



African Journal of Biological Sciences



ADVANCES IN UNDERSTANDING AND MANAGING SKIN CANCER: A COMPREHENSIVE REVIEW

¹ANITA SINGH, ²AMITA JOSHI RANA, ¹MAHENDRA RANA, ¹HANSIKA BANSAL
¹MANISHA JOSHI, ³MONIKA, ³AJAY SINGH BISHT*

1. Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Campus, Bhimtal (263136), Kumaun University, Nainital, Uttarakhand, India
2. College of Pharmacy, Graphic Era Hill University, Bhimtal, Uttarakhand
3. School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun, Uttarakhand.

*Corresponding Author: Ajay Singh Bisht, Email-ajaysinghbisht@sgrru.ac.in

ABSTRACT:

Skin cancer is an important public health issue which is prevailing all over the world, especially in areas which receive sunlight throughout the year. Due to increasing pollution and global warming, a large population has been suffering from this illness. Skin cancer is known as the unwanted and uncontrolled proliferation of skin cells. It is classified as either malignant melanoma skin cancer or non-melanoma skin cancer. Melanoma is responsible for large number of deaths in humans. This review article comprises of a brief account about skin cancer, its types, epidemiology, risk factors, pathogenesis, detection and treatment approaches. The major causative agent found for this underlying disease is exposure to ultraviolet radiation. Other risk factors include aging, genetic factors, weak immunity, family history, etc. These tumors differ in characteristics, thus they can be easily identified physically and can be confirmed through biopsy or histopathological examination. The common treatment approaches for skin cancer are surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, herbal medicine, nanotechnology, dermal therapy, etc. Furthermore, early diagnosis plays an important role in curing this disease. The purpose of this paper is to give a thorough understanding of skin cancer and this knowledge is currently the need of the hour so as to reduce mortality and help mankind to combat this disease.

KEYWORDS: Basal cell carcinoma (BCC), melanoma, tumor, biopsy, squamous cell carcinoma (SCC)

INTRODUCTION

The biggest organ in the human body is the skin which covers a total of 16% body mass. There are two primary layers into which the skin is bifurcated, i.e. epidermis and dermis which further constitute components such as epithelial, mesenchymal, glandular and neurovascular. The peripheral layer that comes in contact with environment and acts as a physiochemical barrier against the stressors and irritants is the epidermis(1). The stressors include pathogens, chemicals, harmful ultraviolet radiations, etc. The layer that lies under the epidermis is dermis. Dermis is originated from the mesoderm and it helps to secure the cutaneous tissues like sebaceous glands, sweat glands, nerves, and hair follicles. Epidermis is composed of keratinocytes and dermis is composed of immune cells and fibroblast cells, both of which together aids in the physiological responses in the skin(2).

Cancer is called as the uncontrolled and unwanted cell growth, in which cell loses its ability to grow normally. Skin cancers are considered to be very common type of cancers occurring in Homo sapiens, particularly in white population. Skin cancers are mostly nonmelanomatous which originate from keratinized epithelial cells(3). They are named according to their place of origin and thus, the three most prevalent types of skin cancer are cutaneous malignant melanoma, squamous cell carcinoma, and basal cell carcinoma. In the basal cell carcinoma, the patient is affected by lesions that occur on head, scalp, nose and neck or any other area which is under contact of ultraviolet radiation. Squamous cell carcinoma is the second most prevalent type of skin cancer, and it includes risk factors such as long sun exposure, tanning, male sex, fair skin, older age groups, etc. Malignant melanoma is associated with high death rate due to the high influence of harmful ultraviolet radiation (4).

Skin cancer has now become a global threat. Due to increasing global warming and UV index, the cases of skin cancer are known to increase tremendously in the upcoming years. Early diagnosis makes skin cancer curable and in the upcoming years, skin cancer is expected

to overtake heart illnesses as the leading cause of death (5). The major cause of skin cancer includes abnormal cell proliferation, unrepaired cellular DNA, DNA mutations and genetic abnormalities. Cancer cells which occur due to mutation in melanocytes are malignant melanoma while those occurring from epidermis are non-melanoma skin cancer. The treatment approaches for skin cancer are surgery, radiotherapy and chemotherapy. But these treatment affect the normal skin cells too and causes toxicity (6). Nowadays, nanoparticles are also used for treatment because they are target specific and site specific and they cross the physiological barriers easily. They also provide high efficacy at low doses and thus, reduce the toxicity and adverse drug reactions(7). The use of traditional medicines has also been practiced for the treatment of skin cancer as these bioactive phytochemicals are less toxic and highly effective. The phytoconstituents commonly used are epigallocatechin-3-gallate, eugenol, curcumin, capsaicin, luteolin, apigenin, silymarin, proanthocyanins, resveratrol, genistein etc and these are found in various leaves, fruits, herbs and roots(5).

A crucial factor in treating such cancers is timely diagnosis. Skin cancer can be detected by biopsy i.e. removing a sample lesion and determining whether it is cancerous or not. However, biopsy is painful and time-consuming(8). Skin cancers can be prevented upto 80% by reducing the exposure to UV radiation and primary care(9).

EPIDEMIOLOGY AND RISK FACTORS

Skin cancer prevails globally; it has been tremendously increasing over past decades, especially melanoma. Skin cancer risk is higher in people with pale skin tones, light-colored hair, and light-colored eyes due to reduced melanin levels. Melanin acts as a protective shield against the harmful UV rays and it is present in less amount in fair individuals(10). Individuals with darker skin tones are less likely to be victims than those with lighter skin tones. Due to their high levels of sunshine exposure, nations like Australia and New Zealand have high rates of skin cancer occurrence. People who live in places with high altitude are

also easily affected. However, the prevalence of skin cancer is not only limited to sunny regions(11).

High exposure to UV radiation from the sun or artificial light sources, such as tanning beds, is the main environmental risk factor for skin cancer (12). People who have gone through radiation therapy earlier also have great chances of skin cancer. Intense and frequent sunburns occurring since childhood due to negligence and lack of knowledge increase the chances of skin cancer. Though melanoma is a kind of cancer that primarily affects younger people, the risk of skin cancer also rises with age. The male sex is more prone to skin cancer than the female sex(13). Compared to melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) are more prevalent but less malignant. Melanoma can travel to other areas of the human body and spread, which raises the death rate(14).

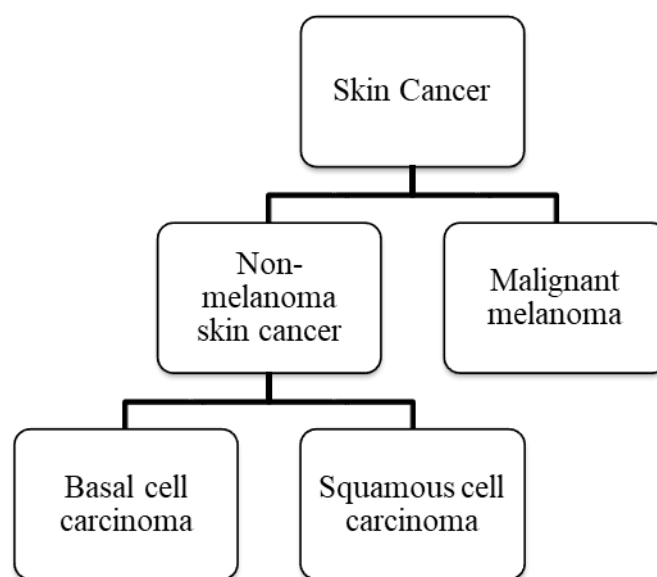
Patients having moles that are more numerous, weakened immune system, a history of sunburns, and a family history of skin cancer are also prone to skin cancer(15). Genetic factors also play a vital part in the emergence of skin cancer. Also, people who have suffered from skin cancer previously have the audacity to suffer from skin cancer again. Moles can be atypical or dysplastic and they should be observed and monitored closely if they are unusually increasing in number. Immunocompromised patients like those suffering with HIV/AIDS, taking medications or having organ transplant have high risk of skin cancer(16). Individuals suffering from chronic skin problems like scars, burns, chemical exposure may lead to skin cancer. Skin cancer can also occur due to occupational hazards like over exposure to harmful radiations or chemicals, thus care must be taken at such places.

Sufficient sun protection measures must be implemented to mitigate the risk factors associated with skin cancer. These measures include using sunscreen, wearing covered and protective clothes, avoiding unnecessary sun exposure. Good general awareness and skin

examinations can also help to lower skin cancer morbidity and death. In case of suspicion, a dermatologist must be contacted as soon as possible.

TYPES OF SKIN CANCER

Malignant melanoma and non-melanoma carcinoma (NMSC) are the two main forms of skin cancer. In addition, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are subtypes of non-melanoma skin cancer. Keratinocyte skin cancer(KSC) is another name for non-melanoma carcinoma (17).



CHAR

T 1: TYPES OF SKIN CANCER

Non-melanoma skin cancer

This particular form of carcinoma targets skin cells except the melanoma cells. The major causative factor for NMSC is ultraviolet radiation, especially in people with fair skin. It can also occur due to genetic mutations in cytochrome P450 family, p53 and glutathione S-transferase family(18). Viruses are another factor that causes some types of NMSC, for example- bowenoid papulosis, Kaposi sarcoma, SCC, verrucous carcinoma, merkel cell carcinoma and epidermodysplasia verruciformis. Two kinds of non-melanoma skin cancer are basal cell carcinoma and squamous cell carcinoma (19).

Basal cell carcinoma (BCC)

BCC is very common category of skin malignancy with low fatality rate. Despite of its low mortality rate, the morbidity rate of BCC is quite high. 50% of the skin carcinoma patients are found to be suffering from BCC(20). Basal cells are also included in the category of keratinocytes. This cancer is least dangerous and it appears in the form of fleshy bumps, pinkish patches over the skin. The most affected organs are face, neck, hands, legs and abdomen including all the other areas which are exposed to sun rays. Apart from UV rays, the main causative agents include human papilloma virus and human immunodeficiency virus. Hyper activation and mutations of hedgehog/patched intracellular signaling pathway causes the emergence of BCC(5). The treatment for BCC is radiation and topical treatment.

Squamous cell carcinoma (SCC)

This is also referred to as CSCC (cutaneous squamous cell carcinoma) and it is the second most common type of skin malignancy. It has the capacity to metastize locally and appears as scaly patches and red firm bumps on the upper layer of epidermis. Like BCC, it also occurs in lighter shade people upon over contact with harmful ultraviolet radiation. Other factors influencing SCC are burns, scars, skin ulcers, aging, suppression of the immune system, chemicals, carcinogens, etc(21). The main treatment for SCC is surgery.

Melanoma skin cancer

These tumors originate from melanocytes and are malignant and aggressive. The basal layer of the epidermis contains melanocytes. The mechanism behind the development of melanoma is when a person comes in contact with ultraviolet rays; genetic alterations occur which causes the oncogens to active and tumor suppressor genes to deactivate. This prevents DNA repair and triggers the uncontrolled growth of melanocytes. This type of cancer is associated with mortality. For diagnosis of melanoma, ABCE rule is followed i.e. asymmetry, border-

irregularity, color and diameter. The subtypes of invasive cutaneous melanoma are lentigo malign, acral lentiginous, superficial, and nodular (5). Superficial melanoma appears like moles and pigmented lesions, nodular melanoma appears as polypoid nodules and are developed often in old people, lentigo malign are macules which appears to be irregular, small, flat and asymmetric while acral lentiginous are rare and appears on toes, soles, fingers, nail beds and palms(22).

PATHOGENESIS

Skin cancer etiology is impacted by lifestyle, environmental, and hereditary factors. UVA and UVB rays are two types of ultraviolet radiation that are important in the development of skin cancer. These rays cause DNA damage, mutations in genes TP53 and BRAF respectively. This leads to the disruption of normal cell cycle and cell proliferation which ultimately causes apoptosis and cancer(23). Another factor influencing the pathogenesis is chronic inflammation. The UV rays trigger the inflammatory responses which in turn causes tissue damage and development of tumor. Immunosuppressant also facilitate the progression of skin cancer as they diminish the natural immunity of the body system and thus body is unable to detect and eliminate the malignant cells(22). Mutation in tumor suppressor genes also enhances the susceptibility to skin cancer. Exposure to carcinogens like arsenic and polycyclic aromatic hydrocarbons also lead to development of skin cancer.

BCC is majorly resulted from ultraviolet radiation. UVB rays having wavelength 290-320 nm cause suppression of immune system and inhibit factors that prevent the formation of tumors. This in turn leads to mutation of tumor suppressor genes and thus, skin cancer(24). Basal cell carcinoma is also known to be caused by abnormal hyperactivity of HH (hedgehog) cycle(25).

SCC takes place in Bowen's disease or actinic keratosis. Over exposure to sunlight also leads to a disease known as photokeratosis. Bowen's disease is also a type of skin damage caused

by arsenic poisoning, ultraviolet radiation and HPV (human papilloma virus). SCC also occurs due to the accumulation of UV rays and long term use of immunomodulators. Previous actinic keratosis lesions also lead to SCC(1). Other factors that influence squamous cell carcinoma are defect in DNA repair, mutations in tumor suppressor gene p53, accumulated UV rays, burn scars and exposure to carcinogenic agents(18).

Environmental and genetic factors are the causes of malignant melanoma but there are no efficacious anticancer drugs for this type. Hence, early diagnosis is really important otherwise the patient will have to go for surgery(26). People who are indulging in outdoor activities and have fair tone, blue eyes, red or blonde hair possess higher risk for melanoma. Mutations in B-RAF gene is often linked with melanoma. If a person is exposed to artificial tanning at young age, then the chances of melanoma is accelerated(27).

DIAGNOSIS

Skin cancer is a broader term which is classified into several types. Each type has distinct characteristic features and diagnostic criteria. BCC is the most popular type of skin cancer and its detection involves skin examination for flat, pearly bumps, lesions, flesh-colored, brown scars or reddish patches. Biopsy is also performed by taking a sample lesion and examining it under microscope. The lesions may bleed, ooze or crust over(28). Squamous cell carcinoma is the second most popular of skin carcinoma whose appearance is a firm, reddish, nodules or lesions which are flat, scaly or crusty. It can be examined physically or through biopsy. Melanoma is malignant, aggressive and can develop from previous moles. It appears as pigmentation and spots. Melanomas are identified by ABCDE rule i.e. asymmetry (both sides of wound are not similar), border-irregularity (edges of melanoma cells are not systematic or ordered), color variation (black, brown, tan, blue, red, etc), diameter (diameter of affected area is greater than 6mm approximately) and evolution (changes in shape, size, color or symptoms). It can be diagnosed through dermoscopy and physical examination and

is further confirmed through biopsy. If condition worsens, imaging tests like MRI, CT scans and PET scans can be conducted. Merkel cell carcinomas appear to be nodules or lumps on the skin and are firm and painless. It is diagnosed by biopsy and histopathology(26). Kaposi sarcomas are often linked with HIV and AIDS and they appear to be red or purple lesions on mucous membrane of the skin. It is diagnosed by biopsy and testing for human herpes virus (HHV-8) in the skin tissue. For the successful management of skin cancer, early detection, skin examination and evaluation is very crucial to cure the illness.

PREVENTION AND CONTROL

Prevention of skin cancer means to reduce the associated risk factors and opting for a healthier lifestyle. It can be done through various protective measures which cut down the long term sunlight exposure and prevent ultraviolet rays from causing harm to the skin. Even on cloudy days, use a broad spectrum sunscreen with high SPF (sun protection factor) on the exposed areas of the skin(29). Avoid going out during the peak sunlight hours, typically in afternoon so as to prevent yourself from coming in contact with sun rays. Wear full-length clothes and use sunglasses which have ultraviolet protection so as to protect eyes from sun rays. Tanning beds must not be utilized as they emit ultraviolet rays. Monitor your skin regularly for the presence of lesions, moles or any unusual growth. Skin must be kept hydrated so that it can withstand chronic conditions. People with lighter skin tones should especially be alert because they have more chances of having skin cancer. People who smoke have increased chances of suffering from skin cancer, quitting it will improve the overall lifestyle and minimize the risk of cancer(30). A diet rich in antioxidants, vitamins and minerals must be intake to improve skin health. Stress management techniques should be adopted because they enhance the immunity. A healthcare professional must be consulted if any type of unusual skin issue is noticed.

APPROACHES TO COMBAT SKIN CANCER

There are several ways by which we can attempt to treat skin cancer but surgery has been the preferred treatment since decades. Chemotherapy and topical treatment have also been developed for treatment at the site of tumor but they are accompanied with severe toxic effects. Traditional medicines also hold great potential for treating cancer along with less adverse effects(2).

Surgery: In this method, the cancerous tissues are removed with the help of surgical instruments. Earlier, scalpel was used to a certain depth in order to eliminate the carcinoma. Different methods of surgery are simple excision, mohs microscopic surgery, electrodesiccation and curette. In simple excision, whole cancerous area is withdrawn along with normal cells and the cuts are stitched. After that, the cancerous cells are examined that the total area is removed. Mohs microscopic surgery is used for untreatable and risky NMSC which has spread in vast areas of the body. The tumorous tissue is removed and the area is analyzed by microscope during the surgery. The advantage of this surgery is that healthy cells are preserved. Electrodesiccation and curette (ED & C) is a technique in which doctor densities the tumor area with the help of local anesthetic and then remove it with a surgical tool known as curette(31).

Phototherapy: Photo thermal therapy is a process the cancerous area is treated with topical medication and then exposed to light of certain wavelength. The key elements used in this therapy are oxygen, light and photosensitizer. These elements together lead to photochemical process and ultimately cause apoptosis of cancerous cells(6).

Immunotherapy: it is a novel approach that utilizes interferons for the treatment of cancer. Interferons exhibit antiproliferative action and enhance the immunity so that body can fight with cancer causing agents(26).

Targeted therapy: This treatment is preferred especially for melanoma cancer at different stages. In this technique, drugs are targeted at the specific site of cancer like molecules and mutated genes of cancerous cells. This stops the uncontrolled growth and proliferation of myeloma cells(7).

Chemical peel: Trichloroacetic acid is applied on cancerous cells directly by doctors(32). Chemical peels are of several types i.e. superficial peel (which eradicates the topmost layer of skin), medium peel (which removes middle layer of the skin) and deep peel (which is able to penetrate deep into the skin and eliminate the deepest layers of the skin). This treatment is cheap and easy to do but it can make the skin appear reddish and patchy for almost a month and may also cause discolouration of the skin.

Radiotherapy: It is one of the most widely used non-surgical techniques for conservation of normal cells. It is practiced in patients where surgery isn't possible for example in elderly patients. The radiation is focused on tumorous areas of the outer layer of the skin and To prevent deep tissue penetration, low intensity X-rays or electron beam beams are utilized (33).

Dermal chemotherapy: It utilizes the transdermal and topical administration of dosage forms into the skin. It has very less side effects and is painless. It helps to enhance the bioavailability of the active pharmaceutical ingredients. Drugs used for dermal therapy are 5-fluorouracin, retinoid, ingenol mebutate, IMQ, colchicines, gingerol, quercetin, curcumin, etc.

Systemic treatment: Chemotherapy has always been the first choice in the management of cancer. BCC is treated with the HH pathway inhibitor vismodegib. An inhibitor of epidermal growth factor receptors called cetuximab is used to treat SCC. Studies are going on to investigate bevacizumab, sorafenib and sunitinib as tyrosine kinase inhibitors for the

treatment of SCC. Capecitabine is used for the treatment of advanced or recurrent SCC, it is a prodrug of 5-fluorouracil(34).

HERBAL THERAPY FOR SKIN CANCER

Chemotherapy has been widely used for the treatment of cancer but several synthetic drugs used in this therapy have severe side effects. It makes chemotherapy challenging. However, to overcome this drawback, plant based drugs are developed for cancer as an alternative therapy. The plants which have cancer curing ability are used to extract drugs and they have less to zero side effects. Also, traditional medicines are nowadays combined with synthetic drugs and are used as hybrid drugs for the treatment of any disease. They are less resistant and more potent than the already marketed drugs(35). Active constituents such as flavanoids, carotenoids and terpenoids have the cancer curing properties. Quercetin is a flavonol and is found in tea, grapes, apples, ginkgo, tomatoes, etc. Carotenoids like retinol helps to reduce DNA damage when exposed to UV light, hence cosmetic products containing retinol are applied on face and body. Terpenes are originated from mosses, liverworts, lichens, algae, mushroom etc and they help to limit the cancerous cells to one part of the body and inhibit them from invading to other parts of the body.

Gingerol is present in ginger and is used to treat epidermal cancer cells, aids in preventing the expansion and proliferation of cancer cells. Aloin and emodin, which are present in aloe species, help to prevent the growth of cancer and prevents the process of cell union. Eupatilin, a flavanoid found in Artemisia plant helps to regulate the G2/M stage of the cell cycle, particularly the skin cancer cells. The Alpinia plant contains bisdemethoxycurcumin, which functions as a growth-resisting mediator and inhibits the proliferation of cancer cells. Tea tree oil and terpinen-4-ol inhibit cancer cells' growth during the cell cycle and causes destruction of cancer cells. Sunflower seed oil contains oleic and linoleic acids have defensive properties against skin cancer. Constituents like sesamin, sesamol, sesamin

present in sesame seeds helps in defending the skin from UV rays. Nutmeg seeds are also being studied for their properties against cancer(5).

NANOTECHNOLOGY FOR SKIN CANCER

Nanoparticles range from 1nm to 100 nm in size and due to their large surface area and volume; they are widely utilized today for skin cancer diagnosis and treatment therapy. Nanoparticles can be easily encapsulated in excipients and thus provide targeted drug delivery in the body systems(36). Nanoparticles are used in imaging as quantum dots, gold nanoparticles and carbon nanotubes and they enhance the fluorescence and photo acoustic imaging and thus help in diagnosis of skin cancer. Nanoparticles ease the chemotherapeutic drug delivery to the skin cancer cells and thus minimize the harm to normal cells and reduce toxicity. They enhance drug solubility, stability and enhance bioavailability(37). Nanoparticles such as titanium dioxide and zinc oxide are used in topical sunscreen formulations and they offer optimum protection to harmful UV radiation.

The composition of vehicle also plays an important role in effective dermal drug delivery system. Some of the factors influencing it are: the nature of excipients, equipments, environmental conditions, route of delivery, etc. Nano biosensors are used to identify skin related disorders. It uses electrochemical identification for respective biomarkers for different types of cancers and provides a highly sensitive and specific diagnosis(38). Immunosensor containing SiO₂ nanoparticles and polypyrrole nanocomposite are used for early detection of malignant melanoma cancer. SPION (super paramagnetic iron oxide nanoparticles) are found to be very efficient in targeted drug delivery in the form of transdermal patches containing drugs like 5-fluorouracil and doxorubicin(39). CNP (cerium oxide nanoparticles) helps to make the cancer cells ready for radiotherapy by triggering them. Polymer Nano-micelles are deposited in hair follicles to deliver drug such as terpinolene or paclitaxel. Lipid nanoparticles such as nanoemulsions, liposomes, solid lipid nanoparticles, cubosomes,

nanodispersion and niosomes are developed which are then loaded with anticancer drugs to target them towards skin cancer cells. Other types of nanoparticles used for cancer therapy are dendrimers, magnetic nanoparticles, nanostructured lipid carriers, etc. As a result, nanotechnology has many applications in the fields of diagnosis, treatment therapy, and prevention of skin cancer(40).

EMERGING THERAPIES FOR FUTURE

To improve the management and mortality rate of skin cancer, many advanced approaches have been developed. They are immunotherapy, targeted therapy, nanotechnology, combination therapy and precision medicine. Immunotherapy basically focuses on enhancing body's immunity to fight against the cancer cells. Drugs like nivolumab and pembrolizumab show good results in the case of melanoma skin cancer. Adoptive cell therapy like CAR (chimeric antigen receptor), T-cell therapy are also be utilized. BRAF inhibitors and MEK inhibitors are being employed as targeted therapy approaches for melanomas. Drugs used are vemurafenib, dabafenib and trametinib. Precision medicine provides a personalized and customized treatment for each patient according to his features like genetic factors, tumor biology and immunity. Combinatorial therapies are used to overcome resistance and provide better treatment approach. Nanotechnology also holds promisable treatment regimens for skin cancer and therefore is being used widely. Many advancements have taken place and new trials are going on in order to search for optimum treatment approaches, thereby reducing adverse drug reactions, reducing toxicity and enhancing potency and efficacy(41) .

CONCLUSION

This review article emphasizes on following key points:

- Skin cancer is the development of uncontrolled skin cells which loses its ability to grow normally.

- Most skin cancers are originated from keratinized epithelial cells.
- There are two types of skin cancer: melanoma and non-melanoma, respectively.
- Non-melanoma skin cancer is further categorized into basal cell carcinoma and squamous cell carcinoma.
- Early diagnosis is essential.
- It can be diagnosed by physical examination, dermoscopy or biopsy.
- Prevention method includes avoiding sun exposure and using sunscreen.
- Treatment is done through surgery, radiotherapy and chemotherapy. New technologies developed for the management for cancer are immunotherapy, nanotechnology, targeted therapy and combinatorial therapy.

To conclude this article, we must note that skin cancer is an emerging threat to humankind. Careful steps must be taken for reducing the morbidity rate of skin cancer. Early diagnosis is really important for the cure. Melanoma should be taken very seriously as it is life threatening. With the increasing environmental depletion and global warming, it is predicted that skin cancer will be at its peak in the next few years. So, precautions should be taken while stepping into the sun, sunscreen should be used and tanning beds must be avoided. It is the duty of each individual to spread awareness about these diseases to promote good public health and well being.

ACKNOWLEDGEMENTS

I would like to express my gratefulness to my institution, “Department of Pharmaceutical Sciences, Sir J.C. Bose Technical Campus, Bhimtal, Kumaun University, Nainital” for the successful completion of my work.

CONFLICT OF INTEREST

The author has no conflict of interest in this article.

REFERENCES

1. Losquadro WD. Anatomy of the skin and the pathogenesis of nonmelanoma skin cancer. *Facial Plast Surg Clin.* 2017;25(3):283–9.
2. Simoes MF, Sousa JS, Pais AC. Skin cancer and new treatment perspectives: A review. *Cancer Lett.* 2015;357(1):8–42.
3. Linares MA, Zakaria A, Nizran P. Skin cancer. *Prim Care Clin Off Pract.* 2015;42(4):645–59.
4. Garrubba C, Donkers K. Skin cancer. *Jaapa.* 2020;33(2):49–50.
5. Hasan N, Nadaf A, Imran M, Jiba U, Sheikh A, Almalki WH, et al. Skin cancer: understanding the journey of transformation from conventional to advanced treatment approaches. *Mol Cancer.* 2023 Oct 6;22(1):168.
6. Cullen JK, Simmons JL, Parsons PG, Boyle GM. Topical treatments for skin cancer. *Adv Drug Deliv Rev.* 2020;153:54–64.
7. Chandra J, Hasan N, Nasir N, Wahab S, Thanikachalam PV, Sahebkar A, et al. Nanotechnology-empowered strategies in treatment of skin cancer. *Environ Res.* 2023;235:116649.
8. Dildar M, Akram S, Irfan M, Khan HU, Ramzan M, Mahmood AR, et al. Skin cancer detection: a review using deep learning techniques. *Int J Environ Res Public Health.* 2021;18(10):5479.
9. Jones OT, Ranmuthu CKI, Hall PN, Funston G, Walter FM. Recognising Skin Cancer in Primary Care. *Adv Ther.* 2020 Jan;37(1):603–16.

10. Armstrong BK, Kricger A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B.* 2001;63(1–3):8–18.
11. Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol.* 2002;146(s61):1–6.
12. Kraemer KH. Sunlight and skin cancer: Another link revealed. *Proc Natl Acad Sci.* 1997 Jan 7;94(1):11–4.
13. Gandhi SA, Kampp J. Skin cancer epidemiology, detection, and management. *Med Clin.* 2015;99(6):1323–35.
14. Leiter U, Keim U, Garbe C. Epidemiology of Skin Cancer: Update 2019. In: Reichrath J, editor. *Sunlight, Vitamin D and Skin Cancer* [Internet]. Cham: Springer International Publishing; 2020 [cited 2024 Jan 21]. p. 123–39. (*Advances in Experimental Medicine and Biology*; vol. 1268). Available from: https://link.springer.com/10.1007/978-3-030-46227-7_6
15. Leiter U, Eigentler T, Garbe C. Epidemiology of Skin Cancer. In: *Sunlight, Vitamin D and Skin Cancer* [Internet]. New York, NY: Springer New York; 2014 [cited 2024 Jan 21]. p. 120–40. Available from: http://link.springer.com/10.1007/978-1-4939-0437-2_7
16. Gordon R. Skin cancer: an overview of epidemiology and risk factors. In: *Seminars in oncology nursing* [Internet]. Elsevier; 2013 [cited 2024 Jan 21]. p. 160–9. Available from: <https://www.sciencedirect.com/science/article/pii/S0749208113000326>
17. De Gruijl FR, Tensen CP. Pathogenesis of skin carcinomas and a stem cell as focal origin. *Front Med.* 2018;5:165.
18. Didona D, Paolino G, Bottoni U, Cantisani C. Non melanoma skin cancer pathogenesis overview. *Biomedicines.* 2018;6(1):6.

19. Ciężyńska M, Kamińska-Winciorek G, Lange D, Lewandowski B, Reich A, Sławińska M, et al. The incidence and clinical analysis of non-melanoma skin cancer. *Sci Rep.* 2021;11(1):4337.
20. Samarasinghe V, Madan V. Nonmelanoma skin cancer. *J Cutan Aesthetic Surg.* 2012;5(1):3–10.
21. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. *The lancet.* 2010;375(9715):673–85.
22. Rüniger TM. Role of UVA in the pathogenesis of melanoma and non-melanoma skin cancer: A short review. *Photodermatol Photoimmunol Photomed.* 1999 Dec;15(6):212–6.
23. Apalla Z, Nashan D, Weller RB, Castellsagué X. Skin Cancer: Epidemiology, Disease Burden, Pathophysiology, Diagnosis, and Therapeutic Approaches. *Dermatol Ther.* 2017 Jan;7(S1):5–19.
24. 병호오. Pathogenesis and prevention of skin cancer. *J Korean Med Assoc.* 2018;61(11):644–8.
25. Cohen PR, Schulze KE, Nelson BR. Basal Cell Carcinoma with Mixed Histology: A Possible Pathogenesis for Recurrent Skin Cancer. *Dermatol Surg.* 2006 Apr;32(4):542–51.
26. Ahmed B, Qadir MI, Ghafoor S. Malignant Melanoma: Skin Cancer- Diagnosis, Prevention, and Treatment. *Crit Rev Eukaryot Gene Expr [Internet].* 2020 [cited 2024 Feb 5];30(4). Available from: <https://www.dl.begellhouse.com/journals/6dbf508d3b17c437,7b107f23667462f0,6971f7cb0e03a2e5.html>

27. Perez HC, Benavides X, Perez JS, Pabon MA, Tschen J, Maradei- Anaya SJ, et al. Basic aspects of the pathogenesis and prevention of non- melanoma skin cancer in solid organ transplant recipients: a review. *Int J Dermatol.* 2017 Apr;56(4):370–8.
28. Nahata H, Singh SP. Deep Learning Solutions for Skin Cancer Detection and Diagnosis. In: Jain V, Chatterjee JM, editors. *Machine Learning with Health Care Perspective* [Internet]. Cham: Springer International Publishing; 2020 [cited 2024 Feb 5]. p. 159–82. (Learning and Analytics in Intelligent Systems; vol. 13). Available from: http://link.springer.com/10.1007/978-3-030-40850-3_8
29. Leffell DJ, Brash DE. Sunlight and skin cancer. *Sci Am.* 1996;275(1):52–9.
30. De Hertog SA, Wensveen CA, Bastiaens MT, Kielich CJ, Berkhout MJ, Westendorp RG, et al. Relation between smoking and skin cancer. *J Clin Oncol.* 2001;19(1):231–8.
31. Ganiev AA, Abdullaev SY, Abdurahmonov SZ. Combined treatment for early-stage skin cancer of the head and neck area. *World Bull Public Health.* 2021;4:3–6.
32. Slavkova M, Tzankov B, Popova T, Voycheva C. Gel Formulations for Topical Treatment of Skin Cancer: A Review. *Gels.* 2023;9(5):352.
33. Narayanan DL, Saladi RN, Fox JL. Review: Ultraviolet radiation and skin cancer. *Int J Dermatol.* 2010 Sep;49(9):978–86.
34. Cortes H, Reyes-Hernandez OD, Alcalá-Alcalá S, Bernal-Chavez SA, Caballero-Floran IH, Gonzalez-Torres M, et al. Repurposing of drug candidates for treatment of skin cancer. *Front Oncol.* 2021;10:605714.
35. Abbas SR, Baig S. Treatment of skin cancer by medicinal plants [A review]. *J Biotechnol Sci.* 2020;137(2):131–7.

36. Hu JK, Suh HW, Qureshi M, Lewis JM, Yaqoob S, Moscato ZM, et al. Nonsurgical treatment of skin cancer with local delivery of bioadhesive nanoparticles. *Proc Natl Acad Sci.* 2021 Feb 16;118(7):e2020575118.
37. Krishnan V, Mitragotri S. Nanoparticles for topical drug delivery: Potential for skin cancer treatment. *Adv Drug Deliv Rev.* 2020;153:87–108.
38. Marzi M, Osanloo M, Vakil MK, Mansoori Y, Ghasemian A, Dehghan A, et al. Applications of metallic nanoparticles in the skin cancer treatment. *BioMed Res Int [Internet].* 2022 [cited 2024 Feb 6];2022. Available from: <https://www.hindawi.com/journals/bmri/2022/2346941/>
39. Amatya R, Kim D, Min KA, Shin MC. Iron oxide nanoparticles-loaded hydrogels for effective topical photothermal treatment of skin cancer. *J Pharm Investig.* 2022 Nov;52(6):775–85.
40. Zeng L, Gowda BHJ, Ahmed MG, Abourehab MAS, Chen ZS, Zhang C, et al. Advancements in nanoparticle-based treatment approaches for skin cancer therapy. *Mol Cancer.* 2023 Jan 12;22(1):10.
41. Mehan N, Kumar M, Bhatt S, Shankar R, Kumari B, Pahwa R, et al. Self-assembly polymeric nano micelles for the futuristic treatment of skin cancer and phototoxicity: therapeutic and clinical advancement. *Crit Rev Ther Drug Carr Syst [Internet].* 2022 [cited 2024 Feb 6];39(2). Available from: <https://www.dl.begellhouse.com/journals/3667c4ae6e8fd136,5dbe384d1c93b099,797334931667ffae.html>