Skin Cancer: An Overview of Epidemiology and Risk Factors

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Objectives: *To provide a general overview of malignant melanoma and non-melanoma skin cancer, with an emphasis on epidemiology, clinical presentation, and the multiple and varied risk factors associated with skin cancer.*

Data Sources: *Peer-reviewed journal articles, government health reports, book chapters, and Web-based resources.*

Conclusion: *Skin cancer is the most common carcinoma, affecting millions worldwide. Incidence is increasing yearly, making it a pre-eminent public health threat. Myriad factors increase the risk of skin cancer and may serve as important prognostic indicators for the disease.*

Implications for Nursing Practice: *To provide nurses with a clearer understanding of the causative mechanisms of skin cancer and an improved awareness of the risk factors associated with the disease.*

Key Words: *Skin cancer, skin cancer epidemiology, skin cancer clinical presentation, skin cancer risk factors, melanoma, non-melanoma skin cancer*

CUTANEOUS carcinoma, or skin cancer, is a pre-eminent global public health problem. Skin cancer encompasses every ethnicity, socioeconomic and demographic cohort, geographic region, and covers the entire lifespan.[1] Skin cancer represents the most common worldwide malignancy and its incidence shows no signs of plateauing.[2,3] The American Cancer Society estimated in excess of 1.6 million new reported cases of cutaneous malignancy in 2012, and 12,190 deaths from skin cancer.[4] Most new cases were non-melanoma skin cancer (NMSC); however, among new cases, 76,250 were malignant melanoma and most of the 9,180 skin cancer-related deaths were from malignant melanoma.[4] The World Health Organization estimated over 200,000 cases of malignant melanoma and 65,000 malignant melanoma-related deaths worldwide in 2012.[3] Table 1 displays the increased incidence of malignant melanoma in selected countries over a 10-year interval.[5]

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TABLE 1.
Estimated Annual Percentage Change in Melanoma Incidence by Country, Time Period, and Gender

Country*	Time Period	All Ages, Men	All Ages, Women
Australia	1995-2004	0.7	0.2
Canada	1993-2002	1.7	1.3
Costa Rica	1993-2002	4.3	4.2
Denmark	1999-2008	3.6	5.2
Finland	1999-2008	3.4	3.2
New Zealand	1996-2005	1.6	0.9
UK, England	1998-2007	6.7	5.4
USA, (white)**	1999-2008	2.1	2.3
Spain	1991-2000	7.8	4.9

*Statistics are presented for available registries with at least 10 years of data and with annual incidence rates 1/100,000 person-years.
**With the exception of the United States, race was not mentioned in the datasets.
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Although the death rate for malignant melanoma in the United States has been declining in whites younger than age 50 years, the rate among whites older than age 50 years continues to increase each year, particularly in men.[4,6] It is, therefore, incumbent upon health care providers to be knowledgeable about and recognize skin cancer. This article provides a general summary of types of skin cancer, anatomy of normal skin, skin cancer pathophysiology, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), malignant melanoma, skin cancer risk factors and comorbidity, and psychosocial factors.

Types of Skin Cancer

Skin cancer is commonly categorized as malignant melanoma and NMSC, the latter including BCC and SCC as the major subtypes. The actual number of NMSC is difficult to estimate because BCC and SCC cases are not required to be reported to national cancer registries. Researchers both in the United States and several other countries advocate that NMSC registration standards be revised.[1,5] The overall upward NMSC trend observed in most parts of Europe, Canada, the United States, and Australia shows that the increase in NMSC incidence averages between 3% and 8% per year.[6,7] One report on NMSC occurrence in the United States estimated that 3.5 million cases were diagnosed and 2.2 million persons were treated for the disease in 2006—some diagnosed with multiple skin cancers.[4] Even more alarming is the predicted doubling of NMSC incidence over the next 30 years.[6] The majority of NMSC is highly curable, particularly if diagnosed in early stages. Malignant melanoma is the most egregious and least predictable form of skin cancer, particularly if diagnosed at advanced stages.

Anatomy of Normal Skin

To better understand skin cancer, clinicians need basic knowledge of the skin itself. Normal skin consists of the layers of the epidermis, papillary and reticular dermis, and subcutaneous fat (Fig. 1).[8] The epidermis is composed of four sublayers and four major types of cells. These sublayers represent different stages of maturation of the actively dividing cells (keratinocytes), which occur over a 30-day period. The stratum basale (basal layer), the deepest sublayer, is comprised of keratinocytes, which push existing cells to

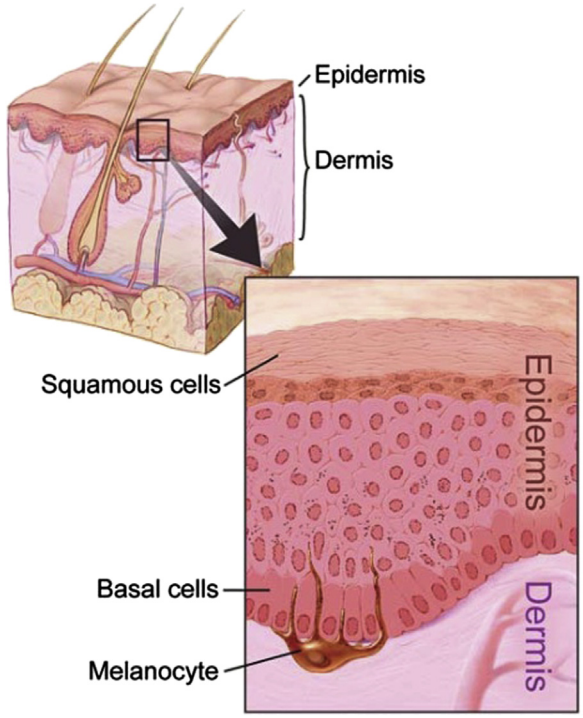

FIGURE 1. **Normal anatomy of the skin. (Source: The National Cancer Institute, available at https://commons.wikimedia.org/wiki/File:Layers_of_the_skin.jpg). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)**

a higher layer. Next are the differentiating cells of the stratum spinosum sublayer, then the stratum granulosum sublayer, where the cells lose their nuclei and secrete lipid into the intercellular spaces. The most superficial of these sublayers is the stratum corneum, which is composed of several laminated and loosely attached keratinized cells. The stratum corneum provides an important barrier function, protecting the underlying layers. Melanocytes reside in the stratum basale and produce the pigment melanin, which protects the skin from ultraviolet radiation (UVR). Langerhans' cells participate in immune system activation; Merkel cells contribute to the sensation of light touch.[9]

Underlying the epidermis is the dermis, which provides support and nutrients for the epidermis. The dermis is composed of fibers and ground substance, and within it are some specialized cells including the hair follicles, sebaceous glands (oil glands), apocrine glands (scent glands), and eccrine glands (sweat glands), as well as blood vessels and nerves that allow sensations of touch, temperature, and pain. Fibroblasts in this area produce collagen and elastin. The subcutaneous tissue layer varies in thickness from person to person, contains fat, connective tissue, some larger blood vessels, and nerves. It contributes to fat storage, regulation of temperature of both the skin and the body, and shock absorption.[9]

Skin Cancer Pathophysiology

The pathogenesis of skin cancer is multifactoral. UVR in sunlight is the main etiological agent in the development of malignant melanoma and NMSC.[6] There are two main types of UVR rays: ultraviolet A (UVA) and ultraviolet B (UVB). UVA rays pass deeper into the skin and can induce deeper skin damage, such as elastosis, than UVB rays.[10] UVB rays predominantly cause erythema or sunburn. UVR produces DNA damage, gene mutations, immunosuppression, oxidative stress, and inflammatory responses, all of which play a pivotal role in photoaging of the skin and skin cancer genesis.[6,7] UVB rays directly damage DNA. The damage to DNA from UVA rays is indirect, mediated by free radical formation and damage to cellular membranes.[6,7] Researchers have suggested an association between skin cancer genesis and UVR-induced immunosuppression. UVR is a complete carcinogen in that it not only initiates tumorigenesis by inducing mutations in tumor suppressor genes, but also promotes tumor development.[11] UVA rays have an important role in the carcinogenesis of stem cells of the skin, and UVB rays induce DNA damage through inflammatory responses and tumorigenesis.[6,12,13]

When UVR penetrates the skin, much of its energy is absorbed by the DNA of epidermal keratinocytes. Researchers hypothesize that DNA is the photoreceptor in the skin, and that UVR-induced cyclobutane pyrimidine dimer formation is the initial molecular step that leads to immune suppression.[11] The mechanics of UVR-induced damage progressing to skin cancer are detailed and complex. UVR creates mutations to *p53* tumor suppressor genes,[11] which are involved in DNA repair or the apoptosis of cells that have DNA damage. Therefore, if *p53* genes are mutated, they are no longer able to aid in the DNA repair process.[10,11] This dysregulation of apoptosis leads to unchecked mitosis of keratinocytes, and initiates skin cancer growth.

A major mechanism of carcinogenesis is UVR-induced free radical damage, and genetically determined ability to metabolize free radicals may also predispose patients to skin cancer. The glutathione S-transferase (GST) enzymes play an antioxidant role by limiting the toxic effects of reactive oxygen species. The glutathione S-transferase polymorphisms (GSTP) enzyme is widely expressed in the dermis and epidermis of the skin, and may be an important mediator of skin cancer development. Deletion of the *GSTP* gene (in animal studies) resulted in a greatly increased susceptibility to skin tumor growth.[14]

Important clinical signs of cutaneous carcinoma include changes in size, shape, color, or texture of a mole or other skin lesion or the appearance of a new growth on the skin. Changes that occur over a few days are usually not cancer, but changes that progress over a month or more should be evaluated by a health care provider.

Basal Cell Carcinoma

Approximately 80% of NMSC is BCC.[15,16] Intermittent UVR exposures and UVR exposures during childhood are cited as predisposing factors.[16] Approximately 80% of all BCC occurs on the head and neck, and clinical diagnosis is fairly straightforward.[17] BCC is a malignant neoplasm derived from the basal cells (Fig. 1).[15] BCC generally appears without precursor lesions (as compared with SCC). Most commonly, BCC presents as a small papule that may enlarge slowly over

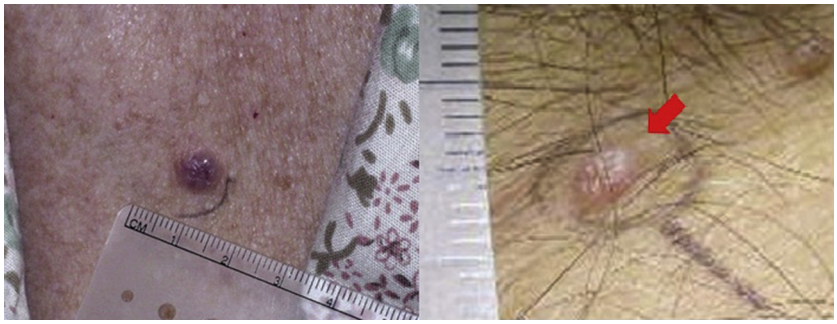

FIGURE 2. Basal cell carcinoma (Image print with permission of Gulf Coast Dermatology). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)

months or years. BCC develops characteristically into shiny papules, with pearly borders, prominent engorged vessels (telangiectasias) on the surface, and a central ulcer (Fig. 2). Variants appear as yellowish-white flat, scar-like patches.[7] Recurrent crusting or bleeding is common. Ambiguous symptoms may include tenderness and itching. BCC may be difficult to distinguish clinically from benign growths; it is often mistaken by patients as pimples. Occasionally, BCC may involute and appear to heal, which may lessen a person's concern about the significance of the lesion. Metastasis is rare, but local growth can be highly destructive.[7]

Squamous Cell Carcinoma

SCC comprises approximately 16% of skin cancer cases.[16] Cumulative habitual sun exposure has a strong association with the incidence of SCC.[7] SCC is a malignant tumor of epidermal keratinocytes that invades the dermis (Fig. 1). Local tissue destruction may be extensive, and metastases via lymphatic or hematogenous spread may occur in advanced stages. The overall metastatic rate is estimated to be 3% to 10%,[16] depending on tumor location, underlying medical conditions, cell differentiation, and size. The clinical presentation of SCC is highly variable, but any nonhealing lesion on sun-exposed surfaces should be suspect. Clinical manifestations include papules, plaques, or nodules, and smooth, hyperkeratotic (crusty), or erosive lesions. The tumor may begin as an erythematous papule or patch with a scaly or rough surface and may become nodular, sometimes with a warty surface or plaque. The tumor may bleed with minimal provocation. Eventually the tumor ulcerates and invades the underlying tissue.[16,18] In some cases, the bulk of the lesion may lie below the level of the surrounding skin (Fig. 3).

The prognosis for small SCC lesions removed early and adequately is generally considered to be excellent. SCC variants include noninvasive and invasive (poorly differentiated) tumors. Initially the cancer spreads regionally to surrounding skin and lymph nodes and eventually to nearby organs. SCC that occurs near the ears, the vermilion border of the lip, and in scars is more likely to metastasize, and may require extensive surgery.[7] Approximately one third of lingual or mucosal cancers have metastasized before diagnosis.[16]

Malignant Melanoma

Malignant melanoma represents only 4% of skin cancer cases,[16] yet accounts for 65% of all skin

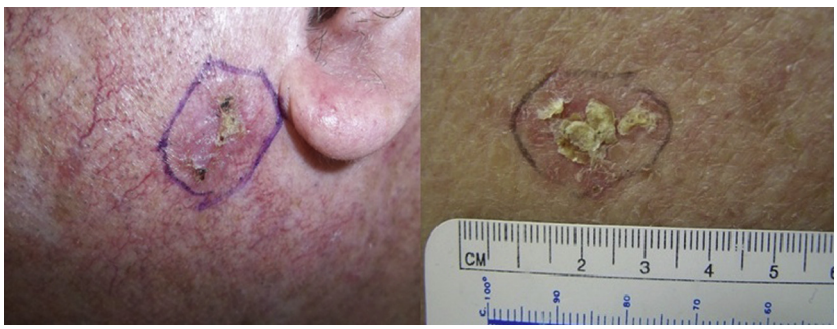

FIGURE 3. Squamous cell carcinoma of the skin (Image print with permission of Gulf Coast Dermatology). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)

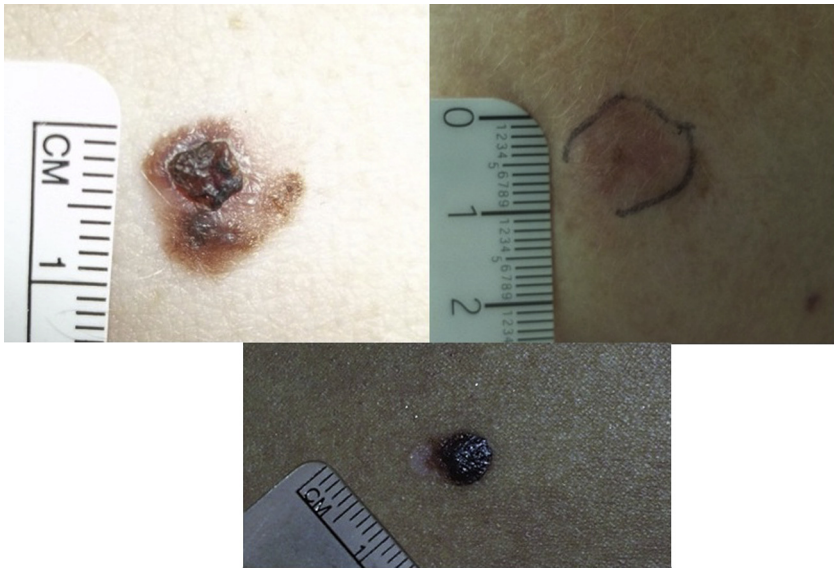

FIGURE 4. Malignant melanoma (Image print with permission of Gulf Coast Dermatology). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)

cancer-related deaths.[19] Incidence rates of malignant melanoma in whites are five times higher than in Hispanics and 20 times higher than in African Americans.[4,6] Malignant melanoma is derived from epidermal melanocytes (Fig. 1) and can occur in any tissue that contains these cells.[19] Malignant melanoma is induced through multiple mechanisms, including suppression of the immune system of the skin, induction of melanocyte cell division, free radical production, and damage of melanocyte DNA. Identification of the melanoma susceptibility gene, *p16*, has elucidated the association between genetics and malignant melanoma. UVR exposure to *p16*-mutated cells allows uncontrolled proliferation of the damaged melanocytes. Random mutations at the *p16* location are responsible for many sporadic (nonfamilial) cases of melanoma.[13,19]

Most malignant melanoma arise on the skin surface and are therefore detectable by visual examination. Clinical features of malignant melanoma vary greatly. The ABCDE rule outlines the clinical presentation and warning signals for most melanomas. "A" stands for asymmetry (one half of the mole does not match the other half); "B" stands for border irregularity (the edges are ragged, notched, or blurred); "C" stands for color (the pigmentation is not uniform, with variable degrees of tan, brown, or black); "D" stands for diameter greater than 6 mm (about the size of a pencil eraser); and "E" represents evolution, elevation, and/or enlargement of a lesion.[4,19] Many lesions suggestive of melanoma will have some but not all of these characteristics (Fig. 4). Approximately 2% to 8% of melanomas are reportedly amelanotic (without pigment).[19]

Skin Cancer Risk Factors

Multiple risk factors exist for all types of skin cancer. These include endogenous factors (phototype, skin and eye color, number of melanocytic nevi, presence of dysplastic nevi, and individual or family history of skin cancer), and exogenous factors (type and degree of cumulative sun exposure, history of sunburn, and sun protection behavior).[20] The main constitutional and environmental risk factors are well known, but it remains unclear how they interact to contribute to the development of skin cancer.[21] Several relative risk factors may serve as important prognostic indicators for the disease (Table 2).[22] Therefore, clinicians must appreciate the importance of taking a detailed patient history, including a social, family, and UVR-exposure history. A discussion of the most common risk factors follows; however, it is not exhaustive.

Ultraviolet Radiation

The chief environmental risk factor for all types of skin cancer is solar UVR exposure. It is often difficult to separate the interrelations among sunburn history, sun exposure habits, ability to tan, and other phenotypic factors. Researchers have suggested that reducing sun exposure during childhood and adolescence through

TABLE 2.
Risk Factors and Relative Risk for Melanoma

Phenotype/Genetic Risk Factors	Relative Risk for Melanoma[22]
Strong family history of malignant melanoma (greater than 3 first degree affected relatives)	35-70
Multiple benign nevi (more than 50) or atypical nevi	11.0
Personal history of melanoma	8.5
Freckles and fair complexion	2.5
Red or blond hair color	2.4
Sun sensitivity (the tendency to burn in the sun rather than tan)	1.7
Blue, green, or gray eye color	1.6

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sun-protective behaviors could reduce the lifetime risk of developing NMSC by as much as 78%.[23] The pattern and amount of sun exposure are significant. Gandini et al[13] investigated sun exposure patterns and made a positive association between intermittent sun exposure and a higher incidence of malignant melanoma. These researchers concluded that the pattern and amount of sun exposure several decades before the diagnosis of malignant melanoma is an important factor. Other research has demonstrated a correlation between cumulative and chronic sun exposure and skin cancer.[12]

Timing of sun exposure appears to be a key factor as well. Karagas et al[24] demonstrated a higher associated risk for skin cancer with sun exposure between 10 AM and 2 PM. While total and occupational sun exposure appear to be mostly associated with the development of SCC, both malignant melanoma and BCC are associated with non-occupational or recreational sun exposure.[25] The geographic variation in incidence of NMSC is associated with ambient sunlight intensity, providing further strong evidence for the relation between NMSC and sun exposure.[7] People who live in locations with year-round bright sunlight, or those who spend a lot of time outdoors without protective clothing or sunscreen, have greater risk for skin cancer.

Precancers

Actinic keratosis (AK), or solar keratosis, develops as a keratotic lesion that occurs on habitually sun-exposed skin (Fig. 5). AK is the most common premalignant skin lesion.[26] AK can be very superficial and may go unnoticed by patients. Davies[26] estimated that 60% of individuals older than age 40 years who are exposed to UVR will develop at least one AK. If untreated, AK lesions carry the risk of malignant transformation to SCC.[15] Researchers have estimated between 25% and 60% of SCC arises from AK.[18,27]

Phenotype/Genetic Factors

Persons who have phenotypic markers of UVR susceptibility, such as fair skin, freckles, light colored eyes and hair, and an inability to tan, have an increased risk of skin cancer.[7] Gender appears to influence relative risk. Men are approximately two times more likely to develop BCC and three times more likely to develop SCC compared with women, a factor that also may be related to increased UVR exposure. Genetic factors include inherited risk. Approximately 8% to 10% of patients with malignant melanoma have a first-degree relative with the disease.[21] Other possible explanations for family incidence could be that the family tends to spend more time in the sun, family members share a similar skin type, or both.[13]

Fitzpatrick[28] created a standard method for classifying individual skin types, according to

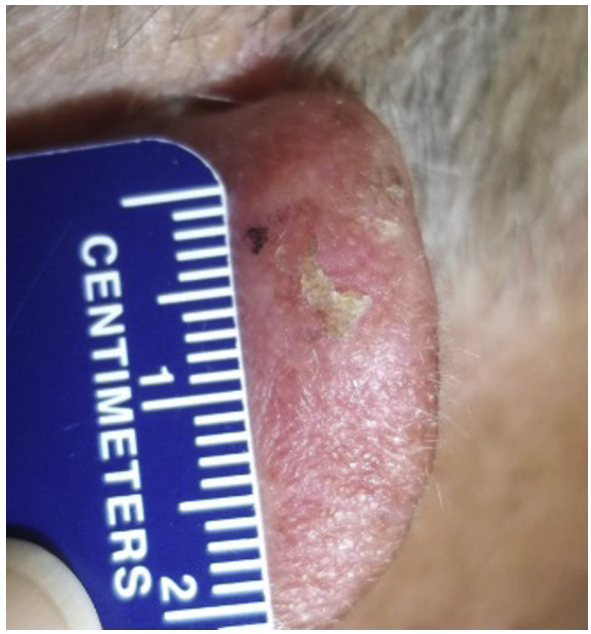

FIGURE 5. Actinic keratosis (Image print with permission of Gulf Coast Dermatology). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)

skin color and burning and tanning responses to UVR exposure. The four categories of skin type range from type I (always burn, never tan) to type IV (never burn, tan easily). Clinicians use these categories widely to assess photosensitivity (skin tendency to sunburn rather than tan).[21]

Atypical and Multiple Nevi

The term *atypical nevus*, also called dysplastic nevus, is used to describe dysplasia underlying a benign congenital or acquired nevus. Concordance among dematopathologists is lacking for making a diagnosis of atypical nevi using the clinical phenotype and histologic criteria.[21] Researchers have estimated that an individual who has dysplastic nevi and at least two family members with malignant melanoma has a 500-fold increase in malignant melanoma risk.[29] UVR may act as both an initiator of new nevi (through sunburn) and a promoter of nevus growth. One risk factor specifically for malignant melanoma is the presence of atypical or numerous moles (more than 50).[29] Families with multiple cases of malignant melanoma often exhibit the dysplastic nevus syndrome, a syndrome characterized by multiple atypical moles that continue to appear in adulthood.[13]

Comorbidity

Basal cell nevus syndrome, also known as Gorlin syndrome, is a rare genetic condition that affects the skin, endocrine, central nervous, and skeletal systems. An individual with basal cell nevus syndrome often develops numerous BCC over his or her lifetime; usually beginning at the onset of puberty.[16] In this condition, BCC occurs on body areas *not* generally exposed to UVR, such as the palms of the hands and soles of the feet, possibly delaying early detection.

Xeroderma pigmentosum (XP), another inherited disease that affects the skin's ability to repair UVR damage, also increases the risk for developing skin cancers, particularly at an earlier age.[16] Nowhere is the linkage between UVR damage and carcinogenesis more clearly demonstrated than in patients with xeroderma pigmentosum, in whom the normal DNA repair machinery is faulty. In these individuals, UVR exposure leads to a high incidence of malignant melanoma and other skin cancers.[19]

Concurrent disease and treatment may influence the overall risk of skin cancer. Psoriasis treatment, specifically psoralen and ultraviolet A light treatment (PUVA) can increase the risk of developing SCC, and potentially other forms of skin cancer. Individuals who have received radiation treatment for skin conditions such as eczema and acne, or for solid tumor reduction such as breast or prostate cancer, may have an increased risk of skin cancer, particularly BCC. Infection with certain types of human papilloma virus (HPV), particularly those that affect the anal or genital area, may increase skin cancer risk.[30]

Organ Transplantation

Medically induced immunosuppression, common in organ transplantation recipients, is well documented in the literature as a significant skin cancer risk factor.[15,27,31-33] In white transplant recipients, the risk of SCC increases 65- to 250-fold compared with the non-transplanted population, and the risk of BCC increases 10- to 16-fold (Fig. 6).[7,18] Incidence rates are likely different based on concomitant risk factors.[27] The key to managing the organ transplantation recipient lies in a multidisciplinary approach of patient education (including decreasing known risk factors), skin self-examination and dermatologic screening, and regular follow-up.

Secondary Malignancies

SCC antigen is a subfraction of the tumor-associated antigen TA-4 and shows a high specificity in a variety of squamous cell cancers in humans. Serum SCC has been established as

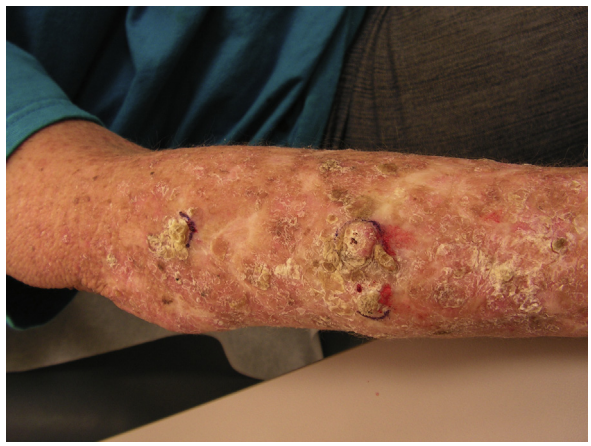

FIGURE 6. Squamous cell carcinoma of the skin in an organ transplant recipient (Image printed with permission of the Skin Cancer Institute at the University of Arizona Cancer Center). (This figure is available in color on the journal's Web site at www.nursingoncology.com.)

a valuable tumor marker in SCCs of the uterine cervix, of the lung, and of the head and neck region. Research demonstrates a good correlation of the serum SCC with the extent of disease prognosis and prediction of recurrence of the primary tumor. Nevertheless, there are a large number of benign diseases, such as inflammatory conditions, exhibiting an elevation of serum SCC, which may limit the value of this marker.[34]

Risk of skin cancer recurrence after treatment is influenced by multiple factors besides treatment modality, including the location, size, and histological subtype of the tumor and the age, sex, and immune status of the patient.[18] Risk of recurrence for patients with NMSC approximates 4% within the first 5 years, rising to 9% within 10 years.[35] However, researchers have not reached consensus on the incidence of developing new or subsequent skin cancers.[1,7,16,18,36] One key risk factor for subsequent skin cancers is the number of previous skin cancers. One study that tracked 300 patients in Australia over 10 years found at least one new skin cancer developed in 67.8% of patients previously diagnosed with NMSC and multiple skin cancers in 51.8%.[37] Men who had a NMSC were eight times more likely than the general population to develop malignant melanoma, while women who had a NMSC were four times more likely.[35,38] One probable explanation for this relatively steep acceleration in the incidence rate and number of cases is a heightened index of suspicion regarding any new or changing skin lesion. These findings strongly support the need for careful and frequent follow-up.

Psychosocial Factors

Many theorists suggest that people with higher perceived vulnerability to illness (higher perceived risk) are more likely to practice health-promoting behavior.[39] Several health psychological factors associated with health-promoting behavior are risk perception, including perceived susceptibility, the seriousness and treatability of a disease, and the effectiveness of preventive actions.[40] According to researchers, people concerned about skin cancer are aware of UVR exposure as an important risk factor for skin cancer, but may fail to use this information to change sun exposure behavior in a consistent way.[40] In addition to these psychological factors, age, income, and education vary in association with risk perceptions and behavior.[39]

In recent decades, indoor tanning has become a common source of UVR. During a typical 2- to 15-minute session in a tanning bed, the controlled dose of UVR absorbed by the skin is two to three times stronger than the sunlight striking the equator at noon.[41] One study among college students found appearance-based factors to be the strongest motivating factor for tanning bed use.[42] Another study revealed tanning bed use was associated with a 1.5-fold increase in the risk of BCC and a 2.5-fold increase in the risk of SCC.[18] Relative risk estimates for NMSC steadily increased with younger age at first exposure to a tanning device. However, previous research may have greatly underestimated the risk. According to a meta-analysis of 27 European studies between 1981 and 2012, tanning bed use increased the risk of skin cancer by 20%, and rose to 87% if exposure was before the age of 35.[43]

Socioeconomic factors such as a lower level of education and lack of health insurance may affect an individuals' knowledge of skin cancer. As a result, these individuals may have a poor sense of risk-reducing strategies for skin cancer. Uncertainty and inaccurate perceptions may be more frequent in the risk perceptions of the elderly, ethnic minorities, and those with less education.[44] Socioeconomic factors may influence individuals to labor in environments that increase their sun exposure, such as farming or construction. Workers exposed to chemicals secondary to occupational hazards, including arsenic, industrial tar, coal, paraffin, and certain types of oil, may have increased risk for certain skin cancers.[45] Numerous national agencies have launched cost-effective public education campaigns directed toward those at greatest risk of skin cancer and populations at risk for high morbidity and mortality.

Conclusion

Skin cancer is the most common carcinoma, affecting millions of people worldwide. The incidence of skin cancer is increasing, making it a pre-eminent public health threat. A variety of endogenous and exogenous risk factors increase the potential for skin cancer to develop. Many risk factors may serve as important prognostic indicators for the disease. Clinicians should be encouraged to: 1) remain vigilant regarding visual

surveillance of patient's skin, 2) possess a high index of suspicion regarding skin lesions involving any patient who might be at increased risk for skin cancer, 3) identify skin cancer early, and 4) promote better health for patients by reducing modifiable risk factors.

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