Ministry of Defence

Synopsis of Causation

Ultraviolet radiation and the skin

Author: Dr Tony Fisher, Medical Author, Medical Text, Edinburgh
Validator: Professor LE Rhodes Photobiology Unit, University of Manchester, Salford Royal Foundation Hospital

April 2010

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.

The Ministry of Defence accepts full responsibility for the contents of this synopsis, and for any claims for loss, damage or injury arising from the use of this synopsis by the Ministry of Defence.

1. Definition

1.1. **Ultraviolet radiation** (UVR) is a component of the non-ionising part of the electromagnetic spectrum, just beyond the violet end of visible light. It has a wavelength of 100-400 nanometres (nm) and it is arbitrarily classified as **UVA** (320-400 nm), **UVB** (280-320 nm) and **UVC** (100-280 nm).UVA can be further subdivided into **UVA I**, or far UVA (340-400 nm), and **UVA II**, or near UVA (320-340 nm). UVR falls beyond the range of human vision but has a number of important effects on health.

1.2. **Solar UVR** By far the most important source of UVR is the sun. The degree of exposure to solar UVR depends on a number of factors, including geographical location, altitude, season, time of day, reflectance from the ground, and behavioural factors such as the use of sunscreens and protective clothing, and avoidance of exposure. In contrast to UVA, all UVC and approximately 90% of UVB is filtered by the ozone layer, so no UVC reaches the earth and only 10% of UVB does so. Approximately 95-98% of the solar UVR at the earth's surface is UVA.

1.3. **Artificial sources of UVR** are widespread, and devices which produce it may do so as part of their original function, or incidentally. However, few cause greater exposure to UVR than natural sunlight. Exceptions include medical sources, which are designed to assist diagnosis and provide specialised therapy for certain diseases, and cosmetic tanning devices. Certain types of industrial lamps and arc welding devices also emit UVR but rarely in significant quantities.

1.4. **Penetration of UVR** The depth of penetration of UVR into the body apart from the skin and eyes is very limited. The skin has 2 main layers, ie the epidermis, which contains the sensitive basal cells, and the deeper dermis. As described, solar UVC is absorbed by the atmosphere, and any UVC arising from artificial sources does not readily penetrate to the sensitive basal layer of the epidermis. The main health effects of UVR are attributable to UVA and UVB. The depth to which UVR penetrates the skin depends upon the wavelength, with longer wavelengths having deeper penetration. About 90% of UVB is absorbed by the epidermis, while 50% of UVA reaches the dermis.

2. The cutaneous effects of UVR

2.1. The UV component of sunlight is responsible for almost all solar-induced cutaneous disease in humans, but the action spectrum for the specific effects of sun exposure is not known with great precision.

2.1.1. **Beneficial effects of UVR** Vitamin D, which is essential for bone metabolism throughout life, is synthesised in the skin, and small amounts of natural sunlight are necessary for this process to occur. Both UVB and UVA are used therapeutically in the treatment of certain dermatological diseases, notably psoriasis, eczema, vitiligo, pruritic (itching) skin conditions and photosensitivity disorders.

2.1.2. **Adverse effects of UVR** The main adverse health effect of UVR is on the skin and eyes although it is known that it also has an effect on the immune system. The molecular configuration of animal proteins, enzymes and nucleic acids is such that they absorb radiation of UV wavelength and may be disrupted when exposed to it. The resulting new molecules may cause inflammation and under certain circumstances, neoplasia.[1] The adverse effects of UVR on the skin are considered in more detail later in this section.

2.2. **Factors which modify the response of the skin to UVR** Individuals vary greatly in their reaction to exposure of the skin to UVR, and the consequences of exposure may be modified by a number of variables. These include anatomical and constitutional factors, genetic and acquired diseases, age-related factors, the use of some medications, and behavioural factors. These are discussed below.

2.2.1. **Anatomical factors** Certain anatomical factors influence the site and severity of erythema ie sunburn following exposure to UVR. For example, the face, neck and trunk are approximately four times more sensitive to UVR than the limbs. Furthermore these anatomical differences are compounded by the variations in solar exposure on different parts of the body. The vertical surfaces of an upright person receive only about 50% of the ambient UVR, whereas horizontal surfaces, such as the upper aspect of the shoulder receive up to 75%.

2.2.2. **Constitutional factors: skin phototypes** The concept of skin phototypes (the "Fitzpatrick sun reactive types") was introduced in 1975.[2] It represents a system of classification which is based on skin colour and the sunburn and suntanning responses of the skin to UVR exposure. It is outlined in Appendix A.

2.2.3. **Genetic disorders** There is marked susceptibility to UVR in a number of inherited disorders, including xeroderma pigmentosum, Bloom's syndrome, Rothmund-Thomson syndrome, Darier's disease albinism, the porphyrias, phenylketonuria, dysplastic nevus syndrome, and basal cell nevus syndrome. Some porphyries (biochemical disorders of porphyrin metabolism) are also acquired.

2.2.4. **Acquired disorders** There are many acquired diseases in which there is increased susceptibility to non-ionising radiation (ie ultraviolet and/or visible radiation). Examples include chronic active dermatitis, polymorphic light reaction, actinic reticuloid, polymorphous light eruption, solar urticaria, hydroa aestivale, hydroa vacciniforme, actinic prurigo, lupus erythematosus, dermatomyositis, and

disseminated superficial actinic parakeratosis. The underlying aetiology of these disorders is uncertain although many have an underlying immune abnormality. Several of these conditions are described in more detail in section 2.5.

2.2.5. **Age-related factors** A variety of age-related factors are thought to influence the susceptibility of the skin to UVR-related damage. For example senescent keratinocytes are more resistant to the normal processes of apoptosis,[3] thus giving an opportunity for UVR-related DNA- and protein damage to accumulate. The skin undergoes both the effects of chronological ageing and those attributable solely to chronic exposure to UVR (photoageing); so called intrinsic and extrinsic skin ageing show different, but overlapping features..

2.2.6. **Medications** A number of therapeutic drugs increase the sensitivity of the skin to UVR. These include such diverse groups as psoralens, certain antibiotics, antihypertensive drugs, hypoglycaemic agents, immunosuppressive agents, phenothiazines and nonsteroidal anti-inflammatory drugs (NSAIDs). This aspect is explored further in section 2.7.

2.2.7. **Behavioural factors** Individuals may modify their exposure to solar UVR by avoidance of sunlight, the application of sunscreens, and the wearing of protective clothing. In contrast, the fashion for cosmetic tanning has led to the widespread use of sunbeds and recreational sunbathing. These factors are discussed further in paras 4.12, 4.17 and 4.18.

Adverse effects of UVR on the skin

2.3. **Effects of acute exposure to UVR** In acute sunburn the exposed areas are erythematous, tender and oedematous [4].Vesiculation occurs in severe cases and may require a week or longer to resolve. Secondary infection may occur but is infrequent. A few days after an acute exposure peeling or scaling usually ensues, and in severe cases constitutional symptoms such as nausea, abdominal pain, tachycardia, malaise, pyrexia and headache may also occur. Following acute overexposure to UVR there is increased production of melanin in the skin, but this tanning effect only confers limited protection against further solar damage and contrary to popular belief is not an indication of good health.[1,5]A tan is the response of the skin to injury produced by UVR.

2.4. **Effects of chronic exposure to UVR**

2.4.1. **Age-like effects; "photoaging"** Cumulative exposure to the sun is responsible for a number of dermatological lesions, including actinic keratoses (discussed below), wrinkles, lentigines, telangiectases, and loss of translucency and elasticity.

2.4.2. **Actinic keratoses** Typically, these very common lesions appear in fair-skinned individuals with a history of extensive sun exposure and on skin which shows signs of solar damage. They are small, usually multiple scaly erythematous lesions which occur on exposed areas such as the dorsum of the hands and the face. They are regarded as pre-malignant lesions and a small proportion may progress to squamous cell carcinoma.[6] These lesions increase in prevalence with advancing age, and in Caucasians their prevalence is less than 10% in the third decade of life, but more than 80% in the seventh decade of life. Apart from their occasional propensity to advance to squamous cell carcinoma, their importance lies as a surrogate for lifetime solar UVR exposure.[7]

2.4.3. **Cancer** Certain cutaneous cancers have exposure to UVR as their major causative factor. These include **non-melanoma skin cancers** (NMSC), a term which refers inclusively to **basal cell carcinoma** (BCC) and **squamous cell carcinoma** (SCC); and **melanoma** itself. These conditions are all considered in later sections and melanoma is further addressed in the Synopsis *Melanoma*. **Merkel-cell carcinoma** (MCC) is a rare form of skin cancer of neuroendocrine origin. It is thought to arise from the Merkel cell or skin-pressure receptor and has the propensity to invade locally and metastasise to distant sites.

2.4.4. The process of carcinogenesis due to UVR exposure is a stepwise accumulation of specific genetic changes in the cell, with ensuing clonal expansion. In other words DNA damage due to UVR exposure leads to the formation of mutations, followed by malignant transformation. UVR is what is termed as a complete carcinogen in that it initiates the DNA damage that can lead to mutations and promotes cancer development, including by causing immunosuppresion.

2.5. **The photodermatoses** Certain individuals exhibit abnormal cutaneous reactions to UVR. In these conditions, the photodermatoses, there are symptoms and/or an eruption following exposure to UVR[8]. The commonest group are the idiopathic, probably immunologically determined photodermatoses, in which abnormal host immunological responses appear to be responsible. They include:

- Polymorphous light eruption
- Actinic prurigo
- Hydroa vacciniforme
- Chronic actinic dermatitis
- Solar urticaria

2.5.1. **Polymorphous light eruption** This is a common, sunlight-induced eruption affecting individuals of all races, with a slight predominance in women. The onset occurs most commonly during the second and third decades. Attacks are intermittent and usually follow within minutes to hours (occasionally minutes or days) of exposure to sunlight or artificial UVR exposure. Characteristically, the lesions consist of pruritic, erythematous papules, vesicles or plaques which heal without scarring. Usually it is more severe in the spring or early summer, often diminishing in severity as summer progresses, before disappearing completely during the winter.

2.5.2. **Actinic prurigo** This is a sunlight-induced, pruritic, papular or nodular, eruption of both uncovered and, to a lesser extent, covered skin. It occurs more frequently in children and it is generally more severe in summer.

2.5.3. **Hydroa vacciniforme** This is a rare, intermittent, vesicular scarring disorder of some or all exposed skin. Attacks are provoked by sunlight and the course and distribution are somewhat similar to that of polymorphous light eruption although unlike polymorphic light eruption it involves pain and is followed by scarring. It usually begins in childhood and often resolves by adolescence or young adulthood.

2.5.4. **Chronic actinic dermatitis** This is a rare, persistent, severe eczematous disorder

which affects the uncovered- and to a lesser extent covered skin. It is caused by exposure to UVR and occasionally to visible light. It usually affects older men although has recently been described in younger people, and may be severe all year round as it is produced by very low amounts of ambient radiation.

2.5.5. **Solar urticaria** is a condition in which transient cutaneous wheals appear following exposure to UVR or visible light. It is often severe and debilitating, and may significantly affect the patient's quality of life.

2.6. **The defective DNA-repair diseases** These conditions are rare, for example xeroderma pigmentosum, an autosomal recessive condition, has an estimated incidence of one per million in newborns in Western countries, and 1 per 40,000 to 100,000 newborns in Japan. Other examples include:

- Bloom's syndrome
- Cockayne's syndrome
- Rothmund-Thomson syndrome
- Trichothiodystrophy
- Kindler syndrome

All the above are autosomal recessive disorders except Kindler syndrome, whose mode of inheritance is probably autosomal dominant with incomplete penetrance.

2.7. **Photosensitivity produced by external agents** can be broadly divided into two categories; phototoxicity and photoallergy.

2.7.1. **Phototoxicity** is the result of direct tissue injury following the UVR-induced activation of a phototoxic agent. All persons exposed to the agent are susceptible to the disorder in the presence of UVR but the degree of sensitivity is variable. Common phototoxic agents include certain diuretics, nonsteroidal anti-inflammatory drugs, phenothiazines and tetracyclines. In general their phototoxic effects cease when the drug is withdrawn.

2.7.2. **Photoallergy** on the other hand is a delayed hypersensitivity response consisting of a sensitisation phase, an incubation period of 7 to 10 days after the first exposure, and a clinical reaction following any subsequent exposure to the agent. Common photoallergic agents include sunscreen fragrances, antibacterial agents and certain therapeutic drugs.

2.8. **Photosensitivity produced by endogenous agents** The cutaneous porphyrias, a group of conditions associated with specific enzymatic defects, are the most noted examples of photosensitivity induced by endogenous agents. In these, the photosensitivity is to visible light rather and ultraviolet radiation.

2.9. **Other UVR-related cutaneous lesions**

2.9.1. **Melanocytic naevi** (“moles”)These are common benign neoplasms composed of melanocytes, the pigment-producing cells of the epidermis. Their appearance is

variable. Generally dark brown, they may vary in colour between almost black, and nearly colourless. Their aetiology is complex and multifactorial, and is incompletely understood. **The congenital variety** may be due to a local failure of melanocytes to migrate from the neural crest during embryogenesis. **The acquired variety** commonly form during childhood, and it is suggested that exposure to UVR may be one factor in the causation of this type. Both congenital and acquired melanocytic naevi hold some risk for the development of melanoma, particularly if they are present in large numbers. Congenital naevi present the greater risk, particularly if large (>20 cm).

2.9.2. **Dysplastic or atypical naevi** are variants of the above that are relatively flat, broad and papular. They may exhibit a target-like appearance, with a central papular zone and a macular surrounding area. They frequently occur in families, and affected individuals may present with many such lesions. Most of these patients have fair skin and are of Northern European origin. In those individuals with only a few dysplastic naevi the risk of melanoma may not be much higher than normal. Those with large numbers of such lesions however have a high lifetime risk of melanoma. If in addition the individual has a family history of melanoma there is an extremely high risk that they will be affected also, and vigilant clinical surveillance is indicated.

2.9.3. **Actinic keratosis** (*syn.* solar keratoses) appears as a flat or thickened, scaly or warty, skin-coloured or red lesion which is often multiple. These lesions are very common on skin sites exposed to the sun, especially the backs of the hands and the face. They are especially common in older fair-skinned individuals or those who have worked outdoors for long periods.

2.9.4. **Bowen's disease** This condition is a carcinoma *in situ*. It is similar in appearance to actinic keratosisbut tends to be larger with a better defined border. It can progress to invasive squamous cell carcinoma.

2.9.5. **Actinic porokeratosis** This UVR-related lesion is most commonly encountered on the lower legs and appears as a raised, circular patch with an elevated border.

2.9.6. **Actinic granuloma** This lesion, often multiple, is thought to arise as a result of degeneration of dermal collagen. It presents as a circular or oval elevated area with a raised margin.

3. UVR-related skin cancer: clinical features

3.1. **Non-melanoma skin cancers** (NMSC) 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.

3.1.1. **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 cancer among Caucasians. The incidence in UK is around 90 per 10,000[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]

3.1.2. Approximately 80% of BCCs occur on the head and neck, and most of the remainder on the trunk and lower limbs. In people 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.

3.1.3. Treatment modalities include:

- Surgery
    - Curettage and cautery
    - Excision
    - Moh's micrographic surgery
- Radiotherapy
- Cryotherapy
- Photodynamic therapy
- Topical treatment (fluouracil, imiquimod)

3.1.4. **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. 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, is most likely to metastasise.[6]

3.1.5. SCC precursor lesions include:

- **Actinic keratoses** These common lesions are now considered by some to be a form of SCC in situ but in the UK are regarded as pre-malignant rather than malignant conditions. They are related to UVR exposure (see 2.9.3)

- **Arsenical keratoses** These are rare, discrete, warty lesions that appear 20 or more years after chronic arsenic ingestion. Lesions are most common on the palms and soles

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

- **Bowen's disease** This form of carcinoma *in situ* 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. (See 2.9.4) They are related to UVR exposure.

- **Erythroplasia of Queyrat** (squamous cell carcinoma *in situ* of penis)

3.2. **Melanoma** (*syn* malignant melanoma) is a condition in which melanocytes undergo malignant change. It occurs at a relatively younger age compared with other forms of malignant disease, and in some of its forms shows a marked propensity to spread locally and metastasise early and widely. As well as arising in the skin it may occur in the nail bed, in mucosal tissue including that of the nose, mouth, vagina, anus, urinary tract, and oesophagus, and the eye. Cutaneous melanoma has doubled in incidence in the UK in the past 20 years (now approximately 10 new cases per year per 100,000 population). The death rate from melanoma has however fallen in recent years and this may be allied to greater public awareness of the condition leading to earlier diagnosis. Melanoma is now one of the commonest malignant diseases, but it is usually recognised at an early stage, when survival rates are high. Nevertheless the fatality rate from melanoma is approsimately 25%. The condition occurs throughout the adult years, and when diagnosed sufficiently early it is easily treated by surgery alone. However the marked tendency of the disease to spread and metastasise renders advanced melanoma extremely difficult to treat.

3.2.1. The incidence of melanoma is greater in individuals with large numbers of pigmented naevi, and in particular those with atypical naevi. It is also commoner in people with fair skin and fair or red hair who do not tan on exposure to the sun (Fitzpatrick types I and II). Individuals with variants of the gene encoding the melanocortin-1 receptor (MC1R), which contributes to traits such as fair skin, freckling, and red hair, have a much greater risk of developing melanoma when associated with mutations in the BRAF oncogene. The mechanism underlying this association is unclear but appears to be independent of the effect of MC1R on

pigmentation.[12]

3.2.2. As previously indicated, the condition frequently arises from malignant transformation of a pre-existing melanocytic naevus, and any such lesions which exhibit a change in size, configuration, character or colour require biopsy and histological examination. However melanoma may also develop in an area of apparently normal skin and individuals who possess risk factors for the condition merit close surveillance. Patients may report border irregularity or variegated pigmentation in a pigmented naevus, a change in the size or colour of a pigmented lesion or itching or bleeding.

3.2.3. Cutaneous melanoma may be classified on clinical and biological grounds as follows:

- Superficial spreading melanoma
- Lentigo maligna melanoma
- Nodular melanoma
- Acral-lentiginous melanoma
- Mucosal lentiginous melanoma

The first three of these groups account for some 85% of all cases.

3.2.4. **Superficial spreading melanoma (SSM)** This form of cutaneous melanoma accounts for approximately 70% of all melanomas. It generally arises in a pre-existing lesion and is the form most commonly associated with dysplastic naevi. Often, the patient presents with changes in a precursor lesion, such as an increase in size. At first the SSM is flat, with irregular borders and usually multicoloured. Amelanotic areas may appear, representing areas of regression. Notching of the border is particularly characteristic and it may develop an irregular surface. SSM may occur throughout adult life, with a peak incidence in the fifth decade. It most commonly occurs on the head, neck, and trunk in males and on the limbs in females.

3.2.5. **Lentigo maligna melanoma (LMM)** This form accounts for some 10% of all melanomas. It arises from the lesion known as lentigo maligna and this precursor may have been present for a number of years before malignant change develops. LMM is most commonly found on the skin of elderly individuals exposed to the sun. The median age of development is 70 years. The lesions are often 3 – 4 cm in diameter, flat and with irregular borders. They vary in colour from tan to dark brown, and like SMM, hypopigmented areas represent foci of regression.

3.2.6. **Nodular melanoma (NM)** NM comprises some 10 to 15% of all cutaneous melanomas and may develop on any area of the body. However it occurs most commonly on the male trunk. The lesion is frequently of a dark uniform colour, and symmetrical in appearance, but occasionally it becomes polypoid. This variety of melanoma is associated with rapid growth and invasion of the dermis.

3.2.7. **Acral-lentiginous melanoma (ALM)** This variety represents approximately 3% to 5% of all cutaneous melanomas. It occurs on the palms, soles, and subungual

regions. Most are large with irregular borders and occur in older individuals (median age, 59 years). The subungual variety most commonly occurs on the first toe or thumb. ALM usually presents as a tan to dark brown macule with an irregular border, but as it advances ulceration may occur or it may present as a fungating mass. It resembles LMM, but is a much more aggressive lesion.

3.2.8. **Mucosal lentiginous melanoma (MLM)** This type is similar in appearance to acral-lentiginous melanoma. It occurs in a variety of mucosal sites, including the mouth, oesophagus, anus, vagina, and conjunctiva.

3.2.9. **Growth phases of cutaneous melanoma** In general, cutaneous melanoma has two distinct growth phases, radial and vertical. During radial growth, neoplastic cells grow in a radial fashion, either above or just below the basal lamina. The lesion does not metastasise during this phase, which may last many years in the case of superficial spreading melanoma and lentigo maligna melanoma, but is generally brief or undetected in nodular melanoma. In due course, the lesion commences the vertical growth phase, the malignant cell population invades the dermis, and the potential for cells to metastasise begins.

3.2.10. **Staging of melanoma** The **Clark level** is an anatomical measurement of tumour invasion but it indicates the prognosis of melanoma only in the more superficial lesions (<1 mm depth). Melanoma is also staged by means of **Breslow's microstaging method**, which uses an ocular micrometer to measure the thickness of the tumour from the granular layer of the epidermis, or the base of an ulcer, to the deepest identifiable melanoma cell. This method is now widely accepted as a useful and accurate prognostic guide. In general, the thicker the melanoma, the greater the risk for developing metastatic disease. However in the presence of a positive sentinel node the Breslow thickness is of no prognostic value. Ulceration, which may only be recognised histologically, is a poor prognostic sign.

3.3. **Merkel-cell carcinoma** This rare and aggressive tumour occurs most commonly in elderly individuals. Although reasonably satisfactory results can be achieved with early diagnosis and the integration of surgery, radiation, and chemotherapy, treatment can be challenging as these lesions commonly occur in difficult sites such as the head and neck, and lower leg.[13]

4. UVR and the pathogenesis of skin cancer

4.1. 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.

4.2. **Skin pigmentation** There is a greater risk of developing either principal type of NMSC ie BCC and SCC with increased exposure to sunlight, and 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. Subjects with red hair and those who always burn and tan poorly on UVR exposure are particularly vulnerable, especially those of Celtic descent. Similarly, individuals with oculocutaneous albinism are at increased risk of NMSC.

4.3. **UVR and 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 activities.[14]

NMSC and exposure to UVR

4.4. 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.[15,16] In addition, the respective relationships between UVR exposure and BCC and SCC are qualitatively and quantitatively different.

4.5. **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. However, like melanoma, intermittent UVR exposure, ie of sites normally covered, appears important in its causation. Research appears to indicate an elevated risk of BCC in individuals exposed to recreational UVR under the age of 20 years[17] but outdoor occupation after this age does not appear to be associated with an increased risk of BCC.[18] An increasing incidence of BCC with overall greater childhood exposure and recreational vacation exposure has also been observed,[19] 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.[20,21]

4.6. **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.[22] One study found a correlation with chronic sunlight exposure in the 10 years before diagnosis.[5,23] A population-based study on over 11,000 patients demonstrated the close correlation between chronic cumulative sun exposure and SCC.[24]

Other risk factors

4.7. **Basal cell carcinoma** Other risk factors include male sex and older age.[11] There is also a strong relationship to a family history of skin cancer of all varieties.

4.8. **Squamous cell carcinoma** 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 hemangiomas). 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 but not BCC. The reasons for this difference between the two types of NMSC are unknown.

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

- **Heat-burned or scarred skin**

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

- **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]

- **Therapeutic immunosuppression and HIV infection**

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

Melanoma and exposure to UVR

4.10. **The components of UVR and their relation to melanoma** It is not in doubt that exposure to sunlight is a major factor in the aetiology of cutaneous melanoma. However difficulties have arisen in identifying precisely the wavelength of UVR responsible. UVB is considerably more effective in producing sunburn, tanning and DNA damage than UVA. It is more strongly absorbed by DNA than UVA, and induces the formation of agents (thymine dimers) which interrupt cell regulation, suppress the immune response and interfere with the rejection of cells which UV exposure has caused to mutate. As a result, in the past most research was focused on UVB as the agent more probably responsible for melanoma. More recently however UVA has also been shown to damage DNA although it does so by a different mechanism, involving the creation of free radicals which lead to DNA strand breakage, nuclear base damage and mutations. As a result, the role of UVA in this respect is coming under increasing scrutiny.[26,27]

4.11. **The pattern of exposure to UVR** The exact mechanisms by which sunlight causes melanoma and as indicated above the wavelengths responsible, have still to be identified with certainty. From the results of many years' research into the problem, it has become evident that the association between total UVR exposure and melanoma incidence is not a simple relationship.[15] A recent systematic review demonstrated a statistically significant relationship between intermittent exposure and melanoma risk, but no increased risk of

melanoma in more continuous (occupational) solar exposure.[28] Intermittent recreational sunburn may therefore play an important role in the development of this tumour, rather than long-term chronic exposure. Childhood sunburns in particular have been linked to the development of melanoma in later life and this connection appears to be supported by experimental work. There is increasing evidence that the cause of melanoma is probably variable and multifactorial and it is now thought likely that UVR exposure interacts with genetic factors to cause the disease. However the pattern of solar exposure that is most likely to be responsible is not yet fully known. Paradoxically, outdoor workers have been found to have a decreased risk of melanoma compared with indoor workers, suggesting that chronic sunlight exposure can have a protective effect.

4.12. **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.[29] 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.

4.12.1. There is no evidence to suggest that UVR exposure from any type of sunbed is less harmful than solar UVR exposure, 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.

4.12.2. To date, evidence from epidemiological studies and clinical observations are inconclusive but appear to suggest that there is a potential role for UVA in the pathogenesis of melanoma. A large number of studies have focused on this question but inconsistencies in methodology have made consensus difficult to achieve. However in one of the most recent, a large prospective cohort study on 106,379 Norwegian and Swedish women conducted between 1991 and 1999 provided evidence for a significant, moderate increase in melanoma risk among regular sunbed users.[30] More recently, a systematic review of the literature investigated the association between sunbed use and cutaneous cancers.[31] Although evidence of a dose-response relationship was lacking, strong evidence of a positive association between cutaneous melanoma and the use of sunbeds was demonstrated. In particular, the authors concluded that the risk of melanoma was significantly increased where the first exposure to sunbeds occurred before the age of 35. An increased risk of squamous cell carcinoma was also found but for basal cell carcinoma no association was identified. Overall, there is accumulating evidence that sunbed use is associated with melanoma when started before approximately 35 years of age.

Other non-solar sources of UVR and cutaneous cancer

4.13. **Fluorescent lamps** The issue of whether ultraviolet radiation (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.

4.14. **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 very safe and poses no additional skin cancer risk.[32] Nevertheless, there is strong evidence that UVA therapy plus a psoralen drug (known as PUVA therapy) causes NMSC[33]

Clothing and sunscreens

4.15. **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 to the detergent of a UV absorber significantly reduced their UV transmission. A significantly greater percentage transmission of UVA, as compared with UVB, occurs through clothing and people wearing summer clothing may receive substantially more UVA than UVB even in clothed areas of the body.[34] Closely worn fabrics can be very protecting.

4.16. **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. It was generally assumed therefore that their use would be effective also in reducing the risk of melanoma but controversy persists regarding their prophylactic value in this respect. A number of studies have examined the relationship between sunscreen use and melanoma but results have been inconsistent. Indeed in some of the studies a statistically significant positive association between sunscreen use and increased risk for the development of melanoma has been demonstrated. It is thought that this might be explained by a greater sunscreen use by those inherently predisposed to melanoma, and by the fact that sunscreen use enables individuals to increase their hours of sun exposure without the risk of sunburn. 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 [35] and are effective in preventing sunburn and actinic keratoses and reducing the risk of squamous cell carcinoma.[36,37,38] The degree of protection they afford in respect of melanoma, however, remains less certain.

5. Prognosis

NMSC

5.1. **BCC** In general, the prognosis of BCC is good. The lesion grows slowly, and metastasis rarely occurs. Most recurrences are observed during the three years following treatment. The risk of development of another BCC is approximately 45% within 5 years and patients treated for the condition should be followed up for 5 years after diagnosis.[39] The overall 5-year cure rate with Moh's micrographic surgery is 99% for primary tumours and up to 95% for recurrent BCC. The 5-year cure rates for other treatments (which may be preferred according to the patient's age and other clinical criteria) vary between 70% and 90%[40].

5.2. **CC** 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 in the case of 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.[41]

Melanoma

5.3. Most metastases occur in the first 3 years after treatment of the primary lesion, and regular follow-up is strongly indicated during this time, particularly with thicker primary lesions. Since some 5% of patients with a history of melanoma develop a new primary melanoma, annual examinations are recommended for life. The risk is increased where there are multiple dysplastic naevi or a family history of melanoma. The two most important adverse prognostic factors in localised primary melanoma are greater tumour thickness and the presence of ulceration. Other statistically significant prognostic factors are the age of the patient, gender, site of the tumour, and the level of invasion.

5.3.1. The outcome for patients with **regional metastases** depends upon:

- The number of metastatic lymph nodes
- The size and number of metastatic foci
- The presence of ulceration of the primary melanoma
- Satellite or in-transit metastases

5.3.2. In patients with **advanced disease**, the prognosis depends on:

- The site of metastases; lung or other visceral organ involvement carries a less favourable outlook than subcutaneous or distant lymph node metastases
- The number of metastatic sites
- Elevated serum lactic dehydrogenase (LDH) levels, which are associated with decreased survival

5.3.3. **Early diagnosis** If the diagnosis of melanoma is made early in its course, cure is usually achieved by simple surgical excision. Subtle signs such as irregular borders and variegated colour are more common in early melanomas and a change in size, configuration, character, or colour in a precursor lesion should alert patient and carer. Pigmented lesions exhibiting any change, particularly in patients with high-risk attributes, should undergo biopsy and expert histological examination.

6. Summary

6.1. Ultraviolet radiation (UVR) is a component of the non-ionising part of the electromagnetic spectrum. It is arbitrarily classified as UVA, UVB and UVC and by far the most important source is the sun. Sunbed use may contribute significantly to total UVR exposure in some individuals. UVR possesses a number of beneficial effects including the synthesis of vitamin D in the skin, and both UVA and UVB are used therapeutically in the treatment of certain dermatological diseases. The main adverse health effect of UVR is on the skin and eyes although it is known that it also has an effect on the immune system.

6.2. Individuals vary greatly in their reaction to UVR. Anatomical and constitutional factors, genetic and acquired diseases, age-related factors, the use of some medications, and behavioural factors may all modify the consequences of exposure of the skin to UVR.

6.3. A wide variety of genetic and acquired disorders are linked to UVR exposure, and most of these pursue a chronic, refractory course. The cutaneous cancers are of particular importance in the current context. These conditions 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.

6.4. There appears to be an elevated **risk of BCC** in individuals exposed to recreational UVR under the age of 20 years, but outdoor occupation after this age does not appear to be associated with an increased 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.

6.5. **Melanoma** occurs at a relatively younger age compared with other forms of malignant disease, and in some of its forms shows a marked propensity to spread locally and metastasise early and widely. It occurs most commonly in fair-skinned individuals and is increasing in prevalence. UVR exposure is a major factor in the aetiology of cutaneous melanoma, and intermittent recreational sunburn plays an important role in the development of this tumour, rather than long-term chronic exposure. Childhood sunburns in particular have been linked to the development of melanoma in later life.

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

6.7. 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 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.

6.8. Like SCC the **prognosis of melanoma** depends upon early diagnosis and treatment and on the histopathological type. Greater tumour thickness and ulceration of the primary tumour are important adverse prognostic factors.

7. Related Synopses

Melanoma

8. 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 with difficulty
III	White	Moderately sensitive: may burn with prolonged exposure	Tans with ease
IV	Olive	Relatively tolerant of UVR: burns rarely	Tans on minimal exposure
V	Brown	Relatively insensitive: burns rarely though some individuals may burn despite pigmentation	N/A
VI	Black	Relatively insensitive: rarely burns	N/A

9. 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.
action spectrum	Relative effectiveness of radiation of different wavelengths to produce a given biological effect.
apoptosis	Cell death.
basal lamina	Extracellular matrix characteristically found underneath epithelial cells.
bullous	Consisting of large blisters.
carcinoma *in situ*	Cancer in the stage of development when the cancer cells are still confined to their site of origin.
clonal expansion	Production of daughter cells all arising originally from a single cell.
collagen	Fibrous connective tissue.
cryotherapy	The therapeutic use of cold as an agent in the removal of unwanted tissue.
erythema	Redness of the skin produced by congestion of the capillaries. Hence *erythematous*.
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.
lentigines	Small brownish macules resembling, but histologically distinct from freckles.
leukoplakia	Circumscribed, firmly attached, whitish patch on the tongue and other mucous

	membranes. A pre-cancerous lesion arising in response to chronic irritation.
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.
oedematous	Refers to excessive fluid in the subcutaneous tissues.
oncogene	A gene having the potential to cause a normal cell to become cancerous.
psoralens	Phototoxic substances found in many plants, which are used in the treatment of skin diseases, especially vitiligo.
p53 gene	A tumour suppressor gene.
sentinel node	The first lymph node to receive lymphatic drainage from the site of a primary tumour.
telangiectases	Abnormal dilation of small superficial blood vessels located just below the surface of the skin.
vesiculation	Small blisters

10. References

[1] NRPB. Health effects from ultraviolet radiation: Report of an Advisory Group on Non-Ionising Radiation. Documents of the NRPB 2002;13(2).
[2] Fitzpatrick TB. Soleil et peau J. Med. Esthet 1975;2:33-4.
[3] Gniadecki R, Hansen M, Wulf HC. Resistance of senescent keratinocytes to UV-induced apoptosis. Cell Mol Biol 2000;46(1):121-7.
[4] Rhodes LE and Lim HW. The Acute Effects of Ultraviolet Radiation on the Skin. In: Principles and Practice of Photodermatology. Editors. Lim HW. Honigsmann H, Hawk JLM. Informa Healthcare 2007, pp75-89.
[5] Young AR. Acute effects of UVR on human eyes and skin. Prog Biophys Mol Biol 2006;92:80-5.
[6] Anwar J, Wrone DA, Kimyai-Asadi A, Alam M. The development of actinic keratosis into invasive squamous cell carcinoma: evidence and evolving classification schemes. Clin Dermatol 2004;22(3):189-96.
[7] Salasche SJ. Epidemiology of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42(1):S1-S7.
[8] Haylett and Rhodes 2009 LE. Evaluation of the patient with photosensitivity. In: Allergy Frontiers: Diagnosis and Health Economics. Editors. Pawankar R. Holgate ST. Rosenwasser LJ. Springer 2009, pp387-402
[9] Hawk JL. Lim HW. Photodermatoses. In: GBolognia JL. Jorizzo JL, Rapini RP, editors. Dermatology , London: Mosby 2003;42(1): S1-S7
[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] Landi MT, Bauer J, Pfeiffer RM et al. MC1R germline variants confer risk for BRAF-mutant melanoma. Science 2006;313(5786):521-2.
[13] Poulsen M. Merkel-cell carcinoma of the skin. Lancet Oncol 2004;5(10):593-9.
[14] Tran H, Chen K, Shumak S. Epidemiology and aetiology of basal cell carcinoma. Br J Dermatol 2003;149(S66):50-2.
[15] Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: a brief review. Prog Biophys Mol Biol 2006;92:119-31.
[16] Wong CS, Strange RC, Lear JT. Basal cell carcinoma. Br Med J 2003;327:794-8.
[17] 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.
[18] Gallagher RP, Hill GB, Bajdik CD et al. Sunlight exposure, pigmentary factors, and risk of nonmelanocytic skin cancer. Arch Dermatol 1995;131:157-63.
[19] 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.
[20] 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.
[21] 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.
[22] 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.
[23] 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.
[24] 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.
[25] Harwood CA, Proby CM. Human papillomaviruses and non-melanoma skin cancer. Curr Opin Infect Dis 2002;15:101-14.
[26] Abdulla FR et al. Tanning and skin cancer. Pediatr Dermatol 2005;22(6):501-12.
[27] Wang SQ et al. Ultraviolet A and melanoma: a review. J Am Acad Dermatol 2001;44(5):837-46.
[28] Gandini S, Sera F, Cattaruzza MS et al. Meta-analysis of risk factors for cutaneous melanoma: II sun exposure. Eur J Cancer 2005;41:45-60.
[29] Mackie RM. Long-term risk to the skin of ultraviolet radiation. Prog Biophys Mol Biol 2006;92:92-6.

[30] Veierød MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003;95(20):1530-8.
[31] 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;120(5):1116-22.
[32] 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.
[33] Stern RS. Liebman EJ and Vakeva L. Oral Psoralen and ultraviolet – A light (PUVA) treatment of psyoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-Up Study. J Natl. Cancer Inst 1998;90(17): 1278-84
[34] 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.
[35] Nash JF. Human safety and efficacy of ultraviolet filters and sunscreen products. Dermatol Clin 2006;24(1):35-51.
[36] 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.
[37] Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. N Engl J Med 1993;329:1147-51.
[38] 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.
[39] Randle HW. Basal cell carcinoma: identification and treatment of the high-risk patient. Dermatol Surg 1996;22:255-61.
[40] Morton CA. McKenna KE and Rhodes LE: on behalf of the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee and the British Photodermatology Group, Guidelines for Topical Photodynamic Therapy: Update. Br J Dermatol. 2008; 159;1245-66
[41] 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.