Ministry of Defence

Synopses of Causation

Non-Melanoma Skin Cancer

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Skin cancers encompass a very wide array of malignant conditions of both primary and secondary origin. Because they are so numerous, diverse, and in many cases uncommon, the focus in this Synopsis is confined to those with a high prevalence or relevance in the military context.[1]

Common skin cancers

1.2. The commoner cancers of the skin are simply classified according to the type of cell involved in the malignant process, namely:

1.2.1. **Non-melanoma skin cancers** (NMSC), a term which by convention refers inclusively to **basal cell carcinoma** (BCC) and **squamous cell carcinoma** (SCC)

1.2.2. **Melanoma**

The conditions in 1.2.1 are the main focus of this Synopsis. An overview of these conditions is provided in the Synopsis *Ultraviolet Radiation and the Skin* and melanoma is further addressed in the Synopsis *Melanoma*.

Rare skin cancers

1.3. In addition, a considerable variety of uncommon skin cancers are recognised.[2,3] These are not considered in detail in this Synopsis. They include:

1.3.1. **Mammary Paget's disease** (MPD), an adenocarcinoma which is confined to the epidermis of the nipple. It is often associated with a carcinoma of the lactiferous ducts of the underlying breast. The disease may occur in either sex. **Extra-mammary Paget's disease** shares several features with MPD but usually occurs in the vulval, perineal or peri-anal region.[4] In a proportion of cases it is indicative of an underlying visceral cancer. As it is often associated with adenocarcinoma of the apocrine gland it is sometimes classified as an adnexal tumour (see below).

1.3.2. **Adnexal tumours** This group of conditions encompasses tumours which affect the sebaceous, apocrine, and eccrine glands of the skin. Some are malignant, such as carcinoma of the sebaceous gland (which is important as a marker of the Muir-Torre syndrome which causes non-polyposis colon cancer and gynaecological malignancies), eccrine porocarcinoma, clear cell carcinoma, and mucinous carcinoma.

1.3.3. **Merkel-cell carcinoma** (MCC) is a form of skin cancer of neuroendocrine origin which is thought to arise from the Merkel cell or skin-pressure receptor. This rare and aggressive tumour occurs most commonly in elderly individuals and has the propensity to invade locally and metastasise to distant sites. Merkel-cell carcinoma has recently been linked to a previously unknown polyomavirus and it is expected that further research will clarify this association.[5,6,7]

1.3.4. **Cutaneous sarcomas** This group of conditions are more accurately referred to as

atypical fibroxanthomas, which are rare cutaneous neoplasms typically found on the sun-exposed areas of the head or neck of the elderly.

Cutaneous metastatic disease

1.4. Metastatic spread of malignant tumours to the skin is not uncommon and such lesions may be the first sign of the process, particularly in patients with melanoma, breast cancer, or cancers of the head and neck.[8]

2. Clinical features

2.1. **Non-melanoma skin cancers** are the most common human cancers (about 15% of registered malignancies in the UK) but they account for only 0.3% of all cancer deaths. They occur mainly on exposed areas of skin (face, hands, scalp) and the incidence increases with age. They are distributed throughout the world but mainly affect light-skinned individuals.

2.1.1. **Basal cell carcinoma** (BCC) (*syn* basal cell epithelioma, rodent ulcer, basalioma, Jacob's ulcer) arises from cells in the basal layer of the epidermis or follicular structures. It accounts for approximately 75% of all skin cancers and is the commonest of all cancers among Caucasians. The annual incidence in the UK is around 90 per 100,000 population.[9] It is much higher in Australia, at 726 per 100,000.[10] Although the mortality rate is low, about 5% of BCCs grow aggressively and cause considerable tissue destruction. They rarely metastasise. BCCs are usually grouped according to their histological structure, and the major types are classified as nodular, micronodular, superficial and morpheaform BCC. Mixed types do occur, with the nodular-micronodular combination being the most common. Nodular and superficial varieties are often considered as non-aggressive types, whereas morpheaform and micronodular BCC is often more aggressive and associated with a higher risk of local recurrence.[11]

2.1.2. Approximately 80% of BCCs occur on the head and neck, and most of the remainder on the trunk and lower limbs. In individuals who develop a BCC on the trunk there is an increased risk of developing multiple BCCs, and these lesions develop at a faster rate than BCC located elsewhere on the body. Patients with BCC are at increased risk of developing squamous cell carcinoma and melanoma.

2.1.3. Treatment strategies[12] include:

- Surgery
    - Curettage and cautery
    - Excision
    - Moh's micrographic surgery
- Radiotherapy (contraindicated in genetic forms of BCC)
- Cryotherapy
- Photodynamic therapy
- Topical treatment (fluorouracil, imiquimod)

2.1.4. **Squamous cell carcinoma** (SCC) of the skin is the second most common type

of NMSC. Unlike BCC, cutaneous SCC is associated with a significant risk of metastasis. SCC of the skin can arise *de novo* or from a precursor lesion such as actinic keratosis. The condition includes many subtypes with widely varying clinical behaviours, ranging from indolent, slow-growing lesions to aggressive tumours with significant metastatic potential. SCC arises in the epidermis from the malignant transformation and proliferation of keratinocytes. Invasive SCC initially appears as skin patches, plaques, and nodules that enlarge and develop central areas of inflammation, induration, and necrosis. SCC metastasises by direct, lymphatic, and haematogenous spread. Metastasis is most likely in a cutaneous SCC that grows rapidly to larger than 2 cm, invades deeply to 6 mm, has been previously treated, or is located at high-risk areas such as the nose, ear, or lip. Other factors influencing the degree of malignancy include the level of differentiation, histological evidence of perineural involvement and the immunological status of the patient. SCC first metastasises to regional lymph nodes in the majority of cases.

2.1.5. Treatment strategies[13] include:

- **Surgery**
    - Excision
    - Moh's micrographic surgery
- **Radiotherapy** As a primary form of treatment, radiotherapy is usually reserved for patients who are unable to undergo surgical excision but it may be used as an adjuvant to surgery
- Adjuvant topical treatment (fluouracil, imiquimod)
- Metastatic disease is managed by local tumour removal, along with radiation therapy and/or chemotherapy

2.1.6. **SCC precursor lesions**:

- **Actinic keratoses** These common lesions are considered by some to be a form of SCC *in situ* but the rate of progression to invasive SCC is so low (~0.1% per annum) that they are better regarded as a marker of solar damage increasing the likelihood of SCC elsewhere. Their significance is chiefly cosmetic
- **Arsenical keratoses** These are rare, discrete, warty lesions that appear 20 or more years after chronic arsenic ingestion. Lesions most commonly occur on the palms and soles
- **Bowen's disease** This condition presents as a slightly elevated, slowly growing, red, scaling patch, found most often on the scalp and ears of men and on the lower limbs of women. The rate of malignant transformation is low (~3% per annum). It shares the same risk factors as SCC
- **Keratoacanthoma** is a relatively common rapidly-growing lesion which

many consider as being closely allied to SCC. Some regard it as a precursor lesion but since it may in rare cases progress to invasive or metastatic carcinoma, aggressive surgical treatment is often advocated

- **Radiation-induced keratoses** These lesions are associated with therapeutic ionising radiation, frequently used in the middle of last century to treat a variety of dermatological conditions

- **Porokeratoses** This group of conditions are caused by a disorder of keratinisation, and some forms are thought to be premalignant. They are characterised by atrophic patches surrounded by a ridge-like border. One variety, disseminated superficial actinic porokeratosis, is often associated with the diffuse solar cutaneous damage present in some patients with NMSC

3. Aetiology

3.1. **Ultraviolet radiation (UVR)** is thought to be of primary importance in the pathogenesis of skin cancers. Its role in this respect is threefold. Firstly it produces DNA damage in epidermal cells; secondly it causes mutations in the p53 gene, and thirdly it has been observed to cause immunosuppression. The role of UVR is considered in more detail in the Synopsis *Ultraviolet Radiation and the Skin*.

3.2. **Quantifying exposure to UVR** The association between UVR exposure and NMSC is undisputed. However the exact relationship between the amount, timing and pattern of exposure to UVR and the subsequent development of NMSC is not yet fully understood.[14] In addition, the respective relationships between UVR exposure and BCC and SCC are qualitatively and quantitatively different.

3.2.1. **BCC and UVR** Since a significant number of BCCs arise on non-sun-exposed areas of the body it is very likely that other, as yet unidentified factors – probably genetic – play a role in the development of the disease. Research appears to indicate an elevated risk of BCC in individuals exposed to recreational UVR under the age of 20 years,[10,15] but outdoor occupation after this age does not appear to be associated with an increased risk of BCC.[16] An increasing incidence of BCC with overall greater childhood exposure and recreational vacation exposure has also been observed,[17] and two studies demonstrated an increased risk of BCC in individuals who had been exposed to UVR in a beach environment before the age of 20.[18,19]

3.2.2. **SCC and UVR** In contrast, it appears that the risk of SCC is more probably related to total lifetime exposure or to chronic (occupational) exposure to UVR rather than to exposure in childhood or early adulthood.[20] One study found a correlation with chronic sunlight exposure in the 10 years before diagnosis.[5,21] A population-based study on over 11,000 patients demonstrated the close correlation between chronic cumulative sun exposure and SCC.[22]

3.3. **Skin pigmentation** A pigment-related variation in susceptibility exists, with darker skinned individuals being at less risk of developing skin cancer for a given amount of exposure than those with lighter skin. NMSC occurs about 70 times more frequently in individuals with lightly pigmented skin than in those with deeply pigmented skin. These so-called skin phototypes are described in Appendix A. Subjects with red hair and those who always burn and never tan on UVR exposure are particularly vulnerable, especially those of Celtic descent. Similarly, individuals with oculocutaneous albinism are at increased risk of NMSC.

3.4. **Geographical factors** Other associations include a higher incidence with decreasing latitude and with increasing altitude. The incidence of both types of NMSC is greater in certain parts of the world, being highest in northern Australia. This may be allied to the increase of UVR exposure with decreasing latitude, but may also be linked to behavioural factors such as an outdoor lifestyle and open air activities.

Other risk factors

3.5. **BCC** Other risk factors for BCC include male sex and older age.[11] There is also a strong

relationship to a family history of skin cancer of all varieties.

3.6. **Genetic factors** There is no doubt that fair skin genes are significant in NMSC,[23] and this has been demonstrated by recent genetic genome association studies. However recent research has demonstrated that common variants on 1p36 and 1q42 are also associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits.[24]

3.7. **Gorlin syndrome** (nevoid basal cell carcinoma syndrome) is an autosomal dominant disorder characterised by multiple BCCs and other dermatological and skeletal abnormalities.

3.8. **SCC** Exposure to chemical carcinogens such as arsenic and polycyclic aromatic hydrocarbons confers an increased risk of SCC, as does radiation dermatitis (an uncommon disorder related to the therapeutic use of ionising radiation in the 1940s and 1950s for such conditions as acne, tinea, and haemangiomas). There is also an association with certain chronic inflammatory disorders, such as dystrophic epidermolysis bullosa and necrobiosis lipoidica, and with diseases such as leukaemia and lymphoma. Owing to the long-term necessity for immunosuppressant therapy, organ transplant recipients are at greater risk for developing SCC, and to a lesser extent, BCC. The reasons for this difference between the two types of NMSC are unknown.

3.9. Other risk factors common to both types of NMSC include:

- **Heat-burned or scarred skin** (Marjolin's ulcer)

- **Chronic skin inflammation and ulceration** Areas of skin which are chronically inflamed or ulcerated are particularly vulnerable to the development of NMSC

- **Male pattern baldness** is an important but underrated risk factor for NMSC of the scalp

- **Infection with human papillomavirus (HPV)** There is undoubtedly an association between HPV infection and the development of both types of NMSC. However the exact role of this organism requires clarification, and further research is required to establish the nature of the causal link. In particular, the specific interactions between the virus and ultraviolet radiation have still to be clearly identified[25,26,27]

- The first evidence for the involvement of HPV in NMSC was reported in patients with **epidermodysplasia verruciformis** (EV), a rare inherited disorder affecting the skin, which is characterised by chronic infection with HPV. The lesions in these patients may show malignant transformation especially on sun-exposed areas, usually after the age of 30 years. It has been shown that the HPV types detected in skin tumours of these patients carry a higher risk for NMSC

- **Therapeutic immunosuppression and HIV infection** The recipients of organ transplants who are treated with immunosuppressive drugs are at increased risk of NMSC. It is notable that in these patients SCC is more common that BCC. Those individuals whose immune system is compromised due to disease, e.g. HIV AIDS, are also more vulnerable to the development of NMSC

- **Xeroderma pigmentosum**, a group of autosomal recessive disorders characterised by defects in DNA repair

3.10. **Sunbeds** The desire to acquire a tan for cosmetic purposes has led to the development of a large artificial tanning industry, mostly in Western countries where many residents have pale skins. These facilities have proliferated considerably over the last 15 years as the fashion for indoor tanning has increased.[28] In general sunbeds predominantly emit UVA radiation, which was thought to be the least damaging component of the UV radiation spectrum. However in recent years, sunbeds have been manufactured that produce higher levels of UVB in order to mimic the solar spectrum more closely and attempt to accelerate the tanning process.

3.10.1. There is no evidence to suggest that UVR from any type of sunbed is less harmful than solar UVR, and additional exposure to UVR from sunbeds is likely to enhance the detrimental consequences of excessive solar UVR exposure. Pre-cancerous actinic keratoses and Bowen's disease have been found in sunlight-protected but sunbed-exposed skin in fair-skinned users after just two to three years of regular sunbed use.

3.10.2. A recent systematic review of the literature investigated the association between sunbed use and cutaneous cancers.[29] An increased risk of squamous cell carcinoma was found but for basal cell carcinoma no association was identified.

Other non-solar sources of UVR and cutaneous cancer

3.11. **Fluorescent lamps** The issue of whether UVR from fluorescent lamps poses a health hazard has been investigated by a number of researchers, including the National Radiological Protection Board (now part of the Health Protection Agency). They concluded that at commonly used illumination levels, the UVR emissions produced by fluorescent lamps presented neither an acute nor a significant chronic hazard.

3.12. **UVB phototherapy**, a common treatment for psoriasis and other dermatological diseases, has given rise to anxiety regarding an accompanying risk of skin cancer. However a recent review has concluded that UVB phototherapy is safe and poses no additional skin cancer risk.[30] It is well established that PUVA (photochemotherapy with oral or topical Psoralen plus UVA) has been widely used in the past for the treatment of psoriasis and is still in use for refractory cases and in selected other disorders. Under the action of UVA, psoralen intercalated in DNA is crosslinked to form photoadducts. This has been clearly demonstrated in many studies to cause cumulative skin damage and carcinogenesis including melanoma.[31]

Clothing and sunscreens

3.13. **Clothing** As a result of the longer wavelength of UVA, it is able to pass through most vehicle, office, and household windows, whereas UVB is blocked by window glass. Recent studies have investigated the protection against UVR afforded by clothing and found that the type of cotton fabrics commonly used in summer wear have only a limited protective effect. However conventional laundering improved their efficacy in this respect, and dyeing the fabrics and the addition of a UV absorber to the detergent significantly reduced their UV transmission.[32]

3.14. **Sunscreens** The use of sunscreens has been shown to be effective in preventing sunburn and actinic keratoses and in reducing the risk of squamous cell carcinoma. Despite concerns regarding their safety, current evidence supports the efficacy and safety of UV sunscreens and filters. The present consensus is that properly applied they help reduce the risk of solar damage[33] and are effective in preventing sunburn and actinic keratoses, and in reducing the risk of SSC.[34,35,36]

Occupational exposures causing NMSC

3.15. **Arsenic** is used in a number of industrial processes, including the manufacture of pesticides and herbicides and glass production. Early signs of exposure include the development of arsenical keratoses, which may then progress to SCC or BCC.

3.16. **Polycyclic aromatic hydrocarbons** (PAH) These organic compounds are emitted in the course of a number of industrial processes, including the production of gas from coal, and coke plants. Polycyclic aromatic hydrocarbons from creosote, asphalt and chimney soot have been associated with NMSC.[37]

3.17. A population-based, case-control study conducted among males in Alberta, Canada investigated the role of non-UVR risk factors for SCC and BCC of the skin. After adjustment for age, skin and hair colour, ethnic origin, and sunlight exposure, elevated risks for SCC were seen in subjects exposed to insecticides, herbicides, fungicides and seed treatments. Elevated risks of BCC were seen in subjects exposed to fibreglass dust and dry cleaning agents. Prior therapeutic irradiation for skin conditions increased the risk of both SCC and BCC (see also sections 3.18 and 3.19).[38]

Ionising radiation and NMSC

3.18. **Ionising radiation of therapeutic origin** The carcinogenic properties of ionising radiation have been known since reports of NMSCs on the hands of workers using radiation-emitting devices in the first decade of the last century. Since then the untoward effects of therapeutic ionising radiation have been investigated over many decades and a number of studies have found an association between radiation treatment, particularly if experienced before age 20, and the subsequent development of both BCC and SCC.

3.19. Until about 40 years ago therapeutic radiation was employed in a variety of benign conditions, including acne vulgaris, tinea capitis and other skin diseases, ankylosing spondylitis, facial hirsutism and certain gynaecological disorders (see para 3.8). The untoward effects of therapeutic ionising radiation have been investigated over several decades and many studies have found an association between radiation treatment, particularly if experienced before age 20, and the subsequent development of both BCC and SCC.[39,40,41] Although records are sparse it is likely that dosage would have been at the level of a few grays (Gy) up to possibly 10 Gy. This compares with the current level of doses associated with standard diagnostic radiology which are generally at the mGy level or less for radiography, in the tens of mGy for fluoroscopy procedures such as barium enemas, and would only reach 100 mGy for certain interventional treatments such as in cardiac stent insertions where doses may be at the 1 to 5 Gy level. (J Williams, personal communication, 2008.)[a]

[a] One gray is the absorption of one joule of radiation energy by one kilogram of matter. One thousandth of a gray (10^{-3}Gy) is one milligray (1mGy).

3.20. For example a group of children treated with ionising radiation for ringworm of the scalp in Israel from 1948 until 1960 has been studied for radiation-induced skin malignancies. The mean scalp dose was 6.8 Gy. The relative risk of non-melanoma skin cancer in this group was 4.2, with 98% of these cancers being basal cell carcinoma in the irradiated population. The mean interval of time between radiation treatment and the development of the malignancy was 21.6 years.

3.21. In another study, 2,224 children given X-ray therapy for tinea capitis were followed for up to 50 years in order to determine the incidence of cancer. They were compared with a control group of 1,380 tinea capitis patients given only topical medication. The study found a relative risk of 3.6 for BCC of the head and neck in the irradiated group (124 irradiated cases and 21 control cases), in response to a scalp dose of about 4.8 Gy. No melanomas of the head and neck were seen, and only a few cases of SCC.[42]

3.22. In most recent investigations of the link between therapeutic ionising radiation and NMSC, an elevated incidence of NMSC was found only at the site of radiation exposure. The risk appears to increase the younger the age at exposure and the link is strongest with BCC. In some studies it was shown that the addition of chemotherapy also appears to increase the risk in a manner not well understood. The accessory roles of subsequent UVR exposure and skin type on the individual's vulnerability to post-radiation NMSC remain uncertain.[43,44]

3.23. **Ionising radiation encountered at work** Individuals such as radiographers exposed to long-term ionising radiation in the workplace are also thought to be at slightly increased risk of NMSC.[45,46] However most studies relate to those first exposed in the 1940's and 1950's, when dosages were considerably greater and safety measures less stringently applied. Some controversy exists regarding the influence of skin pigmentation on the risk of NMSC in occupationally-exposed individuals. One study found that the relative risk of BCC was elevated in long-term chronically exposed workers and this was greater among those with lighter eye and hair colour. To date, there is no clear evidence of an increased cancer risk in medical radiation workers exposed to current levels of radiation doses.[46]

3.24. **Ionising radiation derived from military sources** The radiation-related risk for NMSC among atomic bomb survivors of Hiroshima and Nagasaki is primarily due to the excess risk of BCC, with no demonstrable excess in squamous cell carcinoma.[47] All available studies demonstrate that the risk of NMSC is greater from radiation exposure at young ages than at older ages. Available evidence indicates that the excess risk of skin cancer lasts for 45 years or more following irradiation. It has also been shown that skin susceptibility to ultraviolet exposure modifies the excess risk of skin cancer from ionising radiation, and African-Americans exposed to ionising radiation suffer few excess skin cancers as compared to Caucasians with a comparable dose.[48] This has not been satisfactorily explained.

3.25. **Cosmic radiation** is a very low-level source of ionising radiation which at sea level contributes about 13% to the natural background radiation. It consists mainly of protons, electrons, and heavier ions, along with secondary particles, e.g. neutrons. The effect of exposure to higher amounts of cosmic radiation has received particular attention in air crew personnel, in whom cumulative cosmic radiation is likely to exceed that of the general public. Although some influence of cosmic radiation on NMSC cannot entirely be excluded there does not appear to be a clear or consistent association.[49,50] In one

study, an excess risk for NMSC was observed but this was thought to be attributable to sun exposure during leisure time in holiday destinations.[51]

3.26. **Rare skin cancers** The aetiology of the rare skin cancers is in many cases unknown. Merkel-cell carcinoma has recently been linked to a previously unknown polyomavirus and it is expected that further research will clarify this association.[6]

4. Prognosis

4.1. **BCC** In general, the prognosis of BCC is good. The lesion grows slowly, and metastasis rarely occurs. The choice of treatment will depend on the patient's age and other clinical criteria, but for primary excision and destructive approaches, 5-year cure rates vary between 70% and 90%. Moh's micrographic surgery is more time consuming but has an overall 5-year cure rate of 99% for primary tumours and up to 95% for recurrent BCC. Most recurrences are observed during the three years following treatment. The risk of development of another BCC is approximately 45% within 5 years, and the patient should be made aware of this. High risk patients[52] may require specialist monitoring.

4.2. **SCC** Since the risk of both metastasis and recurrence is significantly greater for SCC than BCC, careful follow-up is essential. The location, size, and node involvement of the primary tumour will determine the frequency and nature of follow-up, but in general these patients should be examined every 6 months or so for the first few years as the 5-year survival among patients with metastatic SCC is less than 50%. However with regard to small SCCs arising from actinic keratosis on sun-exposed surfaces, the rate of metastasis is very low; somewhere in the region of 0.5%, and in these cases 6- to 12-monthly review is adequate.[53]

4.3. It is important also to note the increased risk for new skin cancers in patients who have been treated for NMSC. In one Australian study, 300 NMSC patients were followed up for 10 years after treatment for NMSC. 67.8% developed new skin cancers and 51.8% developed multiple skin cancers. Men who had a NMSC were 8 times more likely than the general population to develop a melanoma while women with NMSC were 4 times more likely.[54]

4.4. A recent community-based, prospective cohort study found that individuals diagnosed with NMSC had a greater risk of developing a subsequent cancer other than NMSC, after adjusting for age, sex, body mass index, smoking status, and educational level. The authors conclude that NMSC may be a marker of a high cancer risk phenotype regardless of sun exposure history.[55]

5. Summary

5.1. The cutaneous cancers are by convention classified as non-melanoma skin cancer (NMSC) and melanoma. There are two main types of NMSC: **basal cell carcinoma** (BCC) and **squamous cell carcinoma** (SCC). Of these, BCC has less tendency to spread locally, and metastases are rare. In contrast, SCC ranges in character from an indolent, slow-growing lesion to an aggressive tumour with significant metastatic potential. In addition, a considerable variety of uncommon skin cancers are recognised.

5.2. There appears to be an elevated **risk of BCC** with intermittent exposure to UVR especially where it occurs under the age of 20 years, but chronic outdoor occupational exposure after this age has not been shown to increase overall risk. The **risk of SCC** is more probably related to total lifetime exposure or to chronic (occupational) exposure to UVR, rather than to exposure in childhood or early adulthood.

5.3. While cutaneous cancers are strongly associated with exposure to UVR, other factors including genetic susceptibility probably play a part in their causation.

5.4. The prognosis of BCC is good, and the overall 5-year cure rate approaches 100%. SCC is more malignant but the prognosis is good if the disease is identified and treated at an early stage. In the case of small SCCs arising from actinic keratosis on sun-exposed surfaces, the rate of metastasis is very low.

5.5. **Additional sources** The relevant guidelines of the British Association of Dermatologists (BAD) may be obtained at the website of the organisation:

http://www.bad.org.uk/site/622/default.aspx

Recent guidance issued by the National Institute for Health and Clinical Excellence (NICE) is available at:

URL:http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf

6. Related Synopses

Melanoma

Ultraviolet Radiation and the Skin

7. Appendix A: Skin phototype and reaction to UVR exposure

Skin phototype	Unexposed skin colour	UVR sensitivity	Tanning
I	White	Extremely sensitive to UVR: always burns on minimal sun exposure	Never tans
II	White	Very sensitive: burns very readily	Tans slowly
III	White	Moderately sensitive: may burn with prolonged exposure	Tans relatively slowly
IV	Light brown	Relatively tolerant of UVR: burns rarely	Tans rapidly on minimal exposure
V	Brown	Sensitivity variable: some individuals may burn despite pigmentation	N/A
VI	Black	Relatively insensitive: rarely burns	N/A

8. Glossary

actinic	Relating to the ability to cause photochemical effects through having a significant short wavelength or UV component.
actinic keratosis	Small, usually multiple scaly erythematous lesions which occur on exposed areas such as the dorsum of the hands and the face. (See *keratinocytes* below).
adenocarcinoma	A form of cancer that involves cells from the lining of the walls of many different organs.
apocrine gland	One of the types of sweat-producing gland that occur in human skin, the other being eccrine glands (*qv*). Apocrine glands are restricted mainly to the axilla and groin.
autosomal dominant disorder	An inherited characteristic which requires only one affected parent have the trait to pass it to offspring. See *autosomal recessive disorder* below.
autosomal recessive disorder	Disorder characterised by the fact that two copies of an altered gene must be present for an individual to be affected with the condition. See *autosomal dominant disorder* above.
carcinoma *in situ*	Cancer in the stage of development when the cancer cells are still confined to their site of origin.
cryotherapy	The therapeutic use of cold as an agent in the removal of unwanted tissue.
eccrine gland	A coiled tubular sweat gland that occurs in the skin on almost all parts of the body.
erythema	Redness of the skin produced by congestion of the capillaries. Hence *erythematous*.
haemangioma	A malformation of the blood-vessels.
keratinisation	Formation of the horny superficial layer of

	the skin.
keratinocytes	Epidermal cells which synthesise keratin and undergo characteristic changes as they gradually move upward from the basal layers of the epidermis to the outer layer of the skin.
lactiferous ducts	The ducts which drain the lobes of the mammary gland.
melanocytes	Specialised cells in the skin and the eye that synthesise melanin pigments.
Moh's micrographic surgery	A surgical technique which involves the removal of serial samples of a cutaneous tumour which are microscopically examined to determine the presence of malignant cells.
necrosis	Tissue death.
neuroendocrine	Pertaining to the anatomical and functional relationships between the nervous system and the endocrine glands.
p53 gene	A tumour suppressor gene.
photodynamic therapy	Mode of treatment for cancer and other conditions that uses the interaction between laser light and pre-sensitised cells.
perineural	Relating to the tissue surrounding a nerve.
sarcoma	A form of cancer that arises in the connective or supportive tissues such as bone, cartilage, fat or muscle.
sebaceous gland	One of the types of gland found in the skin. It produces sebum, an oily semi-fluid substance which softens and lubricates the hair and skin.
tinea	A fungal infection.

9. References

[1] Skidmore RA, Flowers FP. Nonmelanoma skin cancer. Med Clin North Am 1998 Nov;82(6):1309-23.
[2] National Institute for Health and Clinical Excellence. Improving outcomes for people with skin tumours including melanoma. [Online]. 2006 [cited 2009 9 Feb]. Available from: URL:http://www.nice.org.uk/nicemedia/pdf/CSG_Skin_Manual.pdf
[3] Cook TF, Fosko SW. Unusual cutaneous malignancies. Semin Cutan Med Surg 1998 Jun;17(2):114-32.
[4] Kanitakis J. Mammary and extramammary Paget's disease. J Eur Acad Dermatol Venereol 2007 May;21(5):581-90.
[5] Poulsen M. Merkel-cell carcinoma of the skin. Lancet Oncol 2004;5(10):593-9.
[6] Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008 Feb 22;319(5866):1096-1100.
[7] Buck CB, Lowy DR. Getting stronger: the relationship between a newly identified virus and Merkel cell carcinoma. J Invest Dermatol 2009 Jan;129(1):9-11.
[8] Lookingbill DP, Spangler N, Helm KF. Cutaneous metastases in patients with metastatic carcinoma: a retrospective study of 4020 patients. J Am Acad Dermatol 1993 Aug;29(2 Pt 1):228-36.
[9] de Gruijl FR. Skin cancer and solar UV radiation. Eur J Cancer 1999;35(14):2003-9.
[10] Wong CSM, Strange RC, Lear JT. Basal cell carcinoma. Br Med J 2003;327:794-8.
[11] Tilli CM, Van Steensel MA, Krekels GA et al. Molecular aetiology and pathogenesis of basal cell carcinoma. Br J Dermatol 2005;152(6):1108-24.
[12] Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. Br J Dermatol 2008;159:35-48.
[13] Motley R, Kersey P, Lawrence C. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. Br J Derm 2002;146:18-25.
[14] Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: a brief review. Prog Biophys Mol Biol 2006;92:119-31.
[15] Kricker A, Armstrong BK, English DR et al. Does intermittent sun exposure cause basal cell carcinoma? A case control study in Western Australia. Int J Cancer 1995;60:489-94.
[16] Gallagher RP, Hill GB, Bajdik CD et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. Arch Dermatol 1995;131:157-63.
[17] Rosso S, Zanetti R, Martinez C et al. The multicentre south European study 'Helios'. II: different sun exposure patterns in the aetiology of basal cell and squamous cell carcinomas of the skin. Br J Cancer 1996;73:1447-54.
[18] Naldi L, DiLandro B, Parazzini F et al. Host-related and environmental risk factors for cutaneous basal-cell carcinoma: evidence from an Italian case-control study. J Am Acad Dermatol 2000;42:446-52.
[19] Corona R, Dogliotti E, D'Errico M et al. Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. Arch Dermatol 2001;137:1162-8.
[20] Vitasa BC, Taylor HR, Strickland PT, et al. Association of nonmelanoma skin cancer and actinic keratosis with cumulative solar ultraviolet exposure in Maryland watermen. Cancer 1990;65:2811-7.
[21] Gallagher RP, Hill GB, Bajdik CD et al. Sunlight exposure, pigmentation factors, and risk of nonmelanocytic skin cancer. II. Squamous cell carcinoma. Arch Dermatol 1995;131:164-9.
[22] Franceschi S, Levi F, Randimbison L, La Vecchia C. Site distribution of different types of skin cancer: new aetiological clues. Int J Cancer 1996;67(1):24-8.
[23] Pharoah PD. Shedding light on skin cancer. Nat Genet 2008 Jul;40(7):817-8.
[24] Stacey SN, Gudbjartsson DF, Sulem P et al. Common variants on 1p36 and 1q42 are associated with cutaneous basal cell carcinoma but not with melanoma or pigmentation traits. Nat Genet 2008 Nov;40(11):1313-8.
[25] Harwood CA, Proby CM. Human papillomaviruses and non-melanoma skin cancer. Curr Opin Infect Dis 2002;15:101-14.
[26] Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Dis Markers 2007;23(4):247-59.
[27] Akgül B, Cooke JC, Storey A. HPV-associated skin disease. J Pathol 2006 Jan;208(2):165-75.
[28] Mackie RM. Long-term risk to the skin of ultraviolet radiation. Prog Biophys Mol Biol 2006;92:92-6.

[29] International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer. The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: a systematic review. Int J Cancer 2007 March 1;120(5):1116-22.
[30] Lee E, Koo J, Berger T. UVB phototherapy and skin cancer risk: a review of the literature. Int J Dermatol 2005;44(5):355-60.
[31] Stern, R.S et al. Risk of Squamous Cell Carcinoma and Methoxsalem (Psoralen) and UV-A radiation (PUVA). Arch Dermatol 1998;134:1582-85
[32] Wang SQ, Kopf AW, Marx J et al. Reduction of ultraviolet transmission through cotton T-shirt fabrics with low ultraviolet protection by various laundering methods and dyeing: clinical implications. J Am Acad Dermatol 2001;44:767-74.
[33] Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. Dermatol Clin 2006;24(1):35-51.
[34] Naylor MF, Boyd A, Smith DW et al. High sun protection factor sunscreens in the suppression of actinic neoplasia. Arch Dermatol 1995;131:170-5.
[35] Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147-51.
[36] Green A, Williams G, Neale R et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. Lancet 1999;354:723-9.
[37] Gawkrodger DJ. Occupational skin cancers. Occup Med 2004;54:458-63.
[38] Gallagher RP, Bajdik CD, Fincham S et al. Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. Cancer Epidemiol Biomarkers Prev. 1996 Jun;5(6):419-24.
[39] Karagas MR, McDonald JA, Greendberg ER et al. Cancers after ionizing radiation therapy. J Natl Cancer Inst 1996;88(24):1848-1853.
[40] Fitzgerald TJ, Jodoin MB, Tillman G et al. Radiation therapy toxicity to the skin. Dermatol Clin 2008;26:161-72.
[41] Lichter MD, Karagas MR, Mott LA et al. Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. Arch Dermatol 2000;136:1007-1011.
[42] Shore RE, Moseson M et al. Skin cancer after X-ray treatment for scalp ringworm. Radiat Res 2002 Apr;157(4):410-8.
[43] Karagas MR, Nelson HH, Zens MS et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. Epidemiology 2007 Nov;18(6):776-84.
[44] Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. J Am Acad Dermatol 2006;54(1):28-46.
[45] Davis MM, Hanke CW, Zollinger TW et al. Skin cancer in patients with chronic radiation dermatitis. J Am Acad Dermatol 1989;20:608-16.
[46] Yoshinaga S, Hauptmann M, Sigurdson AJ et al. Nonmelanoma skin cancer in relation to ionizing radiation exposure among U.S. radiologic technologists. Int J Cancer 2005 Jul 10;115(5):828-34.
[47] Ron E, Preston D L, Mabuchi K et al. Skin tumor risk among atomic-bomb survivors in Japan. Cancer Causes Control 1998;9(4):393-401.
[48] Shore RE. Radiation-induced skin cancer in humans. Med Pediatr Oncol 2001;36(5):549-54.
[49] Pukkala E, Aspholm R, Auvinen A, et al. Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. Br Med J 2002;325(7364):567.
[50] Buja A, Lange JH, Perissinotto E et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. Toxicol Ind Health 2005;21(10):273-82.
[51] Gundestrup M, Storm HH. Radiation-induced acute myeloid leukaemia and other cancers in commercial jet cockpit crew: a population-based cohort. Lancet 1999;354(9195):2029-31.
[52] Randle HW. Basal cell carcinoma: identification and treatment of the high-risk patient. Dermatol Surg 1996;22:255-61.
[53] Wood GS, Bagheri M, Gharia M et al. Nonmelanoma skin cancers: basal cell and squamous cell carcinomas. In: Abeloff MD, Armitage JO, Niederhuber JE et al, editors. Abeloff: Clinical Oncology, 3rd ed. Philadelphia: Churchill Livingstone; 2004. p. 1589-604.
[54] Czarnecki D, Sutton T, Czarrnecki C, Culjak G. A 10-year prospective study of patients with skin cancer. J Cutan Med Surg 2002;6:427-9.

[55] Chen J, Ruczinski I, Jorgensen TJ et al. Nonmelanoma skin cancer and risk for subsequent malignancy. J Natl Cancer Inst 2008 Sep 3;100(17):1215-22.