Epidemiology of basal cell carcinoma *

Epidemiologia do carcinoma basocelular

Valquiria Pessoa Chinem 1  
Hélio Amante Miot 2

Abstract: Basal cell carcinoma is the most common malignant neoplasm in humans and its incidence has increased over the last decades. Its high frequency significantly burdens the health system, making the disease a public health issue. Despite the low mortality rates and the rare occurrence of metastases, the tumor may be locally invasive and relapse after treatment, causing significant morbidity. Exposure to ultraviolet radiation is the main environmental risk factor associated with its cause. However, other elements of risk are described, such as light skin phototypes, advanced age, family history of skin carcinoma, light eyes and blond hair, freckles in childhood and immunosuppression. Behavioral aspects such as occupational sun exposure, rural labor and sunburns at a young age also play a role. Between 30% and 75% of the sporadic cases are associated with patched hedgehog gene mutation, but other genetic changes are also described. The tumor is commonly found in concomitance with skin lesions related to chronic sun exposure, such as actinic keratoses, solar lentigines and facial telangiectasia. The prevention of basal cell carcinoma is based on the knowledge of risk factors, early diagnosis and treatment, as well as on the adoption of specific measures, particularly in susceptible populations. The authors present a review of the epidemiology of basal cell carcinoma.

Keywords: Injections, intradermal; Review; Skin; Therapeutics

Resumo: O carcinoma basocelular é a neoplasia maligna mais comum em humanos e sua incidência vem aumentando nas últimas décadas. Sua grande frequência gera significativo ônus ao sistema de saúde, configurando problema de saúde pública. Apesar das baixas taxas de mortalidade e de rara ocorrência de metástases, o tumor pode apresentar comportamento invasivo local e recidivas após o tratamento, provocando importante morbidade. Exposição à radiação ultravioleta representa o principal fator de risco ambiental associado a sua gênese. Entretanto, descrevem-se outros elementos de risco: fotótipos claros, idade avançada, história familiar de carcinomas de pele, olhos e cabelos claros, sardas na infância e imunossupressão, além de aspectos comportamentais, como exercício profissional exposto ao sol, atividade rural e queimaduras solares na juventude. Entre 30% e 75% dos casos esporádicos estão associados à mutação do gene patched hedgehog, mas outras alterações genéticas são ainda descritas. A neoplasia é comumente encontrada concomitantemente com lesões cutâneas relacionadas à exposição solar crônica, tais como: queratoses actínicas, lentigos solares e telangiectasias faciais. A prevenção do carcinoma basocelular se baseia no conhecimento de fatores de risco, no diagnóstico e tratamento precoces e na adoção de medidas específicas, principalmente, nas populações suscetíveis. Os autores apresentam uma revisão da epidemiologia do carcinoma basocelular.

Palavras-chave: Injeções, intradérmicas; Pele; Revisão; Terapêutica

Approved by the Editorial Board and accepted for publication on 29.04.2010.

* Work conducted at the Department of Dermatology and Radiotherapy, Faculty of Medicine of Botucatu, Sao Paulo State University (FMB-UNESP), Botucatu (SP), Brazil.
Conflict of interest: None / Conflito de interesse: Nenhum
Financial funding: None / Suporte financeiro: Nenhum

1 MSc - Dermatologist, Department of Dermatology and Radiotherapy, Faculty of Medicine of Botucatu, Sao Paulo State University (FMB-UNESP), Botucatu (SP), Brazil.
2 PhD - Assistant Professor, Department of Dermatology and Radiotherapy, Faculty of Medicine of Botucatu, Sao Paulo State University (FMB-UNESP), Botucatu (SP), Brazil.

©2011 by Anais Brasileiros de Dermatologia

INTRODUCTION

Basal cell carcinoma (BCC) is the most common malignant neoplasm in humans, especially in fair-skinned individuals. The cumulative risk of development of the disease throughout life in the German white population is over 30%. It shows a locally invasive behavior and low metastatic potential and is easily treatable by surgical excision, as long as it is diagnosed early. Due to its frequency and sanitary relevance, there is a vast literature on its epidemiology.

BCC was first described by Jacob in 1827, who called it "ulcus rodens"; its current nomenclature was proposed by Krompecher in 1903.

No precursor lesions have been described for BCC and the cells involved in its origin are still a matter of some controversy. Despite resembling the basal cell layer of the epidermis, there is evidence that these cells are derived from immature pluripotent cells of interfollicular epidermis and those present in the outer sheath of the hair follicle. This is based on experiments with activation of the hedgehog signaling pathway in different compartments of the epidermis and on the expression of cytokeratins 5, 14, 15, 17 and 19 with a follicular pattern, which has defined it as a malignant neoplasm of follicular germinative cells (trichoblasts). Furthermore, there is an association of BCC with abnormalities of the sonic hedgehog gene. This hypothesis is further strengthened by the rarity of palmoplantar and mucosal lesions, where no hair follicles are found.

Exposure to ultraviolet radiation (UV) is the main risk factor associated with the genesis of BCC, as evidenced by a higher frequency of the disease in sun-exposed areas, population frequencies related to latitude, association with photosensitive genetic disorders and by patterns of sun exposure among patients. There is also a higher incidence of BCC in African albinos than in blacks. The risk attributed to solar radiation for malignant keratinocytic neoplasms may reach 90%.

It is believed that the development of BCC occurs in a period of 10 to 50 years after sun damage. Recreational exposure to high doses of UV rays in childhood and youth is a strong element of risk, as evidenced by studies of people who immigrated to low-latitude countries. These studies showed BCC rates similar to those of natives if immigration occurred before 10 years of age. Other studies have associated melanoma and BCC with intense acute sun exposure and sunburns before the age of 20, which would triple the risk of BCC; chronic sun exposure is more important in the genesis of squamous cell carcinoma (SCC).

However, the coexistence of BCC and actinic skin lesions as well as the increased risk of occupational chronic exposure to UV rays, such as that of farmers, also suggest the involvement of chronic exposure to UV rays in the development of BCC, with evidence of the existence of a plateau of cumulative chronic exposure, above which the risk of developing cancer appears not to increase.

Probably, different patterns of sun exposure are independent risk factors for certain clinical and histological types, topographies and prognosis of these tumors, being the focus of controversy among researchers. Ethnic, cultural, and professional aspects may also interfere in the epidemiological patterns of BCC in different countries. For example, superficial BCCs are more recurrent and are associated with intermittent and intense exposure, while nodular types are more associated with chronic exposure. Pigmented BCC is more frequent in melanodermic patients.

UVB radiation generates mutagenic photoproducts in DNA, such as cyclobipyrimidine dimers, and mutations in important genes which regulate cell functions such as the p53 tumor suppressor gene. Apoptosis of keratinocytes (sunburn cells) after exposure to UV rays is evidence of its carcinogenic potential. UVB rays have an indirect effect by generating cytotoxic and mutagenic free radicals, favoring the effects of UVB rays. In addition, UV rays have an immunosuppressive action on the skin, harming the local antitumor monitoring activity of dendritic cells.

FREQUENCY

BCC is the most common skin malignancy and represents between 70% to 80% of these tumors. The proportion of occurrence in the population is four to five BCCs for each SCC, and eight to ten for each melanoma diagnosed. Registration of BCC is not compulsory in our country, and many studies combine cases of BCC and SCC in their reports.

The number of new cases of non-melanoma skin cancer estimated for Brazil in the year 2010 was approximately 115,000, representing nearly 2.2% of dermatologic visits; the estimated risk is of 56 new cases per 100,000 men and 61 new cases per 100,000 women. However, the rates vary according to region and ethnic composition of the population, reaching 85 (cases/100,000 inhabitants) in the South and only 25 in Northern Brazil. These data can be translated into an annual estimate of about 90,000 BCCs in the country.

However, it is likely that these numbers have been underestimated, since non-excisional treatment
techniques do not result in notification to anatomical pathology services, affecting the projections. This fact shows that the rate of non-melanoma skin cancer is even more important in our population than estimated by government agencies. 38

The estimated annual incidence of BCC in the United States of America (USA) in 1996 was approximately 500,000 cases, while that of SCC was between 100,000 and 150,000. Together, the incidence of BCC and SCC was 18 times greater than that of melanoma. In 2002, about 900,000 Americans were diagnosed with BCC and in 2005, 1,000,000 patients received this diagnosis, showing an increase in frequency. 38,39

In countries with a phenotypically lighter-skinned population, the numbers are even higher. In Australia, the incidence of BCC is the world’s largest, accounting for 726 cases (100,000 inhabitants/year). In Germany, the incidence is 96 cases (100,000 inhabitants/year) for men and 95 (100,000 inhabitants/year) for women. In Canada, 87 (100,000 inhabitants/year) for men and 68 (100,000 inhabitants/year) for women. In Finland, 49 (100,000 inhabitants/ year) for men and 45 (100,000 inhabitants/ year) for women. In Switzerland, 52 (100,000 inhabitants/year) for men and 38 (100,000 inhabitants/year) for women. In the Netherlands, 53 (100,000 inhabitants/year) for men and 38 (100,000 inhabitants/ year) for women). 9,32,35

The incidence and morbidity rates of BCC, SCC and melanoma have been increasing in recent decades at a rate of over 4% per year in all countries and social classes. It is estimated that approximately 50% of fair-skinned individuals over 60 years old will develop some type of skin cancer. 1,34 to 36

In England, the incidence of BCC increased from 173.5 to 265.4 per 100,000 inhabitants/year in 10 years. In the white population in the U.S., Canada and Australia the annual increase has averaged 3.7%. 8

In the U.S., it has doubled in 20 years. 38 In Brazil, the growth rate of skin cancer increased about 113% between 2001 and 2006 37. In the Clinical Hospital of UNESP, Botucatu-SP, an absolute increase of 90% in the incidence of BCC was observed in the past 11 years, representing an increase of 61% compared with the number of hospital attendances for the period (unpublished data). With an annual growth rate of 10%, BCC will soon surpass the incidence of all other malignancies combined. 40

One hypothesis for this increase may be greater awareness of the population based on prevention campaigns, as well as greater attention from general practitioners to diagnosis and referral of patients. 9,39

Other factors discussed are greater cumulative exposure to UV rays, time available for leisure (unprotected), popularity of tanned skin, ozone layer depletion (2% in the last 20 years), increased longevity and the proportion of elderly individuals in the population. 8

Men are more affected than women (1.5-2:1), which is probably for professional reasons, and males are also associated with a greater number of tumors. 41 There are, however, some studies that suggest a recent increase in the proportion of female patients, including those who are less than 40 years of age, because most women seek dermatologic care. The role of tanning beds (odds ratio = 1.5) and photoexposed leisure is described as a potential risk factor. Moreover, BCCs excised in women tend to have smaller diameters, suggesting greater health care and early medical attention. 29,30,42,45

BCC occurs more often in the elderly. More than half of the cases occur between 50 and 80 years of age and the incidence of the disease increases with age. However, the age group affected is younger than that of SCC. 7 An increasing incidence of BCC in individuals younger than 40 years has been observed, which already accounts for more than 5% of the diagnoses. BCC is rare in childhood and youth. The hypotheses for this phenomenon are not clear but appear to indicate intense recreational unprotected sun exposure, which can also be suggested by the fact that adolescents show more lesions on the trunk, of the superficial subtype, which relate more to this type of exposure. We also observed a trend toward higher incidence in more affluent classes. The habit of sunbathing is associated with a five-fold increased risk of development of BCC on the trunk. 37,44,45

Still, a higher proportion of young women have been diagnosed with BCC, which may be associated, in addition to the above factors, with natural and artificial tanning in the last decades. 30,37,46-49 The relationship between patterns of sun exposure, age of onset and histological aggressiveness of BCC is controversial among researchers; therefore, more epidemiological studies involving different population groups need to be conducted in an attempt to elucidate this matter. 38,39

The most important constitutional risk factors for the development of BCC are: light phototypes (I and II by Fitzpatrick classification), positive family history of BCC (30-60%), freckles in childhood, light skin, eyes or hair. Fair-skinned individuals are 10 to 20 times more likely to develop BCC than those with dark skin, even when they live in the same region. 4,30,52,53

Moreover, BCC is rare in blacks, Orientals and Hispanics; there are reports that its incidence is lower in patients with a history of acne and oily skin. 54,55 Blacks have a lower incidence of BCC in sun-exposed areas, but in unexposed areas the incidence is similar.
Epidemiology of basal cell carcinoma

The most relevant behavioral and exposure factors are: unprotected professional exposure to UV rays (rural activity, fishermen and builders), sports and outdoor recreation, sunburns in youth, radiotherapy treatments, phototherapy (PUVA or UVB) and arsenic exposure.

Dark hair dye colors, diets rich in fat and artificial tanning beds have been suggested in some studies as factors associated with the development of BCC, but they need to be further clarified in other studies with their own specific designs. 52,57,60

Prolonged use of photosensitizing drugs such as tetracyclines, sulfonamides, fluoroquinolones, phenothiazines, and diuretics was associated with risk of BCC in a study conducted in the USA. 67

Exposure to paraffin, coal, tar (coaltar), pitch, industrial oils, agricultural chemicals, pesticides, ionizing radiation, chronic scarring (burns, discoid lupus, vaccines), and tattoos have been sporadically reported. 4,60 to 72

Tobacco and alcohol use remains controversial; however, most authors did not find a significant association after adjustment for other risk factors. 4,10,73-78

The intake of statins or antioxidants like vitamin C, vitamin E, carotenoids and selenium was not associated with risk of BCC; however, the role of flavonoids, polyphenols, zinc and vitamin D has not been fully explained. 79-82

It was identified that elevated serum levels of vitamin D are associated with a risk of BCC, but these levels may represent only a marker of unprotected sun exposure, rather than suggest a direct oncogenic effect. 90

The consumption of high daily doses of coffee (> 6 cups) was associated with a reduction of up to 30% in the prevalence of non-melanoma skin cancer in Caucasian women. Indeed, caffeine showed a photoprotective effect and reduced UVB-induced carcinogenesis by inhibiting apoptosis in the skin of mice. The same was observed in cultured keratinocytes, in which caffeine increased the potential of apoptosis by inhibiting the ATR-Chk1 pathway. 52,84 to 86

BCC is most commonly found together with skin lesions associated with chronic sun exposure such as actinic keratoses on the face, actinic cheilitis, solar lentigines, facial telangiectasia, cutis romboidealis nuchae and Racouchot-Favre syndrome. 2,10,17,53,58

Paradoxically, solar elastosis has been described both as a risk marker and protection factor against BCC in different studies. 10,18,58

Immunocompromised patients, those with AIDS or with a history of other BCC or other malignant skin tumors are more prone to the development of BCC. Transplant patients have an incidence 5 to 16 times higher than the general population; SCC affects 40 to 250 times more this group of patients. 3,40,87

The occurrence of consecutive tumors is common, and recurrence is more common in the first year. In three years the risk of a patient with BCC to present with another injury ranges from 27% to 44%, reaching 50% in five years. With each new tumor the risk of recurrence increases progressively. Patients with more than ten BCCs have more than a 90% chance of presenting with a new lesion. Male patient, over 60 years of age, BCC located on the trunk, of the superficial type upon histological examination, and presence of multiple actinic keratoses on the skin are predictive factors for the emergence of new lesions. 1,4,27,35,88

There are geographic variations in the incidence of BCC; the incidence is higher in low latitudes, such as in some regions of Australia (1,600/100,000 inhabitants per year) due to proximity to the Equator, than in Southern U.S. (300/100,000 inhabitants / year) and northern Europe (40-80/100,000 inhabitants per year). 1,4,89

**CLINICAL FORMS**

BCCs may have varying sizes. Lesions of a few millimeters can already be identified and, as they develop reaching up to several centimeters, clinical features become more evident. Oftentimes, however, differential diagnosis with other papulonodular and solitary ulcerated skin diseases is necessary. It is commonly referred to by patients as a wound that does not heal or an acne lesion due to its typical slow and asymptomatic growth.

They are clinically divided into five types: nodular-ulcerative, pigmented, sclerodermaform or fibrosing, superficial and fibroepithelioma, although there is disagreement with regard to the classification by some authors. 9,27,30,53 The frequency of clinical forms differs among populations. An overview of the distributions in different studies is shown in Table 1.

The nodular ulcerative form is the most common, usually in isolation, affecting mainly the head and neck. It is characterized as a papule or nodule with a pearly aspect, often with typical telangiectasia seen on dermoscopy, which subsequently ulcerates and may invade underlying tissues.

The pigmented subtype is morphologically similar to the nodular ulcerative, although there are superficial and sclerodermaform variations. It should
be differentiated from melanoma and pigmented seborrheic keratosis. It is the most commonly found variant in melanoderma patients. Due to contrast with the surrounding tissue, lower rates of positive margins are referred in this group. 94,95

The sclerodermiform type has a worse prognosis, with greater chance of recurrence and infiltration. It mainly affects the face as a depressed plaque with ill-defined borders, which can rarely ulcerate. Due to the monotony of the symptoms and clinical presentation, diagnosis may be delayed, causing higher surgical morbidity.

Superficial tumors are located mainly on the trunk and shoulders and may be multiple. 23,27 They are characterized as erythematous-scaly plaques with little infiltration and of slow growth. Differential diagnosis should be done with Bowen's disease, Paget's disease, psoriasis, eczema and dermatophytosis.

Fibroepithelioma is a rare form of BCC, preferably located in the lumbosacral, pubic or genitocrural region. It begins as papules or erythematous plaques that may become pedunculated. Due to the atypical clinical manifestation and rarity of the disease, the diagnosis is often not clinically suspected, and is only revealed in histopathology.

### HISTOPATHOLOGICAL CLASSIFICATION

BCC is a malignant epithelial neoplasm of basaloid cells with large nuclei in relation to the cytoplasm and with loss of intercellular bridges, but with rare mitotic figures. The most suggestive characteristic for the diagnosis of BCC is the presence of clusters of cells peripherally arranged in palisade, usually with a gap between the stroma and tumor parenchyma.

There is diversity among the classifications of histopathological subtypes adopted by different authors. 4,27,96-99 The frequencies of histological types adapted to a reductionist classification described in different studies are shown in Table 2. 100-101

The macronodular form is the most common. It shows nodular masses of basaloid cells separated from the dermis by a typical artifact of separation. They eventually express adnexal, adenoid or cystic differentiation. Pigmented tumors follow the same structure; however, they produce melanin. Occasionally, central necrosis or cystic changes are seen within the tumor lobules. There are micronodular forms, where tumor blocks are smaller, with fewer than 15 cells in diameter, and more uniform than the macronodular type.

The superficial type is characterized by budding and irregular proliferation of basaloid cells forming peripheral palisade fixed to the bottom surface of the skin, usually atrophic. Fibroblasts surround the tumor cells and there is chronic inflammatory infiltrate in the upper dermis. They may have a multifocal aspect, with discontinuous epithelial tumor budding, intermingled with unaffected epidermis, complicating the assessment of margins in surgical specimens.

In fibroepithelioma of Pinkus, the tumor is histologically constituted by long, thin branching strands of BCC, some connected to the epidermis, anastomosing in fibrovascular stroma.

The sclerodermiform variant is composed of numerous tumor islands, usually infiltrating the reticular dermis and promoting an intense fibromatous reaction. The infiltrative variant is constituted by small and irregular basaloid cell islands invading the dermis, similar to what occurs in the sclerodermiform variant, but with smaller cell clusters.
Metatypical BCC (basosquamous) is a skin tumor that shares characteristics of BCC and SCC, with particular behavior and histological features. Although morphologically similar to BCC, basosquamous BCC is more aggressive and metastasizes more frequently (> 7.4%). Some authors have questioned the existence of this subtype as an independent entity, since it can be difficult to differentiate it from collision tumors in which other cancers, such as SCC, appear side by side with a typical BCC in the same surgical specimen.

In most cases (37-43%), there is an association of histological types in the same tumor; however, there is clear predominance of one.

The sclerodermiform, infiltrative and micronodular variants are considered to have infiltrative growth, with more aggressive clinical behavior and increased risk of recurrence. The macronodular, superficial, pigmented, and cystic variants are considered expansive, with a milder behavior. BCCs with multifocal characteristics tend to recur if the excision margin is small.

**PRIMARY LOCATION**

BCC mostly occurs on sun exposed areas of the skin. In approximately 80% of the cases it is located on the face (30% in the nasal area) and neck, although it has been described in the genital and areolar areas, groin, axillae, umbilicus, scalp, interdigital area and mucous membranes.

Involvement of the trunk occurs in 15-43% of cases. The frequencies of topographies of involvement of BCC described by case studies are shown in Table 3.

The occurrence of BCC in areas less exposed to the sun, about 20% of cases, and the rare involvement of other typically exposed areas, such as the backs of hands, indicate that other factors play a role in its genesis. Neoplasms that affect photoprotected and intertriginous areas are usually larger in diameter due to delayed diagnosis and may lead to worst prognosis, surgical morbidity and metastasis.

**GENETICS**

The development of BCC results from the interaction between various genes and environmental factors. Mutations in the PTCH gene (patched hedgehog), a tumor suppressor located in the 9q22 (PTCH1) and 1p32 (PTCH2) loci were associated with the appearance of BCC in 30% to 75% of sporadic cases and almost with all cases associated with basal cell nevus syndrome.

Patched receptor is a receptor for ligands of the hedgehog protein family (HH) and is present in the plasma membrane of cells. Binding of HH to PTCH induces the release and activation of another protein located in the membrane – smoothened - expressed by the SMO gene. Activation of smoothened activates Gli-1 factor, which induces the transcription of several oncogenes involved in the development of BCC and other malignancies. PTCH gene mutations stimulate the hedgehog pathway due to the inability of the mutated patched protein to suppress smoothened (Figure 1). Mutations in the SMO gene are present in 10-21% of sporadic BCCs and mutations in the p53 gene are present in more than 50% of cases, although the p53 gene is more related to the progression than the origin of BCC.

Animal models were developed from transgenic mice that express the smoothened protein in tissues. These animals have, in addition to multiple BCCs, numerous bone abnormalities, simulating basal cell nevus syndrome.

Extragenic DNA also plays a role in tumor
development. Microsatellites, which are short repetitive sequences of one to six nucleotides located throughout the genome, are important. The DNA of tumor cells usually shows changes in the number of repeated units in one or more microsatellites, and this is called microsatellite instability; the complete loss of a microsatellite is known as loss of heterozygosity. Changes in 12 of 18 microsatellites have been detected in BCCs; two of them are close to the TP53 and MSH2 suppressor genes. Many changes also occur near the PTCH gene. In 60% of familial and sporadic BCCs, alterations in the microsatellite D6S251 in the 6q14 region are described. All BCCs with some instability showed high histological risk (46%).

Other changes were identified in patients with BCC based on genome sequencing studies. Mutations in pigment genes, such as melanocortin 1 receptor (MC1-R), are associated with susceptibility to melanoma and BCC. Nucleotide polymorphism in the loci 9p21, 7q32 (rs157955 [T]), rs11170164 and in genes associated with DNA repair - XPD, XRCC, XRCC1 and 3 - were more prevalent in groups with BCC than controls. However, gene variants that encode proteins involved in immune response, such as CTLA4 and XRCC3, reduce the risk of BCC; expression of HLA-DR4, as well as expression of the TNF allele haplotype a2b4d5, was associated with multiple lesions.

Specifically, involvement of the trunk and development of multiple BCCs were related to genetic polymorphisms in glutathione S-transferase, NADPH
and cytochrome P-450. In addition, trisomy of chromosome 6 was linked to increased aggressiveness of BCC.

Mutations in the CDKN2A locus, which encodes the proteins p16 and p14, were also detected in sporadic BCCs; however, mutations of oncogenes (ras) were found in an even less evident proportion (0-30%), suggesting that the oncogenesis of BCC depends primarily on the failure of tumor suppression. In addition, another gene polymorphisms have been studied in families of BCCs without significant risk association. Changes in apoptosis pathways, such as increased expression of BCL2, apoptotic pathway gene, TGF-β, MAPK (mitogen-activate protein kinase), calcium channels, Wnt, catenin and cell cycles also contribute to the oncogenetics of BCC, but they are beyond the scope of this text.

UV rays can lead to a degree of immunosuppression by depletion of dendritic cells and altered expression of cytokines that result in the diversion of cellular immune response to Th2 cells, inhibiting the ability of antigen presenting cells to induce antitumor activity, which may be relevant in tumor progression.

Some cancers express the enzyme COX-2 as an antipoptotic mechanism. Inhibition of this enzyme led to a 30% reduction in the incidence of new lesions in patients with basal cell nevus syndrome. However, the use of non-steroidal anti-inflammatory drugs did not provide significant protection against the recurrence of sporadic BCCs.

Similarly to SCC, HPV viral particles were identified in 36% of BCCs, and only involvement of the superficial layers of the tumor was described; however, its pathogenetic role is not clear. Moreover, the presence of HPV serology was similar for cases with BCCs and controls.

Patterns of gene expression that lead to phenotypic diversity of clinical presentations, histopathological subtypes and biologic behavior of BCCs have not yet been elucidated. Some genetic syndromes are associated with risk of BCCs, which should be suspected when there are multiple tumors or incidence at a young age.

Basal cell nevus syndrome (Gorlin-Goltz syndrome) is autosomal dominant and results from mutations in the PTCH gene. It is clinically characterized by multiple BCCs, especially on the face, but also in less exposed areas such as trunk and axillae, milium, epidermoid cysts, hyperkeratotic, depressed and punctate lesions in the palmoplantar regions (pits), bone deformities, especially mandibular cysts, which can lead to tooth loss, spina bifida, kyphoscoliosis and deformities in the ribs, with frequent calcification of cerebral falx observed in X-ray examination. There are usually changes in body proportions, with a disproportionate head to body and elongated limbs. There may be hypertelorism, prognathism, frontal bossing, syndactyly, cataracts, and other tumors such as ameloblastomas, cerebellar medulloblastomas, cardiac fibromas and fibrosarcomas. The presence of numerous acrodiodons in children may be a marker of the syndrome.

Bazex syndrome is an X-linked (Xq24-q27) dominant disorder characterized by multiple BCCs associated with follicular atrophoderma mainly located in the back of hands and feet, elbows and face, milia, facial anhidrosis and widespread hypotrichosis.

In linear and unilateral basal cell nevus syndrome, patients present with papules and nodules linear and unilaterally distributed, characterizing BCC, permeated by comedones and striae.

In Rombo syndrome there is atrophoderma vermiculata, milia, hypotrichosis, trichoepitheliomas and peripheral vasodilation, telangiectasia, as well as risk of BCC development. Rasmussen’s syndrome and cutaneous albinism are characterized by lack of melanin in the eyes, skin and hair and are associated with increased risk of malignant neoplasms.

In xeroderma pigmentosum, there is a deficit in DNA defect repair that increases the risk of malignant skin cancer by more than 1000 times. Clinically, skin lesions usually begin early in life in sun exposed areas. There may be diffuse hyperpigmentation, lesions similar to ephelides, scaling and erythema with telangiectasia. Later, keratoses and malignant tumors such as SCC, BCC, and melanoma develop, and less frequently, sarcomas, fibromas, angiomas, histiocytomas, tumors in the tongue and gums. Patients present with photophobia, conjunctivitis, keratitis, corneal opacities and ectropion; there is higher frequency of malignant tumors in the lung, kidney, breast, uterus, gastrointestinal tract, pancreas, testicles and central nervous system. As for neurological abnormalities, patients may have mental retardation, abnormal reflexes, nerve deafness, microcephaly, ataxia, spasticity, choreoathetosis, sexual underdevelopment and dwarfism.

The prevalence of BCCs developed from sebaceous nevi ranges from 2.0% to 6.5%. When all adnexal tumors with potential origin in sebaceous nevi are considered, they occur in 30-50% of cases, typically after puberty.

Other unusual syndromes associated with increased incidence of BCC are familial cylindromatosis, familial multiple trichoepithelioma, multiple infundibulocystic BCC, basaloid follicular...
hamartoma, Brooke-Spiegler, Muir-Torre, Cowden and Banayan Riley-Ruvalcaba.\textsuperscript{145-151}

**PROGNOSIS**

The prognosis of BCC appears to have improved in recent decades in all countries, probably due to earlier diagnosis, leading to surgical interventions that result in less sequelae, greater access to health services and possible public awareness raised by educational campaigns.\textsuperscript{9,152} The average duration of lesions from the onset to diagnosis was 57.1 months for both genders.\textsuperscript{27}

Cure rates exceed 90% with surgical excision, and specific mortality by BCC is inferior to 0.1%. There are other effective therapeutic choices, but they go beyond the scope of this text.\textsuperscript{9,9}

There are cases where infiltrative behavior affects all adjacent tissues, causing significant local morbidity, disfigurement, and mutilating surgery. The risk of recurrence increases if the tumor has more than two centimeters in diameter (stage II). This shows the importance of early diagnosis.

The staging of non-melanoma skin cancer depends on the largest diameter of the lesion, the involvement of adjacent tissues and systemic dissemination. Stage I is characterized by lesions smaller than two centimeters and disease limited to skin; stage II is represented by lesions larger than two centimeters, but the disease is still confined to the skin and subcutaneous tissue; stage III occurs by the invasion of underlying tissues, such as muscle, cartilage and bone, or lymphatic spread, and stage IV occurs by disease dissemination to other distant organs such as lungs and bones.

Recurrences can occur due to tumor remnants resulting from therapy. It was demonstrated that surgical excision without microscopic control of margins had a recurrence rate ranging between 3.1 and 6.8% in five years. The latent period between surgery and onset of recurrence varies, on average, from two months to two years; however, it occurs more frequently in the first six months, but there are reports of more than five years.\textsuperscript{155-157}

Surgical excisions with positive margins recur in 15% to 67% of cases; however, they may occur after the report of histopathologically free margins (1.3 to 4.0%). This occurs more commonly in multifocal superficial and sclerodermiform tumors.\textsuperscript{155,156,158-165} These factors stress the need for the oncologic treatment of all patients. Nonetheless, the immediate systematic reevaluation of all BCCs with positive margins is not consensual.

The regions of embryonic fissures - retroauricular perinasal, periorbital, peripalpebral and scalp are considered at higher risk for recurrence.\textsuperscript{162-164}

The recurrent tumor has a worse prognosis because the relationship between the tumor and its stroma may be altered as a result of treatment primarily established, facilitating its dissemination. It may show exulcerations,\textsuperscript{156} more evident cellular dysplasia, loosening of the tumor cell cords, stromal fibrosis and reduction of peritumoral inflammatory reaction, increasing the spread of cancer cells.\textsuperscript{156}

The incidence of metastasis of BCC is rare and ranges from 0.0028% to 0.55%; less than 400 cases have been reported in the literature.\textsuperscript{4,105,106}

The dependence of the BCC on its stroma may be a factor associated with reduced metastatic dissemination. The most frequent site of involvement is the regional lymph node in 68% of cases. Hematogenous dissemination may also occur affecting the lungs and pleura, liver and bones. Some authors claim that BCC only metastasizes when it is a mixed or metatypical tumor, while others associate this complication to previous radiotherapy of the tumor or lesions that have relapsed multiple times, usually over 5-10 cm and evolution over five years.\textsuperscript{9} Recurrent and invasive BCCs are little responsive to chemotherapy and five-year survival rate is only 10%.\textsuperscript{1,165}

**FINAL CONSIDERATIONS**

The prevention of BCC is based on knowledge of risk factors, early diagnosis and adoption of preventive measures, especially in susceptible populations.

Due to evidence of involvement of UV rays on BCC development, educational measures on intense and unprotected sun exposure should be encouraged, such as information about times of lower incidence of UVB, occupational and leisure protection, prevention of sunburn, use of appropriate clothing, hats, protective films for cars and use of a broad-spectrum sunscreen.

There is controversy regarding the protective action of sunscreens alone. Some authors suggest that their use would encourage risky behavior in which the individual would expose himself more to the sun, believing to be fully protected.\textsuperscript{34,167} Failure to reduce the incidence of BCC, despite the prolonged use of sunscreens, has also been shown.\textsuperscript{1,168-170}

One possible explanation for this is that the studies were based on sunscreens with low UVA protection, use for less than ten years, effectiveness of application, frequency and reaplication of the product, thus reducing their function.\textsuperscript{167-174} However, other studies suggest that regular use of sunscreens in
the first 18 years of life may decrease the risk of these tumors by 78%. A lower risk of multiple tumors was observed in the groups who used them for prolonged periods.

Still, one can notice a tendency to protective effect based on the frequency of use of sunscreens, but these results were not statistically significant.

Frequent use of sunscreens and sun protection measures are recommended to reduce costs to the health system due to actinic dermatoses, especially actinic keratoses and SCC. In this study, with a five-year follow up, there was a 10% reduction in the incidence of BCC, although not statistically significant.

Drugs such as isotretinoin, acitretin and beta carotene did not show benefits in preventing BCC in the general population, although retinoids are indicated to treat Gorlin syndrome, with a 26% regression rate and reduction of up to 40% of new BCCs.

Another point of concern related to skin carcinogenesis is the demand for artificial tanning beds, especially by young women, who use these services three or four times more often than men. The emission spectrum of UV rays in tanning booths resembles that of the solar spectrum in terms of UVB, but it may be 10 to 15 times higher for UVA. The tanning industry makes billions of dollars annually, and there is a growing demand for the service, which requires solid evidence for prohibition or recommendation. In 1988, only 1% of adult Americans reported using artificial tanning beds, whereas in 2007 this percentage rose to 27%.

The literature presents conflicting results. A possible limitation would be confounding factors such as natural sunlight exposure, since individuals who seek artificial tanning also expose themselves to the sun for the same purpose, as well as the long latency period between exposure and onset of cancer. Some studies did not find evidence of risk of non-melanoma tumors, whereas others have associated the habit of artificial tanning with BCC (OR = 1.5) and SCC (OR = 2.5), even when adjusted for sunburns, sunbathing and sun exposure. There is also a strong association with melanoma, even though a relationship between dose and response is not quantified.

One of the supposed benefits of tanning beds would be the production of vitamin D; however, oral intake of this vitamin is more efficient and accessible to the population. Another misconception is that artificial tanning would provide protection against subsequent sun exposure, but this protection corresponds to an FPS 2 or 3, something easily achievable by use of sunscreens.

The World Health Organization warned about the dangers of artificial tanning and warned that children under 18 years old should not undergo this procedure. The education of patients regarding risk factors, attention to the diagnosis of minor lesions by self-examination, as well as participation in prevention campaigns are essential in prevention and improved prognosis.

Campaigns to prevent skin cancer have a potential impact on early diagnosis and education of the population. In 1990, more than 100,000 people were examined and about 10,000 skin cancers, detected in the US. However, due to the high cost of examining the general population, the follow-up of risk groups may be a more optimal strategy in prevention.

The Brazilian Society of Dermatology has held annually since 1999 the national skin cancer prevention campaign, screening on a single day more than 30,000 people across the country, with detection rates of up to 10%. BCC affects between 6% and 7% of those examined. There is intense dissemination of information in the media.

The high frequency of BCC and the progressive increase in its incidence make it an environmental and occupational disease, with a clear impact on the patients’ quality of life. This causes a significant burden to the health system, especially in cases of invasive behavior and relapse after treatment.

The study of the epidemiology of BCC allows the identification of behavioral and phenotypical elements for the establishment of risk groups. This leads to the development of sanitary measures for primary prevention in the population; it also improves screening campaigns, encourages the promotion of educational programs in schools and communities, optimizes actions in public and occupational health, and reduces morbidity and health system expenditures by early recognition and treatment of lesions.
REFERENCES


How to cite this article/Como citar este artigo: Miot HA, Chinem VP. Epidemiology of basal cell carcinoma. An Bras Dermatol. 2011;86(2):292-305.