A Practical Guide to Skin Cancer

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Editor
Allison Hanlon, MD, PhD
Department of Medicine
Division of Dermatology
Vanderbilt University Medical Center
Nashville, TN, USA

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To Gar Bo, Alannah and Mary, thank you for your encouragement, patience and love.

Contents

Contributors

Saud Aleissa, MD Department of Dermatology, Tufts Medical Center, Boston, MA, USA

Eileen Larkin Axibal, MD Department of Dermatology, University of Colorado Denver, Aurora, CO, USA

Trisha Bhat, BA Washington University in St. Louis, School of Medicine, St. Louis, MO, USA

Jeremy S. Bordeaux, MD, MPH University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH, USA

Mariah Ruth Brown, MD Department of Dermatology, University of Colorado Denver, Aurora, CO, USA

Jose A. Cervantes, MD Tucson Hospital Medical Education Program, Tucson Medical Center, Tucson, AZ, USA

Maggie Chow, MD, PhD Department of Dermatology, University of Southern California, Los Angeles, CA, USA

Anna S. Clayton, MD Dermatology, Vanderbilt University of Medicine, Nashville, TN, USA

Charles Thomas Darragh, MD Dermatology, Vanderbilt University of Medicine, Nashville, TN, USA

Jennifer Divine, MD Divine Dermatology and Surgical Institute, Fort Collins, CO, USA

Matthew C. Fox, MD Division of Dermatology, Dell Medical School, University of Texas at Austin, Austin, TX, USA

Allison Hanlon, MD, PhD Department of Medicine, Division of Dermatology, Vanderbilt University Medical Center, Nashville, TN, USA

Shauna Higgins, MD Department of Dermatology, University of Southern California, Los Angeles, CA, USA

Kavita Mariwalla, MD Mariwalla Dermatology, West Islip, NY, USA

Paul R. Massey, MD Division of Dermatology, Dell Medical School, University of Texas at Austin, Austin, TX, USA

Vineet Mishra, MD Department of Medicine, University of Texas Health Science Center – San Antonio, San Antonio, TX, USA

Amy Musiek, MD Dermatology, Washington University in St. Louis, School of Medicine, St. Louis, MO, USA

Bichchau Michelle Nguyen, MD, MPH Department of Dermatology, Tufts Medical Center, Boston, MA, USA

Claire Noell, MD Department of Dermatology, Tufts Medical Center, Boston, MA, USA

Allison Pye, MD Dermatology, McGovern Medical School, UT Houston, Houston, TX, USA

Anthony C. Soldano, MD Division of Dermatology, Dell Medical School, University of Texas at Austin, Austin, TX, USA

Mary L. Stevenson, MD The Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY, USA

Sheena Tsai, MPH University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, Cleveland, OH, USA

Daniel Wallis, MD Dermatology, Texas Tech University Health Sciences Center, Lubbock, TX, USA

Ashley Wysong, MD Department of Dermatology, University of Southern California, Los Angeles, CA, USA

Sarah Yagerman, MD The Ronald O. Perelman Department of Dermatology, NYU Langone Medical Center, New York, NY, USA

Nathalie C. Zeitouni, MDCM, FRCPC Dermatology, St. Joseph's Hospital and Medical Center, Dignity Health, Phoenix, AZ, USA

Jeffrey P. Zwerner, MD/PhD Department of Medicine, Division of Dermatology, Vanderbilt University, Nashville, TN, USA

Chapter 1
Skin Cancer: At-Risk Populations and Prevention

Claire Noell, Saud Aleissa, and Bichchau Michelle Nguyen

Abstract Skin cancer is the most common malignancy worldwide. Genetic and environmental factors increase the risk of developing skin cancer. Identifying at-risk individuals is important in skin cancer diagnosis and management. This chapter discusses in detail the risk factors, at-risk populations, and prevention of skin cancer.

Keywords Basal cell carcinoma · Squamous cell carcinoma · Melanoma · Skin cancer · Prevention · At-risk populations · Risk factors

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
BAP	BRCA1 associated protein-1
BCC	Basal cell carcinoma
BCNS	Basal cell nevus syndrome
BRAF	B-Raf proto-oncogene
BRCA	Breast cancer susceptibility gene
CDK	Cyclin-dependent kinase
CDKN	Cyclin-dependent kinase inhibitor
CLL	Chronic lymphocytic leukemia
DNA	Deoxyribonucleic acid
EVER	Epidermodysplasia verruciformis gene
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
MAPK	Mitogen-activated protein kinase
MC1R	Melanocortin-1 receptor

C. Noell (✉) · S. Aleissa · B. M. Nguyen
Department of Dermatology, Tufts Medical Center, Boston, MA, USA
e-mail: cnoell@tuftsmedicalcenter.com

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MITF	Microphthalmia-associated transcription factor
NMSC	Non-melanoma skin cancer
OCA	Oculocutaneous albinism
PTEN	Phosphatase and tensin homolog
PUVA	Psoralen and ultraviolet A
RR	Relative risk
SCC	Squamous cell carcinoma
SHH	Sonic hedgehog
TNF	Tumor necrosis factor
UV	Ultraviolet

Non-melanoma Skin Cancer: Risk Factors, At-Risk Populations, and Prevention

Basal cell carcinomas and cutaneous squamous cell carcinomas are the most common cancers in the United States [1]. The precise incidence of these cancers is unknown, as they are typically not reported to cancer registries. Recent data from the American Cancer Society estimates that 3.3 million people were diagnosed with non-melanoma skin cancers in 2012, with basal cell carcinomas comprising 80% [2].

Risk Factors

Ultraviolet Radiation

Ultraviolet (UV) radiation is a well-known risk factor in the development of non-melanoma skin cancers (Table 1.1). Ultraviolet radiation is comprised of wavelengths 100–400 nm and is subdivided into UVA, UVB, and UVC. Ultraviolet exposure consists of 95% UVA and 5% UVB as UVC is filtered out completely by the ozone layer [3]. A study evaluating the relationship between non-melanoma skin cancers and ultraviolet B exposure in Maryland shore watermen found that squamous cell carcinomas are significantly associated with cumulative ultraviolet B radiation, which is further increased with high levels of exposure; the association with basal cell carcinoma was unclear [4].

Indoor tanning, largely composed of ultraviolet A, is a modifiable risk factor shown to significantly increase the risk of skin cancer. A meta-analysis of indoor tanning and non-melanoma skin cancer evaluated studies comparing populations ever using versus never using indoor tanning. It demonstrated that the relative risks of developing squamous cell carcinoma and basal cell carcinoma were 1.67 and 1.29, respectively, in patients who had ever used tanning beds; the relative risks were further increased to 2.02 and 1.40 in patients reporting use before 25 years of age [5].

Table 1.1 Non-melanoma skin cancer risk factors

Environmental
UV radiation
Indoor tanning
Ionizing radiation
Psoralen UVA (PUVA) therapy
Chemical exposures
Arsenic
Polycyclic aromatic hydrocarbons
Chronic cutaneous inflammation
Immunosuppression
Fair phenotype
Previous history of skin cancer

In contrast, the association between non-melanoma skin cancer and narrowband ultraviolet B therapy appears to be less clear. Several small studies found varying levels of association, while a large retrospective analysis reviewing the Scottish Cancer Registry records of 3867 patients who received a median of 29 narrowband UVB treatments determined that its use was not significantly associated with the development of skin cancers; a notable limitation of this study was that only a small fraction of the study population (352) had received >100 treatments [6].

Psoralen, a phototoxic drug, and ultraviolet A (PUVA) is an effective and established treatment modality most notably for psoriasis, but long-term therapy has been limited due to its cutaneous carcinogenicity. A 30-year prospective cohort study by Stern followed the development of biopsy-proven non-melanoma skin cancers in 1380 psoriasis patients treated with PUVA, with 25% developing 2973 squamous cell carcinomas. Patients exposed to 351–450 and more than 450 treatments had, respectively, 6-fold and almost 35-fold increased risks of squamous cell carcinoma compared to those who had received fewer than 50 treatments, suggesting a dose-dependent relationship. The association between basal cell carcinomas and PUVA was not found to be significant [7].

Ionizing Radiation

While ionizing radiation was historically used to treat benign conditions such as acne, it carries an increased risk of non-melanoma skin cancer. A case-control study using surveys in New Hampshire evaluated the relative risk of non-melanoma skin cancer after receiving therapeutic ionizing radiation. The risk of non-melanoma skin cancer was further increased in patients who first received treatment prior to 20 years of age compared to older populations. The risk for both basal and squamous cell carcinomas was highest in patients receiving treatment for acne, and there was a twofold increased risk of basal cell carcinoma only in patients receiving radiation for cancer treatment. The risk of developing squamous cell carcinoma was only increased in patients with lighter skin types [8].

Survivors of childhood malignancies treated with radiation therapy have an increased risk of non-melanoma skin cancer. A survey of 13,132 5-year survivors from the Childhood Cancer Survivor Study demonstrated that radiation therapy increases the risk of non-melanoma skin cancer to greater than sixfold. Two hundred thirteen participants developed 615 occurrences of non-melanoma skin cancer (97% basal cell carcinomas and 1% squamous cell carcinomas). Forty-six percent of the patients had multiple skin cancers, with a median onset age of 31 years [9].

Medications

Voriconazole, a potent antifungal typically used to treat fungal infections and for prophylaxis in immunosuppressed patients, has been linked with photosensitivity and squamous cell carcinoma. In a retrospective analysis of 3 academic centers, 8 pediatric and adult patients on long-term voriconazole developed 51 squamous cell carcinomas [10]. A recent larger, single-institution study evaluating the relationship between squamous cell carcinomas and long-term antifungal prophylaxis in lung transplant patients demonstrated a significantly increased risk of squamous cell carcinoma incidence in patients exposed to voriconazole-containing regimens independent of other risk factors; furthermore, cumulative voriconazole exposure increased the risk of recurrent squamous cell carcinoma [11].

The growth of squamous cell carcinomas and keratoacanthomas is a common development in patients with melanoma treated with (B-Raf proto-oncogene) BRAF inhibitors. Molecular analysis has demonstrated that a significant number of these malignancies contain Ras gene mutations; the proposed mechanism is the paradoxical activation of mitogen-activated protein kinase (MAPK) signaling, leading to increased growth [12].

Chemical Exposures

The association between arsenic-contaminated drinking water and incidence of several malignancies, including non-melanoma skin cancer, has been reported in developing countries, as well as in the United States. A retrospective study using the National Taiwan Cancer Registry Center evaluated the incidence of non-melanoma skin cancers in the black foot disease endemic areas of Taiwan (an established disease resulting from arsenic-containing water wells) compared to other areas between 1979 and 2007. During this interval, there were 11,191 occurrences of squamous cell carcinoma and 13,684 occurrences of basal cell carcinoma. There was a four- to sixfold increase in squamous cell carcinomas and three- to fourfold increase in basal cell carcinomas in black foot endemic areas compared

to the remaining areas [13]. Arsenic ingestion through private wells in the United States can also increase the risk of skin cancer. A meta-analysis of six studies evaluating arsenic levels and skin cancer within the United States was conducted, which suggested that even arsenic concentrations below the maximum level permitted by the Environmental Protection Agency may increase the risk [14].

Exposure to arsenic and other carcinogens can occur during the production and use of pesticides, herbicides, and fungicides, leading to an increased risk of squamous cell carcinoma. Finally, contact with polycyclic aromatic hydrocarbons, a by-product of the manufacturing of coal products, steel, iron, and diesel exhaust fumes, increases the risk of squamous cell carcinoma, but not basal cell carcinoma [15].

Pre-existing Lesions and Conditions

Chronic inflammation in conditions such as non-healing wounds/ulcerations, burns, venous stasis, discoid lupus erythematosus, lichen sclerosus, and lichen planus can stimulate malignant transformation, typically squamous cell carcinoma. The term "Marjolin's ulcer" was classically used to describe the development of squamous cell carcinoma in burn scars. In 1 study following 21 Marjolin's ulcer patients, 16 developed squamous cell carcinoma, while 4 had basal cell carcinoma and 1 had basosquamous cell carcinoma. Transformation can occur over weeks to decades, with an average interval of 19 years in the study described [16]. Discoid lupus-related squamous cell carcinomas tend to occur earlier and in sun-exposed areas, with the lip being the most common location [17]. The hyperkeratotic and erosive variants of lichen planus carry malignant potential necessitating periodic surveillance, with a reported transformation incidence of 0.4–1.5% in oral lichen planus [18]. Vulvar lichen sclerosus has also been shown to hold malignant potential, with an increasing risk of vulvar squamous cell carcinoma of up to 6.7% after 20 years [19].

Porokeratosis is a disorder of keratinization encompassing several subtypes of lesions with a cornoid lamella, a distinct raised border of angled hyperkeratosis. While historically thought to be a benign condition, certain subtypes carry an increased risk of skin cancer. A literature review following 30 years of porokeratosis revealed that the linear subtype carries the highest risk of skin cancer with a 19% malignant transformation rate, while punctate porokeratosis and disseminated actinic superficial porokeratosis confer the lowest risk (3.4% and 0%, respectively) [20].

While rare, basal cell carcinoma is the most common malignancy that can develop within nevus sebaceus, a benign congenital tumor. In a retrospective microscopic analysis of 596 cases, 0.8% was found to contain basal cell carcinomas; syringocystadenoma papilliferum and trichoblastoma were the most common benign neoplasms [21].

At-Risk Populations

History of Non-melanoma Skin Cancer

Patients with a history of non-melanoma skin cancer have an increased risk of developing subsequent skin cancers. The 3-year cumulative risk of a second squamous cell carcinoma is 18%, while the risk of a second basal cell carcinoma is 44%, demonstrating the need for continued monitoring for subsequent skin cancers in these patients [22].

Skin Types

Skin types play an important role in determining the risk of non-melanoma skin cancer in certain populations. Fitzpatrick skin types I and II, as seen in Caucasians, have the highest risk of both basal cell and squamous cell carcinomas overall [23]. Basal cell carcinomas are the most common skin cancer seen in Caucasians, Hispanics, Japanese, and Chinese [24], while squamous cell carcinoma is the most common skin cancer found in African-Americans. Squamous cell carcinomas in African-Americans tend to be more aggressive, with increased mortality and overall worse prognosis [25]. Similarly, squamous cell carcinomas in Asian populations tend to occur in sun-protected areas and have an increased risk of metastasis as they are usually advanced at the time of diagnosis [24].

Immunosuppressed Populations: Organ Transplant, Immunosuppressive Medications, Cancer, and HIV

Due to the need for lifelong immunosuppression, organ transplant patients are at an increased risk for skin cancers. A cohort study of 26 transplant centers following10,649 organ transplant patients revealed an increased overall incidence rate of 1437 per 100,000 person-years. Squamous cell carcinoma was the most common, accounting for 94% of the skin cancers. The incidence of squamous cell carcinoma in transplant patients was 1355 per 100,000 person-years, compared to the rate in the general population of 38 per 100,000. The study also highlighted predictors of posttransplant skin cancer, including a history of pretransplant skin cancer and undergoing a thoracic transplant due to requiring higher levels of immunosuppression [26]. The type of immunosuppressant can also affect a patient's risk for skin cancers. Patients on the antimetabolite drug azathioprine were more than twice as likely to develop squamous cell carcinomas, while patients taking mycophenolate were recently found to have a lower risk. Azathioprine was not significantly associated with basal cell carcinomas [27]. In contrast, sirolimus historically has been

shown to have a protective effect against skin cancers in transplant patients, with the largest decrease in risk of non-melanoma skin cancer and other malignancies seen in transplant patients who converted from other immunosuppressants to sirolimus-containing regimens [28].

Immunomodulating agents and immunosuppressants used in treating autoimmune conditions such as psoriasis, inflammatory bowel disease, and rheumatoid arthritis have also shown to carry an increased risk of skin cancer. Methotrexate use for rheumatoid arthritis increases the likelihood of a second non-melanoma skin cancer in patients, and combining tumor necrosis factor-α (TNF) inhibitors with methotrexate further increases that risk. More studies are needed to conclude whether TNF inhibitors increase the risk of skin cancer when used as monotherapy [29].

Patients with hematologic malignancies, particularly chronic lymphocytic leukemia (CLL), are predisposed to develop skin cancers. The risk of skin cancer in CLL patients alone is increased eightfold [30]. Furthermore, these skin cancers tend to demonstrate more aggressive behavior, with studies demonstrating a 7-fold and 14-fold increased likelihood of recurrence of squamous cell and basal cell carcinomas previously treated with Mohs micrographic surgery, respectively [31, 32].

Finally, patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) are immunocompromised and therefore at a higher risk of skin cancers. Several studies have shown that HIV/AIDS patients have an almost threefold increased incidence of non-melanoma skin cancers, with male patients over three times as likely. Fortunately starting antiretroviral therapy (ART) in these patients is protective, with treated patients carrying a decreased risk compared to ART-naïve patients [33].

Genodermatoses with Increased Risk of Basal Cell Carcinomas

There are several familial cancer syndromes that carry an increased risk of skin cancer (Table 1.2). Basal cell nevus syndrome (BCNS), or Gorlin's syndrome, is an autosomal dominant disorder caused by germline inactivating mutations in *PTCH1*, leading to unchecked sonic hedgehog (SHH) signaling and increased cell proliferation. Patients with BCNS characteristically develop multiple basal cell carcinomas, which can initially appear within the first two decades of life with a

Table 1.2 Genodermatoses associated with non-melanoma skin cancer

Basal cell carcinoma
Basal cell nevus syndrome (Gorlin)
Bazex-Dupré-Christol syndrome
Squamous cell carcinoma
Xeroderma pigmentosum
Oculocutaneous albinism
Epidermodysplasia verruciformis

median number of 8, though some patients can have >1000 basal cell carcinomas. They also develop several benign and malignant neoplasms, including medulloblastomas, fibrosarcomas, rhabdomyosarcomas, meningiomas, and odontogenic keratocysts, as well as cardiac and ovarian fibromas. Characteristic developmental defects include palmoplantar pits, craniofacial anomalies such as frontal bossing, bifid ribs, spina bifida occulta, corpus callosum dysgenesis, calcification of the falx cerebri, and coarse facies [34].

Bazex-Dupré-Christol syndrome (follicular atrophoderma with basal cell carcinomas) is an X-linked dominant disorder with increased development of basal cell carcinomas. The constellation of findings includes follicular atrophoderma, basal cell carcinomas, and hypotrichosis, as well as less common features such as milia, hypohidrosis, facial hyperpigmentation, and trichoepitheliomas. Patients usually develop basal cell carcinomas within the second decade of life, which can have atypical features [35].

Lastly, Rombo syndrome is another autosomal dominant syndrome with an increased risk of basal cell carcinomas. Features of Rombo syndrome usually manifest prior to 10 years of age (a later onset than seen in Bazex-Dupré-Christol syndrome) and include vermiculate atrophoderma, telangiectasias, hypotrichosis, milia, and basal cell carcinomas [36].

Genodermatoses with Increased Risk of Squamous Cell Carcinomas

Xeroderma pigmentosum is a collection of disorders with defects in deoxyribonucleic acid (DNA) repair, making affected patients exquisitely sensitive to the damaging effects of UV radiation and thereby at greater than 20,000-fold increased risk of skin cancers. Sun exposure in these patients can lead to non-melanoma skin cancer development prior to 10 years of age [37, 38].

Oculocutaneous albinism (OCA) is characterized by mutations leading to absent or reduced melanin production, leaving patients vulnerable to DNA damage and subsequent skin cancers. These patients can have absent to variable levels of pigmentation and are at an increased risk of non-melanoma skin cancers without adequate photoprotection; squamous cell carcinomas are overwhelmingly the most common [39].

Epidermodysplasia verruciformis is a rare, autosomal recessive disorder due to epidermodysplasia verruciformis 1 or 2 genes (EVER1 or EVER2), rendering them more susceptible to human papillomavirus infections. Patients present with diffuse scattered verrucous lesions on their extremities during infancy or childhood. Half of these patients develop squamous cell carcinomas, typically in a sun-exposed distribution [40].

Melanoma: Risk Factors, At-Risk Populations, and Prevention

Melanoma is a skin cancer with significant morbidity and mortality. Each year over 65,000 people are diagnosed with melanoma, and over 9000 people die from the disease each year [41]. It is the fifth leading cancer among men and the seventh among women. Malignant melanoma incidence rate is increasing in the United States, surpassing the rates of any other potentially preventable cancer. The increase in incidence may be partially due to improved detection with increased screening and better reporting systems [42].

Although melanoma only represents 5% of all new skin cancer diagnoses, it accounts for the majority of deaths related to skin cancer [43]. Death rates and mortality have been largely unchanged over the years, with the exception of white men [44].

This incidence rate differs among different ethnic groups. Among whites it is approximately 18.4 per 100,000 persons. Among Hispanics the incidence rate is 2.3. From 2008 to 2012, 6623 cases of melanoma were diagnosed among Hispanics. The incidence rate among other ethnic groups was 0.8, 1.6, and 1.0 for African-Americans, American Indians, and Asians, respectively. Lower extremity and acral lentiginous melanomas were the more common sites of presentation in these groups. The diagnosis of acral melanoma is often delayed, resulting in more advanced stages of disease at presentation [45].

Per the CDC, skin cancer costs an estimated $1.7 billion to treat and results in $3.8 billion in lost productivity [46].

Risk Factors (Table 1.3)

UV Radiation and History of Sunburn

Numerous clinical and epidemiological studies have demonstrated a correlation between increased incidence of melanoma and sun exposure. Sunburn history, defined by five or more severe sunburns in childhood, has shown to play a considerable role as a risk factor for melanoma and can carry a relative risk of 2.02 [47–49].

Table 1.3 Melanoma risk factors

Greater than five sunburns
Indoor tanning
Psoralen UVA (PUVA) phototherapy
Fair phenotype
Parkinson disease
Immunosuppression
Personal and/or family history of melanoma

The link with sun exposure in melanoma is strongly associated with intermittent sun exposure [48], in contrast to non-melanoma skin cancers (NMSC) where cumulative sun exposure plays a larger role. This explains the higher incidence of NMSC in areas maximally exposed to the sun [47]. Furthermore, there is a higher incidence of melanoma in equatorial regions, where ultraviolet B radiation (UVB, wavelengths 290–320 nm) is most intense. This suggests that UVB may play a larger role in the development of melanoma than ultraviolet A (UVA, wavelengths 320–400 nm) [50, 51].

Indoor Tanning

Indoor tanning has emerged as a popular trend, gaining in popularity over the last 50 years, especially among adults aged 18–25 years. The UVA output of some of these devices can be up to four times higher than midday sunlight [46]. Up to one third of young white females reported indoor tanning in the past year. Melanoma incidence is increasing at a faster rate among this group, suggesting that indoor tanning is a likely driver of these diverging trends [52].

PUVA

UV exposure can be iatrogenic as well. Phototherapy and especially PUVA have been used to treat a variety of dermatological conditions. The risk of melanoma appears to increase with the passage of time (RR of 2.3), approximately 15 years after first exposure to PUVA, with the highest incidence in patients receiving >250 treatments (RR of 5.5). These data emphasize the importance of long-term monitoring in these patients [53, 54].

Nevi

Some studies have demonstrated the association between melanoma and the number, size, and type of nevi, illustrating an increased risk with the presence of 25–100 nevi or 1 atypical nevus. (Olsen, 2010) Newer studies, however, have shown that this relationship is not as strong as previously thought, suggesting that physicians and patients should not rely on the total number of nevi as the sole criteria in determining a patient's risk status [55].

Moreover, the risk of melanoma in congenital nevi is strongest with large congenital nevi, defined as greater than 20 centimeters, compared to small and medium congenital nevi, with a lifetime incidence of developing melanoma of around 2% [56, 57].

Phenotypes and Lentigines

Other phenotypic traits, like the Fitzpatrick skin phototype scale describing a patient's ability to tan, hair color, freckles, and eye color, can also affect individual skin cancer risk. The risk of melanoma is 3.5 times higher in red-haired individuals and almost doubled in blond-haired individuals compared to dark-haired counterparts. Light eye color (green, hazel, blue) versus dark showed an approximately 1.5-fold relative risk. Lastly, individuals with high freckle density showed twice the risk compared to lower density individuals [58].

Parkinson Disease

Melanoma can be associated with other comorbidities. Parkinson disease has an overall decreased risk of cancer diagnoses, with the exceptions of breast cancer and melanoma [59]. These patients have a statistically significant increase in the incidence of melanoma with a relative risk almost twice as high compared to the general population [60]. Some have proposed a link between the use of levodopa in the treatment of Parkinson disease and the development of melanoma; however, that increase in prevalence often precedes both the neurologic onset of the disease and initiation of treatment [61]. Another proposed mechanism is the mutation of the melanocortin-1 receptor (MC1R) gene, as it is more likely to develop in patients with Parkinson disease than in controls [59].

At-Risk Populations

Immunosuppressed Patients: Organ Transplant, Lymphoma, and HIV

Immunosuppressed populations, including those on immunosuppressants or those with solid organ transplantation, hematologic malignancies, or HIV, carry a higher risk of melanoma. In solid organ transplant recipients on immunosuppressive therapies, the risk of melanoma is two- to fivefold higher than the general population. Such an increase can be due to the direct carcinogenic effect of these medications or partially due to increased screening of this population, as they are at a higher risk of developing non-melanoma skin cancer [62].

Malignant melanoma was first reported in patients with lymphoma in 1973. Patients with chronic lymphocytic leukemia or small lymphocytic lymphoma have a two- to threefold increased risk of developing malignant melanoma [63]. A large retrospective cohort study showed the posttransplant incidence rate of melanoma is about 125 per 100,000 person-years [26].

Since the emergence of HIV/AIDS in the 1980s, a modest increase in the incidence of melanoma was reported prior to the introduction of highly active antiretroviral therapy (HAART) in the latter part of the 1990s. In the HAART era, the incidence of melanoma in the HIV population remains as high as 50%. That risk, however, is possibly confounded by increased longevity and closer surveillance in these patients [64].

Personal History of Skin Cancer

Patients with a personal history of melanoma should be monitored closely, as the risk of developing a second melanoma can be as high as 8% [65]. The increased risk is observed for patients with both invasive and in situ melanomas [66].

Personal history of NMSC also increases the risk of melanoma, likely due to the fact that both conditions have similar risk factors. Some studies have reported that a history of NMSC can increase the risk of melanoma from 2.80 to 6.55 times compared to those without a history of NMSC [58]. Some studies have also demonstrated not only an increase in the risk but also an increase in the mortality associated with melanoma in patients with a history of basal cell or squamous cell carcinomas [67, 68].

Family History of Melanoma

Family history of melanoma is associated with a higher risk of developing the disease. Approximately 8–12% of all patients diagnosed with melanoma have a family history of the disease independent of any known mutations [69, 70]. The relative risk of developing melanoma approximately doubles with a positive family history in one first-degree relative [71] but can increase ninefold if two first-degree relatives are affected [60].

Familial Syndromes (Table 1.4)

Hereditary melanoma syndromes (familial atypical multiple mole syndromes) are a group of autosomal dominant disorders that present clinically with hundreds of dysplastic nevi and a high incidence of melanoma [70].

Over the years, numerous genes have been studied and identified as a cause of germline mutations that increase the risk of melanoma (Table 1.4). Depending on the specific mutation, that risk can be between 4- and 1000-fold [70]. Germline mutations represent about 10% of all melanomas diagnosed worldwide [72]. These mutations work by three main mechanisms: activation of oncogenes, loss of tumor suppressor genes, and chromosomal instability [73].

Table 1.4 Genetic syndromes and mutations associated with melanoma syndromes

Familial atypical multiple mole syndrome
Xeroderma pigmentosum
PTEN mutations (Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome)
Oculocutaneous albinism type 2
Genetic mutations
Microphthalmia-associated transcription factor (MITF)
Melanocortin-1 receptor (MCR1)
CDKN2A
CDK4
BRCA1
BRCA2
BAP1 in uveal melanoma

Some of the most well-established gene mutations are cyclin-dependent kinase inhibitor 2A (CDKN2A) and less commonly cyclin-dependent kinase 4 (CDK4). They control the transition between the growth phase in the cell cycle (G_1) and the synthesis phase (S_1). They carry a 60–90% lifetime risk of melanoma and have been associated with pancreatic cancer [70]. Testing for this mutation is recommended for patients with a diagnosis or family history of three melanomas, two melanomas, and one pancreatic cancer or one melanoma and two pancreatic cancers [47, 74].

Patients with BRCA1 (breast cancer susceptibility gene 1) or BRCA2 mutations have a twofold increase in melanoma due to mutations affecting DNA repair and stability. These mutations are also associated with breast, ovarian, prostate, and pancreatic cancers, necessitating close monitoring [70].

BAP1 (BRCA1 associated protein-1/ubiquitin carboxy-terminal hydrolase) mutations are more commonly associated with uveal melanoma than cutaneous melanoma. They are also associated with mesothelioma and tumors of the kidney, gallbladder, and brain [75].

MITF (microphthalmia-associated transcription factor) mutations have also been associated with an increased melanoma risk and feature a high nevus count in association with renal cell carcinomas [76].

MCR1 (melanocortin-1 receptor) mutations increase the risk of melanoma through increased pheomelanin production, which is less protective against UV radiation than eumelanin. This imbalance alters skin pigmentation, leading to red hair and fair skin [77].

Xeroderma pigmentosum is a rare autosomal dominant disease that affects approximately 1 in 250,000 births. It is caused by a mutation in DNA repair genes that are responsible for nucleotide excision repair, which play a major role in UV-induced DNA damage repair by removing radiation-induced pyrimidine dimers. This leads to extreme, early onset photosensitivity and significant incidence of basal cell carcinoma, squamous cell carcinoma, and melanoma (600- to 8000-fold risk) [38].

Cowden and Bannayan-Riley-Ruvalcaba syndromes are a group of phosphatase and tensin homolog (PTEN) hamartoma tumor syndromes that are associated with melanoma [78, 79].

Oculocutaneous albinism type 2 is the most common subtype of albinism, which carries an increased risk of melanoma. It is caused by mutation in the OCA2 gene, leading to defects in melanin synthesis and a subsequent increase in melanoma [80]. A substantial challenge in this population is that they can present with the amelanotic variant of melanoma. Amelanotic melanoma typically lacks the usual clinical and dermatoscopic signs of melanoma, which often lead to delays in diagnosis and worse outcomes [81].

Prevention and Screening of Non-melanoma Skin Cancer and Melanoma

Skin cancer prevention focuses on decreasing risk factors through photoprotection, immunosuppression changes, and keratinocyte development.

Consistent and appropriate application of sunscreen has been shown to decrease the number of precancerous actinic keratoses and squamous cell carcinomas after 1–4 years of follow-up [82–84]. Unfortunately, sunscreen has not demonstrated the same beneficial effect with basal cell carcinomas [84]. The relationship between sunscreen and melanoma reduction is unclear and requires more probative studies [85]. This incongruence illustrates the need for additional photoprotection other than sunscreen, which includes photo-protective clothing, limiting sun exposure outdoors at times of highest UV radiation, and seeking shade. Vitamin D deficiency can develop in patients who follow strict sun protection making supplementation necessary.

The degree and duration of immunosuppression in solid organ transplant recipients are associated with increased incidence of skin cancer [86]. In collaboration with the transplant team, there is a reduction of immunosuppression to mimimal levels for graft tolerance. In patients with metastatic, rapidly aggressive, or increasing numbers of skin cancers, a change in immunosuppression to a mTOR inhibitor may be indicated [87, 88].

Retinoids, a vitamin A derivative, affect keratinocyte differentiation and proliferation [89]. The oral retinoid acitretin is advantageous in reducing actinic keratoses and squamous cell carcinomas. A prospective trial evaluating renal transplant patients given oral acitretin for 1 year demonstrated a significantly decreased incidence of squamous cell carcinomas, with a similar but not statistically significant reduction in basal cell carcinomas [90]. Acitretin also reduced the number of actinic keratoses by nearly 50% in renal transplant patients receiving varying doses of the drug [91]. With regard to longitudinal benefits, a retrospective study of renal transplant patients receiving acitretin for 1–16 years demonstrated a significant decrease in the number of squamous cell carcinomas within the first 3 years of taking acitretin [92].

Once discontinued, acitretin is no longer effective, and tumor development recurs. While oral retinoids are beneficial as a chemopreventive agent, topical retinoids, such as tretinoin, are not effective in reducing squamous cell carcinoma incidence [93].

Nicotinamide, vitamin B3, is a precursor of nicotinamide adenine dinucleotide and necessary cofactor in adenosine triphosphate production (ATP). UV radiation depletes cellular ATP as well as damages DNA. ATP is needed for DNA repair. Nicotinamide replenishes ATP thereby enhancing DNA repair [94]. In an Australian study, oral nicotinamide 500 mg twice a day reduced the incidence of NMSC in high-risk skin cancer patients by 23 percent relative rate reduction. Subjects with the highest number of skin cancers prior to enrollment had the highest relative reduction in skin cancers with nicotinamide. Importantly, the benefit was with nicotinamide, not nicotinic acid [95]. Larger randomized controlled trials are needed to further understand the nicotinamide's benefit in reducing skin cancers.

Skin screening examinations theoretically are an important aspect of detecting and reducing the burden of skin cancers. A recent literature review evaluating screening examinations and skin cancers, most notably melanoma, by the US Preventive Services Task Force did not demonstrate a clear benefit with regard to mortality and screening; however, few studies were incorporated due to the inclusion criteria, and few were specific to the United States, illustrating the need for further research [96]. The skin exam includes examination of the skin and provides counseling to patients on the signs and symptoms of skin cancer and to perform their own skin self-examination monthly. A non-healing, bleeding, or changing skin lesion needs evaluation by a trained dermatologist.

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