International Journal of Scientific Research and Engineering Development-– Volume 8 Issue 5, Sep-Oct 2025
Available at www.ijsred.com

RESEARCH ARTICLE OPEN ACCESS

A Comprehensive Review of Skin Cancer: Pathogenesis, Current Therapies, and Emerging Nanotechnological Solutions

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Abstract:

Skin cancer remains a growing global health challenge, with its incidence expected to rise sharply in the coming decades if timely detection is not achieved. Although treatable in the early stages, significant obstacles persist, such as limited success in developing new therapeutic agents, clinical effectiveness, and the issue of drug resistance. To address these concerns, it is vital to gain deeper insight into the underlying causes of skin cancer, the mechanisms driving abnormal cell growth, and the factors that contribute to resistance against treatment. This article discusses the various forms of skin cancer and explores current treatment strategies, including phytocompounds, chemotherapy, radiotherapy, photothermal therapy, surgical interventions, and combination approaches, alongside molecular targets that influence cancer progression and metastasis. Furthermore, it highlights the promising role of nanotechnology in reducing disease severity particularly through the use of nanoparticles to combat drug resistance and provides an overview of relevant clinical trials.

Keywords- **Carcinogenesis, Early diagnosis, Cell proliferation, Chemotherapy, Combination therapy.**

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INTRODUCTION

Skin cancer is one of the most prevalent malignancies of the present decade, which is not surprising given that the skin is the largest organ of the human body. It is broadly categorized into two groups: melanoma and non-melanoma skin cancers (NMSC). Melanoma, though relatively rare, is highly aggressive and accounts for a disproportionate number of skin cancer-related deaths. According to the American Cancer Society, melanoma represents about 1% of total skin cancer cases but contributes to a significantly higher mortality rate. It arises from melanocytes, the pigment-producing cells of the skin, which begin to grow uncontrollably and form malignant tumors. Diagnosis often begins with visual examination by dermatologists, which has an estimated accuracy of around 60%. Dermoscopy, a non-invasive imaging technique, improves diagnostic accuracy to nearly 89%, yet the detection of early melanomas without distinct dermoscopic features remains a challenge. The incidence of skin cancer continues to rise across the United States and globally. While the mortality rate of NMSC is relatively low, it causes significant morbidity, including cosmetic disfigurement and functional impairment. In contrast, melanoma, although less common, can be life-threatening if not detected and treated promptly. The economic burden is also substantial, with NMSC ranked among the five most costly cancers for Medicare in the United States.

The etiology of skin cancer is multifactorial, involving genetic, environmental, and behavioral influences. Ultraviolet (UV) radiation remains the most important environmental risk factor, causing DNA damage that drives carcinogenesis. Cumulative sun exposure is strongly linked to basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), whereas melanoma is more closely associated with intermittent, intense sun exposure and blistering sunburns. Other risk factors include genetic susceptibility, family history, immunosuppression, and exposure to carcinogenic chemicals. Individuals with fair skin, light-colored hair, and a tendency to sunburn are particularly vulnerable, as are organ transplant recipients and those with genetic conditions such as xeroderma pigmentosum. Prevention, early detection, and

timely treatment are essential strategies to reduce the incidence, morbidity, mortality, and healthcare costs associated with skin cancer. This article provides an overview of the epidemiology, clinical features, etiology, treatment approaches, and prognosis of skin cancer.[1]

TYPES OF SKIN CANCER

Skin cancer is mainly divided into three common types, based on the kind of skin cells where the cancer starts. These include, Basal Cell Carcinoma (BCC) , Squamous Cell Carcinoma (SCC), Melanoma.

BASAL CELL CARCINOMA

Basal cell carcinomas are the most frequent skin cancers in the fair-skinned adult population over 50 years of age. Their incidence is increasing throughout the world. Ultraviolet (UV) exposure is the major carcinogenic factor. Some genodermatosis can predispose to formation of basal cell carcinomas at an earlier age. Basal cell carcinomas are heterogeneous, from superficial or nodular lesions of good prognosis to very extensive difficult-to-treat lesions that must be discussed in multidisciplinary committees. Recent guidelines have updated the management of basal cell carcinoma. The prognosis is linked to the risk of recurrence of basal cell carcinoma or its local destructive capacity. Characteristic molecular events in these tumours are: activation of the hedgehog pathway, which has allowed the development of hedgehog inhibitors for difficult-to-treat lesions that are not accessible to surgery or radiotherapy; high mutational burden, which suggests that hedgehog inhibitor refractory tumours could be offered immunotherapy; some trials are ongoing. The standard treatment for most basal cell carcinomas is surgery, as it allows excision margin control and shows a low risk of recurrence. Superficial lesions can be treated by non-surgical methods with significant efficacy.[2-3]

Indeed, mutations in *TYR* gene may cause ocular albinism, a genetic condition associated with an increased risk of NMSCs . Regarding the genetic predisposition to multiple BCCs, some studies found an association between the number of BCCs and polymorphisms shown by the cytochrome (*CYP*) supergene family and the glutathione S-transferase (*GST*) supergene family, having a crucial role in metabolic and detox cellular mechanism .Most BCC were diagnosed on female patients (53,8%, n=1131) revealing a statistically significant association (p=0,04). The average age of this group was 70,3(±13,6) years old, showing no variation when considering only male (70,6±12,8 years old) or fema le patients (70,0±14,2 years old). These results clearly demonstrate the predominance of elderly patients ($p<0,001$ for age >70 years), as only 19,8% of the patients were aged 60 or less at the time of diagnosis. The great majority of BCC were identified on the face (n=1321, 62,9%) - table 1. Of those, 29,4% (n=388) were on the nose, 21,4% (n=283) on the zygomatic prominence and 14,7% (n=194) on the forehead. The remaining BCC were located on the cheek (n=114, 8,6%), the inner eye canthus (n=98, 7,4%), the ear (n=64, 4,8%), the upper lip (n=53, 4,0%), the mandibular region (n=45, 3,4%), the lower eyelid (n=43, 3,3%), the upper eyelid (n=6, 0,4%) and the lower lip (n=5, 0,4%). BCC location within the face was not specified in 28 cases (2,1%). Excluding the face, the scalp was the skin area.

SQUAMOUS CELL CARCINOMA

Oral squamous cell carcinoma (OSCC), which develops in the oral mucosa, is a common type of head and neck malignancy. According to data collected by the Global Cancer Observatory (GCO), there were 377,713 cases of OSCC worldwide in 2020, with the majority occurring in Asia. OSCC affects more males than females, with middle-aged to elderly men being the most susceptible. OSCC results in disfiguration and functional impairments, including swallowing, speech, and taste, which have a substantial impact on the life quality of patients. [4-6] Oral squamous cell carcinoma (OSCC) generally manifests as a lesion with red-and-white or purely red discoloration, often displaying a slightly irregular surface and clearly demarcated borders. In its early stages, OSCC tends to be asymptomatic, but as the disease advances it may

cause discomfort and present with ulceration, tissue induration, or nodular growths. Ulcerative lesions are particularly characteristic, showing an uneven base, irregular edges, and a firm consistency on palpation.

The posterior lateral border of the tongue represents the most frequent site of occurrence, accounting for nearly half of all cases. Other commonly affected areas include the floor of the mouth, soft palate, gingiva, buccal mucosa, and hard palate. Metastatic spread usually occurs through the lymphatic system, most often to the ipsilateral cervical lymph nodes, though contralateral or bilateral involvement is also possible. Distant metastases typically develop in the lungs, bones, and liver [7-8]. Squamous cell carcinoma is the second most common skin cancer, comprising 20 percent of all cases of nonmelanoma skin cancer. This is the most common tumor in elderly patients, and it is usually the result of a high lifetime cumulative dose of solar radiation. However, other irritants and exposures may lead to squamous cell carcinoma Up to 60 percent of squamous cell carcinomas occur at the site of a previous actinic keratosis.Changes in an actinic keratosis that suggest evolution to squamous cell carcinoma include pain, erythema, ulceration, induration, hyperkeratosis and increasing size .Squamous cell carcinomas may grow aggressively and are associated with a 2 to 6 percent risk of metastasis. Risk factors for metastasis include poor cell differentiation, increasing lesion depth and location on the lip or ear. The most common locations for metastatic spread are the regional lymph nodes, lungs and liver. Once metastasis occurs, the five-year cure rate for squamous cell carcinoma is 34 percent. Recurrence and metastasis typically occur within three years of initial treatment.

Table 1: Clinical Features and Common Sites of Oral Squamous Cell Carcinoma (OSCC)

Feature	Description
Appearance	Red-and-white (erythroleukoplakic) or purely red lesion
Surface	Slightly irregular / uneven
Borders	Well-defined, distinct
Symptoms (early stage)	Usually painless
Symptoms (advanced stage)	Discomfort, ulceration, induration, nodularity, tissue fixation
Ulcer characteristics	Irregular floor and margins, hard on palpation
Common sites	Posterior lateral tongue (≈50%), floor of mouth, soft palate, gingiva, buccal mucosa, hard palate
Regional spread	Mainly to ipsilateral cervical lymph nodes; may involve contralateral/bilateral nodes
Distant metastases	Lungs, bones, liver

MELANOMA

Melanoma is a malignancy of melanocytes, melanin (pigment) producing cells in the basal layer of the epidermis. Melanocytes are of neural crest origin, and therefore express many signaling molecules and factors that promote migration and metastasis after malignant transformation. Despite representing only 1% of skin cancers, melanoma accounts for over 80% of skin cancer deaths . Melanoma can be divided into many clinical subtypes that differ in presentation, demographics, and molecular profile. Among cutaneous melanoma, superficial spreading melanoma (SSM) is the most common type, especially among fair-skinned individuals, and tends to carry a good prognosis due to a low Breslow thickness, which also depends on the earlier time of diagnosis. Acral lentiginous melanoma, which arises from the glabrous skin of the palms, soles, and nailbeds is more likely to arise in darker-skinned ethnicities. More rarely, and likely independent of sun exposure, melanoma can arise from mucosal or uveal tissue. Uveal melanoma has a particularly

poor prognosis, with over 50% of patients developing stage IV disease.

The incidence of melanoma has increased in developed, predominantly fair-skinned countries over the past decades . Melanoma is now the fifth leading cancer diagnosis in the US . Our review uses 2020 global statistics (GLOBOCAN) for incidence, mortality, and survival. We also present the latest international initiatives for the prevention of melanoma [9-11]. Melanoma develops from melanocytes, specialized cells responsible for producing melanin. While this cancer represents only a small proportion of skin tumors, it is the most lethal due to its tendency for rapid progression and early metastasis. For many decades, treatment options for advanced melanoma were extremely limited, and outcomes were poor. However, the introduction of targeted therapy and immune checkpoint blockade has completely reshaped the outlook for patients. Today, long-term survival is achievable in a subset of individuals with advanced disease. This review article provides a comprehensive overview of melanoma, integrating biological, clinical, and therapeutic perspective.

CAUSES AND RISK FACTORS

A large proportion of mortality and disease in humans is caused by cancer. Environmental, exogenous and endogenous factors such as causal hazardous or chemical agents like heavy metals, radiation, and genetic predisposition contribute to cancer development. The development of chemical usage and types, including diversified new workers' exposure, is of significant concern to occupational disease, and the application of chemicals has increased due to more industries. According to the current state of knowledge, epidemiological studies have proved that 80-90% of humans' main factors responsible for developing malignant neoplasia are external environmental factors and can be seen in human behaviour, smoking and excessive alcohol consumption. It is concluded that the interaction of these risk factors has an enormous contribution to cancer development. The cancerous process is due to disturbance in cell function by the accumulation of many genetic and epigenetic changes within the cell, such as the accumulation of chromosomal or molecular aberrations leading to genetic instability. Over the years, epidemiological research has focused on the mortality rate and the development of malignant tumors caused by the determinants of environmental and genetic factors of cancer incidence. They have a long latency period with malignancies; for this reason, they are usually found at an older age, probably after workers' retirement. Therefore, it is suggested that management policies must be established to prevent occupational cancers from occurring among workers. In this article, two important environmental risk factors were classified and discussed, the occupational cancers that are often seen with these risk factors, the formation of cancer, and how exposure to occupational cancer can be avoided. It is vital to understand environmental/occupational risk factors and help maintain sustainable and appropriate measures to guarantee workers' safety and health [12-14].

SIGNS AND SYMPTOMS

The pathophysiology of skin cancer is not fully understood, but various etiological factors, with UV light being the most prominent, interact with risk factors that likely contribute to the development and neoplastic proliferation of skin cancer.[15] These proliferations may be benign or malignant; benign proliferation typically results from dysregulation, while malignant proliferation is driven by genetic and molecular alterations associated with UV radiation [15]. Exposure to UV light from solar radiation is the most significant modifiable risk factor for developing both nonmelanoma skin cancer and melanoma.[16] UV radiation can be categorized into UV-A, UV-B, and UV-C based on their respective wavelengths approximately 320 to 380 nm for UV-A, 280 to 320 nm for UV-B, and 100 to 280 nm for UV-C.[17] Sunlight is primarily composed of UV-A (~90%) and UV-B (~10%) radiation, while UV-C rays are absorbed mainly by the atmosphere. UV-A, with its longer wavelength, penetrates the dermis and generates free radicals.[18] UV-B, with a shorter wavelength, penetrates to the level of the stratum basale of the epidermis, leading to the formation of pyrimidine

dimers, such as thymidine dimers.[19][20] Both UV-A and UV-B contribute to carcinogenesis, with UV-A significantly impacting skin aging.[21] UV radiation causes cell injury and apoptosis and impairs DNA repair mechanisms, leading to DNA mutations.[22]

The development of cutaneous malignancy following DNA damage from solar radiation is multifactorial and influenced by genetic factors, Fitzpatrick skin type, and immunosuppressed status. Most (90%) cutaneous squamous cell carcinomas exhibit UV-induced *p53* gene mutations, leading to uninhibited keratinocyte proliferation.[23] DNA mutations associated with basal cell carcinoma include mutations in the *PTCH* and *p53* genes.[24] Melanoma-related DNA mutations include alterations in CDKN2A, MCR1, *BRAF*, and DNA repair enzymes, such as UV-specific endonuclease in xeroderma pigmentosum.[25][26] The complete list of genetic mutations and risk factors remains incomplete, but ongoing research continues to uncover new genes and targets involved in each subtype of skin cancer.[27]

DIAGNOSIS

Skin cancer refers to the abnormal proliferation of the skin cells. Although sun exposure is the leading cause of skin cancer, other factors that including genetic disposition, skin type, and environmental factors may be attributed to skin cancer. An estimated 2,001,140 new cases of cancer are expected to occur in the United States in 2024, with 611,720 deaths from the disease predicted to occur. In contrast, an estimated 108,270 cases of skin cancer are also expected to happen in the US that year, with the estimated number of cases causing fatalities at 13,120. All these numbers bring to light a tremendous public health concern about skin cancer and the importance of early detection and treatment.[28-30] A physical examination of the skin diagnoses skin cancers, and if there are any doubtful areas, a biopsy can be performed. In identifying and classifying skin lesions, imaging the skin for skin cancer plays a crucial role. The images have a lot of features and patterns, all of which are used in the analysis to differentiate between cancerous and non-cancerous lesions. Skin cancer treatment is done early in the same way treatment is given in other types of cancers. Early detection of cancer helps to detect the disease at earlier stages and start treatment. Artificial intelligence and deep learning techniques have been employed in the early cancer diagnosis due to their capability to process large datasets and identify complex patterns . These are applied in various areas, including defense, agriculture, natural language processing, and large language models, among others, which include early diagnostics of cancers.

When it comes to the artificial intelligence and deep learning techniques employed in the early cancer diagnosis, convolutional neural networks (CNNs) are the most widely applied deep learning technique for medical image processing and early cancer diagnosis . Capabilities in image data processing and analysis have been noted with CNNs. In medical diagnosis, such a model can be trained to detect cancerous tissues, cells, or lesions. For instance, it could be applied to detecting abnormalities on MRI or CT scans or classifying cancer cells from a histopathology image. The use of CNNs has excellent potential for tasks in the diagnosis of skin cancer, which includes the classification of skin lesions and the detection of cancerous lesions. Furthermore, the next generation of deep learning models, such as the Vision Transformer (ViT), has also presented great potential in diagnosing cancer in medicine. The ViT model proposes something entirely different from traditional CNN-based methods for feature extraction from image data.[56][57] These models can manage large-scale image data, identify complex patterns, and, to an increasing extent, be used on issues in medical imaging, such as skin cancer detection. In most cases, however, CNNs can afford better performance than ViTs. The earlier the deep learning technologies are used, the more effectively the presence of cancerous lesions can be detected in the case of skin cancers, which leads to more effective processes for the treatment. [31-34]

TREATMENT OPTIONS

Skin cancer represents a major health concern due to its rising incidence and limited treatment options. Current treatments (surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy) often entail high costs, patient inconvenience, significant adverse effects, and limited therapeutic efficacy. The search for novel treatment options is also marked by the high capital investment and extensive development involved in the drug discovery process. In response to these challenges, repurposing existing drugs for topical application and optimizing their delivery through nanotechnology could be the answer. This innovative strategy aims to combine the advantages of the known pharmacological background of commonly used drugs to expedite therapeutic development, with nanosystem-based formulations, which among other advantages allow for improved skin permeation and retention and overall higher therapeutic efficacy and safety. The present review provides a critical analysis of repurposed drugs such as doxycycline, itraconazole, niclosamide, simvastatin, leflunomide, metformin, and celecoxib, formulated into different nanosystems, namely, nanoemulsions and nanoemulgels, nanodispersions, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, hybrid lipid–polymer nanoparticles, hybrid electrospun nanofibrous scaffolds, liposomes and liposomal gels, ethosomes and ethosomal gels, and aspasomes, for improved outcomes in the battle against skin cancer. Enhanced antitumor effects on melanoma and nonmelanoma research models are highlighted, with some nanoparticles even showing intrinsic anticancer properties, leading to synergistic effects. The explored research findings highly evidence the potential of these approaches to complement the currently available therapeutic strategies in the hope that these treatments might one day reach the pharmaceutical market [35-36][54-55].

Various methods including chemotherapy, photothermal therapy (PTT), immunotherapy and gene therapy are used as secondary intention treatment of tumor resection surgery [37]. Wherein, chemotherapy can prevent the continued growth of tumors by utilizing one or more drugs such as doxorubicin (DOX), cisplatin and trastuzumab [38]. However, the side effects with high toxicity and low utilization rate limit its clinical application [39]. Thus, anticancer drugs are wrapped in biodegradable nanocarriers to achieve controlled drug release [40]. Poly (lactic-co-glycolic acid) (PLGA) is an organic polymer compound with excellent biocompatibility and biodegradability, which has wide applications in the field of biomedical engineering . Electrospun PLGA nanofibers possess the structural characteristics of high specific surface area and porosity, which can serve as a good drug carrier [41,42].

PREVENTION AND PROTECTION

Skin cancer, a prevalent cancer type among fair-skinned patients globally, poses a relevant public health concern due to rising incidence rates. Ultraviolet (UV) radiation poses a major risk factor for skin cancer. However, intentional tanning associated with sunburns remains a common practice, notably among female adults. Appropriate prevention campaigns targeting children and adolescents are needed to improve sun protection behavior particularly in these age groups. The aim of our study was to investigate if an AI-based simulation of facial skin aging can enhance sun protection behavior in female adults. In this single-center, prospective, observational pilot study at Department of Dermatology at the University Hospital of Basel, we took photographs of healthy young females' faces with a VISIA-CR camera (Version 8.2; Canfield Scientific Inc., Parsippany, NJ, USA) between February and March 2021. Digital images were performed in three angles (straight, left 45°, and right 45°). All participants received an AI-based simulation of their facial skin with continuous aging to 80 years. A newly created anonymous questionnaire capturing participants' sociodemographic data and also tanning and sun protection behavior was completed in pre- and post-aging simulation. To observe long-term effects, a 2-year follow-up was conducted between March and April 2023. The 60 participants (mean age 23.6 ± 2.5 years) evaluated the importance of sun

protection significantly higher after skin aging simulation with VISIA-CR camera ($p < 0.0001$; 95% CI: 8.2–8.8). Post-intervention, 91.7% (55/60) of the females were motivated to reduce UV exposure and to intensify UV protection in the future since the individual UV-dependent risk was perceived significantly higher ($p < 0.001$; 95% CI: 5.9–6.7). At 2-year follow-up, 96% (24/25) indicated persistent effort reducing UV exposure. The preference for SPF 50+ sunscreen increased to 46.7% (28/65) directly after the skin aging simulation and continued to rise up to 60.0% (15/25) after 2 years. Our data emphasize the potential of AI-assisted photoaging interventions to enhance motivation for UV protection in the short and the long term. We encourage that different age and gender groups are addressed in a personalized, generation-specific manner with the appropriate media and by considering the Hawthorne effect. Campaigns with visual AI support can improve the intent of cancer-preventative behavior. [43-44] [53]

RECENT ADVANCES IN RESEARCH

Skin cancer is a global threat to the healthcare system and is estimated to incline tremendously in the next 20 years, if not diagnosed at an early stage. Even though it is curable at an early stage, novel drug identification, clinical success, and drug resistance is another major challenge. To bridge the gap and bring effective treatment, it is important to understand the etiology of skin carcinoma, the mechanism of cell proliferation, factors affecting cell growth, and the mechanism of drug resistance. The current article focusses on understanding the structural diversity of skin cancers, treatments available till date including phytocompounds, chemotherapy, radiotherapy, photothermal therapy, surgery, combination therapy, molecular targets associated with cancer growth and metastasis, and special emphasis on nanotechnology-based approaches for downregulating the deleterious disease. A detailed analysis with respect to types of nanoparticles and their scope in overcoming multidrug resistance as well as associated clinical trials has been discussed.[45-46] [51-52]

CONCLUSION

Skin carcinogenesis and its consequences show uncontrolled or aberrant expression of factors such as exposure to different genetic, epigenetic, drug, environmental, and pharmacological factors. The number of evidence indicates that NF-κB, STAT, and activator protein 1 promote genetic alterations while maintaining the stemness of cancer cells. Factors associated with skin cancer include exposure to UV rays, age, immunogenic responses, and viral agents. Various kinds of approaches are available till date such as chemotherapy, surgery, radiotherapy, chemical peel, immunotherapy, photothermal therapy, etc. Herein, we have outlined various examples of chemicals and pathways that appear to have promise for more efficient and secure therapies for several kinds of skin carcinoma. The dysregulation of several targeting sites orchestrates mediators and signaling pathways that converge toward skin cancer progression and metastasis, as evidenced by the complexity and heterogeneity of skin cancer cells. Therefore, it should be a top priority for research and clinical trials to identify novel therapeutics with multi-targeting potential from natural and non-natural resources that have fewer negative side effects.[58-59] Nanotechnology is a growing approach that can overcome the stumbling block of existing approaches, such as undesired off-target effects, unspecific distribution, and suboptimal efficacy. Encouraging combination therapies using immunotherapy, phytocompounds, and chemotherapy can be a boon to overcoming the limitations of traditional therapy. Herein, we have discussed various kinds of chemotherapeutic agents, phytocompounds, and their combination for regulating the prognosis and metastasis cascade of skin cancer. To address the highlighted clinical problems in skin malignancies, more information regarding single-as well as combined therapy methods based on verified basic, translational, and clinical research are still desired.[47-50][60]

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