Chapter 7

Skin Cancer Prevention Strategies

Lisa Passantino, Max Costa and Mary Matsui

Additional information is available at the end of the chapter

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1. Introduction

Ultraviolet radiation (UVR) has been identified as the primary etiologic agent for the induction and promotion of most skin cancers. The first associations between solar UVR and skin cancer were acknowledged by the scientific community in 1927. Since then, increasing evidence for the role of UVR in the causation of skin cancer has resulted in the listing of solar and artificial UVR as a human carcinogen by the International Agency for Research on Cancer (IARC) in 1992. Broad spectrum (UVA and UVB) UVR was categorized as a human carcinogen by the National Toxicology Program in 2005. UVR from the sun causes approximately 90% of malignant melanomas and non-melanoma (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC]) skin cancers [1]. The non-melanoma skin cancers make up one third of all cancers around the world [2]. According to the National Cancer Institute, in the United States melanoma has one of the fastest increasing incidence rates. It is estimated that more than two million new cases of skin cancer will be diagnosed in 2012 [3-5]. Prevention of skin cancer is possible since UVR is known to be the central causative agent. National educational programs have emerged globally to deliver the message that unprotected sun exposure increases the risk for developing skin cancer, and present multiple behaviors that when followed together reduce the risk of photocarcinogenesis.

The goal of this chapter is to present a variety of skin cancer prevention strategies in the context of existing scientific knowledge on photocarcinogenesis. The connection between UVR exposure and skin cancer has been shown in numerous epidemiological, *in-vivo*, and *in-vitro* studies. Health professionals and government agencies have been communicating the dangers of UV exposure and the benefits of adopting primary and secondary prevention practices to lessen skin cancer incidence and mortality [1, 6]. Primary prevention strategies to protect against skin cancer are to wear broad spectrum sunscreen, seek shade, avoid the outdoors during peak daytime hours, and to wear protective clothing. Intentional UVR exposure for the purpose of tanning (indoor or outdoor) or stimulation of vitamin D synthesis is strongly

discouraged. There is scientific evidence that indicates oral and topical supplementation with antioxidants, vitamins, and phytochemicals is beneficial for chemoprevention. Secondary prevention for skin cancer is performing periodic examinations of the skin for suspicious growths, and having dangerous-looking growths excised by a dermatologist. Practicing a combination of these skin cancer prevention strategies will reduce the risk of skin cancer.

2. Photocarcinogenesis

Solar UVR is composed of UVA (320-400 nm), UVB (290-320 nm), and UVC (200-290 nm). The atmospheric ozone layer inhibits all UVC and some UVB from reaching the surface of the Earth. The composition of UVR that reaches humans is approximately 95% UVA and 5% UVB, depending on factors such as cloud coverage, weather, thickness of the ozone layer, and latitude. UVA can penetrate deep into the dermis, while most UVB is absorbed by the stratum corneum in the epidermis but some passes into the upper dermis [7]. Human skin has evolved protective mechanisms against solar UVR. Melanocytes produce melanin that absorbs and scatters light in the lower epidermis [8]. The stratum corneum scatters UV light, and stratum corneum, spinosum, and basale can absorb UV light. Endogenously produced antioxidants and DNA repair enzymes protect skin cells from the damaging effects of UVR [9, 10].

Irradiation of the skin with UV damages the tissue and cellular components, and contributes to skin aging and carcinogenesis. The characteristic adverse effects of UVB include sunburn, inflammation, immunosuppression, erythema, and DNA damage. UVA exposure is primarily associated with the generation of reactive oxygen species (ROS), some oxidative DNA damage, cell membrane oxidation, and can result in immunosuppression. UVA indirectly causes oxidative DNA damage through the generation of ROS. The oxidation of guanine bases to 8-hydroxy-2'deoxyguanine (8-OH-dG) is primarily associated with UVA irradiation. UVB can induce oxidative stress indirectly through the activation of the inflammatory cells. Signature mutagenic DNA lesions caused by UVB consistently found in skin cancers are cyclobutane pryimidine dimers (CPD), pyrimidine-(6-4)-pyrimidine photoproducts, and C → T transitions [6, 7, 11-16]. Signature UVB mutations, CPDs and G:C → A:T transitions, have been found to localize in the superficial epithelial layers of human SCC samples, while signature UVA mutations, 8-OH-dG and A:T → C:G transversions, localized in the basal layers [15]. This distribution of DNA lesions is consistent with knowledge that UVA penetration into the skin is deeper than UVB penetration. Signature gene mutations found in skin cancers are those of tumor protein 53 (p53) tumor suppressor gene and proto-oncogene B-raf. Mutations to p53 are particularly detrimental because p53 plays a central role in pausing the cell cycle to allow time for DNA repair [2, 13]. UVR exposure can induce signal transduction pathways, such as mitogen-activated protein kinase (MAPK) and activation of transcription factor AP-1 that regulate cell growth, differentiation, apoptosis, and production of pro-inflammatory cytokines [17].

Inappropriate cell proliferation and survival contributes to carcinogenesis. Severely damaged DNA that cannot be repaired triggers skin cells to undergo apoptosis. Cells that survive the

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damage could carry mutations if the repair was not carried out perfectly [18]. There is a greater tendency for damaged keratinocytes to undergo apoptosis than damaged melanocytes, possibly to preserve melanin-producing cells for photoprotection [19]. In addition to genotoxic effects, UVB exposure increases cell proliferation as is observed in animal models where hyperproliferation of the epidermis and inflammation are the result of prostaglandin and epidermal growth factor receptor activation by UVB [9].

UV exposure causes immunosuppression that promotes the development of skin cancer because the immune system is less likely to detect and eliminate cancer cells. UVA and UVB separately can suppress cutaneous immune responses in humans, and the magnitude of immunosuppression is greater when they are combined [20]. UVR induces physical alterations to cell surface proteins in the epidermis. These structural changes create neoantigens that would be attacked by the immune system. It is believed that the human adaptive immune system has evolved such that recognition of antigens is suppressed by UVR, thus reducing the risk of auto-sensitization. Langerhans cells, the antigen presenting cells of the skin, migrate out of the epidermis to local lymph nodes for several days after UV exposure [18]. The Langerhans cells activate T helper type 2 cells, which suppress immune reactions by releasing immunosuppressive cytokines [13, 21]. The downside to this mechanism is that cancer detection capabilities are suppressed in addition to autoimmune reactions [18].

UVR is considered to be a complete carcinogen since it can induce tumor formation by itself, and both UVA and UVB contribute to skin carcinogenesis. Since UVB is a more potent and direct inducer of DNA damage than UVA, it is thought to play more of a role in the initiation stage of tumorigenesis while the effects of UVA are thought to promote the development of the tumor [7]. UVR can be coupled with other chemical carcinogens to promote tumor development. The combination of solar UV and sodium arsenite causes SCC in mice, but sodium arsenite alone cannot cause SCC. This is an example of how UVR can act as a cocarcinogen [22].

3. Susceptibility factors for UV-induced skin damage and cancer

Relative endogenous protection capacity against UVR is a major factor in determining susceptibility to skin cancer. Individual differences in skin pigmentation, DNA repair, endogenous antioxidant levels, and impact the biological response to UVR [17]. The Fitzpatrick skin type (FST) was created in the 1970s as a method to classify people by the intensity of their erythema response to UVR. It can be used to predict response and susceptibility to skin cancer since lighter-skinned individuals with low FST tend to be more sensitive to UVR than darker-skinned individuals with high FST. There are six FSTs, with FST I being the most sensitive to sunlight and FST VI being the least sensitive. People that are FST I have white skin, may have freckles, blue or green-colored eyes, and red hair. People that are FST VI have black skin and hair, dark-brown eyes, and rarely experience sunburn [8]. Constitutive skin color should not be confused with FST because FST is based on the biological response not ethnicity [23]. It is no coincidence that the highest incidence rates of non-melanoma skin cancer are found in

regions with light-skinned populations such as Australia, Switzerland, and Ireland [2], and that the highest registered incidence of melanoma is found in Australia (Geller et.al, 2012). There is a 20 times greater incidence of malignant melanoma in Caucasians than in African-Americans in the United States [19]. One reason for this difference is that darkly pigmented skin responds to UVR differently than light pigmented skin. In African-Americans, DNA damage is not prominent below the epidermis, and damaged skin cells are more likely to undergo apoptosis. It is believed that the melanin in more highly pigmented individuals provides a higher level of protection than in light skinned individuals. By absorbing UV light, melanin is protective, but it is not enough to give 100% protection, so more highly pigmented people are still prone to UV-induced skin damage and can still get skin cancer [23].

The effects of UV damage on the skin are cumulative. The total number of severe sunburn incidences and lifetime dose of UVR are important factors to consider when determining skin cancer susceptibility. Outdoor workers have a greater risk of developing SCC than indoor workers because their skin experiences chronic irradiation with solar UV. Spending long periods of time outdoors for recreational purposes is associated with increased risk of melanoma [17]. Major risk factors for developing melanoma are the number of nevi and number sunburns experienced during childhood and adolescence [6, 17].

4. Photoprotective behaviors

Acute UVR exposure has deleterious effects on the skin, and contributes to the cumulative effects of lifetime UV exposure. Cellular damage and DNA mutations caused by UVR, if not repaired, can accumulate in the skin and contribute to skin aging and increase skin cancer risk. Melanomas typically develop in areas of the skin that are occasionally exposed to sunlight, while non-melanomas tend to develop in areas of the skin that are frequently exposed to sunlight [19]. Therefore, it is important to protect all areas of skin from UVR by practicing a combination of photoprotective behaviors. The most common form of sun protection that comes to mind is sunscreen, but it is not the only method. Comprehensive sun protection programs endorsed by healthcare professionals include the use of broad spectrum sunscreen, wearing protective clothing, staying in the shade and limiting sun exposure especially at times of peak intensity (10am-2pm), and avoiding indoor tanning devices [8, 9, 24]. Sand, water, and snow reflect UV rays, so protective measures should be taken seriously when in these environments[19]. These core photoprotective methods should be followed by all people regardless of skin color and FST, and especially followed by susceptible populations. However, only 60.6% of adults surveyed in the United States in 2010 reported that they usually or always follow at least one photoprotective behavior when spending time outdoors [25].

Wearing protective clothing means that the clothing should be a physical barrier to sunlight, and should cover as much of the body as possible. Protective clothing includes wearing long pants or a long skirt, and long sleeves. Hats that shade the face, neck and ears are part of protective clothing. Most men wear a baseball cap for protection, but these caps do not shade the face, neck, and ears as well as a wide-brimmed hat that offers more coverage

[25]. Sunglasses also fall under protective clothing as they protect the eyes and areas around the eyes from UVR and reduce the risk of developing ocular melanoma. The best protection against solar UVR would be obtained by through a combination of protective clothing and sunscreen [26].

Consumers are advised to select sunscreens that offer broad spectrum (UVA and UVB) protection with a sun protective factor (SPF) of 15 or greater by the United States Food and Drug Administration (FDA) [1]. Sunscreens are applied directly onto the skin and they reduce UVR penetration by reflection or absorption [9]. Broad spectrum sunscreens can protect against UV-induced erythema and immunosuppression [21]. Sunscreen use is a method of chemoprevention, meaning it can suppress or prevent the progression of premalignant skin lesions into cancer [19]. Sunscreen with SPF of 15 or greater reduces skin cancer risk, and prevents both melanoma and non-melanoma skin cancers [24]. The amount of protection is related to the SPF level and the amount of sunscreen applied. Lower SPF sunscreens are less effective, especially when applied inadequately, than higher SPF sunscreens [27].

Consistent daily application of sunscreen is especially recommended for individuals who are more susceptible to developing melanoma [19]. Consistent long-term daily application of broad spectrum sunscreen to the head and arms was shown to decrease the incidence of malignant melanoma compared to discretionary sunscreen use in a randomized controlled prospective study of Australians [28]. Fewer melanocytic nevi develop on Caucasian children who routinely used SPF 30 broad spectrum sunscreen when going outdoors for more than 30 minutes than children who do not use sunscreen [29]. Sunscreen itself is safe and does not increase the risk of skin cancer. Meta-analysis of 11 case-control studies did not find an association between sunscreen use and increased risk of developing melanoma [30]. Some studies have reported an association between topical sunscreen use and melanoma, but this relationship is probably connected to inappropriate and compensatory use of sunscreen.

The compensation hypothesis is that people tend to wear less protective clothing and/or prolong the amount of time spent in the sun when they use higher SPF sunscreens. This compensatory behavior actually defeats the purpose of using sunscreen, and it increases risk of skin cancer because the risk of sunburn is increased [1, 17, 24]. In an observational study of European sunbathers, it was found that the duration of time spent sunbathing was up to 25% longer for those who used SPF 30 than those who used SPF 10 [31]. Sunscreen is meant to be used as an adjunct to other methods of photoprotection and not to extend the amount of intentional sun exposure time. Consumers generally have a false sense of security when wearing high SPF sunscreens, especially those of SPF of 50 and greater, and they often forgo other methods of photoprotection, such as wearing protective clothing. Interestingly, the consumers who wear sunscreen and spend more time sunbathing are generally those who are more sensitive to UVR. This likely explains why the incidence of melanoma continues to increase despite more people wearing sunscreen [26].

Another behavior that compromises the effectiveness of sunscreen is inadequate sunscreen application thickness. Sunscreen accumulates in fissures on the skin, so it is necessary to apply enough product to fill in the fissures and to fully cover epidermal ridges [32]. Most consumers apply sunscreen below the standard thickness used for the international SPF test, which is 2

mg/cm^2 [1]. Consumers apply between 0.5 and 1.2 mg/cm^2 sunscreen and consequently do not receive the expected amount of sun protection. The actual SPF of the sunscreen can be decreased by 20-50% compared to the rated SPF when it is applied improperly [19, 27, 32]. The reduction of actual SPF as a function of application thickness was recently demonstrated during a study in which Chinese women applied SPF 4,15, 30, or 55 sunscreen at 0.5, 1, 1.5, or 2 mg/cm^2. The actual SPF was calculated for each individual after exposure to solar simulated UVR. It was determined that at the standard application thickness of 2 mg/cm^2 the observed SPF was similar to the rated SPF. However, as application thickness decreased there was an observed linear decrease in actual SPF for SPF 4 and 15 sunscreens, and an exponential decrease in the actual SPF for the SPF 30 and 55 sunscreens [27]. Inadequate application of lower SPF sunscreens may put consumers at greater risk of sunburn and skin cancer than inadequate application of higher SPF sunscreens.

To compensate for inadequate application thickness, the American Academy of Dermatology recommends using a minimum of SPF 30 sunscreen, which is higher than the FDA's recommendation of 15. High SPF sunscreen should especially be used when going outdoors on days when the UV index is predicted to be high and there is greater risk of overexposure. Spending even 45 minutes outdoors unprotected on a day of moderate UV index value can cause skin damage [33]. One application of sunscreen may not be enough if an individual stays outdoors for long periods of time and/or is involved in activities that cause the skin to perspire or get wet.

Proper use of sunscreen includes reapplication every two hours, and more frequently when sweating, swimming, or towel drying [24]. It is important to reapply sunscreen because the active components may become unstable and lose activity during exposure to sunlight [27]. The FDA does not currently require a photostability test for sunscreens [1]. The duration of water resistance is limited, so water resistant sunscreens need to be reapplied frequently when swimming or sweating [24]. It is required by USFDA monograph that the duration of water resistance (40 or 80 minutes) be indicated on the label to instruct consumers about when they should reapply the sunscreen [1]. Spray on sunscreen is thought to be less effective than traditional sunscreens because it is not rubbed directly onto the skin. The FDA is currently investigating the effectiveness of spray on sunscreens, and is performing inhalation safety testing as well [24].

Indoor tanning is a popular alternative to natural tanning because it can be done at any time of the year, but it is actually very dangerous because the skin is intentionally exposed to intense UVR repeatedly over short periods of time. Tanning bulbs emit predominantly UVA, which is known to cause high levels of oxidative stress in the skin and contribute to greater risk of melanoma [26]. They also emit a small amount of UVB that primarily damages the DNA in skin cells during indoor tanning sessions. Artificial UVR from indoor tanning equipment is considered to be carcinogenic along with solar UVR, yet approximately 28 million people expose themselves to it annually in the United States [34].The likelihood of developing SCC is 2.5 times greater for people who use tanning beds, and the likelihood of developing BCC is 1.5 times greater [35]. Individuals who have ever used tanning beds have a 15% greater risk of developing melanoma than individuals who have never

been in a tanning bed [19]. The age at which people start using indoor tanning technologies is a risk factor for developing skin cancer as well. The lifetime risk of developing melanoma is 75% higher in people who first use indoor tanning beds before the age of 35 [35]. Younger people have a greater tendency to use indoor tanning devices, possibly because of the social perception that having a tan is attractive. More people between the ages of 18-24 used indoor tanning devices than people over the age of 25 in 2010. In both age groups, females exposed themselves to artificial UVR to obtain a tan more than males did. Most of these adults were non-Hispanic whites [25]. The high skin cancer risk associated with indoor tanning coupled with the addictiveness of the behavior has caused many states in the U.S. to pass laws restricting the use of indoor tanning devices by minors in 2012 [19].

Consumers should be aware of their skin's reaction to sunlight when they are outdoors, and take appropriate action when noticing adverse reactions to sun exposure. Regardless of sunscreen application and whether sun exposure is intentional or unintentional, if the skin becomes red (indicative of cellular damage) and uncomfortable at any time it is prudent to immediately find shade and put on protective clothing [26]. Parents should be vigilant of signs of redness in their childrens' skin as well. Infants and children should be kept in the shade out of direct sunlight [2]. Self-examination of skin for suspicious growths and nevi is also recommended for early detection of skin cancer [2, 17].

5. Chemoprevention with topical and dietary antioxidants, phytochemicals, and vitamin supplementation

Chemoprevention is the use of natural or synthetic agents to prevent or reverse the development of cancer [21]. Sunscreen use is considered a form of chemoprevention because it contains compounds, such as avobenzone and octyl salicylate, that inhibit UVR from damaging the skin. Supplementation of sunscreens with various phytochemicals and antioxidants has been shown to improve the function of sunscreens in preventing photodamage [13]. Oral intake of certain vitamins, antioxidants, and plant extracts can provide systemic protection as well.

A diet rich in fruits and vegetables has generally been associated with lowering the risk of a variety of diseases and cancers, including skin cancer. Regular consumption of fruits and vegetables was associated with a decreased risk of SCC in a dietary study of 1360 adults in Nambour, Australia. In this study it was also found that a diet high in meat and fat was positively associated with the development of SCC but not BCC [36]. Fruits and vegetables contain bioactive phytochemicals, such as flavonoids, polyphenols and carotenoids. These compounds can boost antioxidant and immune system defenses in the body, including in the skin [37]. Carotenoids and flavonoids naturally protect plants from solar UVR, and consumption of these phytochemicals can provide systemic photoprotection for humans [8]. Polyphenols from tea have been shown to protect against UVB-induced contact sensitization, inflammation, carcinogen-induced cancer of the skin, lung, and esophagus in rodent models [37].

Photooxidative damage occurs when the antioxidant defense mechanisms of the skin are overwhelmed by UV-induced ROS, particularly from UVA. ROS that contribute to photocarcinogenesis and photoaging include singlet oxygen, superoxide radical anion, hydroxyl radical, perhydroxyl radical, and hydrogen peroxide [10, 13, 37-39]. Endogenous antioxidants that scavenge for ROS include superoxide dismutase, glutathione peroxidase, ascorbate, alpha-lipoic acid, and catalase [16]. Excessive ROS generated during UV exposure depletes endogenous antioxidants, and causes a state of oxidative stress in cells that can damage cellular proteins, lipids, DNA, trigger apoptosis, and contribute to photocarcinogenesis [14]. Incorporating antioxidants into sunscreens can ameliorate UV-induced tissue damage and promote DNA repair [13].

Human studies with antioxidant supplementation to sunscreens have been successful at demonstrating the benefits of including antioxidants in the formulation. In a human study, the combination of a several antioxidants, including ascorbyl phosphate, tocopherol acetate, *Echinacea pallida* extract, chamomile extract, and caffeine, with sunscreen best protected the skin compared to sunscreen alone after repetitive irradiation with solar simulated UVR [40]. A significant inhibition of UVR-induced melanin synthesis was observed in the presence of antioxidants alone. There was a synergy between the antioxidants and broad spectrum sunscreen, making the combination more protective than either the antioxidants or sunscreen alone. The antioxidant alone was able to prevent hyperproliferation and thickening of the epidermis that is a typical biological response to chronic UVR exposure. UV-induction of cytokeratin 16 and MMP9 was also suppressed by antioxidant cocktail and sunscreen combination [40]. In another study using a similar combination of antioxidants, sunscreen with antioxidants or sunscreen alone were equally able to protect against immunosuppression as measured by immunohistochemical staining for Langerhans cells. Less induction of tissue remodeling protein MMP1 was observed with the sunscreen plus antioxidant formulation [13]. Taken together, this data demonstrates additive or synergistic effects of antioxidants for photoprotection.

5.1. Green tea

Tea (*Camellia sinensis*) drinking has been associated with health in many cultures. Green tea consumption has been associated with reduced cancer risk, including SCC [17]. It has been demonstrated in mouse skin tumor models that green tea inhibits photocarcinogenesis [37]. Epigallocatechin-3-gallate (EGCG) makes up approximately 40% of all the polyphenols found in green tea, and it is believed to be the main polyphenol responsible for the beneficial health effects of green tea [12, 37]. White and black teas also have protective effects. Theaflavins, the polyphenols found in black tea, can inhibit the UVB-induced activation of cell signaling through AP-1, MAPK, and extracellular matrix receptor-activated kinase [17]. Topical application of white or green teas have been shown to protect against the loss of Langerhans cells after solar simulated UVR exposure in both human subjects and in an *ex vivo* skin explant model [21]. In another human study, EGCG inhibited UVB-induced erythema and inflammation. Fewer leukocytes infiltrated the skin when EGCG was applied prior to irradiation with UVB, and less prostanoids were synthesized [37]. In addition to being able to suppress the

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inflammatory and immunosuppressive effects of UVB, topical application of green or white tea has been shown to completely prevent the formation of 8-OH-dG adducts in human skin [21]. The reduction of DNA damage, aberrant cell signaling, inflammation, and immunosuppression are mechanisms exhibited by teas and tea extracts that contribute to their anti-cancer properties.

The amount of pre-treatment time and concentration of green tea polyphenols required to obtain optimal protection on human skin was elucidated in a study by Elmets et.al. In this study, skin on the back of six human subjects was pre-treated for 30 minutes with 0.25-10% solutions of green tea polyphenols. The skin was then irradiated with a solar simulator at twice the individual's minimal erythema dose (MED). At 24, 48, and 72 hours post-exposure erythema was quantified with a chromameter and biopsies were taken from the exposed sites. Erythema was found to be reduced in a dose-dependent manner at all time points and with all doses of green tea polyphenol that were used (figure 1). Pre-treatment with the polyphenols was noted to work best when applied immediately before exposure as opposed to several hours before exposure. Analysis of the biopsies revealed a 66% reduction in the number of sunburn cells, significantly less Langerhans cell migration at 4 days post-exposure, and a 55% reduction in DNA lesions. Subjects were also irradiated with 135 J/cm^2 UVA only, and pre-treatment with 5% green tea polyphenols significantly protected against UVA-induced erythema in that experiment [9]. The results of this study indicate that the use of green tea polyphenols is most effective at protecting the skin from UVR when used at a concentration of 0.25% or greater, with the greatest protection observed when applying a 10% solution 30 minutes before irradiation. Adding green tea polyphenols to sunscreens could enhance broad spectrum protection since they have been demonstrated to reduce UVA-induced erythema.

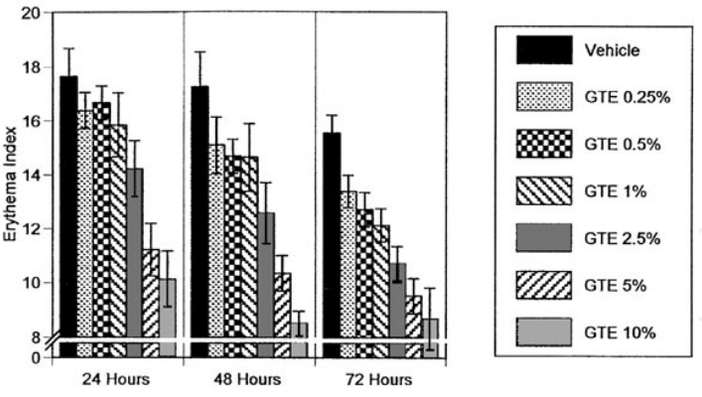

Figure 1. Effect of green tea polyphenols (GTP) on the erythema response evoked by 2-MED solar simulated radiation. Data represent the mean ± standard error of the mean erythema index at 24, 48, and 72 hours after irradiation with a solar simulator. Measurements were made with a chromameter on 6 volunteers. Areas of skin were pretreated with indicated concentration of an extract of green tea (GTE) 30 minutes before UV exposure. Reprinted from Cutaneous photoprotection from ultraviolet injury by green tea polyphenols, Journal of the American Academy of Dermatology, 44(3):425-32, Elmets CA, Singh D, Tubesing K, Matsui M, Katiyar S, Mukhtar H, (2001) with permission from Elsevier.

In a parallel experiment, Elmets et.al tested separate green tea polyphenols for ability to inhibit erythema on human subjects irradiated with solar simulated UVR. The polyphenols tested

were 5% solutions of EGCG, epicatechin (EC), epigallocatechin (EGC), or epicatechin-3-gallate (ECG). EC and EGC were not effective at inhibiting erythema, but EGCG and ECG were. The authors were intrigued by this finding because EGCG and ECG both contain a galloyl group at the 3 position, and this common structure between them could be the source of their effectiveness compared to the other polyphenols that were tested [9]. These results confirmed that EGCG is one of the polyphenols that contributes the most to the photoprotective effects of green tea.

5.2. Resveratrol

Resveratrol is a chemopreventive phytochemical found in grape skin and seeds, red wine, peanuts, and fruits. Topical application of resveratrol in hairless mice has been shown to reduce signs of oxidative stress and inflammation induced by UVB exposure [12]. Daily topical application of resveratrol in humans prior to irradiation with solar simulated UVR for four consecutive days provided significant protection against erythema, melanin synthesis, tanning, and sunburn cell formation compared to unprotected skin [10].

5.3. Pomegranate

Pomegranate is known for its strong anti-inflammatory, antioxidant, anti-proliferative, and anti-tumorigenic properties. Anthocyanidins and hydrolysable tannins are polyphenols found in pomegranate. In an animal study, hairless mice were irradiated with 180 mJ/cm^2 UVB after consuming 0.2% (wt/vol) pomegranate extract for two weeks. Analysis of skin biopsies taken from the mice revealed that pomegranate consumption resulted in the inhibition of UVB-induced skin edema, cell proliferation, infiltration of leukocytes, NFκB activation, COX-2 expression, CPDs, 8-OH-dG, and generation of hydrogen peroxide and lipid peroxidation [11]. These results suggest that regular consumption of pomegranate could provide systemic protection from UVB.

5.4. Lycopene

Lycopene is a carotenoid found in tomatoes, red bell peppers, watermelon and other red-colored fruits and vegetables. Lycopene consumption is believed to aid in the prevention of cardiovascular disease, diabetes, and cancer because of its strong antioxidant property. The bioavailability of lycopene is greater in cooked and processed foods than from fresh fruits. It has been recognized as one of the most powerful quenchers of singlet oxygen of all the carotenoids [41]. Dietary intake of lycopene or foods rich in lycopene can provide systemic photoprotection. Daily consumption of 55 grams of tomato paste with olive oil for 12 weeks protected individuals from solar simulated UVR-induced mitochondrial DNA damage compared to individuals who ate olive oil alone. Less induction of matrix metalloproteinases was also found, and the skin of the group that ate tomato paste tended to have a higher MED than the group that did not [41]. In another human study, individuals that consumed lycopene for 10-12 weeks developed about 40% less erythema than those that did not [8].

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5.5. Chocolate

Fresh cocoa beans contain high levels of polyphenols that are potent antioxidants. Most commercially available chocolate does not contain high antioxidants because conventional chocolate making diminishes antioxidant capacity. Chocolate that is specially prepared to retain high amounts of active flavanols can increase the MED in human subjects who ate it every day for 12 weeks compared to subjects who ate conventional chocolate [42].

5.6. Beta-carotene

β-carotene is a fat soluble antioxidant carotenoid found in many plants, and gives orange color to many fruits and vegetables, such as carrots and yams. It is a precursor to vitamin A, also known as provitamin A [43]. The effectiveness of β-carotene as a systemic photoprotectant in humans is dependent upon the dose and the duration of consumption before irradiation with UVR. Reports suggest that in order for β-carotene pre-treatment to be effective it should be consumed at a dose of 20 mg per day for at least 10 weeks, and moderate intake is insufficient to achieve photoprotection [8]. Meta-analysis of seven human studies on sunburn protection and β-carotene arrived at the same conclusion, and added that the mean photoprotection provided by β-carotene increases for each month beyond 10 weeks of consistent consumption, and β-carotene can provide system photoprotection with a maximal SFP of 4. [43].

While dietary supplementation with β-carotene protects against sunburn, it is not effective for preventing skin cancer when used alone. A data review of randomized control studies did not find a positive association between oral β-carotene supplementation and the prevention of melanoma or non-melanoma [44]. β-carotene supplementation could be used in combination with other photoprotective methods to reduce sunburn. However, dietary supplementation with β-carotene should be done with caution because at high levels it can create a prooxidative state that is damaging to the body. Consuming high amounts of β-carotene is not suggested for smokers, as it has been shown to increase lung cancer risk [44].

5.7. Vitamin C and Vitamin E

Vitamin C (ascorbic acid) and vitamin E (α-tocopherol) are photoprotective antioxidants that can be combined with other antioxidants like β-carotene or added into sunscreen to protect the skin from UVR. Vitamin E is a potent inhibitor of lipid peroxidation, and it is typically found in plant derived oils. Vitamin C has functions as a reducing agent and is an essential vitamin for humans. Vitamins C and E have a synergistic relationship; vitamin C can regenerate oxidized vitamin E at the cell membrane [38, 39]. Oral administration of 200mg/day vitamin C and 1000IU/day of vitamin E for eight days in humans reduces sensitivity to solar simulated UVR as observed by higher MED in subjects [38]. The combination of vitamin E with β-carotene has been shown to suppress UVR-induced erythema better than β-carotene alone when administered orally for 12 weeks [39]. Topical application of vitamin E onto hairless mice prior to irradiation with solar simulated UV has been reported to prevent immunosuppression [16].

5.8. Polypodium leucotomos

An organic extract of the tropical South American fern *Polypodium leucotomos*, given the commercial name "Fernblock", can be used orally or topically to protect the skin from solar UVR. This extract protects against the genotoxic effects of UVB by preventing the formation of CPDs, 8-OH-dG, and mitochondrial DNA damage. It induces the p53 tumor suppressor protein. The extract prevents UVR-induced inflammation through the inhibition of pro-inflammatory molecules (tumor necrosis factor alpha and nitric oxide synthase), COX-2, apoptosis of keratinocytes and fibroblasts, and general reduction of erythema and sunburn. One component of Fernblock, caffeic acid, prevents oxidative stress by inhibiting the formation of peroxide and nitric oxide upon exposure to UVR. Fernblock also prevents the immunosuppressive effects of UVR by suppressing the migration of Langerhans cells and activation of T helper type 2 cells. Remodeling of the dermal extracellular matrix by matrix metalloproteinase 3 is inhibited by the extract, and both collagen and elastin proteins are up regulated indicating that the extract may also fight photoaging. Topical application of the extract on hairless mice was reported to block UVB-induced skin tumor formation. All of these positive protective effects make Fernblock a potentially powerful photocarcinogenesis protective agent [14].

6. Vitamin D

Vitamin D is important for bone health, intestinal uptake of calcium and phosphate, and regulation of calcium and phosphate levels in the blood [2, 4]. Vitamin D is associated with the prevention of autoimmune disease, cardiovascular disease, and believed to have anti-inflammatory and anti-proliferative effects [45, 46]. The current recommended daily allowance for vitamin D is 400 IU for infants under 1 year old, 600 IU for persons 1-70 years old, and 800 IU for persons older than 70 years [47]. People who have vitamin D insufficiency are recommended to take 1,000 IU of vitamin D daily [48].

Lack of vitamin D results in poor enteral absorption of calcium that causes decreased blood levels of ionized calcium. This decrease promotes the breakdown of bone by osteoclasts to release calcium. By this mechanism, vitamin D insufficiency in adults can lead to osteoporosis. Childhood vitamin D deficiency causes Rickets disease. During the late 1800s to early 1900s Rickets disease afflicted more than 80% of North American and European children who lived in industrialized cities. After it was learned that a deficiency in vitamin D was to blame for the bone deformities caused by this disease, increasing exposure to sunlight and fortification of milk with vitamin D in the 1930s helped to reduce the incidence of Rickets in the United States [46, 47]. In addition to dietary sources, vitamin D can be obtained by cutaneous synthesis upon exposure to sunlight (figure 2). Upon irradiation with UVB, 7-dehydrocholsterol (provitamin D) in the skin is converted into pre-cholecalciferol (previtamin D_3). Pre-cholecalciferol undergoes a spontaneous isomerization into cholecalciferol (vitamin D_3). Vitamin D-binding protein (DBP) transports vitamin D_3 to the liver where it is hydroxylated by cytochrome p450 27A1 into 25-hydroxyvitamin D ($25(OH)D_3$) [2]. Further hydroxylation in the kidney or at the

http://dx.doi.org/10.5772/55241

skin modifies the vitamin into its active form called calcitriol ($25(OH)_2D_3$) [49]. Calcitriol binds to the nuclear vitamin D receptor (VDR), which then forms a heterodimer with the retinoid-X receptor and becomes a transcription factor that regulates the expression of cell cycle, cell proliferation, and apoptosis genes [2].

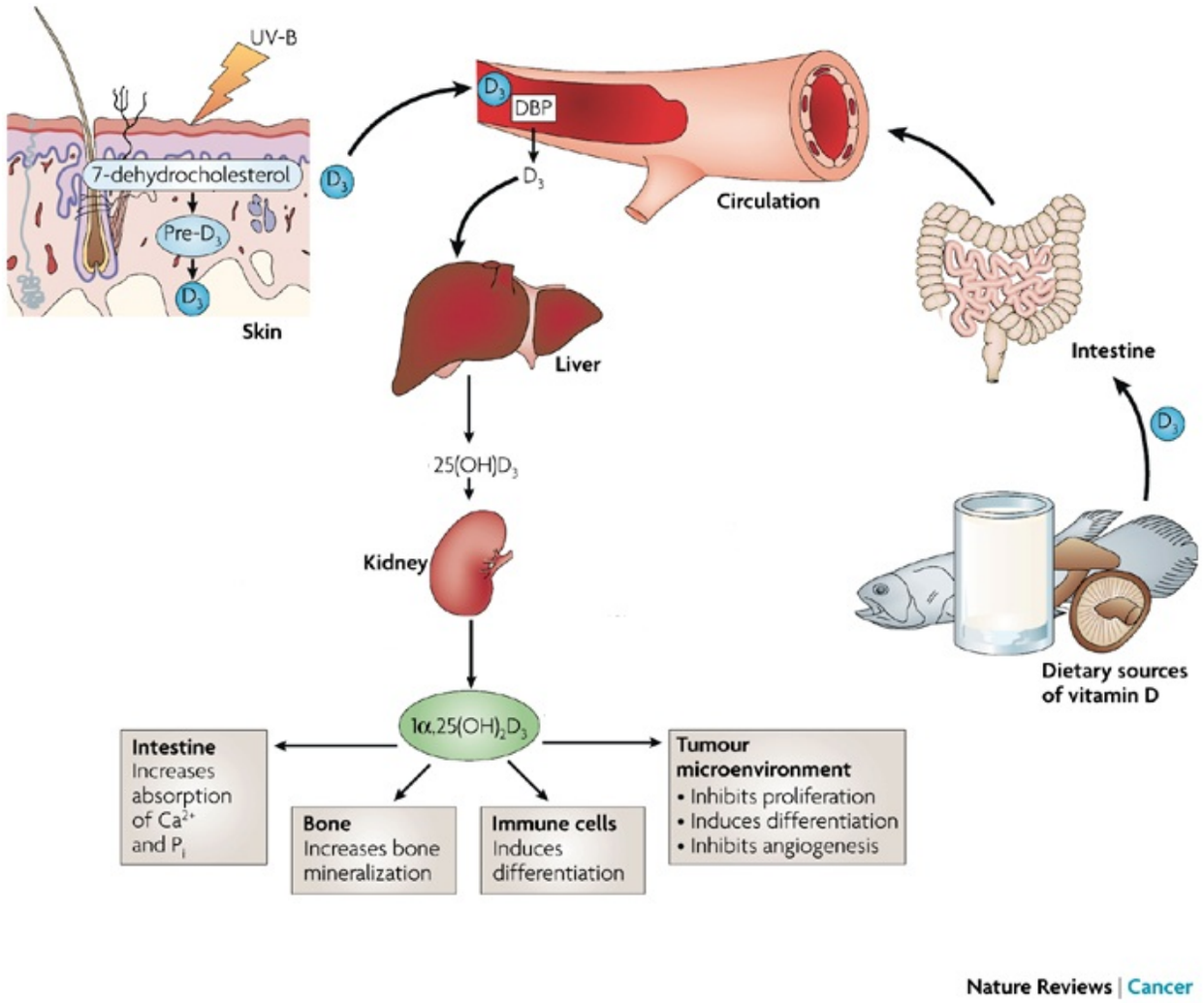

Figure 2. Vitamin D synthesis and biological effects. Reprinted by permission of Macmillan Publishers Ltd: Nature Reviews Cancer, Deeb KK, Trump DL, Johnson CS, Vitamin D signaling pathways in cancer: potential for anticancer therapeutics, 07(9):648-700 (2007).

There is contradictory evidence about whether vitamin D protects against cancer. A study conducted by the National Institutes of Health did not find a correlation between vitamin D levels and internal cancers [49]. Other studies have found that vitamin D can reduce the risk of internal cancers, particularly prostate and colorectal cancer [48]. It was reported in an observational study that individuals with the lowest serum levels of $25(OH)D_3$ had a 26% higher mortality rate when compared to those with higher vitamin D levels [45]. It is hypothesized that high blood levels of $25(OH)D_3$ result in higher levels of calcitriol that regulates cell proliferation. A number of cells in the body, including breast, colon, and skin, have the

enzymes required to make calcitriol. It is suggested that when vitamin D levels are high local production of calcitriol keeps cell proliferation in check and reduces risk of carcinogenesis [46]. Thus, it is speculated that vitamin D production in the skin is protective and sunscreen use diminishes protection by inhibiting vitamin D synthesis.

There is almost no evidence supporting the idea that the vitamin D deficiency epidemic is correlated to the overuse of sunscreen [48]. Sunscreen use may diminish photosynthesis of vitamin D, but it is not necessary or recommended to obtain vitamin D from intentional sun exposure. To maximize cutaneous synthesis of vitamin D, individuals would have to expose themselves to sunlight for the amount of time required to achieve one third of their MED, meaning the skin would incur damage to make vitamin D. Incidental sun exposure for 10-20 minutes on skin protected with SPF 15 or greater sunscreen could maximize cutaneous vitamin D synthesis while protecting the skin because sunscreen does not block all UV [48]. While some people find the idea of synthesizing their own vitamin D through intentional sun exposure holistic and appealing, the better option is to continue protecting skin from solar UVR with sunscreen and protective clothing, and to obtain vitamin D from dietary sources and incidental protected sun exposure. A variety of foods including milk, bread, cereal, yogurt, and multi-vitamins are fortified with vitamin D in the United States and are good alternatives to intentional exposure to sunlight. The use of indoor tanning beds to increase vitamin D levels is not advised [4, 48, 50].

Populations susceptible to vitamin D deficiency are the eldery, people with darkly pigmented skin, breastfed infants, and obese people. The suggestion that elderly and darkly pigmented populations intentionally expose themselves to UVR is not a good solution because these susceptible populations generally have poor cutaneous vitamin D synthesis. The ability to photosynthesize vitamin D in the skin decreases with age because there is less 7-dehydrocholesterol in the skin. People with darkly pigmented skin have increased melanin in the epidermis that inhibits cutaneous vitamin D synthesis [2, 46, 48]. It does not make sense for the elderly or people with darkly pigmented skin to intentionally expose themselves to sunlight to make vitamin D since the process is inefficient in their skin. Rather, they should take dietary supplements and incorporate foods fortified with vitamin D. Obesity is also a risk factor for deficiency of vitamin D. Vitamin D_3 is stored deep in the body fat of obese individuals and is not readily bioavailable to them during winter months, so they can only mobilize about half the amount of vitamin D_3 as persons with healthy weights [46]. Human breast milk contains less than 78 IU vitamin D per liter so it is recommended that infants also receive vitamin D supplementation [47]. Infants should not be exposed to solar UV to increase vitamin D synthesis [2]. Dietary supplementation with vitamin D is the best option for all people, especially those with reduced ability to synthesize and maintain vitamin D levels in their body.

7. Sun protection education

Social perceptions and miscommunications about the dangers of UVR exposure contribute to the continued incidence of sunburns and skin cancer. The message that sun safety should be

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practiced daily is not widely followed, as evident by the fact that people are more likely to follow skin protection methods while on vacation or at the beach than when participating in other outdoor recreational activities [19]. Intentional unprotected sun exposure for cosmetic purposes is prominent in young adults because of the perception that tanned skin is more attractive [48]. About 50% of people in the U.S. between the ages of 18 and 24 years old report having a sunburn in the last year, compared to about 35% of people over the age of 25 who reported having a sunburn in the last year [25]. This is coincides with the tendency for young people to expose themselves to solar and artificial UVR for tanning. Over one million people go to tanning salons on an average day in the United States [34], and most are under the age of 25 [25]. This risky behavior may contribute to melanoma being the second most common cancer in young adults between the ages of 15 and 29 years old [4]. In 2004, it was found that 69% of youths between the ages of 11 and 18 reported in a cross-sectional study survey that they had been sunburned that summer [19]. Summertime sunburns should not be taken lightly or treated as a normal occurrence. The risk of developing melanoma more than doubles for individuals who report having five or more severe sunburns during adolescence [19]. A study by the University of Miami on sun protection behavior in high school students found that white-Hispanics were not likely to use sunscreens, more than twice as likely to go tanning, and generally did not believe that they had a risk of getting skin cancer compared to white non-Hispanics [23]. This is an example of the need to educate young adults and teenagers who are unaware of the health risks associated with sun exposure.

Physicians play in important role in educating patients about sun protection. Primary care physicians should actively promote broad spectrum sunscreen use, and review proper application techniques with patients to reduce sunburn. They should educate patients about the use of sunscreen as an adjunct to the other sun protection methods, and warn patients not to use sunscreen as a tool for prolonging sun exposure because that behavior increases the risk of sunburn [19, 26]. They could point patients towards many informative public education websites about sun protection and skin cancer prevention that are available from government and non-profit organizations.

Skin cancer prevention awareness is spreading with the help of government organizations, such as the National Institutes of Health and National Council on Skin Cancer. Increasing numbers of advertisements for skin cancer prevention are seen on television, heard on the radio, and posted in public places. Major awareness advocates, programs, and campaigns include the SunSmart campaign in Australia and the United Kingdom, the European Skin Cancer Foundation, the SunAWARE non-profit educational organization in the U.S., the USEPA SunWise program, American Academy of Dermatology, the Skin Cancer Foundation in the U.S., and the American Cancer Society. These groups and programs aim to educate the public about skin cancer and encourage multi-step behavioral modifications to reduce the risk of developing skin cancer. The SunAWARE organization uses AWARE as an easy acronym to help people remember the steps of sun protection (figure 3). Skin cancer incidence rates have been stabilizing when compared to the rapid increases seen before the rise in establishment of government-sponsored sun protection programs [19]. The message is starting to be heard, as evident by an overall increase in adult sunscreen use between 2005 and 2010 [25]. Sun safety

awareness is encouraged by campaigns such as national "Don't Fry Day" that takes place on the Friday before Memorial Day in the U.S. and is supported by the National Council on Skin Cancer and SunWise program [5, 51].

Figure 3. Sun protection advice displayed on SunAWARE website using the acronym AWARE. http://www.sunaware.org/be-sunaware/

Product labeling is another means for providing specific information on how to protect the skin. Sunscreen labels are strictly regulated by the USFDA. In the most recent law passed on sunscreen labeling in 2011, known as the "final rule", the USFDA required a new indication statement, simpler labeling, and clearer instructions for the usage of water resistant sunscreen [1]. Instead of indicating protection against UVA and/or UVB, labels are required to state "broad spectrum" to simplify the choice for consumers. The effectiveness rating of the sunscreen must be listed next to the broad spectrum phrase in the same size and style font to encourage consumers to look for broad spectrum sunscreens with a high SPF rating. To teach consumers that broad spectrum sunscreens with SPF 15 and greater are more protective when combined with other sun protection measures than sunscreens with low SPF that are not broad spectrum, the following indication statement is required on all broad spectrum SPF 15 and greater sunscreens:

"**Sun Protection Measures**. Spending time in the sun increases your risk of skin cancer and early skin aging. To decrease this risk, regularly use a sunscreen with a Broad Spectrum SPF of 15 or higher and other sun protection measures including: • limit time in the sun, especially from 10 a.m. - 2 p.m. • wear long-sleeved shirts, pants, hats, and sunglasses" [1]

Previous labeling requirements were confusing and misleading about water resistance. Sunscreens resistant to water must be called "water resistant" and not "waterproof" because there is a limit to the amount of time that they are effective on wet skin. Likewise, the term "sweatproof" is also not permitted. Previous labeling indicating that a sunscreen was "water resistant" or "very water resistant" did not clearly differentiate between the two. It is now required that the label state how much time can be spent in the water, for example "water resistant (40 minutes)" or "water resistant (80 minutes)" is very clear about the duration of protection. Emphasis on the duration of water resistance encourages re-application of the sunscreen at appropriate time intervals [1].

Screening for skin cancer is an effective means of secondary prevention. There is a good chance that skin cancer is curable when detected early enough. Simple excision of the lesion that can be performed as an outpatient procedure by a dermatologist is an effective means of removing the cancer and increasing survival [17]. Designated skin cancer screening days help to identify malignant lesions before they progress to more dangerous stages. Organized skin cancer screenings in Germany have resulted in a 50% reduction in melanoma mortality in the screened population, indicating the usefulness and success of mass skin cancer screenings [6].

8. Conclusion

It is predicted that 40-50% of Americans will have non-melanoma skin cancer at least once before the age of 65 [25]. The lifetime accumulation of skin damage contributes to the development of skin cancer. Skin damage incurred by natural and artificial UVR affects cellular proteins, cell signaling, damages DNA, suppresses the ability of the immune system to detect cancer cells, causes tissue damage, and cell death. Fortunately, melanoma and non-melanoma skin cancers can be prevented by reducing exposure to UVR through a number of behavioral practices. These practices include avoiding excess UV exposure, applying adequate amounts of broad spectrum sunscreen with SPF of 15 or greater and remembering to reapply when necessary, wearing protective clothing including hats and sunglasses, seeking shade, avoiding cosmetic tanning, acquisition of vitamin D from dietary sources rather than intentional UV exposure, and routinely checking the body for suspicious growths on the skin. Dietary intake of phytochemicals and antioxidants has been shown to provide systemic protection from erythema and is a good addition to the recommended sun protection program. Many of these photoprotective compounds are currently included in sunscreen formulations for added protection. It is strongly encouraged that all individuals regardless of ethnicity or skin type follow these sun protection measures to reduce skin cancer risk. Public education through awareness programs is critical for correcting social perceptions and teaching sun protective behaviors.

Author details

Lisa Passantino[1*], Max Costa[1] and Mary Matsui[2]

*Address all correspondence to: lisa.passantino@gmail.com

1 Nelson Institute of Environmental Medicine, New York University, New York, N.Y., USA

2 Estee Lauder Companies, Inc., Melville, N.Y., USA

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