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Advances in skin cancer prevention: From UV radiation and risk factors to effective public health interventions

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ABSTRACT

Skin cancer remains a significant public health concern, with rising incidence rates worldwide. Our literature review examines current knowledge on skin cancer prevention, focusing on key areas such as epidemiology, risk factors, ultraviolet (UV) radiation exposure, pathophysiological and genetic mechanisms, and prevention strategies. A comprehensive literature search was conducted across databases including PubMed, Scopus, Web of Science, and Google Scholar, focusing on peer-reviewed articles published from 2013 to 2023. Non-peer-reviewed articles, non-English studies, non-human research, and studies published before 2013 were excluded. Our study highlights the significant role of UV radiation in skin cancer pathogenesis and underscores the importance of comprehensive prevention strategies. Sunscreen use and protective behaviors are effective but underutilized. Community-based interventions show promise in increasing public awareness and promoting protective measures. Screening and chemoprevention offer additional avenues for reducing skin cancer burden. The findings emphasize the need for continued public health efforts to enhance skin cancer prevention and early detection. Future research should focus on optimizing prevention strategies and exploring novel approaches to reduce the incidence of skin cancer.

Keywords: skin cancer, malignancy, melanoma, non-melanoma, prevention, public health

INTRODUCTION

Skin cancer is one of the most common cancers worldwide. Epidemiological studies on skin cancer have shown that it is a major public health problem that affects all age groups and genders because its incidence has been increasing steadily over the past few decades [1]. In this article, we will review the epidemiology of skin cancer and its risk factors [2]. Skin cancer is a malignant growth of skin cells that can be classified into three main types: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. BCC and SCC are non-melanoma skin cancers (NMSCs), which are the most common types of skin cancer, whereas melanoma is less common but more aggressive and has a higher risk of metastasis [3]. According to a study published in JAMA Dermatology, NMSC, including BCC and SCC, is the most common form of skin cancer, with an estimated 5.4 million cases diagnosed in the United States in 2012. This figure is higher than all other cancers combined, making skin cancer a major public health concern [4].

The incidence of skin cancer varies by region and is generally higher in areas with higher levels of ultraviolet (UV) radiation exposure [4]. The incidence of skin cancer is considered to be the highest in Australia, New Zealand, and the United States, with rates in Australia being among the highest in the world. Australia had the highest skin cancer incidence rates globally in 2020, with approximately 37 cases per 100,000 people for melanoma alone. New Zealand's melanoma incidence rates were around 40% higher during summer compared to equivalent latitudes in the northern hemisphere, primarily due to higher UV radiation levels. In the

United States, there were about 100,350 new cases of melanoma diagnosed in 2020. The incidence of melanoma has also been increasing in many countries, including the United States, Canada, and Europe [4]. Melanoma incidence rates are generally higher in fair-skinned populations (as they have less melanin, which protects the skin from UV radiation). and are strongly associated with UV radiation exposure, especially in early life. In addition, people with a family history of melanoma or with a personal history of NMSC have an increased risk of developing melanoma [5, 6]. Risk factors for skin cancer include fair skin, red or blonde hair, blue or green eyes, a history of sunburns, a family history of skin cancer, and exposure to UV radiation from the sun or tanning beds. The use of indoor tanning beds has been identified as a significant risk factor for NMSC, especially among young people [7-9].

Prevention and early detection are critical in the management of skin cancer. Primary prevention strategies include reducing UV radiation exposure by wearing protective clothing, using sunscreen, and avoiding indoor tanning [10]. Public health campaigns and educational programs aimed at increasing awareness of the risks of UV radiation exposure and promoting sun-safe behaviors have been effective in reducing the incidence of skin cancer in some populations. The American Cancer Society recommends that people protect their skin from the sun by staying in the shade during peak hours, wearing protective clothing, such as long sleeved shirts and hats, using broad-spectrum sunscreen with a minimum SPF of 30, and avoiding indoor tanning [10]. Early detection of skin cancer is important for improving treatment outcomes. Regular skin self-examination and clinical skin examinations by a healthcare professional can help identify suspicious lesions early. The ABCDE rule is a simple tool that can be used to identify potential melanomas: asymmetry, border irregularity, color variation, diameter greater than 6 mm, and evolution over time [11].

As such, skin cancer is a significant public health issue that is increasing in incidence worldwide. As analyzed below prevention and early detection are critical in the management of skin cancer, and individuals should be encouraged to adopt sun-safe behaviors and seek medical attention for suspicious skin lesions. Public health campaigns and educational programs can play an important role in reducing the burden of skin cancer [12].

MATERIALS & METHODS

Literature Search Strategy

A comprehensive literature search was conducted to gather relevant studies on skin cancer prevention. The databases utilized included PubMed, Scopus, Web of Science, and Google Scholar. The search strategy incorporated a combination of keywords such as “skin cancer,” “malignancy,” “melanoma,” “non-melanoma,” “prevention,” and “public health.” The search was limited to peer-reviewed articles published in the last ten years (2013-2023) to ensure the inclusion of the most recent and relevant findings.

Inclusion and Exclusion Criteria

Inclusion criteria

- Studies focusing on modifiable and non-modifiable risk factors for skin cancer.
- Research examining exposure to UVA and UVB radiation.
- Articles detailing the pathophysiological mechanisms of skin cancer induced by UV radiation.
- Studies evaluating the effectiveness of sunscreen protection and other protective measures.
- Research on community-based interventions to prevent skin cancer.
- Articles discussing screening methods for skin cancer.
- Studies on chemoprevention of skin cancer.

Exclusion criteria

- Non-peer-reviewed articles.
- Studies not available in English.
- Articles focusing on non-human subjects.
- Studies published before 2013.

Data Extraction and Synthesis

Data extraction was performed independently by two reviewers to minimize bias and errors. Extracted data included study design, population characteristics, key findings, methodologies, and conclusions. Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer. The collected data were synthesized qualitatively, with findings categorized into thematic chapters.

Analysis

A narrative synthesis approach was employed to integrate findings from the included studies. This method allowed for the identification of common themes and discrepancies within the literature. Key findings were summarized and discussed in relation to existing knowledge, highlighting the unique contributions and implications for public health and future research.

RESULTS

Modifiable and Non-modifiable Risk Factors for Skin Cancer (Melanoma/Non Melanoma)

Skin cancer (melanoma and non-melanoma) is an example of a multifactorial disease in which genetic (non-modifiable) and environmental (modifiable) factors are involved and interact. Age, gender and genetic predisposition are the most important risk factors in the first group, while exposure to UV radiation is the most dominant and potentially modifiable environmental risk factor due to genotoxic effects.

Genetic risk factors for skin cancer include naturally lighter skin color, blue or green eyes, blond or red hair, dysplastic moles or a large number of common moles, and burning, freckled skin that flushes easily or is painful after excessive sun exposure [13, 14]. People with red hair may be particularly at

risk for melanoma. Genetically, this phenotype is often the result of inactivation of polymorphisms in the gene encoding the melanocortin-1 receptor (MC1R). MC1R encodes an AMP-stimulating cyclic G protein-coupled receptor that controls pigment production. Minimal receptor activity, such as in the red hair/light skin polymorphism, produces red/yellow pheomelanin pigmentate, which has weak UV-protection compared to eumelanin and has been shown to enhance UV-A-induced reactive oxygen species (ROS) [15].

Certain phenotypic traits are often associated with race and ethnicity. As a result, people of European descent and non-Hispanic Caucasians have the highest melanoma morbidity and mortality rates because they generally have lighter natural skin color. In contrast, Blacks and Asians/Pacific Islanders have the lowest morbidity and mortality rates from melanoma, followed by American Indians/Alaska Natives and Hispanics. Overall, the lifetime risk of developing melanoma is about 2.4% for Caucasians, 0.1% for Blacks, and 0.1%.5% among Hispanics [16].

Melanomas are about 1.5 times more common in men than women. It has been shown that there is no significant difference in incidence rates up to the age of 40, but after the age of 75 the incidence in males is almost three times higher than in females [17]. Age is the most important non modifiable risk factor for NMSC, with the risk increasing as individuals get older. According to the American Academy of Dermatology, people over the age of 50 are at higher risk of developing skin cancer [18, 19].

In addition, people with a family or personal history of skin cancer, particularly melanoma, are at increased risk. A study about families with hereditary melanoma showed a clear pattern of autosomal dominant inheritance, with many family members being more affected than in the first generation [20]. In some families, susceptibility results from mutations in one of the genes known to predispose to high penetrance melanoma: CDKN2A, CDK4, BAP1, POT1, ACD, TERF2IP, and TERT. Cyclin-dependent kinase (CDK) 2A inhibitor (CDKN2A or p16) mutations were the most common genetic abnormalities found in these families, while CDK 4 (CDK4) mutations were less common.In addition, patients with familial cancer syndromes such as familial retinoblastoma, Li-Fraumeni cancer syndrome and Lynch (II) syndrome have a higher risk of melanoma [21].

Approximately 25% of melanoma cases are due to a pre-existing birthmark. The total number of moles is positively correlated with melanoma risk and varies with the number, size, and type of moles. The results of a recent meta-analysis underline that patients with more than 100 nevi have a sevenfold risk of melanoma. In terms of size, larger (> 5 mm) and giant (> 20 cm) nevi are associated with a significantly higher risk of melanoma [22].

Last but not least, melanocytic nevi, benign congenital or acquired accumulations of melanocytes or nevus cells, play a very important role. Most melanomas are believed to arise de novo since only one-third of primary melanomas are associated with a histologically identifiable nevus precursor. On the other hand, an increased number of melanocytic nevi is an important risk factor for the development of melanoma, including melanomas that do not arise from nevi [23, 24].

As for the modifiable risk factors, exposure to UV radiation from the sun or tanning beds is the most important environmental risk factor for melanoma and NMSC. UV radiation damages the DNA in skin cells, which can lead to the development of cancer. In fact, it is estimated that up to 90% of melanomas are caused by exposure to UV radiation. The extent to which exposure to UV light increases the risk of skin cancer depends on many factors, including a person's skin type, the amount and type of sunscreen used, whether exposure is chronic or intermittent, and the age at which the exposure occurs [25, 26].

Sunburn history may indicate intense and intermittent sun exposure; moreover, the greatest risk is associated with sunburns in childhood [27]. As for the artificial sunlight, the risk is even greater with increased use of tanning beds, which highlights the dose-response relationship, and in people who were first exposed to tanning beds at a young age [28]. A recent international meta-analysis found that people who reported tanning indoors had a 16% higher risk of developing melanoma than those who never tanned indoors [29]. UV-A photochemotherapy psoralen, used to treat psoriasis, is also associated with an increased risk of melanoma [30].

Modifiable risk factors include certain medical conditions like immunosuppression. Primary immunodeficiencies increase the incidence of skin cancer [31], but accurate risk indicators are still lacking due to their low incidence. Regarding secondary immunosuppression, available data indicate that skin cancer is the most common malignancy in organ transplant recipients [31]. More than half of patients develop at least one and 44% develop two or more, accounting for 95% of these NMSC, particularly cSCC [32-34]. Indeed, the ratio of cSCC to BCC is reversed in the OTR, with cSCC being favored over BCC (4:1). The underlying pathogenesis of the association between organ transplantation and increased cancer risk is attributed in part to impaired immune surveillance, but also to activation of oncogenic viruses, chronic inflammation, immunosuppressive drugs, and pre-existing risk factors for cancer [35]. The incidence of melanoma is especially high in heart transplant recipients possibly because heart transplants are often performed later in life and require higher levels of immunosuppression to prevent transplant rejection.

Interestingly, human papillomavirus beta (β-HPV) was identified in 80-100% of NMSCs and in precancerous OTRs, compared to 30% in the general population [36]. High exposure to the most common immunosuppressive regimens used in OTR, including the nucleotide inhibitors (mycophenolate mofetil or azathioprine) and calcineurin inhibitors (tacrolimus or cyclosporin-A), is directly related to the duration and dose of treatment and is strongly associated with the incidence of both cases and mortality from skin cancer [37]. Other modifiable risk factors for skin cancer include smoking, alcohol consumption, and obesity. Also, links between folate, citrus, caffeine, and alcohol with BCC are notable; thus, high dietary folate intake, citrus, and alcohol consumption, are associated with an increased risk of BCC, whereas caffeine is associated with a lower risk [38-40]. While the mechanisms by which these factors increase the risk of melanoma are not fully understood, research has shown that they are associated with an increased risk of developing disease.

Exposure to UVA-UVB Radiation

UVA

The range of UV rays is composed of 3 parts. The first one is UVC wavelengths (100-280 nm), which may be stopped by the ozone layer. The second one is UVB wavelengths (100-280 nm) which can be stopped by ozone and the meteorological conditions and solar inclination and the third is UVA wavelengths (320-400 nm). The UVA wavelengths can be divided into longwave UVA or UVA1 (340-400 nm) and in shortwave UVA or UVA2 (320-340 nm). The UVA wavelengths are less affected by these factors, especially the UVA1 which represents the 80% of total UV that reaches the surface of Earth. Also people during phototherapy or in sunbed tanning sessions can be exposed to UVA1 wavelengths [41].

The UV radiation can interact and penetrate with skin cells, with fibroblasts and keratinocytes. The cellular senescence occurs from factors such as chemokines,cytokines, growth factors and MMPs (matrix metalloproteinases),which is a phenotype senescence-associated. The formation of premutagenic factors for UVA radiations occur form 8-hydroxy-2-deoxyguanosine (8-OHdG), which can cause damage to the DNA structure of humans, from the excessive skin exposure [42].

UVB

UVB radiation is a type of UV radiation with shorter wavelengths (280-315 nm) than UVA, being a major risk factor for skin cancer development. Exposure to UVA and UVB radiation occurs through outdoor exposure to sunlight or even indoor exposure, for example tanning beds [41]. Even though the exposure to sunlight can be beneficial for human health by inaugurating the vitamin D metabolism, this exposure is responsible for inflammations in the skin, DNA mutations, oxidative stress, skin aging and skin cancers [43, 44].

Nowadays, both UVA and UVB radiation are considered to be carcinogens (class I) for humans due to their mutagenic effect on their DNA. More specifically, in [45] it was mentioned that this mutation results in DNA nucleotide alterations for example, cytosine (C) transforming into thymine (T) or even the transformation of thymine (T) to guanine (G). A single mutation can have a large effect, but in many cases, evolutionary change is based on the accumulation of many mutations with small effects. Depending on the background or the location on the genome, this replacement may have a beneficial or a harmful or a neutral impact on gene expression. Also, it is important to mention that the fewer base pairs are affected, the less the effect of the mutation is and its likelihood to be harmful. In this case, the replacement of a C by T or the replacement of T by G may lead to mutation in BRAF oncogene, which is present in the 50% cases of all melanomas. Furthermore, there are other gene mutations that can be observed, for instance mutations in NRAS, CDKN2A, and NF1 or the C-KIT genes, in melanoma cases which happen in parts of the body that are seldom exposed to the sun [46]. Moreover, it is believed that both UVA and UVB radiation are responsible for immunosuppression having effect on the control of dysplastic and neoplastic skin lesions [45].

However, in recent literature it is presented that numerous factors contribute to skin's response to UV radiation. Among these factors are the color of the hair, the type of the skin, the genetic background and the latitude of the zones. It is important for people who are extremely sensitive to sun exposure, to be aware of the sunlight at shaded places [47].

Pathophysiological Mechanisms of Skin Cancer Induced by UV Radiation

Genetic mechanisms

As mentioned above, the pathophysiology of skin cancers is multifactorial with one of the major contributing factors being UV radiation. UVA radiation is accountable for formation of cancer stem cells through indirect DNA damage, while UVB and UVC radiation have a direct effect, through the formation of various photoproducts such as pyrimidine–pyrimidon (6-4) photoproducts, the 'Dewar' isomer and cyclobutane pyrimidine dimers (CPDs) [48]. UVB and UVC destroy the ability of DNA to act as a primer and result to the formation of nuclease-resistant sequences in DNA, through the linkage of two adjacent pyrimidines, formed at 5′-TC and 5′-TT dinucleotide sites and less frequently at 5′-CC and 5′-CT sites [49]. High level of CPDs have been associated with erythema, induced by the production and release of cytokines TNF-α, IL-1β and IL-6 by keratinocytes, as well as impaired immune responses both locally and systemically. Immunosuppression has been observed in xeroderma pigmentosum (XP) patients with CPDs. However, these findings have not concluded if XP is attributed to CPDs or intrinsic factors [50].

The p53 tumor suppressor gene (TSG) has a protective role against UV radiation, arresting G1 phase which leads to apoptosis of damaged cells [51]. Interestingly, p53 mutations have been associated with several pre-lesions and NMSCs, with a higher p53 mutation prevalence in BCC, compared to SCC. Cutaneous squamous cell carcinoma (cSCC) stems from precursor actinic keratosis (AK) lesions, which operate as predictive factors for metastasis [52]. Majority of BCCs and SCCs have signature mutations such as C → T transitions and nonsignature mutations such as CC → TT tandem substitutions at dipyrimidine sites, with a frequency of 60% and 5%, respectively [53]. These mutations are present both in aggressive and non-aggressive NMSCs, highlighting the role of p53 mutations in tumor initiation rather than progression [52].

In addition, p16 and protein patched homolog 1 (PTCH1) are TSGs associated with NMSC and melanoma incidence, respectively. The former is normally expressed in the granular cell layer of the epidermis and encodes a low molecular weight protein, which belongs to the INK4 class of CDK inhibitors. Hence, p16 binds to CDK4/6, inhibiting its kinase activity and preventing pRb phosphorylation. This inhibits the transition from G1 phase to S of the cell cycle and protects epidermal cells from apoptosis induced by UVR [54]. Inactivation of p16 through homozygote deletion or variants has been detected in cases of head and neck squamous cell carcinomas (HNSCCs) [55]. In fact, elevated levels of p16 and p53 expression have been identified as significant prognostic biomarkers in cases of HNSCCs [56]. The latter encodes a protein which participates in the sonic hedgehog-signaling pathway and plays a detrimental role in tumorigenesis. Under normal conditions, PTCH1 regulates cell proliferation and differentiation through the deactivation of genes that were previously activated

through the Hedgehog pathway. In the case of PTCH1 mutations, this balance is disrupted through phosphorylation of Gli repressor (GLIR), that is responsible for repressing the expression of the Hedgehog signalling pathway. This results to uncontrolled signalling, cell proliferation and tumorigenesis [57]. Current findings from both clinical samples and animal models indicate the pathophysiological importance of Hedgehog signaling and suggest the potential application of PTCH in cases of BCC [58].

Another gene that has been associated with skin cancer risk is the Glutathione S-transferase P1 (GSTP1) gene. This gene is expressed in dermis and epidermis, and encodes GST, an antioxidant enzyme crucial for the detoxification of ROS. One of the mechanisms of carcinogenesis is production of ROS, which triggers a cascade of DNA damage and abnormal signal transduction. The family of GST enzymes consists of four isoenzymes, namely mu (GSTM), pi (GSTP), omega (GSTO) and theta (GSTT). These isoenzymes are believed to modify DNA or lipid damage, prohibiting carcinogenesis through a mechanism that is yet to be defined. The opposite effect is observed in cases of GST homozygote deletion or GSTP1 variants. Studies show a predisposition of GSTM1- and GSTT1+GSTM1- genotypes to the development of NMSCs and BCC, respectively [59]. Also, there is a correlation between the GSTP1*C allele and increased cancer risk. However, it is not clear whether 105Val alone or combined with 114Val amino acid change is the culprit polymorphism [48].

Epigenetic mechanisms

The term epigenetic mechanisms refers to the modifications of gene expression and function, without alteration of DNA sequence. It involves multiple modifications such as DNA methylation, histone remodelling and chromatin structure change. DNA methylation can occur through either hypermethylation of the aforementioned TSGs or hypomethylation of proto-oncogenes. Hypermethylation of E-cadherin and 14-3-3 gene has been associated with skin cancer progression. E-cadherin is an essential cell adhesion molecule in maintaining cellular integrity, expressed by epithelial cells. Thus, UV-induced downregulation of E-cadherin leads to detachment of adherent cell groups from the primary tumor and metastasis. Low cytoplasmic expression of E-cadherin is prevalent in cases of poorly differentiated tumors with lymph node metastases [60]. In addition, 14-3-3ε, β, η, γ, σ, θ and ζ are members of the 14-3-3 family, which interact with oncogenic proteins. High expression of 14-3-3ε, ζ and low expression of 14-3-3β, σ are observed in epithelial cell cancers. Underexpression of the latter is induced by ubiquitin-proteasome degradation or hypermethylation of the 14-3-3β promoter [61]. In vitro studies in BCC tissue show that low expression of E-cadherin and 14-3-3σ is prone but not directly linked to carcinogenesis [62, 63]. Fragile histidine triad tumor (FHIT) gene is another TSG, widely expressed in liver and kidney tissues under healthy conditions and underexpressed in BCCs. While immunohistochemical analysis shows negative FHIT staining in all of BCC specimens, there is substantial hypermethylation of the FHIT promoter and subsequent loss of gene function. Additional studies are required to shed light on FHIT expression due to the discordant in vitro results [64].

Similarly, promoter hypermethylation induces silencing of p15, p16 genes observed in cases of HNSCCs and cSCCs, respectively. High levels of p16 methylation were found in 48% of cases and associated with increased cancer cell migration, tumor invasiveness, aggressive phenotype and clinical parameters. These include a lymphocytic, mainly T-cytotoxic, host response and a non-keratinising phenotype [55, 65, 66]. In fact, promoter hypermethylation is linked to methylation of 5' CpG islands. The latter are regions rich in cytosine–guanine that are located at the 5' end of a gene. CpG islands that undergo DNA methylation are associated with epithelial cell carcinomas, compared to CpG islands that remain unmethylated [67]. The impact of p16 silencing has been confirmed in cases of gastric adenocarcinoma and ulcerative colitis, although little is known about p15 silencing [68, 69]. Overall, patterns of promoter hypermethylation have direct impact on disease progression. The methylation state of CpGs can be utilized in classification of cSCC into actinic keratosis, early cSCC, non-metastatic carcinoma and metastatic cSCC. Great knowledge can be derived from methylation signature patterns regarding disease classification, diagnosis and prognosis [65].

With regards to melanoma, multiple candidate TSGs have been investigated. These primarily include Ras association domain family (RASSF) [70], protein phosphatase 1 regulatory subunit 3C (PPP1R3C) [71], metallothionein 1E (MT1E) [72], tumor protein p53-inducible nuclear protein 1 (TP53INP1) [73] and retinoic acid receptor responder 1 (RARRES3) [74]. Among the eight RASSF1 subtypes RASSF1A and RASSF1C have been extensively studied, due to the encoded microtubule protein that regulates cell growth and metastasis. Loss of microtubule protein leads to loss of TSG properties and subsequent genomic instability through the degradation of centrosomes and mitotic structures [70]. Promoter methylation of RASSF1A has been associated with melanoma progression as well as overall survival in cutaneous malignant melanoma (CMM) patients, who received chemotherapy in combination with immunotherapy [71]. Similarly, loss of RASSF10, another member of the RASSF family, has been identified in 68% of malignant melanoma samples. Emerging evidence indicates that RASSF10 gene silencing and promoter methylation is not limited to melanoma but expands to other neoplastic diseases, such as prostate cancer, thyroid cancer, paediatric leukemia and chronic lymphocytic leukemia [71]. Moreover, PPP1R3C, MT1E and TP53INP1 are potential TSGs that encode protein phosphatase 1, metallothionein 1E and p53, which regulate cellular function, proliferation and autophagy, respectively. In vitro studies show reduced PPP1R3C mRNA expression and promoter methylation in melanoma cells compared to melanocytes [72]. Similar results from melanoma samples showed correlation of MT1E, TP53INP1 and RARRES3 with disease progression and clinical response [72-74].

Nevertheless, in few cases hypomethylation of genes and sequences seems to drive tumorigenesis. Under healthy conditions, melanoma-associated antigen 1 (MAGEA1) and mammary serine protease inhibitor (maspin) are heavily methylated genes in normal epithelial cells. In contrast, poor methylation status is observed in melanoma cell lines, with MAGEA1 being more frequently hypomethylated, in comparison to maspin [75]. Sequences long interspersed

element-1 (LINE-1) and Alu are retrotransposons, with over one million copies in the human genome, whose expression is regulated by DNA methylation [76]. Similarly to the aforementioned genes, LINE-1 and Alu are heavily methylated in normal melanocyte cells [75]. Hypomethylation of LINE-1 and Alu sequences has been associated with disrupted gene expression and recombination, resulting to the formation of genes such as BRCA1, BRCA2. The role of these sequences has been investigated in cases of breast cancer and several other malignancies such as gastric cancer, ovarian cancer, lung adenocarcinoma and multiple myeloma [76].

Completing the pathophysiological factors is the role of histone and chromatin conformation in disease progression. Histones and chromatin are no longer merely regarded as building blocks of nucleosomes. Instead, they are recognized as regulators of gene activity, with the ability to undergo acetylation, methylation, phosphorylation, ubiquitylation and sumoylation, at a post-translational stage. Post-translational modifications of nucleosomes are detrimental for chromatin structure and gene expression. Such changes in gene expression patterns can subsequently lead to tumorigenesis and onset of skin cancers [77].

Molecular mechanisms

The aforementioned genetic and epigenetic mechanisms are implicated in multiple pathways. More specifically, inactivation of the following genes: patched homolog 1 (PTCH1), melanocortin 1 receptor (MC1R), CDK inhibitor 2A (CDKN2A) and xeroderma pigmentosum complementation group C (XPC), is detrimental to the pathogenesis of skin cancers. Loss of function of PTCH1 leads to reduced Hedgehog signaling by G-protein-coupled receptor smoothened (SMO) and loss of control over differentiation and proliferation. This pathway regulates stem cell growth, and its dysregulation has been associated with birth defects and malignancies [78]. Another significant pathway is the MCR pathway which involves 5 different G protein-coupled receptors: MC1R, MC2R also known as corticotropin receptor (ACTHR), MC3R, MC4R, and MC5R. Polymorphisms of MC1R have been associated with individual sensitivity to UV exposure due to reduced synthesis of photoprotective eumelanin by melanocytes, which is accountable for dark pigmentation. There seems to be a positive correlation between MC1R R151C, R160W and V92M polymorphisms with BCC and melanoma risk. Despite the positive correlation of MC1R polymorphisms, their association with NMSCs remains unclear due to lack of large-scale studies [79].

CDKN2A and XPC are UV-responsive genes whose dysregulation is associated with the development of multiple skin cancers. The former encodes p16, a key protein in cell cycle progression, which regulates G1 to S phase transition, through the inhibition of CDK4. Mutations of CDKN2A and p16 have been associated with uninhibited cell cycle progression and uncontrolled epithelial cell proliferation. Upon p16 mutation, cyclooxygenase-2 (COX-2) overexpression and prostaglandin production take place, leading to the establishment of an inflammatory environment, which is favourable for the development of BCCs and SCCs. Exon 2 mutations of the CDKN2A gene have been identified in 5 out of 21 SCC cases and 1 out of 28 BCC cases, with a 10,000-fold risk for XP patients, due to heightened sensitivity to UV radiation. XP has heterogenous clinical manifestations–including NMSCs and melanomas–and is attributed to mutations of XPC gene. The latter encodes a DNA repair protein, which is responsible for restoring the standard DNA copy, through the nucleotide excision repair (NER) pathway. XPC mutations lead to NOX-induced ROS production and subsequent inactivation of TSGs and activations of oncogenes [80]. However further studies are required to illustrate the implication of the aforementioned genes in melanocyte cell pathways.

Sunscreen Protection

Sunscreens are products with a defensive role when they are being applied topically to the skin. Their role is to protect the skin from UVA and UVB radiation, whose significance is mentioned above, and prevent erythema, skin aging, rhytids and skin cancer [1]. They can be found in many types with different composition, for example there are lotions, sticks, sprays and creams while their combination varies to water/oil (W/O), oil/water (O/W) cream O/W spray and gel. Both different types and compositions provide protection against UVR, but they have different usage recommendations [80, 81].

In their studies, Hendersson et al. and Heidi et al, highlight the importance of sunscreen application by mentioning that daily use of sunscreen can reduce the risk for skin cancer by 9.3% for SCC and 14% for melanoma [81] and comparing to those who do not use sunscreen protection daily, individuals who apply sunscreen every day present 40% lower BCC rates [81]. Based on the reference of [82], it was related to the impact of UV radiation on ROS, it is highly possible to activate mitogen-activated protein kinase (MAPK) which leads to the formation of transcription factor complexes (AP-1 and NF-κB) that regulate the transcription of MMPs or the release of inflammatory cytokines. UV radiation can also inhibit the production of extracellular matrix (ECM) proteins such as collagen and elastin [82]. In addition, the re- activation of ROS can occur by the exposure to UVA radiation causing damage to DNA [83].

The effectiveness of sunscreen protection is described by and indicator called sun protection factor (SPF) and it represents the ratio of energy required to produce a minimal erythema dose (reddening of the skin) through the sunscreen compared to the energy required to produce the same reaction without the sunscreen. For example, if someone would normally get a sunburn in 10 minutes without sunscreen protection, applying sunscreen with an SPF30 would mean that it would take 300 minutes (5 hours) to observe reddening of skin [84]. It is highly important to mention that a sunscreen with a higher SPF will provide a higher protection, however it does not mean longer exposure to sun [81]. The challenge in sunscreen application is linked with the underapplication, where most of individuals do not apply the proper amount of sunscreen. According to Hendersson et al. the proper amount of sunscreen is about 35 ml for a full adult body cover [80] while there is a need for re-applying sunscreen on the exposed sites in about 15- 30 minutes after sun exposure and after activities which can remove the sunscreen [81].

While sunscreen products are a necessary tool in skin protection from UVA and UVB radiation, it should not be relied

upon as the only protective measure [80]. More specifically, individuals have to be informed for other sun protection measures such as shady places, protective clothing and sun avoidance in peak hours [84]. However, it is suggested that people should use combined protective measures.

According to [85], sunscreens contain some ingredients which can reflect or absorb UVR, in order to protect the skin. These ingredients can be either physical or chemical and constitute the UVA and UVB filters [80]. Recently, these filters are categorized into 3 groups with a GREASE status, the first group includes physical blockers like TiO_2 and ZnO, the second group includes chemical absorbers which decrease the photon energy from the UVR, and the third group have a variety of chemical compounds with insufficient data to categorize filters as safe or not safe. Moreover, the GREASE status refers to their safety and effectiveness and classifies the first group of filters as "safe" and the second group as "not safe", whereas the chemical ingredients of the third group cannot be classified yet [86]. Thus, based on their GREASE status, sunscreens with TiO_2 and ZnO provide a better protection against UVA and UVB radiation [85]. Furthermore, sunscreen products include a group of factors which have antioxidative properties or even DNA repair enzymes. In their study, Singer et al. mention that both vitamins A, C, E, and flavanones present antioxidative properties protecting skin cells from free radicals, which can cause harm to them. Also, it is mentioned that some sunscreens have DNA enzymes with a repairing role trying to decrease the damage from CPDs and immunosuppressive cytokines [86].

Another factor with a major role on UV radiation and skin cancer development is the skin type, based on the study of Serpone et al. the reason why different skin types have totally different response to UVA and UVB radiation and in the development of skin cancer, is associated with the skin color and melanin levels. For instance, people with higher melanin levels-darker skin phototype (SPT) have lower incidence to skin cancer compared with individuals with a fair SPT. The reason why light SPT individuals are at higher risk, is linked with the high melanin concentration in upper skin layers of epidermis but also is associated with the higher pheomelanin ratio. High melanin concentrations provide protection against UV radiation by stopping the penetration into basal layers [85]. Hence, the DNA in the upper layers of dark skin is more likely to be damaged compared to the damage that occurs in basal layers in fair skins. However, despite the fact that darker SPT is naturally protected from UVB radiation, it is more susceptible to UVA. Thus, it is important to use sunscreen protection which will have to be skin-color-matched for more effective application [87].

Additionally, it was studied the effect of a hydrogel sunscreen based on yeast/ gelatin which provided a great shield against UVA and UVB radiation. Moreover, the hydrogel sunscreen was able to absorb a wide range of UV wavelengths, protecting individuals against the harmful effects of UV radiation. The hydrogel sunscreen offers a high protection against UV due to yeast cells property of absorbance, also a reduction of ROS was observed with an increasement of yeast cells, giving a better UV resistance [88].

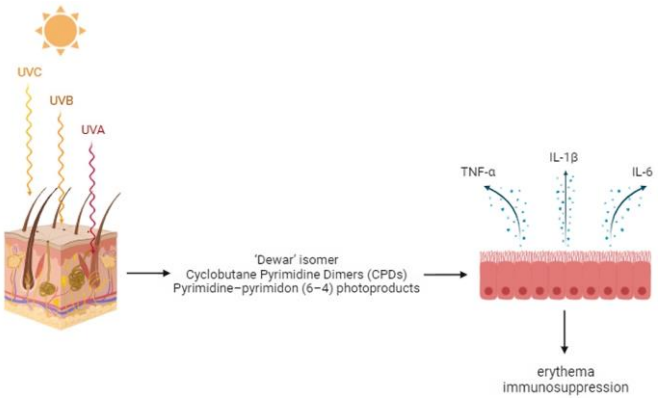

Figure 1. Schematic representation of the formation of various photoproducts triggered by different types of UV exposure (created with BioRender.com [Accessed: 17 January 2024])

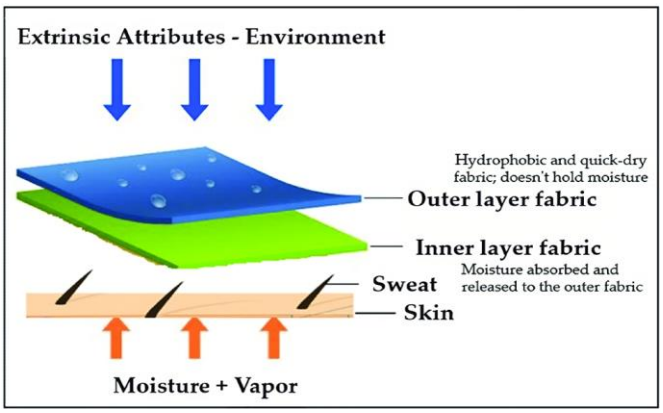

Figure 2. Structure of bi-layer knitted fabrics [93] (https://www.mdpi.com/1996-1944/14/22/6863)

Other Protective Measures

UV radiation exposure can be controlled based on health promotion practices and primary prevention strategies. Health promotion focuses on healthy populations in order to prevent risk factors by restraining exposure (physical protection), applying sunscreen protection (topical protection) and controlling oxidative stress (systemic protection) [89]. Physical protection can be accomplished by using proper clothing for example long-sleeved shirts, and clothes made with bi-layer knitted fabrics [89, 90]. According to [84], the degree of protection by proper clothing depends on color, material, fiber, yarn and fabric structure which is referred as one of the most important factors based on its porosity.

It is mentioned in the recent literature that bi-layer knitted fabrics provide high protection in UV radiation [90]. This type of material consists of two layers of fabric which are knit together to form a single, thicker fabric (**Figure 1**) The layers have been designed to offer improved moisture management, breathability or insulation. It is widely used in sportswear and summer outfits [91] (**Figure 2**).

https://www.zotero.org/google-docs/?vjYo3OIn accord with [90, 91], this fabric is preferred in sportswear due to the fact that outdoor activities demand high exposure to UV radiation. Moreover, based on the body part, the equipment is designed with different combinations of materials, for

example polyester microfiber with lycra and 70/30 bamboo/ cotton, which seems to be the best option [90].

Community-Based Interventions to Prevent Skin Cancer (School Education, Mass Media, etc.)

Both health promotion and primary prevention strategies promote educational, behavioral and environmental interventions while there is an effort to integrate all these single- methods into a one program.

School education

One of the main roles of school is to promote healthy behaviors among the students. Thus, there is an urgent need to educate children from younger ages in subjects concerning prevention. It is well known that exposure to sunlight can be harmful for human health, so for that reason education programs related to skin cancer prevention are mandatory for the awareness of adolescents. So far many educational projects have been conducted around the world, such as *Slip, Slop, Slap, Seek, Slide and SunSmart* in Australia, the *Danish Sun Safety Campaign* and other campaigns based on the Australian model [92]. The Australian prevention model studies children's behaviors referring to sun protection policies and practices enhancing implementation of their proper application [93].

Another way the education system can modify students' behavior is to participate in surveys related to health promotion. According to the cluster-randomized clinical trial (RTC), it was conducted in secondary high-schools in Brazil, using a face-aging mobile application based on interventions on skin cancer protection [94]. Specifically, this RTC had a total duration of six months accompanied by two interventions. The first one referred to the daily usage of sunscreen for six months and the second intervention included the usage of sunscreen for three months, at least one skin examination via the application in the survey period and at least one tanning session the last 30 days. The results of this survey presented an improvement in student's sun protection practices and makes the face- aging mobile application a useful tool for public health policies with great potential [94].

Mass media

Nowadays more and more people are using social media for their health information. In the United States it was found that 2 to 5 people use social media to get informed about preventive measures in health and symptoms [95]. Awareness-raising efforts and marketing that make use of social media's fast communication and wide audience serve as the focal point of these initiatives. In order to reach more people and encourage additional education and healthy behaviors, these efforts frequently transform knowledge and information into dialogues and conversations. Utilizing social media channels to develop and post content is affordable and productive [96].

Even while research on the impact of social media use in health campaigns is still in its early stages, some studies have found that it may be useful for promoting a range of various healthy behaviors. In a review of public health initiatives using social media to address eating habits and physical inactivity, nine out of ten studies demonstrated improvements in those components of health behaviors [97].

Patients are increasingly turning to the Internet for direct information about skin cancer prevention, treatment, and emotional support as social media use among dermatology patients rises. various social media channels tend to be used in various amounts to raise awareness about skin cancer. Implementing skin cancer prevention projects via social media could broaden their audience and relevance, specifically among young people. Social networking and the beauty industry have recently been closely linked [98]. Many of the most popular, active Instagram accounts are owned by beauty companies, including dermatologic. 95 million posts and 3.5 billion "likes" are made on Instagram every day, reaching 1 billion users each month. 90% of users are younger than 35, and 60% of users log in every day [97].

Screening for Skin Cancer

Screening tests and/or exams are the keystones of secondary prevention strategies. They enable the diagnosis of disease in asymptomatic people by identifying those with certain risk factors. Patients' self-examination and medical examination are two techniques for obtaining early detection. The ABCDE rule and the ugly duckling sign should be the basis for both of these evaluations, which should also ideally be assisted by total-body photography [99]. Current international guidelines suggest that all cutaneous screenings should be performed using dermoscopy, a non-invasive imaging technique allowing improving considerably the diagnostic performance. If necessary, biopsy and histopathologic evaluation should be done. Recently, many innovative skin cancer detection technologies have been developed to increase diagnostic accuracy for skin cancers. These noninvasive technologies offer benefits over biopsy but are limited by expense, training, and poor specificity [100]. Skin cancer screening with a total body skin examination is arguably the safest, easiest and possibly the most cost-effective screening test in medicine [101]. Compared to the well-established screenings in the US for colorectal, breast, prostate, cervical, and endometrial cancers, this non-invasive screening check is conducted significantly less frequently [102, 103].

There are no recommendations for the early identification of skin cancer from the American Cancer Society. Instead, early identification of melanoma and keratinocyte carcinomas is done opportunistically in most countries, either by the patient presenting for a routine skin check or with a lesion of concern, or by the clinician incidentally spotting a lesion [104].

Despite the fact that early skin cancer detection and treatment can enhance patient outcomes and lower mortality, there is insufficient evidence to support the use of widespread screening programs [105]. There is worry that melanoma screening may result in overdiagnosis, or an increase in the discovery of small lesions that would not have been found otherwise and are unlikely to develop into lethal malignancy [106, 107].

As a result, there is much disagreement on who should be screened, who should perform the screening, and how frequently screening should be done–with the exception of very high-risk individuals, for whom periodic screening is universally advised once a year. Even though further clarification should be done, 'high risk' groups include adults with personal history of skin cancer or immunodeficiency,

family history of melanoma, certain physical features such as light skin, red or blonde hair, freckles, > 40 nevi, history of sunburns or indoor tanning [102].

Chemoprevention of Skin Cancer

Several natural compounds and antioxidants have shown promise in preventing skin cancer by counteracting the damaging effects of UV radiation. Polyphenols found in green tea, such as epigallocatechin gallate (EGCG), exhibit potent antioxidant and anti-inflammatory properties. These compounds can neutralize free radicals generated by UV exposure, thereby reducing DNA damage and inhibiting the initiation of skin cancer [108-111]. Similarly, resveratrol, a polyphenol present in red grapes and berries, has demonstrated anti-cancer effects by modulating cellular pathways involved in UV-induced apoptosis and inflammation. These natural compounds not only protect the skin from oxidative stress but also have the potential to interfere with the progression of precancerous lesions [112].

Retinoids, derivatives of vitamin A, have long been recognized for their role in promoting healthy skin. Studies suggest that topical application of retinoids can help prevent skin cancer by enhancing cell turnover, promoting the differentiation of keratinocytes, and inhibiting the formation of UV-induced DNA mutations. The retinoid signaling pathway plays crucial roles in the physiology and pathology of the skin, impacting the prevention and treatment of NMSCs. NMSCs form a diverse group of skin cancers derived from non-melanocyte cells, posing significant challenges to both patients and healthcare systems. This category encompasses BCC and cutaneous SCC, collectively referred to as keratinocyte carcinomas, as well as cutaneous lymphomas and Kaposi's sarcoma, among others. Retinoids, regulating various biological processes in the skin such as proliferation, differentiation, angiogenesis, and immune regulation, collectively exhibit the ability to suppress skin carcinogenesis. Clinical trials exploring both topical and systemic retinoids as prophylactic and therapeutic agents for NMSC have demonstrated desirable efficacy and tolerability. Consequently, health regulatory bodies have approved the use of retinoids in the management of NMSC. Additionally, vitamin D, synthesized in the skin upon exposure to sunlight, plays a crucial role in skin health and has been associated with a reduced risk of skin cancer [113, 114].

Nicotinamide, also recognized as niacinamide, is a water-soluble derivative of vitamin B3. It acts as a preventive measure against NMSCS by diminishing UV-induced immunosuppression and enhancing DNA repair.The well-tolerated dosage of 500 mg twice daily demonstrated a favorable safety profile compared to acitretin. Nicotinamide, an inexpensive over-the-counter vitamin supplement, does not necessitate laboratory monitoring [115].

Acitretin, an oral analog of vitamin A, serves as a preventive measure against NMSC, although the exact mechanism of prevention remains unknown. Potential mechanisms may involve the induction of normal cellular differentiation, immunomodulation, and inhibition of tumor differentiation and promotion through the induction of growth arrest and apoptosis in tumor cells. A recent systematic review revealed a substantial 60% reduction in the development of SCC in SOTRs. Limited studies assessing the effect of acitretin in immunocompetent patients exist, primarily due to small sample sizes [113].

In addition to natural compounds, researchers are exploring synthetic drugs with chemopreventive potential. Nonsteroidal anti-inflammatory drugs like aspirin have demonstrated promising effects in reducing the incidence of skin cancer. These drugs work by inhibiting inflammation and modulating pathways involved in the development of skin tumors [116].

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