health. Additionally, a loss in skin flexibility brought on by photoaging results in uneven discolouration, lentigines, and tiny pimples on the skin. It is already demonstrated that blue light causes oxidative stress, damages the skin barrier, and encourages prolonged skin pigmentation, which in turn causes premature ageing both *in vitro* and *in vivo* [10].

In one study, exposure to blue light over an extended period regularly caused skin cancer. Red, green, as well as white light, on the other hand, are not responsible for skin cancer. Irradiation with blue light boosted neutrophil expression as well as that of the neutrophil chemotactic factor CXCR1. Furthermore, there was a spike in the amounts of ROS and neutrophil elastase released by neutrophils, as well as the generation of CitH3 and PAD4, markers of neutrophils-induced NETs. In addition, blue light radiation raised the blood levels of IL-6 and IL-23 as well as the quantity of M1-type macrophages [11]. Generally speaking, whenever the skin is subjected to UV radiation along with additional stimuli, blood vessel neutrophils congregate at the triggered region and release a surplus of neutrophil elastase, which breaks down both collagen and elastin that comprises the outermost layer of the skin. Blue light exposure also emphasized the generation of neutrophils and the CXCR1, a neutrophil chemotactic element [12]. In response to inflammatory stimulation, neutrophils relocate to the nearby region where they use phagocytosis and degranulation to shield the human body from outside threats. Moreover, extracellular neutrophil traps (NETs) are produced by stimulated neutrophils, suggesting a significant involvement of these cells in immunological activity. The disintegration of the neutrophil nuclear membrane, chromatin enlargement, and cell membrane rupture are the hallmarks of the development of NETs [13].

NETs are created via the citrullination of histones (citH3), which are crucial factors for NETosis. Peptide deiminase (PAD4) converts arginine to citrulline in this process.CitH3 and PAD4 expression rose, indicating a possible rise in NET synthesis. In addition to acting as molecules linked to damage that trigger complement systems

and inflammasomes and intensify inflammatory processes, NETs are a form of defence by the host response [14]. It has just been demonstrated that NETs play a great role in the spread and development of tumours. Through the stimulation of the EGFR/ERK pathway, NETs induce epithelial-mesenchymal cells to differentiate and cause alteration, which is important in cancer cell migration and metastasis. Additionally, they awaken inert kinds of cancerous cells and encourage the growth of cancerous cells. The research thus proposed that exposure to blue light triggers NET activation, which leads to tumorigenesis and cell proliferation [15].

On the other hand, after being exposed to blue light, a rise in macrophages was seen, suggesting that these macrophages were M1 types. Cytokines that promote inflammation are secreted by M1 macrophages. Within these, STAT3 signalling is one that IL-6 causes carcinogenesis. Moreover, it was recently demonstrated that IL-23 aids in the development of cancer. M1 macrophages, on the other hand, typically decrease malignancy [16]. Furthermore, the milieu encompassing cancer changes from being dominated by Th1 cells to being dominated by Th2 cells when carcinogenesis is caused by humoral variables obtained by macrophages, and macrophages change to the M2 type in response. To decrease the immunity against tumours and stimulate angiogenesis, M2 macrophages produce TGF-β and IL-10, which modifies the surroundings in a way that promotes the growth of cancerous cells. Moreover, blue light causes the overexpression of MMP-1, a decline of type-1 collagen production, and an inhibition of fibroblast growth [17]. Furthermore, it has been documented that blue-light-induced skin ageing is influenced by JUN, TGF, and EGFR signalling mechanisms. It was believed that an intricate structure evolved in the present research just because immune cells like neutrophils and macrophages played a role in the transduction pathway. Moreover, exposure to blue light enhanced the rate of ROS generated. ROS are crucial to the formation of tumors [18].

It is said that NADPH oxidase might be activated by the colour blue. The primary immune-system cells that directly combat germs by generating reactive oxygen species are macrophages. Brain-specific angiogenesis inhibitor 1 (BAI1), a binding member of receptors associated with G proteins (GPCR)s, triggers the oxidising enzyme NADPH activity and activates the Rho-family GTPase Ras-related C3 botulinum toxin substrate 1 (Rac1), that in turn increases $O2^{-}$ production in macrophages [19]. The accurate pathways by which blue light activates macrophages to make up more ROS are currently undefined. Furthermore, skin cancer was brought on by a whole year of regular interaction with blue light. Type 1 macrophages and neutrophil extracellular matrix (NET) play an essential part in the development of skin cancer. On the other hand, as type 1 macrophages boost the immune system, cancer decreases as long as it remains [20]. As a result, cancerous cells cause macrophages to switch to type 2, thereby encouraging the growth of cancer. The transition from type 2 to type 1 macrophages was not examined in the present investigation whereas more thorough research is required. Furthermore, it continued to be unclear if NETs genuinely contribute to neutrophil tumour formation [21]. Thus, more research is required to figure out how blue light affects NETs. Additionally, there exist numerous methods to avert blue light. Today's generation spends a lot of our time using smartphones and desktops on an everyday basis. Consequently, if you use screens at late hours, wear blue light-cutting spectacles. Additionally, it is advised to be outdoors in the early morning due to the impact of the sun's blue light on the body's circadian rhythm. However, it could be preferable to wear blue light-blocking glasses and base makeup during this time [22]. Further study is necessary, particularly on protective measures, because numerous of the impacts of blue light on creatures of life remain undiscovered.

In addition, the tanning pathway also gets started by destroying DNA. Pro-opiomelanocortin (POMC) transcription of genes is upregulated whenever p53 attaches to and activates the gene involved in keratinocytes in anticipation of damaged DNA. Post-translational cleavage of the POMC molecule yields numerous compounds, one of those being α-melanocyte-stimulating hormones that communicate with melanocytes through the melanocortin 1 receptor (MC1R) [23]. Tan is prevented when the receptor's signalling is interfered alongside, including in the case of red-

haired people who have MC1R malfunctioning polymorphism and sunburn when exposed to the sun without tanning. Put another way, tanning does not appear to occur despite prior destruction of DNA, although UV-mediated destruction of DNA may take place in certain people even in their absence of tanning. Such results seriously question the viability of a genuinely "safe tan" in theory [24].

By claiming that BCC and SCC are typically less severe than melanoma, the tanning company has tried to minimise the severity of the greater likelihood. A case like this misses the truth that non-melanoma skin cancer, particularly SCC, can spread and may be the cause of several thousand avoidable fatalities in the US every year. Furthermore, there is a significant morbidity linked to the operative removal of non-fatal BCC and SCC, as well as the use of healthcare facilities in treating such tumours that can be prevented [25, 26]. Nevertheless, the tanning market has almost solicited research into the relationship involving tanning indoors and risk for melanoma by refocusing the conversation from BCC and SCC to melanoma. As tanning indoors only started to grow more popular in the past three decades, the initial investigations of this connection might have not permitted a long enough post-exposure duration to properly determine the likelihood of melanoma due to the delay that is associated with melanoma expansion, which potentially contributed to the equivocal outcomes [27].

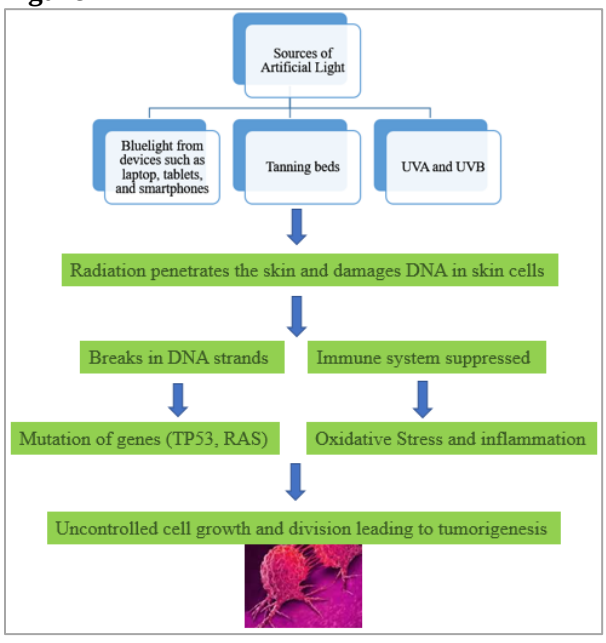
Mechanism of Action

UVB interacts with epidermis cells, but UVA reaches deeper layers of the skin and affects immune cells in the dermis and epidermis as shown in Figure 1. In comparison to infrared radiation, visible light acts more superficially on the skin, but it also penetrates it deeper [28]. Melanin and haemoglobin in the epidermis are highly efficient in absorbing visible light. Blue light has a 0.07–1 mm penetration range. Chromophores are molecules that absorb blue light, including endogenous nucleic acids, aromatic amino acids, urocanic acid, tryptophan, tyrosine, NADPH, NADH cofactors, cytochromes, riboflavins, porphyrins, melanin and melanin precursors, protoporphyrin IX, bilirubin, haemoglobin, carotene, or water molecules. As such, the effects of blue light are dependent on different chromophores, or photoreceptors [11]. The most important photo acceptors are nitrosated proteins, flavins, opsins, and porphyrins such as S-nitro-albumin. One such potential blue light pathway is the activation of flavins and flavoproteins. Flavin adenine dinucleotides (FAD) and flavin mononucleotides (FMN) double the quantity of superoxide generated when reactive oxygen species (ROS) develop when exposed to radiation. Numerous pathways mediate ROS signalling. Among these is an Nrf2-dependent mechanism that entails the activation of a "basic leucine zipper protein" to produce antioxidant substances [29]. Since NF-kB regulates the proinflammatory response, Nrf2 possesses anti-inflammatory qualities. Numerous cell types include proteins that contain flavonoids. Among these proteins are the cryptochromes [30, 31]. According to a recent study, blue light via cryptochrome 1 (CRY1), which is present in the hair follicle after being exposed to light with a wavelength of 453 nm, may be advantageous for the growth of hair. Anagen phase lengthening was observed in ex vivo hair follicles, which could be connected to an increase in CRY1 levels brought on by exposure to blue light [32].

Blue light also triggers the release of free nitric oxide (NO) in the dermis. Chemiluminescence detection (CLD) detected the quantity of NO that developed from S-nitroso albumin and aqueous nitrite solutions at physiological pH when blue light at 420 or 453 nm was present. This process was dependent on Cu^{1+} [29]. When blue light was applied to human skin specimens *in vitro*, electron paramagnetic resonance spectrometry found that the intradermal levels of free NO were significantly increased. When blue light was applied to human skin, CLD *in vivo* testing on subjects in good health revealed both significant NO translocation from the skin's surface into the underlying tissue and significant NO emission from the exposed skin area. Peroxynitrite, which is created when NO combines with superoxide, may damage DNA and cause cell damage, however, apoptosis has not been observed [33]. However, a study found that blue light hindered the proliferation of human keratinocytes and cutaneous fibroblasts. Certain ideas suggest that blue light affects mitochondrial function through cytochrome c oxidase, complex IV of the electron transport chain, which is found

in the mitochondrial membrane. Blue light at a wavelength of 430 nm restores the mitochondrial respiratory function after it is suppressed by NO [34]. Opsin (OPN), which are G-protein receptors, are activated by blue light, so their function is also investigated. Opsins fall into different types based on the locations of expression. OPN2, OPN3, and OPN4 are expressed in the epidermis. The opsin receptor may be stimulated by blue light, resulting in transient receptor potential channels that release calcium and activate calcium/calmodulin-dependent protein kinase-II (CAMKII), which modifies the transcription of genes [35]. Anagen hair follicles were found to express OPN2 (Rhodopsin) and OPN3 (Panopsin, Encephalopsin), in addition to the skin. Blue light irradiation (3.2 J/cm2, 453 nm) extended the anagen phase in hair follicles, according to one of the ex vivo investigations. Studies have also examined the role of optin in regulating melanogenesis and pigmentation, although only in Fitzpatrick skin types III and higher. It was found that blue light has an indirect effect on calcium-dependent melanogenesis through OPN3 and a direct effect on melanocytes. Blue light causes multimeric tyrosinase to develop, which in turn causes tyrosinase stimulation in melanocytes of the higher Fitzpatrick phototype [29].

Figure 1



Possible mechanism of the effect of artificial light and tanning on the development and progression of skin cancer. The sources of artificial light, including laptops, tablets, smartphones, tanning beds, UVA and UVB penetrate the skin and cause harm to DNA such as breaks in DNA strands, suppression of the immune system, genetic mutations, and oxidative stress, ultimately resulting in skin carcinogenesis.

How does Blue Light Cause Skin Damage?

It has been suggested that blue light would interfere with skin cells' nightly pattern, which is essential for skin cell recuperation and maintenance. In addition, blue light at 410 nm lowered the gene transcription of the PER1 gene in keratinocytes, a clock gene that serves an essential part in the rhythm of the circadian cycle, suggesting that human skin cells tend to adjust the synthesis of the clock gene by responding to light perception [36]. Free radicals may be produced by human skin exposed to blue light due to a decrease in carotenoids. This oxidative stress on melanogenic precursors is assumed to be the source of changes in pigmentation, including sudden and persistent skin darkening. The colouring is steady and becomes deeper. Melan-A-positive cells found in skin exposed to blue light provided evidence in favour of it [37]. The melanocytes' ability to operate is disrupted by the quantity of blue light that is administered to the skin, leading to hyperpigmentation, melasma, and uneven and excessive dark patches on the skin. Nevertheless, the only individuals who exhibit hyperpigmentation as a result of exposure to visible light are those with darker skin tones [38, 39]. This behaviour can be explained by the tyrosinase and dopachrome tautomerase protein complex, which is more common in melanocytes seen in darker complexion types. Furthermore, another study showed that blue light activates nuclear factor b (NF-B) and activator protein 1 (AP-1), which in turn stimulates the synthesis of the proinflammatory cytokine TNF. Once an individual's skin is exposed to similar amounts of UVA radiation, this causes redness and swelling [40].

In general, blue light can generate ROS, which are unstable substances that contain oxygen and interact with other molecules. The most common free radical produced by blue light exposure is superoxide (O2), an extremely reactive anion radical produced by the flavins. Research suggests

that the production of superoxide by blue light may contribute significantly to the ageing of the skin and carcinogenesis [41]. Excessive exposure to ROS can damage skin cells, speed up ageing, cause hyperpigmentation, and lead to melisma. ROS can also cause inflammatory processes and the breakdown of healthy collagen and elastin, which further contributes to skin laxity, early ageing, and wrinkles. Blue light triggers the activation of matrix metalloproteinases (MMPs) in skin cells, which have been demonstrated to degrade collagen and accelerate the ageing process [29]. These MMPs inhibit the production of new collagen in addition to degrading the already-existing collagen, which stops healing. In addition, antioxidant levels are impacted in ROS-affected cells. The body becomes depleted of these species after being exposed to blue light because they are removed by antioxidants in the skin. Up to 24 hours may pass before the endogenous healing occurs. It has been discovered that exogenous antioxidants used externally, internally, or both, are beneficial when it comes to UV radiation; the effect of blue light is still being investigated [42]. Hydrogen peroxide swiftly replaces most of the superoxide. It's possible that blue light damages cells more by continuously generating very small quantities of radicals which might evade the body's defenses and permanently damage DNA than by overwhelming antioxidant defenses [43].

Artificial Light at Night and Cancer

Cancer is the primary cause of illness and death globally, accounting for 8.2 million cancer-related deaths and 14.1 million cases reported in 2012. The incidence of cancer is predicted to rise to 22.2 million cases in 2,030. Lung, breast, colorectal, and prostate cancers are the most prevalent cancers worldwide, accounting for four out of every 10 cases of cancer diagnosis [44]. Several risks have been researched and found to be important in the development of cancer. In countries with low or middle incomes, alcohol drinking, smoking, and a diet poor in fruits and vegetables are key risk factors for cancer; in high-income nations, alcohol use, smoking, and obesity are major causes of cancer. Cancers of the lungs, oesophagus, mouth and throat, blood, skin, bladder, liver, colon, kidneys, breast, and prostate have all been related to environmental carcinogens, which also include soil and drinking water contamination [45-47]. Artificial light at night (ALAN), which is a type of light pollution, has been linked to breast cancer in recent times. Melatonin functions as a mediator between the environment and the epigenome. Additionally, night shift workers may be more susceptible to colorectal cancer because of ALAN. ALAN not only has an undesirable impact on people who are directly in contact with it, but it also has a detrimental impact on "protected areas," which are unaltered natural habitats for plants and animals that are essential to human survival [48].

According to the International Union for Conservation of Nature (IUCN), protected areas are "clearly defined geographical spaces, recognized, devoted and controlled, through constitutional or other efficient means that promote the permanent conservation of biodiversity with linked ecological services and cultural values". These areas include national parks, reserves, and wildlife and forests. They additionally safeguard humans from catastrophic events, offer clean drinking water, food, and medicine, and aid in the fight against climate change [49]. However, there is currently no evidence that the phenomenon of ALAN in protected areas can cause cancer in humans, although it can still have this effect. This study discovered that even after controlling for factors such as population density, air pollution-related particulate matter, national energy consumption, and the amount of land covered by forests, artificial light exposure at night causes cancer in humans [50]. This can affect the entire population, not just members of specific professional groups like nurses, and could be caused by the circadian system being disrupted by excessive light exposure at night. Another theory is the relationship between artificial evening light and the hormone melatonin, which is created during the dark and promotes sleep. Consequently, melatonin secretion, which usually peaks in the middle of the night, maybe suppressed by exposure to night light [51].

The artificial light at night raised the likelihood of breast cancer and colorectal cancer in women working rotating night shifts; it should also be noted that the variation in the age-standardized impact rates of breast and colorectal cancer explained by PALI was discovered to be higher when compared to other cancers; in addition, PAHI had a strong association with all kinds of cancer,

lung, breast, and colorectal cancer, and this correlation stayed essential after modification for confounding for colorectal cancer and somewhat significant for breast cancer [52]. Furthermore, the diversity in malignancies demonstrated by PAHI was nearly three times greater in the case of colorectal and breast cancer than it was for PALI. More developed nations had an ASR of 1.8 times greater than less developed nations for all cancer types (except for non-melanoma skin cancers). Consistent results were found, i.e., the ASR rose as the countries' wealth levels rose. The incidence of many malignancies varies according to human development as well. The relationship between PALI and PAHI and the ASR of all cancer types as well as the four most prevalent cancers worldwide was examined according to the nation's income level [53]. PALI showed a strong positive correlation with breast cancer in upper-middle-income nations and colorectal cancer in low-income countries. In low-income nations, PAHI significantly correlated positively with lung cancer; in low-middle-income countries, with colorectal cancer; in upper-middle-income countries, with all types of cancer; and in high-income countries, with breast cancer [52]. This suggests that reducing the risk caused by ALAN can reduce the occurrence of these malignancies in these nations.

It is not possible to comment on the mechanism of cancer causation owing to ALAN in guarded regions because this is the initial study to examine the connection and more thorough research is required. The artificial blue light which is currently widely used since energy-efficient bulbs and LEDs are used, strongly disrupts the melatonin cycle. As a result, lighting systems that maintain the natural melatonin rhythm should be developed and put into use. When ALAN investigates potential causes of lung, breast, colorectal, and prostate cancers, these pathways must be taken into consideration [54]. The study has limitations since it was an ecological investigation rather than a direct examination of the relationship between human exposure to ALAN in protected areas and cancer risk. However, this data allows us to formulate the idea that ALAN may contribute to the causation of cancer in humans [53]. The notion derived from this study needs to be tested by more research. There is a considerable correlation between artificial light at night and all types of cancer, including colon, prostate, lung, breast, and skin cancer [55].

Conclusion and Future Directions

Artificial light and tanning have a substantial correlation with skin cancer due to their intricate signalling and route systems. It has been demonstrated that the skin's response is significantly influenced by both the intensity and wavelength of blue light exposure. Minimal exposure can be therapeutic for many dermatological conditions; however, prolonged exposure can have several negative effects, such as oxidative stress, DNA damage, and enhanced melanogenesis which results in pigmentation and photoaging. Since exposure to blue light pollution is inevitable, people who often get exposed to it must take several precautions. There is a complicated connection between artificial light, tanning, and skin cancer that needs more research. The cumulative consequences of frequent exposure to artificial light, especially from indoor tanning salons and tanning beds, should be studied. Furthermore, studies should look into the interactions between artificial light exposure and other skin cancer risk factors such as genetics, lifestyle, and environmental factors. Furthermore, knowing the precise molecular pathways that artificial light triggers in skin damage and cancer formation is essential and will pave the way for future studies in several areas.

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