CARCINOMAS & KERATOSES

Clinical insights into the world's most common skin cancers
A publication of The Skin Cancer Foundation
President: Deborah S. Sarnoff, MD

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Why Keratinocyte Carcinomas, the Most Common Skin Cancers, Deserve to Be Taken More Seriously

In This Issue

Welcome to Our First C&K

The most common cancers in the world are often referred to as "nonmelanoma skin cancers." We believe it is time to stop talking about what they are not and focus more seriously on what they *are*. We hope *Carcinomas & Keratoses* will help medical professionals keep up with developments in its category just as The Melanoma Letter has done with its topic since 1982.

Keratinocyte cancers and precancers arise in keratinocytes, the most common type of skin cells in the epidermis. They include the two most common skin cancers, basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC), and actinic keratosis (AK), the most common skin precancer. In truth, if not treated at an early stage, these lesions recur with regularity and can become disfiguring and even life-threatening. The latest figures suggest, in fact, that in 2019, more than twice as many people (over 15,000) will die from cSCC in the U.S. than from melanoma (7,230).

Even when caught early, these cancers may sometimes recur, partly depending on the method of removal. Other tumors may also develop in the same vicinity of the face or body. This "field cancerization" can result after years of repetitive exposure to ultraviolet (UV) radiation. The accumulated DNA damage causes mutations that can lead to further malignancies well beyond the clinical margins of the first lesion. Being diagnosed with multiple keratinocyte cancers can seriously affect a patient's quality of life.

Carcinomas & Keratoses will have a lot of ground to cover, from new strategies for early detection and diagnosis to breakthrough treatments for advanced BCC and cSCC.

In our inaugural issue, Mark Teich, The Skin Cancer Foundation's scientific director, and Kishwer Nehal, MD, discuss what keratinocyte carcinomas are and why the traditional term for them, "nonmelanoma skin cancers," is becoming outmoded. She stresses that the dangers of these cancers need to be more widely recognized, especially now when so much exciting research and such far-reaching clinical developments are occurring in the field.

The Feature

We Must Start Thinking Differently About These Skin Cancers

Kishwer Nehal, MD, is director of Mohs and dermatologic surgery and codirector of the multidisciplinary skin cancer management program at Memorial Sloan Kettering Cancer Center in New York City. Dr. Nehal serves on the National Comprehensive Cancer Network (NCCN) panel on nonmelanoma skin cancer and the American Joint Committee on Cancer (AJCC) squamous cell carcinoma expert panel. She recently coauthored a major overview, "Update on Keratinocyte Carcinomas," published in the *New England Journal of Medicine*.

Mark Teich: More than 5.4 million basal and cutaneous squamous cell carcinomas (BCCs and cSCCs) occur each year in the U.S., versus 96,000 invasive melanomas. Yet we call the former "nonmelanoma skin cancers," which almost demeans them, suggesting they are less serious than melanomas. Now, experts like you have suggested calling them "keratinocyte carcinomas." What value do you see in changing this nomenclature?

Kishwer Nehal, MD: The term "nonmelanoma skin cancers" is vague and confusing, lumping together all skin cancers beyond melanoma. You would never call a man a nonwoman or a woman a nonman. It's time for us to use a term for these skin cancers that is distinct and unique. Dr. Martin Weinstock, a professor of dermatology at Brown University, introduced the phrase "keratinocyte carcinomas" (KCs) to describe BCCs and cSCCs, which both arise in epidermal keratinocytes. The term KC allows us to distinguish BCC and cSCC from other skin cancers including Merkel cell carcinoma (MCC), microcystic adnexal carcinoma and sebaceous carcinoma, and more and more of us are using it. I think the terminology is in transition. But old habits are hard to get rid of, and it will take time.

Unlike with melanomas, the tumor registries don't track KCs, and there is a misperception that they are all easily treated. Many are. But there's a large subset involving major morbidity and even mortality, and the mortality rates aren't reported consistently on death certificates because they're not being tracked. All of this contributes to the confusion and misperceptions. As the term KC becomes more recognized, it will allow patients, physicians and researchers to more accurately address BCC and cSCC diagnosis and treatment needs and will help correct the mistaken belief that these skin cancers are less important.

MT: How can we help the public better understand how destructive and dangerous KCs really are?

KN: Compared to melanoma, there has been a definite gap in public awareness of KC. It's important to understand that BCCs and cSCCs outnumber all other cancers worldwide. Their sheer numbers and the increasing rates in both older and younger people present a major health and economic burden on individuals and on the entire health care system. And there is such a wide range of KC disease, from early curable cases that can be easily treated in the office to advanced, potentially lethal cancers that require complex multidisciplinary treatment.

Although deaths from aggressive cSCC represent a small subset of cases, they are approaching or exceeding melanoma deaths. (In 2019, cSCC deaths in the U.S. are expected to be more than double those from melanoma.) And the figures are undoubtedly higher; because of the poor tracking, these cases are underreported.

Furthermore, cure rate and mortality rate aren't everything. Even many BCCs and cSCCs that aren't lethal seriously affect quality of life. They can leave an indelible mark on the face, having a major functional and aesthetic impact. Many physicians and researchers are now focusing on patients' quality of life, on how they cope with wound healing, scarring and issues such as body dysmorphism after treatment. Patients also suffer from cancer-related anxiety, since the risk of a second keratinocyte carcinoma within five years is over 40 percent after a first lesion and over 80 percent after a second. Compounding the anxiety, patients with multiple prior KCs have a higher risk for developing melanoma.

MT: What do medical professionals and researchers need to learn based on the rising mortality numbers and high odds of recurrence?

KN: We have many treatment questions to answer and many areas of research to pursue. Certainly, we need to reduce the odds of recurrence. We must learn to grade tumors better and find better ways of predicting risk, so that we can determine which lesions initially need more treatment. Although we have treatment guidelines for low-risk and high-risk BCC and cSCC based on expert consensus, many treatment approaches have not been prospectively studied to compare recurrence rates. Recently, we developed the first staging systems for cSCC, to define which stages are at risk for nodal and systemic metastasis, but we need trials to guide imaging and lymph node management, and to determine the role of adjuvant radiation and systemic therapy. We also want to home in on molecular markers that can predict which cSCCs have metastatic potential.

In addition, we need to better understand and harness the immune system. cSCCs have a high rate of mutations, and immunosuppressed individuals frequently develop multiple aggressive cSCCs. The first immune checkpoint inhibitor was recently FDA-approved for advanced and metastatic cSCC, and hedgehog pathway inhibitors have had unprecedented success with locally advanced and metastatic BCC. There is growing interest in these areas, with new drugs emerging.

MT: What do we need to learn about prevention? How do we avoid these diseases in the first place, and how can we best prevent recurrence?

KN: It is well established that both intermittent and cumulative ultraviolet A and B exposure from the sun are the main causes of KC — but we need to raise awareness that indoor tanning beds are also harmful. PUVA (psoralen UVA, a traditional UV light therapy) plays a part in people treated for psoriasis, eczema, vitiligo and certain other skin maladies. There are also industrial causes such as chemicals and radiation.

We have learned that that we can effectively counsel children and young adults to improve sun-protective behavior [such as seeking shade and wearing sun-protective clothing], and daily use of sunscreens has been shown to reduce the risk of developing cSCC. We are also studying multiple

strategies to reduce the risk of new or recurring BCCs and cSCCs in individuals with prior KCs, including nicotinamide supplements and topical therapy with 5 percent fluorouracil. Ultimately, successfully preventing KC will require further public education and expanded research efforts to tackle the staggering skin cancer numbers. There is so much to learn, and the knowledge we gain will serve us well down the road.

Editor's View

Désirée Ratner, MD
Editor-in-Chief, *Carcinomas & Keratoses*

It is my great pleasure to introduce this inaugural issue of *Carcinomas & Keratoses*, a new Skin Cancer Foundation digital publication focusing on keratinocyte skin cancers and their precursors. Our goals for the publication are twofold. First, we want to provide current, relevant, accessible information to medical professionals on key issues related to the keratinocyte cancers and precancers, from epidemiology, pathogenesis and prevention to detection, diagnosis and treatment. In so doing, we hope to achieve our second goal, to help you provide the best care possible to patients who have or are at risk for skin cancer. With over 5 million keratinocyte skin cancers likely to be diagnosed in more than 3 million people in the U.S. just this year, we consider this to be important work, and we have many exciting new developments to tell you about from issue to issue — new treatments for AK and for advanced BCC and cSCC, new imaging technologies to help in early diagnosis and new avenues for prevention, to name just a few. We can’t wait to share them with you.

Each issue will focus on a different theme or advance that we consider to be “of the moment.” An original interview with or article by an expert steeped in knowledge of this advance will be the centerpiece of each issue. We will also offer you our analyses of why this development is important and what patients need to know about it.

We hope you enjoy reading *Carcinomas & Keratoses* as much as we have enjoyed planning, researching and writing it; we want you to come away with at least one valuable bit of knowledge from each issue that will help you in your practice or research.

Patient Takeaway

- Keratinocyte carcinomas are the two most common skin cancers, basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (cSCC). Actinic keratosis (AK), the most common skin precancer and often a precursor to cSCC, also arises in the keratinocytes in the skin's outermost layer.
- Keratinocyte carcinomas should not be taken lightly. Delaying detection or treatment can have serious consequences.
- Many patients with one skin cancer develop more. The risk of a second keratinocyte carcinoma within five years is more than 40 percent after a first lesion and about 82 percent after a second lesion.
- New drugs are emerging for patients with advanced keratinocyte cancers. Hedgehog inhibitors have shown efficacy for patients with advanced BCC when surgery, radiation and traditional chemotherapy have failed, and the first checkpoint blockade immunotherapies have been approved for advanced cSCC.

Additional Resources

SkinCancer.org

https://www.cancer.gov/types/skin/hp, The National Cancer Institute website's section on skin cancer for health professionals.

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