# Cutaneous Squamous Cell Carcinoma

Vishwas Parekh, MD[a], John T. Seykora, MD, PhD[b,*]

**KEYWORDS**

• Squamous cell carcinoma • Actinic keratosis • Keratoacanthoma
• Spindle cell squamous cell carcinoma • Desmoplastic squamous cell carcinoma
• Acantholytic squamous cell carcinoma • Pathogenesis

**KEY POINTS**

- There is a persistent trend for an increasing incidence of cutaneous squamous cell carcinoma (cSCC).
- It is crucial to differentiate cSCC from the benign and reactive squamoproliferative lesions and report the high-risk features associated with an aggressive tumor behavior.
- Understanding the molecular mechanisms that drive the development and progression of cSCC is necessary to develop diagnostic and prognostic assays and targeted therapies.

## INTRODUCTION

### *Epidemiology*

Nonmelanoma skin cancer is the most common malignancy worldwide. Historically, cutaneous squamous cell carcinoma (cSCC) has been thought to comprise about 20% of all nonmelanoma skin cancers, thus being the second most common malignancy after basal cell carcinoma (BCC), with a ratio of BCC to SCC estimated to be 4:1.[1,2] However, recent data indicate that there is a significant shift underway in the relative proportion of nonmelanoma skin cancer, with the ratio of BCC to SCC found to be 1.0 in the US Medicare population.[3] Several other studies bear out a trend for an increasing incidence of cSCC compared with BCC, particularly in the aging population.[4–8] An accurate incidence of cSCC is not known because it is not required to be reported to national cancer registries; however, a metaanalysis of population-based studies estimated that in 2012, 186,157 to 419,543 white individuals were diagnosed with cSCC in the United States alone. Note, these estimates do not include squamous cell carcinoma in situ (SCCIS), which likely occurs more frequently.[9]

[a] Department of Pathology, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA, 91010, USA; [b] Department of Dermatology, Perelman School of Medicine, University of Pennsylvania, Room 1011 BRB II/III, 421 Curie Boulevard, Philadelphia, PA 19104, USA
* Corresponding author.
*E-mail address:* john.seykora@uphs.upenn.edu

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### *Etiopathogenesis*

Most cSCC arise in the sun-damaged skin of the elderly white individuals of European ancestry, in the background of preexisting lesions of actinic keratosis (AK).[1] Apart from ultraviolet (UV) radiation exposure, other predisposing factors include chronic immunosuppressed state (solid organ transplantation, human immunodeficiency virus infection),[10–13] chronic skin conditions (burn scars, hidradenitis suppurativa, chronic osteomyelitis, discoid lupus erythematosus, lichen plans, lichen slecrosus et atrophicus),[14–20] inherited genetic conditions (albinism, epidermolysis bullosa, xeroderma pigmentosum),[21–23] exposure to ionizing radiation,[24] chronic arsenic exposure,[25] human papillomavirus infection,[26,27] and treatment with BRAF inhibitors (vemurafenib and dabrafenib),[28] among others.

### *Clinical Features*

AK and SCCIS are considered to be the precursor lesions of cSCC in most instances, and, frequently, patients present with cSCC in association with numerous precursor lesions. AK and SCCIS typically present as flesh-colored, pink, brown, often pigmented, scaly patches, papules, or plaques on an erythematous base. Lesions of cSCC manifest a range of clinical presentations, including papules, plaques, or indurated nodules with a smooth, scaly, verrucous, or ulcerative surface. Cutaneous SCC can be asymptomatic, pruritic, or tender. Local neuropathic symptoms such as numbness, burning, paresthesia, or paralysis are associated with perineural invasion.[29] Although cSCC typically arises on the sun-exposed areas of fair-skinned individuals and often on the sun-exposed areas of dark-skinned individuals, an involvement of the non–sun-exposed areas is more common in dark-skinned individuals.[30,31]

## PRECURSOR LESIONS

### *Actinic Keratosis*

Also known as solar keratosis, AK represents an early precursor lesion that can accumulate additional mutations and in some cases progress to SCCIS and invasive SCC.[32] Clinically, AKs often manifest spontaneous regression and approximately one-third of AKs exhibit regression in 1 year.[33]

Histologically, AK occurs as a proliferation of cytologically atypical keratinocytes that is confined to the lower levels of the epidermis. The lesional cells show loss of polarity, increased size, pleomorphic and hyperchromatic nuclei, and an increased number of mitoses. There is often an increased nuclear:cytoplasmic ratio within lesional cells. There is crowding of the basal portion of the epidermis with variable acanthosis and/or budding of the neoplastic keratinocytes in the papillary dermis, without breach of the basement membrane. By definition, the atypical proliferation does not occupy the full thickness of the epidermis. Hypogranulosis is often seen. The stratum corneum overlying the atypical keratinocytes typically shows hyperkeratosis with parakeratosis. Because the preneoplastic process usually spares the adnexal structures, this results in alternating areas of orthokeratosis and parakeratosis (flag sign). The underlying dermis almost invariably shows solar elastosis, which represents an important diagnostic clue. AKs exhibit a variety of histologic variants with a broad range of histologic patterns.[34,35]

#### *Pigmented actinic keratosis*

This variant shows hyperpigmentation of the lower epidermal layers owing to an increased amount of melanin in the basilar keratinocytes. Melanophages may be present in the superficial dermis. It is important to recognize this entity because it can be