ANTICANCER RESEARCH *38*: 1153-1158 (2018)
doi:10.21873/anticanres.12334

Review

Photocarcinogenesis and Skin Cancer Prevention Strategies: An Update

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Abstract. *UV radiation is acknowledged as the primary cause of photocarcinogenesis and therefore contributes to the development of skin cancer entities such as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and melanoma. Typical DNA photoproducts and indirect DNA damage caused by reactive oxygen species are the result of UV radiation. UV-induced DNA damage is repaired by nucleotide excision repair, which consequently counteracts the development of mutations and skin carcinogenesis. Tumour-suppressor genes are inactivated by mutation and growth-promoting pathways are activated leading to disruption of cell-cycle progression. Depending on the skin cancer entity, some genes are more frequently affected than others. In BCC mutations in Patched or Smoothened are common and affect the Sonic hedgehog pathway. In SCC, cell regulator protein p53 (TP53) mutations are prevalent, as well as mutations of the epidermal growth factor receptor (EGFR), cyclin-dependent kinase 2A (CDKN2A), Rat sarcoma (RAS), or the tyrosine kinase Fyn (FYN). UV-induced mutations in TP53 and CDKN2A are frequent in melanoma. UV-induced inflammatory processes also facilitate photocarcinogenesis. Recent studies showed a connection between photocarcinogenesis and citrus consumption, phytochemicals, alcohol consumption, hormone replacement therapy, as well as oral contraceptive use. Preventative measures include adequate use of sun protection and skin cancer screening at regular intervals, as well as the use of chemopreventative agents.*

The prevalent keratinocyte-derived neoplasms of the skin are basal cell and squamous cell carcinomas. Cutaneous melanoma is less frequent, but associated with high mortality. Photocarcinogenesis follows a multistep model of cancer development in which ultraviolet (UV)-induced DNA damage leads to mutations resulting in activation of oncogenes or silencing of tumor-suppressor genes. This ends in a cellular mutator phenotype even more prone to the acquisition of mutations. DNA repair, especially the nucleotide excision repair (NER) pathway, counteracts mutation formation and skin cancer development. Primary skin cancer preventative strategies therefore include reduction of photodamage to DNA.

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Key Words: Photocarcinogenesis, UV light, skin tumors, DNA repair, prevention strategies, review.

The Electromagnetic Spectrum of Sunlight

Photocarcinogenesis is defined as a multistep progression of skin cancer caused by electromagnetic waves of the optical spectrum. This includes the activation of oncogenes and suppression of tumour suppressors and depends on the applied dosage, the duration of exposure, and the wavelength of the irradiation. The optical spectrum consists of UV radiation (100-400 nm), visible light (400-760 nm), and infrared radiation (IR; 760 nm-1 mm) belonging to the non-ionizing part of the electromagnetic spectrum. UV radiation is further subdivided into three wavelength ranges: UVC radiation (100-280 nm) has the shortest wavelength and is also the most energetic. Its high mutagenic potential does not reach the earth's surface due to the formation of ozone from oxygen in the stratosphere which blocks it. UV-B radiation (280-315 nm) and UV-A radiation (315-400 nm) are able to penetrate the atmosphere and therefore cause direct and indirect DNA damage, resulting in mutations, inflammation, sunburn, immunosuppression, and as a long-term consequence, skin cancer. While UV-B radiation is mostly absorbed by the epidermis, UV-A radiation penetrates into the deep dermal layers of the skin. UV-A radiation (90-95%) presents the largest fraction of UV radiation reaching the earth's surface compared to UV-B radiation (5-10%). IR radiation is also subdivided into three wavelength ranges: IR-A (760-1440

nm), IRB (1440-3000 nm), and IRC (3,000 nm-1 mm). Only IR-A is able to penetrate all three layers of the skin. Comparing the amount of different wavelengths of solar radiation reaching the skin, IR-A radiation represents 54%, while UV radiation only amounts to 7% (1-4). Although IR radiation is known to be imbed in photo aging and photocarcinogenesis (4), research labels UV radiation as the primary cause of photocarcinogenesis and therefore non-melanoma skin cancer (NMSC) such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as well as melanoma (1). Additionally, the effect of IR-A protection in sunscreens is highly contradictory (5, 6). Hence, we subsequently focus on UV-dependent carcinogenesis.

UV-Specific Impact on DNA

DNA is a chromophore for UV radiation, having an absorption maximum at 254 nm. UV-B radiation is directly absorbed by DNA and generates DNA photoproducts such as cyclobutane pyrimidine dimers (CPDs) and 6-pyrimidine-4-pyrimidone dimers (6-4 PPs). At a ratio of 2:1, CPDs are more frequent than 6-4 PPs. These photoproducts lead to bulky lesions in DNA that distort the DNA backbone due to mismatches of bases or photoproducts and therefore block polymerases for transcription and replication (2, 7). Only nucleotide excision repair (NER) removes these errors from the DNA. Defects in NER lead to the rare autosomal-recessive disease xeroderma pigmentosum [a comprehensive review can be found in (8)].

UV-A and UV-B radiation also lead to the formation of reactive oxygen species (ROS) that attack DNA, proteins and cell membranes through oxidation. They can also cause single strand DNA breaks (9).

Clinical Picture of UV-Associated Damage

The clinical picture is dominated by sunburn (*dermatitis solaris*) caused by acute UV-B radiation. The typical erythema is accompanied by oedematous swelling and sometimes blistering, followed by desquamation and pigmentation of the affected skin. Histologically, 12-72 hours after UV-B exposure, apoptotic cells can be found in the *stratum granulosum* (10). As a natural protective mechanism against UV radiation, melanocytes produce the dark pigment melanin. A melanin cap above the nucleus absorbs UV radiation and partially visible light as well as IR radiation. In addition, it functions as a radical scavenger (11). UV-A/UV-B-mediated immediate pigment darkening can probably be accounted for by photo-oxidation of melanin precursors and is rapidly reversible. Long-term late pigment darkening sets in 2 to 3 days after exposure. The pigment production in melanocytes of the basal layer of the epidermis is stimulated, providing melanin for keratinocytes. While UV-A exposure leads to immediate pigment darkening, both UV-A and UV-B exposure are responsible for late pigment darkening. Additionally, chronic UV radiation triggers acanthosis and hyperkeratosis. Radiation has to penetrate deeper to reach the basal layer in order to inflict serious damage. Therefore, actinic acanthosis and skin darkening represent natural protective mechanism of the skin against UV-induced skin damage (12-14).

Cutaneous Cancers and Their Genomic Background

The most common cancers of the skin are SCCs and BCCs. Both entities originate from the same cell type – keratinocytes. However, depending on the cancer type, some genes are more affected than others that drive the entity formation. While Patched (*PTCH*) and Smoothened (*SMO*) mutations that influence the Sonic hedgehog (SHH) pathway are prevalent in BCC, driver genes in SCC include those of the cell regulator gene p53 (*TP53*) producing defective TP53 protein, mutations of the epidermal growth factor receptor (*EGFR*), Rat sarcoma (*RAS*), tyrosine kinase Fyn (*FYN*), and cyclin-dependent kinase 2A (*CDKN2A*) (2, 15). Both types of NMSC are mostly found in the older population, although the incidence in the young population is increasing (15, 16). A precursor stage of SCC is actinic keratosis (AK) that represents an *in situ* transformation. However, only a minor proportion of cases of AK actually progress into invasive SCC, and in many cases these skin lesions regress spontaneously. Melanoma exhibits different UV-induced driver mutations including those of *TP53* and *CDKN2A* (17). Generally, tumour-suppressor genes are inactivated and growth-promoting pathways are activated, disturbing the normal growth behaviour of keratinocytes and melanocytes (11, 15).

Molecular Mechanisms of Photocarcinogenesis

Mutations. Different molecular mechanisms underlie the formation of skin cancer. The proliferation-promoting effect of UV-B radiation is, amongst others, mediated by the mitogen-activated protein kinase (MAPK) pathway. The guanosine phosphate-binding RAS protein is located on the inner cell membrane and represents one of three oncogene family members that are involved in this pathway. Activating RAS mutations lead to a continuous growth signal that no longer depends on receptors. Therefore, it causes tumour development. RAS mutations have been shown to be present in a multitude of epithelial tumours on sun-exposed skin. The reason for its susceptibility to mutations is considered to be the amount of pyrimidine-containing sequences. Both point mutations and gene amplification of RAS are involved in skin cancer development (1).

SHH signalling holds a leading role during embryogenesis. BCCs often exhibit abnormal activation of the SHH pathway causing this neoplasia. This abnormal activation is caused by mutations in *PTCH* (30-40% of all sporadic BCCs), and mutations in *SMO* (approximately 20% of all sporadic BCCs). Mutations uncoupling SMO and PTCH1 from SHH signalling prompt cell proliferation and tumour growth (15, 18).

In its physiological function, TP53 promotes cell-cycle arrest in G1 phase using cyclin-dependent kinases (CDK) to enable DNA repair before the start of S phase. After recognizing DNA damage, a kinase cascade is set in motion [serine-threonine protein kinase] phosphorylates checkpoint kinase 1/checkpoint kinase 2(CHK1/CHK2)] that finally leads to the phosphorylation and, consequently, activation of the cell regulator protein p53T (*TP53*) by the detachment of murine double minute oncogene (*MDM2*), which is an associated ubiquitin ligase. Phosphorylated p53 induces *p21* which in turn halts the cell cycle in G1 phase by binding to and inhibiting CDK–cyclin complexes. Additionally, p53 can induce apoptosis through activation of the intrinsic pathway, which leads to the release of cytochrome *c* from the mitochondria (19-21). By interacting with xeroderma pigmentosum-associated proteins, it facilitates NER and thus suppresses tumour development. BCCs and SCCs exhibit specific mutations in *TP53* that differ from mutations in neighbouring non-cancerous cells. Mutations in *TP53* can initiate skin cancer development (1).

CDKN2A encodes two powerful tumour suppressors that are involved in cell-cycle regulation. $p16^{INK4A}$ prevents cell-cycle progression from G_1 to S phase by binding to CDK4/CDK6 and thereby inhibiting phosphorylation of the retinoblastoma protein. $p14^{ARF}$ stabilizes the level of TP53 and therefore prevents oncogenic transformation (15, 22). UV signature mutations were identified in *CDKN2A* (23).

In 2016, a study identified dysregulated UV target genes in human skin cancer through transcriptome analysis. They first identified conserved UV signature genes and then performed similar tests comparing the transcriptome of human SCC tissue and adjacent normal skin. While significant numbers of down-regulated genes accumulated in top biological pathways, including cell-cycle regulation, chromosomal structure, DNA-damage response and microtubule organization, up-regulated genes accumulated in pathways including apoptosis, defence inflammatory response, ectoderm epithelial development, cell adhesion, and leukocyte activation. A significant proportion of the UV signature genes were shown to be dysregulated in human skin SCCs. The same could not be shown for other human malignancies. Therefore, UV signature genes show potential for clinical diagnosis of UV damage and stratification of skin cancer risk (24).

Photocarcinogenesis-promoting processes. Nuclear factor kappa-light-chain-enhancer of activated B-cells (NFκB) is a transcription factor that is involved in inflammation, cell cycle regulation, and cell survival. In its inactive form, NFκB is bound to inhibitor of kappa B (IκB) in the cytoplasm. By stimuli-dependent phosphorylation of IκB by IκB kinases, NFκB dissociates from IκB. UV radiation is one of such stimuli. NFκB is translocated into the nucleus where it stimulates the transcription of effector genes (25).

Signal transducer and activator of transcription 3 (STAT3) is activated by UV radiation in human keratinocytes and fibroblasts through DNA damage and ROS formation. STAT3 is constitutively active in various human cancer entities and has been shown to be required for cell proliferation and tumorigenesis in SCC cell lines. It also inhibits apoptosis (26-28).

Additionally, inflammation of the skin is promoted by cyclooxygenases (COX), particularly *COX2*. COX2 is a rapidly inducible gene, which can be induced by UV radiation. COX2 synthesizes prostaglandins from arachidonic acid. Hence, it maintains the inflammatory process. Due to UV radiation increasing the amount of arachidonic acid, UV exposure leads to an increased prostaglandin synthesis in the skin. Elevated prostaglandin levels have been shown to be present in BCCs and SCCs, contributing to carcinogenesis and tumour progression (29-31).

Tryptophan is a chromophore for UV-B radiation. UV-B radiation leads to the production of 6-formylindolo[3,2-b]carbazole from tryptophan, which in turn is a ligand of the aryl hydrocarbon receptor (AHR). The AHR is a ligand-activated transcription factor and is an important regulator of drug metabolism. It has been shown that the AHR not only induces COX2 in human keratinocytes but also displays an anti-apoptotic effect due to its influence on checkpoint kinase 1 (*CHK1*) and E2F transcription factor 1 (E2F1). Inhibition of the AHR dampened the anti-apoptotic effect and also reduced the induction of *COX2* (32, 33).

Further Influences on Photocarcinogenesis

The function of vitamin D, a hormone that is mainly produced from precursors in human skin under the influence of UV-B radiation, has long been known to be important in the control of calcium and bone metabolism. Recently, it was discovered that the skin is also a target tissue for vitamin D. The VDR was found to act in conjunction with TP53 and other factors as a tumor suppressor in response to alterations of cell homeostasis such as UV-induced DNA damage. Through VDR binding, vitamin D is able to indirectly regulate the cell cycle and other proteins involved in cell proliferation and differentiation. Other pathways such as SHH signalling that are pivotal for cell growth are also controlled by vitamin D. Vitamin D is also involved in immunological reaction in the skin leading to both immunosuppression and stimulation of distinct immunoregulatory pathways (34).

Lycopene is a potent antioxidant. It has been shown to exhibit strong antiproliferative properties by modulating the cell cycle and apoptosis. A recent study discovered that pre-treatment with lycopene attenuated UV-B-induced cell hyperproliferation and promoted apoptosis in human keratinocytes and SKH-1 hairless mice. Forkhead box O3a (FOXO3a) is important for cell death-related gene expression. It is phosphorylated in response to UV-B-radiation and is sequestered in the cytoplasm. A connection between loss of FOXO3a and reduced lycopene-induced effects point to a significant role for FOXO3a in the regulation of the effects of lycopene (35).

Recent Studies Investigating Dietary Influence on Photocarcinogenesis

A higher skin cancer risk was attributed to furocoumarins, a group of chemicals that naturally occur in citrus products. Furocoumarins exhibit high UV-A absorption and are strongly mutagenic. In their excited state, they react with biomolecules, especially with pyrimidine bases of DNA. The furocoumarin derivate psoralen is often used together with UV-A radiation in psoriasis treatment; this could explain the elevated BCC and SCC risk of patients treated in this way (36, 37).

The dietary influence of pomegranate is attributed to its high anti-oxidative activity, its ability to influence multiple cell signalling pathways, as well as its anti-inflammatory and antiproliferative properties. Pomegranate seed oil, pomegranate fruit extract, and pomegranate juice have been tested in cell culture and reconstituted human skin models and animal models of skin cancer and were found to exhibit a high potential for prevention of UV-B-induced skin cancer (38).

Piperine is a plant alkaloid that is present in black pepper. A recent study showed that it acts as a scavenger for free radicals. It also inhibits DNA damage-mediated cell cycle arrest and apoptosis and inhibits UV-induced activation of NFκB. Therefore, the authors suggest its applicability for human use (39).

Another study correlated an elevated risk for BCC with the consumption of alcohol, irrespective of gender. It has been theorized that on the one hand intermediate byproducts or metabolites of alcohol are directly mutagenic or carcinogenic, while on the other hand, they act as photosensitizers and generate ROS. Furthermore, alcohol-induced immunosuppression may increase cancer risk. High alcohol consumption may also just be an indicator of a general unhealthy lifestyle. UV radiation in combination with alcohol was shown to induce skin cancer (40).

A correlation between the use of oral contraceptives or menopausal hormone therapy (MHT) and NMSC risk was assessed in a nationwide cohort study in the US. As the photosensitizing effects of oestrogen are well recognized, the relationship between exogenous oestrogen use, reproductive factors, and first primary BCC was evaluated, taking sun exposure and personal sun sensitivity into account (41). In particular, women using MHT had a higher risk for BCC (42).

Skin Cancer Prevention

Due to skin cancer incidence dramatically increasing over the last few years, primary prevention has become highly important. In Germany, while in 2003 the number of new melanoma cases was 14,044, in 2013, 20,163 new cases were reported. The number of new NMSC cases in Germany in 2003 was 70,682 and had increased to 134,219 in 2013. Therefore, the number has nearly doubled in that time period (43). As solar UV radiation represents the most important environmental risk factor for the development of skin cancer (44), behavioural protection against UV radiation is a fundamental part of skin cancer prevention. Adequate measures to reduce UV exposure include avoiding direct exposure to midday sun (between 10 am and 2 pm), protection with appropriate clothing, and the use of sunscreens against both UV-A and UV-B radiation with a minimum sun protection factor of 15-20. Regularly performed self-examinations and annual full-body skin cancer examination performed by a dermatologist – at more frequent intervals for high-risk patients if necessary – increase the likelihood of detecting any skin changes that can then be diagnosed at an early and curable stage (45).

Additional strategies for skin cancer prevention are currently being investigated. Particularly high-risk patients who developed NMSC twice within the 5 years showed promising results using 500 mg nicotinamide (vitamin B_3) twice daily as a chemoprevention. A reduced occurrence of NMSC by 23% compared to the placebo-treated group was shown in a phase III study (BCC: 20%, SCC: 30%, actinic keratosis: 13%). This therapy is based on the fact that UV radiation leads to ATP depletion, hindering DNA repair. Nicotinamide prevents ATP depletion and glycolytic blockade, and DNA repair is thereby enhanced. Immunosuppression due to UV radiation is also reduced. The drug is already used in the clinical treatment of autoimmune blistering disorders, such as bullous pemphigoid (46).

Other chemopreventional strategies include the use of phytochemicals as they show low toxicity and anti-carcinogenic properties. Phytochemicals such by those as described in the article by Montes de Oca *et al*. are extracted from plants and are used topically or orally to prevent or protect against skin cancer (47). Hydrophilic hydroxyl groups, often as part of a polyphenol group, act as antioxidants by scavenging ROS or free radicals. Therefore, oxidative damage to DNA, proteins and lipids is inhibited. They also have anti-inflammatory properties and have been shown to modulate the cell cycle, cell proliferation and angiogenesis (48).

A smartphone application, called mISkin, was designed to promote sun protection during holidays taking previously tested interventions into consideration. The application reminds the user to use appropriate sun protection based on their location and provides information about how to apply sunscreen and using other methods of sun protection, elaborating on the risk of unprotected sun exposure. It also includes a Sun Safety Quiz and a Sun Alert Service that alerts the user to use sun protection at a customized rate (49).

In summary, sunlight-induced DNA damage and the resulting mutations in several driver genes for cancer development contribute to a substantial proportion of multistep cancer development. Induction of such mutations can be targeted by personal behaviour and therefore be avoided. In addition, new chemopreventional strategies such as the intake of nicotinamide (vitamin B_3) are emerging that enhance DNA repair at the cellular lever and also lead to a reduction in the mutational load of cells.

Acknowledgements

The Authors would like to thank the German Cancer Aid (Deutsche Krebshilfe e.V.) [111377], the Damp Foundation, and the Deutsche Stiftung Dermatologie for funding. We based this review on our previous publication elaborating on new developments in the field of photocarcinogenesis (2).

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Received November 1, 2017
Revised November 25, 2017
Accepted November 28, 2017