



Review Article

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Comprehensive Study to Decline the Burden of Skin Cancer

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ABSTRACT

Skin cancer is the most common malignancy worldwide, including malignant melanoma and Non-malignant melanoma. The progressive increase in the incidence of skin cancers is observed, mainly in cutaneous melanomas over the last few decades. UV exposure is the most common cause of skin cancer, which occurs due to mutations in the DNA of skin cells. The mutation in MAPK pathway was the main cause of the skin cancer, in which BRAF gene undergoes 75 somatic mutations. The mutation in DNA suppressed the tumor suppressor gene p53, inactivates DNA repair gene and causes mutation in proto-oncogene results in the formation of oncogene which promote the cell growth, cell proliferation and cell reproduction by affecting the process of apoptosis. Skin cancer can be prevented by healthy dietary intervention and regular physical activity. In the current review, we highlight recent global trends in the treatments of skin cancer which involve chemotherapy, radiotherapy, photodynamic therapy, biological therapy and surgery. These therapies show the effectiveness by improving the survival rate and quality of life.

Keywords: Melanoma, skin cancer, UV-radiation, MAPK pathway and tumor suppression mechanism.

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INTRODUCTION

Cancer is a serious global threat in which abnormal cells divide aberrantly and invade other tissues. Cancer is the second leading non-communicable and third fatal disease in the developing nations. [1] Cancer is a group of diseases which is characterized by alteration in gene expression leading to the uncontrolled cell division and differentiation. There are more than 100 types of cancers and most tumors are named for the

organ or kind of cell in which they begin. [2] Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths in 2008. Deaths from cancer worldwide are projected to continue to rise to over 13.1 million in 2030 (WHO 2017). Skin is a protective barrier to protect from heat or cold, chemicals, UV-radiation, bacteria and also helps to control the body temperature and stores water and fat. [3] Skin cancer is destructive cancerous growth of the skin, which is the most

common among all the cancers and its incidence is increasing rapidly all over the world. [4] Skin cancer begins in the epidermis, which is made up of squamous cells, basal cells and melanocytes. Skin cancer can be of two types: Malignant melanoma and Non-malignant melanoma. The incidence rate of melanoma is increasing worldwide, with stable or slightly decreasing mortality. On the other hand, the incidence for Non-melanoma varies widely. Malignant melanoma develops in the cells which give color to the skin (melanocytes) and having great tendency to spread to other parts of the body. [5] Non-malignant melanoma involves Basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC). [6] Ultraviolet (UV) light exposure is the most common cause of skin cancer. The use of tanning booths, HPV, immunosuppression, exposure to unusually high levels of X-rays, genetic susceptibility and contact with certain chemicals (arsenic, hydrocarbons etc) are involved in the etiology of skin cancer. [7-8] Skin cancer occurs when mutations in the DNA of skin cells, due to mutations the cells of skin grows out of control and form a lump. Mutation suppressed the tumor suppressor gene p53, inactivates DNA repair gene and mutation in proto-oncogene results in the formation of oncogene which promote the cell growth, cell proliferation and cell reproduction. [9-10] Skin cancer can be prevented by healthy dietary intervention and regular physical activity. World Health Organization had launched a campaign against cancer, with a three-fold strategy: prevent all the preventable cancers, cure all that can be cured, and reduce pain and discomfort where cure is not possible. [11] There are number of treatments like medications, surgery available for the skin cancer, but these treatment having higher toxicities and less safety. [12] However, Chemoprevention is the administration of natural compounds to prevent, slow down and reverse the occurrence of cancer. Because of the higher safety, low toxicity, antioxidant properties, minimum cost and multiple beneficial effects of the natural products, the chemoprevention attaining great attention in the prevention of cancer.

Development of Skin cancer

The causes of skin cancer are environmental and host factors. [13] Environmental factors associated in skin cancer are Sun exposure, Ozone depletion and chemical exposure where as host factors are immunosuppression, skin tone, HPV and genetic susceptibilities. [14-15] These factors increase the risk of skin cancer by altering the multiple gene expression. Ultraviolet radiation from sun is the most important cause of skin cancer. Sunburns and excessive exposures of UV radiation cause cumulative damage which induces immunosuppression and skin cancers. [16-17] Ozone depletion, the level of UV light, weather conditions, latitude, and altitude and influence the emission of UV radiation reaching the earth's surface.

[18] Organ transplant patients and AIDS patients have a greater incidence of skin cancers.

Types of Skin cancer

The skin cancer has been divided into two main types' malignant melanoma and Non-malignant melanoma.

1. Malignant melanoma (MM): MM is a cancer of pigment-producing cells (melanocytes). [19] Melanocytes can grow together to form non-cancerous lumps. Melanoma can be cured if detected early i.e. before the metastasis. The first sign of melanoma is a change in the shape, color, size, or feel of an existing mole. [20]

2. Non-malignant melanoma: Non-melanoma skin cancer is the cancerous (malignant) growth of cells. Non-malignant melanoma involves Basal cell carcinoma (BCC) and Squamous cell carcinoma (SCC). [21-22] Common symptoms of Non-melanoma skin cancer involve small, smooth, shiny, pale, or waxy lump and a sore which bleeds or develops a crust.

a) Basal cell carcinoma (BCC): BCC is a slow-growing tumor in which metastases is rare. Basal Cell Carcinoma is caused due to the unrestricted growth in the skin basal cells (outermost layer of the skin). [23] BCC arrives on the skin in the form of open sores, red patches, pink growths or scars. [24]

b) Squamous cell carcinoma (SCC): SCC is a cancer of squamous epithelial cells present in skin. Squamous cell carcinoma is mostly caused by DNA damage due to prolonged exposure to UV radiation and sunlight. [25]

Stages of Skin Cancer: The stages of cancer have been classified on the basis of size (width) of the tumor, growth of tumor and spreading to lymph nodes or other parts of body. [26] Skin cancer in the early stage can be cured easily by simple techniques but advanced skin cancer cannot be cured by medicines. So, detection of tumor in early stage is important for effective treatment. [27] The stages of skin cancer are:

Stage 0: The abnormal cells are found only in the epidermis i.e. the outermost layer of the skin. These abnormal cells may become cancerous but does not spread into the nearby normal tissues. This stage affects only the top layer of skin, hence called as melanoma in situ. [28]

Stage I: In stage I, the cancer cells have grown deeply into the skin, but tumor does not spread to the lymph nodes or other parts of the body. The tumor found in this stage is not more than 1 millimeter thick, the surface of the tumor may appear broken down and the mitotic rate is less than 1/mm. [28-29]

Stage II: The stage II of skin cancer is defined by tumor thickness and ulceration. The tumor is between 1-2 millimeters thick or more than 2 millimeters and the surface of tumor appear broken down. There is no evidence that the cancer cells has spread to nearby lymph nodes or to distant sites. [29]

Stage III: In this Stage the cancer cells have spread to a nearby lymph node or lymph gland but not spread to distant organs. [29-30]

Stage IV: Cancer cells have spread to the lung or other organs, skin areas, or lymph nodes far away from the original growth. In this stage cancer commonly spreads to other parts of the skin, tissue under the skin, lymph nodes, and lungs. [27-30]

Mechanism of Cancer: UV radiation induces a variety of free radical and oxidative molecules which alter the molecular structure and damage lipids, proteins and nucleic acids. The changes in our skin cells occur due to continuous formation of reactive oxygen species (ROS), generated by oxidative cellular metabolism. [31] Oxidative phosphorylation in the mitochondria is the major energy-producing step for eukaryotic cells, but this step also results in production of various cell-damaging side products, e.g. free radicals and other ROS. [32] There are two main sources of ROS, mitochondrial sources and non-mitochondrial sources. [33] Mitochondrial sources are the electron transport chain and the nitric oxide synthase reaction however non-mitochondrial source of ROS is Fenton reaction. [34] The mutation in MAPK pathway was the main cause of the skin cancer, in which BRAF gene undergoes 75 somatic mutations. [35] PI3K/AKT/mTOR signaling pathway also lowers the frequency of mutation and produces changes in the immune system. Cancer also occurs due to mutation of cyclic dependent kinase (CDK)-N2A (p16INK) and also CDK-4 gene. [36]

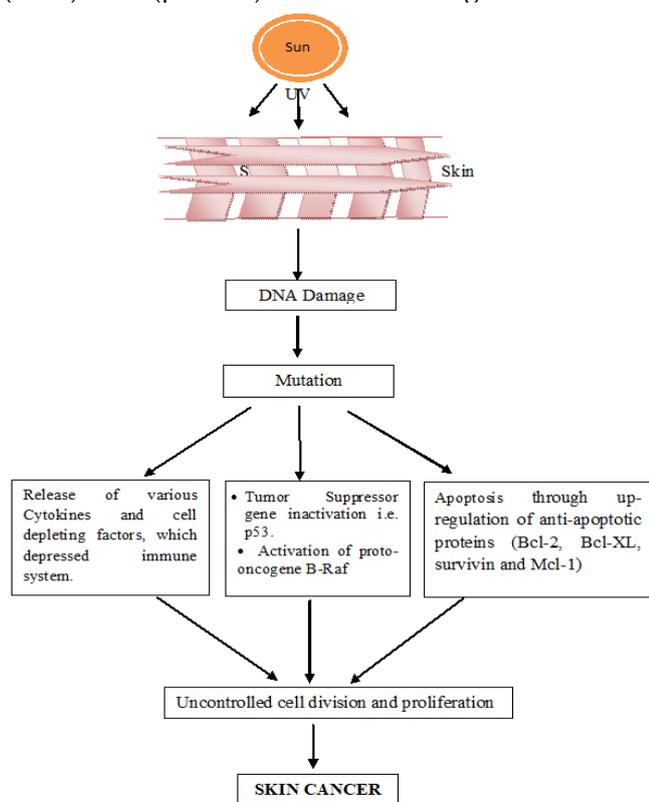


Fig. 1: Basic Mechanism, UV induced skin cancer [37]

UV induced Skin Cancer: The epidermis layer of the skin is more susceptible to damage from UV radiation. The number of cellular and molecular events devote in the development of UV-induced skin cancer. Chronic

exposure to sunlight causes damage to the skin including erythema, edema, hyperplasia, formation of sunburn cells, photoaging and results in the DNA damage. [38] The mutation in various molecular events causes inactivation of Tumor Suppressor gene p53 and activation of proto-oncogene B-Raf. UV induced DNA damaged also causes cell cycle arrest, release various cytokines and cell depleting factors. [39] Apoptosis through up-regulation of anti-apoptotic proteins such as Bcl-2, Bcl-XL, survivin and Mcl-1 is a contributing factor in the pathogenesis of skin cancer. [40] These all contributing factors are for the UV induced skin cancer.

Stages of skin cancer in Chemical Carcinogenesis

Cancer is group of diseases which affected many parts of the body. There are number of studies conducted using animal models in vivo for the investigation of the neoplastic effect. There are initiation, promotion and progression three stages for the induction of skin cancer. The mouse skin model of multi-stage chemical carcinogenesis is one of the effective in-vivo models for the development of tumors. [41] This model helps to understand the stepwise procedure in the development of skin cancer in the mouse. This model is used to evaluate the strategies of skin cancer prevention and to know the impact of genetic manipulation on tumor initiation, promotion and progression. [42] In this model tumor development occurs either after the administration of a single high dose or repeated low doses of a carcinogen or by the continuous exposure to UV radiations. Additionally promoting agents are required for tumor development. The multi-stage chemical carcinogenesis in-vivo models involve three steps for the development of tumor.

1) Initiation: Initiation is the first step of the tumor generation and it is caused by irreversible genetic changes which predispose susceptible normal cells to malign evolution and immortality. [43] The metabolic activation of procarcinogens and covalent binding to DNA results in the cell replication, fixation and mutation in the critical target genes (Ha-ras) in bulge region of hair follicle. [44] The initiated cells undergo mutations and induce the proliferation but not differentiation. [45]

2) Promotion: The second step of the tumor development is tumor promotion in which DNA synthesis is increased, gene expression altered, the population of initiated stem cells is amplified and development of clonal outgrowths as papillomas. [45-46] Promotor is a chemical substance with low carcinogenic effect, which is able to induce cancer under experimental conditions. [47]

Promoter is not directly interacting with DNA. These promoting agents increase cell proliferation, enhance the alterations in genetic expression and cause changes in cellular growth. [48]

3) Progression: This is the last and final step of the tumor generation. Progression is characterized by irreversibility, genetic instability, faster growth,

invasion, metastization, and changes in the biochemical, metabolic and morphological characteristics of cells. [47] In this step additional genetic events occur in which papilloma converted to squamous cell carcinoma and results in metastasis. [46-49]

- **DMBA induced skin papillomas:** This is a classical experimental model of carcinogenesis. This is commonly used model for development of skin cancer in the mouse. Mouse skin is generally most sensitive to epidermal carcinogenesis. DMBA acts as an inhibitor and Croton oil is used as a promoter to induce skin papillomas and Squamous cell carcinomas. [50] Mice are topically applied a single dose of 2.5µg DMBA in acetone on the shaved back. After two weeks of initiation, tumor promotion is started by the topical application of 100µL of Croton oil (1% v/v in acetone), three times in a week, for the next 8 weeks. During the experimentation of 12 weeks, all mice were observed daily and body weight was taken weekly. Tumors appearing on the shaven area of the skin were recorded at weekly intervals in all animals. [51]

Commonly used treatments for skin cancer: There are number of treatments for the skin cancer depends on the type and stage of the cancer. The goal of the treatment of cancer is to stop or destroy the cancer and to improve the quality of life. Cancer is group of diseases which affected many parts of body but if cancer is detected early than most of skin cancer can be cured. The treatments given to the patients with skin cancer involve chemotherapy, photodynamic therapy, radiation therapy and biological therapy. [52] Surgery is also suggested to the patients if the therapies do not destroyed tumor. Skin cancer treatment may damage many healthy cells and tissues due the numerous unwanted side effects. [53] Side effects depend mainly on the type and extent of the treatment. Side effects may not be the same for each person.

1) Chemotherapy: Chemotherapeutic agents are used to kill cancer cells. Chemotherapy agents can be divided into several categories on the basis of chemical structure, mechanism of action and the relationship to another drug. [54] The most important categories of chemotherapeutics agents include alkylating agents (Cyclophosphamide, ifosfamide, melphalan, busulfan), antimetabolites (5-fluorouracil, capecitabine, methotrexate, gemcitabine), antitumour antibiotics (Daunorubicin, doxorubicin, epirubicin), topoisomerase inhibitors (Topotecan, irinotecan, etoposide, teniposide), and mitotic inhibitors (Paclitaxel, docetaxel, vinblastine, vincristine). [55] These chemotherapeutic agents target the cell cycle and affect the frequency of differentiation between the cancer cells and normal cells.

2) Photodynamic therapy: Photodynamic therapy (PDT) is a powerful treatment of skin cancer uses a

drug along with a special light source, such as laser light, to kill cancer cells. [56-57] Methylaminolevulinate (MAL) and 5-aminolevulinic acid (ALA) is most effective topical photosensitizer for the early stage treatments of BCC and SCC. The drug either injected intravenously or may be rubbed into the skin. This treatment is based on the interaction of three elements a photosensitizing compound, light source and oxygen. When the photosensitizer (PS) is activated by light, it provokes a photochemical reaction which produced reactive oxygen species (ROS) and kills cancerous cells. [58] The side effects of PDT are usually not serious but it may cause burning or stinging pain, swelling, redness.

3) Radiation therapy: Radiation therapy, also called radiotherapy uses high-energy rays to kill cancer cells. The radiation comes from a large source and affects cells only in the treatment area. [59] Radiation therapy may be used in areas where surgery could be difficult or for melanoma that has spread to the lymph nodes, brain, bones or other parts of the body. [60] Radiation therapy destroys the ability of cancer cells to multiply, when these cells die our body naturally eliminates them. Healthy cells that grow and divide quickly are also harmed by radiation, but they are able to repair themselves. Superficial radiation therapy is the widely used treatment which utilizes X-Rays, or photons, to deliver electromagnetic energy to rapidly dividing cells in order to effectively stop mitosis. [61] Radiation therapy is a painless procedure which may cause many serious side effects. The side effects mainly depend on the dose of radiation and the part of body that is treated.

4) Biological therapy: Biological therapy is the most effective treatment of cancer that uses the body's natural defense system either directly or indirectly, to fight with cancer. It is a systemic therapy which involves the use of substances called biological response modifiers (BRMs). [62-63] The drugs used for melanoma is interferon and interleukin-2. These drugs injected intravenously or injected under the skin. They can slow the growth of melanoma cells and also helpful in destroying the cancerous cells. [64] Biological therapies commonly cause side effects like rashes, swelling, headache, muscle aches, fever and weakness.

5) Surgery: Surgery is the standard treatment for the skin cancer. The tumor is removed in surgery along with some normal tissues around the tumor in order to reduce the chance that cancer cells will be left in the area. [65-66] If the melanoma was not completely removed during the biopsy the surgeon may do a Cryosurgery, in which surgeon applies liquid nitrogen directly to the skin growth and kill the cancer cells. [67] This treatment may cause swelling and also damage the nerves, which can cause a loss of feeling in the damaged area. If cancer has spread to the lymph nodes, the surgeon may remove some or all of the nearby lymph nodes and additional treatment may be needed after surgery. If a large area of tissue is removed, the

surgeon may do a skin graft in which skin from the affected area is replaced with skin of another part of the body. [68]

Novel Treatments of Skin Cancer

The Novel treatments for skin cancer nowadays gaining the greater attention and may reduce the morbidity. These treatments include the some newer drugs with less unnecessary side effects. Some novel therapeutic agents are:

D, L-alpha-difluoromethylornithine: D, L-alpha-difluoromethylornithine (DFMO) irreversible inhibitor of ornithine decarboxylase, the first and rate-limiting enzyme of polyamine biosynthesis. Polyamines (putrescine, spermidine, spermine) bind to DNA, ribonucleic acid (RNA), and phospholipids and control DNA replication, transcription, and translation. [69] DFMO is an effective cytostatic agent which inhibits carcinogen-induced cancer development in a number of rodent models and also gaining the interest as a preventive agent in cancer. The Randomized controlled clinical trials shows the effectiveness of DFMO in preventing skin cancer in patients who have previously received treatment for early-stage skin cancer. [70]

Perillyl alcohol: It is a hydroxylated monoterpene isolated from essential oils of lavender, peppermint, citrus peels, celery seeds and other plants. Perillyl alcohol induces apoptosis in the tumor cells without affecting normal cells. [71] The agent having antitumor activity in UV-induced skin carcinogenesis and also effective in the suppression of inflammation, oxidative stress, the activity of ornithine decarboxylase, thymidine incorporation into deoxyribonucleic acid (DNA), the Ras pathway. [72]

Interferon: Interferons (IFN) are the cytokines which binds to the receptors located on target cells. The interferons are the important agents for the treatment of skin cancer, including antiproliferative effects (inhibition of mitosis and growth factors, activation of pro-apoptotic genes, and promotion of antiangiogenic activity) and up-regulation of the immune system in the skin. [73]

COX-2 inhibitors: Cyclooxygenase (COX) is the rate-limiting enzyme in the synthesis of prostaglandins from arachidonic acid. The higher production of the prostaglandins may be associated in skin cancer development. [74] Previous studies suggest that the inhibition of COX-2 activity or reduced expression of COX-2 results in the significant reduction of UV induced skin cancer. COX-2 inhibitors having the potent anticarcinogenic effects on various rodents and having the greater potent effect on UV induced skin cancer. [75]

Epidermal growth factor receptor (EGFR) inhibitors: The p53 gene frequently mutates and it often activated Ras. The overexpression of EGFR promotes gene amplification and mutation in the cell proliferation, survival, invasion, metastasis, and tumor. [76] These receptors belong to the tyrosine kinase family. The mutations in epidermal growth factor receptor induce

the signaling pathways downstream and activate the antiapoptotic pathways. EGFR inhibitors are approved for the treatment of lung cancer, colorectal cancer, pancreatic cancer, and squamous cell carcinoma of the head and neck. [77] There are two main classes of EGFR inhibitors the monoclonal antibodies (cetuximab, panitumumab, and matuzumab) which target the extracellular ligand-binding domain and small-molecule tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, and afatinib) which target intracellular domain. The EGFR inhibitors decreased the over expression of the EGFR and results in the inhibition of metastasis, growth, proliferation, differentiation, and angiogenesis and causing apoptosis of cancer cells. [78]

The objective of this review was to give an overview on the development, progression and treatment of skin cancer. In this review, we highlight the important risk factors associated with the development of melanoma and Non-melanoma. Ultraviolet light exposure is the most important etiological factor involve in the development of cancer. Multiple defense mechanism affects in cancer development and this damage alter the deoxyribonucleic acid (DNA) repair, immunosurveillance and cellular growth regulation to protect against malignant progression. Various therapies used for the treatment of skin cancer involve chemotherapy, photodynamic therapy, radiation therapy, biological therapy and surgery. However the chances of recovery by these therapies are less. Nowadays, there are plenty of newly-developed treatments which have showed great potential in skin cancer treatment. These treatments involve some newer agents with high safety and efficacy. The government and non-government organizations are also put their beneficial efforts to diagnose and treat the skin cancer, but all efforts are not up to the required mark. Preliminary precautions like proper lifestyle, nutritional supplements and balance diet will helpful in reducing the risk of skin cancer. These treatments show their effectiveness by increasing the survival and improving the quality of life in cancer.

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