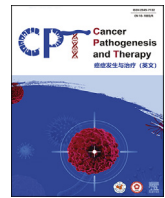




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Cancer Pathogenesis and Therapy

journal homepage: www.journals.elsevier.com/cancer-pathogenesis-and-therapy

Review article

Overview of skin cancer types and prevalence rates across continents

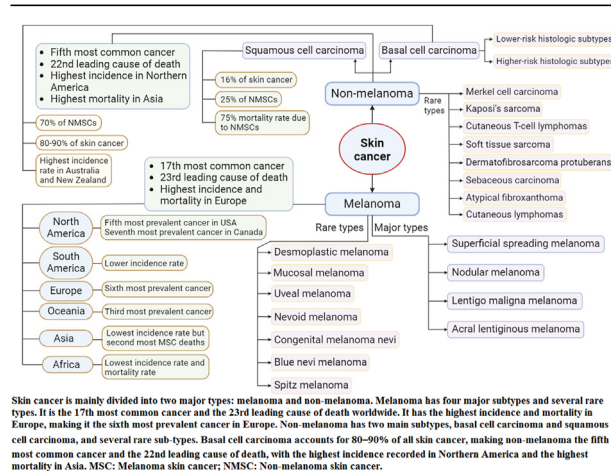
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HIGHLIGHTS

- Skin cancers are highly prevalent in white-skinned populations with sunburns; basal cell carcinoma is the most prevalent.
- Australia and New Zealand have the highest incidence rates of skin cancers.
- The highest incidence and mortality rates of melanoma skin cancer were recorded in Europe.
- The highest incidence and mortality rates of non-melanoma skin cancers were recorded in North America and Asia.
- The incidence of non-melanoma skin cancer is 18–20 higher than melanoma skin cancer, resulting in more deaths.

GRAPHICAL ABSTRACT



ARTICLE INFO

Managing Editor: Peng Lyu

Keywords:

Skin cancer
Prevalence
Melanoma
Non-melanoma
Melanoma types
Mortality rate

ABSTRACT

Skin cancer is one of the most prevalent cancers in the world, and its incidence and mortality rates are increasing continuously, mostly in regions with white-skinned inhabitants. The types of skin cancer vary in their origin and clinical appearances and also differ in their extensiveness. The continents of the world have different scenarios of skin cancer prevalence. This review aims to explore the different types of skin cancer, their clinical features, and their worldwide prevalence based on the literature. Literature from different electronic databases, including Google Scholar, ResearchGate, PubMed, Scopus, Web of Science, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Elsevier, and Springer, were collected through a literature search using specific keywords such as “skin cancer”, “skin cancer types”, “melanoma”, “non-melanoma”, “skin cancer continental prevalence” or similar keywords. The search included English publications from 2000 to 2024. Melanoma skin cancer (MSC) ranks 17th in global prevalence, with the highest incidence and deaths occurring in Europe. However, Australia and New Zealand record the highest incidence and mortality rates. Asia has a lower incidence

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<https://doi.org/10.1016/j.cpt.2024.08.002>

Received 4 March 2024; Received in revised form 1 August 2024; Accepted 4 August 2024

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rate of melanoma, but a higher mortality rate. Superficial spreading melanoma (SSM) is the most common type of MSC. Non-melanoma skin cancers (NMSCs) have the highest incidence in North America, with the highest number of deaths occurring in Asia, Australia and New Zealand have the highest incidence rates for basal cell carcinoma (BCC). BCC is the most commonly diagnosed skin cancer worldwide and the most prevalent form of NMSCs; however, squamous cell carcinoma is the most aggressive form of NMSCs, causing more deaths. NMSCs are the most prevalent cancers worldwide, causing most skin cancer-related deaths. The prevalence of skin cancer rising globally, with several continents experiencing higher incidence and mortality rates. The types and subtypes of skin cancer are becoming more common among clinically diagnosed cancers. This review comprehensively describes skin cancer types and their prevalence worldwide. However, the actual prevalence of skin cancer in these countries should be investigated. Further research on the prevalence of skin cancer across different continents is required to develop more effective cancer management strategies and control the spread of the disease.

Introduction

Skin cancer is a heterogeneous group of cancers and a worldwide epidemic. It is categorized into two major types: melanoma skin cancer (MSC) and non-melanoma skin cancers (NMSCs). These cancers account for >90% of all skin cancers. One of every three diagnosed cancers worldwide is skin cancer, of which NMSCs are the most common.^{1,2}

MSC is a malignant tumor, also known as malignant melanoma or cutaneous melanoma, which arises from dysfunctional and abnormally proliferating melanocytes. Melanocytes are pigment-producing cells that are generated from the neural crest. They produce the brown melanin pigment that gives skin its color and shields it from the harmful radiation of the sun.³ The pathogenesis of MSC involves both biological and non-biological factors. A genetic mutation occurs in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene, which encodes ARF tumor suppressor (p14^{ARF}) and tumor suppressor protein p16^{INK4A} involved in cell cycle regulation. These mutations negatively affect the skin cell cycle, resulting in skin cancers such as MSC.⁴ Moreover, ultraviolet (UV) radiation is a major risk factor for skin cancer and induces melanoma through several mechanisms, including increased deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) damage, genetic mutations, and inactivation of the p53 protein, which induces cell death. UV radiation is more strongly associated with the risk of developing melanoma than basal cell carcinoma (BCC) or squamous cell carcinoma (SCC).⁵ The major types of MSC are (1) superficial spreading melanoma (SSM), (2) lentigo maligna melanoma (LMM), (3) nodular melanoma (NM), and (4) acral lentiginous melanoma (ALM), among which SSM is the most common type.⁶

NMSCs are a combination of two major types, BCC and SCC, which produce epidermal keratinocytes. They are the most common human malignancies and the most common malignancy among Caucasians, with a continuously rising incidence worldwide.^{7,8} BCC and SCC collectively account for 99% of NMSCs incidence.² BCC, which is the most frequent malignant neoplasm in humans, arises from the outermost layer of the epidermis and resembles the basal layer.⁹ SCC is the second most common NMSCs type and arises from epidermal keratinocytes, including squamous and non-squamous epithelial tissues.¹⁰ Other NMSCs include Merkel cell carcinoma (MCC), soft tissue sarcoma (STS), Kaposi's sarcoma (KS), sebaceous carcinoma (SC), apocrine-adenoma carcinoma, and other rare tumors.¹¹ When DNA is damaged by external environmental carcinogens such as UV radiation, mutations in the *p53* gene (90% of SCC and nearly 50% of BCC) occur, which results in the inactivation of the *p53* protein and leads to NMSC formation.¹²

Although skin cancer is one of the most prevalent cancers worldwide, its types and prevalence across different continents, especially those with fewer white-skinned people, have been rarely studied. However, its prevalence is increasing globally, with some forms becoming more aggressive. Discussing the types of skin cancer and their global prevalence based on previous studies from 2000 to 2024 can help us understand the current state of skin cancer worldwide.

In this systematic review, we focused on the prevalence of skin cancer across different continents and countries, along with its types and subtypes. We aimed to comprehensively describe the various forms of skin

cancer and their prevalence across the different continents, fill the knowledge gap, and indicate the direction of future research for better management of skin cancer globally.

We conducted a comprehensive literature search using various electronic databases, including Google Scholar, ResearchGate, PubMed, Scopus, Web of Science, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Elsevier, and Springer. We employed keywords such as "skin cancer", "skin cancer types", "melanoma", "non-melanoma", "skin cancer continental prevalence" or similar terms to identify relevant studies published between 2000 and 2024. This review focuses on the continental epidemiology of different forms of skin cancer and discusses skin cancer types and their histological subtypes.

Skin physiology

The skin is the largest organ of the body, covering the entirety of the human body.¹³ It plays multiple roles, primarily protecting internal organs from the external environment, including microorganisms, pathogens, UV light, dehydration, mechanical and chemical injuries. Additionally, it helps maintain body temperature and excrete waste fluids.^{14–17} The epidermis, dermis, and hypodermis are the primary layers of the skin, each with a specific fundamental structure [Figure 1].¹⁴ The epidermis, the uppermost layer of the skin, comprises keratinocytes. Keratinocytes are a class of cells that produce keratin, a thin and long protein that protects the skin.¹⁷ The epidermis has five layers: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Cells involved in the epidermis include keratinocytes, Langerhan's cells, melanocytes, and Merkel's cells, which contribute to generating different layers.¹³ The stratum spinosum is the thickest layer of the epidermis and contains various cells including Schwann cells, polyhedral cells, dendritic cells, and the Merkel cell–neurite complex, which function as a sensory receptor unit.^{13,18} Similar to cells in the stratum basale, cells in the basal layers of the stratum spinosum exhibit mitotic activity. Most cells in the stratum spinosum are polyhedral keratinocytes with rounded nuclei, containing nucleoli.¹⁹ The mononuclear phagocytic system of the skin is represented by Langerhans cells, which are antigen-presenting dendritic cells originating from bone marrow monocytes. They mimic macrophages physically and functionally.^{20,21} The stratum granulosum comprises approximately five layers of flattened polygonal cells containing nuclei. Small membrane-bound lamellar lipid granules define the cellular cytoplasm of these cells.²² The stratum lucidum, a subdivision of the stratum corneum, is a thin, translucent layer comprising four to six rows of flat and highly reflective eosinophilic cells. Nuclei are rarely visible in this section.¹⁹ The stratum corneum is composed of approximately 15–20 layers of flattened, heavily keratinized cells loaded with keratin. The dead cells in this layer are continuously scraped from the epidermal surface.²² The dermis is a layer of mesodermal origin that supports, nourishes, and connects the epidermis to the hypodermis, providing the skin with strength and flexibility. Fibroelastic tissue supports this layer. The dermis contains the circulatory, lymphatic, and neural systems, sweat pores, and hair follicles. The most prevalent complex extracellular matrix (ECM) protein, dermal collagen, accounts for 90% of the dry weight of the skin. The papillary

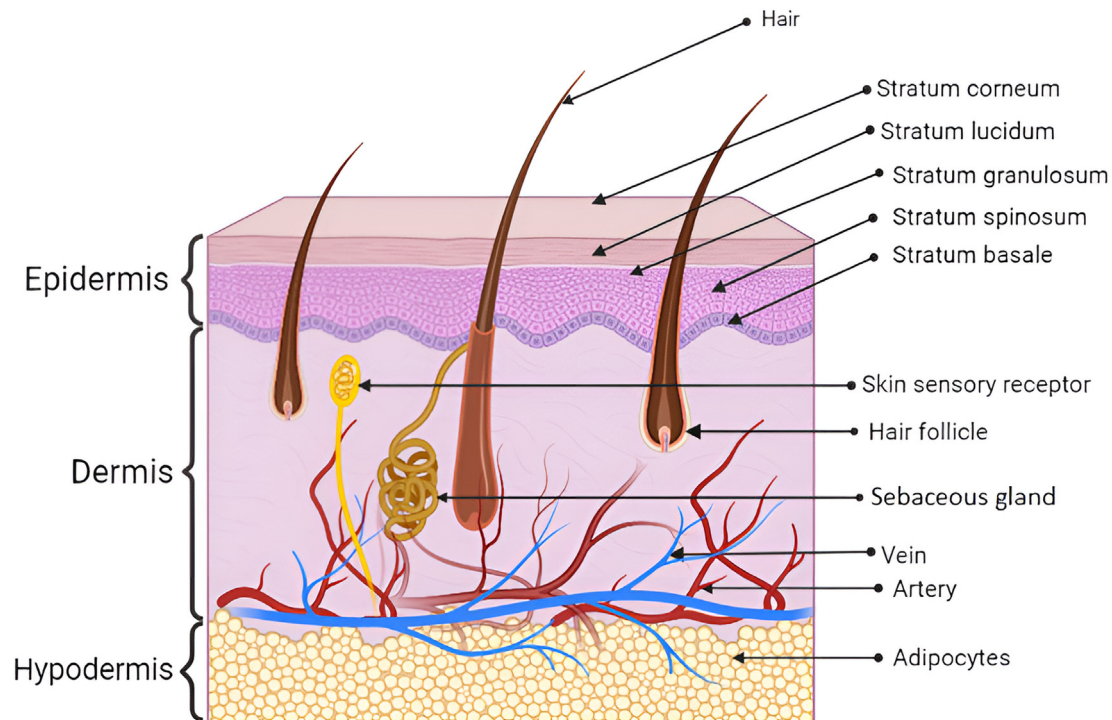


Figure 1. The skin has three layers: the epidermis, dermis, and hypodermis. The epidermal layer is further divided into five sub-layers. The dermis and hypodermis layer contain blood vessels.

and reticular connective tissue layers of the dermis, linked to the epidermis at the basement membrane level, mix without a distinct boundary.^{13,14,19} The hypodermis, commonly called the subcutaneous layer, is the deepest and innermost layer of the skin. Along with various skin appendages, such as hair follicles, blood arteries, and sensory neurons, this layer also contains adipose lobules. The hypodermis contains an enormous capillary network of the circulatory system.^{13,19}

Skin and skin cancer

BCC develops from the basal cells of the epidermis layer, has follicular structures, and is locally destructive but rarely metastasizes. In contrast, SCC arises from keratinocytes of the epidermis but is not as destructive as BCC.^{11,23} Malignant melanoma arises from melanocytic cells of the epidermis layer, is an aggressive form of skin cancer, and has a higher rate of metastasis as it tends to enter the lymphatic system and bloodstream [Figure 2].^{24,25}

Skin cancer prevalence

Table 1 presents the incidence rate of skin cancer at age-standardized rates (ASRs) across different continents in 2022. Australia had the highest incidence rate in 2022.²⁶

According to the World Cancer Report, New Zealand had the highest ASR rate for skin cancer deaths in 2022. Norway had the second-highest mortality rate. Table 2 presents the mortality rates of skin cancer across different continents in 2022.²⁶

Melanoma skin cancer

According to the Global Cancer Observatory (GLOBOCAN) report, MSC is the 17th most common cancer, with 324,635 new cases, and the 23rd leading cause of death among all cancers, resulting in 57,043 deaths in 2020. MSC has the highest incidence in Europe (46.4%) and North America (32.4%). MSC has the highest mortality in Europe (46.2%), followed by Asia (21%), with a 47.3% prevalence in Europe,

33.7% in North America, and 6.2% in Asia in the last 5 years. The worldwide ASR of incidence and mortality in males is 3.8 and 0.7 per 100,000, respectively, which is greater than the incidence (3.0 per 100,000) and mortality (0.4 per 100,000) in females. The worldwide ASR of incidence and mortality is 3.4 and 0.56 per 100,000 individuals, respectively.²⁷ If this prevalence continues, the incidence of melanoma is estimated to rise to 510,000 new cases and 96,000 deaths by 2040.²⁸

The main sign of MSC is often a mole, with changing characteristics including asymmetry (the two halves of the mole are not identical), irregular borders (ragged, notches, uneven, blurred), color variations (black or brown, red, pink, or white), diameter (>6 mm), elevated surface, and other signs such as itchiness and bleeding [Figure 3].²⁹

Melanoma skin cancer across different continents

North America

MSC is the fifth most prevalent cancer in the USA, with 106,000 new cases estimated in 2021, representing 5.6% of all cancer diagnoses. Its incidence grew by >320% from 7.9 per 100,000 in 1975 to 25.3 per 100,000 in 2018.³⁰ According to the American Cancer Society, approximately 97,610 new cases of MSC were diagnosed nationwide in 2023 (58,120 males and 39,490 females), with approximately 7990 deaths from the disease (about 5420 men and 2570 women).³¹ In Canada, melanoma is the seventh most prevalent malignancy in both men and women; comparatively, 2400 new cases and 500 deaths from MSC occurred in 1989, whereas 5800 new cases and 970 deaths were detected in 2011 and 7200 new cases were reported in 2017.^{32,33} The Canadian Cancer Society estimates that approximately 9000 Canadians were diagnosed with MSC in 2022, and approximately 1200 passed away from it.³⁴

South America

MSC incidence rates in Latin American nations such as Argentina, Peru, Chile, Brazil, and Ecuador are <3 per 100,000 individuals, which is

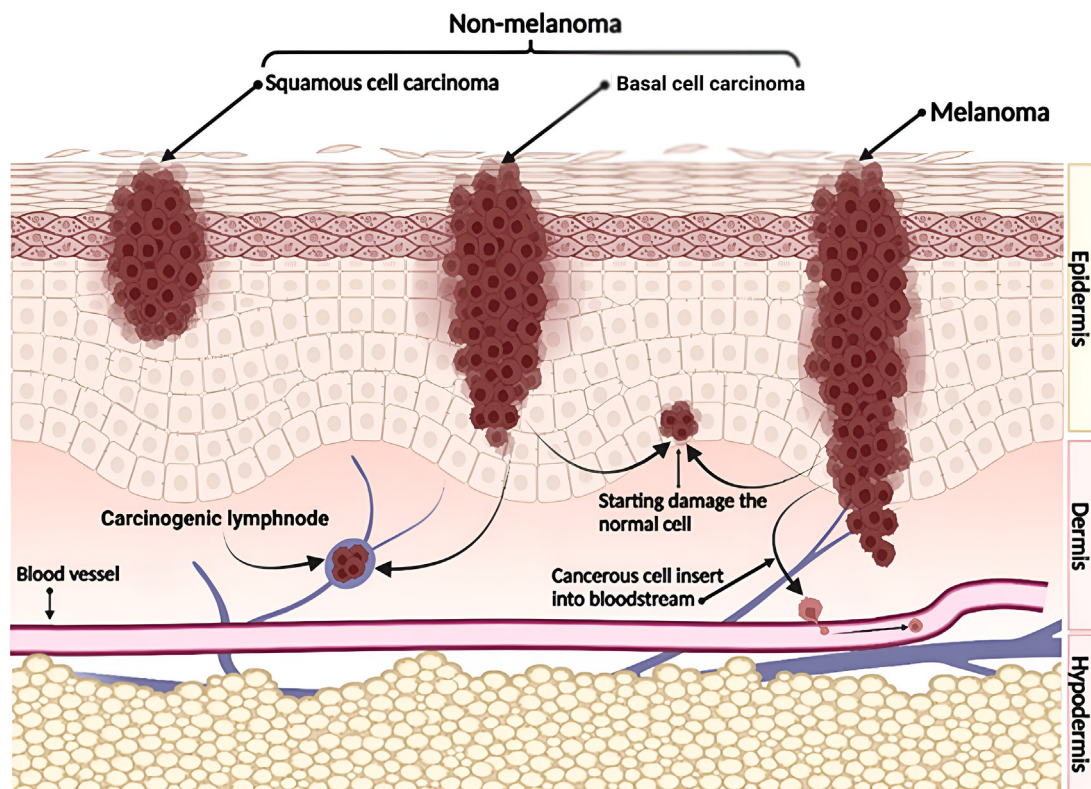


Figure 2. The major types of skin cancer are melanoma skin cancer and non-melanoma skin cancer. Non-melanoma skin cancer includes basal cell carcinoma and squamous cell carcinoma. These types affect different skin cells in different skin layers and demonstrate how cancerous cells infiltrate blood vessels, leading to additional malignancy.

Table 1
Skin cancer incidence rate across different continents in 2022.

Continent	Country	ASR/100,000 population
North America	USA	16.5
	Canada	14.5
South America	Brazil	3.3
Oceania	Australia	37.0
Europe	Germany	12.1
	Italy	12.7
Asia	China	0.37

ASR: Age-standardized rate.

Table 2
Skin cancer mortality rate across different continents in 2022.

Continent	Country	ASR/100,000 population
North America	USA	1.0
South America	Brazil	0.73
Europe	Germany	1.4
	United Kingdom	1.5
	Italy	1.5
	Poland	1.9
Asia	China	0.20
	India	0.16

ASR: Age-standardized rate.

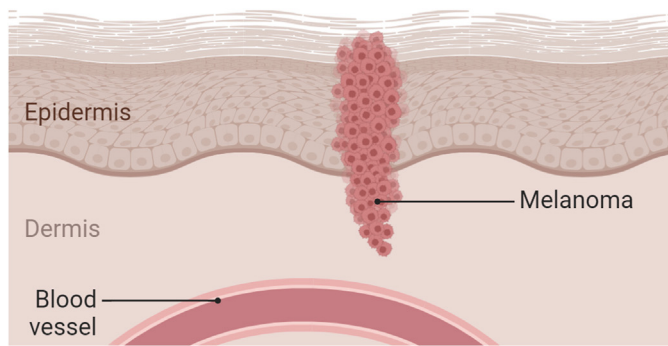
low compared with rates of 19.4–41.8 per 100,000 people in North America, Europe, and Oceania.^{35,36} In Argentina, an estimated 3.8 cases per 100,000 people were reported in 2018, which included 1703 males and females.³⁶ According to a report from the Brazilian National Cancer Institute, 4.03 new cases of melanoma for males and 3.94 new cases for females in Brazil in 2020.³⁷ GLOBOCAN 2020 reported 2051 new cases of melanoma in Mexico.

Europe

In Europe, the incidence of MSC is 10–25 new cases per 100,000 inhabitants, making it the sixth most frequently diagnosed cancer in the continent. Overall, 150,627 people were diagnosed with MSC and 26,360 died from MSC in 2020.^{38,39} In the same year, MSC was the fifth most prevalent malignancy and one of the top 15 causes of cancer deaths in 27 Member States of the European Union (EU-27), accounting for 4% of all new cancer cases and 1.3% of all cancer deaths among the EU-27.⁴⁰ The Netherlands ranks second in terms of incidence rate (27 per 100,000 person-years) and seventh in terms of mortality rate (2.3 per 100,000 person-years).³⁸ In Denmark from 1943 to 2016, MSC ASR increased from 1.1 to 46.5 in men and 1.0 to 48.5 in women, and is predicted to increase to 60.0 and 73.1, respectively by 2036. The MSC mortality rate for men in Denmark increased from 1.4 to 6.7, and that for women increased from 1.2 to 3.7 between 1951 and 2016.⁴¹ In Norway, MSC is currently the fifth and fourth most commonly diagnosed cancer in males and females, respectively, and has experienced the sharpest growth in incidence since 2000, with an annual increase of approximately 3.5%.⁴²

Oceania

New Zealand and Australia have the highest incidence and mortality rates of MSC worldwide, making it the third most prevalent cancer in both males and females in these countries.⁴³ Each year, >15,000 new cases of invasive melanoma are identified, and >1700 people die from melanoma in Australia. The mortality rate increased from 4.7 per 100,000 in 2004 to 5.6 per 100,000 in 2019.⁴⁴ An estimated 17,756 new cases of invasive melanoma (10,374 men, 7382 women) were identified in Australia in 2022.⁴⁵ Melanoma accounts for 10% of all officially reported cancer cases in New Zealand and 80% of skin cancer-related deaths. From 1948 to 2016, the incidence rates in men and women



- Originates from melanocytes
- 17th most common cancer
- 23rd leading cause of death
- UV radiation is a major risk factor
- Four major types

Figure 3. Melanoma skin cancer develops from melanocytes and spreads in the epidermis and dermis. UV: Ultraviolet.

increased from 2.7 to 81.0 and 3.8 to 54.7, respectively. By 2036, both sexes are expected to experience a slight decrease.^{41,46}

Asia and Africa

Most regions of Africa and Asia have the lowest MSC incidence rate, with a mortality rate of <0.5 per 100,000 person-years and an incidence rate under 1 per 100,000 person-years.²⁸ In South Africa, 1777 new cases and 480 deaths owing to melanoma were recorded in 2020, ranking South Africa 22nd globally in terms of mortality rate.⁴⁷

Major types of melanoma

Four main types of MSC exist: (1) SSM (representing 60–70% of melanoma cases), which grows outward of the skin and can develop anywhere on the body; (2) NM (comprising 15–30% of melanoma cases), grow downward into the skin; (3) LMM (accounting for 8% of melanomas), which is typical without melanin and appears red or skin-colored; (4) ALM [Figure 4].^{48,49}

Superficial spreading melanoma

The SSM histologic group includes approximately 70% of melanoma cases, making it the most common among the patient populations. It occurs primarily in populations with fair or lighter skin. SSM may affect any area of the body, although the trunk and proximal extremities are more often affected in young to middle-aged individuals. SSM and long-term intense sun exposure are more commonly related. The lesions have various hues (brown, pink, black, or other colors) and are often larger than other nevi in the patient. They are also commonly asymmetrical, have uneven or ill-defined boundaries, and are typically larger than other nevi. Patients frequently mention a change in color or size. In its initial stages, SSM appears unremarkable. The lesion may initially appear raised; however, it may ulcerate or bleed when cutaneous invasion

intensifies. SSM may also be associated with B-Raf (*BRAF*) mutations.^{50,51}

Nodular melanoma

NM is a dome-shaped, nodular, or pedunculated lesion that can appear anywhere on the body and makes up 15–30% of all melanomas but is responsible for approximately 40% of melanoma deaths. Although NM is occasionally amelanotic, its color is typically dark brown or red-dish brown. No horizontal growth phase is visible, and the NMs frequently and rapidly invade the dermis from the onset. Owing to their potential resemblance to blood blisters, hemangiomas, cutaneous nevi, or polyps, these tumors are commonly misdiagnosed.⁵²

Lentigo maligna melanoma

LMM is a condition with an invasive dermal component and accounts for approximately 4–15% of all melanomas. The hands, neck, and other areas regularly exposed to the sun are most commonly affected by LMM. Owing to the years of sun exposure, older adults are more likely to develop this subtype. Clinically, the lesion appears as a poorly specified, brown-to-black multicolored macule. Changes in size or color are often observed in these patients. Additionally, lesions in the early stages are flat; however, as they progress, they may develop a perceptible component.⁵³

Acral lentiginous melanoma

ALM, which accounts for only 2–3% of MSC, is the most frequent subtype in individuals who are black or have darker skin. It accounts for 58% of all melanomas in Asians but is the least common in Caucasians (1–7%). In the most severe stages, ALM appears as a palpable pigmented macule on the palms, soles, and nail units that can change color. However, UV irradiation does not induce ALM formation. The prognosis is poor because ALM is

Major types of melanoma

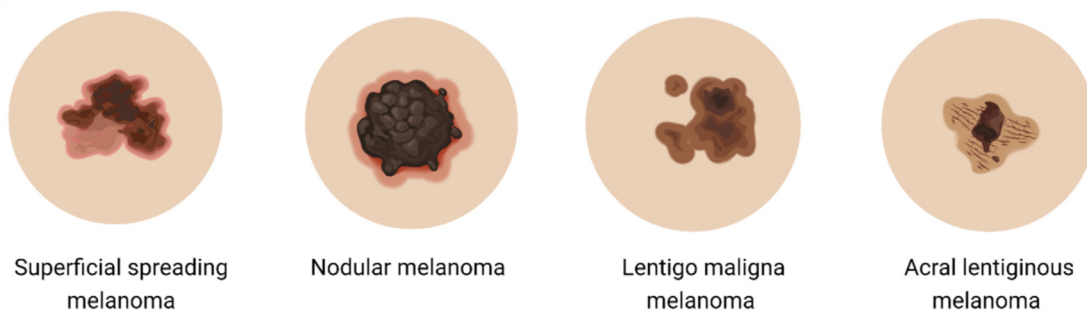


Figure 4. The four major forms of melanoma skin cancer are superficial spreading melanoma, nodular melanoma, lentigo melanoma, and acral lentiginous melanoma.

typically identified later in the course of the disease. Similar to LMM, KIT proto-oncogene (*KIT*) mutations also occur in ALM.⁵⁴

Other rare types of melanoma

Desmoplastic melanoma

About 0.4–4% of all melanoma cases are desmoplastic melanoma (DM). It is strongly associated with sun exposure. Clinically, DM presents as bland-appearing, hard papules, nodules, or plaques that are readily confused with fibromas, scars, or cysts. It has no distinctive color characteristics. DM may occur anywhere in the body, although it often affects the head and neck of elderly individuals. As DM lacks distinctive clinical signs, it is frequently found at higher levels of cutaneous invasion. Moreover, DM is associated with a greater risk of local recurrence after extensive excision.^{55,56}

Mucosal melanoma

MM is an aggressive form of melanomas that mostly appears in the head and neck region and accounts for approximately 1% of all malignant melanomas in the USA.⁵⁷ In areas where melanomas are less common, it represents a greater percentage of instances. For example, >20% of melanoma incidences in Asia are MM, accounting for 30–40% of melanoma incidences in China and approximately 10% of instances in African Americans.^{58,59} Similar to cutaneous melanoma, no recent increase in its incidence has been reported. Moreover, the unfavorable clinical behavior of MM has been linked to its late detection, which may be owing to the tumors' frequently hidden anatomic placements or the extensive network of blood and lymphatic vessels surrounding their mucosal sites. The discovery that mucosal melanoma (MM)s differ genetically or through mutations may explain some variations in biological activity and offer new treatment alternatives.⁶⁰

Uveal melanoma

Uveal melanoma (UM), with annual incidence rates of 0.9 per million for Hispanics, 6.3 per million for whites, and 0.24 per million for blacks, is the most widespread primary intraocular cancer in humans.⁶¹ It is caused by the stromal melanocytes. UM appears in approximately 90%, 7%, and 3% of cases in the choroid, ciliary body, and iris, respectively.⁶² The size and location of the lesion influence the clinical presentation. Ultrasound may aid the clinical diagnosis because it can detect further ocular extension and characteristics specific to UM.⁶³ Additionally, men are more prone to exhibit symptoms than women, and when identified, men also have larger tumors.^{64,65}

Nevoid melanoma

The prevalence of nevoid melanoma is estimated to be between <1% and up to 3% in all melanoma cases.⁶⁶ Nevoid melanoma describes any melanoma resembling or mimicking a melanocytic nevus. Four groups can be derived for nevoid melanoma: (1) those that resemble a primarily cutaneous nevus and are elevated, dome-shaped, or polypoid (nodular non-verrucous); (2) those with a papillomatous or verrucous surface; (3) those that resemble lentiginous melanocytic nevi that develop on the sun-exposed skin of older adults; and (4) those with an intraepidermal nested appearance that resembles a junctional or complicated nevus. As the term “minimal deviation melanoma” was first coined, melanomas have been speculated to resemble melanocytic nevi.^{67,68}

Congenital melanoma nevi

Pigmented birthmarks, known as congenital melanoma nevi (CMN), are commonly termed “moles” when they first appear at birth or during

the first several weeks of life.⁶⁹ Most CMNs in newborns are categorized as tiny (<1.5 cm) or medium (1.5–19.9 cm) according to projected adult size (PAS). Estimates reveal that 1% of neonates have CMNs.⁷⁰ With an estimated frequency of one in every 20,000–500,000 neonates, large CMN (PAS >20 and 40 cm, respectively) are less common.⁶⁹ Although sporadic CMN instances account for most cases, various risk factors have been identified. Moreover, giant CMN is more common in patients with neurofibromatosis type 1 than in the general population, and this risk may be increased by a family history of the disease.^{71–73} Additionally, research on 276 children with 330 CMNs revealed that 43% of children with CMN have a positive family history of the disorder, and children with multiple CMNs are significantly more likely to have a positive family history.^{73,74}

Blue nevi melanoma

An extremely unusual type of melanoma, called a malignant blue nevus, develops from or is associated with pre-existing blue nevus. Without epidermal involvement, it is distinguished by a dense proliferation of spindle cells of various colors. Approximately 80 cases of malignant blue nevi have been reported to date.⁶⁷

Spitz melanoma

The presence of specific Spitz nevi, Spitz melanomas (SMs), and atypical Spitz tumors is a histopathological hallmark of these diverse melanocytic cancers. SMs are more common in individuals aged >20 years; however, children and teens (10–20 years) are more prone to acquiring Spitz tumors.⁷⁵ Spitz cancer generally manifests on the face and extremities. Other lesion locations should be properly assessed for differential diagnosis. A distinctive feature of SMs is their characteristic local lymph node spread. However, distant metastases are seldom observed.^{76,77} According to the 2018 World Health Organization (WHO) classification, SMs are characterized by the presence of certain genetic markers, such as *HRAS* fusions, or mutations in activating genes such as neurotrophic receptor tyrosine kinase 1 (*NTRK1*), neurotrophic receptor tyrosine kinase 3 (*NTRK3*), *BRAF*, proto-oncogene 1 (*ROS1*), mitogen-activated protein kinase kinase 8 (*MAP3K8*), and anaplastic lymphoma kinase (*ALK*).^{78–80} This genetic profile distinguishes SM from other malignant spitzoid tumors. Furthermore, only 36% of 25 spitzoid melanomas analyzed by Raghavan et al.⁸¹ were genetically identified as SM. These findings support the concept that genetic profiling is necessary for precise diagnosis of this subtype.⁸²

Stages of melanoma skin cancer

Melanoma skin cancer develops in five stages [Figure 5]. In stage 0, melanoma development begins and is localized in the epidermal region. In stages 1 and 2, it remains localized, but the thickness increases with each stage. In stage 3, melanoma spreads to the lymph node, and metastasis occurs in stage 4.^{83–85}

Non-melanoma skin cancers

NMSCs, which develop from skin cells other than melanocytes, include BCC and SCC. They are produced in epidermal keratinocytes and are the most common human malignancies, with a continuously rising incidence.^{7,8} Approximately 70% and 25% of NMSCs are BCC and SCC, respectively.⁸⁶ They are more common in people with fair skin who have had long-term exposure to the sun and affect >3 million Americans yearly. The incidence of NMSCs is 18–20 times more than that of MSCs.⁸⁷ According to the GLOBOCAN report, NMSCs were the fifth most common cancer with 1,198,073 new cases (excluding BCC), and the 22nd leading cause of death in all cancers with 63,731 deaths (including BCC) in 2020, with the highest incidence in North America (49%) and the highest mortality in Asia (43.6%).²⁷ Another study published in 2021 revealed

Stages of melanoma

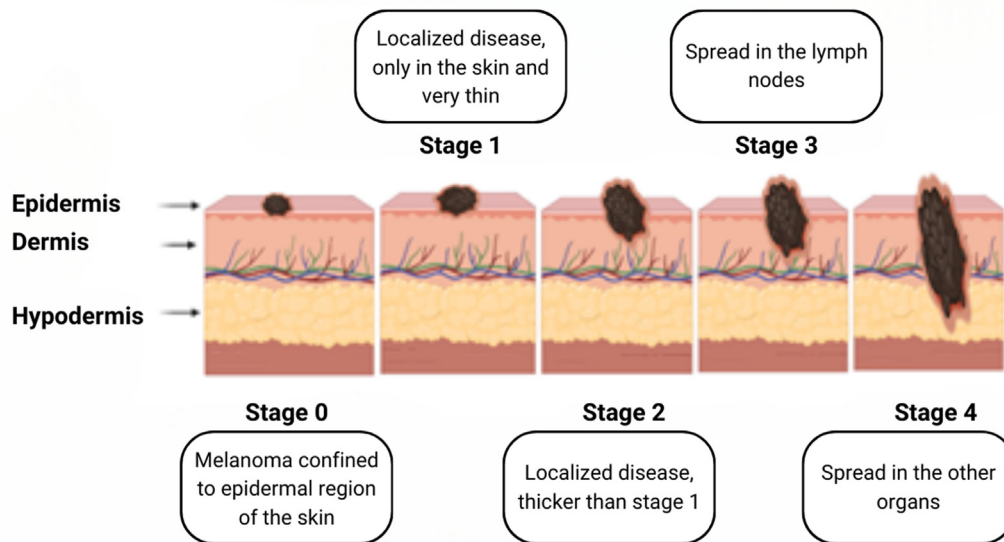


Figure 5. Melanoma has five stages. These are stage 0, stage 1, stage 2, stage 3, and stage 4.

that the prevalence rate of BCC was 525 per 100,000 persons, and that of SCC was 262 per 100,000 persons in the USA.⁸⁸ Although BCC is more prevalent, accounting for 80–90% of skin cancers, it has a lower mortality rate than SCC.⁸⁹ Two patients per 14,000,000 die from locally advanced BCC. In contrast, SCC accounts for 75% of the mortality rate owing to NMSCs.⁹⁰ According to the Global Burden of Disease Cancer Collaboration 2017 data, there were 7.7 million incident cases of NMSCs globally, responsible for 65,000 deaths.⁹¹ Some rare forms of NMSCs include MCC, Kaposi sarcoma, primary cutaneous B-cell lymphoma, carcinosarcoma, and dermatofibrosarcoma.¹¹ NMSCs pose a threat to healthcare worldwide owing to their increasing prevalence. Although curable, lack of knowledge makes it challenging to take preventive measures during the initial phase of the disease.⁹²

Non-melanoma skin cancers across different continents

North America

The estimated annual incidence of NMSCs in the USA is 5.4 million.⁹³ BCC accounts for approximately 80% of all skin cancer cases in the USA, and its incidence is increasing by 4–8% annually.^{94,95} In the USA, an estimated 4.3 million new cases of BCC are diagnosed annually.⁸⁹ The second most commonly diagnosed skin cancer in the USA is SCC, with approximately 1.8 million new cases per year.⁹³ The SCC incidence rate plateaued from 2013 to 2015 and was highest in the 70–79 age group. The incidence was double in men than in women.⁹⁶

Europe

In Europe, the BCC incidence rate is 129.3 in males and 90.8 in females per 100,000 persons per year, with an increasing incidence rate of 5.5% per year.⁹⁷ About 700,00 new cases of BCC are diagnosed annually in Europe.⁹⁸ BCC incidence increases with age in Northern European countries.⁹⁹ In Germany, approximately 76,474 individuals were newly diagnosed with SCC between 2007 and 2015, and the incidence rate was twice as high in males than in females. The incidence increases exponentially with age. Additionally, the annual mortality rate exhibits an increasing trend. The estimated annual percentage change (EAPC) was 7.9% in men and 9.8% in women between 2007 and 2012.⁹⁶ A 13-year study conducted in Germany using data from 11 cancer registries revealed an annual increase in BCC and SCC of 3.3%–11.6%.¹⁰⁰ Moreover, an incidence of

>200 cases per 100,000 inhabitants was reported in Germany in 2020.⁹⁷ In Sweden, the BCC incidence rate increased from 308 per 100,000 individuals in 2004 to 405 per 100,000 individuals in 2017.⁹⁹

Oceania

Australia and New Zealand have the highest incidence rates of BCC, with >1000 per 100,000 individuals per year, followed by the USA and Europe.^{101,102} Recent data have revealed that SCC incidence is 341 per 100,000 men and 209 per 100,000 women. The mortality rates of skin cancer (excluding melanoma) were 2.8 per 100,000 in males and 1.1 per 100,000 in females in 2016.¹⁰³

Basal cell carcinoma

BCC arises from nonkeratinizing cells that develop in the basal cell layer of the skin.¹⁰⁴ It is a less aggressive type of NMSC characterized by cells similar to epidermal basal cells.⁹⁰ White-skinned individuals have an average lifetime risk of developing BCC of approximately 30%.¹⁰⁵ It appears as a small, bumpy or flat, pale or pink patch on the skin [Figure 6]. Constitutive activation of the patched/hedgehog intracellular pathway leads to BCC development. Moreover, Fitzpatrick skin types I and II are more prone to BCC. It is also common in people with light eye color, freckles, and red or blonde hair.⁹⁴ Furthermore, patients with human immunodeficiency virus (HIV) and those who have undergone organ transplants are 5–10 times at greater risk of BCC.¹⁰⁶ Multiple BCC are a sign of basal cell nevus syndrome (BCNS). Subtypes of BCC include superficial, nodular, pigmented (lower subtypes), morpheaform, infiltrative, basosquamous, and micronodular (higher subtypes).¹⁰⁷

Lower-risk histologic subtypes of basal cell carcinoma

Nodular

Seventy-five percent of BCC cases are nodular, making it the most prevalent form of the disease. The tumors appear as well-defined, pearly, clear papules or nodules with rolling edges and telangiectasia. Dermoscopy reveals enormous blue-gray ovoid nests, numerous blue-gray spots, and arborizing arteries. It is a flesh-colored or pink, pearl-like bump that can grow and may contain blood vessels on its surface.¹⁰⁸

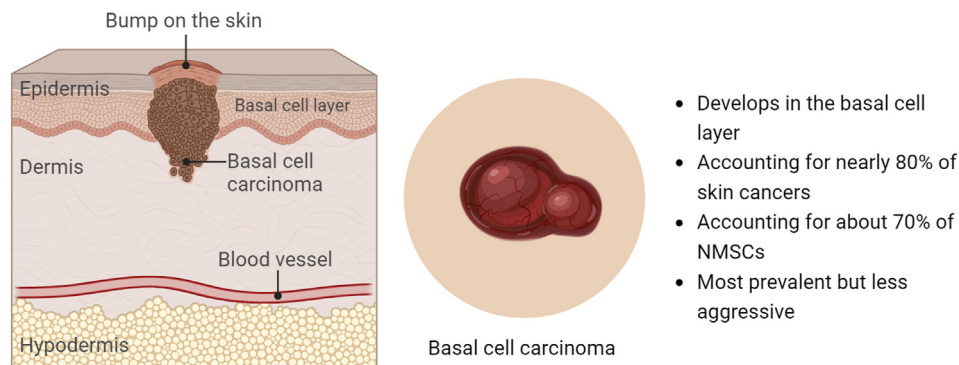


Figure 6. Basal cell carcinoma develops from the basal cell layer of the epidermis of the skin and appears as a small bump on the skin. NMSCs: Non-melanoma skin cancers.

Superficial

It is an indolent variant that resembles a red, scaly patch similar to eczema or psoriasis and usually grows slowly.¹⁰⁹

Pigmented basal cell carcinoma

It is a subtype of nodular BCC that occurs more frequently in individuals with Fitzpatrick skin types III–VI. It appears as a darkly pigmented patch or bump on the skin.¹¹⁰

Higher-risk histologic subtypes of basal cell carcinoma

Micro-nodular

Nodular BCC is formed by aggregated nodules, whereas micronodular BCCs are composed of distributed micronodules. They are small clusters (<1 mm) or nodules of tumor cells within the skin and tend to be more invasive and aggressive than other subtypes.¹¹¹

Morpheaform

This type of BCC accounts for approximately 6% of all BCCs and has a high recurrence rate and perineural invasion. On the head and neck, tumors appear as sunken, waxy, scar-like plaques often accompanied by ulcerations.¹¹²

Infiltrative

It has higher recurrence rates and perineural invasion and spreads to the surrounding skin, making removing it challenging.¹¹³

Fibro-epithelial

They contain both epithelial and mesenchymal components. It has a spindle-like appearance within the tumor stroma.⁸

Other less common subtypes of basal cell carcinoma

Cystic basal cell carcinoma

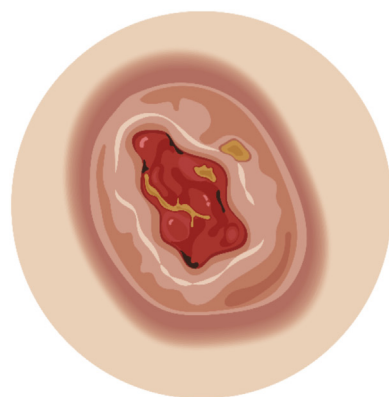
It is a slow-growing tumor with a cystic lesion and a central pore or punctum. Accumulation of fluid within the tumor leads to the formation of a cystic cavity.¹¹⁴

Baso-squamous basal cell carcinoma

It exhibits features of both BCC and SCC. It accounts for 1% of all BCC cases. It appears as a raised, firm, skin-colored, or reddish nodule with ulceration or crusting.¹¹⁵

Squamous cell carcinoma

SCC is the second most prevalent type of NMSC. It emerges from epidermal keratinocytes or adnexal compositions (such as pilosebaceous units or eccrine glands) [Figure 7].¹¹⁶ SCC is more common in light-skinned populations, whereas UV-induced SCC is less common in individuals with darker skin tones.¹⁰ A meta-analysis and review of 45 studies concluded that 13.3% of patients develop a second SCC after receiving a primary diagnosis.¹¹⁷ Unlike BCC, which is associated with intermittent exposure, SCC is associated with long-term exposure to UV radiation. SCC accounts for approximately 16% of all skin cancers. The American Cancer Society classifies SCC based on the location of its appearance: very often found in the skin, lung, cervix, head and neck, and esophagus, and rarely found in the thyroid, pancreas, prostate, and bladder. Conclusively, head and neck carcinomas account for approximately 55% of all cutaneous SCC, with the extensor surfaces of the hands and forearms accounting for 18%. Other common locations include the legs (13%), back and shoulders (4%), upper extremities (3%), and other



Squamous cell carcinoma

- Develops from epidermal keratinocytes
- Accounting for about 25% of NMSCs
- Accounting for nearly 16% of skin cancers
- Accounting for about 75% mortality of NMSCs
- UV radiation is a major risk factor

Figure 7. Squamous cell carcinoma originates from epidermal keratinocytes or squamous cells of the top layer of the skin, which appears as a smooth, firm, or hyperkeratotic plaque or papule, usually with central ulceration.¹¹⁶ NMSCs: Non-melanoma skin cancers; UV: Ultraviolet.

regions (7%).¹⁰ Hence, head and neck SCC is the sixth most prevalent type of cancer worldwide. In 2018, 890,000 new patients and 450,000 deaths were reported worldwide. It is expected to increase by 30% by 2030.^{102,118}

Some rare forms of non-melanoma skin cancers

Merkel cell carcinoma

This is a rare and aggressive type of NMSC with neuroendocrine features. Merkel cell polyomavirus (MCPyV) accounts for approximately 80% of all MCC cases. MCPyV is a typical double-stranded DNA genome common among mammalian polyomaviruses. Although rare, it is associated with a high mortality rate of 45%.¹¹⁹ The worldwide occurrence of MCC spans from 0.1 to 1.6 cases per 100,000 people annually, with the highest incidence in Australia. In the USA, between 2000 and 2013, the incidence of MCC increased by 95%, exceeding that of MSC.¹²⁰ The pathogenesis of MCC is associated with the presence of MCPyV or long-term UV exposure, which can cause a characteristic pattern of multiple DNA mutations. In both non-viral and viral-mediated carcinogenesis, UV exposure likely contributes to DNA damage and immunosuppression. However, the origin of MCC cells remains unclear. Clinical features of MCC include a fast-growing painless plaque or nodule.¹²⁰

Kaposi's sarcoma

It is a type of angioproliferative neoplasm, first discovered by Moritz Kaposi in the late 1800s. It is the most frequently occurring malignancy in people with HIV. It is mostly prevalent in the sub-Saharan region of Africa and is more prevalent in men than women.¹²¹ Any immunocompromised individual affected by the KS-associated herpes virus (KSHV) or human herpes 8 virus is at risk of KS. It is diagnosed when a viral protein known as the latency-associated nuclear antigen (LANA) is detected in a biopsy.¹²² KS lesions exhibit red-blue, purple, or brown-black macules, nodules, and papules that are susceptible to bleeding and ulceration. It is classified into four types based on prognosis and epidemiology: classic, endemic, iatrogenic, and epidemic.¹²³

Cutaneous T-cell lymphomas

Cutaneous T-cell lymphomas (CTCLs) are a set of heterogeneous extranodal non-Hodgkin lymphomas present on the skin without extracutaneous disease at diagnosis. The pathophysiology of this disease is not yet understood owing to its complexity.¹²⁴ However, the annual incidence is approximately 0.5 per 10,000, with a median age of 50–60 years. The most important subtypes of CTCLs include Sezary syndrome, mycosis fungoides (MFs), and primary CTCL.¹²⁵ MFs is the most common type of CTCL, accounting for 44–62% of cases.¹²⁶ The pathological features of CTCLs are characterized by epidermotropism, haloed lymphocytes, exocytosis, large hyper-convolutions, Pautrier's microabscesses, hyperchromatic lymphomas in the epidermis, and lymphocytes aligned within basal cells.¹²⁵

Soft tissue sarcoma

Primary STS is an unusual musculoskeletal tumor and a heterogeneous group of malignancies.¹²⁷ It originates from the mesenchyme of the embryo, which develops into connective tissues and has an average prevalence of 5 per 100,000 annually. STS accounts for <1% of all cancers, with an estimated 12,000 new cases recorded yearly in the USA and roughly 5000 deaths.¹²⁸ The exact cause of this disease is unknown. According to the WHO, 100 different histological subtypes of STS have been identified. Common histological subtypes include liposarcoma (LPS), leiomyosarcoma (LMS), angiosarcoma, rhabdomyosarcoma (RMS), synovial sarcoma (SS), and Ewing sarcoma (ES).¹²⁹

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP) arises from connective tissue cells in the skin. It is a dermal neoplasm that grows steadily and has a high incidence of local infiltration and recurrence but little chance of

metastasis. It usually appears as firm, flesh-colored, raised patches or bumps on the skin that grows slowly over time.¹³⁰

Sebaceous carcinoma

SC accounts for 0.2–4.6% of all malignant cutaneous neoplasms. The approximate prevalence rate of SC is 1–2 per 1 million persons per year, making it the third most prevalent eyelid cancer after BCC and SCC. It affects the sebaceous glands (oil-producing glands) in the skin. It appears as a painless yellowish lump on the skin.¹³¹

Atypical fibroxanthoma

Atypical fibroxanthoma (AFX) is a rare mesenchymal tumor that primarily affects the head and neck in elderly individuals. Clinically, the tumor is characterized by an exophytic development, which grows quickly and frequently results in epidermal ulcers. AFX appears as a firm, dome-shaped, flat, and reddish lesion with a scaly or crusty surface.¹³²

Cutaneous lymphomas

Primary cutaneous lymphomas (CLs) are extranodal non-Hodgkin lymphomas. Its annual incidence is approximately 1 per 100,000 and affects the lymphatic, skin, and blood systems. It originates from immune cells. There are two types of lymphomas: T-cell- and B-cell.¹³³

Ongoing therapeutic experimental studies

Numerous experimental therapeutic trials are being conducted to treat different types of skin cancer. These studies include immunotherapy, targeted treatment, and nonsurgical approaches.

Researchers are investigating the use of immunotherapeutic medications such as nivolumab, pembrolizumab, and ipilimumab as adjuvants after surgery to inhibit MSC recurrence. These medications are used in conjunction with other therapies. Research is also being conducted on mitogen-activated protein kinase (MEK) inhibitors and the proto-oncogene *BRAF* as potential targeted therapeutics for MSC.^{134,135}

Researchers are examining the efficacy of cryotherapy in combination with other approaches for managing BCC and SCC, as well as the use of non-ablative fractional laser therapy to reduce the probability of developing facial keratinocyte carcinoma in the future.¹³⁶ Furthermore, studies are being conducted to determine whether hedgehog pathway inhibitors, such as vismodegib and sonidegib, effectively treat advanced BCC.¹³⁷

Limitations and gaps in knowledge

Different continents and countries employ different methods to determine skin cancer prevalence. Other factors (aside from fair skin) that contribute to the prevalence of skin cancer have rarely been studied. Consequently, variations in skin cancer prevalence across continents are challenging to understand. Additionally, information is limited regarding the incidence of many rare and dangerous types of skin cancers, such as UM, DFSP, and MCC, in different regions worldwide.

Conclusion and perspective

In this study, we discussed the current global epidemiological conditions of skin cancers based on their types. Skin cancers remain aggressive forms of cancer, with a continuous increase in their incidence. They are more common in light-skinned individuals; thus, most incidences are recorded across continents such as North America, Oceania, and Europe, where most of the population is fair-skinned. Australia and New Zealand have the highest incidence rates of skin cancer. Asia has a lower incidence rate of skin cancers; however, it has the highest death rate for NMSCs and the second-highest death rate for MSCs.

BCC is the most prevalent form of skin cancer, followed by MSC and SCC. SCC is the deadliest form of NMSC. Combined, BCC and SCC cause higher mortality rates than MSC globally. SSM is the most common form of MSC, accounting for 70% of the cases. Head and neck SCC is the most

commonly diagnosed form of SCC. Furthermore, MCC is a rare form of NMSC with a high mortality rate, and Australia has the highest incidence rate of MCC. Most skin cancers have a high occurrence across continents with a majority of fair-skinned populations and higher levels of UV exposure, such as Australia and New Zealand, whereas the mortality levels are high on continents with a minority of fair-skinned populations. A lack of public awareness regarding skin cancer prevention and early detection may be responsible for the higher deaths in regions such as Asia.

We suggest focusing future research on skin cancer epidemiology on the following areas, accounting for the information gaps that have been identified to facilitate comparisons across studies and populations (1) establish standardized reporting guidelines for skin cancer prevalence and incidence rates; (2) conduct additional research on the prevalence and risk factors of uncommon forms of skin cancer, such as UM, DFSP, and MCC; (3) examine the efficacy of various early detection and prevention strategies, such as public education campaigns and skin cancer screening programs, in lowering the incidence of skin cancer in various populations and increasing the recovery rate; (4) investigate the potential of new technologies, such as telemedicine and artificial intelligence, in improving the diagnosis and management of skin cancer, especially in settings with limited resources; and (5) conduct clinical investigation and maintain country-wise epidemiological records to design a skin cancers management system in Asia to reduce deaths on this continent.

Funding

None.

Authors contribution

Amdad Hossain Roky: conceptualization, writing the original draft, data extraction, data analysis and editing; Mohammed Murshedul Islam: writing the original draft and data extraction; Abu Mohammed Fuad Ahasan: writing the original draft and data extraction; Md. Saqline Mostaq: writing the original draft; Md. Zihad Mahmud: writing the original draft; Mohammad Nurul Amin: project administration; Md. Ashiq Mahmud: conceptualization, supervision and manuscript revision. All authors read and approved the final manuscript.

Ethics statement

None.

Data availability statement

The datasets used in this study can be obtained from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that generative artificial intelligence (AI) and AI assisted technologies were not used in the writing process or any other process during the preparation of this manuscript.

Acknowledgments

The authors thank Emtiajul Hoque from the Department of Pharmacy, International Islamic University Chittagong, Chittagong, for his valuable contribution to this research.

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