# Basal cell carcinoma

## Epidemiology; pathophysiology; clinical and histological subtypes; and disease associations

Michael C. Cameron, MD,[a] Erica Lee, MD,[a] Brian P. Hibler, MD,[a] Christopher A. Barker, MD,[b] Shoko Mori, BS,[a] Miguel Cordova, MD,[a] Kishwer S. Nehal, MD,[a] and Anthony M. Rossi, MD[a]
*New York, New York*

**Learning Objectives**
After completing this learning activity, participants should be able to recall current understanding of the epidemiology, biology, natural history, and associations of basal cell carcinoma (BCC); discuss new technologies being implemented in the diagnosis of BCC; compare and contrast in an evidence-based fashion standard and new approaches to BCC; and discuss new insights into the gene mutation basis of basal cell carcinoma from a pathology and clinical perspective.

**Disclosures**

**Editors**
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

**Authors**
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

**Planners**
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

As the most common human cancer worldwide and continuing to increase in incidence, basal cell carcinoma is associated with significant morbidity and cost. Continued advances in research have refined both our insight and approach to this seemingly ubiquitous disease. This 2-part continuing medical education article will provide a comprehensive and contemporary review of basal cell carcinoma. The first article in this series describes our current understanding of this disease regarding epidemiology, cost, clinical and histopathologic presentations, carcinogenesis, natural history, and disease associations. (J Am Acad Dermatol 2019;80:303-17.)

***Key words:*** associations; basal cell carcinoma; BCC; cost; epidemiology; genetics; keratinocyte carcinoma; natural history; nonmelanoma skin cancer; skin cancer.

## EPIDEMIOLOGY AND COST

### Key points

- **Basal cell carcinoma and squamous cell carcinoma comprise the keratinocyte carcinomas, which are the most common malignancies worldwide and are increasing in incidence**
- **The lifetime risk of developing basal cell carcinoma in the United States is estimated to be ≥20% and ≥30% for whites**
- **Male sex and age are independent basal cell carcinoma risk factors**
- **The basal cell carcinoma cost burden continues to increase with rising incidence**

From the Dermatology Service,[a] Department of Medicine, and the Department of Radiation Oncology,[b] Memorial Sloan Kettering Cancer Center, New York.
Supported by National Institutes of Health/National Cancer Institute Cancer Center support grant P30 CA008748.
Conflicts of interest: None disclosed.
Accepted for publication March 21, 2018.
Address correspondence to: Anthony M. Rossi, MD, Division of Dermatology, Memorial Sloan Kettering Cancer Center, 16 E 60th St, 4th Floor, New York, NY 10022. E-mail: rossia@mskcc.org.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.03.060
**Date of release: February 2019**
**Expiration date: February 2022**

- **Physician office–based basal cell carcinoma management is less costly compared to ambulatory surgery or inpatient settings**

Keratinocyte carcinomas (KCs) are by far the most common malignancies worldwide and exceed the prevalence of all other cancers combined. Traditionally, approximately 80% of KC cases have been attributed to basal cell carcinoma (BCC) and 20% to squamous cell carcinoma (SCC). However, recent studies point to an increasing SCC incidence relative to BCC, moving the historical 4:1 ratio to 2.5:1 or even closer.[1-4] Some evidence attributes this to a relative SCC increase in the elderly population caused by chronic exposure to ultraviolet (UV) light, while BCC remains much more common in younger populations.[1,5,6] Regardless, the majority of epidemiologic studies still show a higher BCC incidence of at least 2:1.[5,7-16]

Although most cancer registries exclude KCs because of their ubiquity and relatively low mortality rates, numerous studies provide evidence for increasing incidence worldwide. Incidence in the United States has increased by an average rate of 4% to 8% annually.[17] A large US sex-stratified cohort study (1986-2006) showed age-adjusted BCC incidence rate increases from 519 to 1019 cases per 100,000 person-years in women and from 606 to 1488 cases per 100,000 person-years in men.[18] Similar rising incidence rates have been found in Europe, Canada, Asia, and Australia.[11,12,15,19-23] BCCs occur in an estimated 2 million Americans annually.[24] Lifetime risk in the United States overall is greater than or equal to 20%, and greater than or equal to 30% for whites, and could be greater because these estimates are based on data obtained almost 20 years ago.[25,26] Incidence rates are predicted to continue to increase until at least 2040 because of an aging population with historical UV exposure.[27-29]

While BCCs can develop early in life both sporadically and with certain genodermatoses, age is an independent risk factor.[30] Incidence rate doubles from 40 to 70 years of age.[31] The incidence for those <40 years age is also increasing.[32] Men have higher BCC rates (1.5-2:1).[11,24,33-39] However, this sex disparity may not exist in populations <40 years of age.[5]

Unsurprisingly, the BCC cost burden is also increasing. The National Ambulatory Medical Care Survey showed a 70% increase from 1995 to 2007 of KC-related office visits; 59% of visits were associated with a procedure.[40] A study comparing US Medical Expenditure Panel Survey data from periods 2002 to 2006 and 2007 to 2011 found an increased average annual cost for skin cancer of 126.2% (from $3.6 to $8.1 billion annually), while the average annual cost for all other cancers increased by 25.1%.[41] A large cohort study in Australia found that patients diagnosed with KCs consumed significantly more health care dollars than patients without this diagnosis.[42]

Cost varies greatly based on the chosen treatment modality. A study that calculated the average cost of treatment for a standard lesion (BCC on cheek, averaged across the 4 lesion size reimbursement ranges) using the 2008 Resource-Based Relative Value Scale, which included costs of obtaining the biopsy specimen, pathology, repair, and follow-up, found that radiation ($2591-3460) was the most expensive treatment, followed by Mohs micrographic surgery ($1263), standard excision ($1006-1170), topical imiquimod ($959), and electrodessication/curettage ($471).[43,44] Vismodegib was not included in this analysis. While this analysis gives us a basic understanding of cost for various treatment modalities, studies such as this are problematic because of the numerous assumptions incorporated into their design and the possibility of inherent biases and conflicts of interest.

Physician office setting is the most common KC treatment setting in the United States (about 91% of cases), compared to 8% in ambulatory surgical centers and 1% in hospital inpatient settings.[45] While physician office–based procedures account for the greatest percentage of US dollars spent treating KCs, the average cost per care episode is substantially less in the physician office compared to the inpatient or ambulatory surgery center settings.[45,46] Average cost per KC episode treated in the physician office setting ($492 in 1 study) is substantially less than other cancer diagnoses.[45] As such, rising incidence more than cost per episode is driving the increasing BCC cost burden.

## CLINICAL PRESENTATION AND ASSOCIATED HISTOLOGIC FINDINGS

### Key points

- **Patients with BCC often report an enlarging, nonhealing lesion that may sometimes bleed; they may also describe pruritus or deny any symptoms**
- **Many lesions exhibit >1 histopathologic pattern, most commonly nodular-micronodular**
- **Morpheaform (sclerosing, desmoplastic) and infiltrative, as well as lesions with micronodular or basosquamous histopathologic changes, are more aggressive variants**

*Abbreviations used:*

BCC: basal cell carcinoma
Hh: Hedgehog signaling
KC: keratinocyte carcinoma
NBCC: nevoid basal cell carcinoma syndrome
PNI: perineural invasion
SCC: squamous cell carcinoma
Shh: Sonic hedgehog protein
UV: ultraviolet

- **Although rare, perineural invasion indicates an aggressive variant with increased rates of metastasis and locoregional recurrence**

Arising in sun-damaged skin, BCCs present clinically and histopathologically in various ways. Patients often complain of an enlarging, nonhealing lesion that may sometimes bleed. They may also complain of pruritus or report no symptoms at all. Nodular, superficial, infundibulocystic, fibroepithelial, morpheaform (sclerosing, desmoplastic), and infiltrative are well-defined subtypes with distinct clinical and histopathologic findings (Table I). Micronodular and basosquamous are 2 additional descriptors with primarily histopathologic (as well as therapeutic and prognostic) significance. Perineural invasion (PNI) is a primarily microscopic finding that portends aggressive clinical behavior. Age does not vary greatly between subtypes. All variants are most common in the sixth, seventh, and eighth decades of life.[30] While differentiating between these subtypes is helpful in management, many lesions (≤40%) exhibit >1 histopathologic pattern, most commonly nodular-micronodular.[56] When this is the case, it is prudent to guide management based on the most aggressive subtype. In addition, BCCs may histopathologically show a variety of other cell lineage differentiation features that do not impact treatment or prognosis (ie, keratotic, follicular, pleomorphic, eccrine, and myoepithelial differentiation patterns).

As the most common subtype, nodular BCC accounts for approximately 50% to 80% of lesions. With a predilection for the head and neck, lesions typically present as a shiny, pearly papule or nodule with a smooth surface, rolled borders, and arborizing telangiectasias (Fig 1, *A*). While slow-growing, advanced tumors can become large and ulcerate, classically referred to as a "rodent ulcer" (Fig 1, *B*). Advanced, infiltrative tumors can cause distortion of the structures they invade (Fig 1, *C*). Histopathologically, they show large dermal nodules of malignant basaloid keratinocytes, peripheral palisading (secondary to clefting artifact between tumor epithelium and stroma), and mucoid stroma containing plump spindle cells (Fig 1, *D*).

Accounting for approximately 10% to 30% of tumors, superficial BCCs are the second most common subtype. Some epidemiologic studies have shown a somewhat younger average age of onset for this subtype (ie, the fifth decade of life); others have shown a relative increase of incidence in females compared to other subtypes.[30,57,58] Superficial BCCs classically present as a well circumscribed and erythematous thin plaque or patch with scale, central clearing, and thin rolled borders (Fig 2, *A*). They can sometimes be mistaken for inflammatory lesions as well as SCC in situ. These slow-growing lesions are most commonly found on the trunk, but can also often be seen on the legs and, less commonly, the head and neck.[58] Both nodular and superficial lesions can sometimes contain melanin, referred to as pigmented BCCs (Fig 2, *B*). On histopathology, superficial BCCs demonstrate multiple lobular foci of basaloid palisading keratinocyte tumors attached superficially to epidermis with a myxoid stroma and band-like lichenoid infiltrate (Fig 2, *C*).[50,59]

Fibroepithelial BCCs (fibroepitheliomas of Pinkus) are an uncommon, indolent subtype with a predilection for the trunk. Commonly mistaken for a fibroepithelial polyp or nonpigmented seborrheic keratosis, these indolent lesions present as a skin-colored or erythematous sessile plaque or pedunculated papulonodule (Fig 3, *A*). On histopathology, they exhibit multiple collections of delicate strands of epidermal basaloid keratinocytes arranged in a reticular pattern within a spindle cell stroma (Fig 3, *B*).[47]

Usually arising on the head and neck of the elderly, infundibulocystic BCCs present as well-circumscribed pearly papules (Fig 4, *A*). Known for their follicular differentiation on histopathology, these lesions present microscopically as a well-circumscribed tumor of anastomosing strands of basaloid cells and scattered small infundibulum-like cystic structures (Fig 4, *B*).[48] Because of their clinical appearance and indolent nature, they can be mistaken for benign follicular adnexal processes.[50]

Less than 10% of BCCs exhibit morpheaform (sclerosing, desmoplastic) or infiltrative changes.[56] However, these lesions are significantly more difficult to treat because of aggressive biologic behavior with local destruction and subclinical extension, as well as higher local recurrence rates.[49,51] Morpheaform BCCs present clinically as an infiltrated plaque with poorly defined borders and shiny surface. Often resembling a scar or plaque of morphea, they are commonly found on the head and neck (Fig 5, *A*). Infiltrative

**Table I.** Clinical and histopathologic findings of basal cell carcinoma subtypes

| | Clinical features | Histopathologic features |
|---|---|---|
| Nodular | Shiny, pearly papule or nodule with a smooth surface, rolled borders, and arborizing telangiectasias with a predilection for head and neck[47-49] | Discrete nests of malignant basaloid cells in the dermis, peripheral palisading, and mucoid stroma containing plump spindle cells |
| Superficial | Well-circumscribed and erythematous thin plaque or patch with scale, central clearing, and thin rolled borders; most common on the trunk[49] | Multiple lobular foci of basaloid palisading keratinocyte tumors attached superficially to the epidermis with a myxoid stroma and band-like lichenoid infiltrate[50,51] |
| Infundibulocystic | Well-circumscribed pearly papule commonly found on the head and neck of the elderly | Well-circumscribed, anastomosing strands of basaloid cells and scattered infundibulum-like cystic structures[52] |
| Fibroepithelial | Skin-colored or erythematous sessile plaque or pedunculated papulonodule[51] with a predilection for the trunk | Multiple collections of delicate strands of epidermal basaloid keratinocytes arranged in a reticular pattern within a spindle cell stroma[53] |
| Morpheaform | Infiltrated plaque with poorly defined borders and shiny surface commonly found on the head and neck | Thin cords of basaloid cells surrounded by a sclerotic collagenous stroma, with mostly absent peripheral palisading and stromal cleft formation; positive staining of tumor stroma with smooth muscle alpha-actin[54] |
| Infiltrative | Poorly defined, indurated, flat or depressed plaque with white, yellow, or pale pink color that may have overlying crusts, erosions, ulcerations, or papules | Thin cords with angulated ends of few basaloid keratinocytes, embedded in a classic mucinous/myxoid stroma[51] |
| Micronodular | Erythematous macule or thin papule/plaque | Multiple small aggregates of basaloid cells within the dermis, with subtle peripheral palisading and retraction artifact[51] |
| Basosquamous | Majority found on the head and neck[55] | Well-defined nodular or superficial BCC component overlying an invasive front showing BCC and SCC histologic features[51] |

*BCC*, Basal cell carcinoma; *SCC*, squamous cell carcinoma.

BCCs present clinically as a poorly defined, indurated, flat or depressed plaque with white, yellow, or pale pink color (Fig 5, *B*). Overlying crusts, erosions, ulcerations, and papules may be seen. For both morpheaform and infiltrative subtypes, thin cords with angulated ends of few basaloid keratinocytes are seen on histopathology. In the case of infiltrative BCC, basaloid cells are embedded in a classic mucinous/myxoid stroma (Fig 5, *C*).[50] In morpheaform lesions, a sclerotic collagenous stroma surrounds the basaloid cords. Peripheral palisading and stromal cleft formation are mostly absent (Fig 5, *D*), and tumor stroma stains positive for smooth muscle alpha-actin with immunohistochemistry.[53]

Micronodular BCC is a predominantly histopathologic term referring to lesions with multiple small aggregates of basaloid cells within the dermis, often with no appreciable connection to the overlying epidermis. Peripheral palisading and retraction artifact are subtle compared to nodular BCC lesions (Fig 6, *A*).[50] Because of their multifocal nature, these lesions often have subclinical extension and resulting higher recurrence rates. Clinically, micronodular BCCs are often difficult to differentiate from superficial and nodular BCCs and can present as erythematous macules or thin papules/plaques (Fig 6, *B*). Occurring in an estimated 15% of BCCs, micronodular changes are often seen together with other histopathologic patterns.[56] Micronodular, as well as infiltrative and morpheaform patterns, harbor significantly higher percentages of Ki-67 and enhancer of zeste homolog 2–positive cells than nodular, and have been suggested as potential markers for risk stratification in advanced tumors.[60]

Representing <2% of KCs, basosquamous type (metatypical BCC) is another primarily histopathologic term referring to neoplasms that have histologic features of both BCC and SCC.[52,61] Microscopically, there is a well-defined nodular or superficial BCC component overlying an invasive front showing BCC and SCC histologic features (Fig 6, *C*).[50] Because they can be confused with BCC/SCC collision tumors, basosquamous type and

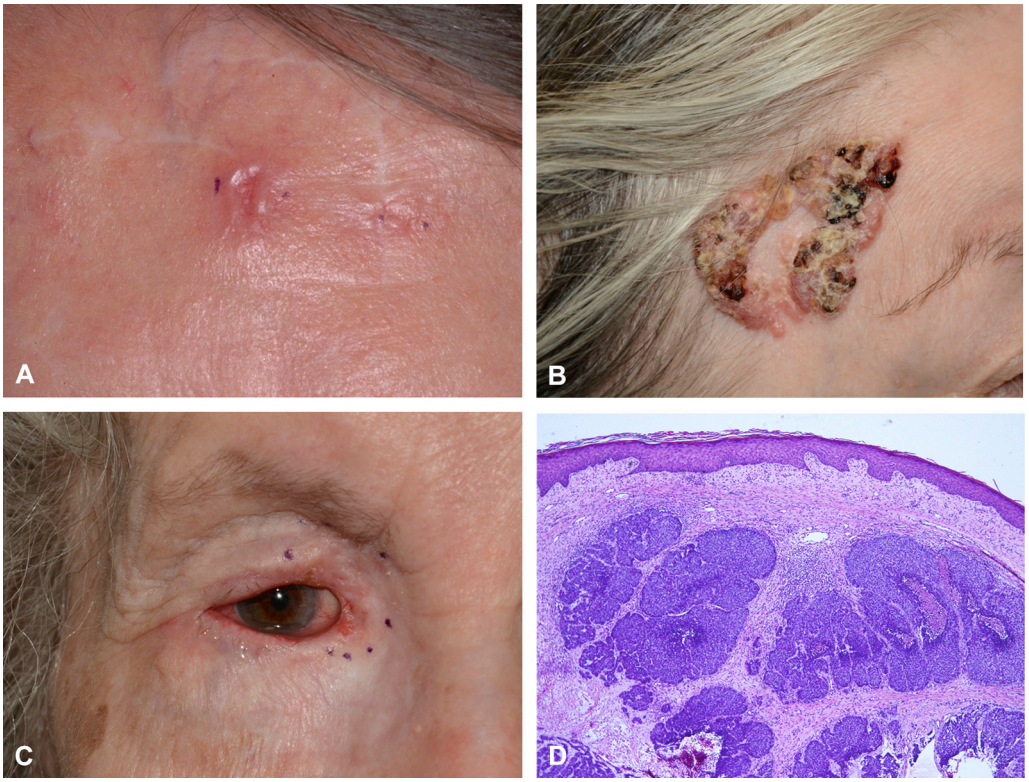


**Fig 1. A**, Nodular basal cell carcinoma (BCC) presenting as a shiny, pearly papule with a smooth surface, rolled borders, and overlying arborizing telangiectasias. **B**, Large, advanced nodular BCC on the temple. **C**, Nodular BCC of the right eye causing free margin distortion. **D**, Hematoxylin–eosin staining of nodular BCC demonstrating large dermal nodules of malignant basaloid keratinocytes, peripheral palisading, and mucoid stroma containing plump spindle cells.

its status as a distinct clinicopathologic entity has been debated.[52] However, immunohistochemical and staining techniques show areas of BCC and SCC with a transition zone, suggesting differentiation from one tumor cell to the other.[62] Given their more pluripotent nature, BCC cells are now believed to differentiate into more aggressive SCC-like cells.[57] Basosquamous is an aggressive subtype with elevated recurrence rates and a significant rate of metastasis (estimated to be >5%).[63] The vast majority of these lesions are found on the head and neck.[52] In addition to BCC/SCC collision tumors, they can be confused with BCCs with squamous metaplasia.[50]

In addition to basosquamous and micronodular histopathologic changes, PNI indicates an aggressive BCC variant. PNI occurs in an estimated 2% to 6% of KC lesions (the majority of which are SCCs) and refers to malignant cells surrounding a nerve sheath and spreading down the length of a superficial or intracranial nerve.[54,55,64-69] If PNI is detected only on histopathology, it is considered microscopic PNI (still high-risk). If a patient exhibits evidence of neuropathy (ie, paresthesia or hyperesthesia) in the vicinity of the tumor or there is gross evidence of perineural tumor invasion on imaging, then the term clinical PNI or perineural spread is warranted.[66,69] Both microscopic and clinical PNI have significantly greater rates of metastasis and locoregional recurrence and are associated with other risk factors including recurrent tumors, high-grade lesions, large lesion size, and aggressive histopathologic subtypes.[54,70-73]

## CARCINOGENESIS AND NATURAL HISTORY

### Key points

- **Predominantly through ultraviolet B light–driven mutagenesis, keratinocyte progenitor cells develop into BCCs**
- **Constitutive activation of the Hedgehog signaling pathway is responsible and alone sufficient for BCC carcinogenesis**
- **BCCs have the greatest mutational burden in coding DNA of any human cancer, perhaps allowing for greater antigenicity and contributing to indolence via heightened immunosurveillance**

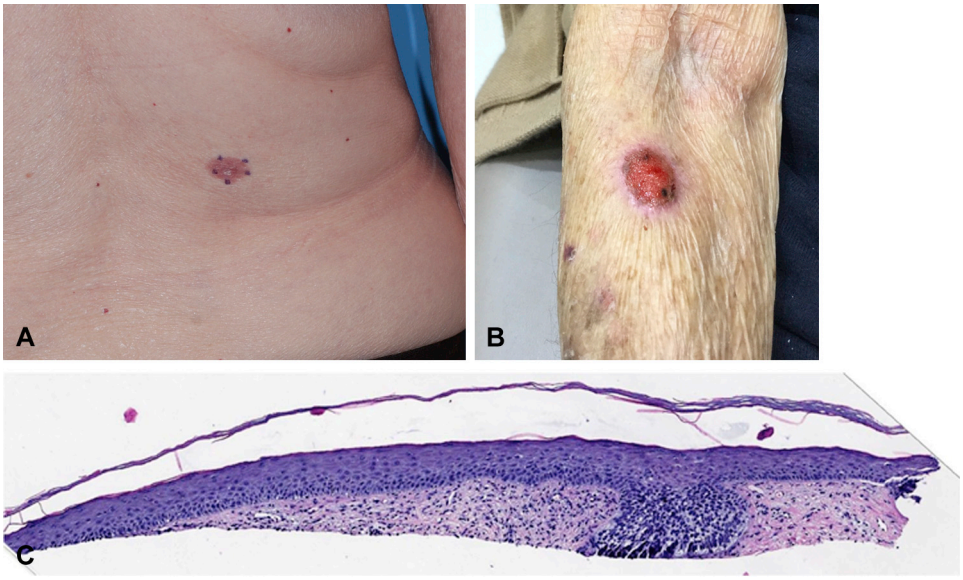


**Fig 2. A**, Superficial basal cell carcinoma (BCC) presenting as a well-circumscribed and erythematous thin plaque. **B**, Pigmented superficial BCC. **C**, Hematoxylin–eosin staining of superficial BCC demonstrating lobular foci of basaloid palisading keratinocytes attached superficially to the epidermis.

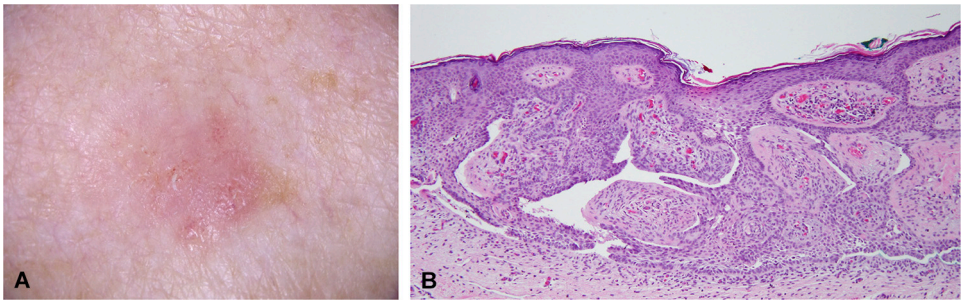


**Fig 3. A**, Fibroepithelial basal cell carcinoma presenting as a pink sessile plaque. **B**, Hematoxylin–eosin staining demonstrating multiple collections of delicate strands of epidermal basaloid keratinocytes arranged in a reticular pattern within a spindle cell stroma.

- **While BCCs grow indolently with local invasion, a small portion progress to locally advanced and metastatic tumors, usually as a result of neglect**

Sporadic BCCs arise from long-term resident keratinocyte progenitor cells of the interfollicular epidermis and upper infundibulum that undergo mutagenesis.[74,75] The majority of these mutations are UVB-induced, with 1 study showing 75.7% of mutations in coding DNA with a "UV signature mutation"—cyclobutane dimer formation attributed to UVB radiation.[76-78]

Nearly all BCCs show constitutive activation of Hedgehog signaling pathway (Hh), and several animal models have shown that amplified Hh is alone sufficient for tumorigenesis (Fig 7).[79,80] Via its effector protein sonic hedgehog (SHH), the Hh pathway is critical for neural, musculoskeletal, hematopoietic, and skin development by governing embryonic development and adult tissue homeostasis, as well as regulating cell type differentiation, patterning, and proliferation.[79] Hh signaling maintains cutaneous stem cell populations and controls development of hair follicles and sebaceous glands.[78]

SHH binding to extracellular receptor PTCH1 relieves PTCH1 inhibition of SMO, which can then activate GLI transcription factors that regulate transcription of Hh pathway target genes; these target genes encode proteins that can execute aforementioned Hh pathway responsibilities.[76] The Hh pathway is also involved in cell cycle regulation, particularly at the $G_2$/M checkpoint. PTCH1 interaction with cyclin $B_1$ prevents the latter protein's

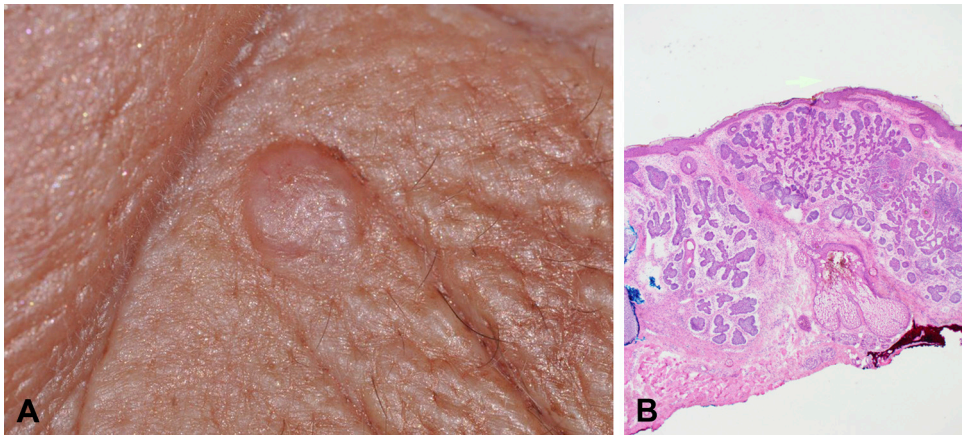


**Fig 4. A**, Infundibulocystic basal cell carcinoma presenting as a well-circumscribed pearly papule. **B**, Hematoxylin–eosin staining of infundibulocystic basal cell carcinoma demonstrating anastomosing strands of basaloid cells and scattered small infundibulum-like cystic structures.

translocation into the nucleus and subsequent promotion of transition to mitosis.[78,81] SHH binding to PTCH1 relieves cyclin $B_1$ of this suppression, allowing its nuclear translocation and cell cycle progression. SHH activity also functions at the $G_1$/S checkpoint, upregulating cyclin $D_1$ (S-phase entry promoter) and inhibiting cyclin-dependent kinase inhibitor 1A (S-phase entry inhibitor).[78,81,82] BCCs exhibit aberrant Hh pathway activation usually either via inactivating mutations of *PTCH1* (chromosome 9q) or activating mutations of *SMO* (chromosome 7q).[75,83-85] A small portion of BCCs exhibit loss of function mutations in *SUFU*, which is a negative regulator of the Hh pathway.[75,83,84,86]

Recent advances in whole-exome sequencing technology have allowed for characterization of the mutational landscape of various cancers. Interestingly, sporadic BCCs show the greatest number of mutations of any human cancer, perhaps because of the ubiquitous nature of the primary source of mutagenesis, UV light.[76] Whether this high mutational burden is, in part, responsible for BCCs indolent nature (via increased antigenicity and heightened immunosurveillance) is a matter of debate.[76] Correspondingly, BCC is one of the cancers increased most by immunosuppression.[76]

While BCCs progress indolently through local invasion, a small subset develops into locally advanced BCC or metastatic BCC tumors. These lesions have usually been neglected for years and developed multiple histologic patterns. Estimated to comprise 1% of tumors, locally advanced BCCs are tumors that are not amenable to curative treatment with surgical excision because of size or anatomic location.[87] Metastatic BCC is extremely uncommon (estimated risk ranging from 0.0028-0.005% of tumors).[88,89] While metastasis can occur hematologically or through subcutaneous spread, lymphatic spread accounts for an estimated 70% of cases.[89,90] All subtypes have been shown to metastasize.[89,91] Common metastatic sites include lymph nodes, bone, lungs, and skin.[89,92] Although median metastatic BCC survival has traditionally been deemed 8 months, recent studies have shown survival lengths of ≥54 months, particularly for disease metastatic to lymph nodes alone.[93-98]

## ENVIRONMENTAL, DISEASE, AND TREATMENT ASSOCIATIONS

### Key points

- **Intermittent intense sun exposure is significantly associated with BCC development via UV-driven mutagenesis and is exacerbated by fair skin, red or blond hair, light eye color, and an inability to tan**
- **Nevoid basal cell carcinoma, multiple hereditary infundibulocystic, Dupre–Christol, Rombo, and xeroderma pigmentosum syndromes are characterized by increased BCC risk**
- **Some autoimmune conditions (ie, rheumatoid arthritis) may be independently associated with increased risk, while evidence exists that others (ie, vitiligo and alopecia areata) may be BCC protective**
- **BCC risk increases secondary to a variety of therapies, including psoralen plus ultraviolet A light phototherapy, immunosuppression in organ transplant patients, and ionizing radiation**

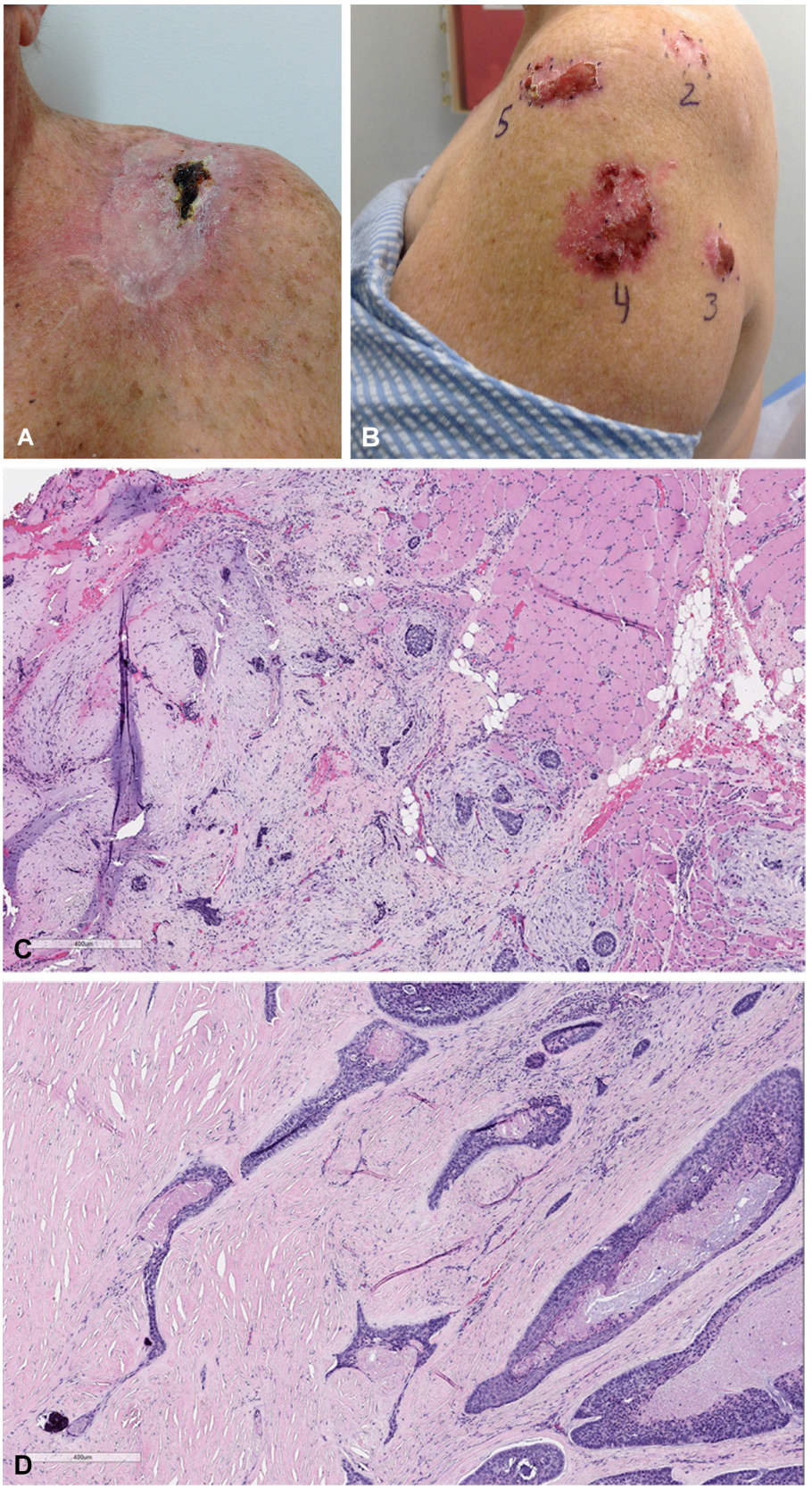


**Fig 5.** **A**, Morpheaform basal cell carcinoma (BCC) presenting as a large, infiltrated scar-like plaque with poorly defined borders and a shiny surface. **B**, Multiple infiltrative BCCs presenting as large, poorly defined plaques with overlying crust, erosions, and ulcerations. **C**, Hematoxylin–eosin staining of infiltrative BCC demonstrating basaloid cells embedded in a mucinous/myxoid stroma. **D**, Hematoxylin–eosin staining of morpheaform BCC demonstrating a sclerotic collagenous stroma surrounding basaloid cords.

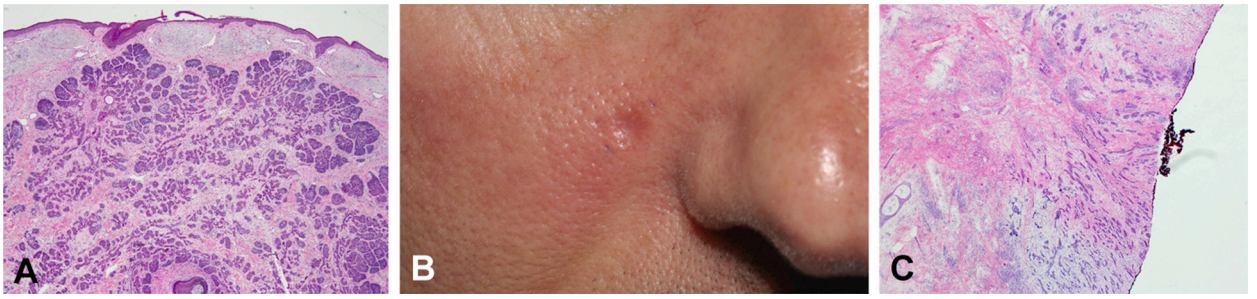


**Fig 6. A**, Hematoxylin–eosin staining of micronodular basal cell carcinoma (BCC) demonstrating multiple small aggregates of basaloid cells within the dermis. **B**, Micronodular BCC presenting as an erythematous indurated thin papule. **C**, Hematoxylin–eosin staining of basosquamous BCC showing features of both BCC and squamous cell carcinoma.

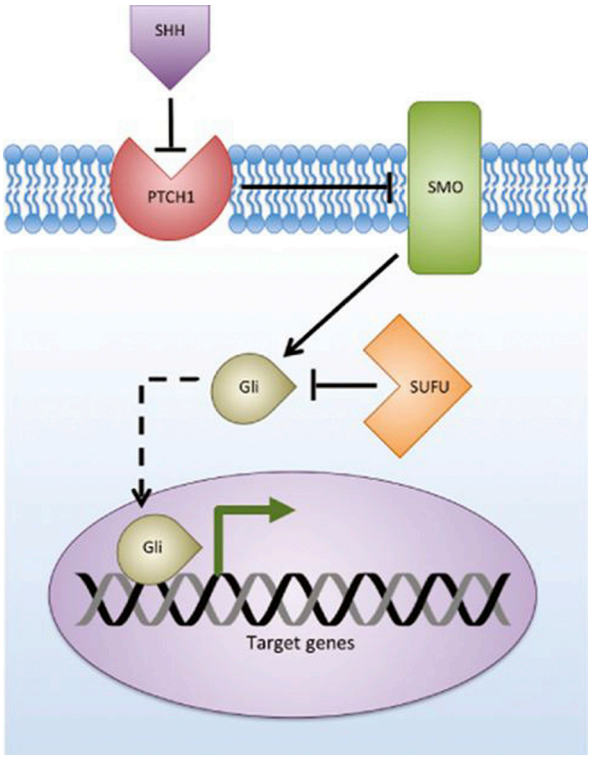


**Fig 7.** Schematic of the sonic hedgehog (SHH) pathway in a representative keratinocyte. Normally, hedgehog ligand activates the pathway by binding to and inhibiting *PTCH1*, allowing the derepression of smoothened (*SMO*), the activation of suppressor of fused gene (*SUFU*), and the downstream upregulation of *GLI1* transcription factors that are involved in cell growth and proliferation. Used with permission from Jaju et al.[136]

Given the predominance of UV signature mutations underlying BCC carcinogenesis, UV exposure via sunlight unsurprisingly is a well-established environmental carcinogen. The nature of this association is complex. A majority of evidence suggests that intermittent sun exposure (ie, recreational tanning, occupational exposure, and childhood sunburns) is a predominant risk factor, while chronic cumulative sun exposure may not play the critical role it does in SCC carcinogenesis.[38,99-110] Other studies show that BCC risk still increases in patients with clinical signs of chronic UV exposure (ie, cutis rhomboidalis nuchae and leukoderma punctata).[103,111] A 20-year observational study involving 73,494 female nurses showed a strong dose-related association between tanning bed use and skin cancer risk; this association was stronger for patients with younger age of exposure and most significant for BCC.[112]

Skin phenotype plays an important role in mitigating the association between UV exposure and BCC. Fair skin, red or blond hair, light eye color, an inability to tan, and a propensity to freckle are independent BCC risk factors.[38,99-107] Skin pigmentation's protective role from carcinogenesis is exemplified by low incidence rates in individuals of African descent.[33] BCC is estimated to occur 19 times less often in such patients compared to whites, although Africans suffering from albinism may develop tumors at early ages.[33] In addition, KC development rates for non-Hispanic whites have been estimated to be 11 times greater than those for Hispanics.[113] As should be expected, variants at melanocortin 1 receptor gene—crucial to tanning response after UV irradiation via melanocyte eumelanin production—are associated with increased BCC incidence.[114,115]

Cigarette smoking does not appear to be associated with increased incidence rates.[116-120] Studies on BCC and alcohol consumption have been limited and contradictory, with some reporting an independent association and others not.[116,117,120-125] The epidemiologic evidence for long-term residential radon exposure and BCC is similarly sparse and contradictory.[126-129] However, substantial evidence exists for a dose-related relationship between arsenic-contaminated water and food and BCC.[130-135]

**Table II.** Summary of select genetic conditions associated with an increased risk of nonmelanoma skin cancer

| Condition | Gene | Locus | Function | Pattern of transmission | Commercial tests |
|---|---|---|---|---|---|
| Basal cell nevus syndrome | *PTCH1*, *PTCH2*, and *SUFU* | 9q22.32, 1p34.1, and 10q24.32 | Hedgehog signaling pathway members | AD | Ambry Genetics, Prevention Genetics, Fulgent Diagnostics, Invitae, and Emory Genetics |
| Bazex-Dupre-Chrisol syndrome | Unknown | Xq25-27.1 | DNA repair and regulation of cell cycle | XLD | |
| Rombo syndrome | Unknown | Unknown | Unknown | AD | |
| Xeroderma pigmentosum* | *XPA-XPG* and *XPV* | 9q22.33, 2q14.3, 3p25.1, 19q13.32, 11p11.2, 16p13.12, 13q33.1, and 6p21.1 | Nucleotide excision repair | AR | Fulgent Diagnostics and Prevention Genetics |
| Rothmund–Thomson syndrome* | *RECQL4* and *C16Orf57* | 8q24.3 and 16q13 | Chromosomal stability, telomere maintenance, trafficking | AR | Fulgent Diagnostics, Prevention Genetics, and Emory Genetics |
| Werner syndrome* | *WRN/RECQL2* | 8p12 | Chromosomal stability | AR | Fulgent Diagnostics and Prevention Genetics |
| Bloom syndrome* | *BLM/RECQL3* | 15q26.1 | Chromosomal stability | AR | Centogene AG-The Rare Disease Company |
| Muir–Torre syndrome† | *MLH1*, *MSH2*, *MSH6*, and *PMS2* | 3p22.2, 2p21, 2p16.3, and 7p22.1 | Mismatch repair | AD | Ambry Genetics and Fulgent Diagnostics |

*AD*, Autosomal dominant; *AR*, autosomal recessive; *XLD*, X-linked dominant.
Adapted with permission from Jaju et al.[136]
*Also includes an increased risk of squamous cell carcinoma.
†Also includes an increased risk of soft tissue tumors and squamous cell carcinoma.

Several genetic syndromes with increased BCC rates have been characterized (Table II). Nevoid basal cell carcinoma syndrome (NBCC, also known as Gorlin syndrome) is an autosomal dominant disorder with an incidence of 1 per 40,000 to 57,000 individuals that is characterized by aberrant upregulation of the Shh pathway and resultant developmental defects and multiple neoplasms, including BCCs (commonly of the infundibulocystic subtype). While some patients may develop >1000 BCCs (and some may develop none), the median number in patients with NBCC is 8.[136] Similar to NBCC, multiple hereditary infundibulocystic syndrome is characterized by autosomal inheritance, upregulation of the Shh pathway, and numerous infundibulocystic BCCs, located commonly on the face; however, there is an absence of palmar pits, jaw cysts, and other developmental stigmata of NBCC.[137,138] Bazex-Dupre-Christol syndrome is a rare (<20 reported sporadic and familial cases) X-linked dominant disorder characterized by the triad of diffuse hypotrichosis, follicular atrophoderma, and BCCs.[136,139] Milia cysts, hypohidrosis, trichoepitheliomas, and facial hyperpigmentation can also be seen. BCCs typically develop on the face by the second decade of life and present atypically, often pigmented and found in comedones, milia cysts, or areas of follicular atrophoderma.[136] Rombo syndrome is a rare autosomal dominant disorder presenting with acral erythema, facial vermiculate atrophoderma, multiple milia, telangiectasias, hypotrichosis, and a tendency to develop milia and BCCs.[136,140] While distinguishing between Bazex-Dupre-Christol and Rombo syndromes is difficult, patients with the latter present later in childhood with a diffuse erythema not seen in the former. Follicular atrophoderma is more prominent in Bazex-Dupre-Christol syndrome.[136] Xeroderma pigmentosum, a group of inherited disorders characterized by

impaired DNA repair and hypersensitivity to UV-induced mutagenesis, have an 1000-fold increased risk of cutaneous malignancies, including BCC. KCs begin to develop at median age of 8.5 years.[136] Other genetic disorders characterized by increased BCC risk (but not necessarily as a prominent and specific finding) include diseases of DNA replication/repair functions (Werner, Rothmund–Thomson, Bloom, Werner, and Muir–Torre syndromes), immune response (cartilage-hair hypoplasia, epidermodysplasia verruciformis), folliculosebaceus unit (Brooke–Spiegler, Schöpf-Schulz-Passarge, and Cowden syndromes), melanin biosynthesis (oculocutaneous albinism and Hermansky–Pudlak syndrome), and epidermal nevus syndromes.[141]

Rheumatoid arthritis patients have a mildly increased BCC risk.[142-145] While some evidence exists for an exacerbation of this association with biologic therapies, a recent large, population-based cohort study showed that this may only apply to SCC.[142,146,147] Antineutrophil cytoplasmic antibody–associated vasculitides may also increase risk.[148] Recent studies have shown a decreased incidence in patients with vitiligo.[149,150] While this association is poorly understood and seems counterintuitive, it is thought to be secondary to keratinocyte upregulation of wild-type p53 and p76 controlling DNA damage/repair.[151,152] Alopecia areata, which shares a similar pathogenesis to vitiligo, may also be associated with decreased incidence.[153]

Increased BCC rates have been associated with a variety of therapies. While the dose-dependent relationship between increased SCC and psoralen plus ultraviolet A light phototherapy is more pronounced, a similar relationship exists for BCC. Increased risk is most apparent for >100 sessions.[54,154-157] Large epidemiologic studies have shown that ionizing radiation increases BCC risk in area of treatment; younger age at time of radiation may increase this association.[158-162] BCC incidence increases 5- to 10-fold secondary to immunosuppression in organ transplant patients (compared to close to 100-fold increase with SCC). Compared to the general population, lesions more often present at a younger age (on average, 15 years earlier), outside the cephalic region, and as the superficial subtype.[54,163-169] Oral contraceptive use may also be associated with increased risk and more aggressive subtypes, potentially helping explain recent data showing a higher rate of incidence increase in women.[10,170-172]

We thank Cristian Navarrete-Dechent for his contribution of the clinical images.

## REFERENCES

1. Rogers HW, Weinstock MA, Feldman SR, et al. Incidence estimate of nonmelanoma skin cancer (keratinocyte carcinomas) in the U.S. population. *JAMA Dermatol*. 2012;2015(151):1081-1086.
2. Staples M, Marks R, Giles G. Trends in the incidence of non-melanocytic skin cancer (NMSC) treated in Australia 1985-1995: are primary prevention programs starting to have an effect? *Int J Cancer*. 1998;78:144-148.
3. Casey AS, Kennedy CE, Goldman GD. Mohs micrographic surgery: how ACMS fellowship directors practice. *Dermatol Surg*. 2009;35:747-756.
4. Nestor MS, Zarraga MB. The incidence of nonmelanoma skin cancers and actinic keratoses in South Florida. *J Clin Aesthet Dermatol*. 2012;5:20-24.
5. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. *JAMA*. 2005;294:681-690.
6. Kaldor J, Shugg D, Young B, et al. Non-melanoma skin cancer: ten years of cancer-registry-based surveillance. *Int J Cancer*. 1993;53:886-891.
7. Brewster DH, Bhatti LA, Inglis JH, et al. Recent trends in incidence of nonmelanoma skin cancers in the East of Scotland, 1992-2003. *Br J Dermatol*. 2007;156:1295-1300.
8. Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977-1978 and 1998-1999 in Northcentral New Mexico. *Cancer Epidemiol Biomarkers Prev*. 2003;12:1105-1108.
9. Hayes RC, Leonfellner S, Pilgrim W, et al. Incidence of nonmelanoma skin cancer in New Brunswick, Canada, 1992 to 2001. *J Cutan Med Surg*. 2007;11:45-52.
10. Karagas MR, Greenberg ER, Spencer SK, et al. Increase in incidence rates of basal cell and squamous cell skin cancer in New Hampshire, USA. New Hampshire Skin Cancer Study Group. *Int J Cancer*. 1999;81:555-559.
11. Staples MP, Elwood M, Burton RC, et al. Non-melanoma skin cancer in Australia: the 2002 national survey and trends since 1985. *Med J Aust*. 2006;184:6-10.
12. Demers AA, Nugent Z, Mihalcioiu C, et al. Trends of nonmelanoma skin cancer from 1960 through 2000 in a Canadian population. *J Am Acad Dermatol*. 2005;53:320-328.
13. Kricker A, English DR, Randell PL, et al. Skin cancer in Geraldton, Western Australia: a survey of incidence and prevalence. *Med J Aust*. 1990;152:399-407.
14. Abbas M, Kalia S. Trends in non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) in Canada: a descriptive analysis of available data. *J Cutan Med Surg*. 2016;20:166-175.
15. Rudolph C, Schnoor M, Eisemann N, et al. Incidence trends of nonmelanoma skin cancer in Germany from 1998 to 2010. *J Dtsch Dermatol Ges*. 2015;13:788-797.
16. Sella T, Goren I, Shalev V, et al. Incidence trends of keratinocytic skin cancers and melanoma in Israel 2006-11. *Br J Dermatol*. 2015;172:202-207.
17. Mudigonda T, Pearce DJ, Yentzer BA, et al. The economic impact of non-melanoma skin cancer: a review. *J Natl Compr Canc Netw*. 2010;8:888-896.
18. Wu S, Han J, Li WQ, et al. Basal-cell carcinoma incidence and associated risk factors in U.S. women and men. *Am J Epidemiol*. 2013;178:890-897.
19. Australian Institute of Health and Welfare. Cancer in Australia 2014: actual incidence data from 1982 to 2011 and mortality data from 1982 to 2012 with projections to 2014. *Asia Pac J Clin Oncol*. 2015;11:208-220.

20. Holme SA, Malinovszky K, Roberts DL. Changing trends in non-melanoma skin cancer in South Wales, 1988-98. *Br J Dermatol*. 2000;143:1224-1229.
21. de Vries E, Louwman M, Bastiaens M, et al. Rapid and continuous increases in incidence rates of basal cell carcinoma in the southeast Netherlands since 1973. *J Invest Dermatol*. 2004;123:634-638.
22. Koh D, Wang H, Lee J, et al. Basal cell carcinoma, squamous cell carcinoma and melanoma of the skin: analysis of the Singapore Cancer Registry data 1968-97. *Br J Dermatol*. 2003; 148:1161-1166.
23. Sng J, Koh D, Siong WC, et al. Skin cancer trends among Asians living in Singapore from 1968 to 2006. *J Am Acad Dermatol*. 2009;61:426-432.
24. Asgari MM, Moffet HH, Ray GT, et al. Trends in basal cell carcinoma incidence and identification of high-risk subgroups, 1998-2012. *JAMA Dermatol*. 2015;151:976-981.
25. Rigel DS, Friedman RJ, Kopf AW. Lifetime risk for development of skin cancer in the U.S. population: current estimate is now 1 in 5. *J Am Acad Dermatol*. 1996;35:1012-1013.
26. Lear JT, Smith AG. Basal cell carcinoma. *Postgrad Med J*. 1997; 73:538-542.
27. Khoo AB, Ali FR, Lear JT. Defining locally advanced basal cell carcinoma and integrating smoothened inhibitors into clinical practice. *Curr Opin Oncol*. 2016;28:180-184.
28. Diffey BL, Langtry JA. Skin cancer incidence and the ageing population. *Br J Dermatol*. 2005;153:679-680.
29. Lear JT. Oral hedgehog-pathway inhibitors for basal-cell carcinoma. *N Engl J Med*. 2012;366:2225-2226.
30. Betti R, Inselvini E, Carducci M, et al. Age and site prevalence of histologic subtypes of basal cell carcinomas. *Int J Dermatol*. 1995;34:174-176.
31. Lomas A, Leonardi-Bee J, Bath-Hextall F. A systematic review of worldwide incidence of nonmelanoma skin cancer. *Br J Dermatol*. 2012;166:1069-1080.
32. Bath-Hextall F, Bong J, Perkins W, et al. Interventions for basal cell carcinoma of the skin: systematic review. *BMJ*. 2004; 329:705.
33. Roewert-Huber J, Lange-Asschenfeldt B, Stockfleth E, et al. Epidemiology and aetiology of basal cell carcinoma. *Br J Dermatol*. 2007;157(suppl 2):47-51.
34. Andersen LK, Davis MD. Sex differences in the incidence of skin and skin-related diseases in Olmsted County, Minnesota, United States, and a comparison with other rates published worldwide. *Int J Dermatol*. 2016;55:939-955.
35. Chuang TY, Popescu A, Su WP, et al. Basal cell carcinoma. A population-based incidence study in Rochester, Minn. *J Am Acad Dermatol*. 1990;22:413-417.
36. Serrano H, Scotto J, Shornick G, et al. Incidence of nonmelanoma skin cancer in New Hampshire and Vermont. *J Am Acad Dermatol*. 1991;24:574-579.
37. Osterlind A, Hou-Jensen K, Moller Jensen O. Incidence of cutaneous malignant melanoma in Denmark 1978-1982. Anatomic site distribution, histologic types, and comparison with non-melanoma skin cancer. *Br J Cancer*. 1988;58: 385-391.
38. Green A, Battistutta D, Hart V, et al. Skin cancer in a subtropical Australian population: incidence and lack of association with occupation. The Nambour Study Group. *Am J Epidemiol*. 1996;144:1034-1040.
39. English DR, Kricker A, Heenan PJ, et al. Incidence of non-melanocytic skin cancer in Geraldton, Western Australia. *Int J Cancer*. 1997;73:629-633.
40. Wysong A, Linos E, Hernandez-Boussard T, et al. Non-melanoma skin cancer visits and procedure patterns in a nationally representative sample: national ambulatory medical care survey 1995-2007. *Dermatol Surg*. 2013;39: 596-602.
41. Guy GP Jr, Machlin SR, Ekwueme DU, et al. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. *Am J Prev Med*. 2015;48:183-187.
42. Rowell D, Gordon LG, Olsen CM, et al. A comparison of the direct medical costs for individuals with or without basal or squamous cell skin cancer: a study from Australia. *SAGE Open Med*. 2016;4, 2050312116646030.
43. Rogers HW, Coldiron BM. A relative value unit-based cost comparison of treatment modalities for nonmelanoma skin cancer: effect of the loss of the Mohs multiple surgery reduction exemption. *J Am Acad Dermatol*. 2009;61:96-103.
44. Wu X, Elkin EE, Marghoob AA. Burden of basal cell carcinoma in USA. *Future Oncol*. 2015;11:2967-2974.
45. Chen JG, Fleischer AB Jr, Smith ED, et al. Cost of nonmelanoma skin cancer treatment in the United States. *Dermatol Surg*. 2001;27:1035-1038.
46. John Chen G, Yelverton CB, Polisetty SS, et al. Treatment patterns and cost of nonmelanoma skin cancer management. *Dermatol Surg*. 2006;32:1266-1271.
47. Pinkus H. Premalignant fibroepithelial tumors of skin. *AMA Arch Derm Syphilol*. 1953;67:598-615.
48. de Eusebio E, Sanchez Yus E, Lopez Bran E, et al. Infundibulocystic basaloid neoplasm. *J Cutan Pathol*. 1996; 23:147-150.
49. Sloane JP. The value of typing basal cell carcinomas in predicting recurrence after surgical excision. *Br J Dermatol*. 1977;96:127-132.
50. Prieto-Granada C, Rodriguez-Waitkus P. Basal cell carcinoma: epidemiology, clinical and histologic features, and basic science overview. *Curr Probl Cancer*. 2015;39:198-205.
51. Litzow TJ, Perry HO, Soderstrom CW. Morpheaform basal cell carcinoma. *Am J Surg*. 1968;116:499-505.
52. Leibovitch I, Huilgol SC, Selva D, et al. Basosquamous carcinoma: treatment with Mohs micrographic surgery. *Cancer*. 2005;104:170-175.
53. Dourmishev LA, Rusinova D, Botev I. Clinical variants, stages, and management of basal cell carcinoma. *Indian Dermatol Online J*. 2013;4:12-17.
54. Bichakjian CK, Olencki T, Aasi SZ, et al. Basal Cell Skin Cancer, Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Cancer Netw*. 2016;14:574-597.
55. Lin C, Tripcony L, Keller J, et al. Perineural infiltration of cutaneous squamous cell carcinoma and basal cell carcinoma without clinical features. *Int J Radiat Oncol Biol Phys*. 2012;82: 334-340.
56. Sexton M, Jones DB, Maloney ME. Histologic pattern analysis of basal cell carcinoma. Study of a series of 1039 consecutive neoplasms. *J Am Acad Dermatol*. 1990;23(6 pt 1):1118-1126.
57. Bastiaens MT, Hoefnagel JJ, Bruijn JA, et al. Differences in age, site distribution, and sex between nodular and superficial basal cell carcinoma indicate different types of tumors. *J Invest Dermatol*. 1998;110:880-884.
58. Scrivener Y, Grosshans E, Cribier B. Variations of basal cell carcinomas according to gender, age, location and histopathological subtype. *Br J Dermatol*. 2002;147:41-47.
59. Crowson AN. Basal cell carcinoma: biology, morphology and clinical implications. *Mod Pathol*. 2006;19(suppl 2):S127-S147.
60. Rao RC, Chan MP, Andrews CA, et al. EZH2, proliferation rate, and aggressive tumor subtypes in cutaneous basal cell carcinoma. *JAMA Oncol*. 2016;2:962-963.
61. Maloney ML. What is basosquamous carcinoma? *Dermatol Surg*. 2000;26:505-506.

62. Jones MS, Helm KF, Maloney ME. The immunohistochemical characteristics of the basosquamous cell carcinoma. *Dermatol Surg*. 1997;23:181-184.
63. Costantino D, Lowe L, Brown DL. Basosquamous carcinoma-an under-recognized, high-risk cutaneous neoplasm: case study and review of the literature. *J Plast Reconstr Aesthet Surg*. 2006;59:424-428.
64. Hassanein AM, Proper SA, Depcik-Smith ND, et al. Peritumoral fibrosis in basal cell and squamous cell carcinoma mimicking perineural invasion: potential pitfall in Mohs micrographic surgery. *Dermatol Surg*. 2005;31(9 pt 1): 1101-1106.
65. Jackson JE, Dickie GJ, Wiltshire KL, et al. Radiotherapy for perineural invasion in cutaneous head and neck carcinomas: toward a risk-adapted treatment approach. *Head Neck*. 2009; 31:604-610.
66. Garcia-Serra A, Hinerman RW, Mendenhall WM, et al. Carcinoma of the skin with perineural invasion. *Head Neck*. 2003;25:1027-1033.
67. Lin C, Tripcony L, Keller J, et al. Cutaneous carcinoma of the head and neck with clinical features of perineural infiltration treated with radiotherapy. *Clin Oncol (R Coll Radiol)*. 2013;25: 362-367.
68. Leibovitch I, Huilgol SC, Selva D, et al. Basal cell carcinoma treated with Mohs surgery in Australia III. Perineural invasion. *J Am Acad Dermatol*. 2005;53:458-463.
69. McCord MW, Mendenhall WM, Parsons JT, et al. Skin cancer of the head and neck with clinical perineural invasion. *Int J Radiat Oncol Biol Phys*. 2000;47:89-93.
70. Williams LS, Mancuso AA, Mendenhall WM. Perineural spread of cutaneous squamous and basal cell carcinoma: CT and MR detection and its impact on patient management and prognosis. *Int J Radiat Oncol Biol Phys*. 2001;49:1061-1069.
71. Galloway TJ, Morris CG, Mancuso AA, et al. Impact of radiographic findings on prognosis for skin carcinoma with clinical perineural invasion. *Cancer*. 2005;103:1254-1257.
72. Balamucki CJ, DeJesus R, Galloway TJ, et al. Impact of radiographic findings on for prognosis skin cancer with perineural invasion. *Am J Clin Oncol*. 2015;38:248-251.
73. Cernea CR, Ferraz AR, de Castro IV, et al. Perineural invasion in aggressive skin carcinomas of the head and neck. Potentially dangerous but frequently overlooked. *ORL J Otorhinolaryngol Relat Spec*. 2009;71:21-26.
74. Youssef KK, Van Keymeulen A, Lapouge G, et al. Identification of the cell lineage at the origin of basal cell carcinoma. *Nat Cell Biol*. 2010;12:299-305.
75. Bonilla X, Parmentier L, King B, et al. Genomic analysis identifies new drivers and progression pathways in skin basal cell carcinoma. *Nat Genet*. 2016;48:398-406.
76. Jayaraman SS, Rayhan DJ, Hazany S, et al. Mutational landscape of basal cell carcinomas by whole-exome sequencing. *J Invest Dermatol*. 2014;134:213-220.
77. Ikehata H, Ono T. The mechanisms of UV mutagenesis. *J Radiat Res*. 2011;52:115-125.
78. Iwasaki JK, Srivastava D, Moy RL, et al. The molecular genetics underlying basal cell carcinoma pathogenesis and links to targeted therapeutics. *J Am Acad Dermatol*. 2012;66:e167-e178.
79. Daya-Grosjean L, Couve-Privat S. Sonic hedgehog signaling in basal cell carcinomas. *Cancer Lett*. 2005;225:181-192.
80. Yang SH, Andl T, Grachtchouk V, et al. Pathological responses to oncogenic Hedgehog signaling in skin are dependent on canonical Wnt/beta3-catenin signaling. *Nat Genet*. 2008;40: 1130-1135.
81. Roy S, Ingham PW. Hedgehogs tryst with the cell cycle. *J Cell Sci*. 2002;115(pt 23):4393-4397.
82. Williams JA, Guicherit OM, Zaharian BI, et al. Identification of a small molecule inhibitor of the hedgehog signaling pathway: effects on basal cell carcinoma-like lesions. *Proc Natl Acad Sci U S A*. 2003;100:4616-4621.
83. Sharpe HJ, Pau G, Dijkgraaf GJ, et al. Genomic analysis of smoothened inhibitor resistance in basal cell carcinoma. *Cancer Cell*. 2015;27:327-341.
84. Reifenberger J, Wolter M, Knobbe CB, et al. Somatic mutations in the PTCH, SMOH, SUFUH and TP53 genes in sporadic basal cell carcinomas. *Br J Dermatol*. 2005;152:43-51.
85. Atwood SX, Sarin KY, Whitson RJ, et al. Smoothened variants explain the majority of drug resistance in basal cell carcinoma. *Cancer Cell*. 2015;27:342-353.
86. Smith MJ, Beetz C, Williams SG, et al. Germline mutations in SUFU cause Gorlin syndrome-associated childhood medulloblastoma and redefine the risk associated with PTCH1 mutations. *J Clin Oncol*. 2014;32:4155-4161.
87. Goldenberg G, Karagiannis T, Palmer JB, et al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: a retrospective cohort study. *J Am Acad Dermatol*. 2016;75:957-966.e2.
88. Mohan SV, Chang AL. Advanced basal cell carcinoma: epidemiology and therapeutic innovations. *Curr Dermatol Rep*. 2014;3:40-45.
89. Ozgediz D, Smith EB, Zheng J, et al. Basal cell carcinoma does metastasize. *Dermatol Online J*. 2008;14:5.
90. von Domarus H, Stevens PJ. Metastatic basal cell carcinoma. Report of five cases and review of 170 cases in the literature. *J Am Acad Dermatol*. 1984;10:1043-1060.
91. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. *J Cutan Med Surg*. 2005;9:10-15.
92. Berlin JM, Warner MR, Bailin PL. Metastatic basal cell carcinoma presenting as unilateral axillary lymphadenopathy: report of a case and review of the literature. *Dermatol Surg*. 2002;28:1082-1084.
93. Jacobsen AA, Aldahan AS, Hughes OB, et al. Hedgehog pathway inhibitor therapy for locally advanced and metastatic basal cell carcinoma: a systematic review and pooled analysis of interventional studies. *JAMA Dermatol*. 2016;152:816-824.
94. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med*. 2009;361:1164-1172.
95. McCusker M, Basset-Seguin N, Dummer R, et al. Metastatic basal cell carcinoma: prognosis dependent on anatomic site and spread of disease. *Eur J Cancer*. 2014;50:774-783.
96. Danial C, Sarin KY, Oro AE, et al. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22:1325-1329.
97. Pfeiffer P, Hansen O, Rose C. Systemic cytotoxic therapy of basal cell carcinoma. A review of the literature. *Eur J Cancer*. 1990;26:73-77.
98. Raszewski RL, Guyuron B. Long-term survival following nodal metastases from basal cell carcinoma. *Ann Plast Surg*. 1990; 24:170-175.
99. Zanetti R, Rosso S, Martinez C, et al. Comparison of risk patterns in carcinoma and melanoma of the skin in men: a multi-centre case-case-control study. *Br J Cancer*. 2006;94: 743-751.
100. Gallagher RP, Hill GB, Bajdik CD, et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. I. Basal cell carcinoma. *Arch Dermatol*. 1995;131:157-163.

101. Ramsay HM, Fryer AA, Hawley CM, et al. Factors associated with nonmelanoma skin cancer following renal transplantation in Queensland, Australia. *J Am Acad Dermatol*. 2003;49:397-406.
102. Kasper ME, Chaudhary AA. Novel treatment options for nonmelanoma skin cancer: focus on electronic brachytherapy. *Med Devices (Auckl)*. 2015;8:493-502.
103. Chinem VP, Miot HA. Prevalence of actinic skin lesions in patients with basal cell carcinoma of the head: a case-control study. *Rev Assoc Med Bras*. 2012;58:188-196.
104. Walther U, Kron M, Sander S, et al. Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case-control study in southern Germany. Clinical actinic elastosis may be a protective factor. *Br J Dermatol*. 2004; 151:170-178.
105. Khalesi M, Whiteman DC, Tran B, et al. A meta-analysis of pigmentary characteristics, sun sensitivity, freckling and melanocytic nevi and risk of basal cell carcinoma of the skin. *Cancer Epidemiol*. 2013;37:534-543.
106. Lock-Andersen J, Drzewiecki KT, Wulf HC. Eye and hair colour, skin type and constitutive skin pigmentation as risk factors for basal cell carcinoma and cutaneous malignant melanoma. A Danish case-control study. *Acta Derm Venereol*. 1999;79: 74-80.
107. Kricker A, Armstrong BK, English DR, et al. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer—a case-control study. *Int J Cancer*. 1991;48:650-662.
108. Radespiel-Troger M, Meyer M, Pfahlberg A, et al. Outdoor work and skin cancer incidence: a registry-based study in Bavaria. *Int Arch Occup Environ Health*. 2009;82: 357-363.
109. Bauer A, Diepgen TL, Schmitt J. Is occupational solar ultraviolet irradiation a relevant risk factor for basal cell carcinoma? A systematic review and meta-analysis of the epidemiological literature. *Br J Dermatol*. 2011;165:612-625.
110. Szewczyk M, Pazdrowski J, Golusinski P, et al. Basal cell carcinoma in farmers: an occupation group at high risk. *Int Arch Occup Environ Health*. 2016;89:497-501.
111. Kaskel P, Lange U, Sander S, et al. Ultraviolet exposure and risk of melanoma and basal cell carcinoma in Ulm and Dresden, Germany. *J Eur Acad Dermatol Venereol*. 2015;29: 134-142.
112. Zhang M, Qureshi AA, Geller AC, et al. Use of tanning beds and incidence of skin cancer. *J Clin Oncol*. 2012;30:1588-1593.
113. Harris RB, Griffith K, Moon TE. Trends in the incidence of nonmelanoma skin cancers in southeastern Arizona, 1985-1996. *J Am Acad Dermatol*. 2001;45:528-536.
114. Suzuki I, Im S, Tada A, et al. Participation of the melanocortin-1 receptor in the UV control of pigmentation. *J Investig Dermatol Symp Proc*. 1999;4:29-34.
115. Box NF, Duffy DL, Irving RE, et al. Melanocortin-1 receptor genotype is a risk factor for basal and squamous cell carcinoma. *J Invest Dermatol*. 2001;116:224-229.
116. Freedman DM, Sigurdson A, Doody MM, et al. Risk of basal cell carcinoma in relation to alcohol intake and smoking. *Cancer Epidemiol Biomarkers Prev*. 2003;12:1540-1543.
117. Sahl WJ, Glore S, Garrison P, et al. Basal cell carcinoma and lifestyle characteristics. *Int J Dermatol*. 1995;34:398-402.
118. van Dam RM, Huang Z, Rimm EB, et al. Risk factors for basal cell carcinoma of the skin in men: results from the health professionals follow-up study. *Am J Epidemiol*. 1999;150: 459-468.
119. Hunter DJ, Colditz GA, Stampfer MJ, et al. Risk factors for basal cell carcinoma in a prospective cohort of women. *Ann Epidemiol*. 1990;1:13-23.
120. Corona R, Dogliotti E, D'Errico M, et al. Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. *Arch Dermatol*. 2001; 137:1162-1168.
121. Wu S, Li WQ, Qureshi AA, et al. Alcohol consumption and risk of cutaneous basal cell carcinoma in women and men: 3 prospective cohort studies. *Am J Clin Nutr*. 2015;102: 1158-1166.
122. Fung TT, Hunter DJ, Spiegelman D, et al. Intake of alcohol and alcoholic beverages and the risk of basal cell carcinoma of the skin. *Cancer Epidemiol Biomarkers Prev*. 2002;11(10 pt 1):1119-1122.
123. Ansems TM, van der Pols JC, Hughes MC, et al. Alcohol intake and risk of skin cancer: a prospective study. *Eur J Clin Nutr*. 2008;62:162-170.
124. Milan T, Verkasalo PK, Kaprio J, et al. Lifestyle differences in twin pairs discordant for basal cell carcinoma of the skin. *Br J Dermatol*. 2003;149:115-123.
125. Kune GA, Bannerman S, Field B, et al. Diet, alcohol, smoking, serum beta-carotene, and vitamin A in male nonmelanocytic skin cancer patients and controls. *Nutr Cancer*. 1992;18:237-244.
126. Brauner EV, Loft S, Sorensen M, et al. Residential radon exposure and skin cancer incidence in a prospective Danish cohort. *PLoS One*. 2015;10:e0135642.
127. Etherington DJ, Pheby DF, Bray FI. An ecological study of cancer incidence and radon levels in South West England. *Eur J Cancer*. 1996;32A(7):1189-1197.
128. Wheeler BW, Allen J, Depledge MH, et al. Radon and skin cancer in southwest England: an ecologic study. *Epidemiology*. 2012;23:44-52.
129. Wheeler BW, Kothencz G, Pollard AS. Geography of non-melanoma skin cancer and ecological associations with environmental risk factors in England. *Br J Cancer*. 2013;109: 235-241.
130. Pesch B, Ranft U, Jakubis P, et al. Environmental arsenic exposure from a coal-burning power plant as a potential risk factor for nonmelanoma skin carcinoma: results from a case-control study in the district of Prievidza, Slovakia. *Am J Epidemiol*. 2002;155:798-809.
131. Karagas MR, Gossai A, Pierce B, et al. Drinking water arsenic contamination, skin lesions, and malignancies: a systematic review of the global evidence. *Curr Environ Health Rep*. 2015; 2:52-68.
132. Hsueh YM, Cheng GS, Wu MM, et al. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. *Br J Cancer*. 1995;71:109-114.
133. Chen YC, Guo YL, Su HJ, et al. Arsenic methylation and skin cancer risk in southwestern Taiwan. *J Occup Environ Med*. 2003;45:241-248.
134. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some drinking-water disinfectants and contaminants, including arsenic. Monographs on chloramine, chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. *IARC Monogr Eval Carcinog Risks Hum*. 2004;84:269-477.
135. Leonardi G, Vahter M, Clemens F, et al. Inorganic arsenic and basal cell carcinoma in areas of Hungary, Romania, and Slovakia: a case-control study. *Environ Health Perspect*. 2012; 120:721-726.
136. Jaju PD, Ransohoff KJ, Tang JY, et al. Familial skin cancer syndromes: increased risk of nonmelanotic skin cancers and extracutaneous tumors. *J Am Acad Dermatol*. 2016;74:437-451.
137. Schulman JM, Oh DH, Sanborn JZ, et al. Multiple hereditary infundibulocystic basal cell carcinoma syndrome associated

with a germline SUFU mutation. *JAMA Dermatol*. 2016;152:323-327.
138. Requena L, Farina MC, Robledo M, et al. Multiple hereditary infundibulocystic basal cell carcinomas: a genodermatosis different from nevoid basal cell carcinoma syndrome. *Arch Dermatol*. 1999;135:1227-1235.
139. Abuzahra F, Parren LJ, Frank J. Multiple familial and pigmented basal cell carcinomas in early childhood - Bazex-Dupre-Christol syndrome. *J Eur Acad Dermatol Venereol*. 2012;26:117-121.
140. Michaelsson G, Olsson E, Westermark P. The Rombo syndrome: a familial disorder with vermiculate atrophoderma, milia, hypotrichosis, trichoepitheliomas, basal cell carcinomas and peripheral vasodilation with cyanosis. *Acta Derm Venereol*. 1981;61:497-503.
141. Castori M, Morrone A, Kanitakis J, et al. Genetic skin diseases predisposing to basal cell carcinoma. *Eur J Dermatol*. 2012;22:299-309.
142. Raaschou P, Simard JF, Asker Hagelberg C, et al. Rheumatoid arthritis, anti-tumour necrosis factor treatment, and risk of squamous cell and basal cell skin cancer: cohort study based on nationwide prospectively recorded data from Sweden. *BMJ*. 2016;352:i262.
143. Chakravarty EF, Michaud K, Wolfe F. Skin cancer, rheumatoid arthritis, and tumor necrosis factor inhibitors. *J Rheumatol*. 2005;32:2130-2135.
144. Mellemkjaer L, Linet MS, Gridley G, et al. Rheumatoid arthritis and cancer risk. *Eur J Cancer*. 1996;32A:1753-1757.
145. Dreyer L, Mellemkjaer L, Andersen AR, et al. Incidences of overall and site specific cancers in TNFalpha inhibitor treated patients with rheumatoid arthritis and other arthritides - a follow-up study from the DANBIO Registry. *Ann Rheum Dis*. 2013;72:79-82.
146. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. *Arthritis Rheum*. 2007;56:2886-2895.
147. Amari W, Zeringue AL, McDonald JR, et al. Risk of non-melanoma skin cancer in a national cohort of veterans with rheumatoid arthritis. *Rheumatology (Oxford)*. 2011;50:1431-1439.
148. Rahmattulla C, Berden AE, Wakker SC, et al. Incidence of malignancies in patients with antineutrophil cytoplasmic antibody-associated vasculitis diagnosed between 1991 and 2013. *Arthritis Rheumatol*. 2015;67:3270-3278.
149. Teulings HE, Overkamp M, Ceylan E, et al. Decreased risk of melanoma and nonmelanoma skin cancer in patients with vitiligo: a survey among 1307 patients and their partners. *Br J Dermatol*. 2013;168:162-171.
150. Schallreuter KU, Tobin DJ, Panske A. Decreased photodamage and low incidence of non-melanoma skin cancer in 136 sun-exposed caucasian patients with vitiligo. *Dermatology*. 2002;204:194-201.
151. Schallreuter KU, Behrens-Williams S, Khaliq TP, et al. Increased epidermal functioning wild-type p53 expression in vitiligo. *Exp Dermatol*. 2003;12:268-277.
152. Salem MM, Shalbaf M, Gibbons NC, et al. Enhanced DNA binding capacity on up-regulated epidermal wild-type p53 in vitiligo by H2O2-mediated oxidation: a possible repair mechanism for DNA damage. *FASEB J*. 2009;23:3790-3807.
153. Mostaghimi A, Qureshi S, Joyce C, et al. Reduced incidence of skin cancer in patients with alopecia areata: a retrospective cohort study. *Cancer Epidemiol*. 2016;41:129-131.
154. Stern RS. The risk of squamous cell and basal cell cancer associated with psoralen and ultraviolet A therapy: a 30-year prospective study. *J Am Acad Dermatol*. 2012;66:553-562.
155. Stern RS, Laird N, Melski J, et al. Cutaneous squamous-cell carcinoma in patients treated with PUVA. *N Engl J Med*. 1984;310:1156-1161.
156. Stern RS, Liebman EJ, Vakeva L. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst*. 1998;90:1278-1284.
157. Archier E, Devaux S, Castela E, et al. Carcinogenic risks of psoralen UV-A therapy and narrowband UV-B therapy in chronic plaque psoriasis: a systematic literature review. *J Eur Acad Dermatol Venereol*. 2012;26(suppl 3):22-31.
158. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. *J Clin Oncol*. 2005;23:3733-3741.
159. Karagas MR, Nelson HH, Zens MS, et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. *Epidemiology*. 2007;18:776-784.
160. Watt TC, Inskip PD, Stratton K, et al. Radiation-related risk of basal cell carcinoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst*. 2012;104:1240-1250.
161. Schwartz JL, Kopecky KJ, Mathes RW, et al. Basal cell skin cancer after total-body irradiation and hematopoietic cell transplantation. *Radiat Res*. 2009;171:155-163.
162. Lichter MD, Karagas MR, Mott LA, et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. *Arch Dermatol*. 2000;136:1007-1011.
163. Park GH, Chang SE, Won CH, et al. Incidence of primary skin cancer after organ transplantation: an 18-year single-center experience in Korea. *J Am Acad Dermatol*. 2014;70:465-472.
164. Jensen AO, Svaerke C, Farkas D, et al. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. *Acta Derm Venereol*. 2010;90:474-479.
165. Hartevelt MM, Bavinck JN, Kootte AM, et al. Incidence of skin cancer after renal transplantation in The Netherlands. *Transplantation*. 1990;49:506-509.
166. Harwood CA, Mesher D, McGregor JM, et al. A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant*. 2013;13:119-129.
167. Brewer JD, Colegio OR, Phillips PK, et al. Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol*. 2009;145:1391-1396.
168. Rashtak S, Dierkhising RA, Kremers WK, et al. Incidence and risk factors for skin cancer following lung transplantation. *J Am Acad Dermatol*. 2015;72:92-98.
169. Fortina AB, Piaserico S, Caforio AL, et al. Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol*. 2004;140:1079-1085.
170. Kuklinski LF, Zens MS, Perry AE, et al. Sex hormones and the risk of keratinocyte cancers among women in the United States: a population-based case-control study. *Int J Cancer*. 2016;139:300-309.
171. Flohil SC, Seubring I, van Rossum MM, et al. Trends in basal cell carcinoma incidence rates: a 37-year Dutch observational study. *J Invest Dermatol*. 2013;133:913-918.
172. Birch-Johansen F, Jensen A, Mortensen L, et al. Trends in the incidence of nonmelanoma skin cancer in Denmark 1978-2007: rapid incidence increase among young Danish women. *Int J Cancer*. 2010;127:2190-2198.