Chapter

# Melanoma Epidemiology: Symptoms, Causes, and Preventions

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## Abstract

Melanoma arises from melanocyte cells. Melanoma spreads faster than basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) if not diagnosed and treated early. Melanocyte tumors cause malignant melanoma. The preponderance of these cells is in the skin, gut, and eye. Melanoma is a rare kind of skin cancer, although it causes 75% of skin cancer deaths. Melanocytes create melanin, a dark pigment, in the skin. Despite years of lab and clinical research, early surgical removal of tiny cancers remains the most successful treatment. The deadliest skin cancer is melanoma. Skin melanocytes are involved. Melanocytes produce skin pigment melanin. Melanin protects skin against ultraviolet (UV) radiation. Skin cancer is the most common form in the United States. When diagnosed early, skin cancer can be treated with topical medications, office therapies, or outpatient surgery. Dermatologists treat skin disorders and conditions. Skin cancer causes less than 1% of cancer fatalities. Detection and treatment of melanoma in its early stages are typically curable. Once melanoma spreads further into the skin or other organs, it becomes incurable and potentially lethal. Early detection of melanoma in the United States is anticipated to result in a 5-year survival rate of roughly 99%.

**Keywords:** Cancer, skin cancer, cancer prevention, Melanoma, BCC, SCC

## 1. Introduction

Melanoma is a form of skin cancer that manifests itself when melanocytes, the cells responsible for giving the skin its brown or tanned appearance, begin to increase uncontrollably.

When cells in the body begin to develop uncontrolled, this is the beginning stage of cancer. Cancer can start in cells in virtually any part of the body, and once it does, it can quickly travel to other body parts [1].

Melanoma is one of the rarest forms of skin cancer, especially compared to other types. Melanoma, on the other hand, poses a greater threat since it has a greater potential to metastasize or spread to other areas of the body if it is not detected and treated in its early stages [2].

When usually healthy cells incur mutations and begin to increase uncontrollably, a mass known as a tumor forms. There are two different sorts of tumors: benign and malignant. Malignant tumors have the ability to metastasize or spread to other parts of the body. The term "benign" means that a tumor can develop but will not spread [3].

More than three million people in the United States are diagnosed with skin cancer each year, making it the most prevalent form of the disease. When detected at an early stage, skin cancer is typically amenable to treatment with topical medicines, treatments performed in the office by a dermatologist, or surgery performed on an outpatient basis. A physician who specializes in treating diseases and ailments that affect the skin is called a dermatologist. Because of this, skin cancer is responsible for fewer than 1% of the total deaths caused by cancer [4, 5].

A dermatologist, a surgical oncologist, a radiation oncologist, and a medical oncologist are typical members of the multidisciplinary teams that are required to address more advanced instances of skin cancer, which can occur under certain circumstances [6]. These physicians will consult with the patient to determine the most effective strategy for treating cancer and present their findings to the patient. When the operation to treat the cancer is too comprehensive to be conducted in an office environment, the surgical oncologist may suggest that the patient undergo surgery instead. This is one of the situations in which an operating room is required. At other times, the team will propose radiation therapy and/or other therapies using medication that is either taken orally or delivered intravenously as an alternative to or in combination with surgery [7].

## 2. Melanoma

Melanoma is a severe kind of skin cancer originating in cells called melanocytes [8]. Despite being less prevalent than basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), melanoma is more deadly due to its tendency to migrate to other organs if not treated early rapidly. Melanoma is a tumor of melanocytes that is malignant [9]. These cells are primarily found in the skin, as well as in the intestine and the eye. Melanoma is one of the less prevalent forms of skin cancer, although it is responsible for most (75%) of skin cancer-related fatalities [10]. Melanocytes are generally present in the skin and are responsible for synthesizing melanin, a dark pigment. Despite many years of extensive laboratory and clinical research, early surgical removal of thin cancers continues to offer the best chance of cure. Melanoma is the most dangerous kind of skin cancer [11]. It begins in the melanocytes of the skin. Melanocytes are the cells responsible for producing melanin, which gives skin its color. Melanin protects the skin's deeper layers from the sun's ultraviolet (UV) radiation [12].

Melanocytes produce two different types of melanin: the black/brown pigment eumelanin and the red/yellow pigment pheomelanin. In contrast to the number of melanocytes, which is largely constant in all skin types, the ratio of eumelanin to pheomelanin in the skin influences skin color. People with darker skin have a lower risk of developing skin cancer, because the darker eumelanin serves as a better UV protection. In addition to providing less protection against UV light, pheomelanin synthesis also creates carcinogens [13].

It has been demonstrated that pheomelanin increases the amount of ultraviolet-A-induced reactive oxidative species (ROS) that cause DNA damage in

response to UV exposure [14]. Melanoma risk has long been associated with skin, hair, and eye coloration: those with light skin that does not tan, blond or red hair, and light eyes have a significantly higher risk of developing the disease than the general population [15].

MC1R is partially responsible for regulating skin, hair, and eyes color. The amount of activity of the MC1R gene is controlled by polymorphisms. Reduced MC1R function caused by MC1R gene variations causes the development of mostly red/yellow pheomelanin pigment, fair skin that does not tan, and light eyes and hair. A fully functional MC1R stimulates eumelanin production. Due to greater exposure of the nuclei to UV radiation, individuals with less functioning MC1R variations accrue more mutations. Skin tumors may develop if mutations gather in the genome's susceptible areas [16].

Only 22.1 out of every 100,000 people in the United States are affected by melanoma, a malignant tumor that develops from melanocytes (cancer statistics from the Center for Disease Control and Prevention). Even though it only accounts for 4% of skin cancer incidences, it is a very fatal illness that causes 75% of skin cancer deaths. There are anticipated to be 96,480 new cases of melanoma detected in 2019 and 7230 fatalities in the United States alone (American Cancer Society). This overview will cover the major methods for diagnosing melanoma, patient prognosis, significant molecular flaws contributing to melanoma progression, and therapy options for melanoma [17].

Melanocytes are skin cells located in the epidermis [18]. They create the pigment melanin, which is responsible for the color of skin. Two types of melanin exist The pigments eumelanin and pheomelanin. Exposure to ultraviolet (UV) radiation from the sun or tanning beds causes skin damage that stimulates melanocytes to make more melanin. However, only the eumelanin pigment aims to protect the skin by darkening or tanning the skin. Melanoma develops when melanocytes incur mutations due to sunburn or tanning-induced DNA damage, leading to uncontrolled cell growth [19].

Early detection and treatment of melanoma is frequently curative. Once melanoma has migrated further into the skin or to other organs, it becomes more difficult to cure and potentially fatal. The expected 5-year survival rate for US patients diagnosed with melanoma early is approximately 99%.

In 2022, an estimated 7650 Americans (5080 males and 2570 women) would succumb of melanoma [20].

When people are exposed to sunshine, their melanocytes produce more melanin, causing their skin to tan. This also occurs while exposing to other ultraviolet radiation (such as in a tanning booth). If the skin is exposed to an excessive amount of ultraviolet radiation, the melanocytes may begin to grow abnormally and develop cancer. This disease is known as melanoma [19].

Approximately 60,000 new cases of invasive melanoma are detected annually in the United States, with males and Caucasians being affected more commonly. It is more prevalent among Caucasian communities living in sunny climates or in individuals who frequent tanning salons than in other ethnicities [21].

According to a WHO estimate, over 48,000 people die annually from melanoma. The treatment consists of tumor excision, adjuvant therapy, chemo- and immunotherapy, or radiation therapy [22].

When people are exposed to sunshine, their melanocytes produce more melanin, causing their skin to tan [19]. This also occurs when other forms of UV radiation are present (such as in a tanning booth). The melanocytes may begin to grow abnormally and develop cancer if the skin is exposed to an excessive amount of UV light. This condition is referred to as melanoma.

Each year, around 60,000 new instances of invasive melanoma are diagnosed in the United States, with males and Caucasians being disproportionately impacted [23]. It is more common among Caucasian cultures living in sunny climes or those who visit tanning salons than among other ethnic groups.

## 3. Diagnosis and prognosis of melanoma

Early melanoma classification was based on the origin of the tumor (existing nevus, acquired melanocytic lesion, and blemish-free skin); however, in the 1960s, a prominent dermatologist, Wallace Clark, proposed that melanoma should be classified based on its histological characteristics, thereby revolutionizing melanoma diagnosis.

To begin, he classified melanoma into three distinct subtypes based on their histological appearance: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and nodular melanoma (NM). Clark was the first to recognize that melanoma is a heterogeneous illness, showing that the variations behave differently and have distinct prognosticates and distinct treatments. Since then, several new variants have been identified, including acral lentiginous melanoma, mucosal melanoma, desmoplastic melanoma, and nevoid melanoma. On the second tier, we have noses and the fact that not all melanomas require the same treatment [24].

Clark also suggested a method for assessing melanoma in 1966 that takes into account the depth to which melanoma cells have penetrated the dermis and subcutaneous fat. Clark identified histologically distinguishable anatomic compartments within the skin; when melanoma cells progressed through each compartment (or "Clark level"), the likelihood of distant dissemination increased.

Melanoma cells are restricted to the epidermis at:

Level 1: Melanoma in situ.
Level 2: Invasion of solitary melanoma cells or extremely tiny nests into the papillary dermis.
Level 3: Melanoma cells "fill and expand" the papillary dermis at the third stage.
Level 4: Invasion of the dermal reticular layer.
Level 5: Invasion into the subcutaneous fat layer.

Some pathologists still include the Clark levels in their melanoma reports because of the information they provide about the risk of disease aggressiveness, but in 1970, Alexander Breslow independently developed a more accurate method for classifying melanoma based on a measured depth of invasion that captured the thickness of the tumor. Breslow's depth classification system was based on the depth of invasion in millimeters rather than the depth by anatomic compartments, which vary in thickness at different anatomic sites.

Breslow initially classified melanoma into five stages:

Stage I: a thickness of less than or equal to 0.75 mm.
0.76–1.5 mm for Stage II.
1.51–2.25 mm in Stage III.
2.26–3.0 mm in Stage IV.
Greater than 3.0 mm in Stage V [25].

## 4. Melanoma detection via noninvasive imaging

Modern scientific advances have enabled the creation of noninvasive imaging methods for the diagnosis of melanoma. The development of mobile apps like SkinVision, UMSkinCheck, and MoleScope has been motivated by a desire to improve patients' access to screenings, lower the financial burden of doing so, and find cancers earlier. Numerous studies, however, have shown that such applications are typically wrong [26]. Three out of four algorithms mistakenly identified as many as 30% of melanomas as low-risk tumors, according to a recent research. The potential for these applications to be a valuable tool in the diagnosis of melanoma would increase significantly if their accuracy could be improved and they were subject to strict regulatory control [27]. Experts warn, however, that patients could be harmed if they put too much faith in these technologies in their current iterations. Until then, consumers should exercise caution when it comes to using these apps for melanoma screening [27].

Some melanomas do not meet the ABCDE rule; thus, you should inform your doctor of any persistent sores, strange bumps or rashes, or changes in your skin or existing moles [28].

The use of immunohistochemistry in the diagnosis of melanoma.

### 4.1 Clinical indicators

For a melanoma diagnosis to be made, a healthcare provider must first identify a lesion as clinically abnormal before doing a biopsy. After a biopsy of a lesion has been taken, further examination at the microscopic level might be conducted. In many cases, melanoma is identified by highly trained pathologists based on a set of well-established histological hallmarks. Histologic subtypes of melanoma can be difficult to distinguish with traditional hematoxylin and eosin (H&E) staining due to the disease's heterogeneity [29]. Also, melanoma has a number of histological imitators, so telling the two apart can be challenging [30]. Immunohistochemistry (IHC) has also been widely employed to interpret difficult cases as knowledge of the molecular mechanisms behind melanogenesis has increased and molecular biomarkers have been developed to aid in melanoma detection [31]. Because of its accessibility in most laboratories, low cost, high reliability, and high reproducibility, immunohistochemistry (IHC) is the most commonly used ancillary test to aid in the diagnosis of melanoma by pathologists. That is why it is not shocking that IHC has been increasingly popular in the last 20 years for the detection of melanoma [31].

Diagnostic and prognostic melanoma biomarkers can be broken down into two categories: melanocytic markers and proliferative markers [32]. An ambiguous lesion can be traced back to its melanocytic origin by testing it for melanocytic markers, which are proteins involved in melanin synthesis, melanosome biogenesis, or melanocyte differentiation. Contrarily, cell cycle activity in a lesion can be assessed with the help of proliferation markers [30]. Counting mitotic figures (mitosis/$mm^2$) is now the gold standard for measuring tumor proliferation; however, new studies have shown that immunohistochemistry (IHC) detection of proliferative markers can be a robust biomarker of proliferative activity with prognostic significance [33].

This is especially true in staging systems, where IHC has become increasingly important. If tumor cells are not apparent on H&E during a sentinel lymph node examination, the seventh edition of the AJCC recommends using

immunohistochemistry (IHC) to improve the detection of micrometastasis [34]. Under the correct conditions, several melanocytic markers provide compelling evidence for melanocytic origin and melanoma. The antibodies melan-A and melanoma-associated resistance to treatment 1 (MART-1) are both responses to the same antigen (melanoma antigen recognized by T-cells) [35]. Detecting melanoma with MelanA/MART-1 is more sensitive than HMB-45, one of the most widely used melanoma biomarkers [36]. Human melanoma black 45 (HMB-45) is an antibody that recognizes gp100, an antigen expressed in melanocytes (also known as Pmel 17) [36, 37]. Melanin polymerization, melanosome biogenesis, and melanogenesis all involve the protein Gp100. The proteins S100, microphthalmia transcription factor (MITF), tyrosinase, and SOX10 are also considered to be typical melanocytic indicators in the diagnosis of melanoma [38]. Some of the most specific markers are melan-A/MART-1 and HMB-45, both of which are expressed only in melanocytic malignancies and a few other, rare kinds of cancer [39, 40]. The melanocytic marker used in the evaluation of a melanocytic lesion is based on the expected outcome. While sensitive indicators like S100 protein and Sox10 can be utilized by pathologists to identify a potentially malignant melanocytic neoplasm, specific markers can be employed to prove beyond a reasonable doubt that the neoplasm in question derives from melanocytes (although some melanocytic tumors may be missed using only these markers). Both high sensitivity and specificity are required of a melanocytic marker.

However, melanocytic markers cannot reliably distinguish between malignant and benign melanocytic growth since they stain all melanocytes [41].

In addition, a false-negative diagnosis may result from the failure to apply more sensitive markers in the case of some types of melanoma (especially desmoplastic melanomas), which lack expression of the most specific melanocytic markers [42].

### 4.2 Causes of melanoma

Most experts agree that overexposure to sunlight, especially when young, is a key risk factor for melanoma. Statistics indicate that 86% of melanomas are caused by the sun's ultraviolet (UV) rays. How does sun exposure lead to skin cancer? UV exposure can damage a cell's DNA, resulting in modifications to specific genes that influence how cells grow and divide. The risk for complications arises when your skin's DNA is broken and its cells begin to proliferate.

The World Health Organization has classified ultraviolet radiation from tanning beds as a carcinogen (a substance that causes cancer). The use of tanning beds may be associated with more than 6000 occurrences of melanoma per year in the United States.

Although anybody can acquire melanoma, those with the following conditions have an increased risk of developing the disease:

*Personal experience with melanoma.*

*A history of melanomas in the family*

*The individual has fair skin, freckles, blonde or red hair, and blue eyes.*

*Sun exposure to the point of blistering sunburns.*

*Living near the equator or at a high altitude may increase your exposure to ultraviolet light.*

*A history of use tanning beds.*

*Numerous moles, particularly unusual moles.*

*A compromised immune system.*

Melanoma is more prevalent among White people; however, all skin types can be affected. Melanoma is typically found on the palms, soles, and nails of those with darker skin [43–45].

### 4.3 Melanoma cancer statistics

Melanoma is the 17th most prevalent form of cancer found all over the world.

Melanoma and non-melanoma skin cancers are the most common forms of the disease, respectively. The most frequent non-melanoma malignancies are basal cell carcinoma and squamous cell carcinoma.

Several factors make it particularly difficult to estimate the incidence of skin cancer [46]. There are numerous subtypes of skin cancer, which might complicate data collection. For instance, non-melanoma skin cancer is frequently not recorded by cancer registries, or registrations of this illness are frequently insufficient due to the fact that the majority of cases are successfully treated with surgery or ablation. It is possible that the estimated global incidence of skin cancer is an underestimate due to these reasons.

Melanoma of the skin is the 17th most prevalent cancer in the world. It is the 13th most prevalent cancer in men and the 15th most prevalent cancer in women.

In 2020, there were more than 150,000 new instances of cutaneous melanoma [47]. Australia had the highest non-melanoma skin cancer incidence rate in 2020, followed by New Zealand [48]. Australia had the highest incidence of cutaneous melanoma in 2020, followed by New Zealand. In 2020, New Zealand had the highest melanoma skin cancer mortality rate, followed by Norway. In 2020, Papua New Guinea had the highest non-melanoma skin cancer mortality rate, followed by Namibia [49].

### 4.4 Melanoma prevention with nutrition

In recent years, there has been a lot of research on dietary factors and/or nutritional aspects that may influence melanoma risk. A vast range of dietary chemicals has been examined. However, just a subset of these will be covered in this review. Many have promised in vitro evidence to back up their potential, and some have been linked to a lower risk of melanoma in epidemiologic studies; nevertheless, data from randomized controlled trials in humans are insufficient. Future research could shed light on the potential involvement of dietary components in melanoma risk reduction.

Vitamin D is a well-studied option for melanoma chemoprevention. Although its primary purpose is to regulate calcium and phosphate balance, vitamin D receptors are found on many cells. It has gained significant interest as a potential preventive or complementary treatment strategy for melanoma and other malignancies [50].

Vitamin E is a class of fat-soluble chemicals that include tocopherols and tocotrienols. Because of its antioxidant effects, it is gaining popularity. Vitamin E has been shown in vitro to inhibit several types of malignant cells, including melanoma cells. Recent research has focused on vitamin E derivatives and their potential anti-melanoma activities [51]. There are numerous fatty acids, including saturated, monounsaturated, polyunsaturated (PFA), and trans-unsaturated fatty acids. Some epidemiologic research suggests that unsaturated fatty acids may reduce the risk of several types of cancer, including melanoma [52]. Nicotinamide, often known as niacinamide, is the vitamin $B_3$ derivative amide form of nicotinic acid. It is a precursor of nicotinamide adenine dinucleotide (NAD+), a cofactor required for energy production, metabolism, and DNA repair. It has recently attracted interest for its potential to counteract UV-induced immunological suppression [53]. Trace amounts of selenium are found in meat, fish, vegetables, grains, and milk. It has been studied as a potential chemopreventive agent cofactor for glutathione peroxidase and thioredoxin reductase antioxidant enzymes. In vitro inhibits melanoma cell growth dose-dependently, halting the cell cycle at G0/G1. Selenium suppresses tumor metastasis in mouse studies but not tumor growth [54].

### 4.5 Conclusion

This is easy-to-spread melanoma. This disease is difficult to identify and treat. Understanding how melanomas escape the immune system will improve diagnostic and therapeutic methods. Improved melanoma detection and prognosis are being developed.

IHC is now frequently used to diagnose melanoma. Tissue immunohistochemistry seeks cancer markers. This diagnostic (and prognostic) method has limitations. IHC scoring can be subjective; diagnostic systems involving several biomarkers require precise interpretation criteria and standardization methods to assure repeatability between labs and pathologists. Newer, more objective methods may change melanoma diagnosis. Parallel reaction monitoring (PRM) is a high-resolution, high-precision ion monitoring approach. PRM uses mass spectrometry (MS) to detect peptides with known masses, such as histone PTMs. This method tells MS to fragment and sequence just certain-sized ions. Discovery-based MS approaches are less sensitive. Melanoma treatment has improved with BRAF, CTLA4, and PD1 inhibitors. To tackle secondary resistance, scientists are researching novel medications and pharmacological combinations. Why do certain therapies work and others fail? Biomarkers to predict patient response are needed, so clinicians may stratify patients and generate personalized treatments based on mutational and biomarker profiles. Individualized melanoma treatment improves prognosis and costs. It will reduce bad drug administration and patient suffering. Metastatic melanoma avoided treatment until recently. Scientists are beginning to comprehend the genetic and mechanical roots of the disease, which may lead to a cure.

## 5. Summary

Melanoma is virulent. It is a heterogeneous, complex condition, making diagnosis and treatment difficult. Understanding melanoma genesis and how melanomas avoid the immune system will lead to improved diagnostic and treatment options. New technologies are being developed to improve melanoma diagnosis and prognosis,

improving patient outcomes. In the last 20 years, IHC has been used more to diagnose melanoma. Tissue immunohistochemistry research focuses on developing sensitive and specific cancer biomarkers. This diagnostic (and presumably prognostic) tool has limitations. IHC scoring can be subjective, so establishing diagnostic systems combining many biomarkers requires precise interpretation criteria and standardization methods to assure repeatability between labs and pathologists. IHC is a good approach for recognizing biomarkers, but newer, more objective, and repeatable methods could change melanoma diagnosis. Metastatic melanoma treatment has improved with BRAF, CTLA4, and PD1 inhibitors. Researchers have learned how secondary resistance develops and are developing new medications and drug combinations to produce a more lasting effect. Ongoing research investigates why and how these treatments work. Biomarker development is a priority, so doctors can stratify patients and design more tailored treatments based on mutational and biomarker profiles. Personalized melanoma treatment improves prognosis and reduces treatment costs. Ineffective drugs will not be given, reducing patients suffering from adverse effects.

Metastatic melanoma is a ferocious and deadly disease that avoided therapy until recently. We are beginning to understand the disease's genetic and molecular roots, enabling more effective therapies and hope for a cure.

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