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SKIN DISEASE AND MALIGNANCY

An Epidemiological Study

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This thesis is dedicated
to the memory of my father
Sigurgeir Guðmundsson

Vits er þörf,
þeim er víða ratar;
dælt er heima hvað.
Að augabragði verður,
sá er ekki kann
og með snotrum situr.

Deyr fé,
deyja frændur,
deyr sjálfur ið sama;
en orðstír
deyr aldregi,
hveim er sér góðan getur.

From Hávamál

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II. Lindelöf B, Sigurgeirsson B, Wahlgren CF, Eklund G. Chronic urticaria and cancer: an epidemiological study of 1155 patients. Br J Dermatol 1990; 123:453-456.

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V. Sigurgeirsson B, Lindelöf B. Lichen Planus and Malignancy. An Epidemiological Study of 2071 Patients and a Review of the Literature. Arch Dermatol 1991;127:1684-1688.

VI. Sigurgeirsson B, Lindelöf B. Positive Patch Tests and Cancer. An Epidemiological Study of 5,858 Patients. Am J Cont Dermat 1992;3:in press.

VII. Lindelöf B, Sigurgeirsson B, Tegner E, et al. PUVA and cancer: a large-scale epidemiological study. Lancet 1991; 338:91-93.

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2. CONTENTS

3. ABBREVIATIONS

5-MOP	5-Methoxysporalen
8-MOP	8-Methoxypsoralen
ACD	Allergic contact dermatitis
AN	Acanthosis nigricans
BCC	Basal cell carcinoma
CI	Confidence interval
CTCL	Cutaneous T cell lymphoma
HPV	Human papilloma virus
LP	Lichen planus
MPD	Minimal phototoxic dose
PUVA	Psoralens and UltraViolet A
SCC	Squamous cell carcinoma
TMP	Trimethylpsoralen
UVA	UltraViolet A
UVB	UltraViolet B

4. ABSTRACT

The aim of this work was to develop a computer program (CANEST) to estimate the risk of cancer in patient populations and to use this program to investigate cancer risk associated with several dermatological disorders. Patients seen at the dermatology departments at the Karolinska Hospital and South Hospital were used for the study of chronic urticaria, condylomata acuminata, basal cell carcinoma, lichen planus and positive patch tests. The national Swedish In-Patient Register was used to find all patients hospitalized for dermatomyositis or polymyositis since 1964. From eleven large dermatological centers in Sweden, details of close to 5,000 PUVA-treated patients were obtained for study.

The computer program CANEST was developed and used to calculate the expected number of malignant tumors in these patient populations, based on incidence data from the Swedish Cancer Register for the years 1958-1987. By matching the patients' records with the Cancer Register the actual number of cancers was obtained.

Of 1,155 patients with chronic urticaria, a malignancy was diagnosed in 36, while the expected number was 41: clearly there is therefore no association between chronic urticaria and malignancy.

In 3,260 patients with condylomata acuminata there was no increased risk of cancer *in situ* of the cervix (relative risk=1.5; 95% confidence interval 0.9 to 2.5) and the number of genitourinary cancers in males was almost three times higher than expected (2.6; 1.2 to 5.0). These results indicate that the risk of developing cervical carcinoma *in situ* is less than previously thought, but the implications of the increase in genitourinary tumors in males are uncertain.

Patients with basal cell carcinoma had an increased risk of malignancy in general. Melanoma risk was seven times greater in males (6.6; 3.0 to 12.5) after the basal cell carcinoma diagnosis. Risks of squamous cell carcinoma of the skin, lung cancer, thyroid cancer and cancer of the uterine cervix were also increased.

No increased risk of cutaneous malignancy was found in 2,071 patients with lichen planus, but for oral cancer it was six times greater in males (5.9; 2.5 to 11.4).

A slight general increase in malignancy risk was found in 2,183 males (1.3; 1.1 to 1.5) with positive patch tests, but not in 3,675 females. When individual sites were analyzed, cancers of the lung, larynx, uterine cervix and prostate were significantly increased. The implications of this are uncertain, but might indicate a common failure of the immune system which might predispose for both conditions, or be a marker of certain occupational exposure.

Risk of squamous cell carcinoma of the skin was increased in 4,799 patients treated with PUVA. Male patients who had received more than 200 treatments had over 30 times the incidence of squamous cell cancer found in the general population. Significant increases were also found in the incidences of some internal malignancies. This study confirms previous reports of dose-dependent increase in the incidence of squamous cell cancer in patients treated with PUVA.

The risk of malignancy was clearly increased in 392 patients with dermatomyositis (2.4; 1.6 to 3.6), but in 396 patients with polymyositis the associated risk was lower (1.8; 1.1 to 2.7). The increase in risk was mirrored in cancer mortality in dermatomyositis patients but not in polymyositis patients. The results suggest that in dermatomyositis patients there is truly an increased risk of malignancy but the increase in incidence of malignancy in polymyositis patients might be due to diagnostic suspicion bias.

5. INTRODUCTION

5.1. Skin diseases and signs associated with malignancy

Dermatologic signs of malignancy have fascinated dermatologists for decades. Considering the number of immunologic, metabolic and endocrinologic changes associated with internal malignancies, it is not surprising that these patients can have various skin signs. Changes in the skin are obvious compared to those in other organs and the patient usually seeks help early. The physician who is confronted with a patient with a possible cancer-associated disease faces a dilemma. Should the patient be investigated internally or not? Excessive evaluation of the patient might waste health-care resources, whereas insufficient or no evaluation may delay diagnosis of a potentially curable malignant disease. This may not be a problem for rare diseases such as acanthosis nigricans when the association between the dermatosis and the cancer is strong, but becomes a problem where the manifestation is very common, such as seborrheic keratoses in the sign of Leser-Trélat, and the presumed association with a wide spectrum of commonly occurring neoplasms. The literature is often confusing, with anecdotal reports. Most conflicts in the literature result from studying highly-selected patient populations that may already be at increased risk for cancer, from incomplete or uneven follow-up of patients, and from lack of data in control populations with which to evaluate any suspected increase in risk. Many of these difficulties can be minimized in population-based studies.

But how to define which diseases are associated with malignancy? A causal relationship between a dermatosis and a malignant disease may exist when the following criteria, which have been suggested by Curth, are fulfilled[1] :

1. *Concurrent onset* - The malignancy and the skin disease begin together, or when the skin disorder appears, it is possible to uncover the cancer.

2. *Parallel course* - If the malignancy is removed the skin disease resolves; and when the tumor recurs, the cutaneous disease also recurs.

3. *Uniform malignancy* - There is a specific site or type of malignancy associated with the skin disease.

4. *Statistical association* - There is evidence based on sound statistical analysis that malignancy is more frequent in patients with a cutaneous disease.

5. *Genetic association* - There are several well-recognized genetic syndromes in which there are prominent skin manifestations and frequent internal malignancy.

It can be difficult to assess an association between a dermatologic sign and malignancy. If the dermatosis is common it is fairly easy to find many cases with the dermatosis and cancer at the same time. Also the great enthusiasm which comes from having discovered yet another association between a benign dermatosis and malignancy sometimes masks the possibility that the association has occurred by chance[1]. Classification of dermatoses which may be associated with malignancy is difficult because of a lack of knowledge about the mechanism which produces the malignancy or the dermatosis. Several classification systems are in use. One of these is presented in Table 1.

TABLE 1.- Classification of cutaneous signs of malignancy. From McLean[2].

I. LESIONS SECONDARY TO THE DEPOSITION OF SUBSTANCES IN THE SKIN
- A. Icterus
- B. Melanosis
- C. Hemochromatosis
- D. Xanthomas
- E. Systemic amyloidosis

II. VASCULAR AND BLOOD ABNORMALITIES
- A. Flushing
- B. Palmar erythema
- C. Telangiectasia
- D. Purpura
- E. Vasculitis
- F. Cutaneous ischemia
- G. Thrombophlebitis

III. BULLOUS DISORDERS
- A. Bullous pemphigoid
- B. Pemphigus vulgaris

C. Dermatitis herpetiformis
D. Herpes gestationis
E. Erythema multiforme
F. Epidermolysis bullosa acquisita

IV. INFECTIONS AND INFESTATIONS
A. Herpes zoster
B. Herpes simplex
C. Bacterial infections
D. Fungi and yeast infections

V. DISORDERS OF KERATINIZATION
A. Acanthosis nigricans
B. Acquired ichthyosis
C. Palmar hyperkeratosis
D. Erythroderma
E. Paraneoplastic acrokeratosis of Bazex

VI. COLLAGEN-VASCULAR DISEASE
A. Dermatomyositis and polymyositis
B. Lupus erythematosus
C. Progressive systemic sclerosis

VII. SKIN TUMORS AND INTERNAL MALIGNANT DISEASE
A. Muir-Torre syndrome
B. Gardner's syndrome
C. Cowden's disease
D. Bowen's disease
E. Neurofibromatosis
F. Basal cell carcinoma
G. Condylomata acuminata

VIII. HORMONE-RELATED CONDITIONS
A. Carcinoid syndrome
B. Glucagonoma syndrome

IX. DISORDERS ASSOCIATED WITH PRIMARY SKIN CANCER
A. Nevoid basal cell carcinoma syndrome
B. Arsenical manifestations

X. VARIOUS DISORDERS ASSOCIATED WITH MALIGNANCIES
A. Pruritus
B. Erythema gyratum repens
C. Subcutaneous fat necrosis
D. Sweet's syndrome
E. Hypertrichosis lanuginosa
F. Clubbing
G. Leukoderma
H. The sign of Leser-Trélat
I. Lichen planus

XI. DIRECT TUMOR INVOLVEMENT IN THE SKIN

The list of dermatoses which have been associated with malignancy is almost endless, especially if rare genetic syndromes associated with malignancy are included. Here however the discussion is limited to those dermatoses which the association with malignancy is considered fairly well confirmed.

5.1.1. Cancer metastases

Direct involvement of the skin by metastatic spread from a distant primary tumor is unquestionably a marker for internal malignancy. Metastasis to the skin occurs in 3-5% of cases with metastatic cancer. In summary, carcinoma is the most frequent cancer that metastasizes to the skin; lung cancer in men and breast cancer in women. Clinically distinctive patterns of cutaneous metastasis of epithelial origin include alopecia neoplastica, morpheaform, and cellulitis-like lesions[3]. The metastases usually appear as firm skin-colored nodules. Metastases from breast cancer can mimic erysipelas. The most common site is the abdomen. Malignant melanoma tends to metastasize to the extremities and the lesions tend to be pigmented. Oropharyngeal tumors often metastasize to the face and neck. Other tumors that commonly metastasize to the skin include lung, colon, stomach, kidney and ovary tumors. Sometimes cutaneous metastases are the first sign of a recurrence of the underlying malignant disease. Recently two patients were described who presented with skin nodules six and ten years, respectively, after their initial cancers were diagnosed[4]. Cutaneous metastases herald poor prognosis, as evidence of systemic spread to other sites is usually quickly apparent.

5.1.2. Leukemia and lymphoma

Skin signs of Cutaneous T cell lymphomas (CTCL) are common and often the presenting symptom. The malignant T cells are epidermotrophic, and these patients often present with erythrodermia or massive infiltrations of the skin which can give the patients a grotesque look. Skin that is damaged allows circulating malignant cells, often of epithelial or leukemic origin, to lodge and proliferate locally (inflammatory oncotaxis). The most usual form of leukemia to affect the skin of elderly males is chronic lymphocytic leukemia. However, when leukemia involves the mucous membranes, acute myeloid leukemia (acute monocytic and acute myelomonocytic leukemia) is the most likely diagnosis. When papules, nodules, or plaques develop on the head or, neck in a middle-aged male accompanied by lymphadenopathy, there must be a high suspicion that these lesions are metastatic lymphomatous deposits[3]. Definitive histologic diagnosis on a skin biopsy specimen is difficult. In this

situation, it is best to rely on histologic patterns seen in lymphoid tissue along with cellular marker studies.

It has been proposed that T-cell lymphoma may be caused by chronic antigenic stimulation with resultant malignant lymphocyte clonality,[5] and recently four patients were described where long-standing chromic dermatitis evolved into cutaneous T-cell lymphoma.

It is possible that these patients may harbor a second internal malignancy in higher percentage than expected[6]. Although the control group was not perfectly matched, Olsen and colleagues in their study of 63 patients with CTCL, found the relative risk compared to population statistics to be about double the expected. There were no predominant tumor sites. T cell leukemias may also present as erythrodermia or massive skin infiltration.

5.1.3. Paget's disease

Paget's disease of the nipple is an erythematous, eczematoid patch that surrounds the nipple and areola and is associated with an underlying mammary adenocarcinoma of ductal origin. The malignant cells from the duct are believed to migrate upwards and infiltrate the skin. Extramammary Paget's disease has been described but its nature is controversial[7, 8]. It appears clinically as an erythematous plaque with an erosive or slightly keratotic surface. Women are more commonly affected. The lesion can also appear in the anogenital region and is believed to arise from sweat ducts or from an underlying organ such as a genitourinary or lower gastrointestinal structure.

5.1.4. Cowden's disease

Cowden's disease has autosomal dominant inheritance and is characterized by multiple hamartomas and neoplasms of ectodermal, mesodermal, and endodermal origin. The most frequent findings are mucocutaneous lesions, which include lichenoid and papillomatous lesions of the facial region, acrokeratotic lesions of the hands, and papillomatous and papular oral lesions. Thyroid disease is the most common internal abnormality, and breast cancer is the most common malignancy associated with this syndrome. Other associated anomalies include a high arched palate, bird-like facies, gastrointestinal polyposis, female genital tract neoplasms, enlarged tongue, and diabetes mellitus. Because of the high incidence of internal malignancy, these signs of Cowden's disease should be recognized as early as possible.

5.1.5. Langerhans' cell histiocytosis

The form of histiocytosis X with endocrine effects is called the Hand-Scüller-Christian disease, but without endocrine effects the Letterer-Siwe disease. The typical skin lesion resembles seborrheic dermatitis in distribution, but yellow or brown papules, which may ulcerate, are present at the edge of the lesions[9]. The brown or red-brown papules tend become confluent, forming a greasy scale. Frequently there are erosions, but frank ulcers are rare.

5.1.6. Bowens's disease

Bowen's disease is an *in situ* sqamous cell carcinoma (SCC) and has been frequently reported to be associated with internal malignancy, although this association has been extremely controversial. In 1959, Graham and Helwig[10] called attention to a possible relationship between Bowen's disease and systemic cancer. They reported 35 patients of whom 28 had "systemic" cancer. However, Andersen and colleagues did not confirm that patients with Bowen's disease had an increased risk of neoplasia[11]. Callen found a 15% risk of internal malignancy in patients with Bowen's disease, and the risk was believed to be higher than a comparable sample from the general population[12].

Recently two studies have failed to show any association between Bowen's disease and internal malignancy. Chuang and colleagues conducted a matched case-control study to evaluate the significance of this link[13]. Ninety patients with Bowen's disease diagnosed between 1972 and 1986 were selected for study. These patients were matched by age, sex, race, and date of biopsy for diagnosis (or treatment) to 90 other patients chosen as controls. Six patients in the Bowen's disease group and three patients in the control group had internal malignancy during the period after the date of biopsy or treatment ($P < 0.4$). The study of Lycka and colleagues uses the technique of meta-analysis to address this issue by pooling the results of the 12 studies published in English that have previously investigated this issue[14]. The results indicated no significant association between the two conditions.

On the basis of the above data the suggested link between Bowen's disease and internal malignancy must therefore be seriously questioned.

5.1.7. Basal cell carcinoma

The patient with basal cell carcinomas (BCC) of the skin has sometimes been thought to run an increased risk of developing other malignancies. Certain exposure such as excessive sun bathing is considered to be a causative fac-

tor both for BCC and malignant melanoma of skin[15] and, therefore, an association of these two cancer types might be expected. Arsenic exposure is another example of a factor which could give an increased risk both of BCC and of other malignancies[16, 17, 18].

On the other hand the association between BCC and other malignancies might not be causal. BCC and other malignancies are common and chronic and it is relatively easy to find small series of patients with both conditions at the same time. There are only two large studies from recent years: one investigation of 196 patients with multiple BCC[19] and one retrospective cohort study of 468 cases[20] have not revealed an increased incidence of cancer in other organs.

5.1.8. Carcinoid syndrome

Carcinoid tumors arise from the bronchiolar gastric mucosa, the pancreas, thyroid gland or from teratomas. They secrete vasoactive substances including serotonin, catecholamines, histamines, bradykinIN, kallikrein, leukotrines and prostaglandines[9]. The vasoactive mediators then result in the flush which is so typical of carcinoid tumors. The vasoactive mediators only reach the circulation when they are produced in the lung or when the gastrointestinal tumor is metastatic.

5.1.9. Glucagonoma

In 1942 Becker and colleagues first described the case of a patient with pancreatic islet cell carcinoma that was associated with a skin eruption[21]. This condition was later given the name "necrolytic migratory erythema"[22]. Most patients are middle-aged and have high plasma glucagon. Erythema, vesicles and erosions are common signs and the condition often starts over the lower limbs, later to involve the intertrigineous areas. Associated symptoms are red, raw tongue, mild normochromic anemia, elevated sedimentation rate, weight loss and weakness.

5.1.10. Neurofibromatosis

At least seven variants of neurofibromatosis are known. The classic variant includes multiple cutaneous neurofibromas and café-au-lait hyperpigmentation. Café-au-lait hyperpigmentation is present in 99% of cases with classic neurofibromatosis. If the patient has more than six such lesions that are larger than 1.5 cm in diameter, he can almost certainly be considered to have neurofibromatosis, even though other signs of the disease are currently lack-

ing. Freckling, particularly of the axillary region and regions of juxtaposed skin surfaces is another clinical marker[23]. Pigmented hamartomatous growths of the ocular iris, known as Lisch nodules, are present in up to 94% of patients who are over six years[23].

Many types of malignancy have been reported to be associated with neurofibromatosis. Malignant schwannoma can appear in up to one third of such patients. Other associated tumors include neurofibrosarcoma, Wilm's tumor, rhabdomyosarcoma and leukemia[24].

5.1.11. Peutz-Jegher's syndrome

The association between hyperpigmented macules on the mucous membranes and the skin and intestinal polyps has been known since the beginning of this century. The pigmented macular lesions vary in size from 1 to 12 mm and in color from brown to black. The macules have predilection for the lips and the buccal and rectal mucosa. Polyposis develops in about 90 % of cases. Malignant degeneration of the intestinal polyps is the major concern and occurs in up to 6% of cases.

5.1.12. Lichen planus

There are at least 36 cases described in the literature where squamous cell carcinoma has developed in lichen planus (LP) skin lesions (V). No large studies, that give any idea of the real cancer risk associated with LP skin lesions. Squamus cell carcinoma has been reported in up to 25% of the cases[25], but some large studies on the natural history of LP do not mention malignant transformation of skin lesions[26]. In the case of oral lichen planus, several epidemiological studies have been done and between 0.09 and 10% cancer development has been reported. Short observation time and heterogeneity of the groups may have contributed to these discrepancies.

5.1.13. Dermatomyositis and polymyositis

Since the proposed association between polymyositis and malignancy was first reported in 1916[27], its validity has been in dispute. Reported results have been contradictory, but there appears to be increased incidence of malignancy in myositis patients, and the risk of malignancy in dermatomyositis patients appears greater than that seen in polymyositis patients[28].

In reviewing the world literature, Andreev reported that bronchogenic carcinoma is the most common tumor seen in association with dermatomyositis, with breast, ovary, cervix, and gastrointestinal tract tumors also reported in a

large percentage of patients[29]. In addition to these neoplasms, almost all other malignant tumors have been reported at least once in association with dermatomyositis. The true incidence of malignant tumors in association with dermatomyositis is quite difficult to define. Bohan and colleagues assessed 153 patients with polymyositis or dermatomyositis and found an associated malignant tumor in 8.5 percent of the total, and in 19.2 percent of men over the age of 50 years[30]. Approximately 37 percent of the 650 patients with dermatomyositis reported in the literature had an underlying malignancy[29].

TABLE 2.- Risk of malignancy in patients with dermatomyositis or polymyositis in studies done after the work of Bohan and Peter[31,32].The number of malignancies/ total number of patients and (% with malignancy) are shown.

STUDY	YEAR	REFERENCE NO	DERMATO-MYOSITIS	POLYMYO-SITIS
Bohan et al	1977	30	8/60 (13%)	5/50 (10%)
Callen et al	1980	36	7/27 (26%)	1/31 (3%)
Vesterager et al	1980	37	9/18 (50%)	*
Henriksson & Sanstedt	1982	38	3/50 (6%)	4/20 (20%)
Hoffman et al	1983	39	1/12 (8%)	1/15 (7%)
Goh and Rajan	1983	40	6/10 (60%)	*
Holden et al	1985	41	4/24 (17%)	0/12 (0%)
Tymms & Webb	1985	42	7/36 (19%)	9/69 (13%)
Benbassat et al	1985	43	10/39 (26%)	3/21(14%)
Manchul et al	1985	44	10/31 (30%)	7/40 (18%)
Hidano et al	1986	45	112/569 20%)	*
Lakhanpal et al	1986	33	11/50 (22%)	18/65 (8%)
Callen	1986	46	10/26 (38%)	*
Cox et al	1990	47	23/53 (43%)	*
Basset-Seguin et al	1990	48	13/32 (41%)	*
Bonnetblanc et al	1990	49	34/118 (28%)	*
Sigurgeirsson et al	1991	Current	94/392 (24%)	52/396 (13%)

**: No information available about polymyositis patients.*

In 1975, Bohan and Peter[31, 32] described five criteria that are now routinely used for the diagnosis of dermatomyositis and polymyositis. Both dermatomyositis and polymyositis are extremely rare diseases and it is therefore difficult for individual centers to get large patient series. In Table 2 the results from studies done after the work of Peter and Bohan are summarized[28]. Most series are based on patients from referral centers. Patients with both dermatomyositis or polymyositis and malignancy are therefore more likely to be referred, and a bias is introduced. This effect has been demonstrated by Lakhanpal and colleagues who found that the highest proportion of cancer among dermatomyositis or polymyositis patients was contributed by the most distant referrals[33].

The cancers are usually identifiable by history and physical examination[34]. The clinical manifestations of dermatomyositis are the same with and without a malignant tumor. A patient with dermatomyositis and metastatic melanoma cleared with extirpation of a known tumor, but dermatomyositis recurred simultaneously with evidence of further metastases[35]

5.1.14. Acanthosis nigricans

Acanthosis nigricans (AN) is the classical example of a cancer-associated disease. Today the disease is considered a complex of symptoms with the following features: papillary hyperplasia, hyperkeratosis and hyperpigmentation. The characteristic sites are the neck, external genitalia and the axillary and inguinal areas. For different types of the disease have been described[1]:

1. Benign AN
2. Benign AN in association with other syndromes
3. Malignant AN, which is associated with adenocarcinoma
4. Pseudoacanthosis nigricans, which occurs as a reaction to friction.

The differences between benign and malignant AN are summarized in Table 3. Exact information about the incidence or the frequency of malignant transformation is hard to find, but is certainly a rare event[50]. The most commonly associated tumor is gastric cancer, but sarcomas, lymphomas and squamous cell cancers have been reported.

TABLE. 3- Differential diagnosis of benign and malignant acanthosis nigricans.[50]

Benign	Malignant
Predominantly women	Both sexes equally affected
Mostly affected are young individuals (only 19% over 25 years)	Mostly affected are elderly persons (only 10% under 30 years)
Rarely pruritic	Pruritus is always present
Family history not rare	No family history
Only the large folds and the neck are involved	Many skin areas are involved
Never generalized and never on the mucous membranes	Mucous membranes involved in at least 50% of the cases
Possible associated disorders: obesity, Cushing's syndrome, diabetes, genetic disorders	No obesity or other endocrine disorders associated

5.1.15. Acquired ichthyosis

It is often not possible clinically or histologically to distinguish acquired ichthyosis from ichthyosis vulgaris, but the flexor surfaces of the large joints may be involved and there may be pronounced pruritus. The family and case histories are important. Ichthyosiform skin lesions can occur as paraneoplastic syndromes in Hodgkin's disease, mycosis fungoides, other malignant lymphomas, and visceral carcinomas.

Sometimes acquired ichthyosis is seen as a concomitant symptom in infectious diseases, e.g., leprosy, tuberculosis, AIDS, typhoid and typhus fever, and in dietary and vitamin deficiencies (vitamin A deficiency, pellagra). The condition is also known to occur in dialysis patients, hypothyroidism, Down's syndrome, and neurotrophic disorders. A sudden development of ichhyosis in an adult can be a sign of internal malignancy, usually a lymphoma[51]

5.1.16. Condylomata acuminata

The clinical features, histologic appearance, and natural history of papillomavirus-associated genital diseases are largely determined by the type of HPV DNA found within the lesions. Human papillomavirus types 6 and 11 mainly induce exophytic condylomata affecting the anogenital skin and lower vagina. In addition, HPV-6 and HPV-11 are also detected within 40% to 50% of flat condylomata and mild dysplasia cases. Histologically, these subclinical cervical lesions show the same picture of basal acanthosis and surface koilocytosis as found in condyloma acuminatum.

Both HPV-6- and HPV-11- induced lesions may also aggregate as huge condylomatous masses termed verrucous carcinomas, which are locally invasive but rarely metastatic. There are many case reports of such malignant conversion, and one large epidemiological study has associated condylomata with cervical dysplasia[52]. Flat cervical lesions induced by HPV-16, HPV-18, and HPV-31 generally show a more severe grade of cervical intraepithelial neoplasia. Dysplasias of the cervix are regarded as precursors of cervical cancer.

5.1.17. Bullous pemphigoid

Many of the bullous diseases have been reported in association with malignancy, but the matter is controversial. In a recent case-control study, the incidence of malignant disease in 84 patients with bullous pemphigoid was

compared with 168 controls. The rate of malignant disease (past, concurrent or during follow-up) in bullous pemphigoid patients was 17.9% compared to 5.3% in the controls. A number of the malignancies occurring in the bullous pemphigoid group may be of doubtful significance, being either temporally very remote or partially attributable to treatment.[53]. Recently, some studies have questioned this association. This relationship was studied among forty patients seen at the Dermatology Clinics of the Puerto Rico Medical Center. The study demonstrated that Puerto Rican patients with bullous pemphigoid do not show an increased incidence of internal malignancy when compared with the general population matched for age, sex and study period[54].

To evaluate the significance of the association of malignant disease with bullous pemphigoid, Lindelöf and colleagues reviewed 497 consecutive cases with positive immunofluorescence tests for circulating antibodies to basement membrane[55]. In 61 patients, a total of 69 malignancies were diagnosed. The expected number of malignancies was 82.6. The conclusion is that pemphigoid is probably not associated with malignancy.

5.1.18. Pemphigus vulgaris

Pemphigus vulgaris has been associated with Hodgkin's disease[56], in which case the two diseases can run a parallel course. The relationship of solid tumors to pemphigus vulgaris is less well defined. Pemphigus vulgaris has been reported in association with many solid tumors, but these have been small series or isolated case reports. It has not been possible from these studies to decide whether there is a greater than expected incidence of malignancy in these patients.

Recently, five patients with underlying neoplasms were described in whom painful mucosal ulcerations and polymorphous skin lesions developed, usually with progression to blistering eruptions on the trunk and extremities[57]. Histologic examination showed vacuolization of epidermal basal cells, keratinocyte necrosis, and acantholysis. Immunofluorescence testing revealed atypical pemphigus-like autoantibodies in perilesional epithelium and serum from all five patients. These five patients with cancer had a novel acantholytic mucocutaneous disease characterized by autoantibodies that were pathogenic after passive transfer. The autoantibodies reacted with an antigen complex composed of desmoplakin I, the 230-kd antigen of bullous pemphigoid and two as yet unidentified epithelial antigens. The authors suggest the term "paraneoplastic pemphigus" for this disease.

5.1.19. Dermatitis herpetiformis

Dermatitis herpetiformis is reported to be associated with intestinal lymphoma[58, 59], but other types of malignancy have also been reported. It is associated with gluten sensitivity, and the presumed etiology of the lymphoma is the resulting chronic antigenic stimulation. The lymphoma, when it occurs, is usually a diffuse histiocytic lymphoma.

In a retrospective study of 109 patients with dermatitis herpetiformis, malignant tumors developed in seven patients, the expected incidence being 2.93; giving a relative risk of 2.38 [60]. In three of the patients the malignancy was a lymphoma, giving a relative risk of 100 for this tumor (expected incidence 0.03). Patients treated with a gluten-free diet appeared to have a reduced risk of developing malignancy compared with those taking a normal diet (relative risk with gluten-free diet 1.01 and with normal diet 3.09).

5.1.20. Pruritus

Pruritus has been associated with malignant disease[61, 62] but must be considered to be a very unspecific sign. In Hodgkin's disease pruritus is common and often worse at night. It starts in the legs and later engages the whole body. The patients describe the itch as burning, and it is seldom the first sign of the disease. Alcohol-induced itch in association with Hodgkin's disease has been described.

Pruritus is also seen in some cases of leukemia, and there are occasional case reports of other malignancies which might be associated with pruritus[63]. The literature provides scant insights, but a number of patients with hematologic malignancies have generalized pruritus at some time during their disease and it seems advisable that all patients with generalized pruritus should have a comprehensive physical examination, a chest x-ray and routine blood tests[62]. Itching associated with polycythemia vera is characteristically provoked by contact with water, and is probably independent of the temperature of the water.

5.1.21. Erythroderma

Erythroderma is well known by all dermatologists. It is characterized by cutaneous erythema, edema and often scaling of most of the skin surface. In roughly half of the cases an etiological factor can be identified and includes an excerption of a previous skin disease in 30%, a drug reaction in 10 to 15 %, and a malignancy in 10 to 15% of cases[64]. The malignancies associated with this sign are listed in Table 4.

TABLE. 4- Malignancies associated with erythroderma.[64]

Lymphoma
Histiocytic
Lymphocytic
Hodgkin's
Acute or chronic leukemias
Myeloid
Lymphocytic
Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
Carcinomas (including lung, cervix, colon, stomach, prostate, pancreas)
Multiple myeloma

5.1.22. The sign of Leser-Trélat

Multiple eruptive seborrheic keratoses characterize the sign of Leser-Trélat. It is difficult to evaluate the significance of this sign as many individuals have many seborrheic keratoses. It is important to notice that in this sign the seborrheic keratosis come suddenly and have an explosive nature.

A 1983 literature review found 39 cases of Leser-Trélat associated with malignancy[65]. The majority of the patients had a gastrointestinal malignancy.

However, we have recently evaluated the possible association of malignant disease with 1,752 consecutive cases with seborrheic keratoses[66].

In the first part of the study the Swedish Cancer Registry was searched for records reporting malignancies in the study population (1958-1983) and the expected number of malignancies was calculated on the basis of age- and sex- standardized incidence data.

In the second part of the study records of individuals with malignancy within one year before or after the diagnosis of seborrheic keratosis were reviewed with regard to the possibility of the sign of Leser-Trélat.

In the third part, a case-control study was performed to evaluate the possibility of eruptive seborrheic keratoses among the non-cancer patients in the study population. The results showed a slightly increased risk of cancer in the study population, (relative risk = 1.2; 95% CI: 1.0-1.3), mainly due to an increased risk of cutaneous squamous cell carcinoma. In 62 patients with seborrheic keratoses, a malignancy (excl. skin) was diagnosed within one year before or after the diagnosis of seborrheic keratosis. Of those 62 patients, 6 were regarded as possibly having presented with the sign of Leser-Trélat. Only one of the 6 had been diagnosed as having the sign. For the other 5 patients, the sudden appearance had been noted in the records but no attention to the sign had been paid. For all of the 62 cases with seborrheic keratosis

and malignancy within one year, an age- and sex- matched control patient without cancer was selected from the study population and the records were reviewed regarding to the possibility of a sudden and eruptive appearance of the seborrheic keratoses . Among the controls, 5 patients were regarded as possibly having presented with the sign of Leser-Trélat.

We conclude that the study gives no evidence to support the opinion that eruptive seborrheic keratoses are related to internal cancer risk.

5.1.23. Erythema gyratum repens

Erythema gyratum repens (gyratum: arranged in rings or convolutions) is a cutaneous eruption that consists of raised erythematous bands that move like waves over the body, mimicking a wood grain. The first patient was described in 1952[67] and today only about 35 patients have been described[68], almost all of whom have had internal neoplasia. The disease often begins on the arms or legs and later becomes generalized. The erythematous bands migrate across the skin surface at daily rates of 0.2 to 0.5 cm[68].

5.1.24. Migratory thrombophlebitis

Multiple-lesion migratory superficial thrombophlebitis is often associated with an underlying carcinoma[69], and when this syndrome is present the patient should be carefully examined for cancer. Each attack only affects a small part of the vein, but is very painful and the vein is intensely inflamed. The attack is usually over within three weeks but during that time another inflamed vein can be found in another part of the body. The thrombophlebitis may precede the detection of the cancer by many months and is thought to be caused by a hypercoagulable state. The underlying carcinoma is usually visceral, but association with many other carcinomas has been described.

5.1.25. Acute febrile neutrophilic dermatosis

Acute febrile neutrophilic dermatosis (Sweet's syndrome) was first described by Sweet in 1964[70]. This disease is characterized by fever; elevated, tender, erythematous plaques on the face, extremities and trunk; polymorphonuclear leukocytosis; and, histologically, a dense dermal infiltrate of polymorphonuclear leukocytes. Extensive search for underlying organisms is fruitless.

The disease occurs mainly in females. In 1982, 88 cases were reported in the English literature of whom 75% were females[71]. Most patients have no identifiable underlying disease, but several have underlying malignancies, mainly myelogenous leukemia[72]; but solid tumors have also been reported[73].

In a recent description of 29 cases of Sweet's syndrome an underlying disease was found in 50%[74]. A streptococcal infection was evident in six cases, inflammatory bowel disease in three cases, malignancy in four cases, and pregnancy in two others.

5.1.26. Chronic urticaria

Urticaria and angio-edema have been reported mainly in association with lymphoproliferative disorders[75, 76], but association with solid tumors has also been noted[77]. It is not clear whether there is any statistical association between malignancy and chronic urticaria, as suspicion about this association is mostly based on case reports.

5.2. PUVA treatment and risk of malignancy

Photochemotherapy is the combined use of a photosensitizing chemical and artificial ultraviolet A (UVA) radiation. The psoralens are the most important chemical in this aspect. Psoralens are found in plants which include lemon and lime. References dating back to 1500 BC describe the use of the plant psoralen corylifolia for the treatment of vitiligo. Already in 1947 it was shown that psoralens combined with natural sunlight were useful in the treatment of vitiligo. Topical psoralens were used for the treatment of psoriasis by Pinkus in 1951. In 1974 the first report was published on the clinical effects of treatment with oral methoxsalen and artificial UVA radiation[78]. The acronym PUVA (Psoralens and UltraViolet A radiation) was suggested as a name for this new treatment. Since 1974 tens of thousands of patients with various dermatological diseases have been treated successfully with PUVA.

5.2.1. The nature of PUVA

The psoralens have effect only when combined with light. The skin is most sensitive to UVA radiation at one to three hours after an oral intake, but remains sensitive for up to 12 hours. The most common psoralens used for oral intake are 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP). For topical treatment, trimethylpsoralen (TMP) is used almost exclusively[79]. It is claimed that the side effects are less with 5-MOP. The absorption maxima of the psoralens lie between 210 and 330 nm, but the spectrum for oral PUVA is between 320 and 335 nm[80]. The rationale of PUVA therapy is to induce remission of the skin disease by repeated, but controlled, phototoxic reactions. How PUVA really works in detail is not known. Neither UVA nor psoralens alone are effective, but together they are very effective. When psoralen-treated skin is exposed to UVA radiation at least two types of reaction occur. Type I reaction does not require oxygen, and the site of cellular damage is primarily in the DNA of cell nuclei. Type II reaction requires oxygen and involves the formation of reactive oxygen species and free radicals. The photoexited psoralen can now react directly with DNA and form single-strand photoadducts with thymidine bases and bifunctional photoadducts with interstrand cross-links between opposite thymidine base pairs. It is believed that psoralens that form bifunctional adducts cause photosensitization, induction of skin cancer, and improvement of psoriasis[81]. Psoralens that form monofunctional adducts do not show this effect. Most hypotheses about the mechanism of PUVA therapy of psoriasis assume photoconjuction of psoralens to DNA and a subsequent suppression in mitosis, DNA synthesis

and cell proliferation. It is also possible that PUVA may affect specific cells of the immune system which are believed to be involved in the pathogenesis of skin disease, and since phototherapy is known to be of value in several other immunologic diseases (mycosis fungoides, vitiligo, atopic dermatitis), it is reasonable to assume that PUVA has an immune-modulating effect[82, 83].

5.2.2. UVA radiation

Artificially produced electromagnetic radiation has been used for treatment in medicine since the beginning of the century. Several treatment systems using electomagnetic radiation of different wavelengths have been used. The following types of UV radiation are commonly used for dermatological treatment:

1. UVB radiation

2. UVA radiation in combination with psoralens (PUVA)

The action spectrum for treatment lies between 320 and 380 nm. Some reports indicate that shorter wavelengths between 320 and 340 nm are more effective, but other have indicated that the 330 to 360 nm range is more appropriate. Today a wide variety of UVA equipment is available commercially. For safe therapy, dosimetry is recommended. The spectral power distribution of the UV system has to be known and the UVA dose must be adjusted accordingly. The UVA doses are expressed as J/cm^2 and are usually measured with a photometer with a maximum sensitivity at 360 nm.

5.2.3. The biological effects of PUVA

PUVA treatment produces an inflammatory reaction in the skin which is manifested by a delayed phototoxic erythema. This reaction is related to the individual, skin type, the dose of the psoralen and the UVA dose. This reaction can therefore be fairly easily predicted. It differs from sunburn and UVB erythema in several aspects. Common sunburn and UVB erythema appear after 4 to 6 hours and peak 12 to 24 hours, while PUVA erythema does not appear before 24 hours and peaks 48 to 72 hours after exposure. The dose response curve rises more steeply and hence a small dose increase can cause intensive erythema. Severe reactions can cause blisters or even skin necrosis. Overdoses of UVA can cause edema, pruritus and sometimes a unique stinging sensation of the skin. The second effect of PUVA is pigmentation. This usually follows erythema, but can occur without preceding erythema. The pigmentation is at its maximum a week after the treatment and can last several months.

5.2.4. Methods of treatment

The common principle in PUVA treatment is to hold the dose of the psoralen steady but vary the patient's UVA dose according to the skin type. The minimal phototoxic dose (MPD) can also be used as a guideline. A MPD is defined as the minimal dose that, after psoralen ingestion, produces erythema when the patient is exposed to various test doses on small areas. The psoralen is administered according to the patient's weight. Treatment is divided in two phases, the clearance phase and the maintainance phase. The intensity and length of treatment vary between diseases.

5.2.5. PUVA treatment

Guidelines exist for selecting patients for PUVA treatment[84]. Children should normally not be treated. The following factors are a relative contraindication: history or presence of melanoma, dysplastic nevi or epithelial malignancy, arsenic intake or ionizing radiation, conditions that can be aggravated by PUVA, history of allergic reactions to psoralens, lactation and history of light-sensitive disorders. Pregnancy is considered an absolute contraindication. Several diseases have been reported to be responsive to PUVA. Two major treatment protocols exist for the treatment of psoriasis, one in the USA and one in Europe. The European protocol is more aggressive than the American one. In the U.S. protocol the patients are skin typed, and then treated two to three times a week with an increase of 0.5 to 1.5 J/cm^2. In the European protocol patients are treated four times a week and doses are kept close to MPD. Obviously the European protocol is more aggressive and its goal is to cure the patient before pigmentation occurs and to use the minimum amount of total energy to achieve this goal. In Sweden treatment is mainly according to the U.S. protocol, although some centers treat according to the European protocol. The following list (Table 5) of indications for PUVA treatment was compiled by Gupta and Andersson in 1987 [85].

TABLE 5.- A list of skin diseases that have been treated with PUVA.

Psoriasis
Mycosis fungoides
Vitiligo
Alopecia areata
Atopic and dyshidrotic eczema
Persistent palmoplantar pustulosis
Urticaria pigmentosa
Polymorphous light eruption
Ichthyosis linearis circumflexa
Hypereosinophilic syndrome
Solar urticaria
Chronic graft-versus-host reaction
Scleromyxedema
Actinic retuculoid
Lichen planus
Nodular prurigo
Pityriasis lichenoides
Keratosis lichenoides chronica
Lymphomatoid papulosis
Hypopigmented sarcoidosis
Transient acantholytic dermatosis
Pityriasis rubra pilaris
Generalized granuloma annulare

5.2.6. General side effects

Some of the side effects of PUVA treatment are directly related to the ingestion of the psoralen. Nausea is seen in up to 20% of patients, but only in a small percentage of treatments. Other frequent side effects, such as erythema and itching, are related to the nature of the treatment. As has been pointed out earlier, PUVA erythema appears late and the dose-response curve is steep compared to that of UVB. A small increase in dose can therefore lead to marked erythema.

Animal studies have shown that PUVA may possibly induce cataracts[86]. Psoralens remain in the eye lens for 24 hours following each PUVA treatment. To date, however, nc cataracts have been reported as caused by PUVA in patients using proper eye protection. As long as there is uncertainty about the actual risk, it is recommended that appropriate protection is worn during the entire period of increased photosensitivity.

Repeated phototoxic injury will generally result in actinic damage. PUVA has effects both on the epidermis and the dermis. UVA affects the dermis to a greater extent than UVB[87]. Clinically PUVA-treated patients show premature

aging of the skin characterized by wrinkling and dryness, as well as the development of discolored spots on the skin[88]. Histologically, hyperkeratosis, acantosis, melanosis and focal dystrophy are seen[85].

During PUVA therapy the leucocytes, while circulating through the dermis, are exposed to the UVA radiation. It is therefore not surprising that PUVA-treated patients show a number of immunological abnormalities. There is a decrease in the total number of T lymphocytes, T suppressor cells and T helper cells[89, 90, 91], possibly as a result of impaired IL-2 production[92]. Dose-dependent effects on lymphocytes have been shown[93]. It has been shown in animal and human studies that PUVA can inhibit cell-mediated immunity[94, 95]. Reduced intensity in the response to contact allergens has been shown in humans[96, 97]. A reduction of Langerhans cells in the skin is noted in several reports[98, 99]. This reduction might affect antigen presentation capacity and, combined with the effect on T suppressor cells, this might lead to increased succeptibility to tumors. However, this is not known, and the long-term effect and significance of the changes described above remain to be elucidated.

5.2.7. PUVA treatment and skin cancer

Several studies have dealt with the potential risk of cutaneous cancers in patients receiving combined psoralen and ultraviolet A phototherapy (PUVA) for treatment of skin disorders[100, 101, 102, 103, 104, 105]. Most of these studies indicate a definite risk of squamous cell cancer of the skin for patients on long-term PUVA treatment (Table 6). A recent report notes that there is an alarming risk of genital tumors among men receiving PUVA, although co-factors such as tar treatment might also contribute to the risk[100].

On the basis of *in vitro* experiments and animal studies, PUVA treatment is known to have both mutagenic and carcinogenic effects[106]. The photochemical reaction involves the interaction of psoralens with DNA and it has been shown that PUVA induces an increased number of sister chromatoid changes *in vitro*[107]. PUVA treatment has also been shown to be carcinogenic in animals. In 1979, in a 16-center study, Stern and colleagues reported an increased risk of non-melanoma skin cancers in patients treated with PUVA only 2 years after the initiation of PUVA. The short latency time and the fact that many of the patients had received other types of potentially carcinogenic treatment, made evaluation of these findings difficult. Several large-scale European studies failed to confirm this increase in skin cancer in PUVA-treated patients[103, 108]. This raised the question whether PUVA itself is oncogenic, or simply acts as a promotor in patients who have been exposed to other risk factors. Long-term evaluation of the American 16-center study has clearly shown an increased risk in long-term PUVA-treated patients[102, 104].

After ten years of evaluation, 162 patients were found to have a total of 391 squamous cell carcinomas and 218 basal cell carcinomas. For high-dose

treated patients, the risk was elevenfold[102]. Similar results were obtained in an independent, but smaller, American study[101]. This high risk has, until recently, not been confirmed by European multi-center studies[103, 108]. Lately Bruynzeel and colleagues in the Netherlands reported a significant increase in both squamous and basal cell carcinomas in 260 PUVA-treated patients, compared to the general Dutch population. The incidence of squamous cell carcinoma was 1.5%, which is low compared to the American 16-center study, where it was 11.2%[102].

TABLE 6.- Comparison between studies of cancer risk in PUVA- treated patients. The table shows the number of patients in the study, the mean observation time, the mean UVA dose, the mean number of treatments and squamous cell carcinoma (SCC) incidence.

Author	No of patients	Mean obs time (years)	Mean UVA dose (J/cm^2)	Mean no treatm.	SCC incidence
Stern 1979	1380	2.1	*	*	2.2
Honigsman 1980	418	1-5	728	27	1.2
Roenigk 1981	631	4	*	92	1.6
Lassus 1981	525	2.1	330	68	0.2
Ros 1983	250	4.1	735	100	0
Stern 1984	1286	5.7	1500	199	8.1
Eskilinen 1985	1047	4.2	499	*	0.4
Tanew 1986	297	5.2	1065	*	3.3
Hensler 1987	1643	8	745	112	2.1
Stern 1988	1380	10	*	*	11.7
Forman 1989	551	4.8	1861	*	3.8
Bruynzeel 1991	261	12.8	824	105	1.5
Present 1991	4799	7.1	400	63	0.5

**: Information about item not available.*

Patient selection, treatment with previous carcinogens, treatment schedules, sun exposure and skin type may explain some of these discrepancies. When total UVA dose is compared the European studies certainly have a much lower dose than the American (Table 6).

The conclusion is that PUVA treatment is probably involved in squamous cell carcinogenesis. The main concern, however, is malignant melanoma; but so far there have been no indications that there is increased risk of malignant melanoma in PUVA-treated patients. Finally, although there is comprehensive clinical experience of PUVA treatment, the risk of potential long-term side effects still remains to be ascertained. As PUVA therapy offers many patients the chance to resume normal lives, this must be considered when evaluating its hazards.

5.3. Risk assessment in dermatology

In modern medicine, new treatments are frequently introduced and it is therefore very important to evaluate the potential risks that can be associated with the treatment. In dermatology many signs, symptoms and even certain diseases have been associated with internal diseases, particularly malignancy. To evaluate the significance of a proposed association can be difficult, especially if the association is based on single reports in different settings. The paradigm for assessing the side effects of a new therapy is the double-blind randomized controlled clinical trial. In the assessment of long-term toxic side effects, such trials may not be practical. Patients may be unwilling to rely on a single form of therapy over long periods of time. This problem is specially likely to occur in the case of chronic diseases such as many skin diseases, the severity of which varies over time. Hence, the most appropriate treatment for an individual will also vary over time.

5.3.1. Case-control studies

The retrospective case-control study has been used to assess the relative risk associated with a given exposure, sign, symptom or dermatosis for the development of a given disease. In the case-control study the individuals with a certain disease are first identified (the cases, ie melanoma) and then compared persons without the disease (the controls). This study design has been used to discover the association between e.g. cigarettes and lung cancer, thromboembolism and oral contaceptives, and stilbesterol and vaginal cancer. After the cases and controls have been identified, information on past exposures and other factors is collected from questionnaires, hospital records, death certificates, cancer registries or other sources. If a higher proportion of the cases were exposed, a link between the disease under investigation and the exposure is suspected. This type of design is probably by far the most frequent type of analytic epidemiologic study and, for a rare disease, often the only practical approach to identifying risk factors. The advantages of case-control studies have been described as follows:

1. Efficient in manpower, cost and time requirements
2. No follow-up required
3. Permit examination of a wide array of factors

4. The ability to consider changes in the amount of exposure over time up to disease onset.

Certain potential problems and limitations of the case-control study are summarized below. Many of these factors also apply to retrospective cohort studies:

1. Information on the potential risk factor may not be available from records or from the subjects' memories.

2. Information on potentially important confounding variables may not be available from records or from the study subjects' memories.

3. Cases may search for a cause of their disease and hence be more likely to report an exposure than controls are.

4. The investigator may be unable to determine with certainty whether the suspected agent caused the disease or whether the occurrence of the disease caused the person to be exposed to the agent.

5. Identifying and assembling a case group representative of all cases can be unduly difficult.

6. Identifying and assembling an appropriate control group can be unduly difficult.

Because of these weaknesses, the case-control study is often considered to be a type of study that merely provides leads to be followed up by more definite cohort studies. Because the actual disease rates in the population at risk, from which both cases and controls are drawn, are not known, the morbidity ratio cannot be determined directly, but can be determined by using the odds ratio. This gives the relative risk ratio (often called the odds ratio) by dividing the odds of the exposed having the disease by the odds of the non-exposed.

5.3.2. Cohort studies

Cohort studies provide a means of establishing with some precision the incidence of events of interest in a defined population. The studies reported in this thesis are all examples of cohort studies. The advantages of such studies include the rapidity with which end points of interest can be assessed and the ability to prospectively document each patient's exposure to both the treatment being studied and other agents.

Cohort studies are often divided into two types, the retrospective and the prospective. In the prospective cohort study the investigator starts with a

group of individuals divided into those who are exposed to a possible risk factor and those who are not. The group is then followed and new cases of the disease under investigation notified. At the end, the number of cases among the exposed individuals is compared to the number of cases among the non-exposed individuals. Obviously this gives a very good control over cofactors, and information is not usually missing. The drawback is that this kind of study takes a very long time and is expensive.

In the retrospective cohort study, the cohort of individuals is identified based on some characteristics in the past. The group is then followed forward in time up to some defined point in the more recent past. During this follow-up time the disease experience is reconstructed by some means. Clearly, if this disease reconstruction relies solely on the patients' memories it is an obvious source of possible error. Some diseases are registered in official records such as cancer registries or in-patient registers which often provide very reliable data over long periods of time. Retrospective cohort studies therefore have the distinct advantage over prospective cohort studies that they can be completed in a much shorter time. This is particularly important when diseases such as cancer are investigated, where the effect of carcinogens can sometimes first be observed after a decade-long latency. The weakness of the retrospective cohort study is that information must be gathered from the past. The study is limited to the information that exists. Information on possible important confounding variables is often difficult or impossible to obtain. This turned out to be a problem in studies (III, VI) in this thesis . Consequently the results can be far from definitive causal relationships. This can sometimes be compensated for by inserting a case-control study into the cohort study, as was done in the present study (VII)[109].

5.3.3. Swedish registers

In Sweden the availability of registers, some intended for research purposes, others mainly for administrative purposes, makes retrospective cohort studies feasible (Table 7). Also, the Swedish personal identification number system makes cross-linkage between various registers possible. By these means a cohort of individuals is identified based on one register, i.e. patients with dermatomyositis in the national In-Patient Register. These patients are then followed forward in time up to some defined point and the outcome, i.e. malignancy, investigated by linking the patient cohort with the national Cancer Register. The national coverage of these registers ensures that no individuals are lost during follow-up, and by comparing the outcome with the general Swedish population, a risk assessment is obtained. Long national documentation of malignancy makes this risk quote very reliable.

TABLE 7.- Some Swedish registries used in epidemiological research.

Cancer Register
In-Patient Register
Cancer-Environmental Register
Cause-of-Death Register
Total Population Register
Census (every five years)
Psyciatric In-Patient Register
Birth Register
Birth Defect Register

The Cancer Register, The Cause-of-Death Register and the In-Patient Register need no further discussion. The Cancer-Environmental Register is created by matching information from the five-yearly census with the Cancer Register. By these means a register is created which includes information from the Cancer Register and occupation. This register has been the basis of many studies of the association between occupation and cancer. The Total Population Register includes all inhabitants of Sweden. Every five years there is a census where information is gathered about occupation, education and household. All psychiatric hospitalizations are registered in a way similar to non-psychiatric hospitalizations in the Psychiatric In-Patient Register. All births in Sweden are registered in the Birth Register, using which a special Birth Defect Register has been created.

6. OBJECTIVES OF THE STUDY

The general aim of the study was to investigate the development of malignancy in patients with dermatological diseases. Specific aims were to:

- Develop a microcomputer program to estimate cancer risk in a patient cohort based on incidence figures from the Swedish Cancer Registry and to use this program to evaluate cancer risks in patients with various dermatological diseases
- evaluate cancer risk in patients with chronic urticaria
- investigate the relation between genital warts and cancer, particularly cancer of the uterine cervix
- investigate the risk of other malignancies in patients with basal cell carcinoma
- study cancer incidence in lichen planus lesions, both in the skin and in the mouth
- investigate cancer incidence in patients with positive patch tests
- evaluate the risk of skin cancer in patients treated with psoralens and ultraviolet A radiation (PUVA)
- study the relation between dermatomyositis or polymyositis and malignancy, and to investigate mortality in these patient groups.

7. Material and Methods

7.1. The Material

7.1.1. The Swedish In-Patient Registry

From 1964 through 1983, the Swedish National Board of Health and Welfare collected information about individuals who were hospitalized in the country. From 1964 through 1969, only some counties were included, but since 1970 this computerized in-patient register has been virtually nationwide. Each time a patient is discharged from a hospital a record is added. The types of information registered are listed in Table 8.

The quality of the register varies. From some centers and for certain periods there has been no check of the personal identification number, resulting in records with incomplete personal identification numbers, which makes linkage with other registers difficult. Generally, after 1977 most regions have checked the personal identification number at the time of registration. In 1977 7% of all records were without complete personal identification numbers, but in 1983 only 2% were without[110]. Between 1964 and 1969 only 0.4% of all records had a wrong diagnosis code, but this has varied, and numbers as high as 1.7% have been noted. About 90% of these errors are missing diagnosis code and in only 10% are the codes wrong. In 1976, 70,000 records were selected randomly and 8% lacked a personal identification number. In 1969, 901 records from three departments were examined. In 1.6% of the cases the diagnosis was wrong. In paper VIII, patients with the diagnosis of dermatomyositis or polymyositis were selected from this register and every tenth original medical record was reviewed. All diagnoses were correctly registered, but in 7% of the cases two dermatologists who reviewed the records considered the diagnosis at the local hospital as not probable.

This is a unique register with over twenty continuous years of registration of in-patients in Sweden. The quality varies, but the errors consist mainly of missing information, not wrong information. The missing personal identification numbers can often be complemented. Too few quality controls have been done. For these reasons it is advisable to use the register only after a quality control.

TABLE 8- Variables recorded in the Swedish In-patient Registry.

Medical region code
County code
Hospital number
Department number
Medical record number
Date of birth
Personal identification number
Sex
Civil status
Insurance number
Date of admission
Admitted from:
Home, acute
Home, not acute
Another hospital, acute
Another hospital, not acute
Earlier admittance for same disease
Date of discharge
Discharged to:
Home
Another hospital
Dead, autopsy
Dead, no autopsy
Leave from hospital
Main diagnosis
Three minor diagnoses
E-code (Classification of accidents....)
Reason for death
Date for operation
Six surgical procedure codes
Six codes for anesthesia

7.1.2. The Swedish Cancer Registry

Nationwide information on the cancer incidence in Sweden has been available since 1958, when compulsory registration began. The Cancer Registry collects information on diagnosed cancers both from clinicians and pathologists. Thus, the majority of cases are notified with two reports. The Cancer Registry contains information about all malignant neoplasms, certain precancerous tumors and some histologically benign tumors (mainly of the central nervous system and the urinary system). The registration follows the guidelines issued by the World Health Organization[111]. The data registered can be seen in Table 9.

At the time of writing computerized information was available about 1,041,388 cancer cases for the years 1958 to 1987. Information from death certificates is available to the Registry, supplying date and causes of death. This information is updated annually. Since 1982 all registration and validation of incoming reports has been done at six local cancer registries and then accumulated at the National Cancer Registry. These registries are associated with the oncological center in each medical region of Sweden.

The following diseases are reported to the Cancer Registry:

1. All definitely malignant neoplasms (e.g. carcinoma, sarcoma, malignant lymphoma, leukemia and malignant teratoma)

2. Carcinoid tumors of digestive organs, granulosa-theca cell tumors of the ovary, thymoma, adamantinoma and chordoma

3. Histologically benign tumors of the central nervous system and meninges, transitional cell papillomas of the urinary tract, all tumors of the endocrine glands (except the thyroid) and the chromaffin system

4. Precancerous lesions of lip, mouth, larynx, bronchus, trachea, cervix uteri, skin, vulva and vagina, gastro-intestinal polyps with suspected malignancy, bronchial adenomas, atypical intraductal proliferations of the breast (carcinoma *in situ* type) and adenoma phyllodes, precancerous endometrial lesions, hydatidiform moles of placental tissue, and ovarial cystadenomas with suspected malignancy.

Basal cell carcinomas are not registered. Diseases mentioned under 1-3 are included in total cancer incidence tables.

TABLE 9.- Data registered in the Swedish Cancer Register.

A. FROM CANCER REPORTS
- Unique personal identification number
- Sex
- Name
- Domicile
- Hospital
- Hospital department
- Hospital-record, number and year
- Pathology/cytology department
- Specimen number, and year when specimen was taken
- Site of tumor. Code based on 7th WHO revision
- Tumor serial number (when more than one primary was diagnosed)
- Malignancy (yes/no)
- Histological type (WHO/HS/CANC/24.1 histology code)
- Basis of diagnosis
  - 1 Clinical only
  - 2 X-ray
  - 3 Histological examination
  - 4 Autopsy with histopathological examination
  - 5 Cytological
  - 6 Gross examination at surgery
  - 7 Autopsy without histopathological examination
- Date of diagnosis
- Died of cancer (yes/no)
- Diagnosis made incidentally at autopsy (yes/no)

B. FROM DEATH CERTIFICATES
- Date of death
- Causes of death

The quality of this register has been the subject of many studies[1,12]. Studies on completeness of the cancer registration showed that the estimated registration deficit was 4 percent when the Cancer Register was compared with the Swedish Cause-of-Death Register and the In-Patient Register in Stockholm. When the diagnosis had been histologically confirmed, the registration deficit was 2 percent.

In conclusion, the Swedish Cancer Register has been nationwide since 1958, all data is checked by the staff of the local registries, and extensive studies have shown that in most cases the quality of the information is good.

7.1.3. The Swedish Cause-of-Death Registry

Information about deaths was first systemically registered in Sweden in 1749. Information is collected about all deceased persons that have been registered in Sweden, whether they have died in Sweden or abroad. The underlying cause of death is generally determined from data on medical death certificates, which are designed in accordance with the internationally established norm. Information registered in this register is shown in Table 10.

TABLE 10.- Variables registered in the Swedish Cause-of-Death Register.

Personal identification number
Date of death
County
Community
Type of death certificate
Disease or condition directly leading to death
Number of antecedent causes
Up to six antecedent causes (diagnoses)
Municipality
Sex
Age
Civil status
Country of birth
Year of Swedish citizenship (if immigrated to Sweden)

7.1.4. The Diagnosis Registry at the Karolinska Hospital

At the Department of Dermatology at the Karolinska Hospital in Stockholm, diagnoses have been registered continuously since 1969. The register contains the name of the patient, personal identification number, address and diagnosis. All patients must have a diagnosis on their medical record. Yearly, all diagnoses made in earlier years are also entered if the patients have been seen at the Department that year. The register includes both in- and out-patients. Since 1949 diagnoses at the dermatopathological section of the clinic for the histopathological investigations done have also been registered.

7.1.5. The Swedish personal identification number

Every person permanently living in Sweden, which has a population of 8.3 million, gets a personal identification number. This number is unique and used in all population statistics, health services and official services in Sweden. It composed of six digits based on year, month and day of birth, supplemented with a registration number (three digits) and a check digit. The check digit makes it possible to validate the number. The identification number is not affected by changes in names. This identification number allows record linkage between different registers.

7.2. The Methods

7.2.1. Statistical methods

Relative risk of death and cancer morbidity were calculated with 95 percent confidence intervals. The follow-up time for each patient was calculated on the basis of the time from registration of the diagnosis of the skin disease under observation, or in study VII fom the time of first treatment, to the last year on-line at the Cancer Registry at the time of study. To allow for deaths during the study period, deductions were made on the basis of life tables for the whole Swedish population. In study VIII, the patient material was linked with the Swedish Cause-of-Death Register to identify patients who died during the follow-up period. These calculations were done with the CANEST program. The program calculates the risk of cancer for each patient individually. The calculation is based on incidence data for the years between the first diagnosis for the skin disease (or first treatment with PUVA in study VII) and the last year on-line at the Registry, at the time of study. Total risk was calculated from the sum of the individual risks. After estimating the ratio between observed and expected numbers of malignancies, the Poisson distribution was used to calculate the relative risk with its confidence intervals.

7.2.2. Computational methods (I)

A model of one patient during a hypothetical study is shown in Fig. 1. The patient enters the study the same year as the dermatosis is diagnosed (YD). At that time there is a certain likelihood that the patient already has cancer. This likelihood is equal to the prevalence in the population at that point. The observation period, or the follow-up period, is defined as the time between the diagnosis of the dermatosis and the last year incidence figures are available on-line in the Swedish Cancer Registry (CR). At the time of writing, this year is 1987. The probability that a certain individual acquires a malignancy during one year of observation (YO), is equal to the incidence of that particular malignancy for the age of the patient, and that particular calendar year, times one (year), minus the mortality rate. This can be expressed with the following formula:

PROBABILITY = INCIDENCE X (1-MORTALITY RATE)

This calculation must be repeated for each cancer form and for each year of observation (YO). As the patient gets older he moves between age groups

and new incidence figures are employed each calendar year. For one patient observed over 10 years, roughly 500 such calculations have to be done. An estimate of the number of malignancies in the group is then the sum of the probabilities for all individuals in the group. The program loop that does these calculations is shown in Table 11. The results are stored in a file.

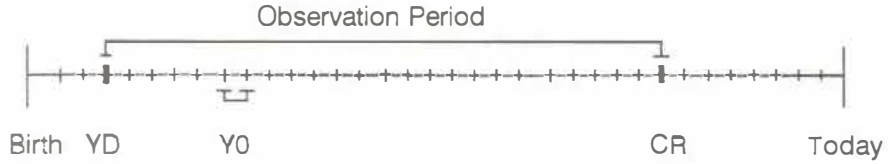

Fig. 1 - Model of a hypothetical patient during the study. See text for details.

Information about the actual number of malignancies in the group is obtained by linking the patient file with the Cancer Register. The relative risk (RR), or standardized morbidity ratio (SMR), is simply computed by dividing the number of observed malignancies by the expected number:

RR = OBSERVED/EXPECTED

Several methods can be used to assess the significance of this ratio. The most classical method is the one proposed by Mantel and Haenszel in 1959. This is only suitable when there is no interaction between the relative risk and the covariate. This does not apply to the Poisson distribution which is traditionally used in this kind of comparison[113]. The Poisson distribution is available from statistical tables or can be computed. The program now looks up the upper and lower intervals for the observed number of cancers based on 95% probability Poisson distribution. By similarly dividing the upper and lower confidence limits for the observed numbers of cancers, by the expected number of cancers, a confidence interval (CI) is obtained for the relative risk (RR) ratio. The results of such calculations can be expressed in the following manner: RR = 1.26; 95% CI: 1.15 - 1.38. In this example the lower CI limit is greater than one, which implies significance at the 95% limit.

7.2.3. The hardware and the software

The CANEST program (I) was developed and tested on an IBM PS/2 computer (IBM Corporation) with an 80386 microprocessor, 120 Mb hard disk and 6 Mb of internal memory. After having reviewed a number of software systems we choose to develop the program with the CLIPPER™ programming language (Nantucket Corporation). Version 5.1 of the compiler was

TABLE 11.- The master loop that calculates cancer risks.

```
SELECT &CXXXXPAT
@ 09,18,16,72 BOX SINGLE
@ 10,19 SAY "RECORDS.....:"
@ 10,43 SAY "RECORDS PROCESSED:"
@ 12,19 SAY "RISK MALES...:"
@ 12,43 SAY "DATASET IN USE....:"
@ 12,62 SAY CXXXXSET
@ 13,19 SAY "RISK FEMALES:"
@ 13,43 SAY "YEARS OF OBSERV...:"
@ 15,19 SAY "TOTAL LOOPS.:"
@ 15,43 SAY "YEAR DIAGNOSED....:"
@ 10,33 SAY ALLTRIM(STR(LASTREC()))
INCCOUNT = 0
DO WHILE .NOT. EOF()
    @ 10,62 SAY ALLTRIM(STR(RECNO()))
    XAGE = DERMAGE
    XSEX = SEX
    XYEAR = DERMYEAR
    YEAR = DERMYEAR
    OBSTIME = INCAREG - DERMYEAR
    SELECT INC58_86
    OBS = 0
    DO WHILE OBSTIME > 0
        OBS = OBS + 1
        @ 13,62 SAY ALLTRIM(STR(OBS))
        @ 15,62 SAY ALLTRIM(STR(YEAR))
        @ 12,33 SAY ALLTRIM(STR(MALRISK[1]/100000))
        @ 13,33 SAY ALLTRIM(STR(FEMRISK[1]/100000))
        * DEFINE DEATHRATE
        TOTDEATH = DEATHRATE(AGEGROUP(XAGE))
        MALDEATH = 1-VAL(SUBSTR(TOTDEATH,1,10))/1000000
        FEMDEATH = 1-VAL(SUBSTR(TOTDEATH,11,10))/1000000
        FOR X = 1 TO NODGN
            INCCOUNT = INCCOUNT + 1
            @ 15,33 SAY ALLTRIM(STR(INCCOUNT))
            TOFIND = STR(ICD7[X],3) + STR(XYEAR,2) + STR(AGEGROUP(XAGE),2)
            SEEK TOFIND
            IF .NOT. FOUND()
                ?? CHR(7)
                ? TOFIND
            ENDIF
            IF XSEX = 1
                MALRISK[X] = MALRISK[X] + (IMALES*MALDEATH)
            ENDIF
            IF XSEX = 2
                FEMRISK[X] = FEMRISK[X] + (IFEMALES*FEMDEATH)
            ENDIF
        NEXT X
        OBSTIME = OBSTIME - 1
        XAGE = XAGE + 1
        XYEAR = XYEAR + 1
    ENDDO && OBSTIME LOOP
    SELE &CXXXXPAT
    SKIP
ENDDO && MASTER LOOP
```

used. CLIPPER is a true compiler originally based on the dBASE III™ programming language (Ashton-Tate Inc).

There are clear advantages in using a compiler, compared with an interpreter. The program runs much faster, the code is protected and it is possible to link together CLIPPER programs and programs written in other languages such as C or assembler. Programs developed with the CLIPPER compiler use a common file format (DBF) shared by many databases and spreadsheets, and this makes it easy to move data to other software programs for further analysis or graphical display. A software link was created to the EXCEL (Microsoft corporation) spreadsheet, and macros were written to format the output for high-quality printing and to do further statistical analysis.

For the patient files, the dBASE IV database was used, and statistical calculations that were not done with the CANEST program were done with the SPSS statistical package.

7.3. The Patients

7.3.1. Chronic urticaria (II)

During the years 1968-83, 1,155 patients with chronic urticaria were seen at the Department of Dermatology, Karolinska Hospital, Stockholm. All had had symptoms for more than 3 months. The patients (Fig. 2) consisted of 704 females and 451 males (median age 32 years, age range 1-85 years). The follow-up period was on average 8.2 years.

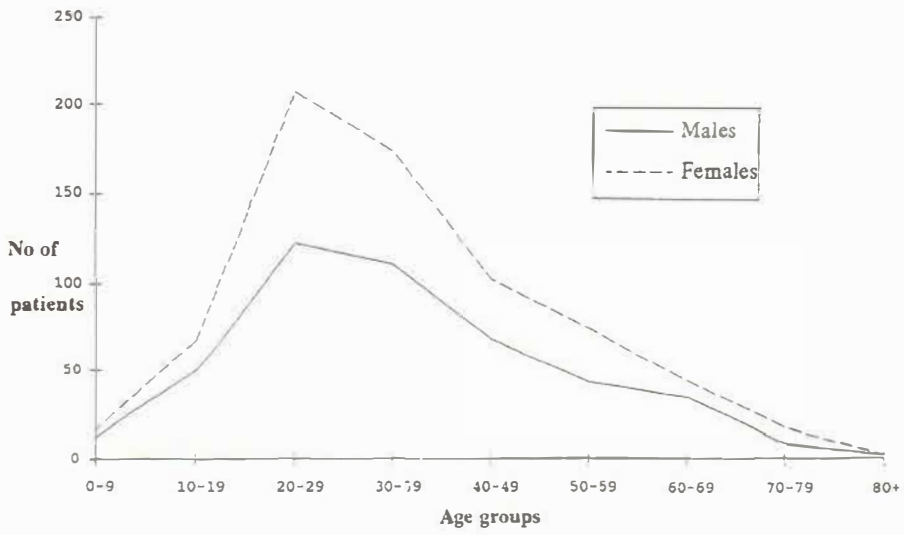

Fig. 2: - Age distribution in 1,155 patients with chronic urticaria.

7.3.2. Condylomata acuminata (III)

During the years 1969-1984, 3,260 patients with condylomata acuminata were seen at the Department of Dermatology, Karolinska Hospital, Stockholm. The patient records were examined and year of diagnosis, age and sex registered. Unfortunately records from patients seen during 1974 and 1975 were not available. The patient population consisted of 2,549 males and 711 females (Fig. 3), median age 23 years, range 1 to 80 years at the time of diagnosis. The follow-up period was 7.8 years on the average.

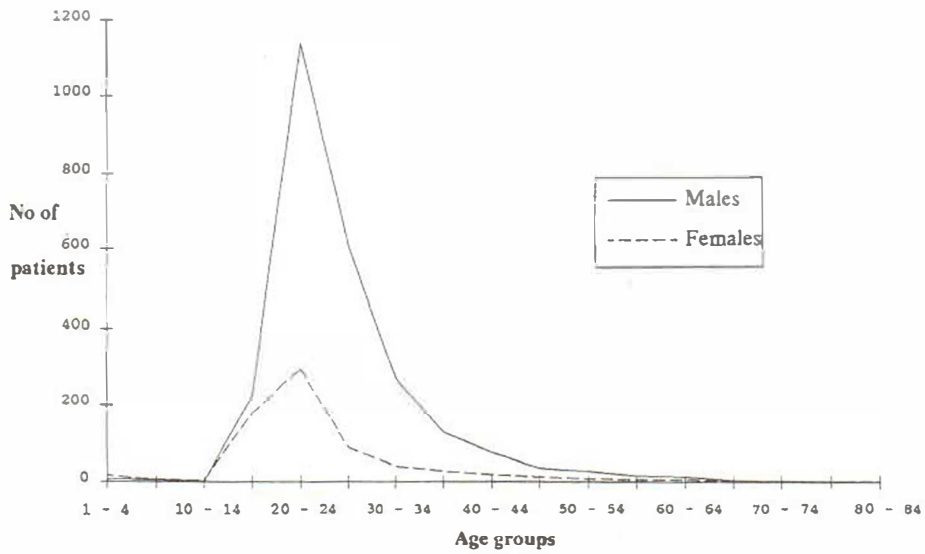

Fig. 3: Age distribution in 3,260 patients with condylomata acuminata.

7.3.3. Basal cell carcinoma (IV)

During the years 1973-1983, 1,151 patients with BCC were seen at the Department of Dermatology, Karolinska Hospital and during the years 1971-1980, 822 patients were seen at the Department of Dermatology, South Hospital, Stockholm, Sweden. All the basal cell carcinomas were histologically verified. The patient population consisted of 934 males and 1,039 females, median age 68 years, range 9-98 in the year of diagnosis (Fig. 4). The follow-up period was 6.5 years on the average.

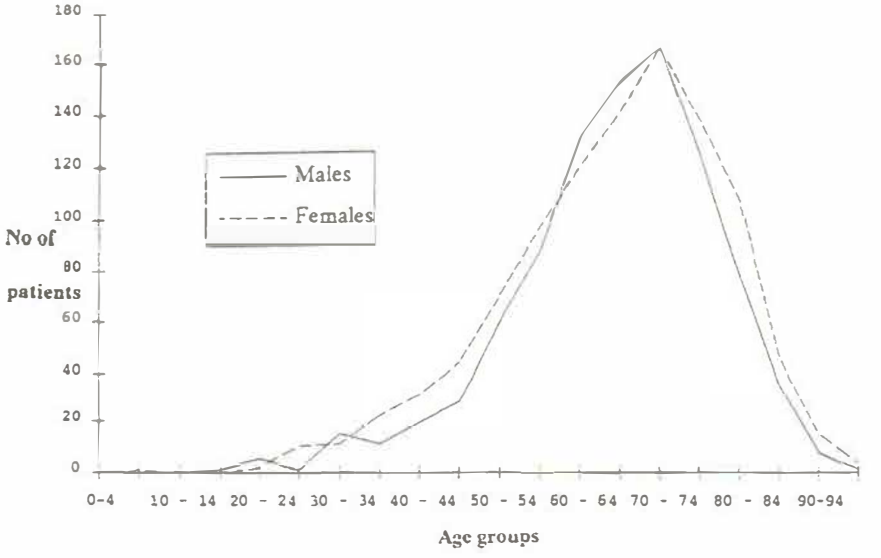

Fig. 4: Age distribution in 1,973 patients with basal cell carcinoma .

7.3.4. Lichen planus (V)

2,071 patients with lichen planus seen between 1969 and 1985 were followed at the Departments of Dermatology, at the Karolinska and South Hospital, Stockholm. From this register, year of diagnosis, age and sex was extracted. Unfortunately records between 1974 and 1978 were not available at the Karolinska Hospital. The patient population consisted of 1,023 males and 1,048 females, median age 52 years, range 1 to 96 years at the time of diagnosis (Fig. 5). The average follow-up period was 9.9 years.

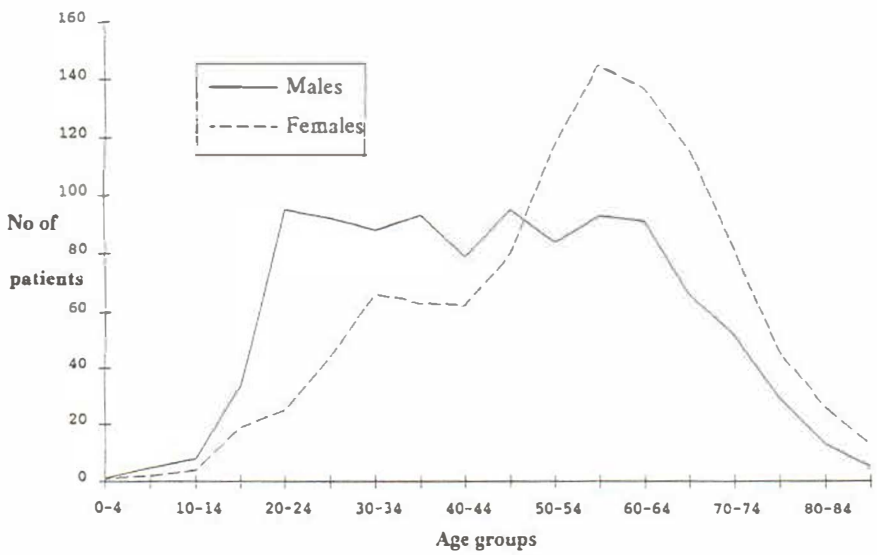

Fig. 5: Age distribution in 2,071 patients with lichen planus.

7.3.5. Positive patch tests (VI)

During the years 1963 to 1983, 5,858 patients at the Departments of Dermatology and Occupational Dermatology, Karolinska Hospital and the Department of Dermatology, South Hospital, Stockholm had positive patch tests in the standard or extended series. The test results were graded as has been recommended by the International Contact Dermatitis Research Group. Patients with +, + + or +++ were included in the study. The patient records were examined and year of diagnosis, age and sex registered. The patient population consisted of 2,183 males and 3,675 females (Fig. 6), median age 41 years, range 6 to 93 years, at the time of first positive patch test. The average follow-up period was 8.8 years.

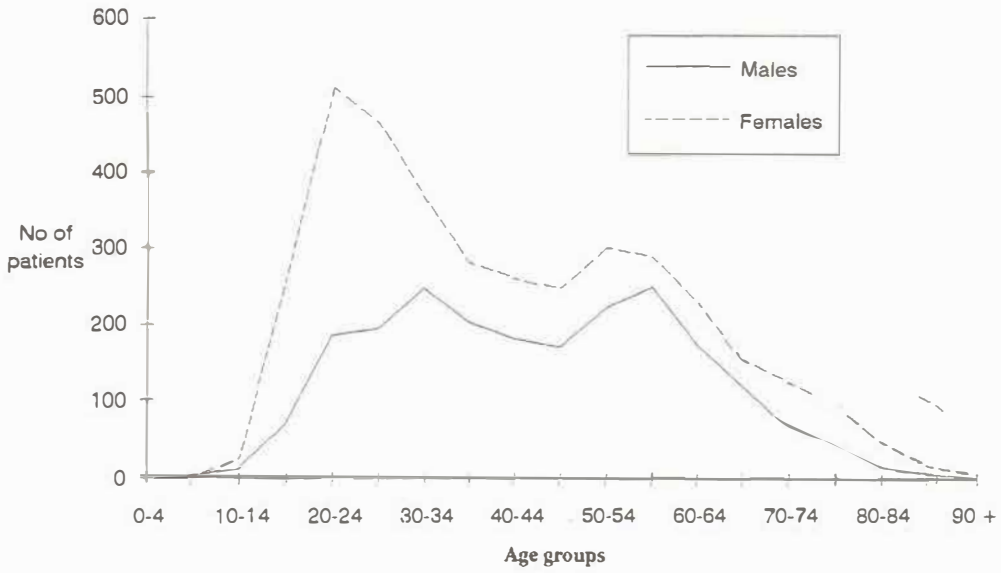

Fig. 6: Age distribution in 5,858 patients with positive patch tests, at the time of the first positive patch test.

7.3.6. PUVA and cancer (VII)

Between 1974 and 1985, 4,953 patients received PUVA for the treatment of skin disorders at eleven dermatological centers in Sweden (Table 12). Seventy-three patients could not be followed because of insufficient information, and 154 patients were excluded because the indication for PUVA was a malignant condition.

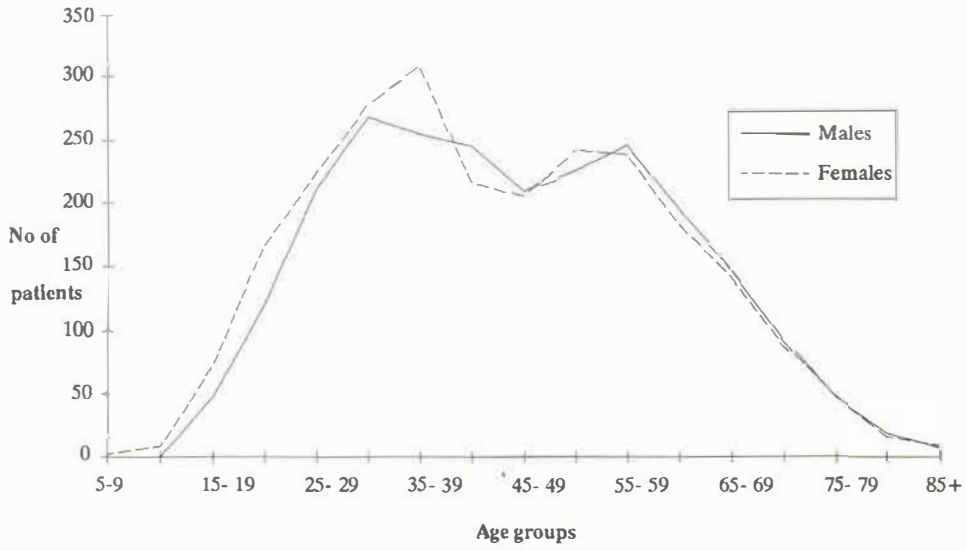

Fig. 7: - Age distribution in 4,799 PUVA treated patients at start of PUVA treatment.

Thus, 4,799 patients were available for the study (Fig. 7). The population comprised 2,343 males and 2,456 females, with a mean age at first treatment of 45.3 years (range 6-93). Average follow-up period was 6.9 years for males and 7.2 years for females. 1,038 patients were followed for more than 10 years. Information obtained from patients' records was: name, date of birth, sex, date of first treatment, diagnosis, site of treatment, type of psoralen, dose of PUVA, number of treatments, and skin type. 77% of patients received oral 8-MOP, 15% had TMP baths, 3.5% had oral TMP baths, and 4.5% had other regimens. Characteristics of patients from individual centers are given in Table 12.

TABLE 12. - Characteristics of patients from individual centers in the "Swedish PUVA cancer study" . No pats: Number of patients; Dose: Total UVA dose (J/cm²);No tm: Mean number of treatments; Obs time: Mean observation time; % 8-MOP: Percent of patients receiving oral 8-methoxypsoralen; % TMP: percent of patients receiving trimethylpsoralen bath PUVA; % Tot body: Percent of patients receiving total body radiation: No SCC: Number of squamous cell carcinomas; Inc SCC: Incidence per 1000 patients of squamous cell carcinomas.

CENTER	NO PATS	DOSE	NO TM	OBS TIME	% 8-MOP	% TMP	% TOT BODY	NO SCC	SCC INC (1000)
University Hospital, Lund	899	218	53	6	99	0	57	8	8.9
Sahlgrenska Hospital, Gothenburg	871	524	63	5.6	100	0	70	3	3.4
Karolinska Hospital, Stockholm	755	580	69	6.3	72	2	64	6	8
Swedish Psoriasis Association	706	511	64	6.2	98	0	85	3	4.3
University Hospital, Uppsala	564	28	50	8.7	0	99	86	1	1.8
Malmö Hospital	391	503	72	5.6	50	26	54	3	7.7
University Hospital, Linköping	285	308	72	7.1	80	7	73	2	7.0
Danderyd Hospital, Stockholm	132	615	58	6.1	98	0	34	0	0
Örebro Hospital	120	534	110	8.3	73	5	98	1	8.3
University Hospital, Umeå	66	386	47	6.5	94	2	68	1	15.1
Huddinge Hospital, Stockholm	10	186	27	2	30	10	40	0	0

7.3.7. Dermatomyositis and polymyositis (VIII)

From 1964 through 1983, the Swedish National Board of Health and Welfare collected nationwide information about individuals who were hospitalized in the country. From 1964 through 1969 only some counties were included (20 %), but since 1970 this computerized in-patient register has been virtually nationwide. From the In-Patient Registry we selected the diagnosis of dermatomyositis and polymyositis, using codes (710.00, 710.01, and 726.30) from the Swedish adaptation of the International Classification of Diseases, seventh revision (ICD-7), for the period 1964 -1968, and codes (716.00, and 716.10) from the eighth revision (ICD-8) for the period 1969 - 1983. Patients seen only as out-patients were not included in the study. Patients with polymyositis from 1964 through 1968 were excluded as the ICD-7 code did not provide a unique number for the diagnosis of polymyositis.

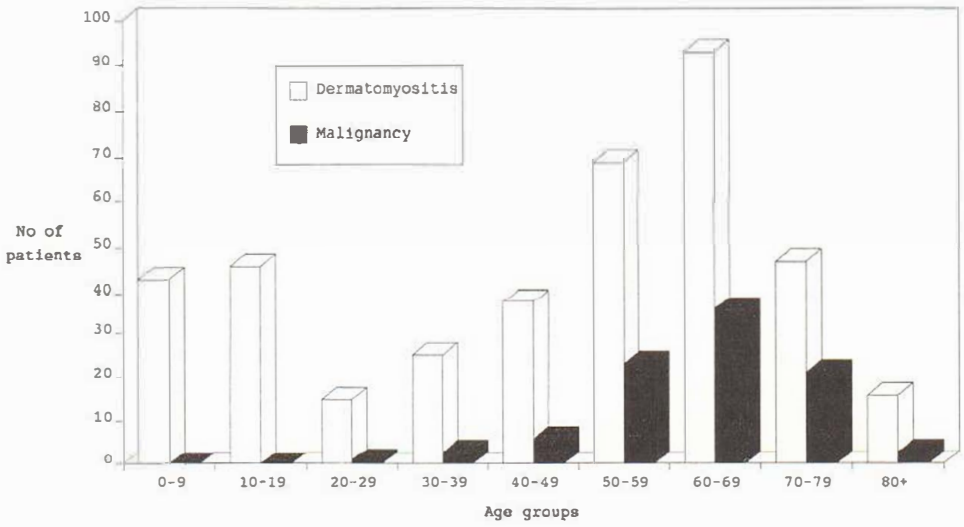

Fig. 8: Age distribution at entry in patients with dermatomyositis. Total number of malignancies is also shown.

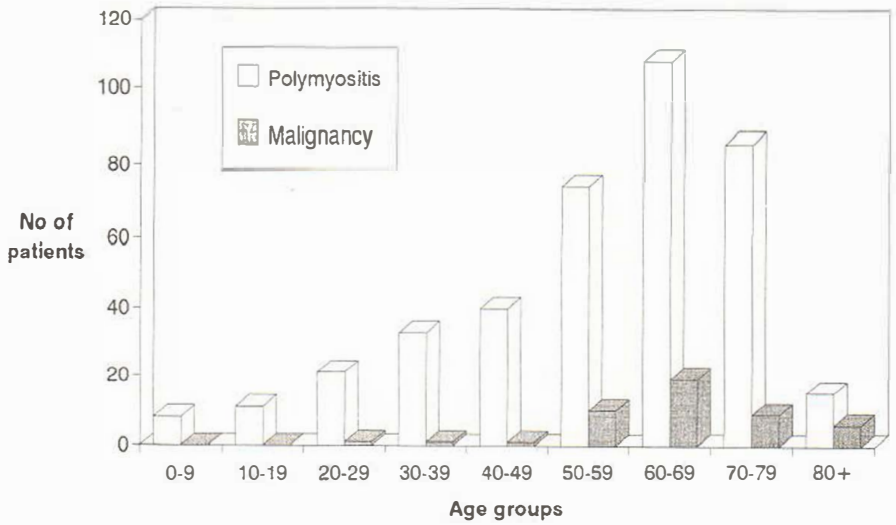

Fig. 9: Age distribution at entry in polymyositis patients. Total number of malignances is also shown.

With these methods we identified 788 patients in whom dermatomyositis or polymyositis was listed in the In-Patient Register for the first time from 1964 through 1983. The patient population consisted of 313 males and 475 females, median age 52 years, range 0 to 92 years at the age of diagnosis (Fig. 8 and Fig. 9). There were 77 (20%) children (0-15 years of age) among the dermatomyositis patients and 12 (3%)children among the polymyositis patients. The average follow-up period was 10.4 years for cancer (through 1987) and 11.4 for death (through 1988). The number of person-years of observation was 5,990, after correction for deaths during the study period.

8. RESULTS

8.1. CANEST (I)

The CANEST microcomputer program was used to estimate cancer and calculate relative risks with confidence intervals in all patients cohorts except (II).

Control of the program is based on pull-down menus as specified by the IBM SAA standard. The program can be controlled with the keyboard or a mouse. Many software programs are based on this standard, i. e. all programs running under the Windows™ (Microsoft Corporation) , OS/2™ (IBM Corporation) and Macintosh™ (Apple Corporation) operating systems. The main menu is at the top row on the screen and information about items selected is shown at the bottom. The area between the top and bottom rows is the working area of the program and is used for displaying results and editing files.

The program is started from the operating system by typing its name CANEST from the operating system prompt. The main menu now appears:

Files	Calculate	Print	Transfer	Setup

Briefly, the program is used in the following way:

1. Feed in patient data (from the keyboard, or another system)
2. Match file with cancer register
3. Estimate cancer in patient population with CANEST
4. Count observed number of cancers in cancer register file with CANEST
5. Compare the results of the match and the estimate with CANEST
6. Print or export data with CANEST or another program

Patient data is first fed into the patient file. The following items are registered:

1. The patient's unique personal identification number

2. The year the dermatological disease was diagnosed

3. The diagnosis if more than one diagnosis is under consideration

If the patient data already exists in another program or in another computer system, data can be imported as an ASCII file. The program now calculates the age and sex of the patient.

When all patient data has been entered, the file is sent to the Cancer Registry for matching. The estimates can now be calculated. This is done by choosing the menu item **Calculate** from the main menu. Cancer probability at the time the individual enters the study is first calculated based on prevalence and the individual probabilities summed. The progress of these calculations can be watched on the screen and takes about 1/10 of total calculation time. Next, cancer probability is calculated for the observation period. These calculations are based on incidence and have to be done for each year each individual is in the study, and are therefore much more time-consuming. As before, the progress of the calculations can be watched on the screen. This feedback is important for the user as these calculations are time-consuming and can take up to 7 hours, for 6,000 patients with an average observation time of ten years, on a microcomputer with a 80386 microprocessor and a 80387 coprocessor. The results of the calculations are now transferred to the output files. If so desired the Poisson distribution can now be calculated for each cancer form and total cancer. The confidence limits based on the Poisson distribution are used later in the calculation of confidence intervals for the relative risk ratio. The objective of the calculation of the estimates is to compare them to the situation in real life, i.e. how many cancers really occurred in the patient population. This can be done by matching the patient file against the Cancer Register. The match is done on a large central computer at the Swedish Cancer Registry. The results of the match are stored in an ASCII (text) file which is then transferred to a personal computer and imported to the CANEST program (CREG file). The files can now be compared and the ratio between observed and expected cancer calculated. This ratio is called the *relative risk*. Several macros (macros are similar to small programs which can be used to do repetitive tasks) have been written in EXCEL™ to do the *relative risk* calculations and compute their confidence interval. A sample of the printout for such calculations is shown in (Fig. 10)

The results can now be printed to a printer by selecting the **Print** option in the main menu. Other files used in the system can also be printed in this option. In the **Transfer** option, data can be imported from other programs or exported to EXCEL™ or to any other programs which accept ASCII or DBF files as input. Data sets can also be transferred to disk for backup. In **Setup** the user can configure the program's various options and name and select data sets.

ICD-7	Malignancy	Mal Obs	Mal Lo	Mal Up	Mal Exp	Mal RR	Conf Lo	Conf Hi
100	All cancers	160	136,17	186,80	126,65	1,26	1,08	1,47
140	Lip	1	0,03	5,57	1,29	0,77	0,02	4,32
141	Tongue	0	0,00	3,69	0,45	0,00	0,00	8,27
142	Salivary glands	0	0,00	3,69	0,34	0,00	0,00	10,76
143	Floor of mouth	0	0,00	3,69	0,20	0,00	0,00	18,92
144	Mouth, other parts and uns	0	0,00	3,69	0,52	0,00	0,00	7,14
145	Mesopharynx	1	0,03	5,57	0,30	3,29	0,08	18,33
146	Nasopharynx	0	0,00	3,69	0,23	0,00	0,00	16,18
147	Hypopharynx	0	0,00	3,69	0,40	0,00	0,00	9,25
148	Pharynx, part unspecified	0	0,00	3,69	0,02	0,00	0,00	160,39
150	Oesophagus	5	1,62	11,67	1,66	3,01	0,98	7,02
151	Stomach	4	1,09	10,24	8,11	0,49	0,13	1,26
152	Small intestine	1	0,03	5,57	0,72	1,39	0,03	7,75
153	Colon	11	5,49	19,68	9,13	1,21	0,60	2,16
154	Rectum and anus	7	2,81	14,42	6,27	1.12	0,45	2,30
155	Biliary passages and liver	3	0,62	8,77	3,58	0.84	0,17	2,45
156	Liver not specified as prima	ma 0	0,00	3,69	0,48	0,00	0,00	7,64
157	Pancreas	7	2,81	14,42	4,61	1,52	0,61	3,13
158	Peritoneum	0	0,00	3,69	0,04	0,00	0,00	94,59
160	Nose and nasal sinuses	0	0,00	3,69	0,27	0,00	0,00	13,67
161	Larynx	6	2,20	13,06	1,46	4,11	1,51	8,94
162	Trach.,bronch,lung & pleura	25	18,18	36,91	14,02	1,78	1,15	2,63
163	Lung, not spec as primary	0	0,00	3,69	0,72	0,00	0,00	5,16
164	Mediastinum	0	0,00	3,69	0,02	0,00	0,00	217,00
170	Breast	0	0,00	3,69	0,20	0,00	0,00	18,54
177	Prostate	40	28,58	54,47	27,13	1,47	1,05	2,01
178	Testis	2	0,24	7,23	0,87	2,30	0,28	8,30
179	Other male genital organs	1	0,03	5,57	0,46	2,16	0,05	12,06
180	Kidney	7	2,81	14,42	5,44	1,29	0,52	2,65
181	Urinary organs (excl. kidney	15	8,40	24,74	8,76	1,71	0,96	2,83
190	Malignant melanoma of skin	3	0,62	8,77	3,29	0,91	0,19	2,67
191	Skin (melanoma excluded)	1	0,03	5,57	4,67	0,21	0,01	1,19
192	Eye	0	0,00	3,69	0,31	0,00	0,00	11,90
193	Nervous system	2	0,24	7,23	3,71	0,54	0,07	1,95
194	Thyroid gland	0	0,00	3,69	0,71	0,00	0,00	5,23
195	Endocrine glands	0	0,00	3,69	1,42	0,00	0,00	2,60
196	Bone	0	0,00	3,69	0,24	0,00	0,00	15,12
197	Connective tissue, muscle	2	0,24	7,23	0,86	2,32	0,28	8,39
199	Other and unspecified sites	3	0,62	8,77	3,44	0,87	0,18	2,55
200	Mal. non-Hodgkin lympoma	3	0,62	8,77	3,49	0,86	0,18	2,51
201	Hodgkin's disease	1	0,03	5,57	0,82	1,22	0,03	6,82
202	Reticulosis and related form	2	0,24	7,23	0,12	17,09	2,07	61,75
203	Multiple myeloma	2	0,24	7,23	1,93	1,04	0,13	3,75
210	Leuk., Polyc ver & myelofib.	0	0,00	3,69	4,03	0,00	0,00	0,91

Fig. 10: - A sample printout from the CANEST program. Only figures for males are shown. ICD7: ICD7 (International classification of diseases, 7th revision) code; Malignancy: Site of malignancy; Mal Obs: Observed number of malignances in males. Mal Lo: The lower confidence limit for the observed number of malignances in males. Mal Up: The upper confidence limit for the observed number of malignances in males. Mal Exp: The expected number of malignances for males. Mal RR: The relative risk for males. Conf Lo: Lower confidence limit for the relative risk. Conf HI: The upper confidence limit of the relative risk.

8.2. Chronic urticaria (II)

A malignant tumor was diagnosed in 36 patients with chronic urticaria. The expected number was 41 and thus the relative risk was 0.88 (95 percent CI: 0.61 to 1.22). In these patients with malignancy, 23 cancers appeared during the same year as the onset of the urticaria or later. The expected number was 25.6. These differences are not significant.

8.3. Condylomata acuminata (III)

Among the 3,260 patients with condyloma, 27 malignances were diagnosed at the same time as, or after, condyloma was diagnosed (Table 13). On the basis of the Swedish national incidence data, 2,549 males and 711 females in the general population would be expected to have 13.4 and 5.6 malignancies respectively. As compared with morbidity in the general population, the morbidity due to cancer produced a relative risk of 1.6 (95%, CI 1.0 to 2.5) for males and 0.9 (0.2 to 2.1) for females. Only 0.6 invasive cervical cancers were expected in the patient group, but one case was observed, relative risk 1.8; (95% CI 0 to 10.1). Nine genitourinary cancers were observed in males, but only 3.4 were expected (2 6; 1.2 to 5.0). Table 14 gives the characteristics of the genitourinary tumors in males and the time interval to diagnosis after diagnosis of condyloma . Cervical carcinoma in situ was analyzed separately; there were 17 cases, but only 11.5 were expected (1.5; 0.9 to 2.5).

To investigate further the risk of genitourinary cancer, the material was stratified according to length of follow-up. A total of 915 (28%) patients were followed up for one to four years, 1351 (41%) for five to nine years, and 994 (30%) for more than ten years. Table 15 gives the relative risks.

TABLE 13.- Observed and expected numbers of malignancies among 3,260 patients with condylomata acuminata.

Site of cancer†	ICD 7 code	Males				Females			
		Expected	Observed	Relative risk	95% Confidence interval	Expected	Observed	Relative risk	95% Confidence interval
All sites	140-210	13·4	22	1·6	1·0 to 2·5	5·6	5	0·9	0·2 to 2·1
Gastrointestinal tract	140-158	2·7	5	1·8	0·6 to 4·3	0·8	0	0	0 to 3·7
Respiratory system	160-164	1·2	2	1·7	0·2 to 6·2	0·2	1	6·3	0·1 to 34·8
Trachea, bronchus, and lung	162	1·0	2	2·1	0·3 to 7·6	0·1	0	0	0 to 3·7
Breast	170					1·4	2	1·4	0·2 to 5·2
Genitourinary organs in females	171-176					1·3	1	0·8	0 to 4·3
Cervix	171					0·6	1	1·8	0 to 10·1
Genitournary organs in males	177-181	3·4	9	2·6	1·2 to 5·0				
Testes	178	1·4	4	2·1	0·8 to 7·2				
Urinary organs excluding kidney	181	0·7	2	3·0	0·4 to 10·9	0·1	0	0	0 to 3·7
Skin	190-191	1·4	0	0	0 to 3·7	0·5	0	0	0 to 3·7
Central nervous system	192-193	1·2	1	0·8	0 to 4·5	0·3	1	2·9	0·1 to 16·4
Other sites	199	0·3	2	6·3	0·8 to 22·6	0·1	0	0	0 to 3·7
Blood and blood forming organs	200-210	2·0	3	1·5	0·5 to 5·1	0·4	0	0	0·0 to 3·7
Malignant lymphoma	200	0·6	2	3·4	0·4 to 12·2	0·1	0	0	0 to 3·7
Cervical carcinoma in situ	171					11·5	17	1·5	0·9 to 2·5

ICD 7= Seventh revision of the International Classification of Diseases.
*Includes malignancies diagnosed at the same time as or after condyloma was diagnosed.
†All sites with two or more cases for either sex.

TABLE 14.- Characteristics of genitourinary tumors in males.

Site of cancer	ICD 7 code	Histological type	Time after diagnosis of condyloma (years)	Age at diagnosis of condyloma (years)
Prostate	177	Adenocarcinoma	−2	71
Prostate	177	Adenocarcinoma	5	58
Testis	178	Seminoma	5	33
Testis	178	Embryonal carcinoma	8	27
Testis	178	Seminoma	−0·5	22
Testis	178	Embryonal carcinoma	7	25
Testis	178	Teratocarcinoma	4	28
Penis	179	Queyrat's erythroplasia	3	47
Penis	179	Queyrat's erythroplasia	1	64
Penis	179	Squamous carcinoma	1	74
Kidney	180	Adenocarcinoma	3	32
Ureter	180	Transitional epithelial cancer	−4	63
Bladder	181	Transitional epithelial cancer	6	27
Urethra	181	Transitional epithelial cancer	3	22

*Includes malignancies diagnosed before condyloma (negative values) and two precancerous lesions.

TABLE 15.- Relative risks of cervical carcinoma in situ and genitourinary cancers in males according to length of follow-up after diagnosis of condylomata acuminata.

	1-4 years		5-9 years		≥10 years	
Site of cancer	No of cases	Relative risk (95% confidence interval)	No of cases	Relative risk (95% confidence interval)	No of cases	Relative risk (95% confidence interval)
Cervical carcinoma in situ	1	1·2 (0 to 6·47)	6	1·6 (0·6 to 3·4)	10	1·5 (0·7 to 2·7)
Genitourinary tumours in males	1	3·1 (0·1 to 17·4)	6	4·4 (1·6 to 9·7)	2	1·1 (0·1 to 4·1)

8.4. Basal cell carcinoma (IV)

In 452 patients with basal cell carcinoma (BCC), another malignancy was also diagnosed. The expected number was 323 and thus the relative risk (RR) was 1.4 (95% CI: 1.3-1.5).

Among 43 cancer sites for men and 47 for women selected primarily for analysis, a significant association with BCC was found in four cancer types for males and in three cancer types for females (Table 16).

For malignant melanoma there was a substantial and significant difference between the patients with BCC and the general population. For males the number of malignant melanomas was more than six times higher than expected after the diagnosis of BCC, and for females more than four times higher. During the period before the diagnosis of BCC there was, however, no significant increase in risk. This was in contrast to skin malignancies other than malignant melanoma. For these tumors there was a more than five-fold increased risk for males before the patients got the BCC and a more than six-fold increase after. For females there was a four-fold increase of other skin malignancies than melanoma before, and a more than three-fold increase after, the diagnosis of BCC.

TABLE 16.- Observed and expected number of other malignances according to basal cell carcinoma diagnosis.

Cancer site	No. of malignancies before diagnosis of basal cell carcinoma						No. of malignancies the same year or after diagnosis of basal cell carcinoma					
	MALES			FEMALES			MALES			FEMALES		
	OBS	RR	95%CI	OBS	RR	95%CI	OBS	RR	95%CI	OBS	RR	95%CI
All sites	81	1.3	1.1-1.7	89	1.2	1.0-1.5	170	1.6	1.3-1.8	112	1.4	1.1-1.6
Malignant melanoma	3	1.4	0.3-4.2	3	1.2	0.2-3.4	9	6.6	3.0-12.5	6	4.2	1.5-9.2
Skin(excl. melanoma)	22	5.0	3.1-7.5	10	4.0	1.9-7.4	37	6.8	4.8-9.4	9	3.1	1.4-5.9
Lung, not primary	0	0.0	0.0-39.2	0	0.0	0.0-68.3	4	5.6	1.5-14.3	1	3.7	0.1-20.4
Thyroid gland	0	0.0	0.0-9.0	0	0.0	0.0-2.8	4	10.1	2.8-25.9	1	1.1	0.0-6.3
Cervix uteri				8	1.7	0.7-3.3				7	4.4	1.8-9.1

Of the 21 malignant melanomas, 7 were located on head and neck, 3 on trunk, 3 on upper limbs, 5 on lower limbs and, for 2 patients, the sites were not specified.

Males with BCC also appear to have an increased risk of cancer of the lung and thyroid gland and females seem to have an increased risk of cancer of the cervix uteri after the diagnosis of BCC.

8.5. Lichen planus (V)

In the 2,071 patients a total of 153 malignancies was observed after the first diagnosis of LP. The expected number of malignancies was 154, producing a relative risk of 1.0 (95 percent CI, 0.9 to 1.2). The material was also analyzed according to 43 (for males) and 47 (for females) individual cancer sites. For none of these sites were significant risks obtained, for either sex, at the 95 percent level. For SCC of the skin, six cancers were observed after the diagnosis of LP, but only 5.2 were expected, producing a relative risk of 1.2 (95 % CI, 0.4 to 2.5). One patient had received arsenic and roentgenographic treatment of the lower legs. Tumors of the mouth were analyzed separately (ICD-7 140, 141, 143 and 144). No significant risk was obtained for individual sites in the males, while for tumors of the mouth as a whole, 1.4 malignancies were expected after the first diagnosis of LP, but 8 SCC were observed, producing a relative risk of 5.9 (95 % CI, 2.5 to 11.4). The location of these tumors and duration of disease on diagnosis of the malignancy are shown in Table 17. No tumors of the mouth were observed in the females, although 0.6 cancers were expected, giving a relative risk of zero (95 % CI, 0 to 6.2).

TABLE 17.- Development of oral squamous cell carcinoma in 2,071 patients with Lichen planus. Age: Age of patient at the time of diagnosis of the cancer. Dur: Duration from first visit for LP until the diagnosis of the cancer (years).

Patient No	Sex	Age	Dur	Cancer site
1	M	83	1	Mouth, unspecified
2	M	76	5	Roof of the mouth
3	M	77	6	Tongue
4	M	69	7	Floor of mouth
5	M	67	11	Lip, unspecified
6	M	61	1	Lip. unspecified
7	M	35	1	Tongue
8	M	29	5	Lower lip

8.6. Positive patch tests (VI)

Among 5,858 cases with a positive patch test, a total of 301 malignancies were diagnosed in 275 patients, after or in parallel with the first positive patch test. On the basis of Swedish incidence data, 2,183 males and 3,675 females in the general population would be expected to have 127 and 137 cancers, respectively. As compared with morbidity in the general population, the morbidity due to cancer produced a relative risk of 1.3 (95% CI, 1.1 to 1.5) for males and 1.0 (95% CI, 0.9 to 1.2) for females (Table 18). The time period before the positive patch test was analyzed separately (results not tabulated). In the males, 39 cancers were observed but 40 expected, producing a relative risk of 1.0 (95% CI, 0.7 to 13). In the females 79 cancers were observed but 95 expected, producing a relative risk of 0.8 (95% CI, 0.7 to 1.0). When individual sites were analyzed, similar results were observed with no significant over-risk of cancer. When the time after the positive patch test was analyzed according to individual sites, the following results were obtained. In the females a significant increase was observed in cancer of the larynx and of the cervix. After the positive patch test, 5.3 cancers of the cervix were expected, but 12 observed, producing a relative risk of 2.3 (95% CI, 1.2 to 4.0). Similarly 0.2 cancers of the larynx were expected, producing a relative risk of 10.7 (95% CI, 1.3 to 38.6). In the males 6 larynx cancers and 25 cancers of the trachea, bronchus, lung, and pleura were observed, producing a relative risk of 4.1 (95% CI, 1.5 to 8.9) and 1.8 (95% CI, 1.2 to 2.6), respectively. Cancer of the prostate was also increased in the males, 40 cancers were observed, producing a relative risk of 1.4 (95% CI, 1.1 to 2.0). No sig-

TABLE 18.- Observed and expected numbers of malignancies among 5,858 patients with positive patch tests. All sites with a significant cancer increase, after the first positive patch test, for either sex, are tabulated.

Tumor site	ICD-7 code	Sex	Exp Ca	Obs Ca	RR	95% CI
All sites	140 - 210	M	127	160	1.3	1.1 - 1.5
		F	137	141	1.0	0.9 - 1.2
Larynx	161	M	1.5	6	4.1	1.5 - 8.9
		F	0.2	2	10.7	1.3 - 38.6
Trachea bronchus & lung	162	M	14.0	25	1.8	1.2 - 2.6
		F	5.0	8	1.6	0.7 - 3.2
Cervix uteri	171	F	5.3	12	2.3	1.2 - 4.0
Prostate	177	M	27.1	40	1.5	1.1 - 2.0

nificant increase was found in other cancer forms. The period after the first positive patch test was divided into 5-year intervals, and a nearly linear rise with time in relative risks was observed until 15 to 19 years after the first patch test (Table 19). After 20 to 24 years the relative risks return to normal. Similar results were obtained for individual cancer sites (results not shown).

TABLE 19.- Observed and expected numbers of malignancies among 5,858 patients with positive patch tests according to observation time.

Years after positive patch test	Sex	Obs	Exp Ca	RR	95% CI
0 - 4	M	2	7.2	0.3	0.03-1.0
	F	5	9.7	0.5	0.2 - 1.2
5 - 9	M	39	45	0.9	0.6 - 1.2
	F	52	44.9	1.2	0.9 - 1.5
10 - 14	M	73	43.5	1.7	1.3 - 2.1
	F	62	50.5	1.2	0.9 - 1.6
15 - 19	M	31	21.6	1.4	1.0 - 2.0
	F	18	9.9	1.8	1.1 - 2.9
20 - 24	M	15	14	1.1	0.6 - 1.8
	F	4	3.8	1.1	0.3 - 2.7

8.7. PUVA and cancer (VII)

After patients' first PUVA treatment, 133 malignances were diagnosed in 2,343 males and 103 in 2,456 females. The expected numbers of malignancies in the general population were 90.5 for males and 67.4 for females; thus, RR of malignancy was 1.5 for both sexes (95% CI 1.2-1.7 for males and 1.3-1.9 for females) (Table 20). Analysis of individual cancer sites showed no significant increase in risk of malignant melanoma among patients receiving PUVA, but risk of squamous cell cancer of the skin was increased more than six-fold for males and more than five-fold for females.

TABLE 20.- Observed and expected numbers of malignances in 4,799 PUVA-treated patients.

SITE	MALES			FEMALES		
	Observed/ Expected	RR	95% CI	Observed/ Expected	RR	95% CI
All sites	133/90.5	1.5	1.2-1.7	103/67.4	1.5	1.3-1.9
Malignant melanoma	3/2.7	1.1	0.2-3.2	2/2.4	0.8	0.1-3.0
Cutaneous squamous cell carcinoma	21/3.3	6.3	3.9-9.6	7/1.2	5.7	2.3-11.7
Trachea, bronchus, lung and pleura	23/10.0	2.3	1.5-3.4	10/2.7	3.7	1.8-6.8
Colon	6/6.5	0.9	0.3-2.0	13/4.8	2.7	1.5-4.7
Kidney	4/4.0	1.0	0.3-2.6	7/1.9	3.8	1.5-7.7
Pancreas	8/3.1	2.6	1.1-5.1	2/1.9	1.1	0.1-3.8

The incidence of respiratory cancer was significantly increased for patients of both sexes ($p < 0.05$). In addition, female patients had greater risks of cancer of the colon and kidney, and male patients had greater risk of cancer of the pancreas. Table 21 shows the relation between total dose of ultraviolet A and relative risk of squamous cell cancer of the skin; men exposed to greater than 1,200 J/cm^2 of ultraviolet A were 27.2 times more likely to have this malignancy than the general population. Men with more than 200 treatments had a greater than thirty-fold increased risk of squamous cell cancer of the skin compared with the general population (results not tabulated).

TABLE 21.- Observed and expected cutaneous squamous cell cancers and total dose of ultraviolet A radiation.

Dose (J/cm^2)	MALES				FEMALES			
	No. of patients	Observed/ expected	RR	95%CI	No.of patients	Observed /expected	RR	95%CI
0-99	841	6/1.4	4.2	1.6-9.2	924	2/0.6	3.7	0.5-13.3
100-199	388	2/0.5	3.8	0.5-13.8	464	1/0.2	4.8	0.1-26.8
200-399	415	1/0.5	1.9	0.1-10.6	427	2/0.2	10.3	1.2-37.1
400-1199	474	4/0.6	7.1	1.9-18.1	461	1/0.2	5.0	0.1-27.6
=>1200	225	8/0.3	27.2	11.3-53.6	180	1/0.1	13.2	0.3-73.3

As the material is heterogeneous with respect to total UVA does, observation time and indications for PUVA therapy, patients observed for more than 5 years, treated for psoriasis with total body PUVA and oral 8-MOP, were analyzed separately. The average UVA dose of this 1264-patient subcohort was 640 J/cm², mean number of treatments 95 and mean observation time 8.8 years, ranging from six to 13. This material is more comparable to some American studies which have followed the same patient cohort of psoriasis patients for a long period (Table 22).

TABLE 22.- Cancer risks in 1,264 patients with psoriasis, treated with total body PUVA and oral 8-methoxypsoralen and observed for six or more years. Obs: Observed number of tumors; Exp: Expected number of tumors.; RR: Relative risk; 95 % CI: 95 percent confidence interval.

	Males			Females		
Tumor site	Obs/ Exp	RR	95% CI	Obs/ Exp	RR	95% CI
All sites	53/35	1.5	1.1-2.0	34/20	1.7	1.2-2.4
Malignant melanoma	3/1.1	2.7	0.6-8.0	1/0.7	1.4	0-7.6
Squamous cell carcinoma	13/1.3	10.2	5.4-17.5	5/0.3	15.0	4.9-35.0
Lung	11/4.0	2.8	1.4-4.9	4/0.8	5.3	1.4-13.4

883 patients treated with TMP baths or oral TMP showed no overall increased risk of malignancy. This will be further elucidated in a seperate study.

*TABLE 23.- Age: Age at start of PUVA treatment. Dur: Duration between start of PUVA treatment and first squamous cell carcinoma. No of tumors: Number of tumors diagnosed from start of PUVA until 1987. Treatm site: Treatment site: Dgn: Diagnosis: Dose: Total UVA dose in J/cm². No: Number of PUVA treatments. Previous treatm: Previous potentially carcinogenic treatment: Ars: Arsenic; UVB: Ultraviolet B radiation; Gr: Grenz rays; MTX: Methotrexat; *: Data missing; None: No previous treatment. Psoralen: Type of psoralen used: 8-MOP: 8-Methoxypsoralen; Bath: Bath PUVA with Trimethylpsoralen; TMP: Trimethylpsoralen per os.*

Sex	Age	Dur, y	No of Tumors	Tumor site	Treatment site	Skin type	Dgn	Dose	No	Previous SCC	Previous Treatment	Psoralen
F	72	4	1	Lower limbs	Total body	M	Psoriasis	1155	100	-	UVB	8-MOP
M	71	5	1	Face	Hand	*	Psoriasis	90	21	-	None	8-MOP
M	66	2	1	Face	Total body	*	Psoriasis	6	6	-	UVB,Tar	8-MOP
F	65	9	2	Lower limbs	Total body	III	Psoriasis	300	72	-	UVB,Gr, Tar,MTX	8-MOP
M	61	1	1	Lower limbs	Total body	*	Psoriasis	2	3	-	*	8-MOP
M	62	8	1	Lower limbs	Total body	III	Psoriasis	670	127	2	Ars,UVB, MTX,Tar	8-MOP
M	58	9	1	Lower limbs	Total body	*	Psoriasis	704	187	-	UVB	8-MOP
M	57	8	1	Upper limbs	Hand & foot	III	Pustul palmopl	777	403	-	Ars,UVB, Gr,Tar	8-MOP +Bath
M	63	1	1	Ear	Total body	III	Lichen simplex	13	16	-	UVB	TMP Bath
F	55	11	1	*	Total body	*	Psoriasis	127	198	-	UVB,Tar	8-MOP +TMP
F	55	11	1	Lower limbs	Total body	*	Eczema	1	4	-	MTX,Tar	TMP Bath
M	56	8	2	Lower limbs	Total body	*	Psoriasis	2170	254	-	Ars,UVB, MTX,Tar	8-MOP
M	50	5	2	Upper limbs	Total body	II	Psoriasis	1732	268	-	UVB,Gr, MTX,Tar	8-MOP
M	55	5	1	Ear	Total body	*	Eczema	54	14	-	Tar	8-MOP
F	51	7	1	Ear	Total body	*	Psoriasis	39	32	-	Tar	8-MOP
M	53	1	1	Trunk	Total body	II	Psoriasis	48	16	-	UVB,MTX ,Tar	8-MOP
M	47	3	1	Lower limbs	Total body	II	Psoriasis	1154	244	-	*	8-MOP
M	43	9	2	Lower limbs	Total body	III	Psoriasis	3411	363	-	Ars,UVB, Gr,Tar	8-MOP
M	41	2	1	Trunk	Total body	*	Psoriasis	150	20	-	UVB, MTX,Tar	8-MOP
M	35	12	1	Lower limbs	Total body	III	Psoriasis	4222	586	-	MTX,Tar	8-MOP
F	33	11	1	Lower limbs	Total body	III	Psoriasis	4525	472	-	Tar	8-MOP
M	31	10	1	Trunk	Total body	*	Psoriasis	172	64	-	UVB,Gr, MTX,Tar	8-MOP
M	29	5	1	Trunk	Total body	II	Psoriasis	1395	370	-	MTX	8-MOP +Bath
M	34	4	1	Lower limbs	Total body	II	Lichen planus	260	68	-	Gr,Tar	8-MOP

Information about skin type was available for 2,388 patients (49.4%). Patients with skin types I and IV had no increased risk of squamous cell cancer of the skin, but males with skin types II and III had a notably increased risk of this malignancy. Characteristics of the 24 patients with squamous cell cancer of the skin are shown in Table 23.

The anatomic location of the tumors was compared to that of the general Swedish population. A marked increase in locations not normally exposed to the sun was observed (Fig. 11).

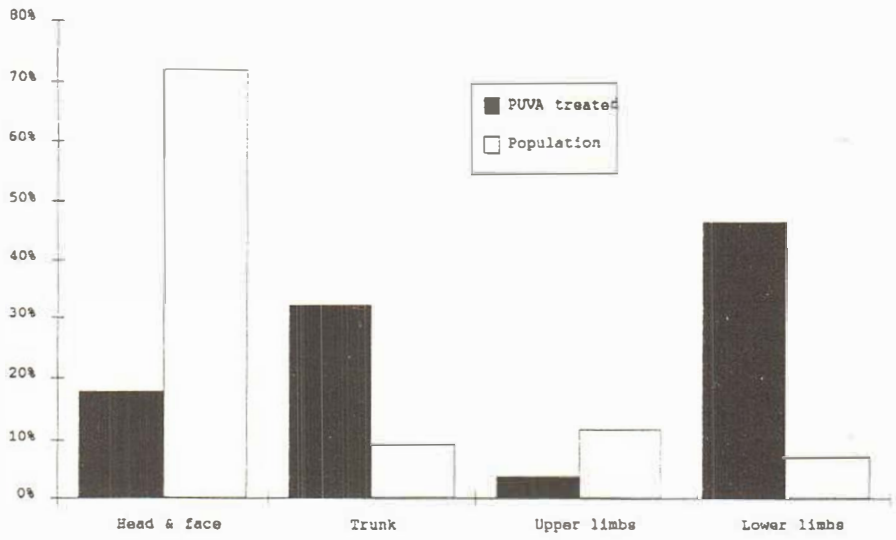

Fig. 11 - Distribution of squamous cell carcinoma in PUVA-treated patients compared with the distribution in the Swedish population.

The main concern in PUVA therapy is not squamous cell carcinoma or basal cell carcinoma, but rather malignant melanoma. There were seven melanomas diagnosed in the material. Two were diagnosed before PUVA therapy was initiated (Table 24).

TABLE 24. - Malignant melanoma diagnosed after the start of PUVA treatment. Age: Age at start of PUVA treatment. Dur: Duration between start of PUVA treatment and first squamous cell carcinoma . Dose: Total UVA dose in J/cm². NO: Number of PUVA treatments. Psoralen: Type of psoralen used: 8-MOP: 8-Methoxypsoralen; Bath: Bath PUVA with Trimethylpsoralen.

Sex	Age	Dur	Tumor site	Treatm site	Skin type	Dgn	Dose	No	Psora-len
M	57	2	Unspeci-fied	Total Body	*	Psor-iasis	127	31	8-MOP
F	55	4	Lower limbs	Total Body	*	Psor-iasis	133	18	8-MOP
M	52	5	Trunk	Total Body	*	Psor-iasis	379	53	8-MOP
F	41	7	Trunk	Total Body	*	Psor-iasis	0.2	3	Bath
M	18	5	Trunk	Total Body	IV	Psor-iasis	151	35	8-MOP

**: Data missing*

8.8 Dermatomyositis or polymyositis (VIII)

A total of 58 malignancies were diagnosed in the polymyositis patients and 94 in the dermatomyositis patients, from 1958 (the first year of cancer registration in Sweden) or birth until 1987 (the last year on-line at the Cancer Registry). The temporal relation of the diagnosis of the malignancy to the

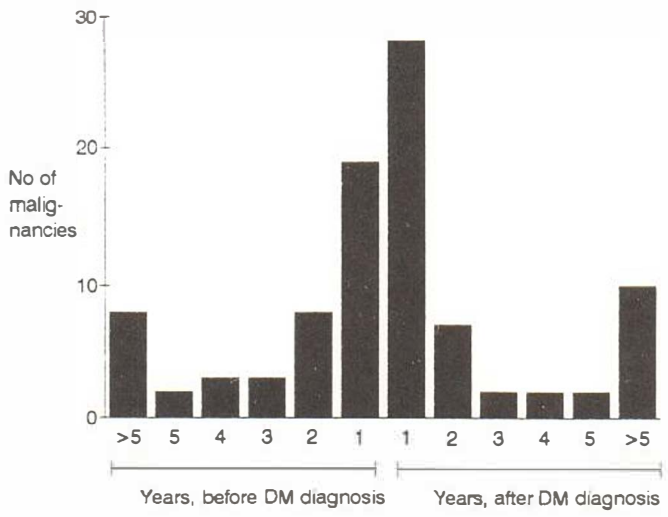

Fig. 12. - Temporal relation of the cancer to the dermatomyositis diagnosis

dermatomyositis and polymyositis diagnosis is shown in (Fig. 12 and Fig. 13).

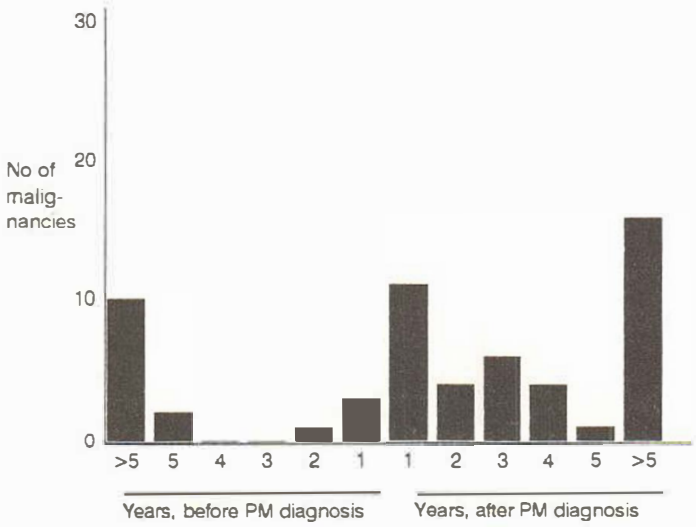

Fig. 13. - Temporal relation of the cancer diagnosis to the polymyositis diagnosis

Among the 396 patients with polymyositis, a total of 42 malignancies were diagnosed, in parallel or after the first polymyositis diagnosis, producing a relative risk of 1.8 (95 percent CI : 1.1 to 2.7) for the males and 1.7 (95% CI: 1.0 to 2.5) for the females. When individual cancer sites were analyzed, significant increase was observed only for cancer of the lung in the males, with a relative risk of 5.6 (95% CI: 2.2 to 11.4) (Table 25).

Among the 392 patients with dermatomyositis, a total of 61 malignancies were diagnosed in parallel or after the first dermatomyositis diagnosis, producing a relative risk of 2.4 (95% CI: 1.6 to 3.6) for the males and 3.4 (95% CI: 2.4 to 4.7) for the females. The risks for individual cancer sites are shown in (Table 26)

TABLE 25.- Numbers of observed and expected malignancies after or in parallel with the first polymyositis diagnosis

		Males			Females		
Site of malignancy	ICD 7	No	RR	95% CI	No	RR	95% CI
All sites	140-209	20	1.8	1.1-2.7	22	1.7	1.0-2.5
Stomach	151	0	0.0	0.0-4.9	1	1.6	0.0-8.9
Colon	153	1	1.2	0.0-6.6	1	0.8	0.0-4.6
Rectum and anus	154	1	1.8	0.0-9.8	2	3.4	0.4-12.4
Biliary passages and liver	155	1	3.0	0.1-16.9	0	0.0	0.0-6.3
Liver, not specif. as primary	156	1	22.2	0.6-123.8	0	0.0	0.0-64.7
Pancreas	157	0	0.0	0.0-8.8	1	2.0	0.1-10.9
Trachea.bronchus.lung	162	7	5.6	2.2-11.4	2	4.1	0.5-14.7
Lung, not spec as primary	163	0	0.0	0.0-54.3	1	23.8	0.6-132.
Breast	170	0	0.0	0.0-204.9	6	1.9	0.7-4.2
Corpus uteri	172	0	0.0	0.0-0.0	1	1.5	0.0-8.4
Ovary. tube & broad ligam	175	0	0.0	0.0-0.0	1	1.4	0.0-7.9
Prostate	177	4	1.5	0.4-3.7	0	0.0	0.0-0.0
Kidney	180	1	2.2	0.1-12.1	0	0.0	0.0-9.0
Urinary organs	181	1	1.3	0.0-7.0	2	5.7	0.7-20.5
Skin (melanoma excluded)	191	0	0.0	0.0-8.5	1	2.7	0.1-14.7
Nervous system	193	1	3.8	0.1-21.0	0	0.0	0.0-9.2
Endocrine glands	195	0	0.0	0.0-36.9	2	7.0	0.8-25.2
Connective tissue	197	1	14.7	0.4-81.9	0	0.0	0.0-45.0
Non-Hodgkin lymphoma	200	1	3.5	0.1-19.3	1	3.3	0.1-18.2

TABLE 26.- Numbers of observed and expected malignancies after or in parallel with the first dermatomyositis diagnosis

		Males			Females		
Site of malignancy	ICD7	No	RR	95% CI	No	RR	95% CI
All sites	140-209	25	2.4	1.6-3.6	36	3.4	2.4-4.7
Nasopharynx	146	0	0.0	0.0-283.8	1	90.9	2.3-506.6
Hypopharynx	147	1	38.5	1.0-214.3	0	0.0	0.0-307.4
Oesophagus	150	1	8.0	0.2-44.6	0	0.0	0.0-63.6
Stomach	151	1	1.3	0.0-7.1	1	2.0	0.1-10.9
Small intestine	152	1	17.9	0.5-99.5	0	0.0	0.0-76.9
Colon	153	3	3.8	0.8-11.0	4	4.2	1.2-10.9
Rectum and anus	154	0	0.0	0.0-7.2	2	4.4	0.5-15.9
Biliary passages and liver	155	0	0.0	0.0-11.2	2	4.5	0.5-16.2
Pancreas	157	3	7.9	1.6-23.1	2	5.0	0.6-18.1
Trachea,bronchus,lung	162	6	6.5	2.4-14.2	1	2.6	0.1-14.4
Breast	170	0	0.0	0.0-230.6	8	3.2	1.4-6.3
Cervix uteri	171	0	0.0	0.0-0.0	1	3.3	0.1-18.6
Ovary, tube & broad ligam.	175	0	0.0	0.0-0.0	5	8.2	2.7-19.2
Prostate	177	2	0.8	0.1-2.8	0	0.0	0.0-0.0
Kidney	180	0	0.0	0.0-9.6	1	3.0	0.1-16.9
Urinary organs	181	2	3.1	0.4-11.3	0	0.0	0.0-13.6
Malignant melanoma	190	0	0.0	0.0-21.0	1	4.0	0.1-22.5
Thyroid gland	194	0	0.0	0.0-82.0	1	7.6	0.2-42.2
Other and unspecified sites	199	0	0.0	0.0-12.9	5	13.0	4.2-30.3
Non-Hodgkin lymphoma	200	2	8.1	1.0-29.3	1	4.2	0.1-23.3
Hodgkin's disease	201	1	17.9	0.5-99.5	0	0.0	0.0-69.6
Reticulosis & related forms	202	1	142.9	3.6-796.0	0	0.0	0.0-527
Leukemia	204-205	1	3.3	0.1-16.9	0	0.0	0.0-12.8

The material was divided into 20-year age groups and relative risks calculated separately for each age group. No malignancies were observed in children. No difference was found for the polymyositis patients, but the cancer risk was close to four in middle-aged dermatomyositis patients.

The mortality was 167/365 (46%) in dermatomyositis patients and 169/385 (44%) in polymyositis patients. Due to incomplete identification numbers, 38 patients could not be matched with the Cause-of-Death Register. In males with dermatomyositis, 57 deaths occurred, producing a mortality ratio of 1.5 (95% CI: 1.2 to 2.0) and in females 110 deaths occurred, producing a mortality ratio of 2.1 (95% CI: 1.7 to 2.5). Similarly, in males with polymyositis, 84 deaths occurred, producing a mortality ratio of 1.3 (95% CI: 1.0 to 1.6) and in the females 85 deaths occurred, producing a mortality ratio of 1.1 (95% CI: 0.9 to 1.3).

The principal cause of death was a malignant disease in 67 (40%) dermatomyositis patients and 24 (14%) polymyositis patients. Seventeen (10%) dermatomyositis and 22 (13%) polymyositis patients died of dermatomyositis or polymyositis. Forty-four (26%) Dermatomyositis patients and 77 (46%) polymyositis patients died of circulatory diseases. For further results see Table 27. The survival of adult dermatomyositis and polymyositis patients is shown in figure 14 and survival according to a modified Bohan and Peter [31, 32] classification in figure 15 (see legend for details).

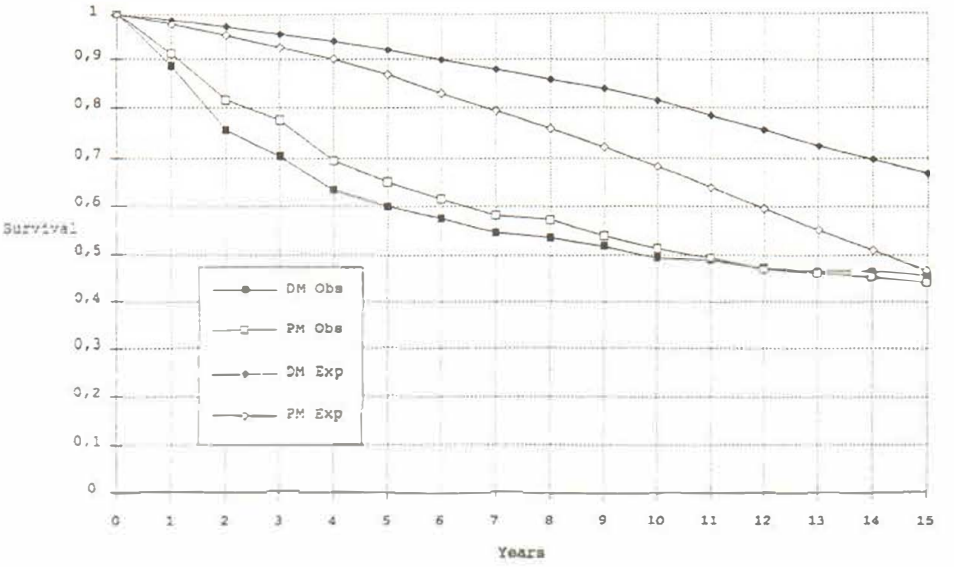

Fig. 14. - Survival of adult (16 years and older) patients with dermatomyositis and polymyositis. Expected survival is also shown.

Table. 27 - Principal cause of death in polymyositis and dermatomyositis patients.

Disorder listed as principal cause of death	ICD 8 Code	Dermato-myosits (n=167)	Polymyo-sitis (n=169)
Infections	000-136	2	1
Malignant neoplasms	140-209	67	24
Hypopharynx	148	1	0
Oesophagus	150	2	0
Stomach	151	4	2
Colon	153	6	2
Rectum	154	2	2
Liver	155	1	2
Gallbladder	156	1	0
Pancreas	157	5	3
Peritoneum	158	1	0
Lung	162	8	5
Other resp. organs	163	1	0
Bone	170	1	0
Skin	173	1	0
Breast	174	9	1
Uterine cervix	180	2	0
Uterus	182	1	0
Ovarium	183	9	0
Other female genitals	184	1	0
Urinary bladder	188	1	1
Kidney	189	1	3
Brain	191	1	1
Other malignancies	195 & 199	4	1
Hematologic malignancies	200-209	4	1
Endocrine & metabolic	240-279	1	5
Neurologic	290-349	4	6
Circulatory	390-458	44	77
Respiratory	460-519	9	6
Gastrointestinal	520-577	8	8
Urogenital	580-678	2	2
Muskuloskeletal	710-738	25	36
Dermatomyositis	716,00	17	0
Polymyositis	716,10	0	22
Accidents	800-999	5	4

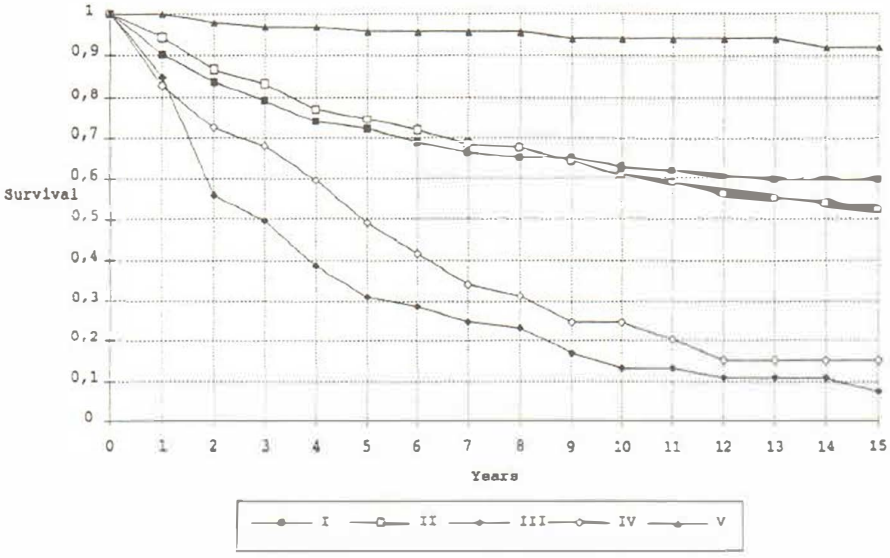

Fig.15. - Survival of dermatomyositis and polymyositis patients. Classification is based on the work of Bohan and Peter. I: Patients with dermatomyositis without neoplasia. II: Patients with polymyositis without neoplasia. III: Patients with dermatomyositis and neoplasia. IV: Patients with polymyositis and neoplasia. V: Children with dermatomyositis or polymyositis.

9. DISCUSSION

9.1. General considerations regarding disease associations

Association between two or more different disorders may, if true, provide valuable clues to the clinician. This is particularly important when the associated disease is a potentially fatal one as most malignant disorders are. Furthermore, if the disease is diagnosed early, the patient's life can often be saved. As skin signs are obvious to the patient and do not require any medical procedures to discover, an association between a skin sign and a malignant disease is particularly important as it may lead to a diagnosis of the malignancy when it is potentially curable. However, if such an association is false it may cause the patient unnecessary fear and waste health resources. Unfortunately, suggesting the existence of a particular disease association by describing such an occurrence in a case report or in a series of clinical patients is easy[114]. Determining whether the association is real or convincingly demonstrating that no true association is present is much more difficult.

9.1.1. Chance association

If two common and chronic disorders are considered, it is relatively easy to find large patient series with both conditions at the same time. Thus, of the estimated 549,000 patients with newly diagnosed malignancies in the United States, almost 32,000 could be expected to have a history of diabetes mellitus due to chance alone, and perhaps would prompt the casual observer to conclude erroneously that the two were related in some way[114]. Often the physician is highly observant of all cases that show such an association, and the great enthusiasm which comes from having discovered yet another association of a benign dermatosis with a malignant tumor sometimes masks the possibility that certain associations have occurred by chance.

9.1.2. The Berkson bias

The Berkson bias was described over 40 years ago by Berkson[115], the joint occurrence of two diseases becomes more likely as a selective referral of patients with both conditions. This is very important, as many studies on rare diseases are based on a highly-selected patient population from referral

centers. Obviously, many adverse conditions will be found more frequently among patients referred to a university hospital than among the general population. It cannot be excluded that this bias obtains in some of the present studies, based as they are on patient populations seen at a dermatology clinic at a university hospital. This effect is eliminated in the study of the association between dermatomyositis or polymyositis (VIII) and malignancy, as the study is population-based, and includes, from the early seventies, close to 90 percent of the Swedish population. However, this probably does not apply in the case of lichen planus (V) as few general practitioners treat this disease in Sweden. Also, patients with chronic urticaria (II) are not likely to be treated by general practitioners. Patch testing is not done outside dermatology clinics (VI). The same applies to PUVA treatment (VII), but basal cell carcinomas are frequently seen by other specialities, mainly plastic surgery. However, it is not likely that more difficult cases are seen at the dermatology clinic. A bias cannot be excluded in the case of the condyloma patients (III), but this is more thoruoghly discussed under the relevant section.

9.1.3. The withdrawal bias

A second bias, the withdrawal bias, occurs when the individuals who remain in the study have a higher frequency of the associated disease. The present study design eliminates this bias, as all patients can be followed-up with the help of the Cancer Registry and the Cause-of-Death Registry

9.1.4. Diagnostic suspicion bias

The third bias, diagnostic suspicion, occurs when patients included in the study are evaluated more thoroughly for the putative associated disease. This bias probably applies in some of the studies, particularly when, as in III and VIII, the association has been suspected for a long time. This would cause more malignancies to be diagnosed soon after the diagnosis of the putative associated disease, because the patients will be investigated at that time. But, as the patients are followed for a long time after the diagnosis of the putative associated disease, this effect is minimized with time.

9.1.5. The problem of multiple comparisons

Concern has been raised about the interpretation of significance tests when multiple comparisons are investigated. The basis for concern rests on the following argument: suppose an association between a disorder and 100 diseases is made. The premise is that that there are no real associations. If sig-

nificance testing is performed at the 5 percent level of significance there will be about five "significant" associations in the data, representing statistically significant associations that occur only by chance. The traditional approach has been to make the significant test more stringent, but a penalty is paid for this, as biologically significant associations may go undetected. Lately it has therefore been seriously questioned whether compensation for multiple comparison should really be made, but it is therefore very important to report even the negative results and the number of comparisons made[116]. Some researches have suggested that the hypothesis to be tested must be formulated in advance[117]. This approach can cause problems when important, but unexpected results are obtained, and is probably too stringent. Finally, it is always difficult to evaluate the significance of an association when multiple tests are done, but a combination of judgement of confidence intervals and the biological background for the tested hypothesis must be included.

9.1.6. The advantages of using the Cancer Registry

The accurate cancer registration in the Swedish Cancer Register is a prerequisite for studies of this type. Since cancer registration is nationwide, no patients are lost on follow-up. Also, the availability of yearly age- and sex-specific national and regional incidence figures for about fifty cancer forms makes it possible to estimate very accurately the expected number of malignancies in the group being studied. This, combined with the national Cause-of-Death Registry, the Swedish In-Patient Registry and the diagnosis register at the Karolinska Hospital, immediately highlights the quality of such studies as few, if any other countries have the infrastructure to produce this type of data.

9.2. Comments on the results of the study

9.2.1. CANEST (I)

The aims of this part of the study was to create a microcomputer program to calculate the expected number of cancers in a group of individuals observed over a number of years, based on Swedish prevalence and incidence figures, and to use this program to investigate cancer risk in patients with certain skin diseases. The estimates are compared to the cancer development in the group, by linking the patient group with the Swedish Cancer Register and thus the risk of cancer development is obtained. This program can of course be used on any patient group, or other groups, i.e. occupational groups.

Before the development of the CANEST microcomputer program, a traditional method was used for estimating cancer development in patient groups with dermatological diseases. This method involves stratification of the patient material into five-year age intervals. The estimated number of cancers is calculated based on the number of years each age group was under observation. The incidence figures used in these calculations are the figures for the year in the middle of the interval, or a cumulative incidence for the years 1971 - 1984. For example for observing patients from 1965 to 1985, the 1975 figures would be used for the calculations. An example of this difference can be seen in patients with chronic urticaria (II), where the cancer incidence was estimated to 41 with the older method but 48 with the computer program. The observed number of cancers was 36. Neither of these estimates indicated a significant risk.

It can be argued that it is not suitable to use national incidence data to estimate cancer development in a regional patient material. CANEST has no limits regarding this aspect : a new data file (INC58_86) with regional incidence data is simply used. At the time of the study regional data was not available in computer-readable form, but the option will be added to the program.

Being able to manipulate the data and do the calculations on a microcomputer has significant advantages compared to the use of a mainframe computer. The data is more accessible to the scientist, who does not have to rely on the help of computer specialists to do all calculations. The data can also be moved more easily to other programs for graphical presentation or further statistical analysis. Mainframe computer time is very expensive so each run of the program costs money. Also, this microcomputer method allows for estimation of cancer cases in a cohort, when personal identification numbers are not complete, if the year of birth and sex are known. The cost of each run of the program on the microcomputer is negligible. It is easy to distribute and

update the program as computers running under MS DOS are widely available.

9.2.2. Chronic urticaria (II)

Urticaria and angio-edema have been reported mainly in association with lymphoproliferative disorders. However, not every case occurring in a patient suffering from malignant disease is causally related. The present study strongly suggests that chronic urticaria is not statistically associated with malignancy and the hypothesis that chronic urticaria is associated with internal malignant disease was based on case reports only, and this association probably occurred by chance. This study does not of course exclude th possibility that single cases of chronic urticaria can be caused by malignancy, but certainly this is rare and there is no indication for an extensive search for malignancy in patients with chronic urticaria if the patient does not have signs or symptoms suggestive of a malignant disease.

9.2.3. Condylomata acuminata (III)

The first epidemiological reports of a possible association between condyloma and cancer go back to 1953, when four cases of vulvar cancer, preceded by a condyloma infection, were described. Since then more than 60 cases of genital cancer in association with condyloma have been reported[118]. Human papillomavirus types 16 and 18 are found in up to 90% of patients with cervical carcinoma[119], and it is not known if the remaining 10%, really are negative for the virus. The oncogenic nature of human papillomavirus is now becoming widely accepted, although direct epidemiological proof is lacking[120]. Most studies to date have been retrospective - that is, the cancer is usually observed first and information about condyloma collected later. Such a study design carries a risk of many biases. It is theoretically possible that the virus entered the lesion after the cancer or cervical intraepithehal neoplasia had developed and that the transformed epithelium is tropic for human papillomavirus. Also it is possible that some other factors - such as other venereal diseases, sperm proteins, smoking, or alcohol intake - are involved in oncogenesis in genital cancer.

In a large retrospective study in Rochester, Minnesota, 746 cases were identified over 29 years[52, 118, 121]. Women were found to carry a four-fold risk of developing carcinoma *in situ* of the cervix. Interestingly, the same ratio of women developed cervical carcinoma *in situ* in both studies, 17 out of 711 (2.4%) in the present study compared with 13 out of 500 (2.6%) in the Rochester study. The Rochester authors estimated the incidence of cervical carcinoma *in situ* in their population by applying the incidence in 1960-1967 to the

follow-up in person-years for patients with condyloma diagnosed during 1950-1978. In the present study more appropriate methods and incidence data are used. Obviously the quality of the incidence data is of crucial importance and strongly affects the relative risks. The results of the present study indicate that the risk of developing cervical carcinoma *in situ* might be less than previously thought.

Male patients with condyloma had an increased risk of developing cancer (at all sites). Most of this increased risk was for genitourinary tumors, which were significantly increased. There was no significant increase in risk for tumors at individual genitourinary sites, but if the single testis cancer which was diagnosed six months before the condyloma was included there was a relative risk of 3.5 (1.1 to 8.4) for developing a testicular malignancy. This approach can be questioned, as traditionally only cancer that is diagnosed after diagnosis of condyloma would be considered. In this case, however, it is not a question of whether condyloma causes cancer, but rather that both the condyloma and the malignancy are caused by human papillomavirus.

A possible explanation of this increased risk is that the virus might, in a similar way as predicted in women, infect the epithelium and predispose to cancer. Oncogenic human papillomavirus types have been found in prostatic tissue[122], but the potential role of human papillomavirus in the etiology of urogenital neoplasia remains to be shown.

It might be argued that the fact that some patients are seen at the gynecological department leads to a selection among female patients, with relatively fewer patients with condyloma on the portio in this study. We do not believe this bias to be important because many "mild" cases of condyloma are diagnosed in the gynecology department when the patients attend for something else (abortion, preventive counselling, etc). Also, Walker and colleagues have shown that 50% of women with "external" condyloma also have cervical involvement[123].

9.2.4. Basal cell carcinoma (IV)

The present study based on a large number of person-years at risk shows that the risk of patients with basal cell carcinoma developing another type of malignancy is increased in comparison to the risk in the general population. Especially the risk of developing other skin malignancies seems to be significantly increased. Excessive sun exposure is probably the most important causative factor both for basal cell carcinomas and other skin malignancies, and thus it is not surprising that patients with basal cell carcinoma run an increased risk of other skin malignancies. The observation that patients with BCC seem to run an increased risk of malignant melanoma after developing BCC, but not before, is of interest, especially when the risks of other malignant skin tumors were increased both during the period before and after the BCC. We have no explanation of this difference, only speculations. The me-

dian age of the population studied was 68 years at the diagnosis of BCC. This elderly population might have developed immunological alterations which cause malignant melanoma to appear. Excessive sun exposure might explain the developments of other skin tumors (mainly squamous cell carcinoma) without immunological disturbances, but for the development of malignant melanomas both these factors might be needed. Also, if malignant melanomas are capable of spontaneous regression, this may explain the increased number after the appearance of the BCC but not before. After the diagnosis of BCC the patients are likely to be checked by dermatologists regularly and, therefore, early malignant melanomas might be detected and removed. These early malignant melanomas might be overdiagnosed by the pathologists or might have healed spontaneously. Before the diagnosis of BCC, only obvious malignant melanomas may have caused the patient to see a doctor.

Since arsenic exposure may be a risk factor for both basal cell carcinoma and lung cancer, it was not surprising to find that males with basal cell carcinoma run a more than five-fold risk of developing lung cancer in comparison to the general population. The observation that males with BCC had an increased risk of cancer of the thyroid gland and that females with BCC had an increased risk of cancer of the cervix uteri is more difficult to explain. Also for these forms of cancer, certain exposure e.g. arsenic might be the explanation of the association with BCC. A general cancer disposition of some of the patients with BCC resulting in an increased risk of cancer development also in other organs could also be an explanation. The excess risk found for these forms of cancer may also be the result of multiple statistical testing rather than a phenomenon of true biologic significance.

In contrast to this study, some earlier studies[19, 20] have not found any increased risk of other malignancies in patients with BCC. However, in these studies the number of malignant melanomas was too low to demonstrate an over-risk and in the largest of the studies[20], squamous cell carcinoma of the skin was not included.

We conclude that patients with BCC run a significantly increased cancer risk, especially of other skin malignancies.

9.2.5. Lichen planus(V)

In this study important information about the natural history of LP has been acquired. In males, there is a steep rise in diagnosis of new cases (first visit) in the late teens with a plateau between ages 20 and 24. This plateau is steady until the age of 60 to 64. The situation is quite different for the females, where an almost linear rise is observed from the early teens to the age of 55 to 59. At this age, almost 50% more cases of LP are diagnosed in women, though on the whole almost equally many cases are diagnosed in each sex.

According to a classic textbook of dermatology[124], women are more affected than men, but the opposite has been demonstrated in small series.

A malignant change in LP skin lesions is rare and only 36 cases of SCC developing in LP skin lesions are described in the literature. The clinical characteristics are summarized in Table 28. Twenty (59%) of the patients were males and fifteen (41%) females and sex was not reported for two patients. Bonnekoh has summarized 24 of these patients who developed squamous cell carcinoma in LP skin lesions[125]. He found that 11 of the 24 (46%) had a history of treatment with arsenic or of X-rays[125]. It is interesting to note that more than half of the malignancies (56%) reported arise in the verrucoid or hypertrophic variants of LP. The conclusion that chronic irritation could be an important carcinogenic factor. The majority of the lesions were located below the knee (69%). It is also well known that the Kobner phenomenon exists in LP and scratching of the lower legs might stimulate the appearance of malignant tumors and LP lesions. The time between diagnosis of LP and the cancer varied between 1 and 22 years, with an average of 12.2 years. Although the latency appears to be long, 12/32 (37%) acquired cancer less than ten years after the diagnosis of the LP skin lesions. The age of the patients at cancer diagnosis ranged from 29 to 78 years, with an average of 59 years.

The results from epidemiological studies on malignant transformation in patients with oral LP are summarized in Table 29. The incidence rates are surprisingly different and very high in some studies. The higher incidence rates are close to what has been reported for oral leukoplakia. It is possible that some of these studies have actually been dealing with oral leukoplakia, which has led to these high incidence rates. The studies of Holmstrup, Jänner, Fulling, Murti and Salem, all which are very large, do not confirm this high incidence. It is therefore logical to conclude that the incidence of malignant transformation is low, somewhere below 1% of all cases. In the literature review of Krutchkoff et. al. in 1978, 222 cases of oral LP with malignant transformation are reported[126]. The authors state that only fifteen cases satisfy the criteria for validity and of these fifteen, eight had been exposed to known carcinogenic factors. The authors rejected the idea of oral LP as a premalignant entity. This approach is probably too rigid. The risk appears to be real, although not very high. A recent case report describes a patient who actually developed under observation the histologic changes of benign oral LP, LP with atypia and finally squamous cell carcinoma[127].

In the present study a large number of patients with cutaneous LP were followed during an extended period. No increase in internal carcinoma was observed. Only one study has suggested that patients with LP might have an increased risk of internal cancer. In a retrospective study of the causes of death of patients with LP, malignant tumors, particularly those of the gut and the bladder, and malignant hemopathies, exceeded the expected prevalence[128].

Only six SCC of the skin, associated with LP, were observed in the present study. This number is no higher than expected. Both SCC and LP are

relatively common diseases and it is not surprising to find patients with both conditions at the same time.

TABLE 28.- Development of Squamous cell carcinoma in patients with cutaneous lichen planus, a literature review. Year: The year of publication. Ref: Number of reference. Sex: M=Male, F=Female. Age: Age at diagnosis of squamous cell carcinoma. Dur: Duration of lichen planus when the squamous cell carcinoma was diagnosed. Localization: Localization of the carcinoma.

Year	Author	Ref	Sex	Age	Dur	Localisation	Variant of lichen ruber
1903	Du Castel	129	M	50	6	Lower leg	Verrucoid
1927	Bartos	130	F	54	11	Lower leg	Verrucoid
1933	Puente	131	M	62	22	Lower leg	Hypertrophic
1935	Hövelborn	132	F	75	*	Lower leg	Verrucoid
1939	Schuermann	133	F	59	4	Thigh	Verrucoid
1940	Hampel	134	M	62	24	Arm	Planus
1951	Lyell	135	M	71	1	Hand	Planus
1952	Ugazio	136	F	*	10	Leg	Hypertrophic
1953	Wilson	137	F	74	8	Lower leg	Hypertrophic
1955	Hansen	138	M	74	*	Lower leg	Atrophic
1955	Bureau	139	F	52	15	Lower leg	Verrucoid
1958	Becker-Brennan	140	M	78	15	Lower leg	Hypertrophic
1960	Jansen	141	F	60	28	Foot	Atrophicus
1961	Brezenko	142	M	61	33	Lower leg	Hypertrophic
1961	Brezenko	142	M	63	23	Lower leg	Hypertrophic
1963	Depaoli	143	M	50	12	Lower leg	Hypertrophic
1966	Potter	144	M	35	18	Leg	Hypertrophic
1967	Midana	145	F	35	5	Hand	Sclerobullous
1969	Témime	146	M	43	*	Chest	Planus
1969	Swanbeck	147	*	*	10	Leg	*
1969	Swanbeck	147	*	*	10	Leg	*
1970	Male	148	F	65	9	Lower leg	Ulcerative
1971	Jänner	149	M	73	14	Shoulder	Planus
1971	Kimmig	150	M	59	*	Penis	Planus
1971	Kimmig	150	F	73	14	Breast	Planus
1971	Kronenberg	151	M	42	18	Leg	Hypertrophic
1980	Crotty	152	F	76	3	Vulva	Planus
1981	Leitao	153	M	29	18	Lower leg	Verrucoid
1982	De Dobbeleer	154	F	61	14	Foot	Erosive
1985	Yesudian	155	M	50	1	Lower leg	Hypertrophic
1985	Yesudian	155	M	39	15	Lower leg	Hypertrophic
1986	Bonnekoh	125	M	41	19	Lower leg	Hypertrophic
1988	Mayron	156	F	76	2	Sole	Ulcerative
1988	Duterque	157	M	72	1	Trunk	Follicular
1989	Ruocco	158	M	70	3	Lower leg	Hypertrophic
1989	Ruocco	158	F	75	5	Perianal	Erosive

**: Information not available*

It cannot be ruled out that the observation period in the present study is too short to detect any increase in SCC incidence, as the average observation time for LP-associated skin cancer, described in the literature, is twelve years. This must be considered unlikely, as 925 patients were followed for ten or more years and, of these, 454 for more than fifteen years. Chronic irritation has been thought to be a possible co-factor in squamous cell carcinogenesis of the skin. SCC has been found in chronic burn scars[159] and leg ulcers[147]. In the present material four of six patients had the hypertrophic variant of LP, which could mean that chronic irritation plays a role in these patients, but the effect is probably no larger than various other irritative effects the human skin is exposed to. We conclude that cutaneous LP is probably not a risk factor for the development of squamous cell carcinoma of the skin, and that the relationship earlier described has occurred by chance only.

TABLE 29.- Development of squamous cell carcinoma in patients with oral lichen planus, a literature review.

Year	Author	Reference No	Observation time	No. of patients with lichen planus	No. patients with oral cancer	Cancer frequency %
1924	Willinger	160	*	20	2	10
1929	Montgomery	161	*	17	1	6
1939	Schuermann	133	*	310	2	0.64
1957	Dechaume	162	*	50	5	10
1959	Sugár	163	11	36	1	3
1960	Warin	164	1-10	53	5	9
1961	Altman	26	6-10	128	1	1
1966	Rhode	165	*	207	6	3
1967	Jänner	149	*	585	9	1.7
1973	Fulling	166	3.6	327	3	1
1985	Silverman	167	5.6	570	7	1.2
1986	Murti	168	5.1	702	3	0.4
1988	Holmstrup	169	7.5	611	9	15
1989	Salem	170	3.2	4,277	4	0.09
1991	Sigurgeirsson	Present	9.9	2,071	8	0.4

*: *Information not available*

The patients in the present study were included on the basis of a cutaneous form of LP. No information is available about how many of these patients had oral involvement. According to a classic textbook of dermatology fifteen

percent of patients with cutaneous LP have oral involvement[124], but numbers up to seventy-five percent have been reported[25]. A five-fold increase in SCC of the mouth was found in the males but no cancers were observed in the females; but as oral cancer is rare in females it is possible that the study is not powerful enough to detect an increase in females, considering the wide confidence limits (0 - 3.7 cases). This observation supports the hypothesis that oral LP can be involved in oral carcinogenesis. The risk in this study is 0.4% for patients with cutaneous LP, but as it is not known how many of the patients had oral involvement, the risk of developing oral cancer among patients with oral LP cannot be determined. However, clearly it is higher than 0.4%. Assuming that between 15 and 75% of patients with cutaneous LP have oral involvement, the risk of cancer development among patients with oral LP lies between 0.5 and 2.6%. It is possible that some other co-factor such as smoking is needed for oral carcinogenesis, and the dominance of the males with SCC supports this hypothesis.

We conclude that patients with LP do not run an increase risk of developing SCC of the skin, but there seems to be an increased risk of developing SCC of the mouth.

9.2.6. Positive patch tests (VI)

Our data demonstrates that males have an increased overall risk of cancer after a positive patch test and that, particularly, there is increased risk of malignant tumors of the larynx, lung and prostate. The relative risk of these tumors varies from 1.5 to 4 for the time after or in parallel with the first epicutaneous test. Women have increased risks of malignant tumors of the larynx and cervix. The relative risk is low the first nine years after the first positive patch test, but clearly increases between ten and nineteen years after the test in both sexes. After twenty years the risk drops to normal.

ACD is a prototype of the delayed hypersensitivity (type IV) reaction and the patch test is an *in vivo* test for delayed hypersensitivity to topically applied chemicals. Many factors determine whether an individual develops contact allergy. Not all chemicals are allergenic, nor can any one chemical sensitize all people. Sensitization depends on the nature of the chemical and most sensitizers have a molecular weight less than 500. Concentration, nature of exposure, genetic susceptibility and nongenetic idiosyncrasies are all important factors. It is therefore obvious that patients with ACD are a very heterogeneous group. Some may have an entirely normal immune system, but have been exposed to highly allergenic chemicals and developed ACD. It is known that certain chemicals, i.e. dinitroclorobenzene, sensitize close to 100% following appropriate contact. In others, disturbances of immune function may lead to ACD. The results presented in this paper could indicate that a common failure of the immune system might predispose to both ACD and cancer.

It is also possible that the results are due to a confounding factor i.e. smoking.

As this paper is based on a retrospective register study with no information about factors other than age, sex, time of positive patch test and the results of the patch test, it was not possible to check for any confounding factors. It is interesting to notice the increase in tumors of the respiratory system which have been related to smoking. Smoking has been shown to be immunemodulating and it is possible that smoking can be a confounding factor in this study. On the other hand if this is so, it must be judged as unlikely that the patients would change their smoking habits in connection with the patch test and one would therefore have expected an increase in lung cancer before the positive patch test as well. This was not the case. It is not known whether patients with ACD smoke more than the general population. Also, patients with ACD might be more likely to have an industrial occupation and the cancer increase might be related to occupational carcinogenic exposure.

Infection with human papilloma virus (HPV) is believed to be one of the possible carcinogenic factors in cervix cancer carcinogenesis. It is possible that some tumors, such as those of viral origin, are under more immunologic control than others, although immunologic control of tumors is probably not a major factor in the etiology of most malignant tumors. It is possible that those ACD patients that have immune abnormalities are more susceptible to HPV and hence run an increased risk of developing cervical carcinoma.

While this study offers evidence of an association between patients with ACD confirmed with epicutaneous testing and cancer, a cautious interpretation of these findings is warranted. This is the first study of this association and it lacks control of possible confounding variables.

9.2.7. PUVA and cancer (VII)

Given the present understanding of the relationship between psoralens and cellular DNA, the long term carcinogenecity of PUVA is of primary concern. The current results show that there is a relation between risk of developing squamous cell cancer of the skin and total exposure to PUVA. Male patients exposed to more than 200 PUVA treatments had at least a thirty-fold greater inicidence of tumors than that expected in the general population, a figure in agreement with earlier findings. Two hundred treatments plus a total ultraviolet A dose of 1,200 J/cm seems to represent a threshold for development of skin cancer, and strategies which reduce the intensity and total dose of PUVA should therefore decrease risk. Also, patients receiving TMP showed no overall increased risk of all types of cancer, in contrast with patients receiving methoxypsoralen. Most of the patients who received TMP were treated topically with bath PUVA. It may be significant in this respect that the dose of ultraviolet A is smaller and only 1/15 of the UVA dose is needed when TMP bath PUVA is used rather than oral 8-MOP. One center used ex-

clusively bath PUVA treatment and when this center was compared with centers using the traditional oral 8-MOP regimen, a striking difference emerged and this is beeing further elucidated in a seperate study and study of the immunologic effects of bath-PUVA-treated patients is in preparation.

Many PUVA patients had received previous treatments. Some of them, such as ultraviolet B and arsenic, are carcinogenic. This fact makes it difficult to evaluate the true carcinogenic effect of PUVA. Patients who received few treatments or low doses of ultraviolet A had increased risks, and that there was also no clear dose response. This finding may be explained by the effects of earlier carcinogenic treatment. A case-control study of the effects of previous treatment in PUVA patients is planned.

Analysis of skin cancer development by skin type shows that patients with skin types II and III have the highest risk. Patients with skin type I (always burn, never tan) are treated conservatively while those with type IV (always tan, never burn) have an inborn shield against ultraviolet A light in their ability to pigment. These "protective effects" are diminished in patients with skin types II and III, therefore they might receive undesirably high doses of ultraviolet A.

The 24 PUVA-treated patients with squamous cell cancer had 6 genital tumors, of which 4 were located on the scrotum. The incidence of genital tumors reported by Stern and colleagues was much higher - 14 among 892 PUVA-treated patients. The average follow-up period in Stern and colleagues' study was longer than in ours[102]. We have, however, followed over 1000 patients for more than 10 years, and included more than five times as many patients in our study.

The genital area was not shielded during PUVA treatment in Sweden during the period studied. One difference between Stern and colleagues' patients and ours is in the use of tars for treating psoriasis[102]. This is less common in Sweden than it is in the USA, and tar itself might cause genital cancer even without PUVA treatment.

When the anatomical location of the skin tumors is studied, it is apparent that their location is quite different from that in the general population, supporting the causative effects of the PUVA treatment. The large numbers of tumors of the lower limbs and trunk, with comparably fewer in the face is most striking.

Many patients in this study received very low doses of UVA and are not likely to contribute much to the risk of cancer development. Some American studies have had much higher mean UVA doses[101, 102] and to make this study more comparable, patients observed for more than five years, treated for psoriasis with oral 8-MOP total body PUVA were also investigated separately. As expected, the risk was much higher in this subgroup: ten-fold in the males and fifteen-fold in the females. This is comparable to the study of Stern and colleagues[102].

The main concern with PUVA treatment is, however, not squamous cell carcinoma, but malignant melanoma. So far no studies have shown any risk of malignant melanoma, and the present study supports this. However, in this

subcohort four melanomas occurred, when only 1.8 were expected, and although these results are not significant, this association must be watched in the future as it is possible that the effects of PUVA will first become apparent after twenty years. The melanomas were diagnosed 2 to 7 years after PUVA treatment was started.

In contrast with other studies of PUVA and cancer, we detected other malignancies as well as skin cancer. Since psoralens are taken orally, one might expect internal side effects. We noted an increased risk of cancer of the respiratory system for males and females. This finding is difficult to explain but could be due to smoking habits among the PUVA-treated patients. The increased risk among males of cancer of the pancreas and among females of cancer of the colon and kidney might be an artifact of multiple comparison testing, especially in view of the discrepancy between the sexes. However, an increased risk of colonic cancer among psoriatics has been reported previously.

The findings of this study indicate that long-term exposure to PUVA increases the risk of squamous cell cancer of the skin. This study also highlights possible risk of internal cancer, which must be further investigated. Careful follow-up and early detection should limit the risk of PUVA treatment.

9.2.8. Dermatomyositis or polymyositis (VIII)

Since the proposed association between dermatomyositis or polymyositis and malignancy was first reported in 1916 [27], its validity has been in dispute. Report results have been contradictory, but there appears to be increased incidence of malignancy in myositis patients and the risk of malignancy in dermatomyositis patients appears greater than that seen in polymyositis patients [28].

In 1975, Bohan and Peter [31, 32] described five criteria that are now routinely used for the diagnosis of dermatomyositis or polymyositis. These criteria have been used in Sweden since then. Bohan and Peter criticized much of the earlier work since strict criteria for myositis had not been applied and it was possible that other disorders such as myasthenia gravis, muscular dystrophy, endocrinopathies, were included. The results of studies done after the publication of the article of Bohan and Peter are summarized in Table 2.

As the present study is based on patients from an in-patient register, we cannot guarantee that no patients with overlap syndromes have been included. As the number of patients was so large, some having up to fifty hospital stays in different hospitals in Sweden from 1964, we judged it impossible to review all the hospital records, though we did review a sample of 76 patients. Two dermatologists (BS and BL) reviewed the records and classified them according to the criteria of Bohan and Peter as described by Caro [171]. Of the 76 records selected randomly, seven were not available at the local hospital, 50 (72%) were classified as definite, 14 (20%) as probable

and 5 (7%) as not probable. Our conclusion is that the material is well defined and that the majority of the patients in the national in-patient register were correctly diagnosed and registered!

In the present study we have demonstrated that there is only a moderate, but significant, increase in the incidence of malignancy in male and female patients with polymyositis. When individual cancer sites were analyzed, cancer of the lung was six times more frequent than the expected number in the males.

There is clearly an increase, although not very large, in the number of malignancies in patients with dermatomyositis. The associated risk is greater in females. This over-risk was mainly carried by "female" and colorectal cancers in the females, and lung and pancreas cancer in the males. In fact if non-genital cancers are compared, the risk is similar in males and females. It is interesting to note the high risk associated with cancer of the ovary, and five more ovarian tumors were diagnosed one to three years before the dermatomyositis diagnosis, making the total number of ovarian cancers ten. These cancers are often diagnosed late and therefore hard to cure, and of these ten patients nine died during the observation period.

Twenty percent of patients with dermatomyositis are children, but the corresponding figure for polymyositis is much lower (3%). This study also clearly shows that there is no associated risk of malignancy in children.

Mortality is slightly increased in male polymyositis patients, but not in females. In dermatomyositis patients, particularly females where the risk is doubled, there is clearly increased mortality. This increase among dermatomyositis patients is caused mainly by cancer deaths (Table 27).

Both dermatomyositis and polymyositis are extremely rare diseases and it is therefore difficult for individual centers to get large patient series. In Table 2 the results from studies done after the work of Peter and Bohan are summarized [28]. Most series are based on patients from referral centers. Patients with both dermatomyositis or polymyositis and malignancy are therefore more likely to be referred, and a bias is introduced. This effect has been demonstrated by Lakhanpal and colleagues who found that the highest proportion of cancer among dermatomyositis or polymyositis patients was contributed by the most distant referrals[33].

The present study design avoids many of the possible biases as has been pointed out earlier. The most important is the Berkson bias [115] in which the joint occurrence of two diseases becomes more likely as a selective referral of patients with both conditions. This effect is completely eliminated as our study is population-based, and includes from the early seventies close to 90 percent of the Swedish population.

The weakness of many previous studies is that they have only stated the cancer incidence among the dermatomyositis or polymyositis patient population, but failed to relate this to the expected numbers of cancers in that particular group. This can only be reliably estimated by applying calendar- and age-specific incidence. This is particularly important when, as in the present study, patients are observed over a long period, as cancer incidence is not

constant. Also, when comparing cancer incidence in patients with dermatomyositis or polymyositis, the age of the patients must be weighed in. This effect can clearly been seen in the present study where 11 cancers in 26 males (42%) aged over seventy produced a relative risk of 1.9, but 4 cancers in 36 females (11%) aged between 30 and 49 produced a relative risk of 3.2 as fewer cancers were expected in this age group. It is therefore obvious that the age distribution of the patient group being studied is of crucial importance and it is very difficult to compare percentages of patients with malignant disease between different groups.

The third bias, the diagnostic suspicion bias, occurs when patients included in the study are evaluated more thoroughly for the putative associated disease. As the suspected association between dermatomyositis or polymyositis and cancer has been known for a long time, it is indeed probable that this bias obtains, and we probably see its effects, at least partly, in the peak of diagnosed cancers around the first diagnosis of dermatomyositis. But since the observation time is at least four years (average ten) after the first evaluation for polymyositis or dermatomyositis, this affect should disappear over time and not effect the total number of cancers during the whole period.

The present study is the largest to date and the only large population-based study which evaluates the risk of cancer development in both dermatomyositis and poiymyositis patients. The expected and observed numbers of cancers are very reliable because of obligatory nationwide registration of malignancies to the Swedish Cancer Registry.

Our findings demonstrate that patients with polymyositis run moderately greater risk of cancer development, as compared with the general population. Apart from complete history, physical examination, routine blood examination and a chest radiography, a nondirected search for tumors is hardly indicated in polymyositis patients. On the other hand patients with dermatomyositis run a large overrisk of developing cancer, and cancer mortality is high in this patient group. This risk seems to be confined to the older age groups and is greater in women. On the basis of these results, a search for malignancy in women over 40 and males over 50 seems to be warranted. In females this over-risk is largely carried by "female" cancers and in the males cancers of the lung and pancreas. In dermatomyositis patients a more extensive search for malignancy is probably warranted.

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12. INDEX

13. PAPERS