JAMA | Review

Keratinocyte Carcinoma
A Review

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IMPORTANCE Keratinocyte carcinomas are skin cancers that arise from keratinocytes and are composed of basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCCs). Keratinocyte carcinomas are common in North America, Australia, New Zealand, and Europe. Approximately 5.4 million keratinocyte carcinomas are diagnosed in the US annually.

OBSERVATIONS Keratinocyte carcinomas are primarily located on the head and neck (40%-64% of BCCs; 35%-45% of cSCCs). BCC typically presents as a pink, smooth, raised lesion or a pink to red, flat lesion. cSCC typically presents as a red, scaly, flat lesion (in situ tumors) or a red, firm, raised lesion with scale or erosion (invasive tumors). UV light exposure is the primary cause, and lighter skin pigmentation and skin phototype (eg, skin that more easily burns) are the primary risk factors. Other risk factors include older age, male sex, indoor tanning, history of precancerous lesions (actinic keratoses), history of keratinocyte carcinomas, and immunosuppression (eg, organ transplant). In-office surgical excision or curettage and electrodessication (in which the tumor is scraped away using a curette and the wound base is cauterized) is typically performed by a dermatologist for keratinocyte carcinomas with lower risk of recurrence, including those that are nonrecurrent and have well-defined borders, small size, and location on the trunk and extremities. After surgical excision, approximately 3% of BCCs and 5% of cSCCs recur; after curettage and electrodessication, approximately 6% of BCCs and 2% of cSCCs recur. For keratinocyte carcinomas at higher risk of recurrence, in-office Mohs surgery (a technique in which a dermatologist with specialized training removes the tumor in stages and evaluates the entire surgical margin pathologically using a microscope after each stage to ensure complete tumor excision) is typically used. After Mohs surgery, approximately 4% of BCCs and 3% of cSCCs recur. Patients diagnosed with keratinocyte carcinoma are at high risk of additional keratinocyte carcinomas (approximately 40% within 5 years). Evidence-based prevention of keratinocyte carcinoma involves use of sunscreen. In a randomized clinical trial, use of daily sunscreen decreased cSCC risk (rate ratio, 0.62; 95% CI, 0.38-0.99; 1587 cSCCs per 100 000 person-years in controls vs 953 per 100 000 person-years in sunscreen group).

CONCLUSIONS AND RELEVANCE Keratinocyte carcinoma, composed of BCC and cSCC, is the most common cancer in the US, with an estimated 5.4 million diagnoses annually. Most keratinocyte carcinomas are effectively treated with in-office surgical procedures. Patients with keratinocyte carcinoma are recommended to undergo a skin examination at least annually due to their high risk of developing additional skin cancers.

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Keratinocyte carcinomas, composed of basal cell carcinomas (BCCs) and cutaneous squamous cell carcinomas (cSCCs), are the most common type of cancer in the US. The latest estimate using 2012 data indicated that there were approximately 5.4 million keratinocyte carcinomas in the US yearly,[1] more than all other cancers combined,[2] although the exact US incidence is uncertain due to absence of keratinocyte carcinoma registry data. Keratinocyte carcinoma primarily affects individuals with lighter skin pigmentation, and rates are highest in North America, Australia, New Zealand, and Western Europe.[1,3-5] Keratinocyte carcinomas most commonly occur on the head and neck (approximately 50%),[6] followed by the trunk for BCCs (15%-35%)[6-9] and upper extremities for cSCCs (25%-35%).[6,8,9] Typical treatments are in-office surgical procedures. For higher-risk keratinocyte carcinomas, Mohs surgery confers a 3% to 4% recurrence rate; for lower-risk keratinocyte carcinomas, standard excision has a 3% to 5% recurrence rate and curettage and electrodessication yields a 2% to 6% recurrence rate (over follow-up periods ranging from 3 months to 10 years).[10-13] The risk of metastasis is low (0.004% of BCCs and 1.2%-1.9% of cSCCs),[14-18] as is risk of mortality (0.08 per 100 000 person-years for BCC[19] and 0.7-3.2 per 100 000 person-years for cSCC[15,20,21]). This Review summarizes epidemiology and risk factors, clinical presentations, pathogenesis, assessment and diagnosis, treatment and prognosis, screening and surveillance, and prevention of keratinocyte carcinomas. The **Box** provides some common questions and answers about keratinocyte carcinomas. This Review does not include mucosal-adjacent cSCCs (eg, anogenital or lip cSCCs) and does not evaluate the role of teledermatology for diagnosing skin cancer.

Box. Commonly Asked Questions About Keratinocyte Carcinomas

What Are the Risk Factors for Keratinocyte Carcinoma?
Common risk factors for keratinocyte carcinoma are exposure to UV radiation (natural sunlight and indoor tanning), lighter pigmentation and skin that more easily burns, red hair, older age, male sex, history of precancerous lesions (actinic keratoses), history of keratinocyte carcinoma, and immunosuppression (eg, organ transplant).

Where Do Keratinocyte Carcinomas Occur Most Commonly?
Approximately half of keratinocyte carcinomas occur on the head and neck. The next most common site is the trunk for basal cell carcinomas and the upper extremities for cutaneous squamous cell carcinomas.

How Often Should Patients With Keratinocyte Carcinomas Undergo Surveillance Skin Examinations?
Patients with keratinocyte carcinomas are at high risk of developing new keratinocyte carcinomas (approximately 40% within 5 years) and are also at increased risk of melanoma, so they are recommended to receive a full-body skin examination at least annually.

Methods

An Ovid MEDLINE search was performed for English-language articles describing randomized clinical trials (RCTs), meta-analyses, systematic reviews, and cohort studies with keratinocyte carcinoma, BCC, or cSCC terms published between January 1, 2013, and July 31, 2025. Relevant studies of the epidemiology, risk factors, clinical presentation, pathogenesis, assessment, diagnosis, treatment, prognosis, screening, surveillance, or prevention of keratinocyte carcinomas were selected based on quality (rigor of study design, sample size, and follow-up). A total of 5871 publications were identified. This Review includes 99 articles (including 22 articles published prior to 2013 identified through reference lists of identified studies): 10 RCTs, 15 systematic reviews or meta-analyses, 7 guideline recommendations, 56 cohort or observational studies, 3 clinical references, 3 online data resources, 2 national/international agency reports, 2 public-facing American Academy of Dermatology websites, and 1 basic/translational science publication. For meta-analyses included in this Review, data are reported on absolute risk differences only when they were provided in the original report. For studies in which data were not reported separately for BCC and cSCC or the outcomes were similar, combined keratinocyte carcinoma outcomes are reported.

Pathogenesis

Keratinocyte carcinomas develop from epidermal keratinocytes. The primary cause of keratinocyte carcinoma is UV radiation. UV radiation causes DNA damage as evidenced by characteristic mutation signatures, such as single base substitution of thymine for cytosine or tandem substitutions, in which an adjacent cytosine pair is exchanged for a thymine pair (UV mutation signatures present in 76% of BCCs[22] and >50% of cSCCs[23]). UV radiation also causes suppression of cell-mediated immune responses that inhibit the identification and destruction of tumor cells as well as tumor promotion that allows growth of damaged cells. The US Department of Health and Human Services and the International Agency for Research on Cancer both classify UV radiation as carcinogenic.[24,25]

Epidemiology and Risk Factors

Epidemiology

Keratinocyte carcinomas are estimated to be among the most common cancers in North America, Australia, New Zealand, and Western Europe but are not included in most national cancer registries, including in the US. Epidemiologic estimates in the US are based on insurance claims for surgical treatment of keratinocyte carcinoma, which do not always distinguish between BCC and cSCC. The most recent comprehensive US estimate, from 2012 data, is that there were 5 434 193 treated keratinocyte carcinomas, which occurred in 3 315 554 patients.[1] In a cohort of US Medicare patients aged 65 years or older in 2009-2018 (4 999 999 persons), the annual incidence was 2.5% in American Indian or Alaska Native, 0.9% in Asian or Pacific Islander, 0.2% in Black or African American, 2.0% in Hispanic, and 11.5% in non-Hispanic White individuals.[26] The Netherlands Cancer Registry, which records keratinocyte carcinoma diagnoses, reported incidence rates of BCC at 292.71 per 100 000 person-years and of cSCC at 86.04 per 100 000 person-years in 2023.[27] BCCs are more common than cSCCs overall, but the ratio of BCCs to cSCCs (including cSCC in situ) is lower among older patients. A commercial US claims-based cohort (468 114 patients; 2012-2016) reported a BCC:cSCC ratio of 9.6:1 in 18- to 39-year-old individuals and 2.9:1 in 40- to 64-year-old individuals.[28] In the Netherlands Cancer Registry (2023), the BCC:

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cSCC ratio ranged from 29.8:1 in individuals aged 30 to 44 years to 2:1 in those aged 75 years or older.[27] Mortality from BCC is rare (reported at 0.08 per 100 000 person-years).[19] The Global Burden of Disease 2021 reports a global cSCC mortality rate of 0.72 per 100 000 person-years, with mortality rates per 100 000 person-years of 3.19 in Australia and New Zealand, 1.69 in Western Europe, and 1.53 in the US, Canada, and Greenland.[21]

Risk Factors

The primary risk factors for keratinocyte carcinoma are pigmentation characteristics and skin phototype (eg, skin response to sun exposure, sometimes described using the Fitzpatrick scale).[29] Having lighter skin pigmentation is associated with higher rates of BCC compared with darker skin pigmentation (odds ratio [OR], 2.11; 95% CI, 1.56-2.86) (meta-analysis of 12 cohort and case-control studies).[30] Having red hair is associated with BCC (OR, 2.02; 95% CI, 1.68-2.44 vs dark-colored hair) (meta-analysis of 13 cohort and case-control studies)[30] and cSCC (OR, 14.44; 95% CI, 4.72-44.18 vs black hair) (multicenter case-control study of 3572 patients).[31] Individuals who report they "burn, never tan" have a higher risk of keratinocyte carcinoma compared with those who report they "tan, never burn" (BCC: OR, 2.03; 95% CI, 1.73-2.38 [meta-analysis of 11 cohort and case-control studies]; cSCC: OR, 2.02; 95% CI, 1.20-3.40 [multicenter case-control study of 3572 patients]).[30,31] However, individuals of all races, ethnicities, pigmentation characteristics, and skin phototypes can develop keratinocyte carcinoma.[26,30,32]

Sunburn also increases the risk of keratinocyte carcinomas. A meta-analysis of 8 cohort and case-control studies with 129 525 individuals reported an association with increased BCC risk (for every additional 5 sunburns per decade, relative risk, 1.91; 95% CI, 1.42-2.58).[33] A meta-analysis of 6 cohort and case-control studies with 283 017 individuals reported an association with increased cSCC risk (ORs, 1.51 [95% CI, 1.26-1.81] for medium frequency and 1.69 [95% CI, 1.39-2.06] for high frequency of lifetime painful, blistering, and/or severe sunburns, compared with none).[34] Indoor tanning is also associated with increased keratinocyte carcinoma risk. A meta-analysis of 10 cohort and case-control studies with 78 375 individuals reported increased risk of BCC among individuals who ever used indoor tanning compared with those who never used indoor tanning (relative risk, 1.24; 95% CI, 1.00-1.55).[35] Another meta-analysis of 9 cohort and case-control studies with 305 360 individuals reported increased risk of cSCC among individuals who ever used indoor tanning (relative risk, 1.58; 95% CI, 1.38-1.81), and the risk of keratinocyte carcinoma was higher among those exposed to indoor tanning before age 50 years and those with more than 10 exposures per year.[35] Selection bias is likely in these studies because individuals who indoor tan may also be more likely to have outdoor UV exposure.

Keratinocyte carcinoma incidence is higher among males than females. In US Medicare patients older than 65 years (2009-2018), keratinocyte carcinoma incidence was 18 973 per 100 000 person-years in men vs 7428 per 100 000 person-years in women.[26] Based on 2023 data, BCC incidence in the Netherlands was 304.8 per 100 000 person-years in men vs 286.4 per 100 000 person-years in women, and cSCC incidence was 107.6 per 100 000 person-years in men vs 69.5 per 100 000 person-years in women.[27] Older age is also associated with increased keratinocyte carcinoma risk: 2023 incidence rates in the Netherlands of BCC were 86.5 per 100 000 person-years in individuals aged 30 to 44 years vs 1221.2 per 100 000 person-years in individuals aged 75 years or older and of cSCC were 2.9 per 100 000 person-years in individuals aged 30 to 44 years vs 622.6 per 100 000 person-years in individuals aged 75 years or older.[27]

Patients with a history of actinic keratosis are at increased risk of developing keratinocyte carcinoma compared with individuals without actinic keratosis. Actinic keratoses are dysplastic skin lesions that can transform into cSCCs (absolute risk of 0.6% at 1 year; 95% CI, 0.5%-0.8%).[36] Although they do not transform into BCCs, their presence is a risk factor for BCC. In a Swedish cohort of 17 651 patients followed up from 2000 to 2014, 21.0% of patients with actinic keratosis developed BCC compared with 4.7% of controls and 18.8% developed cSCC compared with 2.4% of controls.[37] In a cohort of 555 945 US Medicare patients (2009-2018) with actinic keratosis compared with 481 024 patients with a benign skin lesion, patients with actinic keratosis had increased risk of keratinocyte carcinoma (HR, 2.20; 95% CI, 2.18-2.22) and an absolute risk of any skin cancer of 28.5% at 5 years.[38] In a cohort of 1169 patients from the Netherlands, having 10 or more actinic keratoses was associated with higher keratinocyte carcinoma risk (HR, 2.44; 95% CI, 1.65-3.61) compared with having 1 to 3 actinic keratoses.[39]

Compared with the general population, patients who are immunosuppressed, especially those with solid organ transplants, are at increased risk of keratinocyte carcinoma, with the risk varying by the organ transplanted, age, sex, and geographical location. The 10-year cumulative incidence of keratinocyte carcinoma among organ transplant recipients is 13% to 52%.[40] The standardized incidence ratio, which compares the rates of keratinocyte carcinoma in those with organ transplants compared with the general population, is 6.6 for BCC (meta-analysis of 6 cohort studies) and 46 for cSCC (meta-analysis of 5 cohort studies).[41] Mortality rates from cSCC are also increased in solid organ transplant recipients, ranging from 4.9 to 78 per 100 000 person-years.[42,43] Allogeneic stem cell transplant is associated with increased BCC risk by 3-fold (10-year absolute risk, 5.3%) and increased cSCC risk by 18-fold (10-year absolute risk, 0.8%).[44] Chronic lymphocytic leukemia is associated with increased BCC risk by 2.6-fold (10-year absolute risk, 8.5%) and increased cSCC risk by 4.4-fold (10-year absolute risk, 5.9%).[45] Patients with HIV also have an increased risk of keratinocyte carcinoma, with incidence rate ratios of 1.79 (95% CI, 1.43-2.22) for BCC and 5.40 (95% CI, 3.07-9.52) for cSCC in a Danish cohort study that included 25 679 patients with HIV and age- and sex-matched controls.[46]

Clinical Presentation

The **Figure** shows examples of clinical presentations of BCC and cSCC subtypes. **Table 1** summarizes major clinical and epidemiologic characteristics of keratinocyte carcinomas.

Basal Cell Carcinomas

There are 3 common subtypes of BCC. Nodular BCCs, which account for 40% to 70% of BCCs, present as shiny, translucent, or pearly pink raised lesions with a smooth surface, sometimes with visible blood vessels.[7,47,48] Superficial BCCs (approximately 20%-30%) present as well-defined, red, flat lesions, often with some scale, and may be misdiagnosed as eczema.[7,47,48] Infiltrative and morpheaform BCCs (approximately 5%-30%) present as scar-like, white or light pink, flat or depressed lesions.[7,47,48]

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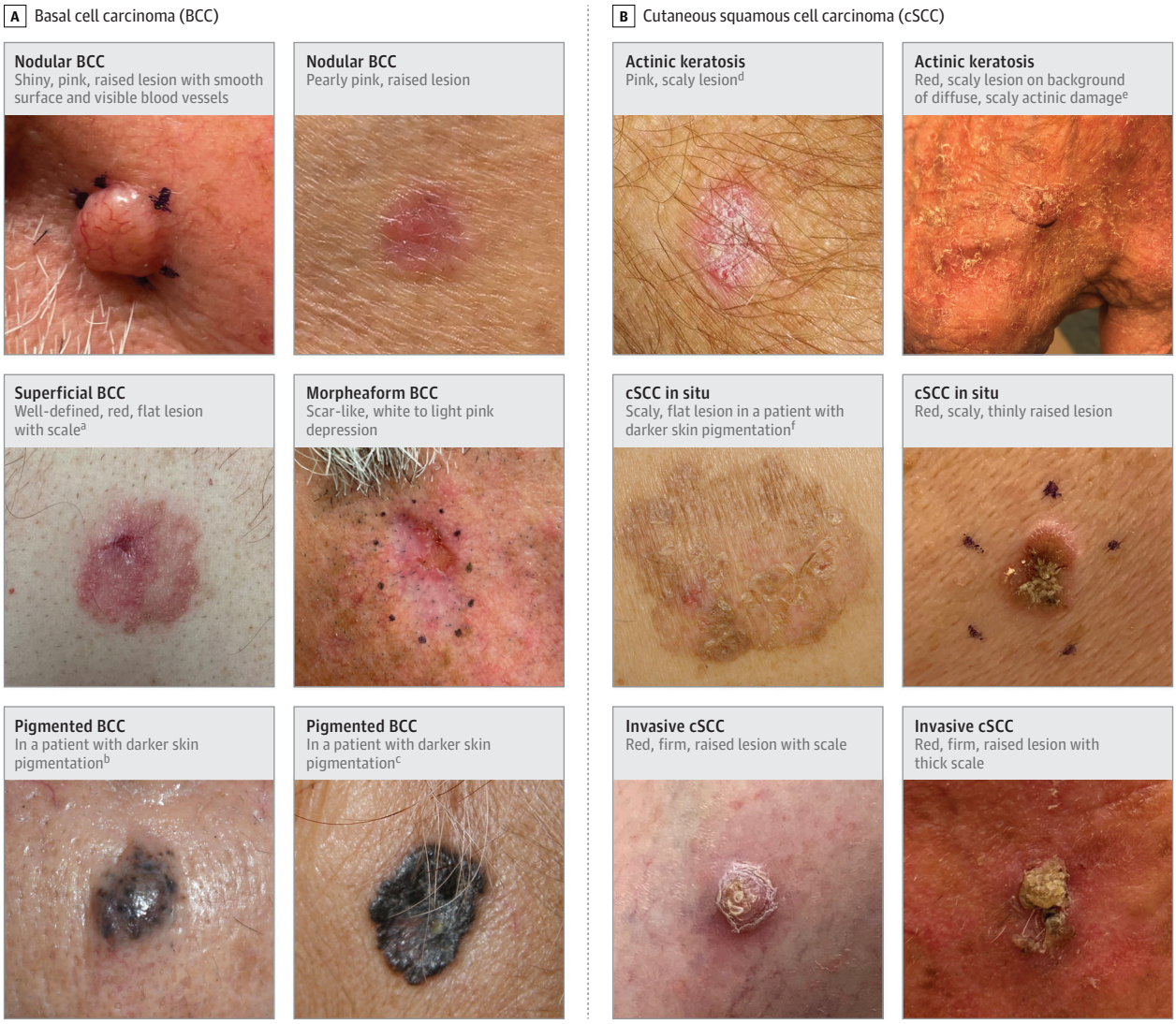
Figure. Examples of Clinical Presentations of BCC and cSCC Subtypes



[a]Image is from the International Skin Imaging Collaboration (ISIC), courtesy of Hospital Italiano de Buenos Aires, Argentina, licensed under CC-BY.

[b]Image is courtesy of the Department of Dermatology, National Cheng Kung University Hospital, Taiwan.

[c]Image is courtesy of Archana Singal.

[d]Image is from the ISIC, courtesy of the Federal University of Espírito Santo (UFES), Brazil, licensed under CC-BY.

[e]Image is courtesy of Megan Rogge.

[f]Image is courtesy of Yung-Tsu Cho.

BCCs can be pigmented (have increased melanin pigment) and include brown, blue, or black colors; pigmentation is more common in BCCs in patients with darker skin pigmentation.[55,56] BCCs most commonly occur on the head and neck (40%-64%, with 28%-54% on the face) and trunk (15%-35%).[6-9] BCCs can be asymptomatic, although approximately 37% of BCCs bleed, 23% to 33% itch, and 16% to 18% cause tenderness or discomfort.[57-59]

Cutaneous Squamous Cell Carcinomas

Actinic keratoses can be precursors to cSCCs and present on sun-exposed areas as rough or scaly lesions that are usually red or pink but can be brown.[8,60] cSCCs in situ (40% of cSCCs) involve only the epidermis or uppermost layer of the skin and typically present as red, scaly, flat or thinly raised lesions.[49] Invasive cSCCs (60% of cSCCs) extend deeper than the epidermis and appear as red, firm, raised lesions, often with thick scaling or erosions.[49] cSCCs most commonly occur on the head and neck (35%-45%, with 23%-36% on the face) and the upper extremities (25%-35%).[6,8,9] Approximately 24% of cSCCs bleed, 44% itch, and 40% to 41% cause tenderness or discomfort.[58,59]

Assessment and Diagnosis

Clinical assessment for keratinocyte carcinoma is performed with a visual skin examination, preferably by a trained clinician with expertise

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Table 1. Major Clinical and Epidemiologic Characteristics of Keratinocyte Carcinomas

	Basal cell carcinoma (BCC)	Cutaneous squamous cell carcinoma (cSCC)
Clinical features[a]	• Most common on the head and neck (40%-64%) and trunk (15%-35%)[6-9] • Asymptomatic or symptoms of bleeding, itching, or pain • Nodular BCC (40%-70%): shiny, translucent or pearly pink, raised lesion with a smooth surface, sometimes with visible blood vessels[7,47,48] • Superficial BCC (20%-30%): well-defined, red, flat lesion, often with some scale[7,47,48] • Infiltrative and morpheaform BCCs (5%-30%): scar-like, white or light pink, flat or depressed lesion[7,47,48]	• Most common on the head and neck (35%-45%) and upper extremities (25%-35%)[6,8,9] • Asymptomatic or symptoms of bleeding, itching, or pain • cSCC in situ (40%): red, scaly, flat or thinly raised lesion[49] • Invasive cSCC (60%): red, firm, raised lesion, often with thick scaling or erosions[49]
Incidence	305 per 100 000 person-years in men and 286 per 100 000 person-years in women (the Netherlands, 2023)[27]	108 per 100 000 person-years in men and 69.7 per 100 000 person-years in women (the Netherlands, 2023)[27]
	5 434 193 treated keratinocyte carcinomas in 3 315 554 patients annually (US, 2012)[1]	
Risk of metastasis	0.004% (Denmark, 14-year cumulative incidence)[14]	1.2%-1.9% (United Kingdom,[16] within a mean of 6.5 years, and the Netherlands, 10-year cumulative incidence,[18] respectively)
Mortality	0.08 per 100 000 person-years[19]	0.72 per 100 000 person-years (Global Burden of Disease, 2021; rates per 100 000 person-years were 3.19 in Australia and New Zealand, 1.69 in Western Europe, and 1.53 in the US, Canada, and Greenland)[21]
Risk factors	• Pigmentation characteristics (eg, lighter pigmentation, red hair) • Skin phototype (eg, skin response to sun exposure, sometimes described using the Fitzpatrick scale)[29] • UV exposure (natural sunlight, sunburn, and indoor tanning) • Male sex • Older age • History of actinic keratosis • History of keratinocyte carcinoma • Organ transplant • Allogeneic stem cell transplant • HIV • Genetic syndromes[50,b] • Smoking (cSCC only)[51] • Human papillomavirus (nonanogenital; cSCC only)[52] • Chronic wounds or chronic skin inflammation (cSCC only)[53] • Chemical exposures (cSCC only)[54,c]	

[a] Less common (<10%) types of BCC include sclerosing, micronodular, infundibulocystic, fibroepithelioma of Pinkus, keratotic, and basosquamous.

[b] Genetic syndromes include basal cell nevus syndrome (BCC), oculocutaneous albinism (BCC and cSCC), epidermolysis bullosa variants (cSCC), Kindler syndrome (BCC and cSCC), epidermodysplasia verruciformis (cSCC), Ferguson-Smith syndrome (cSCC), Huriez syndrome (cSCC), Fanconi anemia (cSCC), Rothmund-Thomson syndrome (BCC and cSCC), Bloom syndrome (BCC and cSCC), and dyskeratosis congenita (cSCC).

[c] Chemical exposures include arsenic, polycyclic aromatic hydrocarbons, and nitrosamines.

in dermoscopy (use of a dermatoscope, a handheld instrument with a magnifying lens and transilluminating light source). For diagnosis of BCC, dermoscopy has a sensitivity of 91% and specificity of 95% among experts[61] (insufficient data for cSCC).[62] The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) suggest a full-body skin examination for patients being evaluated for keratinocyte carcinoma because they may have additional skin cancers on other parts of their body.[63,64]

The diagnosis of keratinocyte carcinoma requires pathologic evaluation of a shave biopsy or punch biopsy (see related video). Shave biopsies use a flexible blade to remove a bowl-shaped slice of the epidermis and dermis, do not include subcutaneous fat, and do not require sutures. Punch biopsies use an instrument with a hollow, sharp end to remove a small circular piece of skin, extend to the subcutaneous fat, and are often closed with sutures.

Treatment

Risk Stratification

BCC is classified as being at low or high risk of recurrence and cSCC is classified as being at low, high, or very high risk of recurrence (risk stratification based on location, size, status as primary vs recurrent, histopathologic features, history of radiation or inflammatory process, and patient immunosuppression) (**Table 2** and **Table 3**), which helps guide choice of treatment modality (**Table 4**).

Surgical Treatments

Standard Excision

Standard excision is appropriate for low-risk keratinocyte carcinomas and is the most common treatment.[11] Standard excision is an in-office procedure using local anesthetic in which the tumor and a 4- to 6-mm margin of uninvolved skin around the tumor or biopsy site are removed with a depth that extends to subcutaneous fat, followed by suturing to repair the defect. After the procedure, standard histopathologic assessment is performed, which visualizes only 1% to 2% of the total surgical margin because the surgical specimen is sampled at intervals rather than the entire peripheral and deep margins.[67] In a network meta-analysis of 16 RCTs with follow-up times of 3 months to 10 years that included 2204 BCCs, local recurrence rates were 3.3% (95% CI, 1.3%-7.8%).[13] In a meta-analysis of 8 cohort and case-control studies of 736 patients with cSCC, local recurrence rates at 2 to 5 years of follow-up were 5.0% (95% CI, 2.3%-8.3%).[11]

Mohs Surgery

Mohs surgery, typically performed by dermatologists with specialized training, is an in-office procedure using local anesthetic in which

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Table 2. Basal Cell Carcinoma Risk Stratification for Determination of Treatment per National Comprehensive Cancer Network Guidelines[63,a]

	Risk of posttreatment recurrence	
	Low	High
Location and size	Trunk, extremities; <2 cm	• Trunk, extremities; ≥2 cm • Head, neck, hands, feet, pretibial, and anogenital area (any size)
Primary vs recurrent	Primary	Recurrent
Borders	Well defined	Ill defined
Immunosuppression	Absent	Present
Site of previous radiation	Absent	Present
Histopathologic subtype	• Nodular • Superficial • Keratotic • Infundibulocystic • Fibroepithelioma of Pinkus	• Morpheaform • Sclerosing • Infiltrative • Micronodular • Basosquamous
Perineural involvement	Absent	Present

[a] Reproduced with permission from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Basal Cell Skin Cancer, version 2.2025.[63]

Table 3. Cutaneous Squamous Cell Carcinoma Risk Stratification for Determination of Treatment per National Comprehensive Cancer Network Guidelines[64,a]

	Risk of posttreatment recurrence, metastases, or death		
	Low	High	Very high
Location and size	Trunk, extremities; ≤2 cm	• Head, neck, hands, feet, pretibial, and anogenital (any size) • Trunk, extremities; >2 cm to ≤4 cm	>4 cm (any location)
Primary vs recurrent	Primary	Recurrent	
Borders	Well defined	Ill defined	
Immunosuppression	Absent	Present	
Site of previous radiation or chronic inflammatory process	Absent	Present	
Rapid growth	Absent	Present	
Neurologic symptoms	Absent	Present	
Histopathologic features	Well or moderately differentiated	Histologic subtype: acantholytic, adenosquamous, metaplastic, or desmoplastic in any portion of the tumor	• Poorly differentiated • Histologic subtype: acantholytic, adenosquamous, metaplastic, or desmoplastic in any portion of the tumor
Depth of invasion	<2 mm and no invasion of subcutaneous fat	2-6 mm and no invasion beyond subcutaneous fat	>6 mm or invasion beyond subcutaneous fat
Perineural involvement	Absent	Present	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	Absent	Absent	Present

[a] Reproduced with permission from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Squamous Cell Skin Cancer, version 2.2025.[64]

the visible tumor is removed, followed by a thin layer (1-2 mm) of surrounding tissue from under and circumferentially around the wound. This thin layer is processed for immediate pathologic evaluation by the surgeon using sections that allow for 100% of the surgical margin to be examined pathologically,[67] typically while the patient waits. If tumor is present in the surgical margin, another thin layer of tissue is excised from the relevant area until the tumor is completely removed, after which the defect is repaired. Mohs surgery is recommended for high-risk BCC and high-risk and very high-risk cSCC by the American Academy of Dermatology[10,12] and the NCCN Guidelines.[63,64] In the aforementioned network meta-analysis of 16 RCTs, local recurrence rates of BCC after Mohs surgery were 3.8% (95% CI, 0.7%-18.9%).[13] In meta-analysis of 7 cohort and case-control studies that included 1116 patients with cSCC, local recurrence rates after Mohs surgery at 2 to 5 years of follow-up were 2.8% (95% CI, 2.0%-3.9%).[11]

Curettage and Electrodessication

Curettage and electrodessication is an in-office procedure using local anesthetic in which the visible tumor and a 2- to 3-mm margin is surgically scraped away using a curette and the wound base is cauterized. Curettage and electrodessication does not include pathologic evaluation and is appropriate for selected low-risk keratinocyte carcinomas on areas that do not have terminal hair (eg, not on the hair-bearing scalp, beard area, underarms, pubic region).[63,73,74] Curettage and electrodessication may be associated with longer healing times and inferior cosmetic outcomes compared with standard excision or Mohs surgery and is typically avoided in visible areas such as the face.[75] Local

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Table 4. Major Treatments Available for Keratinocyte Carcinomas

Treatment type	Indications	Description/mechanism	Efficacy	Risks/adverse effects
Standard surgical treatment modalities				
Surgical excision	First-line treatment for low-risk keratinocyte carcinomas[10,12,63-65]	A 4- to 6-mm margin of clinically uninvolved skin around the tumor or biopsy site is removed down to subcutaneous fat.	Local recurrence rates: • 3.3% (95% CI, 1.3%-7.8%) for BCC[13] • 5.0% (95% CI, 2.3%-8.3%) r cSCC[11]	Pain, bleeding, scarring, postoperative hemorrhage (3%), infection (2%), vasovagal syncope (1%), nerve damage[66]
Mohs surgery	First-line treatment for high-risk keratinocyte carcinomas[10,12,63-65]	Visible tumor is removed, followed by a thin layer of surrounding tissue from under and circumferentially around the wound. 100% of the surgical margin is then immediately examined pathologically using horizontal sections while the patient waits.[67] If cancer is in the surgical margin, another thin layer of tissue is removed only from around the area where the cancer was seen on pathology.	Local recurrence rates: • 3.8% (95% CI, 0.7%-18.2%) for BCC[13] • 2.8% (95% CI, 2.0%-3.9%) for cSCC[11]	Pain, bleeding, scarring, infection (0.44%), dehiscence or necrosis (0.14%), postoperative bleeding and hematoma (0.11%), nerve damage[68]
Curettage and electrodesiccation	Low-risk keratinocyte carcinomas not on terminal hair-bearing skin and not in cosmetically sensitive areas[10,12,63,64]	Tumor is scraped away using a curette, then wound base is cauterized. This can be repeated 3 times during the procedure.	Local recurrence rates: • 5.9% (95% CI, 0.7%-34.9%) for BCC[13] • 2.0% (95% CI, 1.1%-3.0%) for cSCC[69]	Pain, bleeding, scarring, dyspigmentation[70]
Nonsurgical approaches to consider in selected situations				
Topical fluorouracil, 5%	• FDA approved for superficial BCCs • Off-label for cSCCs	• Inhibits DNA synthesis • Twice-daily application for 3-6 weeks	Local recurrence rates • 24.7% (95% CI, 7.1%-58.4%) for BCC[13] • 16.1% (95% CI, 10.3%-21.8%) for cSCC (invasive and in situ)[69]	Erythema (33%-97%), pain (33%-50%), dermatitis (20%), pruritus (17%), scarring (9%-16%), crusting/scabbing (13%), burning/stinging (7%), ulceration (4%-9%), erosion (6%), hyperpigmentation (3%)[71]
Topical imiquimod, 5%	• FDA approved for superficial BCCs ≤2 cm on trunk, neck, and extremities • Off-label for cSCCs	• Immune response modifier, induces production of cytokines, leading to apoptosis of tumor cells • Once-daily treatment 5 times a week for 6 weeks or longer[10]	Local recurrence rates: • 14.1% (95% CI, 5.4%-32.4%)[13] for BCC • 26.6% (95% CI, 16.9%-36.4%) for cSCC (invasive and in situ)[69]	Erythema (63%-100%), edema (3%-92%), pruritus (16%-67%), hypopigmentation (9%-67%), crusting/scabbing/scaling (52%-65%), erosion/ulceration (25%-53%), burning (6%-35%), pain (3%-35%), blisters (3%-17%), scarring (15%), flu-like symptoms (9%)[71]
Photodynamic therapy (topical)	Selected low-risk keratinocyte carcinomas	In-office application of a photosensitizer, incubation period, then irradiation with a specific light source	Local recurrence rates: • 17.8% (95% CI, 9.1%-31.8%) or 16.9% (95% CI, 7.4%-34.4%) for BCC[13] • 29.0% (95% CI, 25.0%-33.0%) for cSCC (invasive and in situ)[69]	Photosensitivity, need for light avoidance and photoprotection for 48 hours, pain (99%), erythema (92%), edema (35%), exudation (23%), hyperpigmentation (27%)[10,72]
Radiation therapy	When surgery is not feasible, is contraindicated, or is not preferred by the patient after a discussion of risks and benefits[10,12]	• External-beam radiation therapy • Brachytherapy (radiation source placed close to or in direct contact with keratinocyte carcinoma; can be done in office) • Typically involves treatments 5 times per week for 3-7 weeks	Local recurrence rates: • 3.2% (95% CI, 0.6%-16.1%) for external-beam radiation in BCC[13] • 6.4% (95% CI, 3.0%-11.0%) for external-beam radiation and 5.2% (95% CI, 1.6%-10.5%) for brachytherapy for cSCC[11]	Local skin toxicities (eg, erythema, desquamation, fibrosis, atrophy), cartilage necrosis, and increased difficulty of treating keratinocyte carcinoma recurrences (increased surgical complexity in previously radiated skin)[10]
Active surveillance/ watchful waiting	Low-risk keratinocyte carcinomas in patients with limited life expectancy or who prefer active surveillance/watchful waiting	No initial treatment; close monitoring	Not applicable	New symptoms, tumor growth, requirement of more invasive treatment if treatment pursued[57]

Abbreviations: BCC, basal cell carcinoma; cSCC, cutaneous squamous cell carcinoma; FDA, US Food and Drug Administration.

recurrence rates after curettage and electrodessication are 5.9% for BCC (95% CI, 0.7%-34.9%) (network meta-analysis of 16 RCTs)[13] and 2.0% for cSCC (1.1%-3.0%) (meta-analysis of 13 single-group observational studies with 2352 cSCCs [invasive and in situ]).[69]

All surgical treatments for keratinocyte carcinoma cause pain (days to weeks) and scarring, although the scarring varies with procedural and individual patient factors. Other adverse events such as infection, postoperative hemorrhage, or wound dehiscence occur in approximately 2% of cases.[76]

Nonsurgical Treatments

For patients in whom surgery is not feasible or is contraindicated (eg, large keratinocyte carcinomas for which surgery carries functional complications, such as facial palsy) or is not preferred (eg, patients who strongly wish to avoid surgery), the NCCN Guidelines[63,64] and/or American Academy of Dermatology guidelines[10,12] suggest considering nonsurgical approaches such as photodynamic therapy, topical medications, radiation therapy, and active surveillance.

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Photodynamic therapy is an in-office treatment consisting of topical application of a photosensitizer (commonly aminolevulinic acid or methyl aminolevulinate), an incubation period of 30 minutes to 3 hours, then irradiation with a specific light source (commonly blue light in the 410- to 420-nm range or red light at 630 nm). Photodynamic therapy, which is appropriate for low-risk keratinocyte carcinomas, is associated with BCC recurrence rates of 17.8% (95% CI, 9.1%-31.8%) or 16.9% (95% CI, 7.4%-34.4%), depending on photosensitizer (meta-analysis of 16 RCTs).[13] Photodynamic therapy used for cSCC is associated with recurrence rates of 29.0% (95% CI, 25.0%-33.0%) (meta-analysis of 99 single-group observational studies with 3798 cSCCs [invasive and in situ]).[69]

Topical therapy (eg, cream applied by patients at home) for treatment of keratinocyte carcinoma includes topical imiquimod, an immunomodulator, and topical fluorouracil, a chemotherapy. For BCC, topical imiquimod 5 times per week for 6 weeks is approved by the US Food and Drug Administration (FDA) for superficial BCCs of 2 cm or smaller on the trunk, neck, and extremities and is associated with recurrence rates of 14.1% (95% CI, 5.4%-32.4%) (meta-analysis of 16 RCTs).[13] Topical fluorouracil twice daily for at least 3 to 6 weeks is approved by the FDA for superficial BCC, with recurrence rates of 24.7% (95% CI, 7.1%-58.4%) (meta-analysis of 16 RCTs).[13] For cSCC, topical therapies are off-label. Topical imiquimod has cSCC recurrence rates of 16.1% (95% CI, 10.3%-21.8%) (meta-analysis of 26 single-group observational studies with 286 cSCCs [invasive and in situ]).[69] Topical fluorouracil has cSCC recurrence rates of 26.6% (95% CI, 16.9%-36.4%) (meta-analysis of 21 single-group observational studies with 430 cSCCs [invasive and in situ]).[69] Adverse events from imiquimod and fluorouracil include local skin reactions, such as erythema, swelling, erosions, crust, vesicles, pain, and itching at the site of administration, and are moderate to severe in 15% to 60% of patients. Approximately 2% to 4% of patients using imiquimod and 5% of patients using fluorouracil discontinue therapy due to adverse events.[71,77,78] Adverse events associated with imiquimod may also include flu-like symptoms (eg, headache, myalgia, fatigue) in 1% to 8% of patients.[77-79]

Radiation therapy for definitive treatment of keratinocyte carcinoma consists of external-beam radiation or brachytherapy and typically involves 3 to 7 weeks of 5 daily treatments per week. Adverse events associated with external-beam radiation or brachytherapy include local skin toxicities (eg, erythema, desquamation, fibrosis, atrophy), cartilage necrosis, and increased difficulty of treating keratinocyte carcinoma recurrences (increased surgical complexity in previously radiated skin).[10] External-beam radiation therapy has recurrence rates for BCC of 3.2% (95% CI, 0.6%-16.1%) (network meta-analysis of 16 RCTs)[13] and for cSCC of 6.4% (95% CI, 3.0%-11.0%) (meta-analysis of 7 cohort and case-control studies with 24-144 months of follow-up in 761 patients).[11] Brachytherapy has recurrence rates for cSCC of 5.2% (95% CI, 1.6%-10.5%) (meta-analysis of 6 cohort and case-control studies with 9.6-55 months of follow-up with 364 patients).[11] Radiation therapy as an adjuvant following surgery should be considered for recurrent cSCC that is resected with margins free of tumor when the lesion is large (≥4 cm), is deeply invasive (>6 mm), or has extensive microscopic perineural invasion or clinical nerve involvement.[80]

Active surveillance (no initial treatment with clinical monitoring) is a potential option for patients with low-risk keratinocyte carcinomas who are older or have limited life expectancy. In 1 prospective cohort of 89 patients with both low- and high-risk BCC who chose active surveillance, 8% developed new tumor symptoms such as bleeding and 38% stopped active surveillance and were treated (more invasive treatment required in only 2.8%).[57] In 2 retrospective cohorts of 148 cSCCs and 411 cSCCs in situ that appeared clinically resolved after biopsy and were managed by clinical monitoring, 1.4% of cSCCs (2/148; median follow-up, 35 months) and 4.1% of cSCCs in situ (17/411; median follow-up, 41 months) recurred locally.[81,82]

Prognosis

Prognosis for most patients with keratinocyte carcinomas is excellent, with low recurrence rates using in-office surgical treatments (Table 4). Local keratinocyte carcinoma recurrences are treated as high-risk tumors and are treated with Mohs surgery or reexcision with wider surgical margins.[63,64] Metastases were reported in 0.004% of 126 627 patients with BCCs in Denmark,[14] in 1.2% of 1122 patients with cSCCs in the UK,[16] and in 1.9% of 11 137 patients with cSCCs in the Netherlands.[18] Metastasis sites of cSCC include regional lymph nodes (52%), the parotid gland (44%), and skin (12%); distant metastases are uncommon (2%).[18] In a Netherlands cancer registry cohort of 217 metastatic cSCCs, most metastases occurred within 4 years of primary cSCC diagnosis (78%).[18] Systemic therapies to treat metastatic disease are outside the scope of this Review.

Screening and Surveillance

Screening for the General Population

The 2023 US Preventive Services Task Force determined that evidence is insufficient to assess the benefits and harms of skin cancer screening (including keratinocyte carcinomas and melanoma) in the general population.[83] The American Academy of Dermatology encourages everyone to perform regular skin self-examinations,[84] although it is not an official guideline.

Risk Stratification and Screening for Solid Organ Transplant Recipients

For solid organ transplant recipients, the risk of skin cancer (including keratinocyte carcinomas and melanoma) can be calculated using the externally validated Skin and UV Neoplasia Transplant Risk Assessment Calculator (SUNTRAC), which incorporates high-risk characteristics, including White race, pretransplant history of skin cancer, male sex, and heart or lung transplant.[85,86] Solid organ transplant recipients are grouped into 4 risk categories, with initial skin cancer screening recommendations ranging from within 6 months of transplant for very high risk (5-year cumulative skin cancer incidence, 45%) to within 10 years of transplant for low risk (5-year cumulative incidence, 1%).[85]

Surveillance After Keratinocyte Carcinoma Diagnosis

Compared with individuals without a history of keratinocyte carcinoma, patients diagnosed with keratinocyte carcinoma are at higher risk of new primary keratinocyte carcinomas as well as at higher risk of melanomas. A prospective cohort study of 1426 patients with keratinocyte carcinoma reported a 40.7% (95% CI, 36.5%-45.2%) absolute risk of developing a new primary keratinocyte carcinoma

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at 5 years.[87] The risk of melanoma in a cohort of 153 576 individuals who were diagnosed with keratinocyte carcinoma and self-identified as White was 116 per 100 000 person-years for men and 79 per 100 000 person-years for women.[88]

Full-body skin examinations are recommended by the NCCN Guidelines after keratinocyte carcinoma: for patients with BCCs, every 6 to 12 months for the first 5 years and then annually,[63] and for patients with low-risk, local cSCCs, every 3 to 12 months for the first 2 years, then every 6 to 12 months for the next 3 years, then annually.[64] However, patients with high-risk and metastatic cSCCs should be examined more frequently.[64]

Prevention

Primary prevention of keratinocyte carcinoma centers on sun protection, which includes shade-seeking behavior, decreased exposure during peak UV hours, sun-protective clothing and hats, sunscreen use, and avoidance of indoor tanning.[89] However, few studies prospectively evaluate the efficacy of sun protection strategies for skin cancer prevention. One large RCT in the 1990s in Australia compared daily use of sunscreen with a sun protection factor (SPF) of 16 with discretionary sunscreen use for 4.5 years and showed a reduced risk of cSCC from 1587 per 100 000 person-years (discretionary use group) to 953 per 100 000 person-years (daily use group; rate ratio, 0.62; 95% CI, 0.38-0.99) 8 years after the intervention ended. That RCT also showed a decreased risk of invasive melanoma 10 years after the intervention ended (HR, 0.27; 95% CI, 0.08-0.97; 11/809 in discretionary use group and 3/812 in daily use group) but did not show a decreased risk of BCC.[90,91] In organ transplant recipients with actinic keratoses, a prospective matched case-control study that provided the intervention group with free sunscreen reported fewer cSCCs in those provided free sunscreen vs controls (0/60 vs 8/60, respectively; $P < .01$).[92] The American Academy of Dermatology recommends use of broad-spectrum protection (UV-A and UV-B) sunscreens with an SPF of 30 or above, reapplied every 2 hours during UV exposure.[93]

Actinic keratosis lesions are typically treated with the goal of preventing cSCC. Actinic keratosis treatments include in-office liquid nitrogen cryotherapy, topical medications such as fluorouracil or imiquimod, and photodynamic therapy.[94]

For patients with a history of keratinocyte carcinoma, over-the-counter nicotinamide (a form of vitamin B_3; 500 mg twice daily) may prevent future skin cancers. In an RCT of 386 immunocompetent patients with a history of at least 2 keratinocyte carcinomas in the prior 5 years, there were 1.8 new keratinocyte carcinomas per patient in the nicotinamide group and 2.4 per patient in the placebo group over 12 months (23% decrease; 95% CI, 4%-38%).[95] However, 2 RCTs of nicotinamide use in organ transplant patients have not shown reductions in skin cancer risk.[96,97] Topical fluorouracil has shown benefit for chemoprevention of cSCC. A trial that randomized patients with at least 2 keratinocyte carcinomas in the prior 5 years to topical fluorouracil on the face and ears as a prophylactic chemopreventive vs placebo reported a 75% (95% CI, 35%-91%; $P = .02$) cSCC risk reduction (5/468 [1.1%] in fluorouracil group and 20/464 [4.3%] in control group) at 1 year.[98] For organ transplant recipients, oral acitretin (a prescription vitamin A derivative) may be beneficial for chemoprevention (56% reduction in keratinocyte carcinomas in a meta-analysis of 3 RCTs and 1 observational study with 103 patients; confidence intervals and P values not provided).[99] However, acitretin has adverse effects such as dryness of skin and mucosal membranes (mucocutaneous xerosis) and teratogenicity. In addition, patients taking this medication need laboratory testing every 3 months (lipids, liver function, blood cell count, creatinine) to monitor for adverse effects.[99]

Limitations

This Review has limitations. First, some relevant articles may have been missed. Second, formal evaluation of the quality of the included articles was not performed. Third, many studies refer to keratinocyte carcinomas as a single outcome rather than separating data for BCCs and cSCCs.

Conclusions

Keratinocyte carcinomas, composed of BCCs and cSCCs, are the most common cancer in the US, with an estimated 5.4 million keratinocyte carcinomas diagnosed annually. Most keratinocyte carcinomas are effectively treated with in-office surgical procedures. Patients with keratinocyte carcinomas are recommended to undergo a skin examination at least annually due to their high risk of developing additional skin cancers.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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