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The risk of cancer associated with immunosuppressive therapy for skin diseases

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ACADEMIC DISSERTATION

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Contents

List of original publications

This thesis is based on the following original articles, which are cited in the text by their Roman numerals:

I Stern RS, Nichols KT, Väkevä LH: Malignant melanoma in patients treated for psoriasis with methoxalen (psoralen) and ultraviolet A radiation (PUVA). N Engl J Med 1997: 336, 1041–1045

II Stern RS, Väkevä LH: Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. J Invest Dermatol 1997; 108, 897–900

III Stern RS, Liebman E, Väkevä LH : Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. J National Cancer Inst 1998; 90, 1278–1284

IV Väkevä L, Pukkala E, Ranki A: Increased risk of secondary cancers in patients with primary cutaneous T cell lymphoma. J Invest Dermatol 2000; 115, 62–65

V Väkevä L, Reitamo S, Pukkala E, Sarna S, Ranki A: Observation by long term follow-up of cancer risk in patients treated with short term cyclosporine. Submitted

Abbreviations

A	nucleic adenine
AK	actinic keratosis
APC	antigen presenting cell
BCC	basal cell carcinoma
C	nucleic cytocine
CI	confidence interval
CTCL	cutaneous T cell lymphoma
DNA	deoxyribonucleic acid
EORTC	The European Organization for Research and Treatment of Cancer
Fc	crystallisable part of immunoglobulin
G	nucleic guanine
HR	hazard ratio
IDEC	inflammatory dendritic epidermal cell
IFN	interferon
IL	interleukin
J	joule
LC	Langerhans cell
MC1R	melanocortin 1 reseptor
MED	minimal erythemal dose
MHC	major histocompatibility complex
MM	malignant melanoma
8–MOP	8-methoxypsoralen
NER	nucleotide excision repair
NMSC	nonmelanoma skin cancer
PPP	palmoplantar pustulosis
p53	p53 gene
PUVA	psoralen plus UVA photochemotherapy
RR	relative risk
ROS	reactive oxygen species
SCC	squamous cell carcinoma
SEER	The Surveillance, Epidemiology, And End Results Programm
SIR	standardized incidence ratio
SUP	selective ultraviolet phototherapy
T	nucleic thymidine
TMP	trimethylpsoralen
TGF	tumor growth factor

TNF	tumor necrosis factor
UV	ultraviolet
UVA	ultraviolet A radiation
UVB	ultraviolet B radiation
UVC	ultraviolet C radiation
W	watt

Abstract

The possible carcinogenic risk of immunosuppressive therapies is an important issue in everyday clinical practice. Carcinogenesis is a slow multistep procedure and there is a long latency period before cancer develops. PUVA is an acronym from psoralen plus UVA. PUVA regimens can be divided into systemic PUVA or topical PUVA according to the administration route (oral or topical). PUVA can be used in many skin diseases including psoriasis, early stage mycosis fungoides, atopic dermatitis, palmoplantar pustulosis and chronic eczema. Systemic PUVA therapy has previously been associated with an increased risk on nonmelanoma skin cancer and especially squamous cell carcinoma (SCC). The increased risk of basal cell carcinoma (BCC) is also documented but it is modest compared to SCC. Most concern has been about the increased melanoma risk that might be associated to systemic PUVA therapy.

This study evaluated melanoma and noncutaneous cancer risk associated with systemic PUVA, and the persistence of nonmelanoma skin cancer risk after systemic PUVA treatment is stopped. In addition, development of subsequent cancer in cutaneous T cell lymphoma patients (CTCL) as a possible side effect of PUVA in immunocompromized persons was studied. The possible cancer risk related to usage of an immunosuppressive drug, cyclosporine, in different inflammatory skin diseases was also monitored.

The first three studies are part of an American PUVA follow-up cohort of 1380 psoriasis patients. The risk of melanoma started to increase 15 years after the first treatment with systemic PUVA. The risk was highest among persons who had received over 250 treatments. In noncutaneous cancer, the overall risk was not increased (RR=1.08, 95% CI= 0.93–1.24), but significant increases in risk were found in thyroid cancer, breast cancer and in central nervous system neoplasms. There was no association between higher PUVA levels and these cancers. The increased risk of SCC was associated to high cumulative UVA exposure in the systemic PUVA regimen and remained high even among patients with little exposure to systemic PUVA during recent years. The patients with high risk had no substantial exposure to other carcinogens. In BCC there was a similar but more modest tendency.

In the two other studies, the patients were from the database of the Finnish Cancer Registry and Department of Dermatology, Helsinki University Central Hospital. CTCL patients are commonly treated with PUVA. In a cohort of 319 patients, the risk of all secondary cancers (SIR) in CTCL

patients was 1.4 (95% CI=1.0–1.9). In separate sites, the risk of lung cancer, Hodgkin and non-Hodgkin lymphomas were increased. PUVA seemed not to contribute to any extent to the appearance of these cancers in contrast to psoriasis patients. The carcinogenity of short term cyclosporine was evaluated in 272 patients with inflammatory skin disease. We did not detect increase in the risk of skin malignancies or overall risk of cancer.

In conclusion, long term use of systemic PUVA therapy increased the risk of malignant melanoma. It did not affect the risk of noncutaneous cancers but was connected with a persistent risk for the development of non-melanoma skin cancer. In CTCL patients, PUVA treatment did not contribute to the development of secondary cancers. There was no evidence that short term cyclosporine treatment is a major risk factor for development of subsequent malignancy. Our studies confirm the increased skin cancer risk related to PUVA treatment in psoriasis patients. In other inflammatory skin diseases (atopic dermatitis, palmoplantar pustulosis and chronic hand eczema) low dose, short-term cyclosporine treatment seems to be without major risk.

Introduction

When conventional topical treatments have failed or are not efficient, immunosuppressive therapy may be considered in skin diseases. These therapies may include photochemotherapies such as PUVA or systemic drugs such as cyclosporine. These treatments have improved the quality of life in many skin disease patients, but adverse effects may appear. Cutaneous carcinogenesis is a long-term multistep process. Therefore, to evaluate the causative factors of skin cancer epidemiological studies with long follow-up times must be performed. UV exposure may take over 20 years to produce skin cancer. Immunosuppressive treatments carry a risk of squamous cell carcinoma (SCC) in psoriasis patients (Stern et al., 1988; Lindelöf et al., 1991), but there are few reports of non-cutaneous cancers related to these immunosuppressive treatments. Fortunately, SCC is less harmful compared to melanoma. Psoriasis patients are often treated with other potentially carcinogenic treatments, thus the adverse effect caused by an individual treatment may be difficult to estimate. The risk of systemic PUVA treatment has been mainly investigated with psoriasis patients. CTCL patients are in the early phase also treated with PUVA, but there are no studies on the effects of PUVA treatment in this group.

Cyclosporine is an effective treatment in inflammatory skin diseases. The carcinogenic information comes mainly from epidemiological studies made in organ transplant patients. There are two studies evaluating the relative risk of malignancy related to cyclosporine use in psoriasis patients (Marcil and Stern, 2001; Paul et al., 2003). In other skin diseases there are no previous studies concerning the risk of cyclosporine to the development of later cancers.

In the PUVA follow-up study, we have investigated the risk of melanoma, noncutaneous cancer and SCC and BCC in psoriasis patients. In further studies the influence of photochemothrapy to the development of secondary cancers in CTCL and the role of cyclosporine in later cancer development in inflammatory skin diseases were evaluated.

Review of the literature

Inflammatory skin diseases commonly treated with photochemotherapy

Psoriasis

Psoriasis is a chronic inflammatory skin disease and its prevalence is around two per cent in various population-based studies (Lomholt, 1964; Farber and Nall 1998). Psoriasis has a clear genetic susceptibility, although the inheritance pattern is still unclear (Henseler and Christophers, 1985). The recent genetic studies have revealed major locus on chromosome 6 (Asumalahti et al., 2002). However, it is assumed that several genes affect the pathogenesis of psoriasis. Other psoriasis susceptibility loci are found in chromosomes 1, 3, 4, 16, 17, 19 (Matthews et al., 1996; Nair et al., 1997; Lee et al., 2000a; Veal et al., 2001; Karason et al., 2005).

Clinically psoriasis presents as a well-demarcated, hyperkeratotic plaques, which favours knees, elbows, lumbar area and scalp (Braun-Falco, 2000). The disease has two peaks of onset: at young adulthood and at middle age. Various environmental factors including infections are well known triggers for psoriasis (Schön and Boehncke, 2005). The severity of psoriasis has clear seasonal variation. Sun exposure is often beneficial, but extensive sunburn can trigger or worsen the lesions. Streptococcal infection can elicit a typical guttate type-psoriasis eruption. Physical trauma can trigger psoriasis to otherwise healthy-looking skin. A few drugs, such as beta-blockers, lithium and interferon-alpha, are able to exacerbate psoriasis. The mechanism of these events is unclear, but some of them are probably related to cytokine release and unmasking of autoantigens.

Histopathologically psoriasis plaques include hyperproliferation of keratinocytes and hyperkeratosis combined with inflammatory cell infiltration (Weedon, 2002; McKee, 2005).

The primary pathogenetic mechanism of psoriasis is not known. Currently, psoriasis is recognized as a T cell mediated immune disease.The epidermal hyperplasia is due to activation of the immune system, which is mediated by accumulating T lymphocytes in the skin. An unknown antigen is taken up by Langerhans cells (LCs) and presented to T lymphocytes in lymph nodes. Eventually, this leads to differentiation of T cells and finally the secretion of proinflammatory cytokines such as IL–1, gamma interferon, IL–6 (Krueger, 2002; Schön and Boehncke, 2005). Recently, an interesting study related to the pathogenesis of psoriasis was published. Epidermal keratinocytes express JunB, a gene, which regulates cell prolif-

eration and differentiation responses (Shaulian and Karin, 2002). Zenz et al. have shown that the expression of this gene is reduced in psoriatic skin. In mice, they showed that deletion of this protein resulted a phenotype resembling psoriasis. The deletion of this protein in keratinocytes triggers the expression of cytokines (e.g. tumor necrosis factor alpha, gamma interferon, IL–2, IL–6, IL–8) and chemokines (Zenz et al., 2005), which can together with adhesion molecules recruit tissue specific lymphocytes into psoriasis plaques.

Mild psoriasis is treated with topical corticosteroids, anthralin, tar, calcitriol or calcipotriol. Phototherapy regimens used in psoriasis are UVB (broad- and narrow-band UVB), SUP (only in children) and PUVA (psoralen + UVA) (Ortel and Höningsmann, 1999). PUVA treatment is divided into systemic PUVA and topical PUVA according to the administration route. Systemic PUVA includes oral intake of psoralen tablets and topically psoralens can be applicated as ointments or bath water. Phototherapy regimens belong to the treatment armamentarium of moderate to severe psoriasis (i.e., 10–25% of body surface area). Widespread, eruptive and relatively superficial forms of psoriasis respond well to UVB treatment. Treatment is usually administered three times a week and the clearance takes 25 treatments in majority of cases (Stern, 1997). All forms of psoriasis, excluding generalized pustular psoriasis and erythrodermic psoriasis, respond well to PUVA treatment, but it is mostly used in plaque-type psoriasis. PUVA treatment is considered to be more effective than broadband UVB in the treatment of psoriasis (Ortel and Höningsmann, 1999), however narrow-band UVB is as effective as bath-PUVA (Dawe et al., 2003; Snellman et al., 2004). Cyclosporine and methotrexate are used in psoriasis if there is no satisfactory response to phototherapy or it is contraindicated. Low-dose methotrexate is highly effective in psoriatic arthritis. Oral retinoid acitretin can be combined with phototherapies. During the last few years, biological treatments have been introduced to treatment for most severe psoriasis cases.

Atopic dermatitis

Atopic dermatitis (atopic eczema) is determined as an itchy, inflammatory skin condition. The predilection sites are the skin flexures in childhood, but in adults it usually affects face, neck and upper part of the torso. Clinically it is a poorly defined erythema. In the acute phase the skin presents oedema, vesicles and weeping and the chronic stage can lead to skin thickening (lichenification) (Williams, 2005). Although atopic constitution is characterized by a tendency to produce IgE as a response to allergens, 40–60% of patients with atopic dermatitis do not have demonstrable IgE mediated hypersensivity (Flohr et al., 2004). The incidence of atopic dermatitis is highest in Scandinavia, the United Kingdom and in the United States (ISAAC, 1998).

The histologic features of atopic dermatitis include epidermal hyperplasia, spongiosis, thickening of the papillary dermis, and a perivascular infiltrate consisting of monocytes, T cells and APC's. (MacKee et al., 2005).

Atopic dermatitis has a familiar occurrence and genetic studies have linked this disease to polymorphic loci in chromosomes 1,3,5 and 11 (Cookson et al., 1992; Cookson, 1998; Lee et al., 2000; Cookson et al., 2001; Tsunemi et al., 2002).

Typical features of atopic dermatitis include a reduced barrier function of the skin, which permits environmental antigens, such as pollen, house dust mite and staphylococcal enterotoxins to enter the skin. These compounds are bound to antigen-presenting cells via IgE and the high-affinity Fc epsilon receptors. The epsilon Fc receptors are abundant in the atopic skin. Antigen presenting cells in the atopic skin include the Langerhans cells and inflammatory dendritic epidermal cells (IDEC). The IDECs are mainly seen during the acute inflammation. The dendritic cells present the processed antigens to the T cells, which proliferate and cause mainly the clinical symptoms of atopic dermatitis. Another pathway is the direct stimulation of the T cells by staphylococcal enterotoxins which is independent of IgE. Therefore the enterotoxins are called "superantigens" (Leung D, 2000; Novak et al. 2003). After antigen presentation the T cells differentiate into Th1 or Th2 cells. The Th1 response is associated with delayed-type hypersensitivity with release of IFN-gamma and IL-2, whereas the Th2 response is related to IgE mediated reaction with the predominance of IL-4, IL-5, IL-13 (van der Heijden et al., 1991; Grewe et al., 1994; Novak et al., 2003). Following repeated contact with the same antigen keratinocytes release cytokines (IL-1 and TNF-alfa) inducing expression of adhesion molecules (Köck et al., 1990), which further allure T cells to the location. In acute atopic dermatitis the lesions express the Th2 cytokine profile whereas in chronic lesions the profile looks more like Th1 type.

In atopic eczema, the standard treatment has included topical corticosteroid emollients until recently, when also topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been shown to be effective (Ashcroft et al., 2005). Broad- and narrowband UVB and selective ultraviolet phototherapy (SUP) are effective treatments in atopic dermatitis. These treatments are usually given three times a week over a period of 15–20 treatments. In chronic atopic dermatitis SUP (UVA/UVB) treatment is found to be more effective compared to broadband UVB therapy (Jekler and Larkö, 1990). The use of systemic cyclosporine is restricted to patients who do not respond to other conventional treatments.

Palmoplantar pustulosis

Palmoplantar pustulosis (PPP) is a common chronic skin disease where the lesions are restricted to the palms and soles. Patients may have psoriasis-like lesions on their forearms and legs, but the relationship to psoria-

sis is controversial. Women are more often affected than men. The disease is more common among smokers (Eriksson et al., 1998). Clinically PPP presents as small 1–5 mm size fresh pustules, dry yellowish lesions and accumulations of crust and scale. These intraepidermal pustules are sterile. Histologically the lesions show vesicles surrounded by neutrophils. The dermis has only mild inflammation (Braun-Falco, 2000).

Treatment options in palmoplantar pustulosis include topical treatment with corticosteroids, topical PUVA treatment, tetracyclines, methotrexate, acitretin and cyclosporine.

Chronic hand eczema

Eczema is a clinically and histologically defined pattern of skin inflammation, which can etiologically be divided into endogenous or exogenous forms. The exogenous form is further divided into irritant or allergic contact eczema depending on the mechanism by which the exogenous agent initiates the reaction. Clinically it is impossible to make a distinction between etiologic factors. Hand eczema shows redness, scaling, and also small papulovesicles.

Chronic hand eczema is treated in a very similar way to atopic eczema. Topical corticosteroid treatments, UVB irradiation localised to hands and topical PUVA treatments are used. Cyclosporine is used for therapy resistant cases.

Skin-associated malignancies treated with photochemotherapy

Cutaneous T cell lymphomas

The European Organization for Research and Treatment of Cancer (EORTC) Cutaneous Lymphoma Project Group recently published new criteria for CTCL classification (Willemze et al., 1997; Willenze et al., 2005). The two most common forms of CTCL are mycosis fungoides, which comprises one half of all CTCLs, and Sezary´s syndrome. Mycosis fungoides can be defined as a clonal proliferation of skin infiltrating T lymphocytes (Diamandidou et al., 1996). These T lymphocytes are small or medium-sized cells with cerebriform nuclei. Clinically the lesions often first present on the trunk and buttocks. In the patch stage the lesions may resemble psoriasis presenting as red-violet, oval, round, serpiginous plaques. In the infiltrative stage the lesions become indurated plaques, but there is usually no lymph node involvement. In the more advanced tumor stage, the lesions enlarge, become ulcerated and invasion to internal organs may occur (Souhami and Tobias, 2005; Willemze et al., 2005). Today mycosis fungoides is classified according to lymph node involvement and invasiveness (Willemze et al., 2005).

The prognosis of mycosis fungoides patients is dependent on the stage and the type of skin lesions and the presence of extracutaneous disease. If a patient has a limited patch or plaque stage mycosis fungoides, the life expectancy does not differ from age-, sex-, and race-matched control population (Willemze et al., 2005). Sezary´s syndrome is the erythrodermic and leukemic variant of CTCL. Lymph node enlargement and hepatomegalia are common features. In the peripheral blood there are typical Sezary´s cells, which are atypical lymphocytes with cerebriform nuclei (Weedon, 2000). Sezary´s syndrome has a poor prognosis with 5-year survival of 11 % (Willemze et al., 1997).

The specific chromosomal translocations for MF have not been identified. In most cases there are clonal T cell receptor gene rearrangements. Many structural and numerical chromosomal abnormalities have been detected (Karenko et al., 1997; Smoller et al., 2003).

Histolopathologically early mycosis fungoides may be difficult to diagnose. The classical histologic features include upper dermal infiltrate with atypical lymphocytes, the number of which can be sparse in the early phases. The malignant cerebriform lymphocytes typically infiltrate to epidermis and form Pautrier microabscesses. As the disease progresses to tumour stage and systemic involvement, the epidermotrophism decreases (McKee, 2005).

CTCL confined to the skin (early stage mycosis fungoides) is treated with photo(chemo)therapy: UVB irradiation and PUVA (Whittaker et al., 2003; Drummer et al., 2003). For small, limited patch stage lesions topical corticosteroids are a good choice.

Human skin

The human skin can be divided into two different layers: the epidermis and the dermis. The epidermis is composed of four different cell types: keratinocytes, melanocytes, Langerhans' cells and Mercel's cells. The most superficial part of the epidermis is stratum corneum, which is comprised of dead, dry cells and it has a filter function. Stratum corneum is biochemically composed of keratin proteins, transglutaminases, free amino acids and other compounds, which can bind water.

LCs belong to a family of antigen presenting cells. In skin, they are located in the basal and suprabasal layers of the epidermis. During contact hypersensitivity induction, the role of LCs is to present antigen-specific signals to T cells, as previously described. Keratinocytes are the main cell type of epidermis. They are mainly responsible for the production of keratins. Keratinocytes also produce inflammatory mediators that are essential in inflammatory skin diseases. Melanocytes are located between basal cell keratinocytes in the basal layer of the epidermis. The main function

of melanocytes is to synthesize melanin, but they also express various cytokines.

The skin is classified into different types according to its erythema response and ability to tan. This Fitzpatrick classification divides skin to types I–VI (Fitzpatrick, 1988). Skin types I–IV are used in white people and types V–VI in dark skinned or black people. People in skin types I–II always or easily sunburn and tan with difficulty, if ever. People with skin types III–IV always tan and burn minimally. In Finland about 60% of people are of skin type III and 25% of skin type II (Jansen, 1989). Skin cancer is most common in types I–II.

UV radiation

The physical properties of UV radiation

UV radiation is electromagnetic radiation. The electromagnetic spectrum of light is presented in Figure 1. The wavelength of UV radiation lies just below visible light.

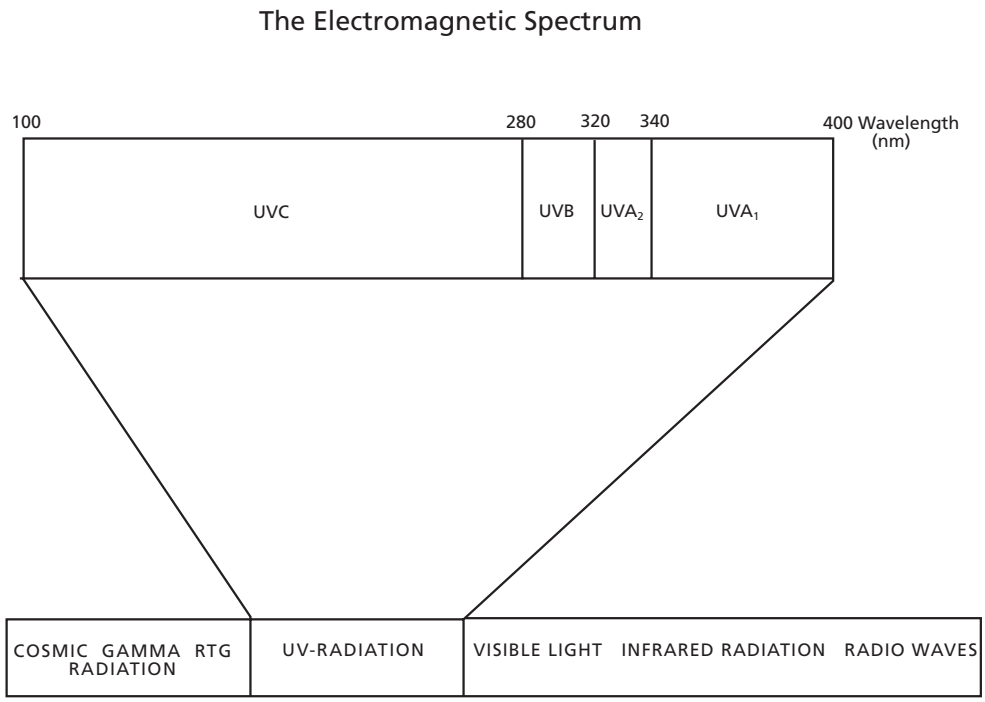


Figure 1 The Electromagnetic Spectrum

UV radiation can be classified artificially, according to wavelength, into three different categories: UVC (200–280 nm), UVB (280–320 nm) and UVA (320–400 nm). The UVA region is further divided into UVA_1 (340–400 nm) and UVA_2 (320–340 nm). The ozone layer blocks wavelengths shorter than 290 nm and thus, in addition to UVC, also part of UVB radiation. On earth, both UVA and UVB reach the surface at significant amounts to be able to influence biological events on the skin. Five per cent all UV radiation reaching the earth is of UVB radiation and 95% is of UVA radiation. UVA radiation passes through windows. In vitro, UVC is a potent mutagen (Evans et al., 1997), and it is used for sterilization and disinfection purposes.

The depth of penetration of UV radiation depends on the wavelength: the longer wavelengths have the capacity to penetrate deeper than shorter ones. Most of the UVB radiation is absorbed to the stratum corneum and epidermis and only 5–10% can reach basal keratinocytes, and dermis. In different studies 19–50% of solar UVA can reach the depth of melanocytes, whereas only 9–14% of UVB reaches that level (Kaidbey et al., 1979; Bruls et al., 1984). Fifty per cent of UVA radiation respectively is absorbed to the stratum corneum and epidermis, but the rest penetrates deeply into the dermis (Parrish, 1983; Bruls et al., 1984).

Radiometric units used in measuring the UV irradiation and its interactions with skin are energy, power, irradiance and exposure dose. Energy is the work or potential of irradiation and it is expressed in joules (J). Power is the rate at which irradiation is expended and is measured in watts (W= J/s). Irradiance is expressed in W/cm^2 and the exposure dose is obtained by multiplying irradiance with exposure time.

The biological effects of UV radiation

Erythema, skin reddening, is a result of increased blood flow in the superficial parts of the dermis. It is caused by the direct effect of UV radiation to the blood capillaries but also through chemical mediators (e.g., histamine, cytokines, prostaglandins) (Soter, 1993). The minimal erythemal dose (MED) is the unit used to determine the ability of UV radiation to induce erythema: it is the lowest UV dose needed to induce weak pink erythema on the skin. The effectiveness of radiation to induce erythema of different wavelengths is called the erythema action spectrum. Shorter wavelengths are the most erythematogenic. Thus both UVB and UVA radiation are capable of inducing erythema to the skin, but UVB radiation is about 1000 times more potent than UVA. UVB radiation is more efficient in inducing sunburn (McKinlay and Diffey, 1987). UVB mediated damage of keratinocytes results in the formation of sunburn cells (Schwarz et al., 1995). These cells have suffered from significant DNA damage and are eliminated through apoptosis. UVA radiation is much more potent in inducing immediate and persistent pigment darkening (Irwin, 1993; Wang, 2001).

Environmental factors affecting UV radiation

Ozone is formed by UV radiation and oxygen and it acts as earth's natural sunscreen. As a consequence of ozone depletion increased levels of UVB and even UVC reach on the earth's surface. Of special concern is the increased UVB radiation, since ozone depletion increases the most carcinogenic part of UV radiation to reach the earths surface. The ozone layer has decreased by 2% during the last 20 years (Armstrong and Kricker, 1995). Some studies estimate that a 1% decrease in ozone concentrations will result approximately in a 3,5% squamous cell carcinoma (SCC) increase and a 2,1% basal cell carcinoma (BCC) increase (Diffey, 1999). In Australia low ozone values has been detected possibly as a reflection of Antarctic ozone depletion (Diffey, 1999).

The latitudinal and altitudinal levels affect the amount of UV exposure. The incidence of SCC in white populations increases with proximity to the equator (Salari and Persaud, 2005).

UV radiation and cutaneous carcinogenesis

Chromophores and DNA damage

To begin a series of photochemical reactions and photobiological events possibly resulting in skin cancer, UV light must first be absorbed by a chromophore. Each chromophore has a characteristic UV radiation absorption spectrum. In skin, DNA and urocanic acid have been identified as such chromophores (Young et al., 1998; Hanson and Simon, 1998). Other endogenous choromophores include e.g., melanin, haemoglobins, porphyrins and tryptophan. Very recently, metabolic products of certain immunosuppressive drugs such as azatiophrine have been identified also to act as a chromophore (O'Donovan, 2005). DNA has an absorption peak around 260 nm in the UVC-region but most of it is absorbed in the UVB region (290–320 nm) and also some in the UVA region (Figure 2). The absorption of photons by DNA opens the double bond of pyrimidines. When this takes place in two adjacent pyrimidines, so-called fingerprint mutations occur in DNA (e.g. C-> T, CC -> TT). These mutations are constantly being repaired by nucleotide excision repair (NER) (Gougassian et al., 2000). This system repairs the damaged base by excision repair, which is followed by DNA repair synthesis and ligation. When this repair fails, the abovementioned mutations characteristic for UV photodamage remain permanent.

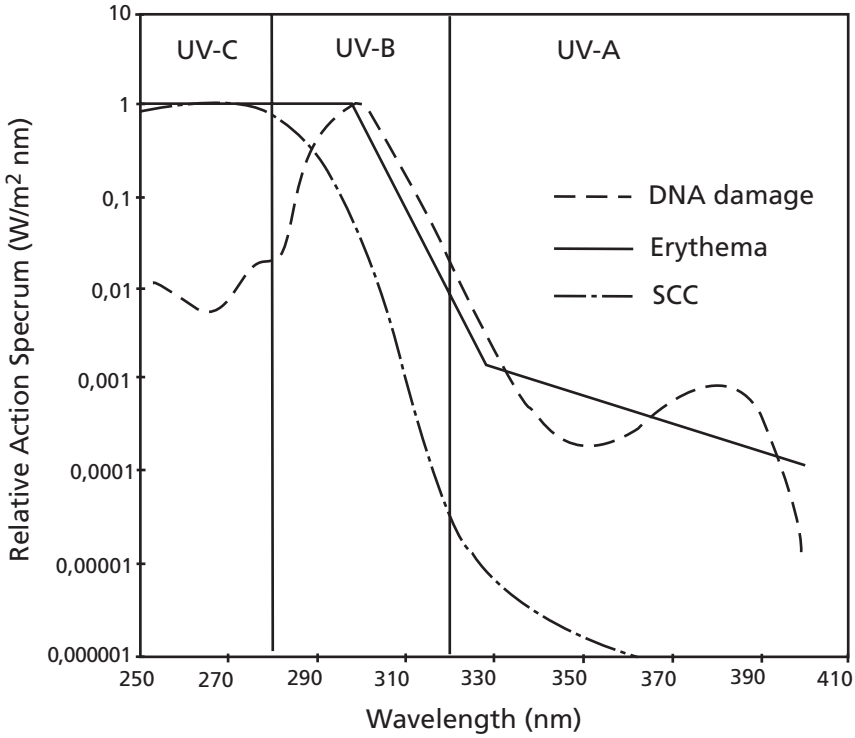


Figure 2 (adapted from the National Agency for Medicines)
The absorption spectrum of DNA damage, erythema and squamous cell carcinoma (SCC)

Mechanisms involved in carcinogenesis

Photocarcinogenesis is a multistep process involving initiation, promotion, progression and finally metastasis. UVB irradiation is shown to be a complete carcinogen (Black et al., 1997). In squamous cell carcinoma UVB initiates as well as promotes cancer and has an effect on the progression of cancer (Pinnell, 2003). The action spectrum of UV irradiation for the generation of squamous cell carcinoma occurs mainly in the UVB spectrum, but there is also activity in the UVA spectrum (320–400 nm): in albino mice model the peak was in UVA radiation (de Gruijl et al., 1993). The action spectrum of DNA damage, erythema and the generation of SCC are shown in Figure 2. In the fish model, the action spectrum for melanoma has been estimated to peak in the UVA region around 365 nm (Setlow et al., 1993). However, only UVB initiated melanoma in the mouse model (De Fabo et al., 2004). UVA radiation has been found to also induce signature mutations, like those in p53 gene, in human skin (Young et al., 1998; Agar et al., 2004), and UVA radiation is proposed to be important in tumor

promotion (de Gruijl, 2000). In cell cultures, the longer UVA wavelengths (340–400 nm) have been shown to induce apoptosis (Godar, 1999).

p53 is a protein whose major physiological role is to suppress the development of cancer. It regulates a number of genes which lead to cell cycle regulation and apoptosis (Lane, 1992). UVB fingerprint mutations can occur in p53 and they are believed to play a major role in the initiation of nonmelanoma skin cancer (Ziegler et al. 1993; Daya- Grosjean et al, 1995).

Initially, failure in repairing photoproducts results in a mutation in keratinocytes. If this occurs in one allele of the p53 gene, the cells fail to undergo apoptosis. If UV related photodamage in the genome is great enough to inactivate the remaining functional allele of p53, this can result in clonal expansion of keratinocytes and squamous cell carcinoma (Lane, 1992; Harris, 1993; Steele and Lane, 2005). Squamous cell carcinoma is thus believed to develop step by step as a result of cumulative excessive lifetime exposure to UV radiation (Kricker et al., 1994). Convincing evidence of the importance of UV radiation in causing DNA damage is given by the studies of xeroderma pigmentosum patients (Cleaver, 1968). In these patients there is a defect in repair of UV radiation induced pyrimidine dimers and the risk of developing cutanous malignancies is approximated to be 2000 times higher compared to the general population (Yarosh et al., 2001).

Reactive oxygen species (ROS) are composed of free radicals and reactive oxygen molecules (Pinnell, 2003). They are formed in the mitocondrial electron chain by the cyclo-oxygenase pathway and by some other cellular enzymes (Ames et al., 1993). Increased oxidative stress and environmental factors, like UV radiation, can cause DNA damage through formation of ROS (Cadet et al., 1997). It has been speculated that the cutaneous UVA effects are mainly from indirect damage by ROS (de Gruijl et al., 1994), but both UVB and UVA radiation are capable of eliciting such a premutagenic oxidative DNA base damage (Kvam and Tyrrel, 1997). However, it seems that UVA must always react with a chromophore (e.g. melanin or porphorin) to generate ROS (Wang et al, 2001).

UV radiation and immunosuppression

UV radiation is proven to be immunosuppressive in laboratory animals (Kripke, 1974). UV induced tumors were rejected upon inoculation in nonradiated syngeneic mice. Skin tumors induced by chronic treatment with UV light grew only when transferred to immunocompromized or UV irradiated mice (Kripke, 1974). In further investigations, it was noticed that UV radiation induced immunosuppression can be divided to local and systemic immunosuppression. These models have been studied in mice with low-dose and high-dose UV exposure settings (Beissert and Schwarz, 1999).

Local immunosuppression is induced with low dose UV irradiation. UV

exposure decreases the number of LCs in the skin. This leads to inability to sensitize mice to contact allergens. Later resensitization with the same allergen through unirradiated skin may again fail to reduce contact hypersensitivity. This tolerance is mediated through antigen specific T cells. In local immunosuppression, contact hypersensitivity reactions were not affected on nonirradiated skin (Beissert and Schwarz, 1999).

UV radiation localized to a limited skin area has been shown to inhibit the induction of the immune response in a distant skin area not exposed to UV radiation (Noonan et al., 1981). This phenomenon is called systemic immunosuppression. Also, this systemic immunosuppressive effect is transferred in T lymphocytes from one animal to another (Fisher and Kripke, 1982). Various cytokines released by UV exposed keratinocytes take part into this process. The most important seems to be IL-10 (Rivas and Ullrich, 1992) and others include TNF-alfa and TGF-beta (Schwartz et al., 1986). The strong induction of IL-10 by UV radiation suggests that UV exposure is capable of shifting cellular immune system responses towards a Th2- type reaction (Ullrich, 1995). Th1 cells help tumor rejection and suppression of the Th1 arm can enhance the carcinogenic properties of UV radiation.

LCs have the major antigen presenting role in the skin and they also present malignant neoantigens. UVB radiation decreases the number of these LCs in a dose-dependent manner (Koulu et al., 1985), and alters also their morphology by destroying the dendrites. UV radiation suppresses the expression of MCH class II surface molecules (Aberer et al., 1981). After high dose UV irradiation, the reduced number of LC's seems to be replaced by LC precursors from the blood (Merad et al., 2002). In animal models, UVA has also caused a significant reduction in the number of epidermal APCs (Bestak and Halliday, 1996). The reduction of LCs induced by PUVA is known to return back to normal within three weeks after stopping of PUVA treatment (Friedman et al., 1983). Thus, it is not surprising that PUVA therapy (topical or oral) can down-regulate hypersensitivity responses (Kripke et al., 1983; Aubin et al., 1991).

Urocanic acid is suggested to be the photoreceptor for UV induced immunosuppression besides DNA. Urocanic acid is postulated to have photoprotective mechanisms such as to protect the skin agains sunburn and to protect DNA in epidermal keratinocytes from actinic damage (Zenisek et al., 1955; Morrison, 1985). Irradiation with UVB isomerizes trans-urocanic acid to cis-urocanic acid. Cis-urocanic acid is known to suppress cell- mediated immunity (Aubin, 2003). To support the immunosuppressive effects of cis-urocanic acid, cis-urocanic acid injected into the skin destroys LCs.

Immunosuppressive treatments have a clear effect on cutaneous carsinogenesis. The risk of skin cancer is increased in patients treated with immunosuppressive agents. This is well documented in organ transplant patients. The role of ultraviolet radiation in the pathogenesis of skin can-

cers is important in this patient group. Skin tumors are typically located on sun-exposed areas like the lip, hands and scalp. The degree of sun exposure is highlighted in studies made in different countries: the frequency of skin cancer after organ transplantation is higher in Australia than in the Netherlands (Hartevelt et al., 1990; Sheil, 1992).

Skin cancer

Human skin cancers can be divided into two types based on the origin of the malignant cell: nonmelanoma skin cancer and malignant melanoma. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) originate from keratinocytes.

Basal cell carcinoma

Basal cell carcinoma (BCC) is the most common skin malignancy arising from undifferentiated basal cells normally capable of differentiation into structures such as sweat glands and hair (Miller, 1991). Histologically they are composed of uniform cells with darkly stained nuclei and they often form typical palisading structures (McKee, 2005). Basal cell carcinomas are most common on sun- exposed areas like the face, scalp, forehead and cheeks. There are three different subtypes of basal cell carcinoma: nodular, superficial and morpheaform (or sclerosing) basal cell carcinoma. Usually, basal cell carcinoma presents as an ulcerated or crusted centre with a distinct raised edge with a pearly appearance. Morpheaform basal cell carcinoma makes a challenge in clinical diagnosis.

Basal cells (keratinocytes) are more tolerant to UV radiation than squamous cells because of their stem cell type properties (Miller, 1991). It is believed that not only cumulative exposure to UV radiation but also intensive skin burning is a major risk factor for the development of basal cell carcinoma (Kricker et al., 1995).

Squamous cell carcinoma

Squamous cell carcinoma arises from differentiated epidermal keratinocytes and it develops step by step from its precursors actinic keratosis and Morbus Bowen (carcinoma in situ). In actinic keratosis (AK) the cells show abnormal epidermal growth and disordered keratinisation. AK may be reversible.

Nuclear atypia is seen in Morbus Bowen, but the changes are above the basement membrane zone. Squamous cell carcinoma arises at the point when atypical keratinocytes invade the dermis. The favourite sites for SCC are the dorsal aspects of the hands and forearms. The clinical appearance is usually a crusted scaly ulcer or more nodular tumour.

Epidemiological evidence of the role of UV radiation in the develop-

ment of squamous cell carcinoma is strong. The incidence of SCC is increased in sunny climates and is related to the skin type. In an Australian study the risk factors for SCC and BCC were compared in a case-controlled study. The risk of both cancers was found to be higher in persons born in Australia than in immigrants with Caucacian ancestors (Kricker et al., 1991). Fair skin type, as well as indicators of previous sun damage (e.g., actinic keratosis, facial teleangiectasia, solar elastosis), were risk factors of SCC and BCC. The incidence of SCC and BCC increases with the age. In a Welsh study, the incidence of SCC among patients aged over 75 years was 35 times higher than that of patients between 50 and 55 years and the figure for BCC was five times higher, respectively (Holme et al., 2000). Thus, the incidence of SCC rises more rapidly than that of BCC. However, in Finland the incidence of BCC has risen more rapidly (Cancer in Finland, 2003). Comparison between different types of skin cancer in different countries is difficult to make due to lack of proper registries. The incidence figures of SCC are comparable only in Scandinavian countries.

Malignant melanoma

Malignant melanoma (MM) is more uncommon than SCC and BCC, but its incidence has risen (Hall et al., 1999). Melanoma is divided into four subtypes: nodular, superficial spreading, lentigo maligna and acral melanoma. Clinically melanomas are dark pigmented, irregularly shaped asymmetrical lesions with colours of black, blue, red, white or brown. Compared to BCC and SCC, melanoma has a different age-distribution. One half of melanomas are found in patients under 55 years of age and one third occurs before the age of 45 (Diepgen and Mahler, 2002).

Cutaneous malignant melanoma arises from epidermal melanocytes. There is variable information, but 17–51% of melanomas arise from pre-existing nevus cells (Skender- Kalnenas et al., 1995). Some families have an increased incidence of melanoma. Most of these patients have dysplastic nevus syndrome. Previous studies have located the gene of this syndrome to chromosome 1 (Bale et al., 1989). In Dutch studies , these patients have been shown to share the same deletion of the p16 gene (van der Velden et al., 2001). In one study patients with 50–100 nevi had a 3.2-fold increased risk and patients over 100 nevi 7.7 times risk for the development of melanoma compared to persons with 0–4 nevi (Bataille et al., 1996). The same study found that patients with four or more atypical nevi had a relative risk for the development of melanoma of 14.3. Other background risk factors related to melanoma are a history of previous melanoma, a positive family history of melanoma and giant congenital pigmented hairy nevus (Roberts et al., 2002). Exposure to UV radiation is accepted to be a major etiological factor, but the role of UV light is complex. In the etiology of melanoma the degree of sunburn seems to be more important than sun exposure per se, since melanoma is thought to be associated with intense

intermitted sun exposure (Holdman et al., 1986; Gallagher et al., 1990). Although some studies claim that the risk is especially increased with a history of five or more sunburn events (Weinstock, 1996), the explanatory mechanism is unclear.

Unlike SCC, most melanomas occur in light-skinned people on parts of the body exposed to the sun intermittently, such as legs in women (47% of all melanoma cases in women) and trunk of men (36% of all melanoma cases in men). Some studies have also shown an increased risk of melanoma in indoor workers compared to outdoor workers (Beral and Robinson, 1981; Vagero et al., 1986). Melanoma risk also increases in fair-skinned people with blond or red hair and a tendency to get freckles easily. The melanocortin 1 receptor (MC1R) is essential in the regulation of variation in normal human pigmentation. MC1R is expressed on melanocytes and melanoma cells. A strong relationship between melanoma risk and the MC1R genotype variants has been shown (Healy et al., 2000; Palmer et al., 2000). One variant of this MC1R genotype appeared to be able to cause fair skin and increased melanoma risk (Healy et al., 2000). The exact mechanism how the risk of melanoma is increased is not known. It has been shown that the same MC1R gene variants have also been linked with an increased risk of SCC and BCC (Palmer et al., 2000; Bastiaens et al., 2001). The world´s highest melanoma risk in detected in Australia, which may be explained by the latitude of the country and large population of Celtic-origin (Mack and Floderus, 1991; MacLennan et al., 1992). The exact spectrum of radiation responsible for melanoma is not known.

In melanoma, the p53 mutations are less prominent (1–9%) than in nonmelanoma skin cancers (41%) (Hartman et al., 1996; Steele and Lane, 2005). Also in melanoma, the observed p53 mutations are found at dipyrimide sites. In melanoma metastases these mutations are more frequent in skin metastases than those of internal organs (Zerp et al., 1999) showing evidence of UV radiation induced mutagenesis of p53.

Photochemotherapy

The different wavelengths of various phototherapy treatments are shown on Figure 3.

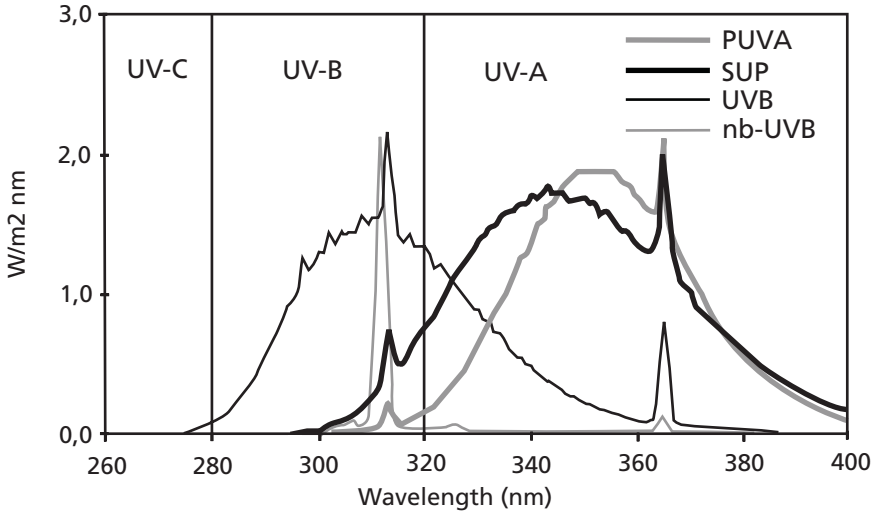
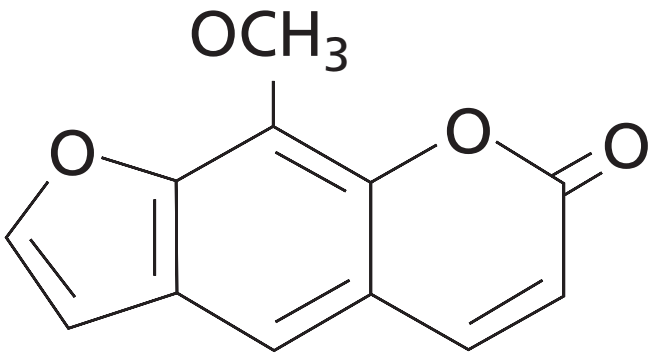


Figure 3 (adapted from the National Agency for Medicines)
The spectral distribution of different phototherapy light sources
(nb-UVB=narrowband UVB)

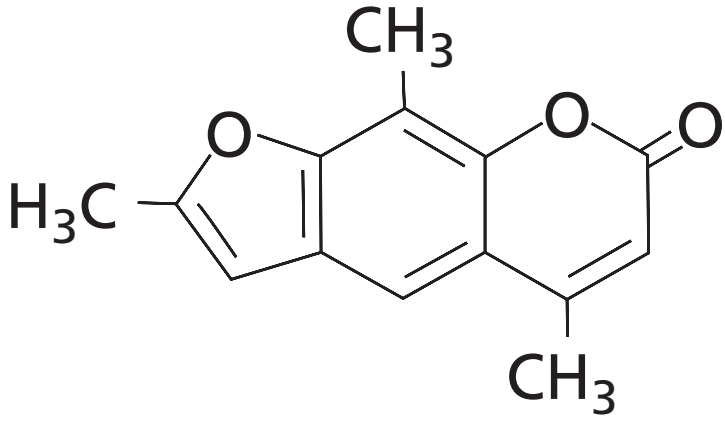
PUVA

Psoralen photochemotherapy (PUVA) is a combination of the drug psoralen and UVA radiation. Psoralens are furocoumarins originally derived from plants. In clinical practice, the most often used are 8-methoxypsoralen (8-MOP) and trimethylpsoralen (TMP) (Figure 4). Psoralens are biologically reactive only if activated with UVA radiation. First, psoralens intercalate in the DNA double strand between adjacent base pairs, then after UVA irradiation psoralens form pyrimidine-psoralen monoadducts and finally, after more irradiation a pyrimidine-psoralen-pyrimidine complex in the DNA duplex is formed. The final result is a covalent interstrand psoralen-DNA crosslink, which inhibits DNA replication and causes the cell cycle arrest (Lauharanta, 1997).

Figure 4
Common psoralens in clinical use



8-methoxypsoralen



trimethylpsoralen

Psoralens can be administered orally or topically. Oral administration has systemic effects such as nausea and ocular side-effects. Therefore, oral PUVA treatment is also called systemic PUVA treatment. Psoralen used in this regimen is 8-MOP. Bath PUVA was developed in the 1970s because it lacks the disadvantages of systemic PUVA. Trioxalen bath +UVA was introduced in Sweden (Fischer and Alsins, 1976). TMP and 8-MOP are both used in bath PUVA. Depending on the route, psoralens are administrated

15 minutes to 2 hours before the irradiation. For psoriasis, the routine oral administration is 0.4–0.8 mg/kg of 8-MOP. PUVA therapy should be given at least 72 hours apart to avoid cumulative delayed cutaneous phototoxicity. Some of the most common indications for PUVA treatment are listed in Table 1.

Table 1

Indications for PUVA therapy
(Atopic dermatitis)
Chronic hand dermatitis
Graft-versus-host-disease
Granuloma annulare
Lichen planus
Lymphomatoid papulosis
Mycosis fungoides
Palmoplantar pustulosis
Prurigo nodularis
Psoriasis
Urticaria pigmentosa

The capability of PUVA to induce apoptosis in lymphocytes is utilized in CTCL and lymphocyte associated skin diseases (Johnson et al., 1996). PUVA has also been shown to have an effect on various cytokines and cytokine secretion, which in turn normalizes the excelerated keratinocyte turnover rate in psoriasis (Averbeck, 1989).

Carcinogenic effects of systemic PUVA therapy

Since the beginning of the use of systemic PUVA therapy there has been concern of the carcinogenic risk of this treatment. 8- methoxypsoralen + UVA is mutagenic in bacteria (Kirkland et al., 1983). PUVA therapy has numerous immunosuppressive effects both in vitro and in vivo: it reduces the number of APCs (Friedmann, 1981; Ree, 1982), the amount of mast cells (Toyota et al., 1990), and the number of helper T cells in psorisis patients (Moscicki et al., 1982). It also depresses natural killer cell activity and suppresses delayed hypersensitivity reactions (Vella Briffa et al., 1981; Viander et al., 1984).

PUVA therapy and UVB generate different types of DNA damage resulting in specific types of p53 mutations (Nataraj et al., 1996). These mutations have been looked for in squamous cell carcinoma of PUVA treated

psoriasis patients. Nataraj et al. found that a significant number (64%) of p53 mutations were of the C-T or CC-TT types, which are usually related to UVB irradiation, whereas PUVA type mutations are usually T-A (Nataraj AJ et al., 1997). Frequent UVB signature C->T transitions were also found in the p53 tumor suppressor gene (Peritz and Gasparro, 1999). Stern et al., found 46% of p53 mutations in PUVA treated patients to be of only UVB type, 5% of only PUVA type and rest (49%) of both types (Stern et al., 2002). However, in tumors in patients with high-dose exposure to PUVA, UVB type mutations were less frequent than the PUVA type. One mechanism, by which PUVA treatment can induce fingerprint mutations in pyrimidine bases, is through generation of the ROS (Reid and Loeb, 1993; Filipe et al., 1997).

Systemic PUVA was introduced for the treatment of psoriasis in the mid 1970´s (Parrish et al., 1974). Almost all epidemiological data about the carcinogenic risk of systemic PUVA is obtained from psoriasis patients. The first report of increased SCC risk was an American PUVA follow up study in 1979 (Stern et al., 1979). In this study, an increased risk of nonmelanoma skin cancer was found only in association with a previous history of NMSC, ionizing radiation and fair skin (type I or II). The subsequent reports from this study have demonstrated a dose-dependent relationship between systemic PUVA exposure and SCC unassociated with other risk factors (Stern et al., 1984; Stern et al., 1988; Stern and Laird, 1994). Since then, many prospective or retrospective cohort studies have been performed. In the 1980's most non-American studies found no increased risk in skin cancer (Lindskov, 1983; Cox et al., 1987;), and in some studies skin cancers were associated with systemic PUVA treatment only with previous exposure to other possible carcinogenic treatments such as arsenic, UVB and methotrexate (Maier et al., 1986; Henseler et al., 1987). Clear co-carcinogenic risk factors for skin cancer are ionizing radiation, previous skin cancer and previous arsenic treatment (Höningmann et al., 1980; Reshad et al., 1984; Stern et al., 1984; Stern et al, 1988).

One large Swedish study of 4799 patients treated with PUVA showed a dose-dependent increase in the risk of SCC. These patients were followed-up for an average of 7 years. The majority of these patients (77%) had received oral 8-MOP. Male patients who had received more than 200 PUVA treatments had over 30 times the risk of SCC compared to the general population (Lindelöf et al., 1991). In a study of Dutch psoriasis patients treated with systemic PUVA, the incidence of squamous cell carcinoma was increased. The average follow up time was 8.6 years, and a 12-fold risk compared to general population was found (Bruynzeel et al., 1991). This study used a quite aggressive treatment schedule resembling more the in American studies. The average total dose was 824 J/cm^2 and all squamous cell carcinomas occurred at doses more than 1000 J.

Systemic PUVA treatment induces pigmented macular lesions, called

PUVA lentigines (Rhodes et al., 1983b). These lesions are histologically composed of large, sometimes atypical melanocytes (Rhodes et al., 1983a). This finding had aroused concern about a possible melanoma risk related to PUVA therapy. Until the year 1997, there were some case reports of melanomas appearing during PUVA therapy. In these individuals, the number of preceding PUVA treatments varied from 40 to 194 (Kemmet et al., 1984; Gupta et al., 1988; Bergner and Przybilla, 1992). In 1998 Wolf et al., reported three melanoma cases in PUVA treated patients. The number of exposures varied between 31 to 501 and none of them had received UVB, methotrexate or x-ray treatment previously (Wolf et al., 1998).

The carcinogenic risk of bath PUVA has been studied extensively in Scandinavia. Trioxalen bath PUVA did not increase the risk of SCC in psoriasis patients (Hannuksela et al., 1996; Hannuksela-Svahn et al., 1999b). The overall cancer risk did not increase in psoriasis patients treated with 8-MOP bath+UVA. In this study, the risk of SCC was not increased (Hannuksela-Svahn et al., 1999a).

Also, in mycosis fungoides patients who had repeatedly received PUVA therapy, a couple of malignant melanoma cases were reported. Reseghetti et al. reported of a patient with a history of 134 times of PUVA treatment (Reseghetti et al., 1994). The diagnosis of melanoma was made 7 months after the start of the therapy. Although the follow-up time in this case was short, both mycosis fungoides (lymphoma) and PUVA therapy could have lowered the patient´s immunity but the authors speculate the finding be due to a change. In a series of 164 CTCL patients, all treated with total skin electron beam therapy, six developed melanoma and three of them had received additional PUVA therapy (Licata et al., 1995).Twenty-four patients developed 34 squamous cell carcinomas and over 37 basal cell carcinomas. In these patients, PUVA therapy was significantly associated with the development of both squamous cell carcinoma and basal cell carcinoma, but not to melanoma.

Other phototherapy regimens

Broad-band UVB, narrow-band UVB

The spectrum of broad-band UVB light sources is seen in Figure 3. The maximal therapeutic effect for psoriasis is between 310–315 nm, whilst the maximum effect of burning is achieved at 290–300 nm (Young, 1995). Narrow-band UVB (311 nm emission) was introduced in the late 1980s as an alternative for conventional UVB therapy and PUVA therapy in clinical practice. It was found to be superior to broadband phototherapy in atopic dermatitis and psoriasis (van Weelden et al., 1988; Grundmann-Kollman et al., 1999). The indications for UVB phototherapy (narrow- and broadband) are shown in Table 2. Narrow-band UVB treatment is as efficient as

systemic PUVA in the treatment of psoriasis (Dawe et al., 2003; Snellman et al., 2004).

Table 2

Indications to broadband and narrow-band UVB
Atopic dermatitis
Generalized dermatitis
Lichen planus
Parapsoriasis
Prurigo nodularis
Pruritus
Psoriasis

SUP

In Finland, sources emitting UVA and UVB light are called SUP devices. The spectrum of SUP is seen in Figure 3. In other European countries the equivalent for SUP is helarine photon therapy. The emission spectrum of SUP devices resembles the spectrum of the sun. There are no reports of the SUP-treatment carcinogenity. The most common indications of SUP are presented in Table 3.

Table 3

Indications for SUP
Atopic dermatitis
Generalized eczema
Lichen planus
Pruritus
Psoriasis (children)

Cyclosporine

Cyclosporine is a cyclic endecapeptide of 11 amino acid residues, which was originally isolated from a soil fungus (Tolypocladium inflatum Gams). The immunomodulatory property of cyclosporine was introduced in 1976 (Borel et al., 1994). The drug was first used in organ transplant patients (du Toit et al., 1985). Also, it has been widely used in various skin diseases e.g.

in psoriasis, different eczemas including atopic dermatitis and pustulosis palmoplantaris (Mueller and Herrmann, 1979, Ellis et al., 1991, Reitamo et al., 1993).

Within the cell, cyclosporine forms a complex with cyclophilin, which binds to and inhibits the activity of the intracellular enzyme calcineurin phosphatase. The inactivation of calcineurin inhibits the nuclear translocation of transcription factors for the transcription of interleukins (Krönke et al., 1984), the most important of which is IL-2. IL- 2 is the main activation factor for T cells. Cyclosporine has also an inhibitory effect on histamine release from mast cells resulting in anti-inflammatory effects (Narita et al., 1998). Cyclosporine targets T cell proliferation and activation and these properties are utilized in various inflammatory skin diseases where the role of T cells is crucial.

Cyclosporine is administered orally and the recommended maximum dosage in skin diseases is 5mg/kg. The median half-life is 6.4–8.6 hours, which gives the possibility of twice a day administration (Ptachcinski et al., 1986). Nephrotoxicity, increased blood pressure and immunosuppression-induced malignancies are the main side effects of cyclosporine. The renal changes are clearly dose dependent (Ellis et al., 1991) but the mechanisms for cyclosporine-induced hypertension is not understood. In long-term treatment almost half of the patients can develop hypertension (Fry et al., 1988). Also, cyclosporine induced hypertension is dose-related.

Cyclosporine and cancer

Basically all drugs that effect the immune system carry a possible risk of increased cancer. In the case of cyclosporine, this can be explained by two different mechanisms. In in vitro models, cyclosporine has been shown to have direct carcinogenic activity (Hojo et al., 1999). Cyclosporine induced non-invasive adenocarcinoma cells invasive, which was speculated to be a result of TGF-beta influence. These cancer cells also developed invasive characteristics. On the other hand, in animal models chronic immunosuppression resulting from medication like cyclosporine is thought to interact with the expression of antigen-induced signals that are needed for the generation of T cell dependent immune responses (Servilla et al., 1987). In mice, cyclosporine shortens the time needed for tumor induction by UV irradiation (Kelly et al., 1987). One recent in vitro study compared the effects of four immunosuppressive drugs on the growth of various tumor cell lines (Casadio et al., 2005). They found that all other immunosuppressive agents, except cyclosporine, inhibited the growth of these cell lines.

In organ transplant patients, immunosuppressive therapy is always combination therapy. Therefore the role of individual drugs is difficult to judge, and the carcinogenic effect of cyclosporine is largely based on data from organ transplant patients. The role of cyclosporine is controversial. Some studies have shown that cyclosporine-based immunosuppression increases

the risk of squamous cell carcinoma more than combination treatments (azathioprine and prednisone) (Glover et al., 1997; Marcen et al., 2003). In another study, patients with cyclosporine and prednisone showed a higher risk of squamous cell carcinoma than patients with azathioprine and prednisolone, but a lower risk when compared to patients taking all three drugs simultaneously (Jensen et al., 1999). One study showed a dose-related link between cancers and cyclosporine. In this study in renal transplant recipients the frequency of skin cancer was significantly higher in a high-dose regimen than in a low-dose regimen. The same effect was detected with noncutaneous cancers, but the difference was not significant (Dantal et al., 1998). In organ transplant patients, the most common skin cancers are squamous cell carcinoma and basal cell carcinoma, which cover over 90 per cent of all skin cancers in this group (Bouwes-Bavink et al., 1996; Webb et al., 1997; Jensen et al., 1999). The other cancers include lymphomas, Kaposi's sarcoma and cancer of the anogenital region (Stockfleth et al., 2001; Euvrard et al., 2003). In organ transplant patients, the risk of cancer is dose-dependent being highest in multiorgan and heart transplant patients (Euvrard et al., 2003). The risk of getting nonmelanoma skin cancers increases rapidly with time, and after 20 years of transplantation, almost half of Caucasian patients in most western countries and 70–80 per cent of Caucasian Australian patients develop at least one nonmelanoma skin cancer (Webb et al., 1997; Jensen et al., 1999; Ramsay et al, 2002).

The carcinogenic risk of cyclosporine in other patients than organ transplant patients has been quite sparsely reported until recently. In a US study with psoriasis patients, cyclosporine use was found to be a risk factor for the development of squamous cell carcinoma. In this nested cohort crossover study, any use of cyclosporine increased the risk of squamous cell carcinoma as much as 200 PUVA treatments (Marcil and Stern, 2001). In another cohort study, the use of cyclosporine was associated with a 6-fold higher incidence of skin malignancies (Paul et al., 2003). When one hundred atopic patients were treated with cyclosporine for 48 weeks, only one basal cell carcinoma was detected (Berth-Jones et al., 1997). Cohort studies without risk analyses have reported two lymphoma cases in psoriasis patients receiving cyclosporine (Krupp and Monka, 1990), but in another study no lymphoma cases were found (Christophers et al., 1992). In addition, some anecdotal reports of lymphomas occurring shortly after discontinuation of cyclosporine treatment have been reported (Koo et al., 1992; Zijlmans et al., 1992; Masouye et al., 1993). Lymphomas have also been detected during cyclosporine treatment in psoriasis patients and autoimmune patients (Cockburn et al., 1989; Cliff et al., 1999).

Methotrexate

Methotrexate is a folic acid antagonist, which was first introduced in the field of dermatology in the late 1950s (Edmundson and Guy, 1958). Its most important mode of action is the inhibition of dihydrofolate reductase enzyme, which blocks the synthesis of thymidine monophosphate. This further results in the inhibition of DNA and RNA synthesis. Methotrexate thus has an antiproliferative effect. The most feared side effects are bone marrow toxicity including pancytopenia, toxicity to gut and to mucous membranes. Others include alopecia, hepatic toxicity, renal failure, pneumonitis and osteoporosis (Souhami and Tobias, 2005). In dermatology, methotrexate is used once a week administration and the dosage is usually 7.5–15 mg but can be elevated up to 30 mg per week. The indications for use of methotrexate are e.g. psoriasis, mycosis fungoides, sarcoidosis, atopic dermatitis, pityriasis rubra pilaris, pityriasis lichenoides, dermatomyositis and SLE (Braun-Falco, 2000; Dadlani and Orlow, 2005).

Methotrexate and cancer

There are no reports on the carcinogenity of methotrexate itself. In patients with rheumatoid arthritis, methotrexate combined with TNF-alpha inhibitor treatment, the hazard ratio of nonmelanoma skin cancer was 1.97, whereas methotrexate treatment alone did not increase the risk (Chakravarty et al., 2005). In a small American cohort (134 patients), the transformation of mycosis fungoides to large cell lymphoma was studied. In patients treated with methotrexate, the incidence of transformation was significantly higher (14.3%) than in patients not treated with methotrexate (1.8%) (Abd-el-Baki et al., 2002). Both these studies suggest that methotrexate may act as a promoter in carcinogenesis. In psoriasis patients, exposure to methotrexate significantly increased the risk of nonmelanoma skin cancer (RR 2.7; 95% CI=1.1–7.3), but the effect of methotrexate was not separately analyzed (Paul et al., 2003). In the PUVA follow up study, high level exposure to methotrexate versus no exposure increased independently the risk of squamous cell carcinoma (RR 2.1; 95% CI=1.4–2.8) (Stern and Laird, 1994). Similar results were found by Lindelöf and Sigurgeirsson, where in psoriasis patients treated with PUVA, previous methotrexate therapy increased the risk of squamous cell carcinoma (RR 3.5, 95% CI= 1,2–9.9) (Lindelöf and Sigurgeirsson, 1993). In a Finnish case controlled study in psoriasis patients, methotrexate was not found to increase the risk of squamous cell carcinoma (Hannuksela-Svahn et al., 2000)

Aims of the study

The main purpose of the present study was to investigate the cancer risk related to two immunosuppressive treatments, systemic PUVA treatment and cyclosporine, widely used in inflammatory skin diseases. The specific aims were:

1. to investigate the possible association between systemic PUVA treatment and melanoma

2. to investigate the possible association between systemic PUVA treatment and noncutaneous cancer

3. to assess the persistence of skin cancer risk among patients treated with systemic PUVA, including also patients without substantial exposure to other carcinogens or patients who have discontinued PUVA treatment

4. to assess the risk of secondary cancer in cutaneous T cell lymphoma patients and to investigate their association with previous photochemotherapy

5. to investigate the risk of cancer related to short term cyclosporine treatment in patients with severe chronic inflammatory skin diseases

Patients and methods

Patients and data collection

Psoriasis patients

Studies I–III are based on a prospective follow-up study conducted in sixteen university centers in the USA. These original centers include Stanford University School of Medicine, University of California Medical School, Baylor College of Medicine, Washington Hospital Center, University of Michigan Medical School, Columbia University College of Physicians and Surgeons, Mayo Graduate School of Medicine, Mt Sinai Medical Center, Temple University School of Medicine, Beth Israel Hospital, Dartmouth Medical School, Yale University School of Medicine, Duke University Medical Center, University of Pennsylvania Hospitals, Massachusetts General Hospital and Harvard Medical School (the cordinating center). During the period from January 1, 1975, through October 1, 1976 altogether 1380 psoriasis patients were enrolled to this study. The study closed at the end of June, 2005. At this time, there were 526 patients in the study. The initial aim of the study was to assess the long-term risks and benefits of PUVA therapy. On average, every 15 months after enrolment, all study patients had interviews and dermatologic examinations regardless of whether or not they continued to use PUVA. Each patient´s exposure to alternative carsinogens (UVB radiation, tar, methotrexate and ionizing radiation) used for their psoriasis treatment were documented before and after initiation of PUVA treatment. The patients had received a standard PUVA protocol consisting of 0.4–0.6 mg/kg oral psoralen and followed 1.5–2 hours later by UVA treatment. The starting dose of UVA was dependent of each patients photosensitivity. Typically, patients reached a maximum UVA dose of 8–15 J/cm2. The treatment was slowly tapered off when their psoriasis cleared. The diagnosis of cutaneous tumors were verified by a pathologist or dermatologist.

Cutaneous T cell lymphoma patients

Study IV was a retrospective study consisting of 319 patients with a histologically confirmed diagnosis of CTCL. The patients were collected from the Finnish Cancer Registry between the years 1953 and 1995. For all subsequent 12 lung cancer cases detected among these CTCL patients, the patient charts were examined to find out their previous treatments.

Skin disease patients

For study V, we analyzed a cohort of 272 patients with a diagnosis of psoriasis, atopic dermatitis, palmoplantar pustulosis or chronic hand eczema during years 1987–1998. All patients were from the Skin and Allergy Hospital, Helsinki. The patients had received at least one month of cyclosporine therapy. The initial criteria for the use of cyclosporine therapy were as follows: in psoriasis and atopic dermatitis moderate or severe disease, in palmoplantar pustulosis at least 20 fresh pustules in palms or soles and in chronic hand eczema therapy resistant disease (Rajka and Langeland, 1983; Reitamo et al., 1993; Granlund et al., 1995; Granlund et al., 1996). From these patients, information regarding cyclosporine duration, dosage of cyclosporine, phototherapy (PUVA, UVB, SUP), methotrexate and dosage of methotrexate was collected from the patient charts.

The mean age and sex distribution of all patients in these studies are shown in Table 4.

Table 4 Age and sex distribution of the patients in each study

Study number (number of patients)	Mean age (years)	Sex distribution
I–III (1380)	44*	65% males
IV (319)	65**	57% males
V (272)	39	43% males

* at the time of enrollment, ** at the time of diagnosis (CTCL)
CTCL=cutaneous T cell lymphoma

Finnish Cancer Registry

The population-based nationwide Finnish Cancer Registry was established in 1952. It is supervised by the National Research and Development centre for Welfare and Health, and run by the Cancer Society of Finland. It is obligatory for all physicians, hospitals, health care centers, pathological and haematological laboratories to report all cancer cases that come to their attention. In addition, the information from all death certificates in which a cancer diagnosis is mentioned comes into the Finnish Cancer Registry. All cancers are registered according their primary site and ICD 1955 codes. The coverage is very high: nearly ninety-nine per cent of cancer cases are included (Teppo et al., 1994).

Statistical methods

Study I

The designation of this study was based on the observation that after 15 years of the first PUVA treatment the incidence of melanoma started to increase or the patients had to have 280 PUVA treatments. Over 250 PUVA treatments were therefore determined as a high PUVA dose and under 250 treatments as a low PUVA dose. Patients were categorised according to their cumulative PUVA exposures to previously mentioned groups. The number of melanomas were calculated based on published data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER, 1995) in each of these four categories (>250 vs. <250 and >15vs. <15 years).

For statistical analyses we used a Poisson regression model and the results were presented as rate ratios and 95 per cent confidence intervals (Gahlinger and Abrahamson, 1993). We used this model to determine if the level of PUVA exposure and the time since the first treatment had any effect on the risk of melanoma development (STATA reference manual, 1997).

We used a Poisson regression model to factor sex, age and the increase in the incidence of melanoma into the calculations of the number of melanomas expected in each group. As independent predictors, we tested the number of PUVA treatments and time from the first treatment.

Study II

The number of expected noncutaneous cancers was calculated on the basis of age-specific data obtained from the SEER. We used age- and sex-specific incidence rates for white people for each year during years 1975–1992. To calculate the expected number of tumors for 1993 to 1996, the incidence rates of 1992 were used. The incidence rate ratios were calculated on the basis of the number of observed and expected cancers and to calculate 95 percent confidence intervals we used the Poisson distribution.

Study III

The risk factors for the development of SCC or BCC were compared for two 10 year periods: before 1985 and after 1985. The cohort was divided into four categories according to the number of PUVA treatments before beginning of 1986: under 100, 100–159, 160–336, over 337. For multivariate analysis, the exposure of different potential cutaneous carcinogens were classified as follows: UVB therapy (high dose >300 treatments), methotrexate (high dose > 208 weeks), topical tar (high dose >45 months). For all the patients that had not developed SCC or BCC by the beginning of January first, 1986, the expected number of tumors were calculated based on age-, sex-, and geographic area specific rates. For SCC and BCC, the head or neck were calculated separately. The expected SCC's or BCC's were

calculated in each PUVA category as described above. The relative risk of both cancers was compared to that expected on the basis of population incidence rates. After that, site specific expected numbers were calculated assuming that in the general population 65% of squamous and basal cell carcinomas occurred on the head and neck and 35% developed on other skin sites (Giles et al., 1988; Gallagher et al., 1990; Magnus, 1991).

To analyse the association of various types of exposure and the risk of the development of SCC or BCC, we used Poisson regression model. The results were presented as rate ratios and 95 per cent confidence intervals. All tests used were two sided.

Studies IV and V

The files obtained from Finnish Cancer Registry and based on personal identification numbers, were linked to cohorts (studies IV, V) to obtain the follow-up for cancer. The follow-up period for subsequent cancers started from the first month following the diagnosis of CTCL (IV) and from the date of starting cyclosporine treatment (V) and ended at the date of death, emigration, December 31, 1995 (IV) or December 31, 2003 (V), whichever came first. The numbers of observed cancer cases and person years at risk were calculated for calendar periods by gender and five-year age groups. To obtain the expected numbers of cancer, age-, sex-, and periodic-specific Finnish incidence rates were applied to the appropriate person-years under observation (studies IV, V).

Standardized incidence ratios (SIR) were defined as the ratio of observed to expected numbers of cases. Assuming a Poisson distribution, we calculated 95 percent confidence intervals (studies IV, V). Cox regression model was used to evaluate the influence of different covariates to the development of subsequent cancer (V). For statistical analyses, we used SPSS for Windows version 12.0 (study V).

Results

Risk of malignant melanoma in psoriasis patients treated with systemic PUVA therapy (study I)

The risk of malignant melanoma in 1380 psoriasis patients treated with oral (8-MOP) PUVA therapy was evaluated over the period from 1975–1976 to 1996. The median follow-up time from first treatment to the most recent follow-up interview was 19 years. We detected 11 melanomas in nine patients during the follow-up time. One patient developed three primary melanomas. The detailed information is shown in Table 5.

Table 5 Patients with malignant melanoma in the PUVA follow-up study 1975-1996

Patient no	Tumor no	Skin type	Sex	Age at enrollment	No of PUVA treatments	Time from first treatment to tumor, years	Tumor location
1	1	III	F	65	55	2	foot
2	1	III	M	47	284	7	upper left calf
	2				284	17	ankle
	3				284	17	under thumbnail
3	1	II	M	41	46	10	upper back
4	1	III	M	68	285	13	upper back
5	1	III	M	60	138	16	upper abdomen
6	1	III	F	29	62	18	shoulder
7	1	III	M	51	470	20	forehead
8	1	II	M	54	52	20	back
9	1	II	M	40	490	20	back

During the first 15 years, the incidence of melanoma observed in the PUVA cohort was similar to that expected from the general population. Beginning 15 years after the first PUVA treatment, the incidence of melanoma in the PUVA cohort elevated significantly and the highest increase in the risk of melanoma was observed in patients who had received 250 treatments or more during the years 1991 to 1996.

In multivariate analysis, the number of PUVA treatments and time from the first treatment gave the highest increase in the incidence of melanoma. The number of PUVA treatments and time from the first treatment had a significant association with the risk of melanoma (incidence rate ratio 4.1, 95% CI=1.3–13.4 and 4.7, 95% CI=1.4–16.1, respectively). In particular, the increase in melanoma risk with the passage of time was striking. During the study, the rate increased from 19 per 100 000 person years to 32 per 100 000 person years (the last figures for years 1991–1996).

Risk of noncutaneous malignant tumors in psoriasis patients treated with systemic PUVA therapy (study II)

During the follow up time (1975 or 1976 to 1996), 195 noncutaneous cancers developed in a cohort of 1380 patients. The overall risk of noncutanous cancer had not increased (RR=1.08, 95% CI=0.93–1.24). For the whole period, the risk of thyroid cancer, breast cancer and central nervous system neoplasms was significantly increased. The site specific RR with 95% CI are shown in Table 6. We examined the risk of cancer also by 10-year periods (1975–1986 and 1987–1996). The risk of breast cancer was elevated in both periods. For the central nervous system, the risk was not elevated for the latter period, whereas for thyroid cancer, the risk was significantly increased only during the latter ten year period (RR=5.0, 95% CI=1.03–14.61). We could not detect any association between higher levels of PUVA (over 300 treatments) and the risk of the aforementioned cancers.

Table 6 Observed and expected number of noncutaneous cancer with RR and 95% CI in PUVA patients from 1975 to 1996 in patients in the PUVA follow-up study

Site of cancer	Observed (no.)	Expected (no.)	RR	95% CI
All sites	195	181.3	1.08	0.93–1.24
GI tract	45	37.4	1.20	0.88–1.61
Resp. tract	37	35.4	1.05	0.74–1.44
Breast	27	14.9	1.81	1.19–2.64
Female genitals	6	7.2	0.83	0.31–1.81
Male genitals*	24	35.7	0.67	0.43–1.00
Urinary tract	18	15.4	1.17	0.69–1.85
CNS	7	2.5	2.80	1.13–5.77
Thyroid	5	1.4	3.57	1.16–8.34
Lymphoma	6	6.8	0.88	0.32–1.92
Leukemia	6	4.6	1.30	0.48–2.84
Others	14			

* excludes squamous cell carcinoma of penis and scrotum

Persistent risk of nonmelanoma skin cancer in psoriasis patients treated with systemic PUVA therapy (study III)

This study evaluated the association of systemic PUVA treatments to the development of SCC and BCC in patients with psoriasis, who had discontinued PUVA therapy long ago or were not substantially exposed to other carcinogens previously. The relative risk of SCC and BCC was elevated at every PUVA dose level. The risk of SCC was elevated more than that of BCC. The incidence of both squamous cell carcinoma and basal cell carcinoma was more than three times higher after 1986 compared to that before 1986. The total numbers for SCC was 375 versus 1047 and 221 versus 821 for BCC respectively in those mentioned time intervals. Among patients who had at least 337 PUVA treatments, the risk of SCC during the last decade was over 100-fold compared to the normal population (RR=104, 95% CI=88.3–121.9). The higher risk of occurrence of tumours on anatomic sites other than head and neck suggested that PUVA was carcinogenic. After year 1985 the risk of SCC increased fivefold on the head and neck and 21-fold on the other parts of the body compared to that expected in the general population. In univariate analysis the role of PUVA, UVB, tar, methotrexate and ionising radiation on the development of SCC was as-

sessed. Other exposures, except exposure to PUVA, did not have an impact to the risk of SCC. Among patients who did not develop SCC during the first decade after the first PUVA treatment, the level of exposure to PUVA was the most important risk factor for the development of SCC (RR=8.6, 95% CI=4.9–15.2).

For BCC, the risk was substantially increased only in those patients who were exposed to high dose levels of PUVA (over 337 treatments). They had a threefold increase in risk compared to those patients exposed to less than 100 treatments.

Risk of secondary cancers in patients with CTCL (study IV)

During the follow-up time (years 1953–1995), 319 patients with CTCL developed 36 subsequent primary cancers whereas the expected number in the normal population was 26 (SIR=1.4, 95% CI=1.0–1.9) (Table 7). The overall risk of lung cancer and lymphomas (Hodgkin's and non-Hodgkin's lymphoma combined) was increased (SIR=2.7, 95% CI=1.4–4.8 and SIR=7.0, 95% CI=1.9–18 respectively). Half of the histologic subtypes of lung cancer represented small- cell lung cancer. PUVA therapy did not appear have an influence on the cancers mentioned above because these cancers were detected in a range of 1 month to 2 years after the start of PUVA treatment. Also, some cancers were detected before PUVA was introduced as a clinical treatment. In nonmelanoma skin cancer, the SIR was 3.5 (95% CI=0.7–10). This finding was not significant. During the observation period, we also found a slight increase in the incidence of CTCL rising from 0.65 to 1.75 during years 1961–1965 and 1976–1980, respectively.

Table 7 Observed and expected number of subsequent cancer, with standardized incidence ratio (SIR) and 95% confidence interval (CI) with cutaneous T cell lymphoma (CTCL) from 1953–1995

Site of cancer	Observed	Expected	SIR	95% CI
All sites	36	26	1.4	1.0–1.9
Stomach	3	2.4	1.3	0.3–3.7
Colon	1	1.4	0.7	0.0–3.9
Rectum	1	1.1	0.9	0.0–5.1
Biliary tract	-	0.4	0.0	0.0–9.4
Pancreas	-	1.1	0.0	0.0–3.4
Lung	12	4.4	2.7	1.4–4.8
Skin melanoma	-	0.4	0.0	0.0–9.2
Nonmelanoma skin cancer	3	0.9	3.5	0.7–10
Kidney	1	0.8	1.3	0.0–7.2
Urinary tract, bladder	1	1.2	0.9	0.0–4.7
CNS	1	0.5	2.1	0.1–12
Hodgkin's disease	2	0.1	21.0	2.6–77
Non-Hodgkin lymphoma	2	0.5	4.1	0.5–15
Myeloma	-	0.4	0.0	0.0–10
Leukemia	2	0.6	3.3	0.4–12
Breast	4	1.8	2.3	0.6-5.8
Thyroid	-	0.2	0.0	0.0–19

Risk of cancer in skin disease patients treated with cyclosporine (study V)

The overall risk for all cancers was not significantly increased in skin disease patients (63 psoriasis, 96 atopic dermatitis, 73 palmoplantar pustulosis and 40 chronic hand eczema) treated with cyclosporine (SIR=1.31, 95% CI=0.7–2.23). We found altogether 13 malignancies (Table 8). In men, we found an increased risk of all cancers in the age range 45–49 years (SIR=3.28; 95% CI=1.06–7.64). These five cancers were: brain tumor (astrocytoma), carsinoid tumor, mouth cancer and two prostate cancers. We did not found any squamous cell carcinomas, but we did detect three basal cell carcinomas.

The median treatment time with cyclosporine was eight months. Most of the thirteen patients (85%) who developed cancer had received medium dosage (2–4 mg/kg) cyclosporine treatment. In analysis of different covariates we did not detect any correlation between phototherapy and these cancers (HR=0.98). The use of methotrexate was a protective factor to the development of subsequent cancer, but not significant. In this study, the relative risk of cancer increased by 7 percent per year.

The SIR comparison between different skin disease groups (atopic dermatitis, chronic hand eczema, palmoplantar pustulosis and psoriasis) showed a significant increase in basal cell carcinomas in the psoriasis group (SIR=6.05, 95% CI=1.25–17.69). There was no evidence that cyclosporine was related to these basal cell carcinomas.

Table 8 Skin disease type, cancer type, duration of cyclosporine treatment and dosage in those 13 patients who developed cancer during the follow-up (study V)

Skin disease	cancer type	csa treatment in months	csa dosage
palmoplantar pustulosis	breast cancer	5	low*
palmoplantar pustulosis	MALT-lymphoma	12	low
palmoplantar pustulosis	lung cancer **	14	medium
psoriasis	lung cancer **	2	medium
psoriasis	cervix cancer	8	medium
psoriasis	prostate cancer	30***	medium
psoriasis	carcinoid tumor	155	medium
atopic dermatitis	brain tumor (astrocytoma)	6	medium
atopic dermatitis	prostate cancer	10	medium
atopic dermatitis	prostate cancer	19	medium
eczema	testis cancer	1,5	medium
eczema	mouth cancer	3	medium
eczema	brain tumor (meningeoma)	3	medium

* low indicates cyclosporine dosage under 2mg/kg, medium 2–4 mg/kg
** patient was a smoker
*** only this patient had received methotrexate treatment

Discussion

Possible methodological sources of error

In the Finnish Cancer Registry, the registration of malignancies is almost complete covering 99 per cent of all Finnish cancers (Teppo et al., 1994). Every solid cancer is registered separately. In nonmelanoma skin cancers, basal cell carcinoma is registered and reported separately and not counted to the overall cancer incidence (Karjalainen et al., 1989). The registration of both SCCs and BCCs is based in histopathological diagnosis. Allthough in study V we did not detect any SCCs, we had no reason to believe that this was an underestimation. It is highly unlikely that SCCs or BCCs in this study were reported less often than those in other population. Since the personal identification numbers are used in the computerized record-linkage procedure, technical inaccuracy is ruled out (Pukkala, 1992) (studies IV, V).

The baseline incidence for melanoma, squamous and basal cell carcinomas and noncutaneous malignancies was obtained from the Surveillance, Epidemiology, and End Results (SEER) data (studies I, II). This database collects information of cancer from tumor registries of hospitals and private laboratory records in certain regions of the USA, and covers samples of about 10 percent of the population (Miller et al., 1993).

In studies I–III there has been criticism about the lack of control group of patients who had never received PUVA (Whitmore and Morison, 1997). PUVA treatment is an extremely efficient treatment in certain types of psoriasis. It is difficult to desing a study where all patients had received exactly same treatments for psoriasis and the only difference being PUVA treatment.

General discussion

The increased dose-dependent risk of squamous cell carcinomas is a well documented side effect of systemic PUVA therapy. The capability of this treatment to induce pigmented lesions on the skin and nails (Rhodes et al., 1983b; Trattner et al., 1990) as well as its carcinogenic potential has raised the issue of the increased risk of melanoma among PUVA treated patients. In fact, PUVA lentigines are proliferations of melanocytes, which are comparable with freckles. Freckles are UV radiation induced clones of mutated melanocytes (Gilchrest, 1984; Kanerva et al., 1984), that are

associated with an increased risk of melanoma (Seykora and Elder, 1996; Pavlotsky et al., 1997). So far, the present American study (I) and its extension (Stern, 2001) are the only studies in which an increased risk of malignant melanoma has been detected in PUVA treated patients. This additional follow-up reported seven new invasive melanomas till the end of 1999. During the last 2.5 years, the incidence of melanomas increased to 3.82 compared to 0.69 during all years (1975–1999) (Stern, 2001). These additional findings confirm the significance of study I.

During the first 15 years, there was no increased risk of melanoma and the risk started to increase about 15 years after the first treatment. During the years 1975–1990, four melanomas were detected, but from 1991–1996 seven cases were found. In two previous large cohort studies of patients treated with PUVA, the average follow-up times have been seven and eight years, and this may be the reason that these studies failed to detect any increased melanoma risk (Henseler et al., 1987; Lindelöf et al., 1991). However, one of these studies has reported updated information after 16 years of follow-up, and yet no increase in the incidence of melanoma has been detected (Lindelöf et al., 1999). In this study, a fifth of the patients (total number 4799 patients) were treated with trimethylpsoralen bath + UVA, which is less carcinogenic than oral 8-methoxypsoralen (Hannuksela-Svahn et al., 1999b). Our data (I) suggests that high levels of PUVA, over 250 treatments, is a risk factor for the development of melanoma. Based on our results, it is not possible to determine the number of PUVA treatments at which the risk of melanoma starts to increase. It is possible that both a certain time (over 15 years) and high exposure to PUVA are needed at the same time to develop this increased risk.

The role of UVA in the development of melanoma is controversial. Epidemiological studies have shown that the incidence of melanoma does not have such a great latitudinal variation than that of SCC. Also, the latitudinal variation of UVB is much greater than that of UVA (Armstrong and Kricker, 2001). The incidence rates of melanoma increase as the latitude decreases (Moan and Dahlback, 1992). Sunbeds and sun lamps emit mostly UVA radiation. A Swedish study reported an increased risk of melanoma in sunbed/sunlamp users (Westerdahl et al., 2000). They showed that the risk of melanoma after tanning salon use was dose dependent and correlated positively to the age of the customers sunlamps were first used.

It is clear that UVA radiation can induce DNA damage in human cells (Marrot et al., 1999). There is also evidence that UVA irradiation increases the frequency of melanoma metastases in the mouse model (Pastila and Leszczynski, 2005). A 12-fold increase in metastasis compared with UVA unexposed controls was detected. UVA irradiation also inducted low- metastatic potential melanoma cells to high- metastatic potential melanoma cells. In the fish model, UVA and visible spectral wavelengths were interpreted to be responsible for 90–95% of melanoma induction (Setlow et al.,

1993). UVA had similar effects to melanocytes and keratinocytes, but UVB showed more pronounced effects on keratinocytes (Larsson et al., 2005). These findings may suggest that UVA irradiation has an important role in the development of melanoma. However, another mouse experiment showed that only UVB initiated melanoma in transgenic mice and the effect of UVA was comparable to a placebo (De Fabo et al., 2004).

Clear risk factors for the development of melanoma are e.g., the number of pigmented nevi, skin type I–II, freckling and red or blond hair, previous skin burn, and dysplastic nevus syndrome (Kanzler and Mraz-Gernhard, 2001; MacKie et al., 1989). In the present study (I), we did not have information of the patients' family history of melanoma or if they had dysplastic nevus syndrome. We do not know if the risk of melanoma was increased already at the beginning of the study.

PUVA induced carcinogenesis is dependent on the total UVA dose. In study one (I), there is no knowledge of the total cumulative dose of UVA. Also, no burning history of these patients was available. However, BCC and malignant melanoma are both related to intensive sun burning. Patients in the PUVA follow up study did have only a modestly increased risk of BCC. This could be a reflection that these patients perhaps did not have a serious burn history.

There has been discussion about the diversity of melanomas arising on chronically sun exposed versus intermittently sun exposed areas. A recent study found different genetic alterations in melanomas with different levels of sun exposure (Curtin et al., 2005). This supports the previous suggestion that the response of melanocytes to UV light may be different at different sites of the body (Whiteman et al., 2003). Malignant melanoma is reported to occur more frequently on facial skin than on the body (Pearl and Scott, 1986). Also, the clinical types can be different: on the face lentigo maligna melanoma is the most common type. In our study (I), the lentigo maligna melanomas occurred in patients who had received the highest PUVA exposure. This data was not published, because the diagnosis of melanoma subtypes was not able to be repeated reliably. Three cases were lentigo maligna melanomas, one was acral melanoma, three were nodular melanomas, three superficial spreading melanomas and one was unclassified.

In the development of melanoma, intermittent extensive exposure to UV radiation is a risk factor and in that way BCC and melanoma resemble each other (Elwood, 1996). Melanocytes are very resistant to apoptosis. This has been explained by the high content of anti-apoptotic proteins, like Bcl-2, in melanocytes (Plettenberg et al., 1995). It it possible that UV radiation induced resistence to apoptosis explains in part the relationship of melanoma risk to extensive, intermitted sun exposure (Gilchrest et al., 1999). Some studies have speculated that sublethal, chronic exposure to UV radiation leads to an increased base level DNA repair capacity (Eller et al., 1994; Le et al., 1998). In the case of melanoma, because of the lack of

continuing exposure to UV radiation, the base line capacity to repair DNA is low resulting in retention of the mutated melanocytes and progression of melanoma (Gilchrest et al., 1999).

The use of UVB has increased in the PUVA follow-up study. However, in patients who developed melanoma, the exposure to high levels of UVB was no more frequent than in the cohort overall (I). This does not emphasize the role of UVB in these melanomas.

Immunosuppression and UV radiation are both risk factors for the development of non-Hodgkin's lymphoma (Fisher and Fisher, 2004). Although PUVA can have immunosuppressive effects, in the present study (II) long-term PUVA treatment was not associated with an overall increased risk of noncutaneous cancer. In contrast to the data of nonmelanoma skin cancer risk in PUVA treated patients, this study (II) suggests that the carcinogenic effect of PUVA is limited to the skin. There are later reports of the increased risk of noncutaneous tumors in PUVA treated patients. In a Swedish study the risk of respiratory cancers was increased and in women the risk of kidney cancer was higher. The majority (64%) of these patients suffered from psoriasis (Lindelöf et al., 1999). In our study (II), an increased risk for thyroid cancer, breast cancer and central nervous system cancer was detected. However, there was no association between the risk of any of these cancers and higher levels of exposure to PUVA. Finnish studies failed to show any increased overall incidence of noncutaneous cancers in patients treated with bath PUVA (Hannuksela et al., 1996; Hannuksela et al., 1999a; Hannuksela et al., 1999b). As to other possible risk factors other than UV irradiation, one of the five thyroid cancer patients had received ionizing radiation for treatment of psoriasis (II).

The increased risk of SCC associated to PUVA treatment was within the first decade after starting PUVA (years 1979–1989) therapy more pronounced in American studies than in European studies. In fact, first in the beginning of 1990s the European Studies confirmed the previous findings from American studies of a dose-dependent increase of SCC (Lindelöf, 1991; Brynzeel et al., 1991). The differences found may be due to a number of factors. The cumulative doses in American studies are higher than in European studies. In European studies the percentage of patients who had received over 1500J/cm2 of UVA varied from 9% to 13% (Ros et al., 1983; Tanew et al., 1986; Henseler et al., 1987). In American studies, a remarkable higher percentage of patients exceeded this 1500 J/cm^2 (Stern et al., 1984; Forman et al., 1989). Also, in a Swedish study (Lindelöf et al., 1991), men exposed to doses greater than 1200 J/cm^2 of UVA were 27.2 times more likely to have SCC than the general population. The baseline incidence of SCC is higher in USA than in Europe, and this means the European studies require at least double of person years of follow-up to have the same power as the American studies.

Most previous studies concerning the risk of nonmelanoma skin cancers deal with patients who are on active PUVA therapy. Based on studies done in organ transplant patients, the risk of SCC increases with the increasing dose of therapy of immunosuppressive therapy. Our study (I) showed that a long interval from the first exposure to the development to melanoma is needed. In the PUVA follow-up study, the intensity of PUVA treatment has decreased. During the years 1975 to 1985 80% of the cumulative PUVA was provided and after 1985 less than half (40%) of the original 1380 patients still had PUVA exposure. However, the incidence of SCC and BCC increased after 1985. This was true in patients who did not have nonmelanoma skin cancer in the first decade. The results (III) support the hypothesis that the carcinogenic risk of PUVA treatment is not restricted to patients with substantial previous exposure to carcinogens. The risk also remains high in patents who had stopped PUVA treatment.

Narrow-band UVB treatment is a relatively new weapon in the phototherapy armament. In Finland, this treatment has been used since 1989 (Karvonen et al., 1989). In study V, we did not separate whether our patients had received broad or narrow-band UVB. Initially, narrow-band UVB light sources were thought to be less carcinogenic than broad-band UVB (Cole et al., 1986). The narrow-band UVB light sources seem to be two to three times more carcinogenic if calculated per MED compared to broad- band light sources (de Gruilj et al., 1994). However, the cumulative numbers of MED of narrow-band UVB irradiation needed to clear psoriasis is usually less than those required with broad-band UVB. This is in line with two recent studies. Weischer at al. conducted a study with 195 psoriasis patients. Two thirds of the patients received narrow-band and one third broad- band UVB treatment. During a follow up of six years no nonmelanoma skin cancer was detected. One in situ melanoma was found within the same year that narrow-band phototherapy was started, and due to this short time-interval, treatment-related photocarcinogenesis can be ruled out in this case (Weischer et al., 2004). In another four year study of 1908 patients treated with narrow-band UVB, no increased incidence of SCC or melanoma was found (Man et al., 2005). The increased incidence of BCC was speculated to be due to diagnostic bias. Also, in this study almost one third of BCCs were excised within three months from the start of treatment.

Broad-band UVB treatment carries a theoretical risk of carcinogenesis, but epidemiological data on carcinogenity in humans has been shown to be only a moderate cancer risk related to UVB treatment. Larkö and Svanbeck conducted a study with 85 psoriasis patients. All patients had received more than 100 UVB treatments. Two BCCs occurred in the psoriasis group and three SCCs in the control group, whereas there were no SCCs in the psoriasis patients. The difference between these two groups was not statistically different in terms of the total number of malignant lesions. Because

of the small sample size no convincing evidence of the carcinogenity of UVB treatment was obtained (Larkö and Svanbeck, 1982). In an American PUVA follow up study a five -fold increase in the relative risk of SCC was detected (95% CI= 4.0–8.7), but UVB was not detected to be an independent risk factor for the development of SCC (Stern et al., 1994). Lim and Stern have recently found that high UVB exposure (over 300 treatments) was significantly associated with an increase in SCC in psoriasis patients (Lim and Stern, 2005). Among patients who had received low-dose PUVA treatment (under 100 treatments), high UVB exposure was not associated with the development of SCC and BCC on chronically sun- exposed sites like head and neck.

Patients with the most common CTCL, mycosis fungoides, are treated with PUVA initially (Whittaker et al., 2003). CTCL patients with limited patch or plaque stage disease have close to normal life expectancy and usually get numerous PUVA treatments. In our clinic, we have seen mycosis fungoides patients developing SCC and BCC. We did not find an increased risk of skin cancers. The three detected nonmelanoma skin cancers did not reach significance. However, CTCL patients showed an increased risk of overall secondary cancer. The overall risk of lung cancer and lymphomas (Hodgkin and non-Hodgkin lymphomas combined together) had increased.

As CTCL is a disease of T lymphocytes, it could be speculated that natural cell mediated immune responses to transformed cells is decreased (Kantor et al., 1989). MF patients have decreased numbers of normal circulating CD4+ T cells as a result of decreased synthesis of IFN-gamma, which results in decreased antitumor cytotoxic T lymphocyte activity. Thus, CTCL patients could have been more sensitive to the effect of immunosuppressive treatments such as PUVA. In this study (IV), PUVA treatment did not have any affect on the development of subsequent lung cancer or lymphomas. In a recently published study of the updated information of the PUVA follow-up study, the risk of lymphomas was increased only in psoriasis patients who had received high dose methotrexate treatment (Stern, 2006). It can be speculated that in CTCL compared to psoriasis patients the development of cancer is mediated through different pathways.

The incidence of CTCL is rising worldwide (Weinstock and Horm, 1988; Hartge et al., 1994). Increased exposure to UV radiation has been speculated partly to explain this increase. p53 mutations are clearly linked to the development of SCC (Steele and Lane, 2005). One study has reported p53 mutations in CTCLs (McGregor et al., 1999). They found typical fingerprint mutations in tumour MF stage patients suggesting that UVB may play a role in the increased incidence of CTCL. Agaist this argues a large population based case- control study (Smedby, et al., 2005). Data analysis showed that high UV exposure was linked to reduced risk of

non-Hodgkin lymphoma. However, the history of skin cancer was associated with a two-fold increased risk of lymphomas. This suggests that the correlation between skin cancer and lymphomas is not mediated via UV exposure. In our study (IV), we did not detect any increase in the incidence of nonmelanoma skin cancers or melanoma.

Study V did not show an increased risk of cancer among skin disease patients treated with cyclosporine. In this study, the majority of patients, two thirds, had some other inflammatory skin disease than psoriasis. In an American study, the risk of squamous cell carcinoma was increased after any use of cyclosporine, but all patients had photochemotherapy treatment before (Marcel and Stern, 2001). A recent study by O'Donovan and colleagues presented a new possible mechanism for the development of skin cancers among organ transplant patients (O'Donovan et al., 2005). They showed that azathioprine, another immunosuppressive agent, sensitizes DNA to UVA radiation. The metabolic end product of azathioprine is incorporated into the DNA of skin cells. With the presence of UVA radiation this metabolic end product turns into reactive oxygen species capable of damaging DNA. They also made another interesting finding: the skin of patients treated with azathioprine became more sensitive to UVA but not to UVB during three months of observation. Marcil and Stern had a very similar setting in their study (Marcil and Stern, 2001): squamous cell carcinomas developed in patients who were exposed to PUVA previously and then treated with cyclosporine. There have been speculations that it would be better to treat patients with PUVA therapy as late as possible in life and avoid the emergence of PUVA indused skin cancer by subsequent immunosuppression like cyclosporine (Murphy, 1999).

Renal transplant patients receiving a cyclosporine based regimen were at high risk for SCC but not for BCC (Glover et al., 1997). The use of cyclosporine was an independent risk factor for development of neoplasms in another study (Marcen et al., 2003). Thus, the role of different immunosuppressive treatments is controversial.

In study V, the median treatment time was 8 months and cyclosporine treatment was given intermittently. A previous European study found an increased risk of malignancies after an average of 1.9 years of cyclosporine treatment. All patients suffered from psoriasis. Almost half of the malignancies were nonmelanoma skin cancer (Paul et al., 2003). The differences between the results of these two previous studies (Marcil and Stern, 2001; Paul et al., 2005) and of study V are probably due to our short median treatment time and the relatively small proportion of psoriasis patients in the study (V). This study (V) is the first one trying to evaluate the risk of cancer in cyclosporine treated patients including also other than psoriasis patients. We did not find any evidence in this study (V) that short term cyclosporine treatment is a major risk factor for subsequent malignancy. With our sample size (272 patients) it was possible to exclude twofold in-

cidence increase in cancer risk with a power of 90% and a two sided significance lewel of 0.05 (Machin and Campbell, 1987). Our results are supported by Dantal et al. who found similar results in their study, where in kidney transplant patients there were significantly less malignancies in the low-dose cyclosporine treatment group compared to those patients treated with normal doses (Dantal et al., 1998). Also, in a study conducted on rheumatoid arthritis patients and thus in patients with no previous history of phototherapy treatments, no increased risk of malignancies was found (van den Borne, et al., 1998).

Immunosuppression clearly predisposes to basal cell carcinoma. In organ transplant patients and PUVA treated patients the normal ratio of BCC to SCC ratio is reversed (Stockfleth et al., 2001; McKenna, 2004). This ratio has been reported to be approximately 4 to 1 in white persons in the United Kingdom and in Australia (Marks et al., 1993; Gray et al., 1997), and in Norway 6 to 1 (Henriksen et al., 1990). This ratio was 1 to 1.3 in organ transplant patients (Stockfleth et al., 2001). In this study (V) we detected three basal cell carcinomas but no squamous cell carcinomas.

In organ transplant patients, nonmelanoma skin cancers are mainly located on sun exposed skin areas. This is associated with the amount of UV exposure (Bavink et al., 1993). Previous studies have shown that also in organ transplant patients the incidence of skin cancer increases as the latitude decreases (Bavink-Bouves et al., 1996; Jensen et al., 1999). Age at transplantation is associated with skin cancer risk (Ong et al., 1999) and that is assumed to be a reflection of lifelong UV exposure. In our study (V), we did not detect any SCC and previous phototherapy did not have any influence to the cancers detected.

Conclusions

This study was conducted to investigate the cancer risk related to immunosuppressive treatments such as systemic PUVA and cyclosporine in different inflammatory skin diseases. Based on the results presented in this thesis, the following conclusions can be drawn:

In psoriasis patients, the risk of malignant melanoma in PUVA treated patients is increased among patients who had received more than 250 treatments or after 15 years of first PUVA treatment. However, PUVA treatment does not increase the risk of noncutaneous cancers. Systemic PUVA treatment increases the risk of SCC in a dose dependent manner especially in patients exposed to high dose PUVA.This risk is persistent even after systemic PUVA treatment is stopped. The same trend is seen with BCC, but it is less pronounced.

In CTCL patients, the risk of developing secondary cancers was increased. Of separate sites, the incidence of lung cancer and lymphomas was increased. These patients did not have high exposure to PUVA treatments. The risk of SCCs was not increased.

In our study, we found no increased risk of cancer or particularly skin cancer in patients treated with short term cyclosporine and consisting mainly of other skin diseases (atopic dermatitis, palmoplantar pustulosis, chronic hand eczema) than psoriasis. In these patients, the relatively short term cyclosporine treatment without other previous immunosuppressive treatments is probably not associated with increased risk of cancer, but the size of our cohort was small.

In clinical practice, these findings have led to a close and permanent follow-up of patients treated with systemic PUVA.

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