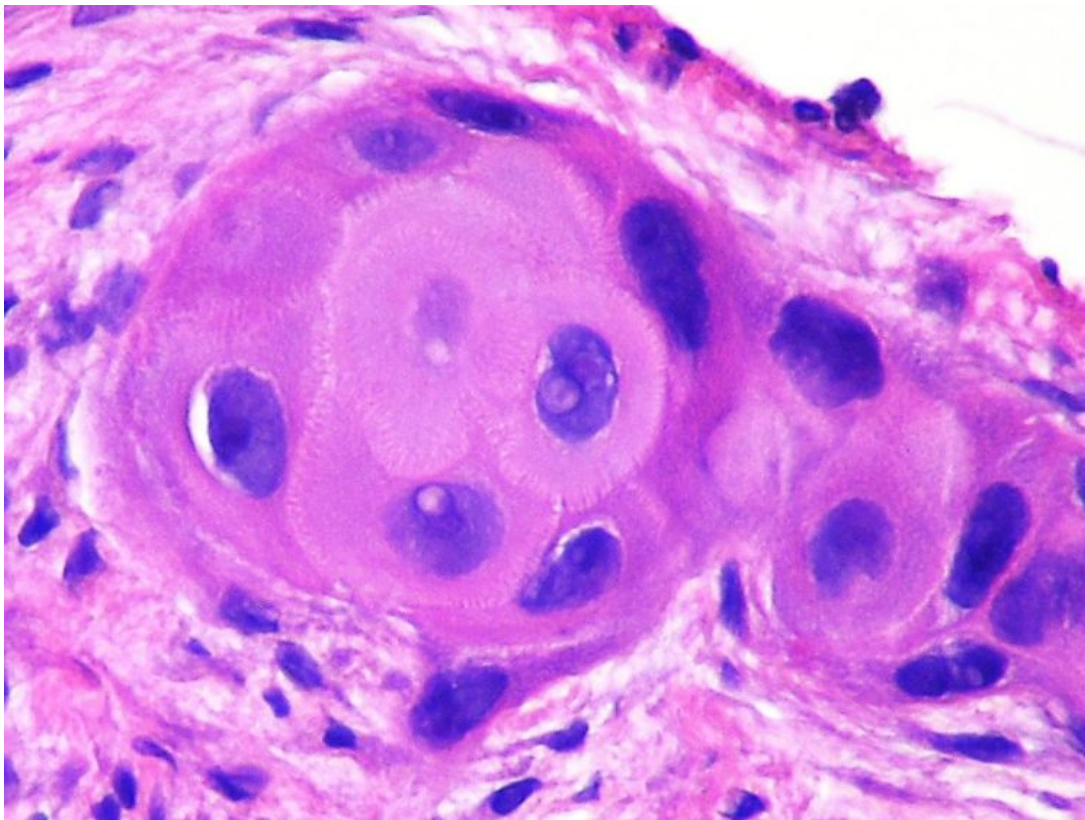


Squamous Cell Carcinoma (SCC, SqCC) — Classification, Symptoms and Treatment

[See online here](#)

Cutaneous squamous cell carcinoma represents one of the most common malignancies in humans. The malignant tumour arises from suprabasal epidermal keratinocytes that invade the dermis and together with basal cell carcinoma, forms the most common malignancies of skin to affect humans. But unlike basal cell carcinoma that is thought to arise de novo, this non-melanoma skin cancer is thought to evolve from precursor lesions of actinic keratosis (AK) and Bowen's disease. The clinical appearance is highly variable but a strong suspicion must be kept in mind if a non-healing lesion presents, specially on sun exposed areas. Histopathological evidence helps in establishing the diagnosis. While a multitude of treatment options are available, prevention in patients with predispositions should attract more attention.



Definition and Epidemiology of Squamous Cell Carcinoma

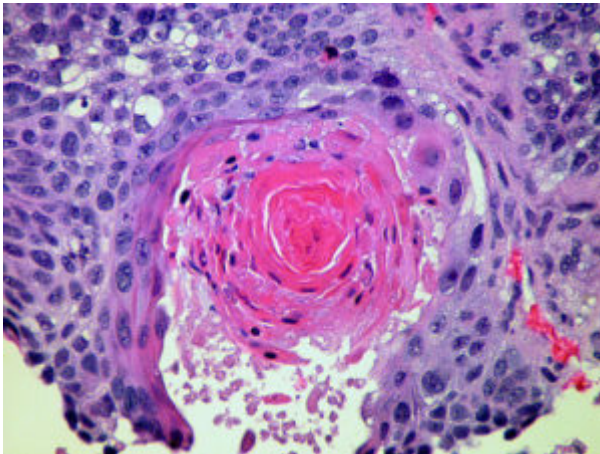
Cutaneous squamous cell carcinoma is a **non-melanoma skin cancer** arising from

suprabasal epidermal keratinocytes.

Non-melanoma skin cancers are the most common types of skin cancers affecting humans. SCC is the **second most common non-melanoma skin cancer** after basal cell carcinoma. It is seen most frequently in sun-exposed areas in people over 40. White males are more likely to be affected by this cancer; however, SCC is the most common skin cancer in patients with darker skin types.

Classification of Squamous Cell Carcinoma

Precursor lesions



[Image](#): "Squamous cell carcinoma" by Yale Rosen. License: [CC BY-SA 2.0](#)

- Actinic keratosis (AK)
- SCC in situ (Bowen's disease)

Direct exposure to the sun

- SCCI (invasive SCC)
- Clear cell SCC
- Spindle cell SCC
- SCC with single-cell infiltrates

Unrelated to sun exposure

- De novo SCC
- Verrucous carcinoma
- LELCS (lymphoepithelioma-like carcinoma of the skin)

Etiology and Pathogenesis of Squamous Cell Carcinoma

SCC is associated with both **acquired** and **genetic risk factors**.

Predisposing factors

Precursor lesions

Most SCCs develop from precursor lesions – AK or Bowen’s disease.

UV exposure

- Predominant risk factor
- A linear relationship between UV exposure and SCC incidence
- Incidence of SCC doubles with every 8-10 degree decline in latitude
- Highest incidence at the equator

Ionizing radiation

Patients susceptible to **sunburns** are more at risk of developing SCC.

Environmental carcinogens

- Other than anthracene and 3-methylcholanthrene, chemical carcinogens generally produce more SCC than BCC
- Alcohol and smoking are associated with SCC of the oral cavity

Chronic immunosuppression

- Patients on long term **corticosteroid**, **azathioprine** or **cyclosporine** therapy found to be susceptible to SCC
- An 18-fold rise in patients with **renal transplant**
- More aggressive behavior in patients with [HIV](#), [leukemia](#), lymphoma

Human papillomavirus

- Verruca pus carcinoma is associated with many variants of HPV
- SCC of head, neck and periungual region are associated with HPV

Thermal factors

Chronic heat exposure is also a risk factor.

Scars and underlying diseases

- Associated with burns and chronic infection
- Vaccination scars are more associated with BCC than SCC

Genodermatoses

- Variety of heritable diseases predispose to SCC
- Xeroderma pigmentosum, a dystrophic form of epidermolysis bullosa, epidermodysplasia verruciformis, and oculocutaneous albinism

Molecular aspects

Genetic alterations

- Chromosomal deletions in chromosomes 3,7,9,11
- Involvement of p53 tumor suppression genes

Involvement of p53 genes

- [Apoptosis](#) of keratinocytes with UV damage is regulated by p53 tumor suppressors, which are a defense against malignant transformation
- Loss of function of p53 leads to increased resistance of UV damaged cells to apoptosis; they proliferate and survive better – increasing the risk for SCC

Other apoptotic regulators

- *Bcl-2* inhibition in vulvar SCC
- *Bcl-XL* in tumor invasion and metastasis
- *Bax* in SCC tongue

Clinical Manifestations of Squamous Cell Carcinoma

Development from precursor lesions



Image: "Actinic keratoses are precancerous lesions common on sun-exposed areas of the skin. They can assume many different appearances, but this image shows a very common presentation of AKs on a balding head." by Future FamDoc - Own work.

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Actinic keratosis

- Multiple lesions
- Pinpoint to over 2cm in size
- Ill-defined borders
- Rough gritty texture

Bowen's disease

- Isolated lesions
- Variable size
- Sharply demarcated lesions
- Non-pruritic scaling papules or plaques

The development of tenderness, induration, erosion, increased scaling, or enlarging diameter indicate evolution into SCC.

Morphologies of SCC

SCC can present in many different ways. The **most common presentation** is a **firm, erythematous, keratotic plaque or papule**; however, ulcers, thick cutaneous horns, or nodules can occur.

In **periungual location**, the **abscess or verrucous form** of SCC is more common. As the tumor progressively invades, it loses its free character and fixes to the underlying

tissue. In the head and neck region, **enlarged lymph nodes** indicate tumor [metastasis](#).

Usual **sites of presentation** include the **oral cavity** (involving the palate and tongue), and more commonly, the **lower lip**, as well as the genital region (most common site being the anterior labia majora of the vulva).

Keratoacanthoma is a clinical subtype of SCC. Usually, it resolves spontaneously, but it can also be locally aggressive and destructive. The hallmark feature is its rapid growth, over several centimeters in a matter of weeks followed by spontaneous resolution over a period of months. The usual presentation for this is an elderly patient presenting with a large, smooth, dome-shaped verrucous lesion with a central keratotic crater on the extremities.

Investigations for Squamous Cell Carcinoma

Biopsy

The diagnosis of SCC is always made with a biopsy. In elevated lesions, a **punch biopsy** is performed, while a **superficial shave technique** is adequate in flat lesions or lesions with minimal elevation (less than 1mm) since it minimizes wound size and scarring.

The biopsy depth should be sufficient to distinguish between in situ carcinoma and invasive SCC.

What to expect in the histopathological report?

- The hallmark of SCC is **atypical keratinocytes** extending beyond the basement membrane and into the dermis
- **The lack of connection** between the epidermis and tumor cells indicates metastatic SCC
- Clues to underlying etiology, such as scar tissue, indicates recurrent SCC, while solar elastosis and keratinocyte atypia indicate actinically derived SCC. These clues hold important implications for treatment and prognosis

Differential diagnosis

- **Bowen's disease** may have an **eczematous appearance** and at first, might be mistaken for eczema, psoriasis, or lichen simplex. In Bowen's disease, the lesions are not pruritic
- For **verrucous lesions** - warts, seborrhoeic keratosis, AK, chromomycosis, metastatic SCC, Merkel cell carcinoma
- For **ulcerative lesions** - trauma, BCC, herpes virus infection
- For **pigmented lesions** - melanoma

Management of Squamous Cell Carcinoma

Selection of the best modality of treatment for SCC is based on an assessment of risk factors for recurrence and [metastasis](#).

Non-excisional ablative techniques



Image: "Shown is close up of surgeons' hands in an operating room with a "beam of light" traveling along fiber optics for photodynamic therapy." License: Public Domain

- Electrodesiccation and curettage
- Liquid nitrogen cryotherapy
- Carbon dioxide laser
- Intralesional chemotherapy
- Photodynamic therapy
- Superficial technique
- Do not allow histological margin control
- **Status:** to be used for in -situ disease only, in special circumstances. Inappropriate for invasive SCC

Surgical techniques

Conventional surgical excision:

- **Treatment of choice for primary SCC**
- Recommended margins - 4mm for low-risk lesions with depth less than 2mm

Mohs microscopically controlled surgery (MMCS):

- Allows for minimal tissue destruction
- Indications of MMCS
 - History of radiation at the site
 - Involvement of nerve, muscle, or bone
 - Immunosuppression
 - Recurrent tumor
 - Infiltrative SCC
 - Important tissue preservation sites (the lip, eyelid, nasal tip, ear, genitalia)
 - Verrucous carcinoma

Radiation

- Used for superficially invasive to moderate risk lesions, particularly in lesions

of the **external auditory canal**

- As adjuvant therapy:
 - To excisional surgery in residual microscopic disease
 - Perineural SCC
- As prophylaxis against metastatic disease

Prevention of Squamous Cell Carcinoma

Patients with a prior history of non-melanoma skin cancer or with any of the predisposing factors as mentioned above must receive **regular complete skin examinations**.

Sun protection

These measures include regularly applying sunscreen, wearing proper clothing, wearing sunglasses, and avoiding exposure to the sun during peak hours.

Treatment of precursor lesions

A variety of treatment options are available for the management of AK. While isolated lesions can be treated with **liquid nitrogen cryotherapy**, multiple lesions are treated with a course of **5-fluorouracil**.

Other preventive measures

- Using condoms and vaccination to prevent the transmission of **HPV**
- Decreasing **alcohol** consumption
- **Smoking** cessation
- Using **low dose retinoids and interferons** as systemic chemopreventive agents, for example, Accutane
- Applying topical **DNA repair enzymes in liposomes**
- Using **topical immune modifiers** that stimulate cutaneous immunity to kill malignant cells

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