Clinical review

Basal cell carcinoma

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The authors of this review aim to provide a comprehensive overview of basal cell carcinoma, concentrating in particular on incidence, risk factors, molecular genetics, clinical features, and treatment

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Basal cell carcinoma is the most common malignancy in white people.[1] Its incidence is increasing worldwide by up to 10% a year. Although mortality is low as basal cell carcinoma rarely metastasises, this malignancy causes considerable morbidity and places a huge burden on healthcare services worldwide. Furthermore, people who have this condition are at high risk of developing further basal cell carcinoma and other malignancies. This review aims to present a concise and comprehensive overview of this important condition, concentrating on recent advances in our understanding of its epidemiology, clinical features, molecular genetics, and treatment.

Summary points

- Basal cell carcinoma is the most common malignancy in white people, and its incidence is increasing worldwide
- Risk factors include skin type 1, red or blonde hair, blue or green eyes, freckling in childhood, sunburn in childhood, family history of skin cancer, immunosuppressive treatment, and ingestion of arsenic
- Development of basal cell carcinoma is likely to result from a complex interaction between genes and the environment, especially ultraviolet irradiation; the exact role of exposure to ultraviolet radiation is still to be determined
- Patients with basal cell carcinoma have an increased risk of developing further basal cell carcinoma
- They also have an increased risk of developing other skin cancers, such as malignant melanoma and squamous cell carcinoma, and possibly non-cutaneous malignancies
- Treatment of basal cell carcinoma includes different forms of surgery, radiotherapy, photodynamic therapy, topical fluorouracil, and imiquimod

Sources and selection criteria

This review is based on information obtained from a recent Medline search with basal cell carcinoma, rodent ulcer, and non-melanoma skin cancer as key words. We also used our extensive knowledge of the literature on basal cell carcinoma. We attached greater importance to more recent studies.

Incidence

The incidence of basal cell carcinoma shows marked geographical variation. The age standardised incidence of basal cell carcinoma in south Wales was estimated at 114.2 per 100 000 population in 1998.[2] The overall age and sex standardised annual incidence in Minnesota, USA, was reported at 146 per 100 000. In Australia, the incidence is much higher at 726 per 100 000.[3] These figures are likely to be underestimates, as basal cell carcinoma tends to be under-reported to the cancer registries.

In white populations in North America, the incidence has increased at more than 10% a year, leading to a lifetime risk of 30% of developing a basal cell carcinoma.[4] With an ever increasing elderly population, the disease is likely to become more of a problem in the future. Indeed, the prevalence of this cancer will probably be greater than that of all other cancers combined.

The age standardised incidence of basal cell carcinoma in white populations is generally between 18% and 40% higher in men (British and Australian data).[5] Sporadic basal cell carcinoma is rarely seen before the age of 20 years, but thereafter the age specific incidence increases. Basal cell carcinoma is extremely uncommon in dark skinned races.

Risk factors

Exposure to ultraviolet radiation is the main causative factor in the pathogenesis of basal cell carcinoma. However, the precise relation between risk of basal cell carcinoma and the amount, timing, and pattern of exposure to ultraviolet radiation remains unclear. Studies are hampered by difficulties in reliably assessing ultraviolet exposure in an often elderly study

population. However, given these concerns, many population based studies have used validated questionnaires to assess exposure. Several studies have shown an association between cumulative ultraviolet exposure and risk of basal cell carcinoma, although the magnitude of risk conferred has been small, with odds ratios in the region of 1.0 to 1.5.[6 7] Other studies have failed to find a significant association between estimated cumulative sun exposure in adulthood and the presence of basal cell carcinoma.[8]

Skin type 1 (always burns, never tans), red or blonde hair, and blue or green eyes have been shown to be risk factors for the development of basal cell carcinoma, with an estimated odds ratio of 1.6.[9] Development of basal cell carcinoma is reported to be more frequent after freckling in childhood and also after frequent or severe sunburn in childhood.[8 10] This is in contrast to history of sunburn as an adult, which does not seem to be associated with the development of basal cell carcinoma.[10] Recreational sun exposure in childhood seems to be an important risk factor; an Italian study calculated an almost fivefold increase in risk for an average summer holiday exposure of more than eight weeks throughout childhood (before the age of 20 years).[8] Outdoor occupation after the age of 20 years was not associated with an increased risk of basal cell carcinoma.[10] This suggests that childhood and adolescence may be critical periods for establishing adult risk for basal cell carcinoma and may explain why studies have failed to find a large impact of increased cumulative sun exposure in adulthood on the risk of basal cell carcinoma.[11]

A positive family history of skin cancer seems to be a predictor of development of basal cell carcinoma, with an odds ratio estimated at 2.2.[11] Other non-ultraviolet environmental exposures that have been associated with increased risk of basal cell carcinoma include ionising radiation, high dietary energy (especially fat), low intake of vitamins, and various chemicals and dust. Exposure to arsenic predisposes to multiple basal cell carcinomas.[12–14]

Patients on immunosuppressive treatment also have an increased risk of basal cell carcinoma. A study in the Netherlands showed that the incidence of basal cell carcinoma in transplant recipients was 10 times higher than in the general population.[15] Smoking does not seem to increase risk of basal cell carcinoma, and neither does fluorescent lighting.[8] Non-solar emitting lamps do not seem to pose a risk unless exposure is combined with oral psoralen as in PUVA (psoralens plus ultraviolet A) treatment for psoriasis, which modestly increases the risk of basal cell carcinoma.[16] However, a recent study looking at the use of sunbeds by young women with basal cell carcinoma has shown a non-significant ($P = 0.351$) increase in the average number of lifetime tanning bed exposures compared with the control population.[17]

Several genetic conditions are associated with the risk of developing basal cell carcinoma. These include albinism, xeroderma pigmentosa, Bazex's syndrome, and the naevoid basal cell carcinoma syndrome (Gorlin's syndrome). Gorlin's syndrome is a rare autosomal dominant condition in which patients develop multiple basal cell carcinoma, pitting of the palms and the soles of the feet, jaw cysts, spine and rib anomalies, calcification of the falx cerebri, and cataracts.

Molecular genetics

Although exposure to ultraviolet radiation is accepted as a critical causative factor in the pathogenesis of basal cell carcinoma, the magnitude of the risk associated with increased exposure seems to be insufficient to explain either why particular people get these tumours whereas others do not, or the considerable phenotypic diversity shown by patients in terms of the number and site of tumour and patterns of presentation.[18 19] Susceptibility to basal cell carcinoma seems to be determined by a complex interaction between duration and intensity of exposure to ultraviolet radiation and polymorphic genes. Two phenotypes are particularly interesting:

- Presentation with clusters of basal cell carcinoma (termed multiple presentation phenotype)[20]
- Development of tumours on the trunk.

These phenotypes seem to be associated with distinct predispositions. In particular, patients with truncal basal cell carcinoma have more basal cell carcinomas, are younger, and develop more clusters of basal cell carcinoma.[18 21] Genes associated with susceptibility (cytochrome P-450 CYP2D6, glutathione S-transferase GSTT1) as well as tumour numbers (vitamin D receptor, tumour necrosis factor) in these phenotypes have been identified.[18] In the case of multiple clustering, associations between the cytochrome P-450 CYP2D6 EM genotype and risk showed a particularly large odds ratio (15.5).

In terms of molecular events in the tumour, the development of basal cell carcinoma seems to be relatively simple. Thus whereas ultraviolet B irradiation is known to produce DNA damage at mutation hotspots in the p53 tumour suppressor gene, leading to the development of skin cancers, mapping of sporadic basal cell carcinoma reveals few chromosomal regions that

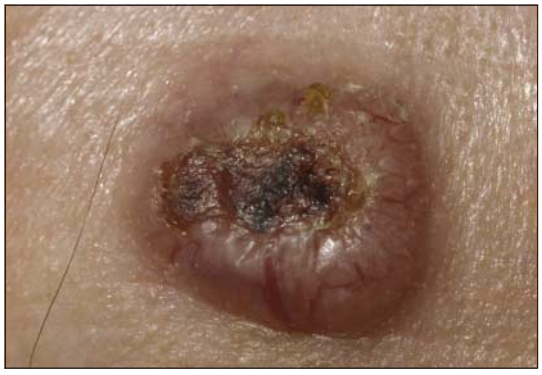

Fig 1 Nodulocystic basal cell carcinoma on the forehead

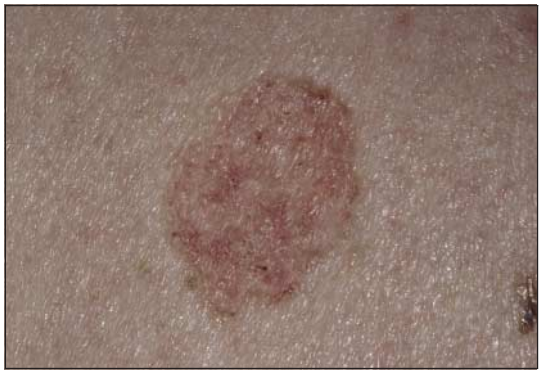

Fig 2 Superficial basal cell carcinoma on the back

display loss of heterozygosity, apart from chromosome 9q22.[22] This region harbours the PTCH tumour suppressor gene, in which germline inactivating mutations have been found in patients with basal cell naevus syndrome. Sporadic basal cell carcinomas also display frequent loss of heterozygosity at 9q22, with inactivating PTCH mutations being described.[22 23] PTCH is the human homologue of the drosophilia ptc gene, which encodes the PTC transmembrane receptor for the hedgehog (HH) morphagen. Dysregulation of the hedgehog morphagen signalling is important for the development of basal cell carcinoma. For example, overexpression of shh (human homologue of HH) in transgenic mice induces features of basal cell carcinoma.[24] The link between events in the tumour and the clinical diversity observed in patients is unknown.

Clinical features

Basal cell carcinomas exhibit several markedly different subtypes and occur at different anatomical locations. Approximately 80% occur on the head and neck, with the rest mainly on the trunk and lower limbs, particularly in women. Basal cell carcinoma on the backs of the hands is rare. The distribution of basal cell carcinoma may be changing, with a recent increase in truncal tumours described. Early basal cell carcinomas are commonly small, translucent or pearly, with raised areas through which dilated vessels may show (telangiectasia). The classic form is the rodent ulcer, which has an indurated edge and ulcerated centre. This tumour is slow growing but, if neglected, can spread deeply to cause great destruction, especially around the eye, nose, or ear. It may even extend into the periorbital tissues and bone.

The other patterns of basal cell carcinoma include nodular or cystic (fig 1), superficial (fig 2), morphoeic (fig 3), and pigmented (fig 4). Superficial basal cell carcinomas tend to occur on the trunk. They are often flat, well demarcated erythematous plaques, which can mimic psoriasis, discoid eczema, and Bowen's disease. They are particularly slow growing. Nodulocystic basal cell carcinoma presents as a solitary, shiny, red nodule with large telangiectatic vessels, often seen on the face.

The most important clinical subtype is the morphoeic basal cell carcinoma. These have a more aggressive natural history and ill defined borders, making complete excision under direct vision difficult. These types of basal cell carcinoma can be difficult to diagnose clinically and often present late. Some of these tumours can be huge and devastating to the patient, needing lengthy plastic surgical reconstructions and causing much cosmetic disfigurement. They account for approximately 5% of all basal cell carcinomas.

Typical basal cell carcinomas are indolent with slow progression. An important, and as yet unexplained, feature of basal cell carcinomas is that they can be extensively locally destructive but have a very limited potential to metastasise. The metastatic rate ranges from 0.0028% to 0.55%. Tumours that metastasise tend to be large, locally aggressive, neglected lesions that have recurred despite repeated treatment. The interval from onset to metastasis ranged in one study from seven to 34 years, with a median of nine years; the five year survival rate was 10%.[25] Differential diagnoses of basal cell carcinoma include squamous cell carcinoma, malignant melanoma (pigmented basal cell carcinoma), melanocytic naevi (pigmented), Bowen's disease (especially superficial basal cell carcinoma), psoriasis (superficial), eczema (superficial), sebaceous hyperplasia, molluscum contagiosum, and appendygeal tumours.

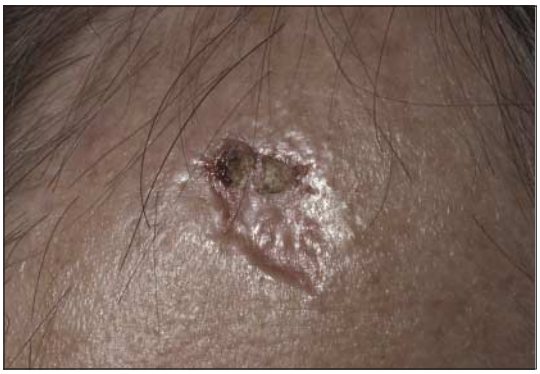

Fig 3 Morphoeic basal cell carcinoma on the forehead

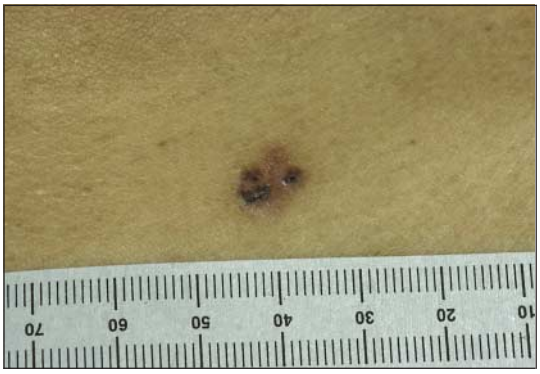

Fig 4 Pigmented basal cell carcinoma on the back

Patients with basal cell carcinoma have an increased risk of developing further basal cell carcinoma. In a recent meta-analysis, the three year cumulative risk varied between 33% and 77%.[26] This risk seems to depend on the number of lesions present. Patients presenting with truncal tumours seem to be at increased risk of developing further lesions (hazard ratio 1.58).[20]

The risk of developing a squamous cell carcinoma is increased slightly after a basal cell carcinoma, with a 6% risk at three years.[26] Patients are at increased risk of developing malignant melanomas—an American study showed a multivariate risk ratio of 2.2, a Danish study found a standardised incidence ratio of 2.64, and a Swedish study showed a sixfold increase in men developing malignant melanomas after a diagnosis of basal cell carcinoma and a fourfold increase in women.[27–29] This risk is presumably related to exposure to ultraviolet radiation.

The association of basal cell carcinoma with other malignancies remains unclear, with some studies showing no association and others suggesting a small increase in risk of cancer of the lung, thyroid, mouth, breast, and cervix and non-Hodgkin's lymphoma.[27–31] The explanation for these observations is unclear, but exposure to carcinogens such as ultraviolet radiation, cigarette smoke, and arsenic may be relevant. The evidence for an association with other cancers has recently been supported by the finding of increased cancer mortality in patients with basal cell carcinoma, with a relative risk of 1.23 (95% confidence interval 1.15 to 1.32) for men.[32] Although the actual increase in

mortality is small, the population effect could be quite considerable given the number of basal cell carcinoma patients worldwide. A better understanding of this issue is important.

Treatment

Treatment of basal cell carcinoma can be surgical or non-surgical (box). It is important to distinguish between studies on primary tumours and those on recurrent tumours, as differences in preferred modalities and cure rates exist. Surgical techniques include curettage and cautery (scraping away the tumour and stopping bleeding with cautery), cryosurgery (with liquid nitrogen), excision, and Mohs' micrographic surgery. In the best hands, five year cure rates for excision, curettage and cautery, and cryosurgery are in the order of 95% or better.[33–35] Both cryosurgery and curettage and cautery can result in wounds that take longer to heal than excision wounds. Furthermore, no tissue is available for histological examination after cryosurgery. Curettage samples do not provide adequate tissue to be able to examine tumour margins histologically. Curettage and cautery is not recommended for the management of recurrent, large, morphoeic tumours or tumours at high risk sites (central face).

The main advantage of surgical excision is that excision margins can be examined histologically to check for tumour clearance. An excision margin of 4 mm around the tumour is recommended where possible.[36] Mohs' micrographic surgery is a specialised technique that offers high cure rates for basal cell carcinoma at high risk sites (central face), morphoiec tumours, and recurrent tumours, with maximal preservation of normal tissues. Serial sections are taken and examined histologically until all margins are clear. The overall five year cure rate with Mohs' micrographic surgery has been estimated at 99% for primary tumours and up to 95% for recurrent basal cell carcinoma.[37 38]

Radiotherapy is a useful treatment that is generally used for elderly patients with extensive lesions when major surgery may not be appropriate. It is not recommended for young patients, as the late cosmetic results are inferior to those of surgery. The five year cure rate has been estimated at about 90%.[39]

Topical photodynamic treatment is effective for superficial basal cell carcinoma and gives good healing and cosmesis.[40] This technique uses δ-aminolaevulinic acid made up in a 20% emulsion and applied topically to the lesion. Tumour tissue absorbing this porphyrin metabolite becomes photosensitive with its conversion to protoporphyrin IX and subject to photodestruction when exposed to light, usually in the wavelength range 620-670 nm. The average clearance rate for superficial basal cell carcinoma from a review on photodynamic therapy was around 87%; it was lower in nodular basal cell carcinoma (53%).[41] This difference may be related to tumour thickness affecting uptake of photosensitiser and penetration of light source.

Another topical treatment for basal cell carcinoma is fluorouracil 5% cream, which is useful in the management of multiple superficial basal cell carcinoma on the trunk and limbs.[42] A newer topical immunomodulatory treatment is imiquimod 5% cream, which has been shown to achieve clearance rates ranging from around 70% to 100%, depending on frequency of application.[43] The more often the cream was applied, the higher the incidence of local side effects. Superficial tumours seem to do better than nodular ones. Long term recurrence rates have not yet been assessed, but many studies are currently being undertaken to confirm the precise role this promising treatment will have in clinical practice.

Intralesional interferon alfa is an experimental treatment. In a series of 140 patients with basal cell carcinoma treated with intralesional and perilesional interferon alfa-2b, 67% achieved cure, sustained over a mean follow up period of three years.[44]

Recurrent tumours generally have poorer cure rates with most treatment modalities compared with treatment of primary tumours. Cryosurgery or curettage and cautery is not recommended for recurrent tumours. The overall five year cure rate for recurrent basal cell carcinoma treated by curettage and cautery is estimated at 60%.[38] In general, recurrent tumours, especially morphoeic tumours or recurrences at high risk sites, are best treated by Mohs' micrographic surgery where this is available.

Treatment options for basal cell carcinoma

- Surgical:
  Curettage and cautery
  Excison with primary closure, flaps, grafts, and secondary intention healing
  Mohs' micrographic surgery
- Radiotherapy
- Cryotherapy
- Photodynamic therapy
- Topical fluorouracil
- Topical imiquimod

Additional educational resources

Professional

British Association of Dermatologists (www.bad.org.uk)—useful site for doctors; provides guidelines for the management of basal cell carcinoma

emedicine (www.emedicine.com/derm/topic47.htm)—very comprehensive article on basal cell carcinoma by an American dermatologist

Patients

Skin Cancer Foundation (www.skincancer.org)—useful site providing information about skin cancers, including basal cell carcinoma, and advice on sun protection; also very good pictures of basal cell carcinoma

American Academy of Dermatology (www.aad.org/pamphlets/bcc.html)—provides a patient information leaflet on basal cell carcinoma

Follow up and prevention

Oral retinoid treatment may prevent or delay the development of new basal cell carcinomas. This has mainly been used in patients with Gorlin's syndrome,[45] in renal transplant patients who are at high risk of non-melanoma skin cancer, and in severely actinically damaged patients. β carotene does not seem to reduce the occurrence of new skin cancers.[46]

Long term hospital based follow up of all patients after treatment of basal cell carcinoma is not practica-

ble given the current state of dermatological service provision. Indeed, some authors have not deemed it necessary in most patients.[36] However, given that patients are at risk of developing further basal cell carcinoma and other cutaneous and non-cutaneous malignancies, it may be prudent to follow up high risk patients with multiple or truncal lesions. Education on sun avoidance and tumour detection may help to prevent further malignancies and facilitate diagnosis of smaller basal cell carcinomas, which, in general, are easier to treat and have less morbidity.

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Interactive case report

A 2 year old child with rash and fever

This child's case was described on 20 September and 27 September (*BMJ* 2003;327:668, 720). Debate on her management continues on bmj.com (bmj.com/cgi/eletters/327/7416/668). On 18 October we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from a general practitioner, a paediatric cardiologist, a specialist in paediatric infectious disease, and the patient's mother.