Classic diseases revisited

Basal cell carcinoma

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Incidence and mortality

Basal cell carcinoma is the commonest skin cancer and is the most common malignancy in Caucasians. Squamous cell carcinoma (often grouped with basal cell carcinoma under the title non-melanoma skin cancer) and malignant melanoma are the two other main forms of skin cancer. Basal cell carcinoma is composed of cells similar to those found in the basal areas of the epidermis and appendages, hence its name. It is rare in black-skinned individuals. Incidence rates of 300 per 100 000 people in 1977 in the USA have been described, with rates up to 1000 per 100 000 seen near the equator in Australia.1 The lifetime risk of a basal cell carcinoma for a child born in 1994 in the USA is 28–33%. Non-melanoma skin cancer will affect approximately a million people in the USA in 1994, leading to predictions that incidence will become similar in magnitude to the total incidence of all malignancies,2 thus placing a significant burden on health service provision.

Incidence rates are highest in Australia and are increasing in many countries. Depletion of stratospheric ozone leading to increased ultraviolet (UV) radiation is predicted to further increase rates.3 There is evidence from four sources, with different ascertainment methods, of a striking increase in incidence of non-melanoma skin cancer in North America during the past two decades.4 Population-based estimates of non-melanoma skin cancer in 1977–78 revealed rates higher for men.4 When compared with a previous study by the same group in 1971–72 an increase of 15–20% had occurred. In Australia, the incidence of basal cell carcinoma increased by 11% between 1985 and 1990.5 Similar increases have been shown in Tasmania,6 UK,7 Sweden,8 and The Netherlands.9

Mortality data is more accurate in most countries.3 Recent estimates suggest a rate of 0.5 per 100 000 whites/year in 1987–88 (0.67 for men and 0.30 for women). These rates have been dropping with a 20–30% decrease from 1969 through to 1988. Although mortality is lower than malignant melanoma, morbidity and cosmetic deformity are important for basal cell carcinoma, although there is no good quantitative assessment of the degree of disability or handicap.

Clinical features

Early basal cell carcinomas are translucent or pearly, with raised, rounded areas covered by thin epidermis through which dilated vessels may show. Occasionally pigment can be seen. As they advance they can have a wide variety of patterns (box 1, figures 1–4), which may make classification difficult. Telangiectasia are characteristically seen, especially in the morphoeform variety. The majority of tumours (80%) occur on the head and neck, particularly the upper central part of the face. The superficial type, however, is found mainly on the trunk.10 Importantly, multiple tumours often occur. The role of a family

Types of basal cell carcinoma

- nodulo-ulcerative (rodent ulcer)
- pigmented (more common in dark skinned people)
- morphoeform (ulceration rare)
- superficial (found mainly on the trunk)
- premalignant fibroepitheliomas (flesh coloured, sessile lesions)

Box 1

Figure 1 Rodent ulcer
Basal cell carcinoma: differential diagnosis

- other cutaneous malignancies: Bowen's disease, squamous cell carcinoma, malignant melanoma
- eczema
- psoriasis
- naevi
- seborrheic and viral warts
- sebaceous hyperplasia
- solar keratosis
- molluscum contagiosum
- granulomatous reactions, eg, sarcoid

Box 2

Basal cell carcinoma: risk factors

- increasing age
- red/blonde hair
- blue/green eyes
- male gender
- skin type 1
- freckling
- actinic keratoses
- UV exposure
- outdoor occupation
- low socio-economic status (giant lesions)

Box 3

history in non-melanoma skin cancer is unclear, with some supportive data\(^{11}\) and other suggestions that inheritance of complexion may explain familial clustering.\(^{12}\) Typical basal cell carcinomas are indolent with a slow progression, although spontaneous fluctuations in size can occur. Diagnosis is based on histological examination of biopsy specimens but many tumours have a characteristic clinical appearance. Differential diagnoses are shown in box 2.

**Predisposing factors**

Patients with albinism and xeroderma pigmentosum are at increased risk. In the naevoid basal cell carcinoma syndrome (Gorlin's syndrome), multiple basal cell carcinomas at an early age (<30 years) are found, together with other manifestations including: milia; punctate hyperkeratosis and circular pits on the hands and feet; dental cysts; spina bifida, bifid ribs; hypertelorism; syndactyly and cataracts. This is inherited in an autosomal dominant fashion with a linked locus on chromosome 9q.\(^{13}\) Although UV radiation is considered to be the major factor predisposing to basal cell carcinoma, exogenous chemicals have also been associated. Arsenic toxicity predisposes to the development of multiple basal cell carcinoma, particularly the superficial type on the trunk, illustrating that exogenous factors can be important, possibly via interactions with UV radiation.\(^{14}\)

**Risk factors and associations with other malignancies (see box 3)**

The study of risk factors enables identification of at-risk individuals in the hope of preventing or modifying the natural history of the condition. This is of great importance in basal cell carcinoma as smaller tumours are more easily dealt with. In the UK there have been relatively few case-control studies on risk factors in basal cell carcinoma.\(^{15}\) It was shown that actinic keratoses, freckling and the number of hours spent outdoors after the age of 60 years were important. Other recognised risk factors include increasing age, red/blonde hair, blue/green eyes and fair skin.\(^{16}\) Outdoor occupation and family history may also be important.\(^{17}\) Smoking, although a risk factor for cutaneous squamous cell carcinoma, has not been consistently associated with basal cell carcinoma.\(^{18}\) The paucity of data on risk factors in the UK indicates that further large studies are needed in the British population.

Low socio-economic status and infrequent physician visits have been shown to be associated with very large basal cell carcinomas. Such patients are less concerned about their general health and pose a significant management problem. Patients with basal cell carcinoma are at high risk of suffering further primary lesions.\(^{19}\) Importantly, this risk depends on the number of lesions present. Thus, in subjects with one lesion the five-year risk is 27%, while in those with 10 or more tumours the risk is 90%, suggesting accrual of lesions is not just dependent on time but that some subjects have an increased susceptibility. Male gender, age over 60 years, burning easily and sun-damaged skin were also associated with an increased risk of subsequent new tumours.

It is interesting to note whether patients with basal cell carcinoma are at increased risk of other skin cancers or internal malignancies. Such observations will have implications for follow-up and give insights into the pathogenesis of this tumour. Several studies show that patients with basal cell carcinoma are at an increased risk of both squamous cell carcinoma\(^{18}\) and malignant melanoma. One study found a relative risk of 17 for the development of malignant melanoma in patients with a prior basal cell carcinoma.\(^{20}\) Other studies have found relative risks between 2.8 to 6.6.\(^{21,22}\) Differences between these rates may
be explained by recruitment bias, histological classification and increasing incidence. The link between these associations is considered to be UV radiation, as in both diseases UV is considered to be a major aetiological factor. Thus, patients with basal cell carcinoma are at high risk for the development of malignant melanoma and could potentially benefit from surveillance, especially as early melanomas in the horizontal growth phase have a much better prognosis than later lesions in a vertical growth phase. Regular total cutaneous examinations have been advocated as a useful, noninvasive, quick surveillance technique to detect new tumours in at-risk individuals. However, a physician skilled in the detection of skin cancers is needed to give the best results and such people are in relatively short supply in the UK.

The association with internal malignancy remains unclear, with some studies suggesting no association and another study suggesting that men with basal cell carcinoma have an increased risk of cancer of the lung and thyroid gland and women an increased risk of cancer of the uterine cervix. The explanation for these observations is not clear but exposure to carcinogens such as arsenic were suggested. Renal transplant recipients are at increased risk of both skin cancer, particularly squamous cell carcinoma, and lymphomas, illustrating the role of the immune system in cancer prevention.

### Treatment, recurrence and metastasis

Basal cell carcinomas can grow very large, become locally invasive, and can metastasise. Therefore treatment is almost always indicated. The principles of management include identifying high-risk patients for prevention and early detection, complete removal of the lesion, careful follow-up to detect local recurrence and new tumours. Available treatment modalities include curettage, primary resection with closure of defect (including flaps and grafts), Mohs' micrographic surgery (see below), radiotherapy, cryotherapy, and laser excision. Some preliminary evidence suggests that vitamin supplementation may reduce the risk of basal cell carcinoma and that interferon reduces recurrence. Further studies are required to confirm these observations. The choice of treatment depends on the size and site of tumour, age of patient, efficacy of treatment modality, cosmetic considerations, and the preferences of patient and physician. In general, the smaller the tumour the easier it is to treat, with minimal morbidity and a favourable outcome. There have been no large randomised prospective studies comparing one treatment modality with another. An ideal treatment would be one with a high cure and low recurrence rate; quick, cheap and easy to perform and with good cosmetic results.

Surgical resection is the commonest form of treatment used in the UK. Removal can be performed easily, usually in an out-patient setting; 80% of lesions can be removed with primary closure but larger, more complex lesions require grafts or rotational skin flaps to close the defect and may need general anaesthesia. The simplest surgical procedure is curettage. It is quick, sutures are not required (haemostasis is achieved via electrodesiccation) and cosmetic results can sometimes be better than resection. However, recurrence rates can be higher than resection especially with inexperienced individuals. Many physicians prefer to use this technique although it seems most suitable in small lesions (<6 mm) at any site, any lesions on the neck, trunk and limbs and in elderly patients. Cure rates of 90–95% can be achieved with selection of patients who fit into the above categories. Primary surgical excision is associated with a 90–95% cure rate in most studies. Ideally the margin of resection should be at least 5 mm because as closer margins are obtained, local recurrences are increased. Bigger tumours often need more sophisticated techniques to achieve complete excision. In 1939, Frederick E Mohs developed a technique to fix skin cancer in situ and a method of systematically excising and pathologically mapping the excised tumour to obtain margins of normal skin. Since 1970, the technique has evolved so that chemical fixation is no longer needed. The technique is, however, slow and tedious, but cure rates of 97% can be achieved, even in large tumours. This method is particularly useful for morpheic basal cell carcinoma where the margins of the lesion are unclear to the naked eye. Grafts or flaps may be needed after Mohs' resection to reconstruct the defect. Mohs' surgery is a highly specialised technique and there are few trained individuals in the UK.

Radiotherapy is a useful and effective treatment modality. Better cosmetic results are achieved by fractionation of dose (10–16 fractions for small tumours (<5 cm) and in 15–30 divided doses for larger tumours). Therefore multiple sessions over a period of weeks are required. However, because of time constraints, often one to three fractions are used. The main advantages and disadvantages of radiotherapy are given in box 4. Radiotherapy is contra-

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**Advantages and disadvantages of radiotherapy**

**Advantages**
- No anaesthesia or surgery needed
- 95% effective
- Effective in troublesome areas (nose, eyes, ears)
- Margins not critical
- Useful in elderly patients

**Disadvantages**
- Time consuming for patient and radiotherapist
- Expensive
- No histological specimen
- Radiation necrosis to skin
- ? Carcinogenesis

Box 4
indicated in those with Gorlin's syndrome as recurrence is high. Patients in whom radiotherapy is particularly useful are the elderly and those with lesions in difficult anatomical sites, such as eyes and ears. However, after radiotherapy, subsequent surgery can be more difficult.

Clinical trials are currently underway to assess the effect of photodynamic therapy in basal cell carcinoma. This makes use of the tumour cell's ability to take up a haematoporphyrin derivative in higher concentrations than the surrounding tissue. This makes the cells photosensitive to light of wavelengths 514.5, 488 and 625–30 nm. The tumour is then exposed to laser light which destroys selectively the tumour cells. Intralosomal interferon-alfa-2b, 1.5 million units three times a week for three weeks gave a cure rate of 85% with excellent cosmetic results. However, large or recurrent lesions were not treated. Further work is needed to establish the role of this therapy in clinical practice. Oral retinoids can produce regression but not cure. They have a role in prevention of lesions in patients with xeroderma pigmentosum or Gorlin's syndrome.

Depending on site, size of tumour and treatment modality, up to 10% of tumours recur, making the treatment of recurrent lesions a common problem. Surgical resection of recurrent tumours gives a cure rate of 65% whereas Mohs' procedure gives 94% cure rates. Factors influencing recurrence are listed in box 5. Treatment of choice for recurrent basal cell carcinoma is therefore Mohs' surgery but access to this facility is extremely limited in the UK and recurrences are usually re-excised via non-Mohs' techniques. Radiotherapy has also been shown to be effective.

Metastatic basal cell carcinoma (box 6) is rare. The reported rate of incidence ranges from 0.0028% to 0.55%. The typical metastatic tumour begins as a neglected, large, ulcerated, locally invasive neoplasm that recurs despite repeated treatment. Tumours greater than 3 cm have a higher incidence of metastasis. The average age of onset is 48 years which is lower than non-metastatic tumours. The interval from onset to metastasis ranges from one to 45 years with a median of nine years. Anatomical location of tumour is no different between metastatic and non-metastatic lesions. Morpheaform and adenocystic types are more aggressive than other variants. Survival after metastasis ranges from one to 192 months with 10% surviving five years. Why basal cell carcinoma metastasises so rarely is not clear. However, its dependence on its surrounding tissue (or stroma) is important. This concept is supported by failed attempts to transplant human basal cell carcinoma without surrounding tissue into other animals or humans.

### The role of UV radiation exposure

UV radiation is considered the major aetiological agent in the pathogenesis of basal cell carcinoma. UV causes mutagenesis in mammalian cells, induces pyrimidine dimers in human skin and is photocarcinogenic in mice. UV has also been shown to invoke a degree of immunosuppression in both animals and humans. Thus, both UV-induced DNA alterations as well as immune modulation are important in cutaneous carcinogenesis. Risk has traditionally been thought to be related solely to cumulative dose received, with a monotonic relationship between cumulative dose and basal cell carcinoma risk. One of the main problems in this area is that information relies on the accurate memory of an often elderly patient to recall exposures from many years previously. The evidence for the relationship between UV and skin cancer has arisen from animal experiments and observations that incidence can be related to occupational sun exposure. However, more recent research has cast doubts on this monotonic relationship between dose and risk. Two studies have found little evidence of increasing risk of basal cell carcinoma with increasing UV exposure and postulated a plateau in risk at higher doses. There is also evidence of higher rates of basal cell carcinoma in North America and Europe than more southerly regions of these continents. The anatomical location of basal cell carcinoma is now seen to increasingly favour sites, mainly trunk, that are not regarded as continuously exposed to the sun when outdoors. Thus, it seems that cumulative dose does not entirely explain basal cell carcinoma risk. Further research is needed to confirm this plateau effect: its implications are that substantial reductions in exposure may be necessary if heavily exposed populations are to reduce their risk of basal cell carcinoma.

The effect of intermittent exposure is still unclear but it was found that a significant increase in risk occurred with increased exposure at the weekend, especially in late teenage years, suggesting infrequent, probably intense increments will increase risk of basal cell carcinoma more than a similar dose delivered continuously. Another study found an increased risk with recreational

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**Factors affecting recurrence**

- tumour size
- location (tumours on eyes, nose and ears more likely to recur)
- deep or marginal invasion on histology
- resection margin < 5 mm
- growth pattern (morpheaform more likely to recur)
- initial treatment modality

**Features of metastatic basal cell carcinoma**

- large size (>3cm)
- long time to first presentation with primary tumour
- locally ulcerative
- recurrent
- younger age of onset
- morpheaform/adenocystic types more common
- median time to metastasis nine years
- 10% five-year survival
sunlight exposure from the ages of 0 to 19 years and no association with mean annual cumulative exposure. These results suggest that childhood may be a critical period for establishing adult risk. Freckling, light skin colour and severe sunburn in childhood were also associated with an increased risk. Therefore, freckling may be a marker for UV damage to the skin. It was suggested that, by extension of these results, sun-avoidance behaviour in adulthood may not markedly reduce risk for this tumour. The usefulness of sunscreens with high protection factors has caused much debate. It seems that sunscreens are associated with a decreased risk of solar keratoses and current trials are assessing the effects on skin cancer incidence.

**Prevention**

As UV is considered the major aetiological agent, prevention focuses on reducing exposure to this, both in childhood and in later life. Much effort has addressed these issues in public health campaigns. Sunscreens have been advocated but there is no hard evidence that they prevent basal cell carcinoma. They do suppress actinic keratoses, a possible precursor to squamous cell carcinoma. Trials are currently underway to assess the effect of sunscreens in basal cell carcinoma prevention.

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