



A REVIEW ON SKIN CANCER

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ABSTRACT

Skin cancer can be of 2 types mainly. They are malignant melanoma and non-malignant melanoma. Skin cancer mainly occurs due to exposure of sunlight. Ozone depletion and chemical exposures are other factors involved in precipitating skin cancer. Mutations of p53 gene are involved in UV- induced carcinogenesis. P53 gene acts vital in development of SCC. So, prevention of skin cancer is the main criteria. Regular application of sunscreens could be one of the primary prevention. The purpose of present review is to outline types, pathogenesis, diagnosis, prevention and treatment of skin cancer.

Keywords: Skin cancer, BCC, SCC, melanoma, UV-light.

INTRODUCTION

Skin

The skin is an organ that separates human body and environment. It acts as a barrier that protects body against UV-radiation, toxic substances, infections.¹ Epidermis is the outermost layer of skin. Keratinocytes, dendritic melanocytes, Merkel and Langerhans cells are different type of cells present in epidermis. The underlying dermis contains connective tissue with antigen presenting dermal dendritic cells, mast cells and memory T-cells.^{2,3}

Skin Cancer

The incidence of skin cancer in people has been increasing day by day. The main reason for skin cancer is due to UV-exposure because large amounts of UV-radiation reach earth's surface due to depletion of ozone layer.^{4,5} Skin cancer can be of two types mainly. 1. Malignant melanoma 2. Non malignant melanoma; which is divided into BCC and SCC; BCC and SCC mainly occur due to chronic exposure of UV-sunlight. MM may be due to intense sun exposure and history of sun burn.^{6,7} 80-85 % of non-melanoma skin cancers are BCC and SCC. SCC is more dangerous and is responsible for many deaths. Skin cancer in early stage can be cured easily by simple procedures or techniques but advanced skin cancer cannot be treated effectively by any medications. So there is a need to detect and treat disease at early stage.⁸ Over all, 80 % of skin cancers are BCC, 16 % are SCC and 4 % are melanoma.⁹



Figure 1: Skin Cancer

Etiology

The causes for NMSC are environmental and host factors. Environmental factors associated with NMSC are sun exposure, ozone depletion, and chemical exposures. Host factors are HPV, genetic susceptibilities, skin tone and immunosuppression.¹⁰⁻¹² Outdoor workers are more prone to skin cancer as they may easily get affected by UV-exposure. Exposure during weekends and holidays are involved in chronic exposure to UV-light in children.^{13,14}

Prevalence

Generally fair skin, red and blond hair, blue or green eyes are more susceptible to skin cancer.¹⁵⁻¹⁸

Signs and Symptoms of Melanoma

- Changes in size, shape or color of mole¹⁹.
- Oozing or bleeding from mole.
- A mole that feels itchy, hard, lumpy or swollen.

Types of Skin Cancer

Basal cell carcinoma (BCC)



Figure 2: Basal Cell Carcinoma

The most common type of skin cancer is basal cell carcinoma. They generally occur in head and neck regions followed by trunk and extremities. They usually arise from basal layer of epidermis.^{7,20} BCC is again classified into 3 types; Superficial, nodular and sclerosing / morpheiform. Superficial form of BCC can be seen in trunk and extremities as an erythematous plaque. Nodular BCC lesions generally seen on the head and neck and appear as pearly, telangiectatic

papules with rolled borders. Morpheaform lesions often resemble scars and usually are the most difficult to identify on visual inspection alone, often lacking the pearly and telangiectatic characteristics seen in superficial and nodular BCCs. Gorlin syndrome patients are often associated with BCC. These people usually have BCC at centre of face or at any anatomical site.²¹ NMSC like BCC and SCC arise from keratinocytes. BCC undergo metastasis rarely but it has tendency to cause more morbidity. But SCC undergoes rapid metastasis. They may occur due to chronic sun exposure and can be seen on different parts of sun-exposed areas of the body.^{22,23}

Epithelial Skin Cancer and Oncogenic Virus Infection

Non melanoma skin cancers like BCC, SCC, AK are most commonly occurring types in transplanted patients. AK is found to be precursor for BCC and SCC. AK was found to occur 15 years prior in transplanted patients compared to normal people. AK is found to be more frequent in heart than in kidney and liver transplants. SCC > BCC can be seen in transplanted patients and it is vice-versa in general population.²⁴⁻²⁸

Kaposi Sarcoma

This is more commonly seen in elderly people. This occurs mainly due to virus named KS associated human herpes virus (KSHV) called as HHV-8.²⁹⁻³³ Lower limbs; trunk and at last upper limbs are the targeted regions for Kaposi sarcoma to occur. It can also involve oral mucosa, lymph nodes, stomach and duodenum.³⁴

Neuroendocrine Skin Cancer (Merkel cell carcinoma)

It usually occurs at head, neck and extremities of elderly people. Immunosuppression plays an important role in formation of such type of skin cancer. MCC in transplanted patients found to be elevated when compared to normal people.³⁵

Melanoma



Figure 3: Melanoma

Melanoma is less common than other skin cancers. However, it is much more dangerous if it is not found early. It causes the majority (75 %) of deaths related to skin cancer.³⁶ This type of skin cancer is associated with melanocytes of epidermal layer. They synthesize melanin pigment that produces cells of skin with photo protection from mutagenic UV-rays. MM is less common compared to BCC and SCC. The treatment for melanoma completely is not familiar. There is less curable rate for melanoma. Prevention is best method for melanoma.³⁷⁻³⁹ It is the only preventable cancer that continues to increase.⁴⁰

Squamous Cell Carcinoma

SCC is considered to be second most common type of cancer in US with 250000 cases diagnosed annually. It is usually seen in black and Asian Indians representing 30 % to 65 % of skin cancers in both races. It occurs on sun exposed sites of head and neck. Generally, the long-term outcome is positive, as less than 4 % of Squamous-cell carcinoma cases are at risk of metastasis (and hence life-threatening)^{39,41}

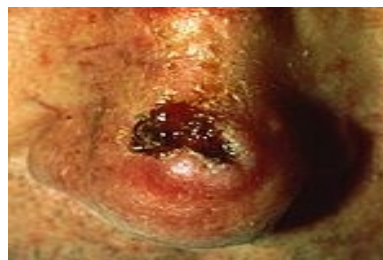


Figure 4: Squamous Cell Carcinoma

Pathophysiology

UV-light is a major cause for skin cancer. Both UV-A and UV-B play a crucial role in causing skin cancer.⁴²

UV-induced DNA Damage

Sunlight can be categorized into three types depending on wavelength UVC (200 – 280 nm), UVB (280 – 320 nm) and UVA (320 – 400 nm). UVC do not reach earth surface as it is filtered by ozone layer. UVB (1 – 10 %) and UVA (90 – 99 %) reaches earth surface.⁵ UVB is primarily responsible for DNA damage. It has the tendency to induce all phases of skin cancer. (Initiation, promotion and progression).⁴³ As the ozone layer is slowly depleted due to environmental changes, large amount of UV-light reaches earth surface. This is responsible for increased incidence of skin cancer all over the world. Research implies that there is positive correlation between skin cancer and past UV exposure.⁴⁴ Sun beds are also involved in etiology of skin cancer. UVA has constituted much higher proportion of total UV released by these devices relative to that in solar radiation since early 1980's.⁴⁵

UVB-induced MAPK Signaling Pathways. UVB has been shown to signal through the MAPK cascade and includes ERK, JNK and p38. In this simplified model, UVB-irradiation activates acidic sphingomyelinases which in turn activates ceramide followed by activation of atypical PKCs. Atypical PKCs (PKC_α or PKC_β) phosphorylate and activate MEK, followed by ERK. ERK phosphorylates and activates TCF which then binds with SRF to an SRE site within the promoter of specific genes. Activation of this pathway results in c-Fos expression followed by AP-1 activation. UVB also activates PKC_α and PKC_β followed by activation of JNK and c-Jun. Another affect of UVB is activation of the p38 pathway. UVB can also induce signaling through the Ras pathway. The ultimate result of these signal transduction cascades is a cellular response such as proliferation, differentiation, apoptosis or tumorigenesis. The postulated molecular targets of the chemoprevention agents EGCG, perillyl alcohol, aspirin, and retinoids are shown.⁵ If a foreign antigen enters into human body, immune system gets activated and fights against foreign antigen. But in case of UV-radiation, this phenomenon doesn't occur because UV can cause the suppression of immune system that leads to inadequate prevention of tumor development.⁴⁶

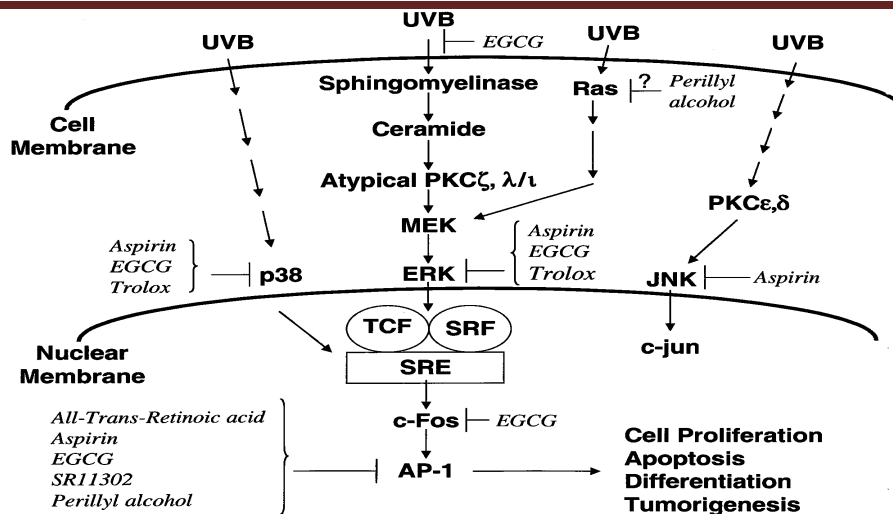


Figure 5: UVB-induced MAPK Signaling Pathways

This is most commonly seen in elderly people; because they have weak immune system power. Immunosuppressive drugs like cyclosporine, steroids and azathioprine can potentially impair SIS defence capacity leading to an increased incidence of different types of skin cancer.⁴⁷⁻⁵⁰

Mutations of p53 Gene in Skin Cancer

P53 is crucial in maintaining genomic integrity by blocking DNA replication in response to DNA damage from exposure to agents like UV-light.^{51,52} Exposure to normal epidermal keratinocytes to UV-light results in transient increase in p53 protein levels and resultant arrest in G1 phase of cell cycle. So, mutations of p53 can be seen in UV- induced carcinogenesis. P53 gene plays a predominant role in development of SCC.^{5,53-56}

Prevention

At most, there is a need to educate the people about skin cancer completely. So, that there might be a chance to prevent skin cancer to some extent. The measures to be taken to prevent skin cancer include staying out of the sun during hottest part of the day, wearing or applying sunscreen when expose to sunlight, avoiding exposure to sunlamps. Use of sun beds need to be prevented.¹⁹ SEB: It is biological event that takes place between exposure and subsequent development of cancer. They acts as predictors to identify persons that are on verge of developing cancer. BCC or SCC incidence and multiplicity, AK incidence and multiplicity are considered to be clinical or histological endpoints that are targets for human skin cancer chemoprevention trials. Wearing protective clothes found to be best method to prevent skin cancer during sun exposure. Even though effective sunscreen lotions prevent direct exposure to sun and UV-light, they have the capacity to prevent formation of BCC and SCC and mixed. Some trials indicates no effect on NMSC incidence can be seen by using sunscreens.^{57,58} Primary prevention involves regular application of sunscreens along with protective measures recommended by the World Health Organization (WHO), the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the European Society of Skin Cancer Prevention (EUROSKIN). Secondary prevention involves early assessment of malignancies that are curable in early stages of development; because skin cancer can't be treated completely

at later or advanced stage. So, there is a need for secondary prevention.¹⁴

Treatment

The first step in the evaluation of skin cancer in patients comprises of thorough history, focusing on general medical and drug history, personal and family history of skin cancer, number of moles including presence of dysplastic naevil and comprehensive social history, carcinogen or sun exposure.^{59,60} The choice of treatment should be determined by the histological type of the lesion, its size and location, and the age of the patient. No single treatment method is ideal for all lesions.⁶¹ The treatment goals are total removal of the tumor, preservation of function, and a good cosmetic outcome. Curettage and electro desiccation, cryosurgery, topical chemotherapy, laser surgery, radiotherapy, immunotherapy, Mohs micrographic surgery, and conventional surgical excision are all effective therapeutic options for selective types of BCC.^{42,62} As the treatment for skin cancer needs to be initiated at early stage, intervention soon after diagnosis is required for effective cure of disease. Radiotherapy is effective in treating early stage lesions.⁶³ New molecular therapeutic approaches for skin cancer include several medications like cryosurgery, immunomodulation with imiquimod, 5-FU, photodynamic therapy and radiation. Small molecule regulators have been identified for variety of pathways that leads to skin cancer. The pathways are SHH, Ras / Raf, P17INK4A/CDK4/Rb and ARF / p53. Research mainly focuses on these pathways and treatment for skin cancer can be augmented by small changes of pathways.⁶⁴⁻⁶⁶

Chemotherapy for Melanoma Skin Cancer

Several chemo drugs may be used to treat melanoma: Dacarbazine (also called DTIC), Temozolomide, Paclitaxel, Carmustine (also known as BCNU), Cisplatin, Carboplatin, Vinblastine, Dacarbazine, temozolomide and paclitaxel may be given either alone or along with some of the other drugs on the list. It is not clear if using combinations of drugs is more helpful than using a single drug, but it can add to the side effects like hair loss, mouth sores, loss of appetite, nausea and vomiting, diarrhea, increased risk of infection (from too few white blood cells), easy bruising or bleeding

(from too few blood platelets), fatigue (from too few red blood cells).⁶⁷

Treatment for BCC

Primary radiotherapy is considered to be treatment of BCC involving nose, lower eyelids or ears. The limitation for radiotherapy is lack of histological control of margins and fault that often leads to inadequate or excessive treatment. Morpheaform of BCC found to be resistant to radiotherapy treatment. Morpheaform, mutotypical, adenoid, basosquamous and infiltrative types can be treated with Mohns surgery or conventional surgical excision.⁶² So, the early detection of skin cancer is the key to cure especially in malignant melanoma. Several sensitive mole imaging systems are available in market that has the tendency to identify lesions that might ordinarily missed using standard clinical tools.⁶⁸

How to Examine

There should be a method to the examination that allows for visual scanning of the entire surface of the patient's skin before focusing on individual suspect lesions. The feet and hands including the palms, nails and areas between the toes and fingers should be examined. The anterior of the body then the posterior surface should be examined, including the intertriginous areas. If the patient gives consent, the border zones of the oral and ocular mucosae and genital area should also be examined. Special attention should be paid to the head and neck region, and the scalp should also be examined with a combination of direct visual examination and palpation. Dermoscopic examination of individual lesions can allow visualization of deeper layers of the skin and, in expert hands, can be useful. However, practitioners must be trained in its use and the significance of dermoscopic changes. In the most common skin cancers, the genetic traits of an individual form the base upon which environmental factors established over a period interplay to result in disease. Pale complexion, light-coloured eyes, red or blond hair (related to nonfunctioning MC1R mutations),⁶⁹ freckles and a Northern European or Celtic background are important risk factors. Squamous cell carcinoma (SCC) is more common in outdoor workers and occurs on body sites of maximum sun exposure. The ears and lower lips are frequently unprotected and may be exposed to cocarcinogens, e.g. tobacco. SCC at these sites is more aggressive, with a significantly higher risk of metastases.⁷⁰

CONCLUSION

The incidence of skin cancer has been drastically elevating day-to-day. Skin cancer in early stage can be cured easily by simple procedures or techniques but advanced skin cancer cannot be treated effectively by any medications. So there is a need to detect and treat disease at early stage. Overall, 80 % of skin cancers are BCC, 16 % are SCC and 4 % are melanoma. UV-A and B are mainly responsible for skin cancer. Outdoor workers are more prone to skin cancer because they get easily exposed to skin cancers. So, precautionary measures like application of sunscreen lotions need to be done. SEB play an important role in identifying extent of skin cancer in particular person. It can be treated at initial stages, as the duration is extended, the chances for treating skin cancer gets hastened. New molecular therapeutic approaches for skin cancer include several medications like cryosurgery, immunomodulation with imiquimod, 5-FU, photodynamic therapy and radiation.

Abbreviations

AK: Actinic keratosis
 BCC: Basal Cell carcinoma
 ERK: Extracellular Signal-Regulated Kinases
 EUROSkin: European Society of Skin Cancer Prevention
 HHV-8: Human Herpes Virus-8
 ICNIRP: Ionizing Radiation Protection
 KSHV: Kaposi's sarcoma-associated herpes virus
 MM: Malignant Melanoma
 MAPK: Mitogen activated Protein Kinase
 NMSC: Non melanoma skin cancer
 PKC: Protein Kinase C
 SCC: Squamous cell carcinoma
 SEB: surrogate Endpoint Biomarker
 WHO: World Health Organization
 UV: ultra violet

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