Epidemiology and Prevention of Cutaneous Cancer

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KEYWORDS

• Nonmelanoma skin cancer • Melanoma • Epidemiology • UV radiation
• Indoor tanning • Screening • Prevention

KEY POINTS

- Nonmelanoma skin cancer is the most common malignancy in the United States; melanoma is the fifth most common cancer in the United States but is the leading cause of death among skin cancers.
- Lack of mandated reporting for nonmelanoma skin cancers hinders the ability to accurately study their incidence, outcomes, and cost.
- Incidence of cutaneous malignancies is rapidly increasing, in association with increased longevity, a growing immunosuppressed population, and changes in patterns of ultraviolet radiation exposure.
- The United States does not have a national skin cancer prevention program, because of lack of consensus regarding the efficacy and evidence of beneficial outcomes.
- Universal skin-cancer screening may not be cost-effective, but targeted screening of high-risk populations is generally accepted by experts as worthwhile.

INCIDENCE

Cutaneous malignancy is the most common human cancer, in the United States and worldwide. The incidence of skin cancer is higher than all other cancers combined. In the United States alone, more than 9500 people are diagnosed with skin cancer every day, and more than two people die of the disease every hour.[1] One in five Americans develop skin cancer by the age of 70.[2] Incidence is difficult to assess accurately because the most common types, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), are not required to be reported to cancer registries.[3] A 2015 study

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using Medicare databases and national survey data found that 5.4 million cases of nonmelanoma skin cancer (NMSC) were treated in 3.3 million patients in 2012.[4] BCC is the most common cutaneous malignancy, accounting for roughly 80% of NMSC, with approximately 4.3 million cases diagnosed in the United States each year, whereas more than 1 million cases of SCC are diagnosed annually.[5]

Invasive melanoma is mandated by law to be reported to cancer registries. Therefore, we better understand the numbers for this disease, although there is evidence that melanomas are underreported. Proposed reasons include the outpatient treatment of many melanomas, which may lead them to go undetected by automated surveillance systems.[6] Despite potential reporting inaccuracies, it is clear that invasive melanoma constitutes a small proportion of all cutaneous malignancies (1% according to the Surveillance, Epidemiology, and End Results database) but is responsible for the preponderance of skin cancer mortality. This year, new melanoma diagnoses will number around 100,350 in the United States, and 6850 people will die of the disease.[7] Although it is orders of magnitude less common than NMSC, melanoma is the fifth most common reported cancer in the United States, trailing only breast, lung, prostate, and colorectal malignancies. Melanoma currently accounts for 5.6% of all reported new cancer diagnoses in this country.[7] Most cutaneous malignancies occur in Whites, which, in combination with climate, dictates the geographic distribution around the globe. According to research cited by Bradford,[8] skin cancer accounts for approximately 35% to 45% of all cancers in Whites, 4% to 5% in Hispanics, 2% to 4% in Asians, and 1% to 2% in Blacks. Sixty percent to 75% of melanomas in Blacks, Asians, and native Hawaiians occur on the palms, soles, mucous membranes, and nail regions, which contain less melanin.[9]

Among Whites, skin cancer risk is highest in those with light skin pigmentation, light hair and eye color, and skin that burns easily.[10,11] Risk of melanoma and NMSC is more common in men and in older people. BCC incidence is 30% higher in men than women. Fifty-five to 75 year olds have a 100-fold higher rate of BCC compared with those younger than 20 years of age.[12] For SCC, incidence is 50 to 300 times higher in those older than 75 years versus those younger than 45 years old.[13] Melanoma is more common in women than men in people younger than 50 years of age, but rates in men far outpace those in women with increasing age, with a 2:1 ratio by age 65 and a 3:1 ratio by age 80. Several factors may explain these differences, including gender and age variations in occupational and recreational exposure to ultraviolet radiation (UVR), and divergences in health care use.[14] Aside from the commonly acknowledged at-risk population of older White patients, cutaneous malignancy is an underappreciated disease in other distinct populations, namely young women, patients of Hispanic ethnicity, and homosexual men.[15] A concerning development is the increase in NMSC diagnoses among American younger than 45 years of age, especially women.[16] Christenson and Borrowman[16] hypothesize that this trend is associated with increased use of tanning beds and increased sun exposure, and greater public awareness of cutaneous malignancy, leading to improved surveillance.

Most NMSCs are curable, especially if the cancer is detected and treated early. Mortality from BCC and SCC is known to be uncommon, but again difficult to track because reporting is not mandated for these cancers. However, given the prevalence of these diseases, the mortality burden is substantial. It is estimated that more than 15,000 people die of SCC in the United States each year, more than twice the number of mortalities from melanoma.[17] Worldwide, more than 5400 people die of NMSC skin cancer every month.[18] Death from NMSC occurs mostly in the elderly, those who present at an advanced stage, and the immunosuppressed. Although melanoma is also frequently curable when detected in its earliest stages, its propensity for regional

and distant metastasis far exceeds NMSC. The overall 5-year relative survival rate for melanoma is 92%.[3] Fortunately, 84% of cases are diagnosed at a localized stage, for which the 5-year survival rate is 99%. Survival drops substantially with regional metastases (65%) and distant metastases (25%). Recent breakthroughs in systemic treatment have led to one noteworthy improvement: more than half of patients diagnosed with distant-stage disease now survive at least 1 year. Black patients have significantly poorer outcomes, with an estimated 5-year overall melanoma survival rate of only 70%.[3] Hispanic and Black patients are typically diagnosed at a more advanced stage than are non-Hispanic White patients; 52% of Black patients and 26% of Hispanic patients are diagnosed with melanoma at an advanced stage, compared with 16% of non-Hispanic White patients.[19]

Already the most commonly diagnosed human cancer, cutaneous malignancy is rapidly growing in incidence. Diagnosis of NMSC in the United States increased by 77% between 1994 and 2014. Between 2010 and 2020, the number of melanoma diagnoses has increased by 47%.[3] Multiple factors seem to contribute to this trend. Developments in outdoor activities over the past five decades, evolution of clothing styles, lengthened lifespan, particularly for patients with immunocompromised immune systems, ozone depletion, and advances in skin cancer detection all seem to play a role.[2]

RISK FACTORS

Ninety percent of NMSC and 86% of melanomas are caused by exposure to UVR,[20,21] a type of electromagnetic radiation that is located between X-radiation and light on the electromagnetic spectrum. UVR is released by the sun and by devices, such as tanning beds, which can emit UVR in amounts 10 to 15 times higher than the sun at its peak intensity.[22] UVR causes cutaneous malignancy through a combination of mechanisms: DNA damage, suppression of the immune system, tumor promotion, and mutations in the *p53* tumor suppressor gene. DNA absorbs UVR, causing base modifications, strand breaks, cross-links, and DNA-protein cross-links. These DNA "photoproducts" lead to gene mutations, triggering cellular responses, such as cytokine release that stimulate tumor promotion, tumor progression, and immunosuppression. One of the most common gene mutations is in the *p53* tumor suppressor gene, found in more than 90% of cutaneous SCC. In fact, specific *p53* mutations caused by C to T or C:C to T:T transitions at pyrimidine-pyrimidine sequences are frequent enough to be considered a trademark of UVR carcinogenesis. These mutations have been found in 74% of sun-exposed normal human skin samples and only 5% of unexposed skin samples. UVR exposure has been shown in multiple studies, in humans and experimental animals, to diminish immune function.[23] Greater epidermal melanin in people with darker skin filters twice as much UVR as does the epidermis in Whites, explaining the demographic differences in skin cancer incidence.[24] Multiple studies have shown variations in the patterns of sun exposure that correlate with different cutaneous malignancies. Total cumulative sun exposure correlates with development of BCC and SCC, whereas intense intermittent exposure, including sunburns and childhood exposure, is more strongly associated with the development of melanoma, including areas of the body only intermittently exposed to the sun, such as the back in men and the legs in women.[25] Several studies have linked occupational sun exposure to SCC, including a case-control study by Schmitt and colleagues,[26] which found an almost two-fold risk of SCC in patients with high levels of sun exposure through their work.

UV-emitting tanning beds are categorized as a group 1 carcinogen by the International Agency for Research on Cancer, an affiliate of the World Health Organization,

placing them in the same class as tobacco and asbestos.[27] More people now develop skin cancer because of indoor tanning than develop lung cancer caused by smoking. Indoor tanning is responsible for more than 450,000 new skin cancers annually, including more than 10,000 melanomas, 245,000 BCCs, and 168,000 SCCs.[28] Any history of indoor tanning increases one's lifetime risk of BCC by 29% and risk of SCC by 83%.[29] More specifically, it increases one's risk of developing BCC before the of age 40 by 69%.[30] A large cohort study of women in Norway over more than two decades demonstrated a dose-response association between tanning bed use and risk of cutaneous SCC.[29] Women with highest cumulative exposure to indoor tanning had a hazard ratio of 1.83 compared with never users for the development of cutaneous SCC. This correlation between cumulative indoor tanning exposure and cancer risk was not impacted by duration of use or age at initiation.[29]

A similar study by the same authors found that risk of developing melanoma also showed a dose-response association with tanning bed use, with highest cumulative exposure to tanning beds having an adjusted relative risk of 1.32. This study showed that age at initiation of use of less than 30 years carried a higher risk of developing melanoma, and at a slightly younger age (2.2 years earlier).[31] A 2012 meta-analysis demonstrated that any use of tanning beds was associated with a summary relative risk of melanoma of 1.20, and a 1.8% increase in risk of melanoma with each tanning bed exposure per year. Age of initiation of use less than 35 years of age increased the summary relative risk to 1.87.[32] Compounding this risk of malignancy is the correlation of tanning booth use with behaviors such as reduced use of protective clothing and shade when outdoors.[33] Even "sunless tanning" can lead people to increase their risk by neglecting to wear sunscreen and otherwise limit their sun exposure. Misguided beliefs about the benefits of tanning beds for seasonal depressive disorder and perceived vitamin D deficiency thwart educational efforts about the risks of UVR exposure.[34]

Family history of NMSC and melanoma has been shown to increase the risk of developing these diseases.[25] Genetic factors are suggested by multiple studies to play a role but is challenging to separate from the influence of shared cutaneous phenotypes and similar environmental exposures among families. There are several rare inherited disorders that markedly increase risk of cutaneous malignancy. Xeroderma pigmentosum and oculocutaneous albinism are associated with heightened risk of BCC and SCC. Nevoid BCC syndrome (Gorlin syndrome) and Bazex-Dupre-Christol syndrome increase risk of BCC, whereas epidermolysis bullosa and epidermodysplasia verruciformis increase risk of SCC. Familial atypical multiple mole and melanoma syndrome and atypical mole syndrome (also known as dysplastic nevus syndrome) increase risk of melanoma.[25]

IMMUNE SYSTEM FACTORS

A variety of immunocompromising conditions have a notable impact on the immune system's capacity to recognize and eliminate cutaneous malignancies. The most striking example of this is organ transplantation. More than half of White transplant recipients (solid organ transplant recipients [SOTRs]) develop cutaneous malignancy, on average 3 to 8 years after transplantation. Most of these are NMSC, with a predominance of SCC over BCC, versus the preponderance of BCC in the general population. SCC has a 65- to 250-fold increased incidence in SOTRs, whereas BCC has a 10-fold increased incidence.[35] Melanoma has a two- to five-fold increased incidence, and work by Fattouh and colleagues[36] demonstrates a steadily increasing incidence over the past two decades. Frequent routine skin cancer surveillance for transplant patients may be a contributing factor. Risk of cutaneous malignancy correlates with

exposure to immunosuppressive medications, because incidence of NMSC increases with higher doses, longer duration, and increased numbers of these drugs. This helps explain why heart and lung transplants have the highest risk of skin cancers, because they require the highest levels of immunosuppression, compared with kidney and liver transplants. SOTRs are characteristically afflicted with many skin cancers, and with more aggressive skin cancers than those in the general population.[34] SCCs in transplant patients often grow rapidly. These patients have a 13.4% local recurrence rate, usually within the first 6 months after resection, and a 5% to 8% rate of metastasis, typically in the second year after resection.[37]

Patients with chronic lymphocytic leukemia, the most common adult leukemia in the United States, have an increased risk of cutaneous malignancy, with an eight-fold increased risk of NMSC and a two- to four-fold increased incidence of melanoma.[35] As in SOTRs, disease recurrence and mortality are more common than in the general population. Patients with human immunodeficiency virus overall have a two-fold increase in risk of BCC and five-fold increase in risk of SCC, and risk increases in those with poorly controlled disease, with lower CD4 counts and higher viral loads.[38] Patients treated with biologic agents for autoimmune diseases (including psoriatic arthritis, rheumatoid arthritis, and inflammatory bowel disease) have an increased risk of NMSC, mostly SCC, but not melanoma. These biologic agents include inhibitors of tumor necrosis factor and the interleukin-17 pathway.[39] Finally, immunosenescence, the gradual deterioration of the immune system that occurs with advancing age, has been linked to increasing risk of cancer, likely associated with deterioration in T-cell function that diminishes tumor immunosurveillance.[40,41]

PREVENTION

NMSC is the most common malignancy in the United States.[1] Melanoma is the fifth most common cancer in the United States but is the leading cause of death among skin cancers.[3] The average annual cost of skin cancer treatment in the United States more than doubled between 2002 and 2011 to $8.1 billion, whereas the costs of all other cancer treatment only increased by 25%.[42] The increasing incidence of NMSC and melanomas, and the increasing health care and economic costs related to the treatment and management of cutaneous cancers, suggests potential benefit of prevention and screening to decrease severity of this disease burden. However, there remains controversy and conflicting evidence regarding many prevention and screening methods including the efficacy of public health campaigns, benefits of sunscreen use, and cost-effectiveness of skin cancer screening.

Some of the best data regarding skin cancer prevention comes from Australia. In the 1980s, Australia implemented a national skin cancer prevention program focused on clothing, sunscreen, wearing hats, and seeking shade.[43] Between 1988 and 2011, the campaign is estimated to have prevented 50,000 cancers and 1400 deaths and produced a net savings of $92 million.[44] In another Australian study, 25- to 75-year-old people who applied sunscreen regularly for 5 years were found to have reduced melanoma incidence 10 years later.[45]

Although there are various programs focused on education and sun safety that have been reported in the United States, there has never been a national skin cancer prevention program.[15,43] A lack of consensus regarding the efficacy and evidence of beneficial outcomes of skin cancer prevention programs is likely responsible for the current state.

There is no consensus regarding recommendations for sunscreen use. This controversy exists because of some studies showing no decrease and other studies actually

showing an increase in skin cancer incidence with sunscreen use.[46–48] The reasons for these conflicting data may be caused by individuals using lower than recommended SPF or insufficient amounts of sunscreen may be applied to their skin.[49] The use of sunscreen may create a false sense of security leading individuals to possibly have longer sun exposure.[50] Some studies may not have followed study participants long enough, because it may take decades to see the beneficial impact of sunscreen use.[51] The annual cost of sunscreen is $200 to $400 for the average adult, which may be a socioeconomic barrier to use.[52] Free sunscreen dispensers have been suggested and exist in many countries.

Children are an especially vulnerable population because their skin is thinner, has finer hair follicles, and allows greater percutaneous absorption of UVR.[53] Children also tend to spend more time outdoors. Thus, approximately 50% of the estimated total lifetime exposure to radiation occurs before the age of 18.[54] Therefore, public health prevention efforts in children are especially important.

Indoor tanning, despite its obvious risks, remains a popular activity among young people, especially White women.[28] UVR from tanning booths is a known carcinogen and efforts to inform and persuade against this destructive practice is important.[55] Yet evidence points to need to use nontraditional platforms of outreach to more effectively convey this public health message to the target population.

SCREENING

In 2016, the US Preventative Services Task Force found insufficient evidence to recommend skin cancer screening for early detection.[56] A recent Cochrane review found similarly no evidence of benefit from universal screening programs for preventing melanoma.[57] Skin cancer screening for the general public might lead to overdiagnosis and a potential surge in treatment costs without significant mortality benefit.[58] It has been suggested that targeted screening of high-risk populations for cutaneous malignancies may be more worthwhile. By focusing on high-risk populations, it may be possible to prevent delayed diagnosis of melanomas or other skin cancers, which could mean avoiding costlier treatment, more invasive surgery, and the need for systemic treatment as opposed to simple excision.

Supporting the benefits of public skin cancer screening is the German experience of its SCREEN campaign, conducted in 2003 to 2004.[59] As part of a population-based skin cancer awareness campaign, the program included clinician and patient education and training and screening of nearly 20% of eligible adults aged 20 or older with a single annual clinical visual skin examination. On average, identified melanomas were 50% thinner, and there was an 8% relative reduction in melanoma mortality by 2009, suggesting earlier diagnosis and a benefit to the screening campaign. Unfortunately, the mortality benefit could not be sustained with further implementation of the German public health campaign.[60]

Although universal screening may not be cost-effective, targeted screening of high-risk populations is generally accepted by experts as worthwhile. Dermatologic societies have typically considered high-risk population groups to recommend for skin cancer screening to include patients with history of skin cancer or melanoma, organ-transplant patients, Fitzpatrick skin type I to III, family history of melanoma, severely sun-damaged skin, or history of indoor tanning.[56] Individuals from high-risk populations may have up to a 60-fold higher risk for developing skin cancer.[46] For example, people with a history of multiple skin cancers have a probability of developing another skin cancer of 50% within 1 year and 70% within 3 years of their last skin cancer diagnosis.[46]

The goal of screening of high-risk populations is earlier skin cancer diagnosis to allow for less radical surgery and eliminate need for systemic therapy. Ultimately, improved survival is the goal. However, the method of screening even for high-risk populations remains unclear. Increased public awareness and skin self-examination practices have been promoted for the general population by the American Cancer Society.[61] However, the prevalence of doing skin self-examinations in even high-risk groups remains low.[62] Full-body skin cancer screenings by health providers is possible but is fraught with different challenges. Given the higher regularity of visits to primary care providers, these providers would seem well positioned to lead in screenings; however, studies have shown primary care providers may lack sufficient preparation and training to identify early skin cancers.[63] Dermatologists, however, may lack sufficient numbers of providers and adequate time during visits to be able to meet the screening needs of even those at most risk.[59,64] But considering the significant cost savings that could be derived by reducing the burden of advanced skin cancer treatment, a concerted effort to improve quality and the resources available to provide comprehensive skin cancer screening for a defined at-risk population seems an important goal.

New research may provide additional tools to facilitate identification and screening of high-risk populations. UVR is a known risk factor for skin cancer; however, there may be decades between sunburn events and visible skin lesions. Studies have identified biomarkers, including p53, E-cadherin, Snail, Slug, and Twist, that are associated with UV-related progression to SCC and their precursor lesions, actinic kerotoses.[65–67] Multiple heritable mutations are known to be associated with risk for NMSC and melanoma, such as xeroderma pigmentosum and basal cell nevus syndrome.[68,69] Use of biomarkers may facilitate better risk-stratification of populations that would most benefit from skin cancer screening.

Artificial intelligence and machine learning may also provide additional tools to improve the accuracy and availability of skin cancer screenings. A recent promising study using artificial intelligence systems and a neural network trained on 129,450 clinical images found similar performance compared with 21 experienced clinical dermatologists.[70] Implementation of such a tool could potentially allow for tele-remote skin cancer screening location by nondermatologic health care providers.

In summary, cutaneous malignancy is becoming an increasing public health burden in terms of morbidity and cost, associated with changing environmental exposures and increased longevity of the general and the immunosuppressed population. Yet the understanding of the scope of this problem is hindered by lack of robust registries for NMSC. The risk factor responsible for most of these cancers (exposure to UVR) can be mitigated. However, greater consensus is necessary to enact effective prevention and screening programs. New developments, including identification of biomarkers and use of artificial intelligence, show promise for targeting screening efforts.

CLINICS CARE POINTS

- Cutaneous malignancy is becoming an increasing public health burden in terms of morbidity and cost, associated with changing environmental exposures and increased longevity of the general and the immunosuppressed population.
- Exposure to ultraviolet radiation is the risk factor responsible for most of these cancers, and tanning booth use substantially contributes to the incidence of cutaneous malignancies, particularly in younger people.
- Screening programs targeted at high risk populations could significantly reduce the morbidity and cost associated with advanced skin cancer treatment.

DISCLOSURE

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