

## The Risk of Cancer Associated with Immunosuppressive Therapy for Skin Diseases

Dr Liisa Väkevä

Department of Dermatology

University of Helsinki

Helsinki, Finland

E-mail: liisa.vakeva@hus.fi

### Background

The possible carcinogenic risk of immunosuppressive therapies is an important issue in everyday clinical practice. Carcinogenesis is a slow multi-step procedure and there is a long latency period before cancer develops. 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 non-cutaneous cancer risk associated with systemic PUVA, and the persistence of nonmelanoma skin cancer



Dr. Liisa Väkevä (*left*) from the Department of Dermatology, University of Helsinki, defended her PhD thesis on the risk of cancer associated with immunosuppressive therapy for skin diseases in August 2006. Professor Olle Larkö (*right*) from Uppsala was the opponent. The thesis was supervised by Professor Annamari Ranki (*middle*) together with Professor Robert S. Stern from Harvard.

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.

### Results

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. 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 first five years, the rate increased from 19 per 100 000 person years to 32 per 100 000 person years (the last figures for years 1991-1996).

During the follow up time (1975 or 1976 to 1996), 195 non-cutaneous cancers developed in this same cohort of 1380 patients. The overall risk of noncutaneous 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. 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.

The study also 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 1042 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 assessed. 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.

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). 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.

When evaluating the risk of cancer in skin disease patients treated with cyclosporine, the overall risk for all cancers was not significantly increased in these patients (63 psoriasis, 96 atopic dermatitis, 73 palmoplantar pustulosis and 40 chronic hand eczema) (SIR=1.31, 95% CI=0.7-2.23). We found altogether 13 malignancies. 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), carcinoid tumor, mouth cancer and two prostate cancers. We did not find 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=1.07). 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% 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.

## Conclusions

This study investigated the cancer risk related to immunosuppressive treatments such as systemic PUVA and cyclosporine in different inflammatory skin diseases.

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

## Original publications

1. Stern RS, Nichols KT, Väkevä LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). *N Engl J Med* 1997; 336: 1041–1045.
2. Stern RS, Vakeva LH. Noncutaneous malignant tumors in the PUVA follow-up study: 1975–1996. *J Invest Dermatol* 1997; 108: 897–900.
3. Stern RS, Liebman EJ, Vakeva LH. Oral psoralen and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA Follow-up Study. *J Natl Cancer Inst* 1998; 90: 1278–1284.
4. Vakeva 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.