REVIEW ARTICLE

CURRENT CONCEPTS

Basal-Cell Carcinoma

Adam I. Rubin, M.D., Elbert H. Chen, M.D., and Désirée Ratner, M.D.

From the Department of Dermatology, Columbia University, New York. Address reprint requests to Dr. Ratner at the Department of Dermatology, Columbia University, 161 Fort Washington Ave., 12th Fl., New York, NY 10032, or at dr221@columbia.edu.

Drs. Rubin and Chen contributed equally to this article.

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According to the American Cancer Society, skin cancer is the most common cancer, accounting for about half of all cancers in the United States. More than 1 million cases of skin cancer will be diagnosed in the United States this year.[1] Basal-cell carcinomas constitute approximately 80 percent of all nonmelanoma skin cancers. This article addresses cutaneous basal-cell carcinoma, which should be differentiated from the uncommon basal-cell carcinoma or basaloid carcinoma that arises in sites such as the prostate, pancreas, lung, cervix, salivary gland, thymus, and anal canal.

INCIDENCE

The absolute incidence of basal-cell carcinoma is difficult to determine, since nonmelanoma skin cancer is usually excluded from cancer-registry statistics. The task is further complicated by the marked geographic variability in the incidence of nonmelanoma skin cancer.[2] However, the trend is clearly toward an increasing number of cases. Australia has the highest rate of basal-cell carcinoma in the world, with certain regions reporting an incidence of up to 2 percent per year. Age-standardized yearly rates in the United States have been estimated at up to 407 cases of basal-cell carcinoma per 100,000 white men and 212 cases per 100,000 white women.[3] Although the rates remain highest among elderly men, patients with this disease are increasingly likely to be young women.[4]

RISK FACTORS

Exposure to ultraviolet radiation is generally accepted as the major cause of basal-cell carcinoma.[5] Whereas squamous-cell carcinoma appears to be strongly related to cumulative sun exposure, the relationship between exposure to ultraviolet radiation and the risk of basal-cell carcinoma is more complex.[6] The timing, pattern, and amount of exposure to ultraviolet radiation all appear to be important. The risk of this disease is significantly increased by recreational exposure to the sun during childhood and adolescence.[5] Intense intermittent exposure to the sun is associated with a higher risk of basal-cell carcinoma than is a similar degree of continuous exposure.[7] Physical factors, including fair complexion, red or blond hair, and light eye color, influence responsiveness to ultraviolet radiation but are also independent risk factors.[8] Exposures to ionizing radiation,[9] arsenic,[10] and oral methoxsalen (psoralen) and ultraviolet A radiation[11] have also been linked to the development of basal-cell carcinoma (Table 1).

Immunosuppression predisposes persons to basal-cell carcinoma. The 4:1 ratio of basal-cell carcinoma to squamous-cell carcinoma seen in immunocompetent patients is reversed in organ-transplant recipients. Among Australian heart-transplant recipients there were 21 times as many cases of basal-cell carcinoma as among Australians who had not received a heart transplant and 123 times as many cases as among Americans who had not received a heart transplant.[12] Renal-transplant recipients have a risk of

Table 1. Risk Factors for the Development of Basal-Cell Carcinoma.

Physical characteristics
Blond or red hair
Blue or green eyes
Light skin color
Exposures
Arsenic
Coal tar
Ionizing radiation
Smoking
Tanning–bed use
Ultraviolet light
Genodermatoses
Albinism
Xeroderma pigmentosum
Rombo syndrome*
Bazex–Dupré–Christol syndrome (Bazex's syndrome)†
Nevoid basal-cell carcinoma syndrome (Gorlin's syndrome)‡
Immunosuppression
Recipients of solid-organ transplants

* This syndrome is an autosomal dominant disorder, characterized by basal-cell carcinoma, atrophoderma vermiculata, milia, hypotrichosis, trichoepithelioma, and peripheral vasodilatation.

† This syndrome is an X-linked dominant disorder, characterized by basal-cell carcinoma, follicular atrophoderma, hypotrichosis, and localized anhidrosis.

‡ This syndrome is an autosomal dominant disorder, characterized by basal-cell carcinoma, palmoplantar pits, odontogenic keratocysts, bifid ribs, frontal bossing, and central nervous system defects.

basal-cell carcinoma that is 10 times that among a population of those who have not received renal transplants.[13]

In a meta-analysis of seven studies, Marcil and Stern[14] showed that after an index case of basal-cell carcinoma, the incidence of subsequent cases among such patients was increased by a factor of 10, as compared with that in the general population. Significant predictors of a greater number of basal-cell carcinomas include an initial truncal occurrence, an age of more than 60 years at the first presentation, the presence of the superficial histologic subtype, and male sex.[15] Susceptibility to a truncal location has been linked with genetic polymorphisms in glutathione *S*-transferase and cytochrome P-450.[16]

CLINICAL PRESENTATION AND HISTOLOGIC APPEARANCE

Basal-cell carcinoma characteristically arises in body areas exposed to the sun and is most common on the head and neck (80 percent of cases), followed by the trunk (15 percent of cases) and arms and legs. Basal-cell carcinomas have also been reported in unusual sites, including the axillae, breasts, perianal area, genitalia, palms, and soles.

Nodular basal-cell carcinoma is the classic form, which most often presents as a pearly papule or nodule with overlying telangiectases and a rolled border, at times exhibiting central crusting or ulceration (Fig. 1A). Occasionally, nodular basal-cell carcinoma may resemble enlarged pores or pits on the sebaceous skin of the central portion of the face[17] (Fig. 1B). Superficial basal-cell carcinoma presents as a scaly erythematous patch or plaque (Fig. 1C). Both nodular and superficial forms may contain melanin, imparting a brown, blue, or black color to these lesions (Fig. 1D). The morpheaform type, also known as sclerosing, fibrosing, or infiltrative basal-cell carcinoma, typically appears as an indurated, whitish, scar-like plaque with indistinct margins (Fig. 1E). Suspicious lesions occurring in high-risk areas, such as the central portion of the face, should undergo prompt biopsy to obtain a timely diagnosis and to expedite definitive treatment. Skin biopsy will also identify amelanotic (nonpigmented) or minimally pigmented melanomas, which can sometimes mimic basal-cell carcinoma.

In a review of 1039 consecutive cases of basal-cell carcinoma, Sexton et al.[18] found that the most common histologic subtypes are mixed (38.6 percent), nodular (21.0 percent), superficial (17.4 percent), and micronodular (14.5 percent). Uncommon variants, including basosquamous, keratotic, granular-cell, adamantinoid, clear-cell, and basal-cell carcinoma with matrical differentiation, have also been described. The value of classifying the histologic appearance lies in the relationship between histologic subtype and clinical behavior. Aggressive histologic variants include the micronodular, infiltrative, basosquamous, morpheaform, and mixed subtypes.[19] Nodular and superficial subtypes generally have a less aggressive clinical course.

MOLECULAR PATHOGENESIS

Inappropriate activation of the hedgehog (HH) signaling pathway is found in sporadic and familial cases of basal-cell carcinoma, medulloblastoma, rhabdomyosarcoma, and other tumors.[20] Originally identified as a determinant of segment polarity in the fruitfly *Drosophila melanogaster*, the HH signaling pathway plays a critical role in vertebrate development.[21] Secreted sonic HH (SHH) protein binds

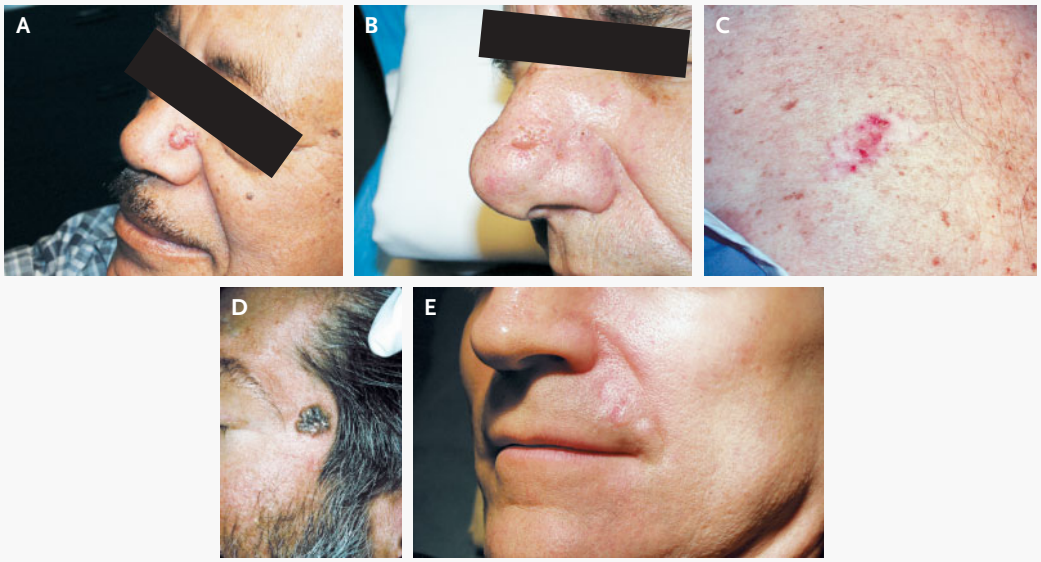

Figure 1. Types of Basal-Cell Carcinoma.

Panel A shows nodular basal-cell carcinoma of the lower nasal sidewall, with telangiectases and a pearly border. Panel B shows nodular basal-cell carcinoma presenting as an enlarged pore. Panel C shows recurrent superficial basal-cell carcinoma of the abdomen at the site of a previous curettage and electrodesiccation. This form could be mistaken for an actinic keratosis, eczema, psoriasis, or tinea corporis. Panel D shows pigmented nodular basal-cell carcinoma of the temple. This lesion may be confused clinically with a seborrheic keratosis, nevus, or even a melanoma. In Panel E, morpheaform basal-cell carcinoma on the cutaneous lip has a scar-like appearance with indistinct clinical margins. Because of its banal appearance, morpheaform basal-cell carcinoma may remain undiagnosed for years.

the tumor-suppressor protein patched homologue 1 (PTCH1), thereby abrogating PTCH1-mediated suppression of intracellular signaling by another transmembrane protein, the G-protein–coupled receptor smoothened (SMO). The downstream targets of SMO include the GLI family of transcription factors (Fig. 2).

Loss-of-function mutations of *PTCH1*, including the germ-line mutation found in patients with nevoid basal-cell carcinoma (or Gorlin's) syndrome, have been identified in 30 to 40 percent of sporadic cases of basal-cell carcinoma.[22,23] In the absence of PTCH1, SMO is constitutively active, resulting in continuous activation of target genes.[24] Other alterations in the HH pathway that have been implicated in the development of this disease include gain-of-function mutations in *SHH*, *SMO*, and *GLI*.[25] Transgenic human-skin models confirm that the activation of the HH pathway is an early event in tumor formation.[26] Small-molecule inhibitors of the HH signaling pathway, such as cyclopamine, hold promise as mechanism-based therapies.[27,28]

Mutations in the *p53* tumor-suppressor gene are found in approximately 50 percent of cases of sporadic basal-cell carcinoma.[29] Many of these mutations are C→T and CC→TT transitions at dipyrimidine sequences, signature mutations indicative of exposure to ultraviolet B radiation. The relationship between basal-cell carcinoma and mutations in the RAS or RAF signaling pathway is less well defined.[30] The presence of nuclear β-catenin has recently been shown to correlate with increased proliferation of tumor cells.[31] The specific roles of these genes have not yet been elucidated.

FEATURES ASSOCIATED WITH RECURRENCE AND METASTASIS

Risk factors for extensive subclinical spread include a tumor diameter greater than 2 cm, location on the central part of the face or ears, long-standing duration, incomplete excision, an aggressive histologic pattern of growth, and perineural or perivascular involvement.[32] Tumors with subclinical extension or indistinct borders are more frequently associated with residual positive margins after excision and have a higher recurrence rate than more limited or well-defined tumors.[32] Metastasis of this disease is

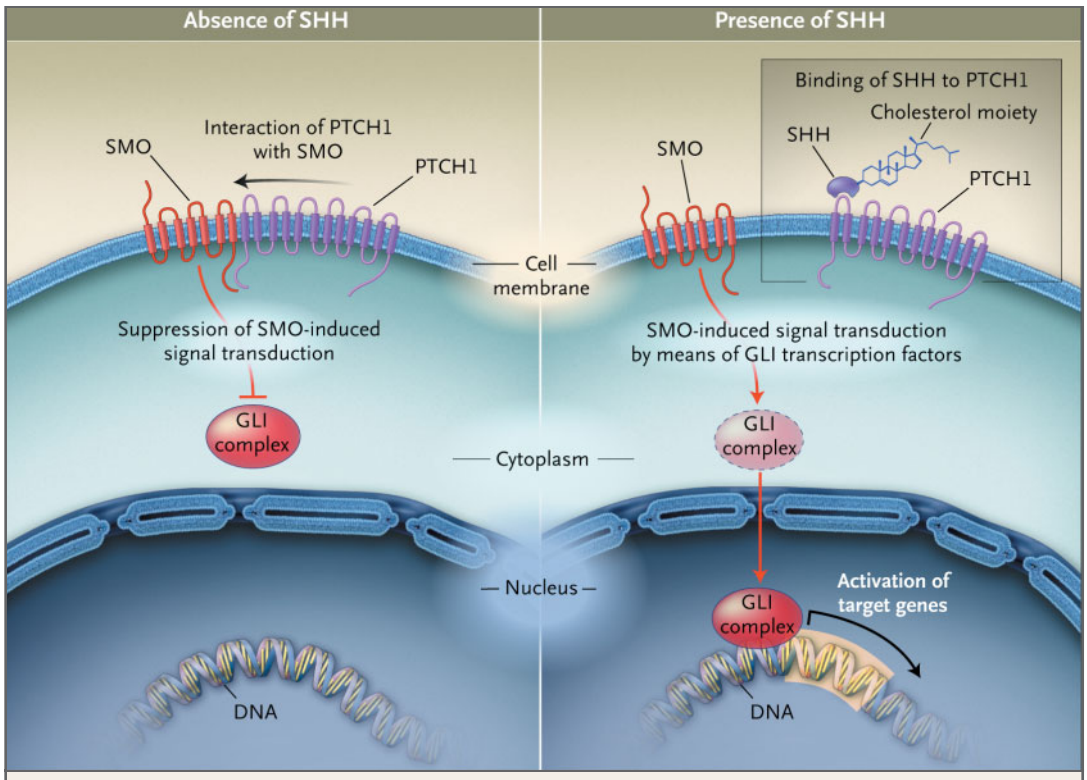

Figure 2. Molecular Pathogenesis of Basal-Cell Carcinoma.

Sonic hedgehog (SHH) interacts with a receptor complex comprising the transmembrane proteins patched homologue 1 (PTCH1) — a tumor suppressor — and smoothened protein (SMO). In the absence of SHH, PTCH1 interacts with and suppresses SMO-mediated signal transduction. Binding of SHH to PTCH1 permits SMO to transduce a signal to the nucleus by means of the GLI family of transcription factors. The lack of functional PTCH1 results in uninterrupted signal transduction by SMO and constitutive activation of target genes.

unusual, with rates ranging from 0.0028 percent to 0.55 percent. Risk factors for metastasis are similar to those for recurrence. Metastases arise most commonly from primary tumors on the face and ear, with the median interval between the appearance of the tumor and metastasis estimated to be nine years.[33] Basal-cell carcinoma most often metastasizes to the regional lymph nodes, followed by bone, lung, and liver.[32] The prognosis for metastatic disease is poor, with mean survival ranging from 8 months to 3.6 years.[32]

TREATMENT

Given its low metastatic potential, treatment of basal-cell carcinoma focuses on local control. Accurate stratification of treatments is difficult, since few randomized, prospective, comparative studies have evaluated the wide range of treatment options. Furthermore, cure rates have improved as practice standards have evolved. When one compares the cure rates for individual treatments in different studies, several factors should be evaluated: the duration of follow-up, the separation of primary from recurrent tumors, the percentage of high-risk tumors, and the method of calculating recurrences.[34,35] In an extensive review of the literature, Rowe found that the greatest risk of recurrence was within the first five years after treatment.[34] Recurrence rates of previously treated cases are higher than those of primary cases and should be reported separately.[35] A modified life-table analysis best approximates the actual recurrence rates. The primary goals of treatment are complete extirpation of the tumor with maximal preservation of function and cosmesis.

Treatment of basal-cell carcinoma can be surgical or nonsurgical. Surgical approaches include curettage and electrodesiccation, cryosurgery, surgical excision, and Mohs micrographic surgery.

Five-year cure rates of 95 percent or higher are possible with the use of either curettage and electrodesiccation or cryosurgery for low-risk lesions — that is, small, well-defined primary lesions on the neck, trunk, and arms and legs, with nonaggressive histologic features. Curettage and electrodesiccation and cryosurgery are not appropriate for recurrent or morpheaform tumors.

Surgical excision and Mohs surgery are excisional treatments that have the advantage of including histologic evaluation. Primary lesions of any size on the neck, trunk, and arms or legs have an extremely high five-year cure rate (more than 99 percent) with surgical excision.[36] Surgical excision of lesions on the head is less effective with increasing tumor size: the five-year cure rate for lesions less than 6 mm in diameter is 97 percent, as compared with a rate of 92 percent for lesions that are 6 mm or larger. Patients with incompletely excised primary lesions should undergo surgical reexcision or Mohs surgery shortly after the initial procedure to confirm the presence of clear margins; such procedures result in improved cure rates and reduce the subsequent need for more complicated resection of recurrent tumors.[37]

Mohs surgery is a technique for the removal of malignant tumors of the skin that includes rapid, in-office examination of horizontal frozen-section specimens processed to include 100 percent of the peripheral and deep surgical margins. If any part of the specimen shows infiltration of the margin by tumor, serial excisions can be limited to the affected area or areas, permitting the narrowest possible excisional margin.[38] Mohs surgery has the lowest five-year recurrence rate of any treatment: 1.0 percent for primary tumors and 5.6 percent for recurrent tumors.[34] Recurrent basal-cell carcinoma is best treated with Mohs surgery, since recurrent tumors may develop a more aggressive histologic subtype.[39] A meta-analysis by Thissen et al.[40] reviewed the treatment of primary disease from 18 large, prospective series with five-year follow-up and confirmed that the lowest recurrence rates were obtained with Mohs surgery, followed by surgical excision, cryosurgery, and curettage and electrodesiccation.

In a recent randomized trial, Smeets et al.[41] found no significant difference in recurrence rates between patients with primary facial disease treated with Mohs surgery (2 percent) and those treated with surgical excision (3 percent) and between patients with recurrent facial disease treated with Mohs surgery (0 percent) and those treated with surgical excision (3 percent). However, the interpretation of these results is potentially biased by issues concerning randomization, crossover analysis, and insufficient duration of follow-up.[42]

Nonsurgical approaches include radiotherapy, topical and injectable therapy, and photodynamic therapy. Radiotherapy is an important option for patients with tumors in difficult-to-treat locations or for those who are not surgical candidates, and it is a useful adjunct in the rare occurrence of unresectable tumors. Radiotherapy is not recommended for patients younger than 60 years of age, given its potential for carcinogenesis and inferior long-term cosmesis.[43] A randomized comparison of surgery with radiotherapy for primary facial basal-cell carcinoma favored surgery on the basis of treatment efficacy (four-year recurrence rate, 0.7 percent vs. 7.5 percent) and cosmesis (rate of "good" cosmetic results, 87 percent vs. 69 percent).[44]

The topical immune-response modifier imiquimod was approved in July 2004 for the treatment of biopsy-proven, small (less than 2.0 cm in diameter), primary, superficial lesions on the trunk, neck, or arms or legs of adults with normal immune systems. Although its precise mechanism of action is unknown, imiquimod binds to toll-like receptor 7 and has been shown to stimulate innate and adaptive immunity through the production of inflammatory cytokines.[45] Once-daily administration of imiquimod 5 days per week for 6 weeks resulted in a histologic clearance rate of 82 percent at 12 weeks.[46] An open-label study is currently assessing the five-year recurrence rate among patients with superficial basal-cell carcinoma treated with this regimen. Interim follow-up data indicate that 79 percent of patients who were clinically free of disease at 12 weeks after treatment remained free of disease at 24 months. The histologic clearance rate for small nodular tumors treated with imiquimod ranges from 42 to 76 percent.[47,48] There is a trend toward improved rates of clearance with increased frequency and duration (weeks) of application; however, the use of twice-daily dosing is often limited by the occurrence of local cutaneous reactions. Imiquimod is not indicated for morpheaform, infiltrative, nodular, or recurrent basal-cell carcinoma or for lesions on the head.

Photodynamic therapy involves the administration of a tumor-localizing photosensitizing agent and its subsequent activation with visible light to cause selective destruction of the tumor.[49] Photo-

dynamic therapy with 5-aminolevulinate is an effective treatment for superficial basal-cell carcinoma, with rates of complete response ranging from 79 to 100 percent. Photodynamic therapy using methyl 5-aminolevulinate as the photosensitizer resulted in the clearance of up to 91 percent of nodular lesions, with excellent or good cosmesis.[50] The main obstacle to expanded use of this type of therapy is the high recurrence rate. Short-term rates of recurrence range from 6 to 44 percent but appear to decrease with multiple treatments.

In summary, we recommend Mohs micrographic surgery for most high-risk lesions, particularly in locations where tissue sparing is essential and in clinical situations in which a high risk of recurrence is unacceptable. Several risk factors are defined by the National Comprehensive Cancer Network as associated with a high risk of recurrence.[51] Clinical risk factors include a tumor size greater than 2 cm; tumor location on the head and neck, particularly the central portion of the face, eyelids, nose, or ears; a tumor with poorly defined borders; a recurrent tumor; previous radiotherapy; and immunosuppression. Pathological risk factors include aggressive histologic growth patterns (morpheaform, infiltrative, and basosquamous types) and perineural invasion.

In patients who are candidates for surgery, surgical excision has high cure rates for lesions on the neck, trunk, and arms and legs, as well as selected well-circumscribed tumors on the head. Curettage and electrodesiccation and cryosurgery are cost-effective and appropriate for low-risk lesions but not for morpheaform or recurrent lesions. Radiotherapy is useful for patients with inoperable lesions or for elderly patients who are unwilling to undergo surgery. There are limited data to support the use of imiquimod beyond the indications stated by the Food and Drug Administration, which currently preclude its use in high-risk basal-cell carcinoma. Photodynamic therapy is another promising treatment associated with excellent cosmetic results but suboptimal short-term rates of recurrence. These recommendations are similar to those published in a consensus statement by the National Comprehensive Cancer Network in 2005.[51] Fluorouracil, topical tazarotene, and intralesional interferon alfa-2b are other, uncommon therapeutic options. Patients who have high-risk basal-cell carcinoma should be referred to an expert for treatment.

PREVENTION

A recent survey of 300 white and Hispanic persons from the United States demonstrated that more than half the respondents were familiar with basal-cell carcinoma.[52] Most of the respondents reported that their main source of information was the media.[52] Analysis of news coverage in the United States between 1979 and 2003 showed a relative lack of attention to skin cancer and preventive measures.[53] Media campaigns increase public awareness of the need for sun protection, but they produce only transient behavioral changes.[54] About 90 percent of the respondents identified a correlation between skin cancer and exposure to sunlight, but less than half reported applying sunscreen regularly.[52] The Australian "Slip! Slop! Slap!" and SunSmart campaigns have changed attitudes and behavior regarding sun protection and skin cancer by delivering a consistent and continuous message for more than two decades.[55] These efforts have begun to affect incidence and mortality trends. Avoidance of the sun and protection against exposure are essential preventive measures against basal-cell carcinoma.[56] Although no randomized trials have shown any effect of the use of sunscreen on the incidence of basal-cell carcinoma, randomized trials have shown a protective effect on the development of actinic keratoses[57] and squamous-cell carcinoma.[58] Finally, the American Academy of Dermatology's Melanoma/Skin Cancer Screening Program has conducted more than 1.4 million free public screenings over the past 20 years, but evidence suggests that targeted skin-cancer screening is more effective.[59]

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