Cutaneous squamous cell carcinoma

Incidence, risk factors, diagnosis, and staging

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Learning objectives
After completing this learning activity, participants should be able to describe the incidence of cSCC and define factors that are independently associated with poor outcomes on multivariate analysis of cSCC; outline the various staging systems for cSCC, the features that upstage a cSCC, and the rate of local recurrence, metastatic disease, and disease specific death at each stage; and identify aggressive cSCC that require further work-up and treatment.

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Cutaneous squamous cell carcinoma (cSCC), a malignant proliferation of cutaneous epithelium, represents 20% to 50% of skin cancers. Although the majority of cSCCs are successfully eradicated by surgical excision, a subset of cSCC possesses features associated with a higher likelihood of recurrence, metastasis, and death. The proper identification of these aggressive cSCCs can guide additional work-up and management. In the first article in this continuing medical education series, we discuss the incidence, recurrence rates, mortality rates, and risk factors associated with cSCC and review the staging systems used to stratify patients into high- and low-risk groups. The second article in this series reviews the treatment options for cSCC, with focused attention on the management of high-stage tumors. (J Am Acad Dermatol 2018;78:237-47.)

Key words: 5-fluorouracil, imiquimod, ingenol mebutate; acitretin; American Joint Commission on Cancer; Brigham and Women's Hospital staging system; capecitabine; *CDKN2A*; cetuximab; chemotherapy; classification; cSCC; CT; cutaneous squamous cell carcinoma; familial cancer syndromes; high-risk; management; MRI; N1S3 staging; nicotinamide; nivolumab; *NOTCH1*; p53; PD-1; pembrolizumab; photodynamic therapy; radiation therapy; Ras; retinoids; risk factors; sentinel lymph node biopsy; sirolimus; staging.

EPIDEMIOLOGY AND ESTIMATES OF INCIDENCE

Key points

- **Cutaneous squamous cell carcinoma is the second most common nonmelanoma skin cancer after basal cell carcinoma, and in some studies approaches the incidence of basal cell carcinoma**
- **The incidence of cutaneous squamous cell carcinoma is increasing yearly in the United States**

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Abbreviations used:

AJCC-8:	American Joint Committee on Cancer, 8th edition
BCC:	basal cell carcinoma
BWH:	Brigham and Women's Hospital
CDKN2A:	cyclin-dependent kinase inhibitor 2A
cSCC:	cutaneous squamous cell carcinoma
EGFR:	epidermal growth receptor factor
HPV:	human papillomavirus
MAPK:	mitogen-activated protein kinase
N1S3:	revised nodal staging system for head and neck cSCC
PD1:	programmed cell death protein 1
SOTR:	solid organ transplant recipient
TP53:	tumor protein p53

- **Estimates of mortality rates of cutaneous squamous cell carcinoma approximate that of renal and oropharyngeal carcinomas and melanoma in the southern and central United States**

Cutaneous squamous cell carcinoma (cSCC) is the second most common nonmelanoma skin cancer/keratinocyte carcinoma. While cSCC traditionally accounted for 20% of skin cancers, a recent study cited a 1:1 ratio between basal cell carcinoma (BCC) and SCC in the Medicare fee-for-service population.[1] Data from the Rochester Epidemiology Project, conducted by the Mayo Clinic, showed an overall 263% increase in the incidence of cSCC between the 1976 to 1984 and 2000 to 2010 periods.[2] Rates are likely increasing with the growing elderly population[3] and the increased focus on skin cancer screening.

Unfortunately, cSCC is not included in the US national tumor registries, making it difficult to know the exact incidence and mortality rates in our country. European data show that the age-standardized incidence of cSCC ranges from 9 to 96 per 100,000 male inhabitants and 5 to 68 per 100,000 female inhabitants (2002-2007 estimates).[4-6] In Australia, the incidence of cSCC was as high as 499 per 100,000 for men and 291 per 100,000 in women (2002 estimates).[7] In 2011, the cSCC mortality incidence in Australia was 2 per 100,000 individuals.[8] A study in Denmark estimated that 3% to 4% of cSCCs diagnosed in 1984 were associated with cSCC-specific mortality.[9]

In the United States, a 2012 estimate by Karia et al[10] suggested that 5604 to 12,572 people with cSCC developed nodal metastases and 3932 to 8791 people died from cSCC in the United States in that year. The incidence of cSCC was higher in the southern and central United States, where the estimated mortality rate approximates that of renal and oropharyngeal carcinomas and melanoma.

Given its increasing incidence and potential for poor outcomes, cSCC is emerging as a public health problem. Understanding the features of cSCC associated with poor prognosis can help dictate an appropriate work-up and management strategy.

PATHOGENESIS AND ETIOLOGIC RISK FACTORS

Key points

- **Genes commonly mutated in patients with cutaneous squamous cell carcinoma include *TP53*, *CDKN2A*, *Ras*, and *NOTCH1***
- **Risk factors that predispose to the development of cutaneous squamous cell carcinoma include light skin (Fitzpatrick skin types I-III), age, male sex, exposure to sunlight or other ultraviolet radiation, immunosuppression, human papillomavirus, chronic scarring conditions, familial cancer syndromes, and environmental exposures, such as arsenic**

Molecular basis

cSCC carries more mutations than other common malignancies—5 times the mutation rates in lung cancer[11] and >4 times the mutation rates in melanoma.[12] Through the accumulation of these mutations and other cellular changes, an area of skin (usually in response to ultraviolet light damage) can progress through increasing levels of dysplasia and transform into a cSCC.

Tumor protein 53 (*TP53*) is the most commonly mutated tumor suppressor gene in patients with cSCC. Most of the *TP53* mutations in cSCC are C→T single-base transition mutations at dipyrimidine sites.[13] *TP53* mutations enable tumor cells to resist apoptosis and expand clonally at the expense of neighboring normal keratinocytes. Other mutations commonly involved are cyclin-dependent kinase inhibitor 2A mutations (*CDKN2A*), involved in cell cycle control proteins[14]; *Ras* mutations, involved in cellular signal transduction; and mutations of Notch homolog 1, a tumor suppressor gene that acts as a gatekeeper event in cSCC carcinogenesis.[15] Most cSCCs have a multitude of other mutations in addition to these 4. Also, mutations in *TP53* and *Ras* have been found in sun-damaged skin (actinic keratosis).[16-19] This suggests that mutations in *TP53*, *CDKN2A*, and *Ras* may be early events from ultraviolet light damage that set the stage for cSCC development, but other additional mutations are likely required for tumor formation and growth.

Understanding this molecular basis can help pave the way for targeted therapy in the future, although the sheer number of mutations in cSCC may make single-agent targeted therapy infeasible. At the