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Impact factors affecting the prevalence of skin cancer (melanoma): A review

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Abstract

The skin of humans is thought to be the primary immune barrier, and repeated exposure to various carcinogens and mutagens can have an impact on it. The ability of these dangerous substances to cause skin cancer (melanoma) depends on a number of underlying factors, including the individual's genetic predisposition, the amount and duration of exposure, their overall health, their age, sex, and race, and their nutritional and lifestyle choices. The elements as mentioned above have the potential to activate oncogenes linked to specific forms of skin cancer. Carcinogens may be chemical substances such as those that alter DNA and cause dimers, a common DNA abnormality, or physical particles such as radiation and prolonged sun exposure. When the body does not eliminate these melanoma-related dimers through proofreading activity, physiological function will continue, and cancer will develop as a result of unchecked cellular proliferation. This review aims to provide an overview of the mechanism(s) underlying the development of cancer (ideally, skin malignancies in general and melanoma in particular), as well as its diagnosis, therapy, and variables contributing to its occurrence in the human body.

Keywords: *Melanoma, Mutagens, Carcinogens, DNA aberrations*

Introduction

Melanoma pathogenesis

Melanin pigment-producing cells, which are primarily found in the skin but can also be found in the lining of the mouth, the ear, the eye, and the gonads, are affected by skin cancer, which is an irregular growth that spreads with necrosis and affects the dermis layer, the skin's outermost layer, or the layer directly beneath the skin (1).

Historical context:

Historical records of cutaneous malignancies trace back to the fifth century AD, underscoring its prevalence and hereditary factors. Initially, observed predominantly in females (2), research has evolved to identify diverse forms of skin cancers, their diagnostic modalities, and therapeutic approaches (3). Ultraviolet (UV) radiation has been recognized as a principal etiological factor, particularly in high-incidence regions such as Australia and New Zealand (4). Figure (1) shows the typical shape of a melanoma (5).

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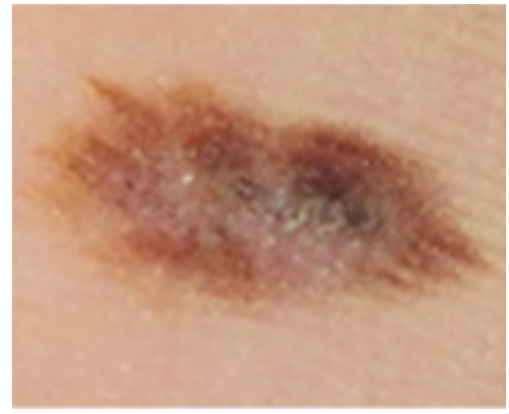

Figure (1): Typical shape of a melanoma (5)

Eighty-five percent of all suspected melanomas worldwide might be due to exposure to ultraviolet radiation; ninety-eight percent have the disease locally, and there are chances of surviving it for five years, which decreases if the cancer spreads to the lymph nodes (1).

The epidemiology of melanoma differs across regions, sexes,

and racial/ethnic backgrounds. It is yet unknown whether there is a genuine biological reason for these differences.
One major drawback of current medical treatment protocols is drug resistance. Chemotherapy, targeted treatment, and/or immunotherapy are currently being used in combination therapy trials.
(6).
The average age of occurrence is approximately 59 years, and out of a total of 73,870 people with skin cancer, 9,940 have died worldwide. Globally, it represents 4% of all cancer cases, with the highest death rates reaching 2000 cases in 2022 (7).

Classification of Skin Cancer:

The primary types of cutaneous malignancies include the following:
- Basal cell carcinoma (BCC): the most frequently encountered form.
- Squamous cell carcinoma (SCC): The second most prevalent type.
Less common variants include ocular melanomas and lymphomas (6). Figure (3) shows the prevalence rates worldwide (6).

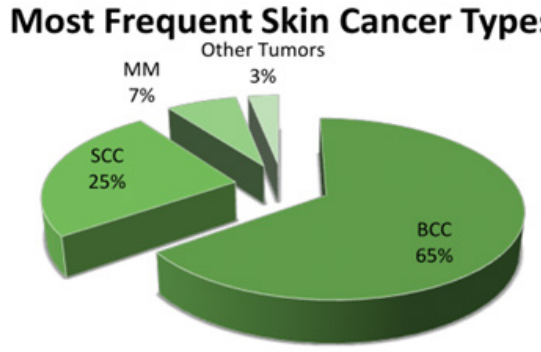

Figure (3): Prevalence of common skin cancer types worldwide.

Risk factors:

- Age: Risk increases with advancing age, especially beyond 59 years (5).
- Skin phenotype: Certain racial groups or origins—such as Caucasian origins—play a part in incidence
- Genetic Predisposition: Hereditary factors and genetic mutations.
- Ultraviolet Exposure: Exposure to UV radiation from natural sunlight or artificial sources.
- Immunocompromised State: Conditions such as acquired immunodeficiency syndrome (AIDS) or certain immunosuppressive treatments.
- Chemical Exposures: Contact with industrial chemicals, mining byproducts, and heavy metals.
- Lifestyle factors: tobacco use, alcohol consumption, dietary habits, and occupational exposures.
- Prior skin cancer cases : Increased risk of neoplastic recurrence.

An uncommon genetic condition called xeroderma pigmentosum (XP) significantly increases the risk of skin cancer, including melanoma. The ability of people with XP to repair UV-induced DNA damage is compromised. Other genetic disorders that increase the risk of melanoma include the following:

1. FAMMM Syndrome, or Familial Atypical Multiple Mole-Malignant Melanoma

This syndrome is characterized by an increased risk of developing melanoma and an abundance of atypical moles. Mutations in the CDKN2A gene, which is essential for controlling cell development, are frequently involved.
Examples: FAMMM frequently affects families with a history of atypical moles and numerous melanomas. This syndrome may put a person at a much increased risk of developing melanoma earlier in life.

2. Gorlin syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome, is characterized by a high risk of basal cell carcinoma as well as other cancers, such as melanoma. It is caused by mutations in the PTCH1 gene. Individuals who have this syndrome may also be predisposed to other cancers and frequently develop numerous basal cell carcinomas.
Examples include numerous basal cell carcinomas, jaw cysts, and skeletal anomalies in individuals with Gorlin syndrome. Although not as severe, the elevated risk of melanoma is still present.

3. Li-Fraumeni syndrome: This disease is associated with mutations in the TP53 gene, which is essential for regulating cell division and preventing the development of tumors. Li–Fraumeni syndrome patients have an increased early-life risk of developing melanoma and other malignancies.
For example, breast cancer, sarcomas, brain tumors, and melanoma are among the cancers that can affect families with Li–Fraumeni syndrome.

4. Cowden syndrome

Cowden syndrome is caused by abnormalities in the PTEN gene and is linked to an increased risk of melanoma, among other cancers. It frequently manifests as several benign tumors and skin blemishes (7).
Examples: People with Cowden syndrome are more likely to develop endometrial, thyroid, and breast malignancies in addition to noncancerous skin growth, such as papillomas and trichilemmomas.

5. Syndrome of BAP1 Tumor Predisposition

Description: BAP1 gene mutations produce this condition, which is linked to a greater risk of melanoma and other malignancies, including mesothelioma, renal cell carcinoma, and uveal melanoma.
Examples: People with BAP1 tumor predisposition syndrome have a family history of several cancers, including kidney tumors and uveal melanoma, and they may develop cutaneous melanomas.

6. Ataxia–telangiectasia: This syndrome, which is mostly linked to a greater risk of lymphoid tumors and leukemia, can also increase the susceptibility of a person to other cancers, such as melanoma. It is caused by mutations in the ATM gene (5).
For example, people with ataxia-telangiectasia frequently experience neurological symptoms such as tiny aneurysms and

ataxia. They may also lead to the development of melanoma or other cancers.

Genetic abnormalities that cause the body to be less able to repair damaged DNA or control cell division are present in all of these syndromes, increasing the chance of developing melanoma and other malignancies. To regulate the risk associated with these disorders, early detection and routine screening are essential (8).

Genetic factors such as inheritance of chromosomal abnormalities, family history, and genetic predisposition to certain types of cancer. Exposure to ultraviolet radiation from a natural or artificial source, exposure to sunlight, some burns, or sensitivity to it, as it has risks of mutation, similar to tobacco, and exposure to ionizing radiation in various applications, nuclear waste, or radiation examinations and medical treatment (2). Weakness of the immune system and diseases leading to it, such as immunosuppression in AIDS patients, as well as taking some medications that cause reactions that lead to skin cancer (by causing photosensitivity, such as hydrochlorothiazide, which is a diuretic commonly used to treat high blood pressure), especially in elderly patients, also after organ transplantation, the treatment of certain types of cancer and age (5). Chemicals, especially industrial materials, some mining derivatives, hydrocarbons and heavy metals. Lifestyle and daily behavior, such as exercise, smoking, alcohol intake, type of food, type of work and work environment, as well as some hormonal changes associated with menopause or physiological changes. Previous occurrences of the disease increase the possibility of recurrence or the emergence of cancerous types in other places (3).

Many scientists believe that any amount of sunlight that a person is exposed to every day for more than twenty minutes may lead to skin complications, the most important of which is skin cancer. The period of exposure to ultraviolet radiation from the sun may extend to three years. Usually, the disease appears on the face because it is more exposed to sunlight. With respect to genetic factors, research indicates that some races or families have more skin cancer than others do (6).

Symptoms and diagnosis:

Diagnosis:

Neoplasia is a process of several steps in which the life cycle of the melanin-producing cell changes, making it more sensitive to the effect, and does not divide or multiply properly (7). Several mechanisms have been suggested depending on the time, exposure, location and type of injury or necrosis (8). The infected skin cells are characterized by irregular edges, are asymmetrical, differ in color and dimensions in the affected area, the area increases over time, starting from 6 mm and gradually increasing in size, and the shape develops from a benign type to a precancerous type (premalignant and then a cancerous type called malignant melanoma) [9].

Histological examination includes morphological examination in terms of the dimensions, color, number of pieces, thickness of the sample, dimensions, symmetry, location, and date of excision of the sample, noting the presence of necrosis and whether lymphocytes have been infected (5). It also includes a microscopic examination, which provides an accurate diagnosis. The degree of disease development and, accordingly, the appropriate treatment should be determined (10). The disease is classified into five stages according to the scientists Clark and Breslow to determine the degree of necrosis, depth, and rate of cell division within a sample (11). Figure (4) illustrates the stages and indications for diagnosing the disease, which are internationally approved.

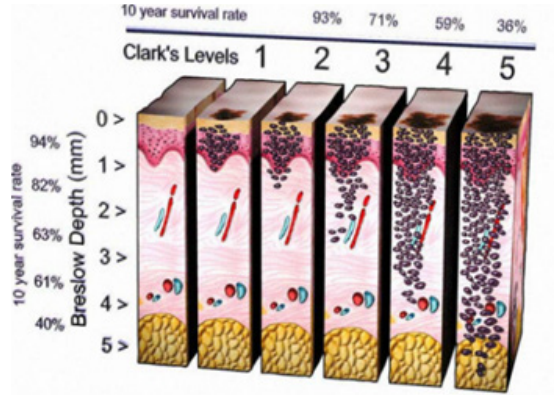

Figure (4): Cancer stages in melanoma diagnosis.

Skin Layers and Melanoma Progression

- Epidermis: The outermost layer is composed primarily of keratinocytes and melanocytes. Melanoma generally originates in this layer.
- Dermis: Located beneath the epidermis, this layer contains vascular networks, sensory nerve endings, and hair follicles. Melanoma infiltration into this layer complicates therapeutic management.
- Hypodermis (subcutaneous layer): The deepest layer, consisting of adipose tissue and connective tissues. Melanoma that advances to this layer may metastasize to distant organs, significantly impacting patient prognosis (9, 10).

Understanding the stratigraphy of the skin is crucial for elucidating melanoma progression from the epidermal layer to deeper tissues, which is integral for effective diagnosis and intervention (11).

Diagnostic criteria

Melanoma commonly presents with lesions characterized by asymmetry, irregular borders, heterogeneous pigmentation, and increased diameter. Diagnostic evaluation involves histopathological examination and staging based on the Clark and Breslow systems (12). Therefore, accurate diagnosis is essential for formulating optimal treatment regimens (13).

Treatment Approaches:

Prevention is limited to raising awareness and avoiding sunlight, especially in the period from early in the day until the afternoon, maintaining a healthy lifestyle within the home and work, and monitoring the skin and duration of exposure (5). In the early stages, the tumor can be discovered and removed by surgery or by X-rays or radium radiation for early diagnosis, which saves much effort, time, and the use of toxic and expensive treatments (11).

Treatment generally depends on the stage of cancer and may include one or more of the following therapeutic methods: surgery, the use of interferons and interleukins (which are im-

mune substances used for treatment and are naturally excreted in humans), radiation or chemotherapy (10). The determination of mutations is important for inferring the possibility of skin cancer in up to 20% of patients because mutations are heterogeneous with a high frequency in melanoma patients (12).

The management of early-stage melanoma may involve surgical resection or radiation therapy. Advanced stages may require immunotherapeutic agents, cytokine-based therapies, or chemotherapeutic regimens (13). Genetic profiling is crucial for assessing individual susceptibility and tailoring treatment (14).

The effect of the causative agents of the disease:

Effects of the sun and radiation:

Many scientists believe that any daily exposure to sunlight for longer than twenty minutes might cause skin problems, the most significant of which is skin cancer (3). We may have been exposed to UV light from the sun for up to three years throughout that time. Owing to increased sun exposure, this condition typically manifests on the face (13). With respect to the genetic component, studies have shown that certain racial or familial groups have higher rates of skin cancer. Numerous scientists have reported that one of the harmful effects of gamma rays on melanin-producing cells in the skin is the stimulation of oxidative, cellular, and genetic toxicity (11).

Chemicals:

Exposure to chemicals does not necessarily cause cancer. There are several factors that determine whether contact or exposure is a direct cause of the occurrence of disease and the susceptibility of an individual or a disease to occur over others, including (3):

-The type of chemical
- Duration of contact or exposure
-The general health of the individual and genetic factors
-Place of exposure (work environment, home, etc.)
-The exposed area of the body
-The method of exposure to the stimulus
-The number of exposure times

The body has certain mechanisms to drive the harmful effects of hazardous chemicals by eliminating them, reducing their effects, or metabolizing them. Thus, it prevents its carcinogenic effects. There are three types of chemicals in this field (12):

A- Substances that directly cause cancer.

B- Procarcinogens, which are substances that do not cause cancer until they are converted to other basic substances.

C- Substances that are associated with other substances to cause cancer.

Damage to genetic material leads to the emergence of cancer, and if the damage is very massive, it is difficult to repair, and the cells may die directly, or this may lead to mutation, genetic changes at certain sites, and the emergence of cancer (9). Mutations may also be inherited, and this genetic predisposition coincides with the presence of various environmental factors (2). The potential for disease between individuals as well as for a certain type of cancer, since the data showed that certain time periods and unique environmental conditions were associated with the existence of a particular type of cancer in a geographical area below another (13). As previously stated, not all chemicals are carcinogenic, and exposure to them does not always result in cancer unless the chemical has a particular ability to attach to its receptors in the body (7).

Immune factors:

A weak immune status is generated by the presence of certain diseases, such as diabetes, AIDS, and cancer, and the use of some medications, such as those used after organ transplantation and advanced age, are among the risk factors for skin cancer (14), and sometimes, the treatment of skin cancer itself leads to the inhibition of the immune response or the generation of a negative immune response. In contrast, some drugs stimulate T cells and stimulate programmed cell death (immune mechanisms specific to resistance to tumors or inflammation) and stimulate toxic T cells, according to different mechanisms specific to each treatment. This depends on the type of treatment (steroids or others) and the doses used and their use with peptide vaccines for the purpose of stimulating antibodies or using more than one treatment (7).

Notably, melanoma cells have several mechanisms to escape from the immune system; for example, they lead to a reduction in antigenic action, so they do not appear to the immune system in the form of foreign bodies, or they block gene expression after encountering immune cells. It also affects the absence of differentiation signals and sequential immune reactions that eventually lead to tumor elimination in normal patients (5). Additionally, the cytokines generated against melanoma cells were studied in mice, and it was found that the host immune response was altered in one way or another in the tumor area, resulting in a disruption of the immune environment.

The scientist Dranoff and his group also conducted several immuno-histochemical studies and reported that cellular secretions initially stimulate maximum immune activity against the tumor, analyze and devour cancer cells, and reduce the chances of tumor growth by macrophages, which explains why the disease may be eliminated and that the patient may recover through the body's immunity, which prevents the development of the disease in its early stages, as the body's immunity may eliminate it (4).

Modern studies and immunotherapies focus on collecting immune cells that present the tumor as a foreign body, as well as toxic T cells, and promote the use of cellular secretions for the purpose of attacking the tumor and reducing the chances of its transformation into advanced stages. The treatments used are still being refined and activated in a more specialized way (15).

Immunotherapy not only includes the use of protein vaccines to generate antibodies but also includes the use of immune cells after being multiplied outside the living body and re-injecting them into the same host from which they are taken to avoid being rejected if they are taken from another host (8). This treatment was attempted on a cancerous cell line, either from a tumor source, once called monoclonal, or from several tumor sources, then called polyclonal, and has proven successful in mice since 1996 and in the following years, it was performed in two directions: monitoring the immune response of the host and an immunological survey of the cells involved in restricting and eliminating the tumor (15). A class of immunotherapeutic drugs known as anti-PDL-1 antibodies works by inhibiting the programmed death-ligand 1 (PD-L1) protein, which strengthens the immune system's capacity to

identify and destroy cancer cells (7).

Genetic factors:

The reason for the difference in the formation of healthy skin from the skin affected by melanoma is the failure to repair the defect in deoxyribonucleic acid resulting from exposure to ultraviolet radiation and the sun; therefore, the percentage of melanin differs and increases from the normal limit owing to a combination of genetic and environmental factors (16). An example of a defect in genetic material is Xeroderma disease, on which several molecular and cellular–cancer studies have been conducted. Individuals who inherit a defect in the ability to repair DNA when exposed to environmental conditions such as sunlight are more likely to attack skin cancer. At an early age, it may reach 16 years or less on average (8).

In the context of the aging process in human cells, the disease may develop into other types of cancer other than melanoma. The resulting mutation, which leads to the emergence of all kinds of melanoma, leads to increased cell division as a result of inhibition of the BRAF and MEK sites (15).

In 2000, the scientist Sisley and his group searched for the relationship of chromosomal changes with the emergence of melanoma and noted the existence of a significant correlation with a percentage of up to 76% of the frequency of mutations, as they occur mainly in chromosomes 1 and 6 and in the second degree in chromosomes 3 and 8, with a less frequent "and all of them responsible for the emergence of the disease, the mutation is due either to the loss or partial deletion of some nitrogenous bases or to the short arm, especially in chromosome No. 1 during the crossing-over phase of nucleic acid replication, point mutation, or defects in micronuclei and chromosomal aberrations" (13).

The defect may be either inherited or due to a defect that occurs via the mechanism of replication itself. Chromosome number 6 is a defect in the sequence of bases without losing them (17). Defects may arise at other chromosomal sites. The occurrence of mutations is not sufficient for diagnosis, but it must be studied at the molecular level, taking into account the effects of external factors such as sunlight. These studies are important because they accelerate treatment in specific places and according to the degree of the defect because of their importance in the diagnosis (16).

The final explanation for the occurrence of the disease is that several environmental and genetic factors combine to affect the natural function of the melanin-producing cells in the skin so that the concentration and secretion of the pigment increases in an unmodifiable manner, and the rate of cancer in the skin or under the skin increases, which is subject to immune factors and other factors related to cellular receptors. of carcinogens and the physiological state of the person (18).

Epidemiological trends and incidence

Global Statistics:

Melanoma incidence is increasing globally, with more than 331,000 new cases documented in 2022. Nations such as Australia, New Zealand, and the United States bear significant melanoma burdens, with Australia exhibiting the highest incidence rate per capita and New Zealand showing the highest mortality rates (16). In the United States, there are over 106,000 new melanoma cases, making it the country with the highest total incidence. Nonetheless, Australia has the highest incidence per population, whereas New Zealand continues to have the highest per capita death rate from melanoma, reflecting substantial regional disparities (17).

Globally, there were more than 58,000 deaths from skin cancer in 2022, highlighting the severity of melanoma and the necessity for improved preventive strategies. The contributing factors include increased UV exposure, an increasing prevalence of indoor tanning, and an aging demographic (18).

Impact of Carcinogenic Agents:

- Ultraviolet and Radiation Exposure

Excessive UV radiation exposure is a primary risk factor for melanoma, particularly in high-exposure areas such as facial regions (19). Ionizing radiation and other forms of radiation exacerbate melanin toxicity, facilitating carcinogenesis (20).

- Chemical exposure

Chemical carcinogens may not invariably induce melanoma, but their effects are influenced by factors such as chemical type, exposure duration, and individual susceptibility (21). Chemical agents can induce genetic alterations that precipitate oncogenic transformations.

Immune system status

Immunosuppression due to disease states, pharmacological treatments, or aging can increase susceptibility to melanoma. Certain therapies may either augment or attenuate the immune system's capacity to combat neoplasms (22). Immunotherapy aims to increase the ability of the immune system to target and eradicate tumor cells (23).

Genetic Factors

Deficiencies in DNA repair mechanisms increase the risk of melanoma. Conditions such as Xeroderma pigmentosum underscore the critical role of DNA repair in melanoma prevention. Chromosomal anomalies, particularly those involving chromosomes 1, 6, 3, and 8, are associated with melanoma development (24).

Prevention Strategies for Melanoma:

Effective prevention strategies include the following:

- Utilizing Broad-Spectrum Sunscreen: The application of sunscreens with an SPF of 30 or higher provides protection against UVA and UVB radiation.
- Employing Protective Apparel: Use of hats, sunglasses, and UV-resistant clothing to minimize direct exposure.
- Avoiding Indoor Tanning: Refraining from the use of tanning beds, which significantly elevates melanoma risk, particularly among younger populations.
- Conducting Regular Skin Assessments: Routine self-examinations and professional skin screenings are vital for early detection, particularly in high-risk individuals, such as those with fair skin, a familial history of melanoma, or extensive sun exposure (25).

Conclusion: Melanoma represents one of the most aggressive forms of skin cancer, yet early detection and intervention can substantially improve patient outcomes. The global rise in melanoma cases underscores the necessity for increased awareness, proactive screening, and robust UV protection. Continued research and public health initiatives are crucial in mitigating the impact of melanoma

Recommendations:

- Skin protection: Regular use of sunscreens and protective clothing.
- Healthy lifestyle: Adherence to a balanced diet and avoidance of known carcinogens.

- Routine evaluations: Regular skin examinations and genetic assessments.
- Chemical Safety: Implementing protective measures in environments with chemical exposures.
- Nutritional supplements: Use under medical supervision to maintain optimal vitamin D levels

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