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Skin Cancer: An Overview



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ABSTRACT

Skin cancer is a most common cancer in United State. Number of skin cancer cases have been going up over the past few decades. In 85 percent of the cases when a person reaches 18 years of age, damage to the skin results in skin cancer. Cancer is most challenging disease to treat and second leading cause of death in the society. Most skin cancers are caused by too much exposure to ultra-violet (UV) rays, also from man-made source such as tanning bed, sun lamp. In human, arsenic is known to cause cancer of the skin. SCC and BCC have been reported to be associated with arsenic alone or in combination with other risk factor. The purpose of the present review is outline types, pathogenesis, diagnosis, treatment of skin cancer. Also discussed anticancer compounds which are derived from different sources as well as provide coverage commentary of novel drug delivery system for skin cancer.



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INTRODUCTION

The skin

The main function of the skin is giving protection to body from heat, injury, and infection. Skin mainly consists of fat and water for maintaining body heat. It acts as a barrier that protects body against UV-radiation, toxic substance (1).

Epidermis is top layer of body which is made up of flat cells called squamous cells. Keratinocytes, dendritic melanocytes, Merkel and Langerhans cells are different types of cells present in epidermis (1). Melanocytes produce melanin, which gives your skin its cover (2).

Dermis is layer below the epidermis which contains different types of cells such as blood vessels, lymph vessels and gland. Some gland secretes sweat and other glands secrete sebum that keeps your skin from drying out. Both reaches skin surface through small opening called pores (2).

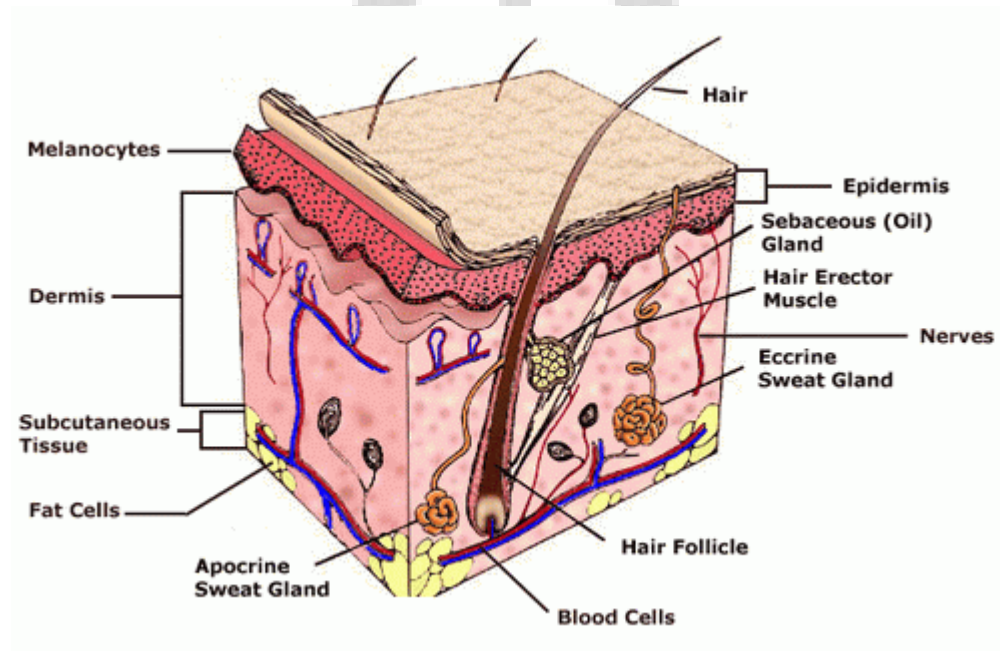


Figure1. Structure of skin. (ref. No.:3)

Cancer

The body is made up of cells and it is normal for them to grow, divide and produce more cells when body needs them. Cancer occurs process sometimes going wrong, when cells keep dividing, even when new cells are not needed.

The mass of extra cells may produce a tumor that can be:

- **Benign (not cancer)**
Being tumors are rarely life-threatening and they do not spread to other parts of body. They often can be removed and usually do not grow back.
- **Malignant (cancer)**
Malignant tumors can harm nearby tissue and spread to other part of body (2). They can be removed but sometimes grow back.

Cell becomes cancer cells because of damage to DNA. DNA is in every cell and direct all its action. In normal cell, when DNA gets damaged the cell either repairs or the cell dies. In cancer cell, the damaged DNA is not repaired, but cell does not die like it should. Instead, this cell goes on making new cells that body does not need. These new cells will all have the same damaged DNA as the first cell does(4).

Skin cancer

Skin cancer mainly two types. 1.malignant melanoma 2. Non-malignant melanoma; which can be divided into Basal cell carcinoma (BCC) and Squamous cell skin cancer (SCC)(1). Carcinoma means cancer that begins in the cells covering or lining an organ(2). BCC and SCC mainly cause due to chronic exposure of UV- sunlight. 80-85% of non-melanoma skin cancer are BCC and SCC. SCC is more dangerous and responsible for many deaths. Overall 80% of skin cancer are BCC, 16% are SCC and 4% are melanoma (1). Melanoma which originates in the pigment-producing cell i.e. melanocytes, is the least common, but most aggressive, most likely to spread and if untreated then fatal. Skin cancers that are not melanoma are called as non-melanoma skin cancer because they develop from skin cells other than melanocytes(4).

Types of skin cancer

Skin cancer is named for type of cell that becomes malignant. Mainly three type of skin cancer are :

- **Melanomas :**

It causes 75% of death related to skin cancer. This type of skin cancer is associated with melanocytes of epidermal layer. They synthesize melanin pigment that produces cell of skin with photo protection from mutagenic UV-rays. It is only preventable cancer that continues to increase(1). Melanocytes can also form benign (non-cancerous) growth called *moles*(5).

Melanoma can occur anywhere on the body, but are more likely to start in certain area. The trunk, chest, back is most common place in men. In women, the legs are the most common site. The neck and face are other common place for melanoma to start(5).

Sign and symptom of melanoma:

The most important warning sign for melanoma is appearance of new spot on the skin or a spot that's changing in size, shape or colour.

The ABCDE rule is another guide to usual sign of melanoma. Be on lookout and tell your doctor about spot that have any of the following features:

- A is for Asymmetry: One-half of mole or birthmark does not match other.
- B is for Border: The edges are irregular, ragged, notched or blurred.
- C is for Colour: The colour is not same all over and may include shades of brown or black, or sometimes with patches of pink, red, white or blue.
- D is for Diameter: The spot is larger than 6 millimetres across (about 1/4 inch-the size of a pencil eraser), although melanomas can sometimes be smaller than this.
- E is for Evolving: The moles are changing in size, shape or colour(5).

Also, another sign is oozing or bleeding from mole and moles that feel itchy, hard, lumpy or swollen(1).

Basal cell carcinoma (BCC)

This is most common type of skin cancer. They usually arise from basal layer of epidermis. BCC is again classified into three type;

- Superficial: Seen in trunk and extremities as an erythematous plaque.
- Nodular: Lesion generally seen on head and neck and appear as pearly, telangiectatic papules with rolled border.
- Sclerosing / morpheaform: Lesion often resembles scars and usually are mostly difficult to identify on visual inspection(1).

BCC are mostly found in areas that get exposed to a lot of sunlight, such as the neck, and arm, but they can develop anywhere on body (5).

Sign and symptoms of BCC:

Look for new growth, spots, bumps, patches or sores that don't heal after several weeks. BCC can appear as:

- Flat, firm, pale or yellow area, similar to scar
- Raised reddish patches that might be itchy.
- Small, pink or red, translucent, shiny, pearly bumps, which might have blue, brown or black areas.
- Pink growth with raised edges and a lower area in their center, which might contain abnormal blood vessels(5).

Gorlin syndrome is often associated with BCC(1). BCC undergo metastasis rarely(6).

Squamous cell carcinoma (SCC)

SCC occurs on sun-exposed site of head and neck. Generally, the long-term outcome is positive, and less than 4% of squamous cell carcinoma cases are at risk of metastasis(1,7).

Sign and symptoms of SCC:

In people with dark skin, squamous cell skin cancer is most common, usually found in place that is not getting in sunlight, such as legs feet. If people are fair skin, SCC usually occurs on skin have been in the sun, such as head, face and neck.

SCC mainly appear as

- Rough or scary red patches, which might crust or bleed.
- Raised growth or lumps, sometimes with a lower area in the center.
- Open sores that don't heal or that heal and come back.
- Wart-like growth(5)

Basal cell carcinoma (BCC) is most common malignancy in United State and comprises 75% of non-melanoma skin cancer, squamous cell carcinoma (SCC) is second most common skin cancer, accounting for 20% of cases of non-melanoma skin cancer(4).

Other skin cancer

They are less common:

- Merkel cell carcinoma
- Kaposi sarcoma
- Cutaneous lymphoma
- Skin adnexal tumors (tumors that in hair follicle or sweat and oil gland)
- Various type of sarcoma

Together, these type account for less than 1% of skin cancer(5).

Risk factor:

UV- radiation

Exposure to ultra radiation is main risk factor. Sunlight is major source for UV-light(5). Tanning equipment is important source of UV light (6). UV-rays damage the DNA of skin cells. Skin

cancers start when this damage affects the DNA of genes that control skin cell growth (5). Sunlight categorised into three types depending on wavelength(1).

- UVA light(320-400nm): These rays are linked to long-term skin damage such as wrinkle, but they are also through to play a role in some skin cancer(5). 90-99% reaches to earth surface(1). Most tanning equipment gives large amount of UVA.
- UVB light(280-320nm): They can damage skin cells DNA directly and are the main rays that cause sunburn(5). 1-10% reaches to earth surface. It has tendency to induce all phases of skin cancer. UVB-induced Mitogen activated protein kinase(1).
- UVC light(200-280): These rays have more energy than other UV rays. But they don't get through our atmosphere and are not in sunlight. They are not normally a cause of skin cancer(5).

UVA and UVB rays can cause skin cancer, and damage skin.

Long term exposure can cause early skin aging, wrinkles, loss of skin elasticity, dark patches and pre-cancerous skin changes as dry, scaly, rough patches called *actinic keratosis*(5).

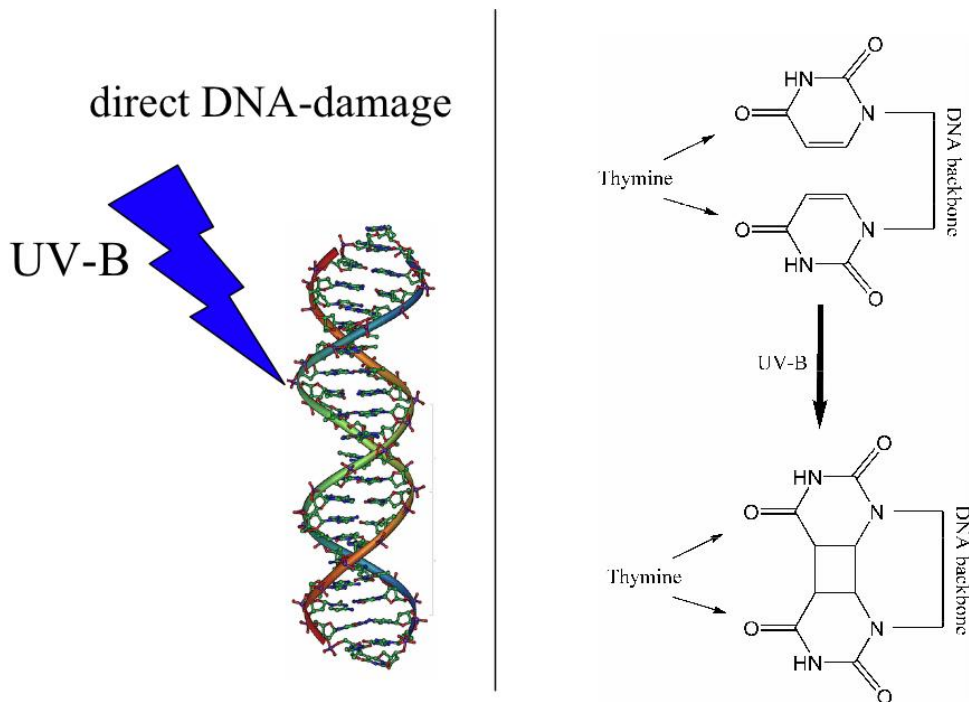


Figure 2. UVB directly damage DNA. (ref. no. 8).

UVB radiation may lead to direct damage of DNA including the development of thymine dimers, whereby adjacent thymine base bond with each other instead of across the DNA backbone ladder. This thymine dimer makes a bulge and the distorted DNA molecule does not function properly(9).

Effect of Arsenic

Arsenic is chemical element. It is semi-metal that comes in three different allotropic forms: yellow, black and gray. The carcinogenic potential of inorganic arsenic exposure through drinking water is cause for considerable concern, especially because hazardous inorganic arsenic is powerful human multi-site carcinogen(9).

The combination of UVB-Arsenic treatment results in antiproliferative and proapoptotic effect by stimulation of caspase pathway in keratinocytes. SCC has repeatedly been reported with association the ingestion of arsenic alone or in combination with other risk factor. Also, report on BCC related to arsenic ingestion is quite common. In addition to SCC and BCC, Bowen's disease is often reported to be associated with arsenic ingestion, which might come from both drinking water and medication (9,10).

The main mechanism regarding arsenic carcinogenicity is induction of chromosomal abnormalities, promotion and oxidative stress(9,11).

Treating for skin cancer

The choice of treatment should be determined by histological type of lesion, its size and location, and age of patient. No single treatment method is ideal for lesion(1). It may also include different therapies such as;

- Radiation therapy: The radiation oncologist uses various form of radiation to treat cancer and other disease.
- Brachytherapy: A special form of radiation that places the radiation source very close to the tumor. This form of radiation tends to shorter in duration than regular radiation therapy.
- Surgery: The cancer cells are cut out and removed.
- Moh's surgery: A form of surgery where the tumors are removed one layer at a time. This technique may allow a dermatologist to preserve more healthy tissue.

- Cryosurgery: The cancer is frozen and removed.
- Laser surgery: Cancer cells are killed by laser beams.
- Electrodesiccation: This cancer is dried with an electric current and removed.
- Photodynamic therapy: This describes a two-part method in which a photosensitive drug, light of specific wavelength and molecular oxygen combine to produce a therapeutic, tumor-killing effect(12).
- Chemotherapy: The cancer cells are attached to drug that is either taken internally or applied to the skin.
- Biologic therapy: Medication given to help your immune system fight cancer better(13).

Anti-cancer compound

Phytochemical compounds from extracts of plant root, bulbs, bark, leaves, stem and other have shown promising potential as anti-cancer drugs, or for serving as lead compound in the synthesis of new compound(14). Natural sources for anti-cancer drugs are plant, animal, marine and microbes(14).

Marine source

The high anti-tumor potency of agents, discovered from marine resources, reflects the high potential of ocean as a possible source of anti-cancer drug(14,15). Extract from sponges, algae and marine cyanobacteria have shown strong anti-cancer activities (14,16). Laminarans, fucoidans, alginic acid and carrageenans are some of the compound isolated from marine source that have been found to exhibit effective anti-cancer activities(14).

The anti-cancer drugs are cytarabine, trabectedin, eribulin mesylate and brentuximab vedotin, derived from *Cryptotethya crypta*, *Ecteinascidia turbinata*, *Halichondria okadai* and *Symploca hydroides*, respectively(14,17).

Microbial source

The chemical diversity and ease of access of microbes with respect to collection, culturing and fermentation make them an extremely relevant source of pharmaceutically active compound. Anthracyclines, bleomycin, staurosporine, and actinomycin group of microbially derived anti-cancer compound in clinical use(14,15). Whole bacteria can be used in their life, attenuated, or

generally modified forms to stimulate immune response, but this may potentially result in side effect that can be avoided by using bacterially derived products instead(14).

Plant source

Over 50% of all drug currently in clinical use are originated from plant. The vinca alkaloids, including vincristine, vinblastine and vinorelbine, were the first plant-derived anti-cancer agent to gain approval for clinical use. Contrary to the vinca alkaloids, taxanes work by stabilizing the microtubule, instead of destabilizing it. The stabilization of microtubules results in an imbalance between tubulin and microtubules, which affects normal cellular function and in turn results in cell death(14).

Phytochemical:

Phytochemicals having anti-inflammatory, immune-modulatory and anti-oxidant properties, generally have the highest potential of exhibiting chemo-preventive behaviour in skin cancer(14,18). Some group of phytochemical with high anti-cancer potential as following are

Phytochemical group with high anti-cancer potential	Properties	Chemical structures of phytochemicals	Reference
Flavonoids	Anti-oxidant, chelating, due to antioxidant property act as trigger of inhibition of tumorigenesis	<ul style="list-style-type: none"> a) Quercetin b) Kaempferol c) Epigallocatechin-3-gallate d) Apigenin e) daidzein 	(14,19)
Carotenoids	Preventing cancer, diabetes, cardiovascular, due to antioxidant activity that reduces DNA damage by free radical after exposure to UV light.	<ul style="list-style-type: none"> a) β-carotene b) retinol c) lycopene d) fucoxanthin 	(14,20)

Terpenoids	Anti-neoplastic, anti-melenoma, flavorants, preservatives, perfume	Structurally assembled from five carbon building unit such as a) hemiterpenoids(C ₅) b) monoterpenoids(C ₁₀) c) sesquiterpenoids(C ₁₅) d) diterpenoids (C ₂₀) e) triterpenoids(C ₃₀) f) tetraterpenoids (C ₄₀) g) polyterpenoides(C ₅) _n	(14)
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Drug delivery for skin cancer:

The new drug delivery approaches and new modes of action represent one of the frontier areas which involve multidisciplinary scientific approaches to provide a major advance in improving therapeutic index and bioavailability at site specific delivery.

The main important objective for the development of these system is to furnish an extend duration of action and thus assure greater patient compliance(4). The advantages of controlled release preparation have been summarised as following:

- Decrease incidence and/or intensity of adverse effect and toxicity.
- Better drug utilization.
- Controlled rate and site of release.
- More uniform blood concentration.
- Improve patient compliance.
- Reduced dosing frequency.
- More consistent and prolonged therapeutic effect.
- A greater selectivity of pharmacological activity(4,21).

Novel drug delivery system includes those based on physical mechanism and those based on biochemical mechanism. Physical mechanism also referred as controlled drug delivery system includes osmosis, diffusion, erosion, dissolution and electron transport. Biological mechanism includes monoclonal antibiotic, gene therapy and vector system, polymer drug adducts and

liposomes. Therapeutic benefit of some new drug delivery system includes optimization of duration of action of drug, decrease in dosage frequency, controlling the site of release and maintaining constant drug level(4,22).

CONCLUSION

Skin cancer cannot be treated effectively by a medication so there is a need to detect and treat disease at early stage. Climate changes, exposure to UVB and high level of arsenic in drinking water as well as several other factors have been reported to be associated with melanoma, SCC and BCC. Incidence rate melanoma and non-melanoma skin cancer are dramatically increasing worldwide. Anticancer activities of plant can be ascribed to a distinct compound or a combination of the effect of different compounds in crude extract in human life.

Traditional use of natural compound in cancer treatment is relatively cheap due to availability of plant and the simple method used in product preparation. Thus, here we discuss an overview to give information about type of skin cancer, pathogenesis, treatment and also anticancer compound.

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