Risk of cancer after coal tar treatment

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General introduction

1

Introduction

Psoriasis

Psoriasis is a very common chronic disease affecting approximately 2% of the population worldwide. Males and females are equally affected. Psoriasis can present at any age, but a bimodal distribution of age at onset is seen with a large peak between 15 and 30 years and a smaller peak at 50-60 years.[1] The pathogenesis of psoriasis is complex and concepts on the etiology have changed over the years. Studies from the 1970s provided evidence for a T-cell mediated skin disease.[2;3] Nowadays psoriasis is conceptualized as an immune mediated disease caused by many interactions between immune cells and keratinocytes, proinflammatory cytokines and chemical mediators.[4-6] Classic linkage analyses and genome wide association studies have identified different genes associated with psoriasis. Population studies clearly indicate that the incidence of psoriasis is higher among first-degree and second-degree relatives of patients compared to the general population. The strongest association was observed in the psoriasis susceptibility 1 region (*PSORS1*), which probably accounts for 35-50% of the heritability of the disease.[7] Other psoriatic gene variants include the genes encoding the interleukin-23 receptor (IL23R) and its ligand (IL12B).[8] Also, an association between a high copy number of beta-defensins on chromosome 8p21.1 and an increased risk of psoriasis has been reported.[9]

Psoriasis is characterized by sharply demarcated erythematous plaques covered with silvery white scaling (Figure 1). The most common type of psoriasis is psoriasis vulgaris, with symmetrically distributed plaques on the extensor sites of elbows,

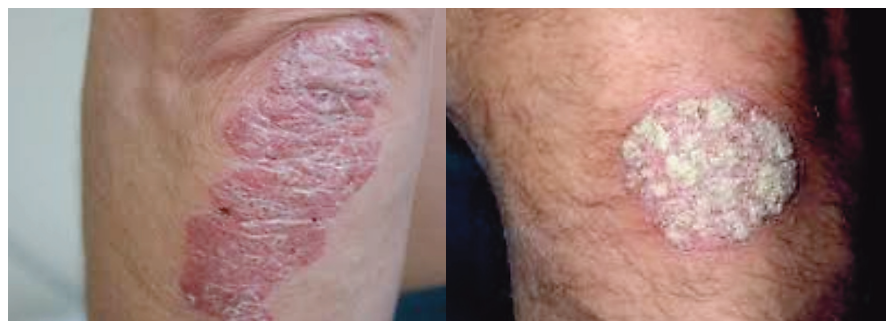

Figure 1 Classical presentation of psoriasis vulgaris with thick, sharply demarcated erythematosquamous plaques on the extensor site of an elbow and on the knee.

knees, scalp and lumbosacral region. Psoriasis inversa involves skin folds of the axillary, inframammary, genital, intergluteal and perianal skin. Scaling in these areas is minimal. Other types of psoriasis are guttate psoriasis, generalized pustular psoriasis (von Zumbusch) and palmoplantar pustulosis. Associated features of psoriasis occur at the nails and joints. Nail psoriasis (psoriasis unguium) is common and is found in 20-50% of patients with psoriasis.[10] Typical signs of nail changes are nail pitting, subungual hyperkeratosis, distal onycholysis and oil spots. The joints are affected in 10-20% of patients with psoriasis.[11;12] In general, the classical psoriatic arthritis may consist of oligoarthritis, distal interphalangeal joint involvement, dactylitis and calcaneal enthesitis.

Different treatment options exist for psoriasis (Table 1.) Topical therapy is the mainstay of treatment for psoriasis, especially in patients with mild disease. First line therapeutic modalities include topical corticosteroids and vitamin D analogues. Second line treatments are ditranol and coal tar ointments. In case of moderate or severe psoriasis phototherapy can be applied. Types of phototherapy used in psoriasis are narrow-band UVB and psoralen-UVA (PUVA). When topical therapies or photo(chemo) therapy are not effective, fail to induce long-term remission or are contra-indicated, systemic treatments can be used. Systemic treatments include methotrexate, retinoids, cyclosporine, fumaric acid esters and the recently introduced 'biologics'. Some of these therapies are potential carcinogenic (e.g. PUVA and cyclosporin) and therefore, patients treated with these therapies may have an increased risk of cancer, such as non melanoma skin cancer and lymphomas.[13-16]

Studies that investigated the risk of cancer in patients with psoriasis showed an increased risk of cancer, especially non-melanoma skin cancer.[17-22] The majority of these patients had been treated with potential carcinogenic therapies and therefore, it is not possible to discriminate between a possible increased intrinsic risk of cancer in patients with psoriasis and the effect of these therapies.

Table 1 Treatment modalities for psoriasis.

Topical therapy	Photoherapy	Systemic therapy
Emollients	UVB	Methotrexate
Corticosteroids	PUVA	Cyclosporine
Vitamin D analogues		Retinoids
Coal tar		Fumaric acid esters
Ditranol		Biologics

Eczematous disease

Atopic dermatitis

Atopic dermatitis (AD) is a very common chronic relapsing inflammatory skin disease that occurs at any age, but usually starts before the age of 5 years. The prevalence of AD has doubled in industrialized countries in the past decades; 15-30% of children and 2-10% of adults are affected.[23] Atopic dermatitis is a multifactorial disease arising as a result of the interaction of many genes with environmental factors (e.g. allergens and microbes) leading to an imbalance in the immune system and disruption of barrier function. In the majority of patients with AD elevated levels of total and allergen specific IgE can be detected. The acute phase of AD is characterized by a Th2-cell response which leads to increased cytokine production of interleukin (IL)-4, IL-5 and IL-13.[24] In chronic atopic dermatitis, there is a shift from a single Th2 cell response to an environment of Th2 cell and Th1 cell type response. Many candidate genes encoding for cytokines involved in the Th2 cell response, e.g. IL-4, IL-5 and IL13 were identified on chromosome 5q31-33, 3q21 and 3p26.[23;25]

The disrupted skin barrier in AD allows penetration of microbes, allergens and irritants, leading to allergen sensitization and inflammation. In the past years, a strong association between mutations in the gene encoding filaggrin (FLG) and AD was observed in different populations. Filaggrin is a key protein in epidermal differentiation and contributes to the keratin cytoskeleton; mutations in the gene coding for filaggrin results in diminished epidermal barrier function.[26;27] Clinically, atopic dermatitis is characterized by itchy erythematous papules and plaques. In childhood, lesions are usually seen on the face, scalp and extensor surfaces of the extremities. Any cutaneous site can be affected, but the diaper area is often spared. During childhood, lesions favor the distal extremities, the poplitial flexures and posterior neck. In adults, AD is seen predominantly in a flexural distribution (Figure 2), but extensive areas of skin may be involved. Some adults present with a head neck

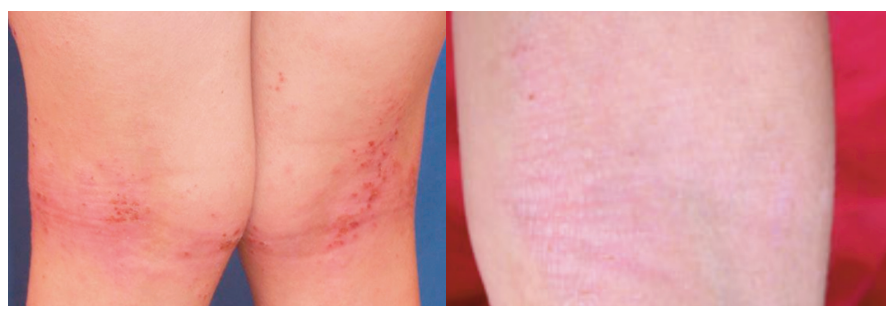

Figure 2 Erythematous papules, plaques and excoriations in the flexural sites of the knees in a patient with atopic dermatitis and lichenification in the elbow.

dermatitis or chronic hand dermatitis. Intense pruritus and a dry scaly skin are observed in the majority of patients with AD.

Because of the dry skin, the use of emollients is important in the treatment of AD. The use of ointments can reduce flares by improving the barrier function of the skin. Topical corticosteroids are first-line treatments in AD (Table 2). To reduce side effects mid-potency preparations are used. However, more potent corticosteroids may be required for lichenified plaques and lesions on the palms and soles. Second line treatments are calcineurin inhibitors and coal tar ointments. In case topical therapy is ineffective or in case of severe AD, phototherapy (narrow-band UVB of PUVA) or systemic therapies can be prescribed. Systemic corticosteroids or cyclosporin should be reserved for the treatment of severe, acute flares that fail to respond to intensive topical therapy. However, disease relapse may make discontinuation difficult. In case of chronic relapsing AD, immunosuppressive therapies, such as methotrexate, cyclosporin or azathioprine can be prescribed to stabilize the disease. Atopic dermatitis causes chronic stimulation of cells of the immune system, leading to randomly occurring pro-oncogenic mutations in actively dividing cells and may therefore lead to increased risk of cancer. In addition, patients with atopic dermatitis are treated with potential carcinogenic therapies. Several studies reported an increased risk of cancer in patients with atopic dermatitis.[28-30] As several of these patients had been treated with systemic therapies, it is not possible to disentangle the effect of treatment on the risk of cancer in these studies.

Table 2 Therapies for atopic dermatitis.

Topical therapy	Photoherapy	Systemic therapy
Emollients	UVB	Corticosteroids
Corticosteroids	PUVA	Cyclosporin
Calcineurin inhibitors		Methotrexate
Coal tar		Azathioprine

Contact dermatitis

Contact dermatitis can be divided in allergic contact dermatitis (ACD) and irritant contact dermatitis (ICD). It is the most common form of occupational skin disease.[31]. The acute phase is characterized by erythema, edema and vesicles, followed by dryness and scaling in the chronic phase. Allergic contact dermatitis is a T-cell-mediated inflammatory reaction which occurs after the exposure of susceptible individuals to sensitizing chemicals.[32;33] These cutaneous antigens are generally low

molecular weight molecules (haptens). ACD is characterized by two phases: the induction phase and the elicitation phase. After the first contact of the skin, the hapten is taken up by cutaneous dendritic cells, which migrate to regional lymph nodes. Contact of these dendritic cells with hapten-specific T-cells result in differentiation of T-memory cells. Challenge of sensitized individuals with the same hapten will result in elicitation of the inflammatory reaction after 48-72 hours by activation of the T-memory cells (elicitation phase). The most common causes of ACD are metals (nickel and chromate), cosmetics (preservatives, perfumes), cloths (dyes), drugs (active ingredient, preservative or vehicle) and plants.[33]

In irritant contact dermatitis the irritant has a direct toxic effect on the keratinocytes, leading to impairment of the barrier function.[32] Damage to the epithelial cells leads to release of IL-1α by keratinocytes, which in turn stimulates other keratinocytes and fibroblast to produce more pro-inflammatory cytokines, such as IL-1α, IL-α, IL-6, IL-8 en TNF-α[32] Substances that are dehydrating or oxidizing agents or keratin solvents may be irritants. The effects of irritants are related to the chemical properties of the irritants, the concentration and duration of exposure.[32]

Coal tar

Coal tar is one of the oldest topical treatments in dermatology and is well-established in the management of various skin diseases, especially psoriasis and eczema. The exact mechanism of action is unknown, but coal tar has anti-pruritic and anti-inflammatory effects.[34] Two coal tar preparations are mainly used in dermatological practice: crude coal tar (pix lithantracis) and its alcoholic extract liquor carbonis detergens. In general, coal tar ointments are well tolerated, but short-term adverse effects, such as folliculitis and irritation can occur. Coal tar can cause a phototoxic reaction and therefore, it is recommended to avoid sun exposure during treatment. Other disadvantages of using coal tar are its messiness, staining and odour. Therefore, these products, especially crude coal tar, are mainly used at dermatological day-care units and in hospitalized patients (Figure 3).

Long-term adverse effects include the potential increased risk of cancer. Coal tar is a complex mixture of more than 10,000 compounds, including high concentrations of polycyclic aromatic hydrocarbons (PAH).[35] Some PAH, such as benzo(a)pyrene are classified as human carcinogens by the International Agency for Research on Cancer[36], based on both animal studies[37-39] and occupational studies[38;40-42], that demonstrated increased risks for lung, skin and bladder cancer after PAH exposure. The carcinogenic potential of coal tar is an important reason for dermatologists to be reluctant to use this therapy. There is still considerable uncertainty about the carcinogenicity of coal tar in dermatological practice, because clear evidence of an increased risk of cancer after coal tar therapy is lacking.

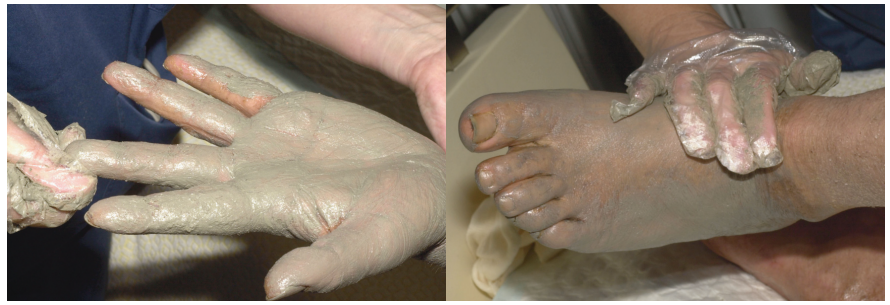

Figure 3 Crude coal tar is applied to the hands and feet of a patient with atopic dermatitis.

Only few studies have investigated the risk of cancer in patients treated with coal tar (Table 3). The majority of these studies did not observe an increased risk of cancer.[19;43-46] Only one study by Stern et al. reported an increased risk of non-melanoma skin cancer in patients treated with coal tar.[47] Differences in cancer risks observed in occupational studies versus studies in patients may be explained by the frequency, level and duration of PAH exposure. Malignancies have occurred after prolonged occupational exposures, whereas the use of coal tar in dermatological practice is limited to a much shorter duration of exposure.[48;49]

Table 3 Epidemiological studies that investigated the risk of (skin) cancer after coal tar treatment (with or without UVB) in patients with psoriasis and eczema.

Author	Study design	Study group	Therapy	Outcome	RR (95% CI)
Hannuksela-Svahn[19]	Nested case-control	Psoriasis	Goeckerman[1]	SCC[2]	1.5 (0.3-7.3)
				NHL[3]	1.2 (0.1-16.8)
Pittelkow[46]	Historic cohort	Psoriasis	Goeckerman[1]	All cancers	No increased risk
Maughan[45]	Historic cohort	Eczema	Goeckerman[1]	All cancers	No increased risk
Jones[43]	Historic cohort	Psoriasis	Coal tar	All cancers	No increased risk
Stern[47]	Nested case-control	Psoriasis	Coal tar and/or UVB	Skin	5.6 (1.9-16.2)

[1] combination of coal tar with UVB
[2] Squamous cell carcinoma
[3] Non-Hodgkin lymphomas

Most of the studies in patients lacked sufficient numbers of patients, follow-up data or did not control for confounding factors (e.g. smoking and treatment).Therefore, more research is needed to provide valid risk estimates of the use of coal tar in patients with psoriasis or eczema.

Aim and outline of the thesis

The main objective of this thesis was to investigate the risk of cancer after coal tar treatment in patients with psoriasis or eczema. For this purpose, we initiated a large historical cohort study: the LAte effects of coal Tar treatment in Eczema and psoriasis; the Radboud study (LATER study).

Chapter 2 comprises a review on the use of coal tar in dermatology. An overview of the preparation, method of action and its current use in dermatology is presented. The second part of the review focuses on the possible carcinogenicity of coal tar.

In **chapter 3** the results of a survey that was conducted among Dutch and Flemish dermatologists are presented. Dermatologists were invited to describe their treatment policy in psoriasis and eczema with special emphasis on the use of coal tar preparations. This study enabled us to evaluate the position of coal tar in the treatment of these skin diseases.

In **chapter 4** we report the results of our large-scale cohort study in which the risk of non-melanoma skin cancer and organ tumours after coal tar treatment was assessed in patients with psoriasis or eczema. In the second part of chapter 4 we present the results of a case-control study on the risk of bladder cancer after coal tar treatment.

The risk of cancer in patients with psoriasis or eczema has been investigated in many studies. However, in these studies it was not possible to disentangle the effect of treatment on the risk of cancer. In **Chapter 5** the results from a cohort study in which the risk of cancer in patients with psoriasis or eczema was compared to the general population are presented. By selecting a group of patients who were only treated with dermatocorticosteroids we were able to exclude the effect of potentially carcinogenic treatments on the risk of cancer. Also, subgroups of patients were selected to assess cancer risk in patients treated with potentially carcinogenic therapies, such as PUVA and systemic therapies.

In **Chapter 6** we report the results of a toxicology study in which the uptake, bioavailability and bio-activation of PAH in patients with psoriasis was compared to healthy volunteers. Patients with psoriasis have an altered skin barrier and this could have implications for the carcinogenic potential of coal tar. Differences in dermal

absorption and metabolic activation of PAH after topical application of coal tar were analyzed in skin biopsies and urine samples of patients with psoriasis and healthy volunteers.

Concluding this thesis, in **Chapter 7** the main results of our studies are summarized and the implications of our findings for the treatment of psoriasis and eczema are discussed.

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Coal tar in dermatology

2

Later-studie

2.1

Coal tar in dermatology

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Abstract

Coal tar is one of the oldest treatments for psoriasis and eczema. It has anti-inflammatory, antibacterial, antipruritic and antimitotic effects. The short-term side effects are folliculitis, irritation and contact allergy. Coal tar contains carcinogens. The carcinogenicity of coal tar has been shown in animal studies and studies in occupational settings. There is no clear evidence of an increased risk of skin tumors or internal tumors. Until now, most studies have been fairly small and they did not investigate the risk of coal tar alone, but the risk of coal tar combined with other therapies. New, well-designed, epidemiological studies are necessary to assess the risk of skin tumors and other malignancies after dermatological use of coal tar.

Introduction

Coal tar has been used in the treatment of skin diseases for many decades. However, some reluctance has evolved recently among dermatologists for several reasons, including the difficulty of obtaining coal tar preparations. In the Netherlands, many pharmacies are no longer able to prepare coal tar products, because of stringent rules from the Dutch government regarding the preparation of such products. Other disadvantages of using coal tar are its messiness, staining and odor. Owing to its staining of clothes and furniture, it is not always possible to use tar preparations at home. The most important reason for the reluctance to use coal tar is its potential carcinogenicity with dermatological use. Animal studies and studies in occupational settings showed an increased risk of non-melanoma skin cancer after chronic exposure to coal tar.[1-5] In epidemiological studies on the dermatological use of coal tar, some revealed an increased risk of non-melanoma skin cancer[6-8], while most studies did not .[9-13] Studies that investigated the risk of internal tumors after coal tar treatment did not find any increased risk of cancer. However, there is still considerable uncertainty about the carcinogenicity of coal tar due to the lack of convincing results from large epidemiological studies with sufficient follow-up. Therefore, the question remains as to whether it is justified to abandon coal tar preparations. To answer this question, two comparisons must be made: the risk versus the efficacy of coal tar and the risks versus the efficacy of other therapies.

In this paper, we present an overview of the characteristics of coal tar and its current use in dermatology. Emphasis is laid on the possible carcinogenicity of coal tar. Furthermore, we discuss the need for further research data on which to draw a well-founded conclusion about the use of coal tar in dermatological practice.

Method of preparation

Tars are products of the destructive distillation of organic materials. The most frequently used tar product in dermatology is coal tar. Other tar products are wood tar (pix liquida) and shale tar (ammonium bituminosulfonate).

Coal tar is obtained by heating coal in the absence of air. It contains more than 10,000 compounds, but only a minor proportion of them have been identified. The composition of coal tar depends mainly on the temperature of distillation. High-temperature coal tars (1000-1300^{o}C) have a higher polycyclic aromatic hydrocarbon (PAH) content than low-temperature coal tars (400-700^{o}C).

Medical pix lithantracis is produced by mixing two thirds of pitch from high temperature sources with one third of tar oils (obtained by fractional distillation at 220-270^{o}C). Liquor carbonis detergens is obtained by the extraction of 20 grams of pix lithantracis with 100 ml of alcohol and the addition of 5 grams of polysorbate.

Wood tar is produced by the destructive distillation of several types of wood (birch, beech, pine or juniper). Shale tar is obtained by the destructive distillation of bituminous stone that contains deposits of fossilized fish.

Modes of action

The precise mechanism of action of coal tar on a molecular level is unknown. Coal tar has anti-inflammatory, antibacterial and antipruritic effects.[14] At the start of coal tar treatment, hyperplasia of the skin is observed. Continued application of coal tar has a cytostatic effect that causes epidermal thinning.[15;16] These changes in keratinisation have also been shown in mouse models. After the application of coal tar, changes occurred in the type of prekeratin. Furthermore, after the application of coal tar to mouse models, parakeratotic regions in the epidermis were replaced by orthokeratotic regions.[17] Coal tar also has a photodynamic effect that makes the skin more sensitive to UV light.[18;19]

Applications

Psoriasis

Several local therapies are prescribed for the treatment of psoriasis. Corticosteroids and vitamin D_3 analogues are applied as first-line therapies. Also tar products and dithranol are frequently prescribed. This can be concluded from a recent survey among dermatologists in the Netherlands and Belgian Flanders on treatment policies for psoriasis and eczema (Table 1).[20] However, a proportion of the dermatologists, approximately 25%, reported that they had stopped or minimized their use of coal tar products. In many cases, patients showed unwillingness to accept or comply with this therapy owing to the risk of staining and possible irritation of the skin.

Several studies have shown the efficacy of coal tar in the treatment of psoriasis.[21;22] However, it is unclear how the efficacy of coal tar compares to the efficacy of other therapies, because only a few studies compared the efficacy of coal tar to an active therapy. One study on the efficacy of coal tar preparations compared to vitamin D_3 analogues observed similar efficacy after one month, whereas other studies found that vitamin D_3 analogues gave better results.[23-25] When itching is extensive and first-line therapies show insufficient improvement, tar products are recommended alternative therapies.

Eczema

Several local therapies are available for the treatment of eczema. Local corticosteroids are very effective and are frequently prescribed by dermatologists (Table 1). Over the past several years, calcineurin inhibitors have been applied to patients with eczema. These therapies have proved effective in adults and children.[26;27] Some indications are present for the use of coal tar preparations in the treatment of eczema

Table 1 The use of local therapies in the treatment of psoriasis and eczema reported by dermatologists in the Netherlands and Belgian Flanders.

	Dutch dermatologists (n=225)		Flemish dermatologists (n=150)	
Local therapies	**Eczema (%)**	**Psoriasis (%)**	**Eczema (%)**	**Psoriasis (%)**
Corticosteroids	100	100	99	99
Vitamin D_3 analogues	-	100	-	100
Tar products*	72	41	49	60
Dithranol	-	56	-	30
Calcineurin inhibitors	92	-	98	-

Data were collected in a survey among Dutch (n=360) and Flemish dermatologists (n=330).[20] The response of Dutch dermatologists was 63.2% and of Flemish dermatologists 41%. *Tar products are pix lithantracis, liquor carbonis detergens and pix liquida.

(figure 1). Coal tar has good antipruritic activity and has proved very effective on eczema lesions.[28] As it difficult to use tar preparations at home (especially pix lithantracis), these products are mainly used at dermatological day-care units and in hospitalized patients. An exception is liquor carbonis detergens that can also be used at home.

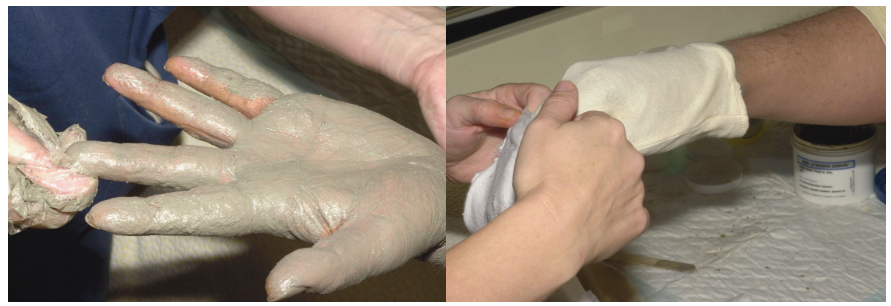

Figure 1 Coal tar treatment in a patient with eczema. (**a**) Coal tar is applied by a nurse. (**b**) After the application of coal tar, the areas are covered with dressings.

Other skin diseases

Owing to the antipruritic and anti-inflammatory activities, coal tar products are also used in the treatment of pustulosis palmoplantaris and prurigo simplex.[19;29]

Adverse effects

Short-term

Coal tar has several side-effects. Folliculitis can occur, especially when high concentrations are used (above 5%); a common location is the lower extremities.[15] Coal tar can cause irritation of the skin in patients with unstable forms of psoriasis, pustular or erythrodermic psoriasis. Another side-effect of coal tar is contact allergy, while cross-allergies may also arise between coal tar and wood tar.[30-33] Coal tar can cause a phototoxic reaction (figure 2). Therefore it is recommended to avoid sun exposure during treatment with coal tar. The part of the UV spectrum that is responsible for this reaction is within the UVA-visible region (340-430 nm). Thus, it is possible to become sunburnt, because UVA penetrates glass.

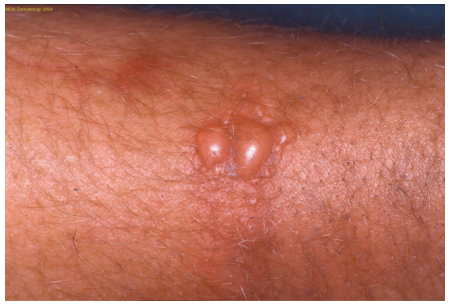

Figure 2 Phototoxic reaction caused by coal tar.

Long-term

Coal tar contains several polycyclic aromatic hydrocarbons (PAH), such as benzo(a) pyrene, benz(a)antracene and diben(a,h)anthracene. These PAH are metabolized into reactive metabolites by cytochrome P450-systems in the liver, skin and blood. The metabolites are able to bind to macromolecules, such as DNA. As a consequence, PAH-DNA adducts are formed. These adducts may be important in tumor initiation.[34-37] Carcinogenicity of PAHs has been shown in animal studies and in workers with chronic exposure to PAHs.[1-5] However, studies in a dermatological setting showed conflicting results.[6;9-13] Occupational exposure to PAH is usually of very long duration at a low concentration level, whereas in dermatological practice, exposure is high and short-term. Also, the uptake route is different: with dermatological use, PAH uptake mainly occurs via the skin, while in occupational settings, the uptake route can also include the respiratory system. Such differences in PAH exposure levels and uptake routes may explain the variation in results found in studies on the risk of cancer after exposure to coal tar.

Although several studies investigated the risk of cancer in patients with psoriasis and eczema, only a few studies specifically addressed the risk of cancer after coal tar treatment (as monotherapy or in combination with UVB). The results of these studies are summarized in table 2.

In two parallel small retrospective studies, data were collected from patients who had been hospitalized in the period 1950-1954 and had received treatment with coal tar and UVB (Goeckerman-regimen) for psoriasis (n=260) or eczema (n=305).[12;13] After 25 years the observed numbers of skin malignancies were compared to the expected numbers. Neither of the studies showed an increased risk of skin cancer after coal tar treatment. However, the treatment durations and dose levels of coal tar varied widely in the study populations and no adjustments were made for other therapies that patients may have received, such as PUVA, cyclosporin or methotrexate.

A case-control study by Stern et al. (1980) found an increased risk of skin cancer in patients with psoriasis who had been treated with coal tar for more than 90 months and had received more than 300 UV light treatments (odds ratio = 5.6; 95% CI: 1.9-16.2).[6] All patients were drawn from the PUVA cohort (n= 1,373 patients) and had therefore been treated with PUVA.

Jones et al. (1985) investigated the risk of skin cancer and internal tumors in 719 patients with psoriasis.[10] These patients had received coal tar therapy intermittently over a 10-year period. None of them had been treated with UVB, PUVA or cytotoxic therapies. No increased risk of (skin) cancer was found.

In 2000, Hannuksela-Svahn et al. published the results of a reasonably large cohort study[9] in which the risk of cancer was estimated in 5,687 hospitalized patients with psoriasis. During follow-up (mean duration 14 years) 533 tumors were observed. The number of expected tumors (n = 425.8) was based on the nation-wide sex-specific and age-specific cancer incidence rates for Finland. The overall cancer incidence was increased (standardized incidence ratio (SIR): 1.3; 95% CI: 1.2-1.4). Increased risks were found for squamous cell carcinoma (SIR= 3.2; 95% CI: 2.3-4.4), non-Hodgkin lymphoma (SIR= 2.2; 95% CI: 1.4-3.4), Hodgkin lymphoma (SIR= 3.3; 95% CI: 1.4-6.4), laryngeal cancer (SIR= 2.9; 95% CI: 1.5-5.0), lung cancer (SIR= 1.5; 95% CI: 1.2-1.8) and liver cancer (SIR= 1.5; 95% CI: 0.9-3.3). A nested case-control study did not show a significantly increased risk of squamous cell carcinoma (30 cases and 137 controls; OR = 1.5; 95% CI: 0.3-7.3) or non-Hodgkin lymphoma (19 cases and 110 controls; OR=1.2; 95% CI: 0.1-16.8) after treatment with the Goeckerman regimen.

Several other studies investigated the risk of cancer in psoriasis and eczema patients regardless of specific therapies.[38-45] A recent study by Olesen et al. (2005) on 2,030 hospitalized patients with eczema revealed an increased risk of cancer (standardized morbidity ratio (SMR): 1.5; 95% CI: 1.2-1.9).[44] This increased risk could almost entirely be explained by an increased risk of non-melanoma skin cancer

(SMR: 2.4; 95% CI: 1.4-3.9). No cases of melanoma were detected during the relatively short follow-up period; the increased risk of non-melanoma skin cancer could partly be explained by detection bias. The skin of patients with chronic eczema is often examined by dermatologists and this may increase the chance of discovering skin cancer compared to individuals in the general population.

Bofetta et al. (2001) conducted a similar cohort study on 9,773 hospitalized psoriasis patients.[40] An overall increased risk of cancer was found (SIR: 1.37; 95% CI: 1.28-1.47). This study did not only show an increased risk of non-melanoma skin cancer (SIR: 2.46; 95% CI: 1.82-3.27), but also increased risks for other types of cancer were found: pharynx (SIR: 2.80; 95% CI: 1.96-3.87), liver (SIR: 1.91; 95% CI: 1.28-2.74), pancreas (SIR: 1.56; 95% CI: 1.02-2.23), lung (SIR: 2.13; 95% CI: 1.71-2.61), vulva (SIR: 3.24; 95% CI: 1.18-7.06), bladder (1.43; 95% CI: 1.03-1.92) and kidney (SIR: 1.56; 95% CI: 1.04-2.25). The study showed a decreased risk of melanoma (SIR: 0.32; 95% CI: 0.10-0.74). These two studies only included a highly selected population of psoriasis and eczema patients, i.e. all patients were hospitalized.

Table 2 Epidemiological studies on the risk of (skin) cancer after coal tar treatment (with or without UVB) in patients with psoriasis or eczema.

Author	Type of study	Psoriasis or eczema	Therapy	Outcome	RR (95% CI)
Hannuksela-Svahn et al.[9]	nested case-control	psoriasis	Goeckerman regimen	squamous cell carcinoma	1.5 (0.3-7.3)
				non Hodgkin's lymphoma	1.2 (0.1-16.8)
Pittelkow et al.[13]	historic cohort	psoriasis	Goeckerman regimen	all skin cancers	no increased risk
				internal tumors	no increased risk
Maughan et al.[12]	historic cohort	eczema	Goeckerman regimen	all skin cancers	no increased risk
				internal tumors	no increased risk
Jones et al.[10]	historic cohort	psoriasis	Coal tar	all cancers	no increased risk
Stern et al.[6]	nested case-control (PUVA study)	psoriasis	Coal tar and/or UVB	skin	5.6 (1.9-16.2)

Discussion

So far, there is no conclusive evidence of the carcinogenicity of coal tar in dermatological practice. Most of the studies were too small and lacked power to detect small increased risks. Although Hannuksela-Svahn et al. studied a large cohort, they did not control for other risk factors, such as smoking, sun exposure and occupational exposure to PAHs.[9] It would be worthwhile for future studies to include a large number of patients with sufficiently long follow-up and to control for other risk factors.

An important risk factor in patients with psoriasis or eczema may be an impaired immune system. Theoretically it is possible that the indication for therapy involves an increased risk, not the therapy itself. However, several studies suggested that atopy is a protective factor for cancer.[46] In most studies, atopy seemed to protect for the development of childhood gliomas and leukemias. Furthermore, most studies showed an inverse relation between atopy and pancreas cancer. No clear explanation has been put forward for the possible protective role of atopy in the development of tumors. Perhaps hyperreactivity of the immune system leads to increased immune surveillance. However, atopy causes chronic inflammation that in turn causes damage to tissues. The result is cell proliferation that could lead to an increased risk of cancer.

It is important that future studies not only investigate the risk of skin cancer, but also the risk of internal malignancies. PAH are able to penetrate the skin, which leads to systemic absorption.[47-49] As described earlier, cytochrome P450 enzymes metabolize PAHs into reactive metabolites. Many polymorphisms of cytochrome P450 enzymes have been described. These polymorphisms lead to variation in activity of enzymes involved in the metabolisation of PAH, such as aryl hydrocarbon hydroxylase and glutathione S-transferase.[50;51] Therefore, a subgroup of patients may be more susceptible to the development of cancer after coal tar treatment. Future studies on the role of these polymorphisms in patients with psoriasis or eczema are needed to provide new insight into the risk of cancer after coal tar treatment.

In 2004, a large historical cohort study (the LATER-study: "Late effects of coal tar treatment in eczema and psoriasis; the Radboud study") was started in the Netherlands. In this study 10,000 patients with psoriasis or eczema, diagnosed between 1960 and 1990, were included. This study investigates whether psoriasis or eczema patients who received coal tar treatment have an increased risk of developing cancer compared to patients who did not receive coal tar and compared to the general population. Data from these patients were collected from medical records and via questionnaires. Subsequently, linkage with the Netherlands Cancer Registry was conducted to assess the cancer incidence in this cohort. The results of this large study are expected in 2008.

Conclusion

Coal tar remains an important therapy for psoriasis and eczema when first line therapies have insufficient effect. More research data are needed to provide valid risk estimates of the use of coal tar in patients with psoriasis or eczema and to compare these risks to the risks of other therapies that are available for the treatment of psoriasis and eczema.

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Treatment policy for psoriasis and eczema

3

Later-studie

3.1

Treatment policy for psoriasis and eczema: A survey among dermatologists in the Netherlands and Belgian Flanders

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Abstract

Today, many therapies are available for the treatment of psoriasis and eczema. One of the oldest topical therapies is coal tar. Coal tar has been used for decades, but over the past years, the use of coal tar has decreased for several reasons, including the supposed carcinogenicity of coal tar. We investigated the current and past treatment policy for psoriasis and eczema with special emphasis on the use of tar products. A postal survey was conducted among all dermatologists in two European countries: the Netherlands (n=360) and the Flemish speaking part of Belgium (Flanders) (n=328). This study was conducted as part of the ongoing LATER-study ("Late effects of coal tar treatment in eczema and psoriasis; the Radboud study"). All practising dermatologists received a questionnaire. Dermatologists were asked to describe their treatment policy in mild/moderate psoriasis, severe psoriasis, mild/moderate eczema and severe eczema. The response rate to the questionnaire was 62.5% for the Dutch dermatologists and 45.7% for the Flemish dermatologists. Almost all dermatologists prescribe topical corticosteroids. In eczema, most of the dermatologists prescribe the recently introduced calcineurin inhibitors (95%). Coal tar is a second choice topical therapy. Dutch dermatologists mainly use tar in the treatment of eczema (72% vs. 48% in Flanders), whereas in Flanders tar is mainly prescribed in psoriasis (60% vs. 41% in Holland). Flemish dermatologists very frequently prescribe PUVA in psoriasis (93% vs. 63%).

Topical treatment, especially topical corticosteroids, is the mainstay in psoriasis and eczema. Coal tar still is an important (second choice) therapy for the topical treatment of psoriasis and eczema, but its use varies from country to country. Despite the carcinogenicity of PUVA, this photochemotherapy is frequently prescribed by dermatologists, mainly in Flanders.

Introduction

Psoriasis and eczema are chronic skin diseases, which often require years of treatment. Many therapies are available for these dermatoses. In recent years, new topical therapies (e.g. calcineurin inhibitors) and systemic therapies (e.g. biologicals) have been introduced. Coal tar has been a well-established therapy for psoriasis and eczema in the past decades, but some reluctance to use coal tar has evolved among dermatologists over the past years. One of the reasons for this reluctance is the suspicion of an increased risk of cancer after coal tar treatment in dermatological practice. This suspicion is based on animal studies and studies in the occupational setting showing an increased risk of nonmelanoma skin cancer after chronic exposure to coal tar.[1-5] However, the results of epidemiologic studies on dermatological use of coal tar are conflicting. One study showed an increased risk of nonmelanoma skin cancer after coal tar treatment,[6] but other studies did not reveal an increased risk.[7-11] The risk of other types of cancer is unknown. Because of a lack of large epidemiological studies with long-term follow-up that specifically investigated the (late) side effects of coal tar treatment, uncertainty about the carcinogenicity of coal tar with dermatological use remains. For this reason the LATER-study ("Late effects of coal tar treatment in eczema and psoriasis; the Radboud study") started in November 2003 in the Netherlands. In this study 10,000 patients diagnosed with psoriasis or eczema before 1990 will be included and the risk of cancer after coal tar treatment will be evaluated.

Because of the possible carcinogenicity and several additional reasons (e.g., use is unpleasant for patients, doubts on efficacy and difficulties in obtaining coal tar from pharmacies) the use of coal tar in the dermatological practice has decreased over the past years. A survey was conducted among Dutch and Flemish dermatologists with special emphasis on the use of coal tar in order to find out the position of coal tar in the treatment of skin diseases. The study was carried out in two countries to get an impression on the variation between countries with respect to use of coal tar. This survey was conducted as part of the LATER- study.

Methods

A questionnaire was developed and pilot-tested among three expert dermatologists (two from the Netherlands and one from Flanders). All dermatologists were asked to describe their treatment policy in case of mild/moderate psoriasis, severe psoriasis, mild/moderate eczema and severe eczema. For these questions, a list with topical, photo-, and oral therapies was provided and dermatologists could mark whether or not they used a listed therapy. In addition, dermatologists could describe therapies

that he/she uses and that were not recorded in the list of questions. They were also asked to list therapies that they had prescribed in the past but stopped prescribing, including the reason(s) and year of stopping. Finally, they were asked about prescriptions of topical therapies in the case of pregnant patients with psoriasis or eczema. In this questionnaire the overall terms 'psoriasis' and 'eczema' were used. As a consequence, these terms included all different types of psoriasis and eczema.

The questionnaires were sent to all practising dermatologists in the Netherlands (N=360) and Flanders (N=328) who were registered as a member of the Dutch or Belgian Association for Dermatology and Venereology. The questionnaire was accompanied by an invitational letter. In this letter we shortly introduced the ongoing LATER-study. We explained that as part of this study (that estimates the risk of cancer after coal tar treatment) we were interested in the position of coal tar in the spectrum of treatment modalities for psoriasis and eczema.

The invitational letters and questionnaires were mailed to the dermatologists in the summer of 2004. After three weeks, a reminder was sent. All collected data were summarised descriptively using the statistical software program SPSS version 12.

Results

A total of 236 questionnaires were returned by Dutch dermatologists (response rate 62.5%) and 153 questionnaires by Flemish dermatologists (response rate 45.7%). Fourteen dermatologists were retired or left the questionnaire blank and were therefore excluded from the study.

Large differences exist in the work setting of Dutch and Flemish dermatologists; the majority of Dutch dermatologists practise in a general hospital (77%) while most Flemish dermatologists practise in a private clinic (51%). The percentage of dermatologists practising in a university hospital is about the same in both countries (16% in the Netherlands, 17% in Flanders).

Treatment of psoriasis (Table 1)

As expected, almost all dermatologists initially prescribe topical corticosteroids and vitamin D_3 analogues to patients with psoriasis. The majority of dermatologists (91%) use class 3 corticosteroids (e.g., bethametasone dipropionate) for patients with mild/moderate psoriasis. In case of severe psoriasis, dermatologists prefer class 4 corticosteroids (e.g., clobetasol dipropionate) (93%). In addition to corticosteroids and vitamin D_3 analogues, 49% of all dermatologists also apply tar products in patients with psoriasis. Overall, the most frequently used tar product is solutio carbonis detergens; the Flemish dermatologists apply this much more frequently compared to Dutch dermatologists (56% *vs.* 30%, respectively). The majority of the Flemish

dermatologists prescribe solutio carbonis detergens in both mild/moderate psoriasis and severe psoriasis (68%), while a considerable part of the Dutch dermatologists prescribe this coal tar product only to patients with mild/moderate psoriasis (42%). Pix liquida (wood tar) is not used by Flemish dermatologists and is used by only 5% of the Dutch dermatologists. Dermatologists practising in a general hospital treat patients less frequently with tar products than their colleagues from the university hospitals or private clinics (44% *vs.* 52% and 58%). Next to coal tar, dithranol is applied as a second choice therapy. Overall, 46% of all dermatologists use dithranol. It is more frequently applied by Dutch dermatologists compared to Flemish dermatologists (56% *vs.* 30%). Dutch dermatologists prefer to use dithranol in both mild/moderate psoriasis and severe psoriasis (52% compared to 41% of the Flemish dermatologists), whereas the Flemish dermatologists prescribe dithranol more frequently to patients with mild psoriasis (25% *vs.* 15%). Dermatologists in university hospitals and in general hospitals prescribe dithranol more often than the dermatologists practising in private clinics (62% and 53% *vs.* 17%).

When topical therapies appear to be insufficiently effective or when skin lesions are increasing, almost all dermatologists will treat their patients with phototherapy. Flemish dermatologists prefer to use PUVA (93% *vs.* 63% of the Dutch dermatologists) whereas the Dutch dermatologists prefer to use UVB as first-choice phototherapy (99% compared to 83% of the Flemish dermatologists). In both countries, the majority of the dermatologists apply UVB in both severe psoriasis and mild/moderate psoriasis (79%). In case of PUVA, a small majority of dermatologists apply this photochemotherapy in severe psoriasis as well as in mild/moderate psoriasis (58%); a considerable part of dermatologists only use this therapy in patients with severe psoriasis (41%).

When psoriasis is resistant to topical therapy or phototherapy, dermatologists can apply oral therapies. Several oral therapies are available for the treatment of psoriasis. In the Netherlands first choice oral therapies include methotrexate and retinoids (81% and 76%) whereas in Flanders first choice therapies are retinoids and cyclosporine (83% and 70%). Fumarates are less frequently used compared to other oral therapies. In addition to the above-mentioned therapies, approximately 15% of the Dutch and Flemish dermatologists reported to apply therapies that were not listed in the questionnaire. Most frequently reported were emollients, salicylic acid containing ointments and Dovobet® (containing betamethasone dipropionate and calcipotriol hydrate). The recently introduced biologicals (*e.g.*, infliximab and efalizumab) were mentioned by 6 dermatologists. Because these agents were not registered and reimbursed at the time of this survey, these agents are likely to be prescribed within a clinical trial setting.

Table 1 Therapies used in the treatment of psoriasis reported by dermatologists in the Netherlands and Flanders by severeness and country.

	All Dutch and Flemish dermatologists (n = 375)				Dermatologists from the Netherlands (n = 225)				Dermatologists from Flanders (n = 150)			
	Total of dermatologists	Only mild/ moderate psoriasis	Only severe psoriasis	Both	Total of dermatologists	Only mild/ moderate psoriasis	Only severe psoriasis	Both	Total of dermatologists	Only mild/ moderate psoriasis	Only severe psoriasis	Both
1 Therapy	% (n)	%	%	%	% (n)	%	%	%	% (n)	%	%	%
Topical												
Topical corticosteroids	100 (374)	3	1	96	100 (225)	4	-	96	99 (149)	2	1	97
Vitamin D_3 analogues	100 (374)	16	-	84	100 (224)	19	-	81	100 (150)	12	-	88
Tar products	49 (183)	23	15	62	41 (93)	22	24	54	60 (90)	23	7	70
Pix lithantracis[1]	20 (73)	12	43	45	24 (54)	11	43	46	14 (19)	16	42	42
1.1 Solutio carbonis detergens[2]	40 (151)	33	11	56	30 (67)	42	18	40	56 (84)	26	6	68
Pix liquida (wood tar)	3 (11)	9	45	46	5 (11)	9	45	46	-	-	-	-
Dithranol	46 (169)	18	33	49	56 (125)	15	33	52	30 (44)	25	34	41
Phototherapy												
UVB	93 (346)	6	15	79	99 (222)	6	12	82	83 (124)	7	21	72
PUVA	75 (280)	1	41	58	63 (141)	1	46	53	93 (139)	1	35	64
Oral												
Methotrexate	72 (269)	1	72	27	81 (182)	1	67	32	58 (87)	2	83	15
Retinoids	80 (297)	3	53	44	76 (172)	3	47	50	83 (125)	4	61	35
Cyclosporine	66 (247)	1	74	25	63 (142)	1	68	31	70 (105)	1	83	16
Fumarates	28 (106)	5	50	45	43 (96)	5	48	47	7 (10)	-	70	30

The first column shows the percentages and numbers of dermatologists prescribing specific therapies. The next columns shows the percentages of the prescribing dermatologists who prescribe the therapy only in case of mild/moderate psoriasis, only in severe psoriasis or in both mild/moderate psoriasis and severe psoriasis.

[1] Pix lithantracis is most frequently used in concentrations of 1.5%-5%; 1 g of 1.5% or 5% pix lithantracis contains 15 mg or 50 mg tar, respectively.
[2] Solutio carbonis detergens is most frequently used in concentrations of 10%; 1 g of 10% solution carbonis detergens contains approximately 16 mg tar.

Treatment of eczema (Table 2)

Similar to psoriasis, topical steroids are the first choice topical therapy in eczema. Class 2 corticosteroids are mostly prescribed to patients with mild to moderate eczema (91%). In severe eczema, dermatologists prefer class 3 corticosteroids (89%). Other first choice therapies include calcineurin-inhibitors tacrolimus (Protopic®) and pimecrolimus (Elidel®). Dutch dermatologists prefer the use of tacrolimus (92% and 40%, respectively) while Flemish dermatologists appear to have no preference (96% *vs.* 93%). Dutch dermatologists use tar products more frequently compared to Flemish dermatologists (72% *vs.* 48%). As with psoriasis, the most frequently used tar

Table 2 Therapies used in the treatment of eczema reported by dermatologists in the Netherlands and Flanders by severeness and country.

	All Dutch and Flemisch dermatologists (n = 375)				Dermatologists from the Netherlands (n = 225)				Dermatologists from Flanders (n = 150)			
	Total of dermatologists	Mild/ moderate eczema	Severe eczema	Both	Total of dermatologists	Mild/ moderate eczema	Severe eczema	Both	Total of dermatologists	Mild/ moderate eczema	Severe eczema	Both
Therapy	% (n)	%	%	%	% (n)	%	%	%	% (n)	%	%	%
Topical												
Topical corticosteroids	100 (374)	1	0	99	100 (225)	0	0	100	99 (149)	1	1	98
Calineurin inhibitors	95 (355)	21	8	71	92 (208)	25	9	66	98 (147)	16	6	78
Coal tar	63 (234)	20	11	69	72 (163)	19	9	72	48 (71)	22	16	62
Pix lithantracis[1]	30 (109)	5	60	35	38 (86)	6	59	35	16 (23)	4	31	35
Solutio carbonis detergens[2]	59 (218)	36	9	55	66 (149)	38	7	55	47 (69)	33	13	54
Pix liquida	9 (34)	21	35	44	13 (30)	13	37	50	3 (4)	75	25	0
Phototherapy												
UVB	82 (308)	2	42	56	91 (205)	2	33	65	69 (103)	1	61	38
PUVA	39 (146)	2	71	27	31 (69)	3	71	26	52 (77)	1	72	27
Oral												
Corticosteroids	59 (222)	1	87	12	66 (148)	1	86	13	50 (74)	0	89	11
Cyclosporine	62 (234)	1	86	13	65 (146)	1	84	15	59 (88)	1	91	8

The first column shows the percentages and numbers of dermatologists prescribing specific therapies. The next columns shows the percentages of the prescribing dermatologists who prescribe the therapy only in case of mild/moderate eczema, only in severe eczema or in both mild/moderate eczema and severe eczema.

[1] Pix lithantracis is most frequently used in concentrations of 1.5%-5%; 1 g of 1.5% or 5% pix lithantracis contains 15 mg or 50 mg tar, respectively.

[2] Solutio carbonis detergens is most frequently used in a concentration of 10%; 1 g of 10% solution carbonis detergens contains approximately 16 mg tar.

product is solutio carbonis detergens. In both countries, most dermatologists apply this therapy in both mild/moderate eczema and severe eczema (55%), while pix lithantracis is mainly prescribed to patients with severe eczema (60%). In contrast to psoriasis, Dutch dermatologists practising in a general hospital prescribe tar products more often than their colleagues practising in a university hospital or a private clinic (74% *vs.* 69% and 63%). In Flanders, tar products are more frequently prescribed in a private clinic compared to a university or a general hospital (56% *vs.* 40% and 40%).

The next step in the treatment of eczema is phototherapy. In both countries, UVB appears to be the first-choice phototherapy. UVB is frequently applied by Dutch dermatologists in both mild/moderate eczema and severe eczema (65%) while Flemish dermatologists prefer to use UVB only in patients with severe eczema (61%). Similar to psoriasis, PUVA is more frequently used by Flemish dermatologists than by their Dutch colleagues (52% *vs.* 31%). In both countries, it is mainly prescribed in patients with severe eczema. In patients with severe eczema or when topical or phototherapy is not effective, oral therapies are applied. In both countries, dermatologists prescribe cyclosporine and oral corticosteroids approximately as many times (62% and 59%, respectively). The most frequently reported therapies that were not listed in the questionnaire were emollients, oral/topical antibiotics and antihistamines.

Topical treatment in pregnant patients

Most dermatologists are reluctant to prescribe tar products to pregnant women with psoriasis or eczema (**Table 3**). Topical corticosteroids appear to be the most prescribed treatment for psoriasis and eczema during pregnancy. A few dermatologists use dithranol when treating pregnant women with psoriasis or eczema.

Table 3 Percentages of dermatologists prescribing topical therapies in pregnant women.

	Yes, during the whole pregnancy (%)	Yes, but not during the 1st trimester (%)	No (%)
Tar products	9	9	82
Dithranol	3	4	93
Corticosteroids	77	17	6

Therapies used in the past

Approximately, one-third of all dermatologists reported using one or more therapies in the past which they less frequently, or not at all, apply nowadays (**Table 4**). The most frequently mentioned therapy was coal tar. Several reasons were given for stopping or minimizing the use of coal tar. Most frequently reported reasons were 1) the difficulty to obtain coal tar from the pharmacy (42 times) 2) the unpleasant use for patients (11 times) 3) possible carcinogenicity (10 times) and 4) difficulties to use tar at home (10 times). Other therapies that are no longer/less used by dermatologists are dithranol, with the main reason its unpleasant use for patients, cyclosporine and PUVA, both because of the adverse effects.

Table 4 Therapies no longer/less prescribed by Dutch and Flemish dermatologists.

Therapy	Number of dermatologists	Most reported reason for stopping
Coal tar	92	difficulties in obtaining tar from pharmacies
Dithranol	26	unpleasant use for patients
Retinoids	6	unsatisfactory effect
Cyclosporine	12	adverse effects/carcinogenicity
Fumarates	2	unsatisfactory effect
Methotrexate	2	adverse effects, better alternatives
PUVA	9	adverse effects/carcinogenicity
Vitamin D_3 analogues	3	unsatisfactory effect
Other	16	-

Discussion

In psoriasis, topical corticosteroids and vitamin D_3 analogues are applied by almost all dermatologists. Tar products and dithranol are second choice therapies. This is in accordance with European surveys conducted in the past among patients with psoriasis.[12-15] American surveys also show that topical corticosteroids and vitamin D_3 analogues are the most frequently prescribed topical therapies.[16;17]

Phototherapy is mainly applied in patients with severe psoriasis or when topical therapy is not effective. In the past years several studies showed an increased risk of nonmelanoma skin cancer after PUVA-therapy.[18-21] Still, more than 60% of the Dutch dermatologists and even more than 90% of the Flemish dermatologists prescribe this photochemotherapy for psoriasis. PUVA and UVB have a comparable efficacy but the long-term safety of UVB therapy is more favourable.[22] Almost all studies that investigated the risk of cancer after UVB therapy did not show an increased risk.[23] PUVA may be considered in case UVB treatment has an insufficient effect.[24]

In case of oral therapy for the treatment of psoriasis, retinoids are frequently applied by dermatologists in both countries. In Flanders, it is the most frequently applied oral therapy. This is remarkable because of the moderate efficacy of retinoids as monotherapy in psoriasis vulgaris, the most common type of psoriasis.[25-27] The guidelines of the Dutch Association for Dermatology and Venereology recommend that methotrexate, and not a retinoid, is the first choice oral therapy.[22] Fumarates are the least frequently prescribed oral therapies by dermatologists, especially in

Flanders. This oral therapy is not licensed in both the Netherlands and Flanders, which is probably the main reason for the limited use of fumarates.

As in psoriasis, in eczema, topical corticosteroids are prescribed by almost all dermatologists. The recently introduced calcineurin inhibitors are also frequently applied by both Dutch and Flemish dermatologists. The European Task Force on atopic dermatitis recommend topical corticosteroids as first choice therapy and they state that calcineurin inhibitors are useful second choice agents.[28] The guidelines from the American Association of Dermatology on the treatment of atopic dermatitis also prescribe topical corticosteroids and calcineurin inhibitors as most useful agents.[29] A major advantage of calcineurin inhibitors, compared to topical steroids, is that these agents do not cause skin atrophy.[30;31] There is a theoretical risk of promotion of skin cancer because these agents modify the immunoregulatory function of the skin.[31;32] These agents were introduced a few years ago. Therefore, results of epidemiologic studies with long-term follow up that have assessed the risk of (skin) cancer after the use of calcineurin inhibitors are not available. So far, available data suggest that the use of calcineurin inhibitors is safe, but a definite place for these agents in the treatment for eczema has to be established.[30]

The use of coal tar products is under discussion. Some dermatologists have stopped using it and other dermatologists still regard tar products as part of the therapeutic spectrum. The main reason for stopping is the difficulty to obtain coal tar preparations from the pharmacies. Due to stringent rules from the Dutch government for preparing coal tar products, many pharmacies are no longer capable of preparing these products. These rules are derived from the rules of the European Union concerning the protection of employees against the risk of exposure to carcinogen and mutagenic agents in the working place (rule 2004/37/EG). PAH are recorded as carcinogenic and mutagen agents by the European Union and therefore, exposure to these agents during work comes under these rules. Another reason is the difficulty of using tar at home. Because coal tar stains furniture and clothes, it is not always possible to use tar preparations at home. Another reason for stopping is the possible carcinogenicity of coal tar (but mentioned by no more than 10 dermatologists). Studies carried out so far on the long-term effects of coal tar in patients with psoriasis or eczema have shown conflicting results[6-11] and therefore large-scale epidemiologic studies are needed that include a large number of patients and have sufficient follow-up. Studies conducted so far mainly focused on the risk of skin cancer after coal tar treatment. However, coal tar penetrates the skin, which leads to systemic absorption of PAH. Therefore it is important that future studies not only investigate the risk of skin cancer but also the risk of internal tumors after exposure to coal tar.

Many dermatologists hesitate to prescribe coal tar preparations during pregnancy. Also dithranol is not frequently prescribed to pregnant women. In general,

topical corticosteroids are prescribed during pregnancy while the safety of some preparations during pregnancy is questionable. According to the Swedish classification of risk of drug use during pregnancy and lactation, preparations like betamethasone, fluticasone and triamcinolone are classified in group C which means that the pharmacological action of the drug may have undesirable effects on the human fetus or newborn infant. However, when the duration and area of application are limited and a mild preparate is used, corticosteroids can be prescribed during pregnancy even in the first trimester of pregnancy.[33]

The present study has indicated that a major part of dermatologists in two European countries still use tar products in the treatment of psoriasis and eczema. The variation between the Netherlands and Flanders with respect to the use of coal tar products is intriguing. However, no guidelines or treatment recommendation of the national or European dermatological societies are available, which explains the highly variable use of topical treatments in psoriasis and eczema, especially with respect to coal tar and dithranol.

Despite the clear or suggested unfavourable effects, many dermatologists still prescribe coal tar preparations. So far coal tar remains an important therapy for psoriasis and eczema. Future research has to assess the risk of (late) side effects of coal tar and compare this to the risks of other therapies that are available for the treatment of these dermatoses.

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The risk of cancer after coal tar treatment

4

Later-studie

4.1

No increased risk of cancer after coal tar treatment in patients with psoriasis or eczema

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Abstract

Coal tar is an effective treatment for psoriasis and eczema, but it contains several carcinogenic compounds. Occupational and animal studies have shown an increased risk of cancer after exposure to coal tar. Many dermatologists have abandoned this treatment for safety reasons, although the risk of cancer after coal tar in dermatological practice is unclear. This large cohort study included 13,200 patients with psoriasis and eczema. Information on skin disease and treatment, risk factors and cancer occurrence was retrieved from medical files, questionnaires and medical registries. Proportional Hazards regression was used to evaluate differences in cancer risk by treatment modality. Patients treated with coal tar were compared to a reference category of patients treated with dermatocorticosteroids (assumed to carry no increased cancer risk). The median exposure to coal tar ointments was six months (range 1-300 months)**.** Coal tar did not increase the risk of non-skin malignancies (hazard ratio (HR) = 0.92;95% confidence interval (CI) = 0.78-1.09), or the risk of skin cancer (HR = 1.09;95%CI = 0.69-1.72). This study has sufficient power to show that coal tar treatment is not associated with an increased risk of cancer. These results indicate that coal tar can be maintained as a safe treatment in dermatological practice.

Introduction

Coal tar is one of the oldest topical treatments in dermatology. It is well-established in the management of various skin diseases, especially psoriasis and eczema. Coal tar is a complex mixture of more than 10,000 compounds, including high concentrations of polycyclic aromatic hydrocarbons (PAH). Coal tar is obtained by heating coal in the absence of air. Medical pix lithantracis is produced by mixing two thirds of pitch of high temperature sources with one third of tar oils. Liquor carbonis detergens is obtained by extraction of 20 gram pix lithantracis with 100 ml alcohol and addition of 5 gram polysorbate. In general, the use of pix lithantracis is restricted to a hospital or day-care setting, because of staining of furniture and clothes and the strong odor, but liquor carbonis detergens can be used at home. It is well-known that some PAH, such as benzo(a)pyrene and benz(a)antracene, are carcinogenic.[1;2] Animal studies[2-4] and occupational studies[3;5-7] showed increased risks of lung and non-melanoma skin cancer after chronic exposure to coal tar. The risk of cancer after coal tar treatment in dermatological practice is still unclear because of the lack of large-scale observational studies. All studies performed so far lacked sufficient numbers of patients, follow-up data or data on potential risk factors, e.g. treatment, smoking, and sun exposure, to accurately estimate the risk of cancer after coal tar application.[8-13] Despite the lack of clear evidence of an increased risk of cancer after dermatological use of coal tar, many dermatologists around the world have abandoned coal tar as a therapeutic option.[14;15] Some dermatologists even consider the use of coal tar obsolete.[16] However, several alternative therapies for psoriasis and eczema, such as psoralen plus ultraviolet light A (PUVA) and ultraviolet B are known or suspected carcinogens as well and therapies such as cyclosporine, methotrexate and topical calcineurin inhibitors may facilitate carcinogenesis by its immunosuppressive action. We therefore question whether it is justified to abandon coal tar before making a valid assessment of the risk of cancer. To assess the risk of cancer after coal tar treatment in patients with psoriasis or eczema, we initiated a large historical cohort study, the LATER study (LAte effects of coal Tar treatment in Eczema and psoriasis; the Radboud study).

Subjects and methods

The LATER study was initiated in 2003. The cohort comprised patients diagnosed with psoriasis or eczema between 1960 and 1990 in one of three large hospitals in the Netherlands. These hospitals include two university hospitals and one teaching hospital. Between January 2004 and June 2006, over 300,000 medical records stored in the paper archives of the Departments of Dermatology at these hospitals were searched manually to identify eligible patients. A detailed description of data

collection is described below. The LATER study was approved by the Institution Review Boards of all three hospitals.

Selection of patients and data collection from medical files

All patients included in this study had to be diagnosed with psoriasis or eczema. Furthermore, patients had to fulfil the following eligibility criteria: 1) The date of diagnosis of psoriasis or eczema should be between 1960 and 1990 to obtain sufficient follow-up for cancer to occur; and 2) the patients had to have visited a dermatologist at least thrice, to support the presumption that the skin disease was sufficiently severe to require medical treatment. A total of 14,009 patients met the eligibility criteria. Administrative data were recorded in a database. In addition, detailed information on the medical history was collected from the medical files.

Data on variables collected from the medical files were complete and of good quality for the majority of the variables. Information on therapies that patients received was available from the medical files. However, it was not possible to extract information on duration of the received therapies. Medical history and data on cancer occurrence during follow-up, especially non-skin cancer, were not always recorded in the medical files. This information was supplemented by questionnaires and linkages to the Netherlands Cancer Registry and Causes of Death Registry. Recent data on vital status were frequently unavailable in the medical files. This was supplemented by linkages to the Hospital Information Systems of the participating hospitals, the nationwide Dutch Municipal Personal Records Database and the Central Bureau of Genealogy (described below).

Updating information

Figure 1 shows the labour-intensive stepwise procedure that was followed to update information on the place of residence and vital status. At the time of inclusion, most administrative data derived from the medical files were outdated, because many patients had not visited their dermatologists recently. This procedure included record linkages to the digital information systems of the participating hospitals, an electronic telephone record database and the Municipal Personal Record Database (MPRD). Additionally, municipalities and the Central Bureau of Genealogy were consulted. By the end of these procedures, addresses and vital status of 88% of the patients was updated (12,272/14,009). A total of 2,656 patients (19%) had deceased and 229 patients had emigrated. In case a patient had deceased, efforts were made to retrieve current information of the partner, whom we considered as a potential proxy. This resulted in the identification of 604 partners of deceased patients (23.3%), but only 412 (68%) were still alive and could be invited for the study.

Data collection through questionnaires

All patients with verified contact information (n=9,387) and 412 partners of the deceased patients were invited to participate in the study. They were sent an invitation letter, an information leaflet and a questionnaire. All subjects were asked for informed consent for participation in the study and for linkage of their personal data to medical registers. They were asked to fill out a detailed questionnaire concerning demographic factors, use of alcohol (yes vs no and number of glasses/day in past year), smoking habits (current/former/never and pack years), skin type, history of sunlight exposure (use of tanning beds [never, 1-4, 5-10, 11-20, 21-50, >50 times/year], residence in tropical areas [never, <1, 1-2, 3-5, 6-10 years]), occupational history (including history of outside occupation), detailed information on the skin disease and history of other (skin)diseases and cancer. Questionnaires were scanned, processed and data were stored in a database (Teleform®, Cardiff, Vista, CA). After three weeks, a reminder was sent. Questionnaires with missing data or unclear information were completed by telephone calls. Data from questionnaires were added to the data retrieved from the medical files. In case information from the questionnaires did not correspond with information from the medical files, information from the medical files was assumed to be superior. A total of 5,927 questionnaires were returned, corresponding with a response rate of 61%.

Data on cancer occurrence through linkage with population-based registers

The occurrence of cancer, as assessed through information in the medical files and questionnaires, was supplemented by record linkage to the Netherlands Cancer Registry (NCR). The NCR has nation-wide coverage since 1989. At the time of linkage, cancer incidence data were complete until 2003. Linkage was performed for all living and deceased patients, except for those who explicitly refused (n=406). Although non-responders and deceased patients did not give explicit consent, linkage to the NCR is allowed using a strict privacy procedure.[17] To assess cancer occurrence among patients who died before 1989, all deaths were linked to the Causes of Death Registry of Statistics Netherlands. This registry has been recording causes of death information in the Netherlands since 1901.

If information retrieved from the NCR did not correspond with the information in the questionnaires and/or medical files, the information from the NCR was assumed to be superior.

Statistical analysis

Multivariable proportional hazards regression models were used to estimate the relative risk of cancer after coal tar treatment. Follow-up for each patient was calculated as the time from date of diagnosis of psoriasis or eczema until date of

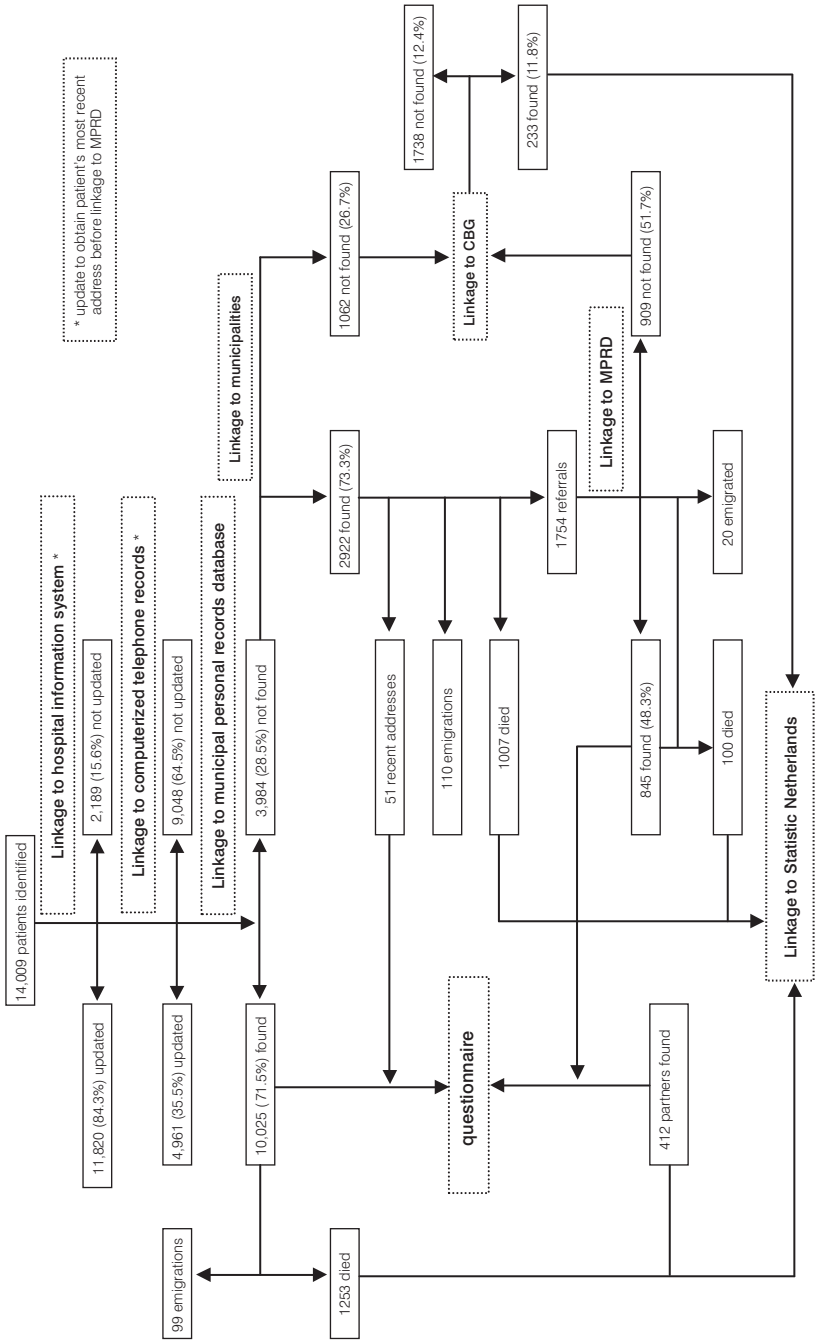

Figure 1 Process of updating personal data and vital status of patients in the cohort.

diagnosis of cancer, date of death, date of loss to follow-up or December 31, 2003, whichever came first. Separate analyses were conducted on specific outcomes: 1) overall cancer (total of all the tumours) 2) skin cancer (excluding basal cell carcinoma) 3) non-skin cancer and 4) different (groups of) tumour sites. If a patient was diagnosed with multiple tumours, only the first tumour was included in the analyses on overall cancer.

Coal tar exposure was divided into two categories: a reference/control category ('non-exposure' category) of patients treated with dermatocorticosteroids only (assumed to carry no increased risk of cancer) and an exposure category of patients treated with coal tar (including PL and/or LCD). As pix lithantracis contains far more carcinogenic PAH than LCD, the analyses were also performed with coal tar exposure divided into three categories: reference (similar to above), 'high exposure' including patients treated with pix lithantracis (regardless of exposure to LCD) and 'low exposure' including patients treated with LCD only. Patients in the exposure categories could also have been treated with other therapies (e.g. ointments, photo(chemo) therapy or systemic therapies).

In all final models, the risk of coal tar was adjusted for age (continuous), gender, severity of skin disease (more than 10% body area affected vs less than 10%), an interaction term of coal tar and severity, calendar period of diagnosis (1960-69, 1970-79, 1980-89), PUVA (yes vs no), systemic therapy (yes vs no) and smoking (current smoking and ever smoked vs never smoked). We chose the moment at which the skin disease was most extensive to assess the maximum severity of the skin disease. We did not use any information on fluctuations of severity in the analyses. The models were not adjusted for skin type, history of sun exposure or alcohol consumption, because these variables did not alter the risk estimates of the treatment effects in the proportional hazards models.

Data on smoking habits were only available from the patients with a completed questionnaire and were consequently missing in a large proportion of the cohort (58%). To handle these missing data, a multiple imputation technique (MI) was used.[18-20] The proportionality assumption of each variable was checked by visual inspection of log-log survival plots and by examining the effect of adding a time-dependent interaction term. Analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC).

Results

Characteristics of the cohort (Table 1)

809 patients in the total cohort of 14,009 patients were excluded from the analyses, because of missing or invalid data on key variables, such as diagnosis of psoriasis or

Table 1 Characteristics of patients in the total cohort and stratified by psoriasis and eczema.

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Gender (male/female %)	47/53	52/48	45/55
Median age at diagnosis (range)	28.4 yr (0 - 95.7)	31.1 yr (0 - 95.7)	27.2 (0 - 91.4)
Calender period of diagnosis			
1960-1969 (%)	2476 (18.8)	931 (21.6)	1545 (17.4)
1970-1979 (%)	4160 (31.5)	1575 (36.5)	2585 (29.1)
1980-1989 (%)	6564 (49.7)	1809 (41.9)	4755 (53.3)
Status at end of follow-up			
Diagnosed with cancer (%)	1048 (7.9)	421 (9.8)	627 (7.1)
Deceased without cancer (%)	1951 (14.8)	725 (16.8)	1226 (13.8)
Censured at December, 31, 2003 (%)	9346 (70.8)	2840 (65.8)	6506 (73.2)
Lost to follow-up (%)	855 (6.5)	329 (7.6)	526 (5.9)
Median duration follow-up (yr)	21	22.5	20.5
1 - 9 yr (%)	1433 (10.9)	502 (11.6)	928 (10.5)
10 - 19 yr (%)	4634 (35.1)	1219 (28.3)	3414 (38.4)
20 - 29 yr (%)	4415 (33.4)	1528 (35.4)	2856 (32.5)
≥30 yr (%)	2718 (20.6)	1063 (24.6)	1654 (18.6)
Severity of skin disease (% area affected)			
<1%	2759 (20.9)	375 (8.7)	2381 (26.8)
2-9%	4528 (34.3)	1290 (29.9)	3234 (36.4)
10-30%	3907 (29.6)	1696 (39.3)	2221 (25.0)
>30%	2006 (15.2)	954 (22.1)	1049 (11.8)
Use of coal tar ointments (%)			
Never[1]	5138 (38.9)	1234 (28.6)	3904 (43.9)
Only liquor carbonis detergens, no pix lithantracis[1]	4927 (37.3)	2256 (52.3)	2671 (30.1)
Pix lithantracis with/without liquor carbonis detergens[1]	3135 (23.8)	825 (19.1)	2310 (26.0)

Table 1 Continued.

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Use of other therapies (%)			
Topical			
Local corticosteroids	96.6	96.6	96.5
Vitamin D3 analogues	11.5	32.4	-
Topical calcineur-inhibitors	1.9	1.0	2.4
Dithranol	3.4	10.2	-
Systemic			
Methotrexate	5.2	14.9	0.5
Retinoids	4.9	13.2	-
Cyclosporin	1.7	3.5	0.8
Fumarates	1.8	5.1	-
Oral prednison	9.6	5.1	11.8
Photo(chemo)therapie			
PUVA	13.1	27.2	6.2
UVB	16.7	33.5	8.6
Goeckerman	3.5	9	0.9
Smoking status (%)[2]			
Never	1499 (11.4)	400 (9.3)	1099 (12.4)
Former	2489 (18.9)	997 (23.1)	1492 (16.8)
Current	1526 (11.5)	559 (13.0)	967 (10.7)
Unknown	16 (0.1)	6 (0.1)	10 (0.1)
Missing (no data from questionnaire)	7670 (58.1)	2353 (54.5)	5317 (59.8)
Alcohol (%)[2]			
<1 days/week	2561 (19.4)	859 (19.9)	1702 (19.2)
1-2 days/week	1062 (8.0)	383 (8.9)	679 (7.6)
3-5 days/week	824 (6.3)	296 (6.9)	528 (5.9)
>5 days/week	973 (7.4)	373 (8.6)	600 (6.8)
Unknown	110 (0.8)	51 (1.2)	59 (0.7)
Missing (no data from questionnaire)	7670 (58.1)	2353 (54.5)	5317 (59.8)

Table 1 Continued.

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Skin type (%)[2]			
Type 1 (always burns, never tans)	426 (3.3)	167 (3.9)	259 (2.9)
Type 2 (burns easily, tans minimally)	1764 (13.3)	555 (12.9)	1209 (13.6)
Type 3 (burns moderately, tans to light brown	2688 (20.4)	977 (22.6)	1711 (19.3)
Type 4 (burns minimally, tans well)	564 (4.3)	226 (5.2)	338 (3.8)
Unknown	88 (0.6)	37 (0.9)	51 (0.6)
Missing (no data from questionnaire)	7670 (58.1)	2353 (54.5)	5317 (59.8)

Abbreviations: PVA, psoraleen plus UVA.

[1] Patients in all three categories could also have been treated with other therapies.

[2] Percentages are based on the part of the cohort that returned the questionnaire (5,530, 1,962 and 3,568 in the total cohort and in patients with psoriasis and with eczema, respectively).

eczema or date of diagnosis. One-third of the cohort consists of patients with psoriasis and two-thirds with eczema. Over 60% of the patients with psoriasis had a severe form, i.e., more than 10% of their body was affected. In eczema, this applied to less than 50%. In the total cohort, 61% of the patients had been treated with coal tar: approximately 60% with liquor carbonis detergens and 40% with pix lithantracis. Many other therapies had also been applied to these patients. Systemic therapies and photo(chemo)therapy had been applied to 25% and 46% of the patients with psoriasis, respectively. These percentages were much lower in the patients with eczema.

Valid information on duration of coal tar therapy could be obtained from approximately 1,100 patients only. This made a robust dose-response evaluation of coal tar exposure and the risk of cancer impossible. The available information showed a median use of pix lithantracis of 4 months (range: 1-300 months) and the median use of liquor carbonis detergens was 6 months (range: 1-500 months).

Risk of cancer after coal tar treatment

The median duration of follow-up was 21 years. During follow-up, 1,327 tumours had been diagnosed (**Table 2**). **Table 3** presents the results of the multivariable proportional hazards regression analyses on the relative risk of cancer after coal tar treatment. No increased risk of skin cancer and non-skin cancer was found after coal tar treatment

Table 2 Observed number of tumours in the total cohort and stratified by psoriasis and eczema and by exposition to coal tar.

Tumour site	Total cohort (n=13,200)	Psoriasis (n=4,315)	Eczema (n=8,885)	Coal tar (n=8,062)	No coal tar (n=5,138)
	N (%)	N (%)	N (%)	N (%)	N (%)
Overall cancer	1327 (10.1)	512 (11.9)	815 (9.2)	794 (9.9)	533 (10.4)
Skin cancer [1]	163 (1.2)	83 (1.9)	80 (0.9)	109 (1.4)	54 (1.1)
Internal malignancies	1192 (9.0)	444 (10.3)	748 (8.4)	707 (8.8)	485 (9.4)
Specific tumour groups					
Haematological	52 (0.4)	18 (0.4)	34 (0.4)	32 (0.4)	20 (0.4)
Lymphoma	53 (0.4)	21 (0.5)	32 (0.4)	30 (0.4)	23 (0.5)
Lung	233 (1.8)	83 (1.9)	150 (1.7)	147 (1.8)	86 (1.7)
Gastrointestinal	218 (1.7)	81 (1.9)	137 (1.5)	114 (1.4)	104 (2.0)
Bladder and urinary tract	58 (0.4)	25 (0.6)	33 (0.4)	35 (0.4)	23 (0.5)
Breast	171 (1.3)	61 (1.4)	110 (1.2)	101 (1.3)	70 (1.4)
Female reproductive organs	113 (0.9)	39 (0.9)	74 (0.8)	79 (1.0)	34 (0.7)
Prostate	108 (0.8)	46 (1.1)	62 (0.7)	62 (0.8)	46 (0.9)

[1] Excluding basal cell carcinoma

Table 3 Hazard ratios (95% Confidence Intervals) for patients with psoriasis or eczema treated with coal tar and stratified by skin disease.

		Psoriasis or eczema		Psoriasis		Eczema
Tumour	**Cases**	**HR (95% CI) ***	**Cases**	**HR (95% CI) ***	**Cases**	**HR (95% CI) ***
Overall cancer	1,180	0.92 (0.79-1.08)	441	0.79 (0.57-1.09)	739	0.96 (0.80-1.15)
Skin [1]	145	1.09 (0.69-1.72)	71	1.08 (0.43-2.72)	74	1.06 (0.62-1.83)
Internal malignancies	1,061	0.92 (0.78-1.09)	383	0.78 (0.55-1.10)	678	0.97 (0.80-1.17)
Specific tumour groups						
Haematological malignancies	48	0.80 (0.38-1.72)	16	0.56 (0.09-3.44)	32	0.95 (0.41-2.19)
Breast	147	1.00 (0.66-1.53)	53	1.03 (0.43-2.50)	94	0.95 (0.57-1.57)
Lung	207	1.22 (0.82-1.83)	71	0.97 (0.38-2.46)	136	1.29 (0.75-2.23)
Gastrointestinal	203	0.64 (0.45-0.92)	73	0.72 (0.36-1.44)	130	0.57 (0.37-0.89)
Bladder and urinary tract	51	1.33 (0.63-2.81)	21	0.51 (0.14-1.92)	30	1.83 (0.73-4.58)
Prostate	96	0.85 (0.46-1.55)	40	0.84 (0.26-2.70)	56	0.75 (0.36-1.59)
Female reproductive organs	101	1.59 (0.85-2.81)	32	0.57 (0.13-2.40)	69	2.03 (0.99-4.14)

Patients treated with coal tar (n=8,062) were compared to the reference group (n=3,705 patients treated with dermatocorticosteroids alone).

* All HRs were adjusted for age, gender, severity of skin disease, calendar period, use of PUVA, use of systemic therapy and smoking

[1] Excluding basal cell carcinoma

(HR = 1.09; 95% CI = 0.69-1.72 and HR = 0.92; 95% CI = 0.78-1.09, respectively). The risk of haematological malignancies seemed to be slightly decreased, especially in psoriasis, but these analyses only included a small number of tumours. In the patients with eczema, the risk of gastrointestinal cancer after coal tar treatment was approximately 50% lower than that in the patients treated with dermatocorticosteroids alone (HR = 0.57; 95% CI = 0.37-0.89). Opposite results were observed regarding the risk of bladder and urinary tract cancer in patients with eczema (HR = 1.83; 95% CI = 0.73-4.58) compared to patients with psoriasis (HR = 0.51; 95% CI = 0.14-1.92). However, these results were based on small numbers (30 and 21, respectively) and were not statistically significant.

Table 4 presents the results of the multivariable analyses on the high (pix lithantracis) and low (liquor carbonis detergens) coal tar exposure categories. Neither of the coal tar categories showed an increased risk of non-skin cancer. The hazard ratio of skin cancer for pix lithantracis in patients with psoriasis or eczema was 0.66 (95% CI = 0.33-1.30), whereas it was 1.28 (95% CI = 0.80-2.06) for liquor carbonis detergens. Comparable results were found in the psoriasis group: HRs for liquor carbonis detergens and pix lithantracis were 1.35 (95%CI = 0.53-3.44) and 0.33 (95%CI = 0.07-1.69), respectively. Similar risk estimates of gastrointestinal cancer were observed in patients with psoriasis and eczema in both the low and high exposure group. In patients with eczema, the risk of gastrointestinal cancer after liquor carbonis detergens was almost 50% lower compared with the reference group (HR = 0.54; 95% CI = 0.33-0.89). In patients with psoriasis or eczema the risk of cancer of the female reproductive organs after pix lithantracis was increased (HR = 1.26; 95% CI = 0.61-2.58). This was caused by a three-fold increased risk of tumours of the female reproductive organs in patients with eczema (HR = 2.89; 95% CI = 1.30-6.43).

Table 4 Hazard ratios (95% Confidence Intervals) of cancer after use of LCD and PL in patients with psoriasis or eczema and stratified by skin disease.

		Psoriasis or eczema			Psoriasis			Eczema	
Tumour	**Cases**	**HR LCD (95% CI)***	**HR PL (95% CI)***	**Cases**	**HR LCD (95% CI)***	**HR PL (95% CI)***	**Cases**	**HR LCD (95% CI)***	**HR PL (95% CI)***
Overall cancer	1,180	0.95 (0.80-1.12)	0.87 (0.70-1.09)	441	0.85 (0.60-1.19)	0.64 (0.40-1.03)	739	0.96 (0.78-1.17)	0.96 (0.74-1.23)
Skin [1]	145	1.28 (0.80-2.06)	0.66 (0.33-1.30)	71	1.35 (0.53-3.44)	0.33 (0.07-1.69)	74	1.13 (0.63-2.03)	0.83 (0.39-1.80)
Internal malignancies	1,061	0.93 (0.78-1.12)	0.91 (0.72-1.15)	383	0.81 (0.57-1.16)	0.70 (0.43-1.14)	678	0.96 (0.78-1.19)	0.98 (0.75-1.27)
Specific tumour groups									
Haematological malignancies	48	0.84 (0.37-1.89)	0.74 (0.24-2.31)	16	0.49 (0.07-3.56)	0.87 (0.07-10.14)	32	1.06 (0.43-2.59)	0.73 (0.20-2.65)
Breast	147	1.00 (0.63-1.59)	1.02 (0.58-1.79)	53	0.97 (0.39-2.46)	1.18 (0.38-3.68)	94	0.97 (0.56-1.69)	0.91 (0.47-1.77)
Lung	207	1.30 (0.86-1.98)	1.06 (0.61-1.84)	71	1.10 (0.42-2.84)	0.68 (0.20-2.36)	136	1.43 (0.89-2.32)	1.20 (0.65-2.25)
Gastrointestinal	203	0.62 (0.42-0.93)	0.72 (0.40-1.28)	73	0.70 (0.33-1.44)	0.81 (0.30-2.20)	130	0.54 (0.33-0.89)	0.60 (0.32-1.11)
Bladder/urinary tract	51	1.23 (0.55-2.79)	1.61 (0.63-4.13)	21	0.47 (0.11-1.95)	0.61 (0.10-3.93)	30	1.72 (0.63-4.70)	2.22 (0.73-6.81)
Prostate	96	0.98 (0.51-1.87)	0.58 (0.22-1.50)	40	1.09 (0.33-3.54)	0.23 (0.02-2.14)	56	0.75 (0.33-1.74)	0.73 (0.26-2.07)
Female genital organs	101	1.26 (0.61-2.58)	2.28 (1.10-4.73)	32	0.63 (0.14-2.82)	0.43 (0.04-4.23)	69	1.51 (0.67-3.44)	2.89 (1.30-6.43)

Patients treated with LCD (n=4,927) and patients treated with PL (n=3,135) (with or without LCD) were compared to the reference group (n=3,705 patients treated with dermatocorticosteroids alone).

* All HRs were adjusted for age, gender, severity of skin disease, calendar period, use of PUVA, use of systemic therapy and smoking

[1] Excluding basal cell carcinoma

LCD = liquor carbonis detergens; PL = pix lithantracis

Discussion

The main conclusion of this study is that, overall, the use of coal tar ointments is not associated with an increased risk of cancer. With regard to the risk of skin cancer after coal tar exposure, separate analyses of pix lithantracis and liquor carbonis detergens showed unexpected results: a higher risk of skin cancer in the "low" coal tar exposure group than in the "high" exposure group (HR = 1.28 vs HR = 0.66). However, these results were not statistically significant. The intensity of PAH exposure is not only determined by the PAH concentration, but also by the duration of exposure. The use of pix lithantracis is restricted to a hospital or day-care setting, because of staining of furniture and clothes and the strong odor. In contrast, liquor carbonis detergens can be used at home and therefore, most patients use these ointments for a longer period of time. Patients treated with pix lithantracis were probably exposed to a high concentration of PAH over a short period, whereas patients treated with liquor carbonis detergens were exposed to a lower dose of PAH over a longer period. Occupational studies have shown that the risk of non-melanoma skin cancer was increased after chronic exposure to low doses of PAH.[3,5-7]

Therefore, it seems possible that tissue (skin) is capable to repair any damage after short-term exposure to PAH, but may not always be capable of doing so during long-term exposure.

Most of the studies that investigated the risk of skin cancer after coal tar treatment did not find an increased risk of non-melanoma skin cancer[8-12]. Only Stern et al. reported an increased risk of non-melanoma skin cancer in patients with psoriasis.[13] However, these patients were drawn from the PUVA cohort and all had therefore received this carcinogenic therapy.

Very few studies have analyzed the risk of internal malignancies after coal tar treatment. A fairly small study by Jones et al. (1985) evaluated the risk of internal malignancies in 719 patients with psoriasis.[9] These patients had received coal tar therapy intermittently over a 10-year period and had never been exposed to UVB, PUVA or cytotoxic therapies. The results indicated that coal tar treatment did not increase the risk of internal tumours. Hannuksela-Svahn et al. (2000) conducted a large cohort study to estimate the risk of cancer in 5,687 hospitalized patients with psoriasis.[8] A nested case-control study within this cohort study showed a non-significant increase in the risk of non-Hodgkin's lymphoma after treatment with the Goeckerman regimen (OR=1.2; 95% CI: 0.1-16.8).

In the tumour-specific analyses, we found a decreased risk of gastrointestinal cancer. This decreased risk seemed to be driven by a decreased risk of colon cancer (HR = 0.57; 95% CI = 0.32-1.03). Although we did not expect the gastrointestinal tract to be

a tumour risk site after coal tar treatment (in contrast with the bladder, lymphatic and haematological system), a decreased risk was unexpected and we cannot think of a logical explanation. The study by Jones et al. reported an increased risk of colon cancer in men, but not in women. However, these results were based on very small numbers of tumours (n=6).[9]

Another remarkable finding in our study was the difference in the risk of bladder and urinary tract cancer between patients with psoriasis (HR = 0.51; 95% CI = 0.14-1.92) and with eczema (HR = 1.83; 95% CI = 0.73-4.58). However, the numbers of tumours were fairly small and therefore this finding may be due to chance.

This is the first cohort study with sufficient numbers of patients and follow-up for assessing the overall risk of cancer after limited coal tar treatment in a valid way. In addition, data on possible risk factors for cancer, such as age, smoking and non-coal tar therapies were collected that made it possible to adjust all estimates for these risk factors.

Unfortunately, we were unable to estimate a dose-response relation of coal tar exposure and the risk of cancer. It was impossible to derive reliable information on the exact duration of coal tar treatment from the medical files. Only a limited proportion of the patients (treated with coal tar) returned the questionnaire and answered the questions on the duration of coal tar therapy (approximately 1,100 patients). The number of cases was therefore too small to reliable estimate the risk of cancer after different levels of coal tar exposure. The information on duration of exposure showed that patients were treated with coal tar for a relatively short period of time. This is consistent with our experience from daily practice in which pix lithantracis is mainly used during hospitalization or in day-care clinic. The duration of treatment with liquor carbonis detergens is somewhat longer, but still limited and frequently alternated with other topical therapies. We therefore believe that our data reflect the duration of coal tar use in dermatological practice.

No distinction could be made between the risk of melanoma and squamous cell skin carcinoma, because we did not make this subdivision in the questionnaire. Although we received type-specific cancer incidence data from the Netherlands Cancer Registry (and Statistics Netherlands), we could not make this subdivision of skin cancer in our final analyses, because we also used data on cancer occurrence from the questionnaires. Basal cell carcinomas are not registered in the Netherlands Cancer Registry. Consequently, we could not include this type of skin cancer in our analyses. Occupational studies on PAH exposure showed an increased risk of squamous cell carcinomas, and hence this type of skin cancer may be more related to PAH exposure than BCC. [2-7]

Besides coal tar, many other therapies have been applied in the treatment of psoriasis and eczema. Most of these therapies have mild-to-moderate or even severe side-effects. The use of topical calcineurin inhibitors in eczema has been increasing since their introduction. These agents modify the immune regulatory functions of the skin and may therefore increase the risk of skin cancer.[21;22] Until now, epidemiological studies have not shown any increased risk of (skin) cancer after the use of calcineurin inhibitors, but only short-term follow-up data are available.[22] If patients have severe skin diseases or do not respond to topical treatment, systemic therapies or photo(chemo)therapies can be applied. Most of these modalities have moderate-to-severe carcinogenic (PUVA and cyclosporine), hepatotoxic (methotrexate, retinoids) or teratogenic (retinoids) side effects.[23-25]

The risk of skin cancer after PUVA has been extensively studied and most studies showed an increased risk of skin cancer [8;26-28]. Several studies showed that patients exposed to long-term treatment with cyclosporine after an organ transplant have a significantly increased risk of non-melanoma skin cancer.[29-33] Some of the studies that analyzed the risk of skin cancer after cyclosporine in psoriasis also showed an increased risk of skin cancer.[34-36] Since their introduction a few years ago, the use of biologicals (e.g. infliximab, etanercept and adalimumab) has been rapidly increasing in the treatment of psoriasis. These biologicals suppress specific parts of the immune system, and hece in theory, they may come along with an increased risk of cancer. Cost-effectiveness and cost-utility studies comparing traditional and new modalities are not yet available.[37;38]

This large study with long time follow-up showed no increased risk of cancer after coal tar therapy in patients with psoriasis or eczema. Coal tar exposure was rather short in our cohort, but this may reflect dermatological coal tar exposure in practice. We conclude that our study showed no reasons for safety concerns with respect to the risk of cancer after the use of coal tar in patients with psoriasis and eczema. It is therefore ungrounded to consider coal tar as obsolete because of its alleged carcinogenic action.

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4.2

Association between psoriasis or eczema and bladder cancer. A case-control study

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Abstract

Background

Coal tar ointments are used as treatment of various skin diseases, especially psoriasis and eczema. These ointments contain several carcinogenic polycyclic aromatic hydrocarbons (PAHs). Metabolites of these PAHs are excreted in the urine and therefore, dermatological use of coal tar may be associated with an increased risk of bladder cancer.

Objective

To study the association between dermatological use of coal tar ointments and bladder cancer.

Methods

A population-based case-control study was conducted including 1,387 cases diagnosed with bladder cancer and 5,182 population controls. Information on the use of coal tar, history of skin disease and known risk factors for bladder cancer was obtained through postal questionnaires. Logistic regression analyses were performed to estimate the risk of bladder cancer after coal tar treatment, adjusted for age, gender, smoking status, duration of smoking and intensity of smoking.

Results

The use of coal tar ointments was approximately equal among cases and controls (3.8% versus 3.0%, respectively). Dermatological application of coal tar was not significantly associated with bladder cancer (adjusted OR = 1.37; 95% CI: 0.93-2.01). An inverse association between bladder cancer and a history of skin disease was observed (adjusted OR = 0.74; 95% CI: 0.61-0.90).

Conclusion

This is the first study that was specifically aimed to study the association between the use of coal tar preparations and bladder cancer. The results suggest that there is no reason for safety concerns with respect to the risk of bladder cancer after the use of coal tar preparations in dermatological practice.

Introduction

Coal tar is an effective therapy in the treatment of chronic skin diseases, such as psoriasis and eczema.[1] It contains more than 10,000 compounds, including polycyclic aromatic hydrocarbons (PAHs) in high concentrations. Some PAH, such as benzo(a) pyrene are classified as human carcinogens.[2;3] Because of the carcinogenic potency of PAHs, concerns have been raised about the risk of cancer after coal tar treatment in patients with skin diseases. The skin is an important route of uptake after dermatological exposure to coal tar.[4] Several studies have therefore investigated the risk of skin cancer after coal tar treatment but most studies[5-8], except one of Stern and colleagues[9], did not observe an increased risk. After application, coal tar is absorbed and metabolized in the skin and body. After metabolisation, several metabolites of PAHs are excreted in the urine.[10] Therefore, dermatological use of coal tar might be associated with an increased risk of non-skin cancer, especially bladder cancer. The risk of non-skin cancer in patients treated with coal tar was investigated in only a few studies and most of these studies did not observed an increased risk of internal malignancies.[6;11-13] However, none of the previously performed studies was specifically aimed at the association between bladder cancer and dermatological application of coal tar preparations. In this case-control study we examined the risk of bladder cancer after exposure to coal tar ointments used in the dermatological practice.

Patients and methods

Study population and data collection

Patients were identified by the Department of Registry and Research of the Comprehensive Cancer Centre The Netherlands, location Nijmegen. All bladder cancer patients diagnosed between 1995 and 2006 under the age of 75 in this region and alive at time of data collection were invited to participate in a study on genetic susceptibility for bladder cancer.[14] Patients filled out a detailed postal questionnaire concerning topics such as demographic factors, life style, history of diseases (e.g. cancer) and medication use. The response rate was 62%. For the current study, only bladder cancer cases with urothelial cell carcinoma were included (n=1,501). Patients with missing data on skin disease, smoking status or use of coal tar ointments were excluded (n=114). A total of 1,387 cases were included in the analyses.

Controls were obtained through the Nijmegen Biomedical Study (NBS), a population-based survey conducted by the Radboud University Medical Centre in 2002.[15] A random selection of inhabitants of Nijmegen were invited to participate in a study on risk factors for (any) disease by filling out a detailed postal questionnaire. In 2008, an

additional questionnaire, more specifically aimed at potential risk factors for bladder cancer was sent to all participants of the NBS who gave consent for further research and were still alive at that point in time. A total of 5,613 (64%) persons returned this second questionnaire. Persons who were diagnosed with cancer (except for basal cell carcinomas of the skin) at the time of data collection were excluded (n=303), as well as controls with missing data on smoking status and skin disease (n=128). Coal tar exposure was measured as "yes" versus "no". People with missing data on this variable (n=1,481) were included in this category as well (assuming that persons who did not answer yes to this question, did not use these preparations). A total of 5,182 controls were included in the analyses. All patients and controls gave written informed consent. The study was approved by the Institutional Review Board of the Radboud University Medical Centre.

Statistical analysis

Descriptive analyses were performed to provide insight in the characteristics of the patients and controls. Logistic regression analyses were performed to estimate Odds Ratios (OR) and 95% Confidence Intervals (95% CI) for the association between the use of coal tar ointments and bladder cancer. These analyses were adjusted for age at completing the questionnaire, gender and smoking. Smoking and male status are strong risk factors for bladder cancer. To exclude the effect of smoking in the association between coal tar and bladder cancer, subanalyses in non-smokers were performed. In addition, subanalyses in men and women were performed. We also analyzed the association between occurrence of skin disease and bladder cancer, because coal tar ointments are applied in patients with skin diseases. All models were not adjusted for height, weight, use of temporary and/or permanent hair dyes and educational level, because these variables did not alter the effect estimates in the models. All statistical analyses were performed in SAS (SAS system for Windows, version 9.2, SAS institute, Cary, NC).

Results

This study included 1,387 patients and 5,182 controls (Table 1). Patients were older at the time of completing the questionnaire compared to controls (67 yr versus 57 yr). Smoking, both current and former, was more frequent in patients. Among current and former smokers, patients had smoked for a longer period of time and the intensity of smoking was higher. Education level among patients was lower compared to controls. The use of coal tar ointments was approximately equal in both groups (3.8% versus 3.0%). Among individuals exposed to coal tar, skin diseases were more prevalent compared to the individuals not-exposed (94% versus 16.4%) (data not shown).

Table 1 Characteristics of the study population.

	Cases (n = 1,387)	Controls (n = 5,182)
Age at completing the questionnaire (y) [1]	67.3 ± 9.4	57 ± 16
Gender (% men)	84	46
Smoking status		
Never smokers (%)	10.7	36.2
Former smokers (%)	64.9	47.6
Number of cigarettes (cig/day) [1]	15.4 ± 4.5	12.6 ± 8.7
Smoking duration (y) [1]	29.2 ± 13.7	20.4 ± 13.6
Age at start smoking (y) [1]	17.5 ± 4.5	17.7 ± 4.6
Current smokers (%)	24.4	16.2
Number of cigarettes (cig/day) [1]	15.3 ± 5.1	13.7 ± 8.1
Smoking duration (y) [1]	42.7 ± 13.1	32.1 ± 15.2
Age at start smoking (y) [1]	17.6 ± 5.1	17.4 ± 5.0
Educational level (%)		
Primary school	15.9	7.2
Technical/professional school	52	53.1
Secondary school	22.3	21.9
University degree	9.8	17.8
Use of temporary and/or permanent dyes (%)	13.9	44.9
Skin disease (%)	14.4	18.8
Use of coal tar ointments (%)	3.8	3.0

[1] Mean ± SD
Abbreviations: (y): years; (cig/day): cigarettes/day

The risk of bladder cancer associated with exposure to coal tar ointments is presented in Table 2. The use of coal tar was not significantly associated with bladder cancer (OR=1.37; 95% CI = 0.93-2.01). The risk of bladder cancer was comparable in men and women. The OR in the subgroup of non-smokers was comparable to the total group (OR=1.20 versus OR=1.37), but this result was based on small numbers (n=4 non-smoking cases).

An inverse association between skin disease and bladder cancer was observed (OR=0.74; 95% CI=0.61-0.90) (Table 2), although this inverse association was restricted to men (OR men=0.68; 0.54-0.85; OR women=1.05; 95% CI 0.70-1.58).

Table 2 Risk of bladder cancer associated with use of coal tar ointments and occurrence of skin disease.

	Coal tar	Skin disease
	OR (95% CI)	**OR (95% CI)**
All[1]	1.37 (0.93-2.01)	0.74 (0.61-0.90)
Gender[2]		
Male	1.32 (0.85-2.05)	0.68 (0.54-0.85)
Female	1.57 (0.72-3.39)	1.05 (0.70-1.58)
Never smokers[3]	1.20 (0.41-3.53)	1.08 (0.68-1.72)

[1] OR were adjusted for age at completing the questionnaire, gender, smoking status, duration of smoking (in years) and intensity of smoking (cigarettes/day).
[2] OR were adjusted for age at completing the questionnaire, smoking status, duration of smoking (in years) and intensity of smoking (cigarettes/day).
[3] OR were adjusted for age at completing the questionnaire and gender.

Discussion

This is the first population-based case-control study specifically aimed at assessing the risk of bladder cancer after dermatological use of coal tar. No association between dermatological exposure to coal tar and bladder cancer was observed. Several studies have shown that occupational exposure to polycyclic aromatic hydrocarbons is associated with an increased risk of bladder cancer.[2;3;16] The increased bladder cancer risk in occupational studies was observed in workers with prolonged occupational exposure, whereas dermatological use of coal tar is most often limited to a much shorter duration of exposure.[10;17] The results from the present case-control study are in accordance with the results found in some other studies, although these studies did not specifically address the risk of bladder cancer.[6;11-13] Differences in cancer risks between occupational studies and studies in patients may be explained by the duration of PAH exposure. Possibly, the body is capable of repairing tissue damage, following short-term exposure to PAH, but not to the same extent after long-term exposure.

We also investigated the association between bladder cancer and skin diseases. An inverse association between the occurrence of skin disease and bladder cancer was observed, although restricted to men. It is difficult to explain this observed association, because no information on the type of skin disease was available from the questionnaires. However, it can be assumed that a major part of the reported skin diseases will be eczema and psoriasis. In both skin diseases, a hyperreactive immune system leads to chronic inflammation. This chronic stimulation of cells of the immune system may lead to randomly occurring pro-oncogenic mutations in actively dividing cells and therefore, to an increased risk of cancer. Also, patients with severe psoriasis or eczema are often treated with potential carcinogenic therapies, such as PUVA and cyclosporine. Several studies have evaluated the risk of bladder cancer in patients with psoriasis or eczema, but showed conflicting results.[5;6;18-20] Several patients in these studies had been treated with carcinogenic therapies and as a result, it is not possible to exclude the effect of these therapies on the risk of cancer. In future research it is worthwhile to only include patients with one type of skin disease to study the association between skin disease and bladder cancer.

Information was assessed after the diagnosis of bladder cancer and therefore, recall bias cannot be excluded. We assume that recall is limited, because questions on these topics were part of a questionnaire with a wide spectrum of questions and we have no reason to assume that patients or controls associate the use of coal tar or occurrence of skin disease with the development of bladder cancer. No information on the type and duration of coal tar preparations was asked in the questionnaires. In dermatological practice pix lithantracis and liquor carbonis detergens are used. Pix lithantracis contains far more PAHs than liquor carbonis detergens. In our earlier performed cohort study no differences in cancer risk was observed between the use of pix lithantracis and liquor carbonis detergens.[13] In the present study it was not possible to confirm these results because no information on the type of coal tar preparations was collected.

We conclude that there is no reason for safety concerns with respect to the risk of bladder cancer after the use of coal tar preparations in dermatological practice.

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Risk of cancer risk in a cohort of patients with psoriasis or eczema

5

Later-studie

5.1

Treatment-independent increased risk of cancer in patients with psoriasis or eczema

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Abstract

Background

Psoriasis and eczema are common skin diseases that often require long-term treatment. Several studies showed an increased risk of cancer, but in these studies it was not possible to disentangle the effects of treatment and the underlying skin disease on the risk of cancer.

Objectives

To assess the risk of cancer in patients with psoriasis or eczema, independent of treatment.

Methods

A cohort study was performed including 13,200 patients diagnosed between 1960 and 1990 with psoriasis or eczema in the Netherlands. Standardized incidence ratios (SIRs) were calculated using gender-, age and calendar year specific cancer incidence rates. To exclude the effect of treatment, sub-analyses were performed in patients treated with dermatocorticosteroids only.

Results

The overall risk of cancer was slightly increased in both psoriasis (SIR= 1.07; 95%CI=0.98-1.16) and eczema (SIR=1.09; 95%CI=1.01-1.16). The risk of cancer in the subgroup of patients treated with dermatocorticosteroids only (*i.e.* treatment-independent risk of cancer) was borderline increased in psoriasis patients (SIR=1.20; 95%CI=0.95-1.48), as well as in patients with eczema (SIR=1.10; 95%CI=0.98-1.22). A non-statistically significant increased risk of lymphomas was observed in untreated patients with psoriasis (SIR=2.66; 95%CI=0.86-6.21) and eczema (SIR=1.67; 95%CI=0.93-2.77).

Conclusion

Our results suggest that patients with psoriasis or eczema have a slightly increased risk of cancer, independent of therapy. A possible explanation may be the chronic stimulation of cells of the immune system due to the chronic state of inflammation in these skin diseases.

Introduction

Psoriasis and eczema are common, inflammatory skin diseases. In both skin diseases, a hyperreactive immune system leads to chronic inflammation. The pathogenesis of psoriasis is complex and not completely understood. Psoriasis is conceptualized as an auto-immune disease caused by interactions between immune cells and keratinocytes, proinflammatory cytokines and chemical mediators.[1;2] Because of the hyperreactive immune status, psoriasis patients may have an increased risk of lymphoproliferative malignancies. Some studies reported an increased risk of lymphomas [3-6], while other studies did not show an increased risk.[7-9] Psoriasis is characterized by an increased turnover of keratinocytes and, as a consequence, an increased proliferation of cells, which may predispose for the development of skin cancer.[7] Most studies reported an increased risk of non-melanoma skin cancer in psoriasis patients.[5-10] Also, increased risks of several non-skin cancers, including larynx, pharynx, lung, pancreas and breast cancer have been reported, although these results are not consistent.[5-10]

Atopic eczema can be regarded as an inflammatory skin disease, linked to an altered T-lymphocyte response with an initial shift toward the Th2 response and altered regulatory T-cells, which leads to increased cytokine production of interleukin (IL)-4, IL-5 and IL-13.[11] It has been hypothesized that this hyperreactive state may lead to increased tumour immunosurveillance, which may decrease the probability of proliferation of aberrant cells and therefore, decreases the probability to develop malignancies.[12;13] On the other hand, atopic eczema causes chronic stimulation of cells of the immune system that may lead to randomly occurring pro-oncogenic mutations in actively dividing cells and therefore, to an increased risk of cancer. This is postulated in the antigenic stimulation hypothesis.[13;14] Several studies investigated the risk of cancer in patients with atopic eczema. Two cohort studies in hospitalized eczema patients found an increased risk of overall cancer.[15;16] Most studies reported inverse associations between atopic disease (including atopic eczema) and the risk of glioma.[13;17] Also, a fairly consistent protective effect of atopic disease for childhood leukemia and adult pancreatic cancer is described in several studies.[13] Concerning other tumours, like breast, lymphoma, colorectal and lung tumours, studies showed inconsistent results.[14-16;18-21] Differences in study design and assessment of atopy (self-reported, medical files or specific IgE measurement) may cause variability in results which complicates comparisons of study results.

In all reported studies of cancer risk in patients with psoriasis or eczema, patients have been treated with several therapies. Most of these studies included hospitalized patients and therefore it can be assumed that these patients have been treated with

potential carcinogenic therapies, such as coal tar, PUVA or cyclosporine. As a result, it is not possible to exclude the effect of treatments on the risk of cancer.

In this cohort study the risk of cancer in patients with psoriasis or eczema was investigated by comparing the number of observed cancer diagnoses in the cohort to the expected number of cancer diagnoses based on cancer rates from the general population. To assess the treatment-independent risk of cancer we selected patients treated with dermatocorticosteroids only. Furthermore, to evaluate the risk of cancer in patients treated with potential carcinogenic therapies, we performed analyses in subgroups of patients treated with coal tar, PUVA and systemic therapies.

Materials and methods

This study is part of a large historical cohort study, the LATER study (Late effects of coal tar treatment in eczema and psoriasis; the Radboud study). This study was initiated in 2003 and designed to assess the risk of cancer after coal tar treatment in patients with psoriasis or eczema.[22] Between January 2004 and June 2006, over 300,000 medical records stored in the archives of the Departments of Dermatology of two university hospitals and one large teaching hospital were searched manually to identify eligible patients. A total of 14,009 patients fulfilled the inclusion criteria. Administrative data and information concerning the medical history, like date of diagnosis, date of last visit to the dermatologist, severity of skin disease, therapies, history of cancer and vital status were retrieved from the medical files. Because data on cancer, especially non-skin cancer, was not systematically recorded in the dermatology files, this incomplete information was supplemented by questionnaires and record linkage to the Netherlands Cancer Registry and Causes of Death Registry (described in section cancer occurrence). At time of inclusion, most administrative data from the medical files were outdated and therefore an update of addresses and vital status was necessary before questionnaires could be sent. A labour-intensive stepwise procedure was performed to update addresses and vital status. Detailed information on this procedure and the data collection by questionnaires has been described previously.[22] Data from the questionnaires were added to the data already collected from the medical files. A total of 5,927 questionnaires were returned, corresponding with a response rate of 61%. 809 patients of the cohort of 14,009 patients were excluded from the analyses, because of missing or invalid data on critical variables like diagnosis of psoriasis or eczema or date of diagnosis. The LATER study was approved by the Institutional Review Boards of all three participating hospitals.

Cancer occurrence

Occurrence of cancer was assessed through information from the medical files and questionnaires. In addition, the cohort was linked to the Netherlands Cancer Registry (NCR). The NCR has nation-wide coverage since 1989 and at time of linkage, cancer incidence data were complete until 2003. Record linkage was performed for all living and deceased patients, except for those patients who explicitly refused linkage to population and health registries (n=406). Although non-responders and deceased patients did not give explicit permission, linkage to the NCR is allowed using a strict privacy protocol.[23] In order to assess cancer occurrence among patients deceased before 1989, record linkage to the Causes of Death Registry of Statistics Netherlands was performed. In case a malignancy was reported as underlying cause of death, cancer site and date of death were used as proxies for cancer occurrence and date of diagnosis. In case the information retrieved from the NCR did not correspond with the already available information from the questionnaires and the medical files, the information from the NCR was assumed to be superior.

Statistical analyses

Standardized incidence ratios (SIR) were calculated to assess the risk of (site-specific) cancer. The SIR is the ratio of the observed and the expected number of cases of cancer.[24] In order to obtain the expected numbers, the national incidence rates stratified by sex, 5-year age group and calendar year for each cancer type were used. These incidence rates were obtained from the NCR for the period 1989-2003. As the NCR was not complete until 1989, cancer incidence rates from the Comprehensive Cancer Centre South were used as proxies for the national incidence rates for the period 1975-1989. The number of person-years at risk was defined as the time between date of diagnosis of the skin disease until date of diagnosis of cancer, date of death, last date of follow-up or December 31, 2003, whichever came first. No information on cancer occurrence before 1989 (start nation-wide coverage NCR) was available for patients who did not return a questionnaire and were not deceased (i.e. censured at December 31, 2003). For these patients (n= 4,240) the number of person-years were calculated from January 1, 1989 until December 31, 2003. In case a patient developed multiple tumours at different sites, only the first tumour was included in the calculations concerning total cancers, but the different tumours were included in the cancer site-specific calculations. In case of multiple tumours at the same site, only the first tumour was included in site-specific calculations. Basal cell carcinomas (bcc) are not registered in the NCR and therefore not included in the analyses.

SIRs were calculated for the total cohort of patients, stratified by skin disease. To exclude the effect of treatment on the risk of cancer, SIRs were calculated in a

subgroup of patients who were treated with dermatocorticosteroids only. These SIRs represent the treatment-independent risk of cancer. Finally, sub-analyses were conducted in patients treated with coal tar, PUVA and systemic therapies. 95% Confidence Intervals (CI) were calculated assuming a Poisson distribution of the number of observed cases.[25] All the analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC).

Results

The characteristics of the patients are shown in Table 1. One third of the cohort consists of patients with psoriasis and two thirds of patients with eczema. Patients with psoriasis had more severe skin disease compared to patients with eczema, *i.e.* 62% of the psoriasis patients had more than 10% of their body affected, compared to 37% of patients with eczema. This difference in severity of skin disease was also reflected by the use of systemic therapies and photo(chemo)therapies; these therapies were more frequently used for psoriasis (25% and 46%, respectively) than for eczema (13% and 13%, respectively). The median duration of follow-up in patients with psoriasis was 22.5 years and in eczema patients 20.5 years. During follow-up, a total of 535 cancers were diagnosed among patients with psoriasis and 855 among patients with eczema.

Psoriasis

The risk of cancer was slightly increased in patient with psoriasis (SIR=1.07; 95% CI=0.98-1.16) (Table 2). The risk of non-basal cell skin cancer (non-bcc) was significantly increased (SIR=1.95; 95% CI=1.56-2.42). Patients with psoriasis also showed an increased risk of cancer of the female reproductive organs. In table 3 the SIRs for the treatment-independent risk of cancer in psoriasis patients are presented. In these 'untreated' patients the risk of cancer seems to be increased as well, although this is not statistically significant (SIR=1.20; 95%CI=0.95-1.48). A 2.7 fold increased risk of lymphomas was observed (SIR=2.66; 95% CI=0.86-6.21); however this result is based on small numbers (n=5). The treatment-independent risk of non-bcc skin cancer was not significantly increased (SIR = 1.38; 95% CI = 0.60-2.72). Table 4 presents the SIRs of patients who were treated with coal tar, PUVA and systemic therapies. Psoriasis patients who used these therapies had a slightly increased risk of cancer, similar to the cancer risk in the total group psoriasis patients and in the untreated subgroup. This increased risk of cancer was largely caused by an excess of non-bcc skin cancer in these treatment groups. In the group of patients treated with systemic therapy, increased risks of overall cancer, non-bcc skin cancer, lung cancer and prostate cancer were observed as well.

Table 1 Characteristics of patients in the total cohort and stratified by psoriasis or eczema.

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Gender (male/female %)	47/53	52/48	45/55
Median age at diagnosis (range)	28.4 yr (0 - 95.7)	31.1 yr (0 - 95.7)	27.2 (0 - 91.4)
Calender period of diagnosis			
1960-1969 (%)	2476 (18.8)	931 (21.6)	1545 (17.4)
1970-1979 (%)	4160 (31.5)	1575 (36.5)	2585 (29.1)
1980-1989 (%)	6564 (49.7)	1809 (41.9)	4755 (53.3)
Status at end of follow-up			
Diagnosed with cancer (%)	1048 (7.9)	421 (9.8)	627 (7.1)
Deceased without cancer (%)	1951 (14.8)	725 (16.8)	1226 (13.8)
Censored at December, 31, 2003 (%)	9346 (70.8)	2840 (65.8)	6506 (73.2)
Lost to follow-up (%)	855 (6.5)	329 (7.6)	526 (5.9)
Median duration follow-up (yr)	21	22.5	20.5
1 - 9 yr (%)	1433 (10.9)	502 (11.6)	928 (10.5)
10 - 19 yr (%)	4634 (35.1)	1219 (28.3)	3414 (38.4)
20 - 29 yr (%)	4415 (33.4)	1528 (35.4)	2856 (32.5)
≥30 yr (%)	2718 (20.6)	1063 (24.6)	1654 (18.6)
Severity of skin disease (% area affected)			
<1%	20.9	8.7	26.8
2-9%	34.3	29.9	36.4
10-30%	29.6	39.3	25.0
>30%	15.2	22.1	11.8
Use of other therapies (%)			
Topical			
Dermatocorticosteroids	96.6	96.6	96.5
Vitamin D3 analogues	11.5	32.4	-
Topical calcineurin-inhibitors	1.9	1.0	2.4
Dithranol	3.4	10.2	-
Coal tar	61.1	71.4	56.1

Table 1 Continued.

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Systemic	17.1	25.4	13.1
Methotrexate	5.2	14.9	0.5
Retinoids	4.9	13.2	-
Cyclosporin	1.7	3.5	0.8
Fumarates	1.8	5.1	-
Prednison	9.6	5.1	11.8
Photo(chemo)therapie	23.4	45.7	12.5
PUVA	13.1	27.2	6.2
UVB	16.7	33.5	8.6
Goeckerman	3.5	9	0.9

* Percentages are based on the part of the cohort that returned the questionnaire (5,530, 1,962 and 3,568 in the total cohort, in patients with psoriasis and in patients with eczema, respectively)

Eczema

A slightly increased risk of overall cancer was observed in patients with eczema (SIR=1.09; 95% CI=1.01-1.16) (Table 2). The SIR of non-bcc skin cancer was 1.14 (95% CI: 0.90-1.42); this was lower compared to psoriasis patients (SIR=1.95; 95% CI: 1.56-2.42). Increased risks were observed for lymphomas, haematological malignancies (leukemia), brain tumours, lung cancer and cancer of the female reproductive organs. The treatment-independent cancer risk in eczema patients was non-significantly increased (SIR=1.10; 95%CI=0.98-1.22) (Table 3). Also, non-significantly increased risks of brain tumours, lung cancer and gastrointestinal cancer were observed in untreated eczema patients.

As only a small number of eczema patients were treated with PUVA (n=550) and subsequently the number of observed tumours was low, no cancer site-specific analyses were performed. The cancer risk in patients with eczema treated with PUVA was increased (SIR = 1.33 (95% CI=1.02-1.81)). Patients with eczema who were treated with coal tar ointments had a slightly increased risk of cancer (SIR = 1.11; 95% CI=1.01-1.22). The risk of gastrointestinal cancer was decreased in patients treated with coal tar (SIR=0.76; 95%CI=0.58-0.97). In the group of patients treated with systemic therapy, increased risks of overall cancer (SIR=1.36; 95% CI=1.11-1.64) were observed, caused by an excess of non-bcc skin cancer (SIR=2.19; 95% CI=1.25-3.55) and cancer of the female reproductive organs (SIR=2.29; 95% CI=1.22-3.91).

Table 2 Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) in patients with psoriasis or eczema.

	Psoriasis (n=4,315)			Eczema (n=8,885)		
Cancer type	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Overall	535	500.0	1.07 (0.98 to 1.16)	855	787.3	**1.09 (1.01 to 1.16)**
Skin	83	42.5	**1.95 (1.56 to 2.42)**	80	70.2	1.14 (0.90 to 1.42)
Hematological	20	15.3	1.30 (0.80 to 2.02)	36	24.3	**1.48 (1.04 to 2.05)**
Lymphoma	21	14.7	1.43 (0.89 to 2.19)	34	24.4	1.39 (0.96 to 1.95)
Bone and soft tissue	4	5.0	0.80 (0.21 to 2.04)	6	8.9	0.68 (0.25 to 1.47)
Brain	3	6.4	0.47 (0.10 to 1.36)	20	10.9	**1.84 (1.13 to 2.85)**
Glands[2]	6	3.6	1.68 (0.61 to 3.66)	10	6.4	1.57 (0.75 to 2.88)
Head and neck	17	16.3	1.05 (0.61 to 1.67)	31	25.1	1.24 (0.84 to 1.76)
Lung	89	78.2	1.14 (0.91 to 1.40)	157	119.0	**1.32 (1.12 to 1.54)**
Gastrointestinal	87	105.6	0.83 (0.66 to 1.02)	147	163.4	0.90 (0.76 to 1.06)
Bladder and urinary tract	28	32.5	0.86 (0.57 to 1.25)	38	49.3	0.77 (0.55 to 1.06)
Kidney	12	9.9	1.21 (0.62 to 2.11)	16	15.1	1.06 (0.61 to 1.72)
Prostate	47	39.4	1.19 (0.88 to 1.59)	67	59.9	1.11 (0.85 to 1.40)
Testis	1	2.5	0.40 (0.10 to 2.19)	3	4.7	0.64 (0.13 to 1.87)
Breast	63	75.4	0.84 (0.64 to 1.07)	112	122.3	0.92 (0.75 to 1.10)
Female reproductive organs[3]	39	27.6	**1.42 (1.00 to 1.94)**	75	47.8	**1.57 (1.23 to 1.97)**
Other	1	1.5	0.66 (0.10 to 3.68)	6	2.4	2.48 (0.61 to 1.72)

Obs = observed number of tumours
Exp = expected number of tumours
[1] Excluding basal cell carcinoma
[2] Includes thyroid, adrenal and salivary glands
[3] Includes vulva, cervix, ovary and endometrium

Table 3 Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) in the subgroup of patients with psoriasis or eczema who were only treated with dermatocorticosteroids and/or emollients.

	Psoriasis (n=578)			Eczema (n=3,130)		
Cancer type	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**
Overall	81	68.1	1.20 (0.95 to 1.48)	323	295.3	1.10 (0.98 to 1.22)
Skin	8	1.4	1.38 (0.60 to 2.72)	28	26.6	1.05 (0.70 to 1.53)
Hematological	3	2.1	1.44 (0.29 to 4.21)	13	9.1	1.43 (0.76 to 2.44)
Lymphoma	5	1.9	2.66 (0.86 to 6.21)	15	8.9	1.67 (0.93 to 2.77)
Bone and soft tissue	0	0.6	-	1	3.1	0.32 (0.01 to 1.77)
Brain	1	0.8	1.27 (0.02 to 7.04)	8	3.9	2.06 (0.89 to 4.06)
Glands[2]	1	0.4	2.27 (0.03 to 12.65)	2	2.3	0.80 (0.10 to 3.16)
Head and neck	4	2.2	1.84 (0.49 to 4.70)	7	9.4	0.75 (0.30 to 1.54)
Lung	12	11.0	1.10 (0.56 to 1.91)	56	44.8	1.25 (0.94 to 1.63)
Gastrointestinal	18	14.9	1.21 (0.72 to 1.91)	75	62.0	1.21 (0.95 to 1.52)
Bladder and urinary tract	7	4.6	1.51 (0.61 to 3.11)	11	18.9	0.58 (0.29 to 1.04)
Kidney	3	1.4	2.20 (0.44 to 6.44)	7	5.7	1.24 (0.50 to 2.55)
Prostate	8	4.7	1.69 (0.73 to 3.32)	27	22.4	1.21 (0.80 to 1.77)
Testis	0	0.2	-	1	1.6	0.63 (0.01 to 3.52)
Breast	8	9.4	0.86 (0.37 to 1.68)	38	44.8	0.84 (0.60 to 1.16)
Female reproductive organs[3]	3	3.8	0.79 (0.16 to 2.31)	19	17.7	1.08 (0.65 to 1.68)
Other	0	0.2	-	3	0.9	3.33 (0.67 to 9.73)

Obs = observed number of tumours
Exp = expected number of tumours
[1] Excluding basal cell carcinoma
[2] Includes thyroid, adrenal and salivary glands
[3] Includes vulva, cervix, ovary and endometrium

Discussion

Our study showed that patients with psoriasis or eczema have an approximately 10% increased risk of cancer. Most studies that investigated the risk of overall cancer in patients with psoriasis showed increased risks of cancer, with SIRs varying from 1.3 to 1.8.[5-8;10] However, Lindelöf and Bhate et al. showed no increased risk of non-skin malignancies in patients with psoriasis.[9;26] Two studies that investigated the risk of cancer among hospitalized patients with atopic eczema reported increased risks of overall cancer (SIR=1.1; 95%CI=1.0-1.3 and SIR=1.5; 95%CI=1.2-1.9, respectively).[15;16]

The treatment-independent risk of cancer was slightly increased in both patients with psoriasis and eczema. This result suggests that the underlying skin disease itself might be a risk factor for development of cancer. A possible explanation for this increased risk may be the chronic state of inflammation in these skin diseases. Today, the association between chronic inflammation and cancer has been widely accepted, but all mechanisms involving this relationship have not fully been resolved yet.[27;28] It can be assumed that the subgroup of untreated patients will have less severe skin disease compared to patients treated with systemic therapy and phototherapy. It is possible that patients with mild to moderate psoriasis or eczema have a less disturbed immune system compared to patients with a severe skin disease. This could be the reason that the intrinsic risk of cancer in the untreated patients was only slightly increased.

The increased risk of cancer in all patients with psoriasis was caused by an increased risk of non-bcc skin cancer and haematological malignancies, brain cancer and lung cancer in patients with eczema. The risk of cancer of the female reproductive organs was increased in both patient groups. Some of the increased cancer risks may be explained by the use of carcinogenic treatments, such as the increased risk of non-bcc skin cancer in patients with psoriasis treated with PUVA and systemic therapies. An association between long-term use of PUVA or cyclosporine and non-melanoma skin cancer has been shown in studies before.[29-32] Other cohort studies in psoriasis patients also observed an increased risk of non-melanoma skin cancer.[5-10] Most of these studies included hospitalized patients and therefore, it can be assumed that the majority of these patients have been treated with phototherapy or systemic therapies.

Also, the increased risk cancer of the female reproductive organs may be therapy related. From studies in renal transplant recipients it is known that female recipients have a high risk to develop human papillomavirus (HPV) related anogenital (pre) malignancies, such as cervical and vulvar cancer.[33] Immunosuppressive medication

Table 4 Standardized incidence ratios (SIR) with 95% confidence intervals (95% CI) in the subgroup of patients who were treated with coal tar , PUVA or systemic therapies (these patients could also have been treated with other therapies).

	Coal tar							PUVA			Systemic therapy					
	Psoriasis (n=3,081)			Eczema (n=4,981)				Psoriasis (n=1,175)			Psoriasis (n=1,096)			Eczema (n=1,164)		
Cancer type	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**		**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**	**Obs**	**Exp**	**SIR (95% CI)**
Overall	383	347.0	**1.10 (1.00 - 1.22)**	451	405.9	**1.11 (1.01 - 1.22)**		129	112.3	1.15 (0.99 - 1.37)	156	123.8	**1.26 (1.07 - 1.47)**	107	78.6	**1.36 (1.11 - 1.64)**
Skin	63	29.8	**2.11 (1.62 - 2.70)**	46	36.6	1.26 (0.92 - 1.68)		27	10.0	**2.70 (1.78 - 3.93)**	33	10.6	**3.10 (2.14 - 4.36)**	16	7.3	**2.19 (1.25 - 3.55)**
Hematological	15	10.2	1.47 (0.82 - 2.42)	21	12.7	**1.65 (1.03 - 2.53)**		7	3.7	1.91 (0.76 - 3.93)	3	3.8	0.80 (0.16 - 2.33)	0	2.8	-
Lymphoma	13	10.6	1.22 (0.65 - 2.09)	18	12.5	1.43 (0.85 - 2.27)		4	3.4	1.17 (0.32 - 3.01)	5	3.8	1.33 (0.43 - 3.10)	4	2.4	1.65 (0.44 - 4.23)
Bone and soft tissue	2	3.5	0.58 (0.07 - 2.10)	3	4.6	0.65 (0.13 - 1.91)		2	1.3	1.56 (0.18 - 5.64)	3	1.3	2.36 (0.47 - 6.90)	1	1.0	0.97 (0.01 - 5.40)
Brain	0	4.4	-	10	5.5	1.81 (0.86 - 3.32)		1	1.7	0.59 (0.01 - 3.31)	0	1.7	-	0	1.3	-
Glands[3]	4	2.5	1.63 (0.44 - 4.18)	5	3.3	1.52 (0.49 - 3.55)		1	0.9	1.12 (0.01 - 6.25)	1	0.9	1.12 (0.01 - 6.25)	3	0.7	4.11 (0.83 - 12.0)
Head and neck	12	11.3	1.06 (0.55 - 1.85)	20	12.9	1.55 (0.95 - 2.39)		5	3.8	1.31 (0.42 - 3.05)	5	4.1	1.22 (0.39 - 2.84)	6	2.7	2.26 (0.82 - 4.91)
Lung	65	54.3	1.20 (0.92 - 1.52)	86	61.4	**1.40 (1.12 - 1.73)**		20	16.3	1.23 (0.75 - 1.90)	36	19.0	**1.89 (1.32 - 2.62)**	13	11.1	1.18 (0.63 - 2.01)
Gastrointestinal	61	73.6	0.82 (0.63 - 1.06)	64	84.3	**0.76 (0.58 - 0.97)**		12	22.1	**0.54 (0.28 - 0.95)**	16	25.6	0.63 (0.36 - 1.02)	12	15.0	0.80 (0.41 - 1.40)
Bladder and urinary tract	17	22.6	0.75 (0.44 - 1.20)	24	25.4	0.94 (0.60 - 1.40)		7	6.9	1.01 (0.41 - 2.08)	6	8.0	0.75 (0.27 - 1.64)	9	4.6	1.94 (0.60 - 3.68)
Kidney	7	6.9	1.02 (0.41 - 2.10)	7	7.8	0.90 (0.36 - 1.86)		2	2.3	0.88 (0.10 - 3.17)	3	2.5	1.20 (0.24 - 3.50)	2	1.6	1.28 (0.14 - 4.63)
Prostate	33	28.7	1.15 (0.79 - 1.62)	34	32.3	1.06 (0.73 - 1.47)		12	8.6	1.40 (0.72 - 2.45)	17	9.4	**1.80 (1.05 - 2.88)**	9	4.8	1.87 (0.85 - 3.54)
Testis	1	1.7	0.58 (0.01 - 3.23)	2	2.4	0.83 (0.09 - 2.99)		1	0.8	1.27 (0.02 - 7.04)	0	0.7	-	0	0.6	-
Breast	47	52.2	0.90 (0.66 - 1.19)	57	62.7	0.91 (0.69 - 1.18)		14	19.2	0.73 (0.40 - 1.23)	16	19.4	0.83 (0.47 - 1.34)	17	13.8	1.23 (0.72 - 1.97)
Female reproductive organs	29	18.3	**1.59 (1.06 - 2.28)**	51	23.7	**2.15 (1.60 - 2.83)**		9	6.5	1.39 (0.63 - 2.64)	11	6.9	1.59 (0.79 - 2.84)	13	5.7	**2.29 (1.22 - 3.91)**
Other	1	1.1	0.95 (0.01 - 5.30)	3	1.3	2.38 (0.48 - 6.96)		0	0.4	-	0	0.4	-	0	0.3	-

Obs = observed number of tumours
Exp = expected number of tumours
[1] Excluding basal cell carcinoma
[2] Includes thyroid, adrenal and salivary glands

can potentiate oncogenic stimuli, such as HPV leading to mutations in proto-oncogens and tumour-suppressor genes. Although dose and duration of the use of systemic medication in dermatological patients differs from renal recipients, it is possible that the observed increased risk of cancer of the female reproductive organs in our study can be explained by the use of systemic therapy.

However, it can be questioned whether the increased cancer risks after treatment with PUVA and systemic therapies can be entirely explained by treatment. As said earlier, these patients will have a more severe skin disease compared to the untreated group of patients. It may be possible that patients with severe psoriasis or eczema have a more disturbed immune system and therefore, may have a higher intrinsic risk of cancer compared to patients with less severe skin disease.

An increased risk of lung cancer in patients with psoriasis and eczema was observed in both the non-treatment group and in patients treated with coal tar ointments or systemic therapies, so the risk seems treatment-independent. Other studies reported an increased risk of lung cancer in patients with psoriasis or eczema as well.[5;7;8;10;15] Our finding of an increased risk of lung cancer could be due to smoking. Most studies showed that patients with psoriasis more frequently smoke compared to the general population.[34;35] Studies in which the association between smoking and eczema was investigated, reported conflicting results.[36;37]

The risk of brain cancer was increased in patients with eczema. An increased cancer risk was also observed in the subgroup of untreated eczema patients, although these results were no longer statistically significant and based on small numbers. Our finding is in contrast with results of other case-control studies showing an inverse association between atopic eczema and brain cancer.[13;17] A recent cohort study of Hwang et al. also showed an increased risk of brain cancer in patients with atopic eczema (SIR = 2.52; 95% CI = 1.15-4.79).[38]

In the analyses on the risk of skin cancer no distinction could be made between the risk of melanoma and squamous cell skin carcinoma, because this subdivision could not be made in the data from the questionnaire. Basal cell carcinomas are not registered in the Netherlands Cancer Registry and therefore, we could not include this type of skin cancer in our analyses.

Cancer occurrence was assessed by linkages to the Netherlands Cancer Registry (NCR), Causes of Death Registry of Statistics Netherlands and information from the questionnaires and medical files. Data from the NCR are complete and of good quality. For patients who died before 1989 information on cancer occurrence was assessed by linkage to the Causes of Death Registry of Statistics Netherlands. It

is likely that some tumours were missed, because some types of cancer, such as prostate cancer have an indolent behaviour and a part of these patients do not die from this tumour.

We collected data on potential confounders such as smoking in our cohort. However, it is not possible to adjust for these factors in the calculation of standardized incidence ratios, because cancer incidence of patients in our cohort was compared to cancer incidence in the Dutch population in which these risk factors are not known on an individual level.

In conclusion, we demonstrated that patients with psoriasis or eczema have a slightly increased risk of cancer, independent of treatment. A possible explanation could be the chronic state of inflammation in these skin diseases. Our study also provided evidence that the increased risk of cancer in non-bcc skin cancer and cancer of the female reproductive organs may be (partly) explained by the use of carcinogenic therapies.

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PAH metabolism in skin after application of coal tar

6

Later-studie

6.1

DNA adducts in skin biopsies and 1-hydroxypyrene in urine of psoriasis patients and healthy volunteers following treatment with coal tar

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Abstract

Coal tar ointments (CTO) are frequently used in the treatment of psoriasis and eczema, but CTO contain carcinogenic polycyclic aromatic hydrocarbons (PAH). PAH are absorbed and metabolized in the skin. In psoriasis, the skin barrier is altered and therefore, absorption and metabolism of PAH may differ from healthy skin. In this study, levels of urinary 1-hydroxypyrene and PAH-DNA adducts in the skin were studied in psoriatic patients and healthy volunteers. Three punch biopsies were taken from the lower back of 10 male volunteers and from a psoriatic plaque in 10 male patients. A surface of 6.25 cm^2 was treated with CTO. After 96 hours CTO was removed and another three skin biopsies were collected from the treated area. DNA was isolated from skin biopsies and urine was collected during and after the exposure period. After 24 h, a twofold lower 1-hydroxypyrene urinary excretion was observed in patients compared to healthy volunteers and after 48 h, this difference reached statistical significance ($p < 0.05$). Over 96 h the median level of the sum of PAH-DNA adducts, analyzed by ^{32}P-post-labeling, increased from 3.5 before CTO administration to 21.1 adducts per 10^8 nucleotides in volunteers, and from 1.0 to 3.6 adducts per 10^8 nucleotides in patients. At 96 h, PAH-DNA levels were higher in healthy volunteers than in patients ($p < 0.05$). Biomarkers for uptake, bioavailability and bioactivation of PAH were lower in patients compared to volunteers. These data suggest a lower risk of carcinogenic effects of CTO in psoriatic skin compared to healthy skin.

Introduction

Coal tar is one of the oldest topical treatments in dermatology. Nowadays, it is still used by dermatologists in the treatment of eczema and psoriasis.[1] It contains more than 10,000 compounds, including polycyclic aromatic hydrocarbons (PAH) in high concentrations.[2] Some PAH, such as benzo(a)pyrene are classified as human carcinogens,[3] based on both animal studies[4-6] and occupational studies[5;7-9], that demonstrated associations between PAH exposure and lung, skin and bladder cancer. Surprisingly, only few studies have investigated the iatrogenic risk of cancer in patients treated with coal tar. Moreover, the majority of these studies did not observe an increased risk of cancer.[10-14] Only Stern et al. found an increased risk of non-melanoma skin cancer in patients treated with coal tar.[15] Recently, we performed a large historical cohort study in 13,000 patients with psoriasis and eczema to study the risk of cancer after dermatological treatment with coal tar ointments (CTO).[16] This study showed that treatment with coal tar did not increase the risk of squamous cell or melanoma skin cancer, nor the risk of non-skin malignancies.

Differences in cancer risks observed in occupational studies versus studies in patients may be explained by the frequency, level and duration of PAH exposure. Malignancies have occurred after prolonged occupational exposures, whereas the use of coal tar in dermatological practice is limited to a much shorter duration of exposure.[17;18] Possibly, the body (and especially the skin) is capable of repairing tissue damage, following short-term exposure to PAH, but not to the same extent in situations of long-term exposure.

PAH require metabolic activation to exert their carcinogenic effects. Metabolic activation can lead to the formation of diol epoxides, which react with DNA to form PAH-DNA adducts, and these were found to be pro-mutagenic.[6;19] Benzo(a)pyrene diol epoxide DNA adducts (BPDE DNA-adducts) are often used as biomarkers of the local balance between bioactivation and detoxification.

A variety of detoxification pathways, including hydroxylation to phenols by cytochrome P450 isoenzymes (CYP), conjugation of epoxides and diol epoxides with glutathione by glutathione S-transferases, and glucuronidation of diols by UDP-glucuronosyl-transferases are competing with this PAH metabolic activation.[20;21] In many studies the role of polymorphisms in the genes coding for these enzymes, as modifiers of cancer risk in people exposed to PAH, was investigated. The results of these studies are inconsistent, but certain genotypes, such as *GSTM1* null genotype have been found to lead to accumulation of p53 protein in CTO treated skin[22] and a higher risk of cancer.[23-25]

Both in the dermatological and occupational setting, the skin is an important route of uptake.[26;27] After exposure *via* the skin, 1-hydroxypyrene (1-OHP), the principal metabolite of pyrene, can be used as a biomarker for the assessment of dermal uptake and bioavailability of PAH.[28] In studies concerning occupational exposure, e.g., in the production of coke, carbon products and aluminum, elevated urinary levels of 1-OHP after PAH exposure were detected.[29-31] In several studies the urinary excretion of 1-OHP in patients with atopic eczema and psoriasis treated with coal tar was investigated.[18;32-38] In all of these studies high levels of urinary 1-OHP were observed after dermal application of coal tar.

Psoriasis is a chronic inflammatory skin disease, characterized by hyperproliferation of keratinocytes, leading to thickening of the epidermis, including the stratum corneum (hyperkeratosis). In addition, the intracellular lipid content was altered, resulting in reduced permeability for lipohilic substances.[39] Changes in this barrier function may lead to an increased or decreased permeability of components in ointments. Barrier function changes of the epidermis in psoriasis will depend on the activity of psoriasis. A study of Ghadially *et al.* showed that the barrier function was much more disturbed in active plaque psoriasis, compared to chronic plaque psoriasis.[40]

Besides altered permeability of the skin, metabolism of PAH may be changed in patients with psoriasis. A study of Chapman et al. reported a reduced activity and inducibility of aryl hydrocarbon hydroxylase (AHH), a microsomal mono-oxygenase in skin from psoriatic patients compared to healthy controls after incubation with benza(a)nthracene. Since AHH converts many PAH to active metabolites, the authors suggest that patients with psoriasis have a lower risk of skin cancer.[41] However it is not known whether the activity of other PAH metabolizing enzymes differs in psoriatic skin compared to the skin of healthy individuals. If PAH metabolism in the skin of patients with psoriasis is altered, this could have implications for the carcinogenic potential of CTO.

The aim of our study was to investigate differences in dermal absorption of PAH and metabolic activation of PAH after topical application of coal tar in patients with psoriasis and healthy volunteers, using established biomarkers of internal absorption and metabolic activation.

Materials and Methods

Study population

The study population consisted of ten healthy male volunteers and ten male patients with psoriasis. Patients and controls were selected from a research database of the department of Dermatology at the Radboud University Nijmegen Medical Centre, The Netherlands. The study persons received an information letter describing the objectives and instructions for the study. All persons were invited to visit the outpatient clinic of the department of Dermatology twice. All patients had chronic stable plaque psoriasis. Four patients did not use any therapy and six patients were treated with topical therapies (3 patients with emollients, two patients with a corticosteroid ointment and one patient with calcipotriol ointment). The patients with psoriasis were asked to stop the use of ointments two weeks before the start of the study (washout period). None of the patients used any systemic therapy. The psoriasis area and severity index (PASI) was used to assess the clinical severity of psoriasis. Self-administered questionnaires were used to obtain information on PAH sources (other than the CTO application), such as smoking, diet and indoor air quality. The study protocol was approved by the regional medical ethics committee (CMO Arnhem-Nijmegen). Written informed consent was obtained from each person before data and sample collection was started.

Skin biopsies and application of CTO

Before the CTO was applied, three 4 mm punch biopsies were taken from the lower back after local anaesthesia with xylocaine/adrenaline (1:100,000 v/v). Biopsy samples were immediately frozen and subsequently stored at -80°C. Subsequently, 1.75 g of 5% crude CTO (pix lithantracis in zinc oxide paste) was applied to an area of 2.5 by 2.5 cm of the lower back of the volunteers (not at the biopsy location). The content of pyrene and benzo(a)pyrene in the CTO was 331.3 μg/g and 263.4 μg/g, respectively. In patients with psoriasis CTO was applied on a psoriatic plaque of the same area size (2.5 x 2.5 cm). CTO was applied in excess, covered with waterproof adhesive tape (Allevyn adhesive®, Smith & Nephew, Engeland) and fixed with Tegaderm Film® (3M Health Care, the Netherlands) (Figure 1). After 96 h the adhesive tape and CTO were removed during a second visit to the outpatient clinic. Subsequently, three punch biopsies were taken from the area that had been treated with CTO.

Urine sample collection

For each subject a urine sample was collected before CTO was applied to establish the baseline excretion of 1-OHP. The following four days (96 h) spot urine samples were collected twice daily (in the morning between 7 a.m. and 9 a.m. and in the evening between 7 p.m. and 9 p.m.) until CTO was removed.

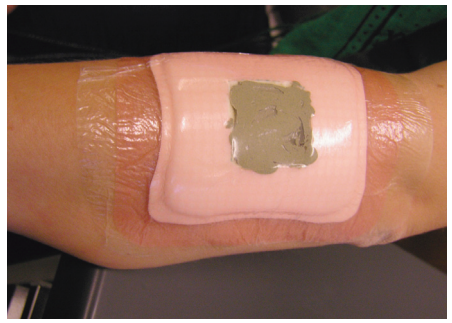

Figure 1 Application of CTO to an area of 2.5 by 2.5 cm on the forearm of a patient with psoriasis. After application of CTO the treated area was covered with waterproof adhesive tape.

^{32}P Postlabelling of DNA adducts

The ^{32}P-postlabelling assay was performed as described earlier.[42] Adduct levels were expressed as adducts that migrated to the same position as the BPDE-DNA adduct standard or as the sum of all detectable DNA-adducts (see Figure 2). In each experiment, parallel analyses were run for the three calibration standards of [^{3}H]-BPDE-modified DNA with known modification levels (1 per 10^6, 10^7 and 10^8 nucleotides).

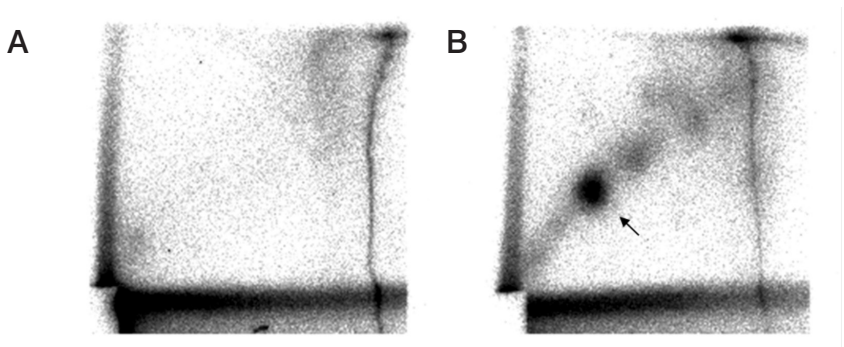

Figure 2 ^{32}P-post-labeling chromatograms of untreated skin (**A**) and skin treated with coal tar ointment (**B**). The major DNA adduct spot (indicated by arrow in panel B), migrated to the same position as the BPDE-DNA adduct standard. Chromatograms were similar for psoriasis patients and healthy volunteers

Analysis of urinary 1-OHP

The analytical procedure to determine urinary 1-OHP levels in the patients was based on the use of reverse-phase high performance liquid chromatography with fluorescence detection and has been described previously.[43] Determination of 1-OHP in the urine samples of volunteers was performed using a GC-MS/MS methodology including a derivatization step to give 1-methoxypyrene as previously reported.[44] Creatinine determined according to the Jaffé method was used to adjust for the variability in urine density.

Statistical analysis

The characteristics of the study groups were summarized by descriptive methods. To compare means of PAH-DNA levels before and after application of CTO, non-parametric Wilcoxon signed rank tests were performed. Mann-Whitney U tests were used to compare median DNA adduct levels between patients and volunteers and between smokers and non-smokers. Pearson correlation coefficients were used to evaluate associations between the sum of PAH and BPDE-DNA adducts. In all analyses a p-value of < 0.05 was considered statistically significant. Analyses were performed using SPSS software, version 16 (SPSS, Chicago, IL, USA).

Results

The mean age of the healthy volunteers (28 y; range 18-68 y) was lower compared to the patients with psoriasis (60 y; range 36-74 y). The number of smokers was comparable in the group of volunteers and psoriasis patients (3/10 and 2/10, respectively). Smokers in both study groups reported a mean number of cigarettes of 9-16/day. The mean PASI-core in patients with psoriasis was 7.2, indicating a mild to moderate psoriasis.

The urinary concentrations of 1-OHP in volunteers and patients with psoriasis before and during CTO exposure are presented in Figure 3. In both study groups, the highest concentration of urinary 1-OHP excretion was observed at 36-48 h after CTO application. At $t = 48$ h, the difference in excretion of 1-OHP between volunteers and patients was statistically significant ($p < 0.05$). No statistically significant difference in urinary concentrations of 1-OHP was observed between volunteers and patients before CTO application ($t = 0$) and after 96 h.

In Table 1 the results are presented for the PAH-DNA and BPDE-like DNA adduct levels in skin biopsies of volunteers and patients, before CTO application and after 96 hours of CTO exposure. Before the application of CTO, BPDE like adducts (expressed

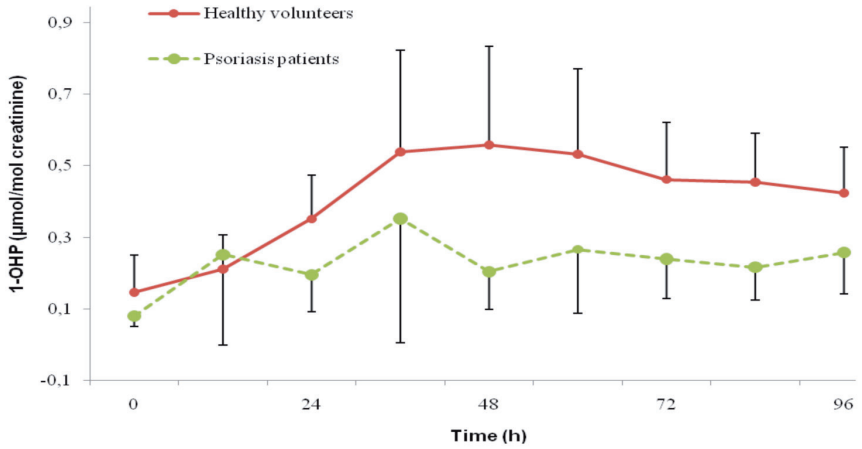

Figure 3 Urinary excretion of 1-hydroxypyrene (error bar indicates standard error of the mean). Time = 0 hours, just before the start of application of CTO.

as medians and ranges in adducts per 10^8 nucleotides) were below the detection limit in both study groups. These adducts levels increased to 8.2 (3.9-13.3) at 96 h in volunteers, but only to 1.1 (0.5-6.7) in patients ($p < 0.05$).

For the sum of PAH-DNA adducts, there was a small but significant difference in adduct levels between patients and volunteers, already before the application of CTO. During the exposure period the sum of PAH-DNA adducts (expressed in adducts per 10^8 nucleotides) increased from 3.5 (1.0-5.2) before CTO administration to 21.1 (12.9-29.1) in healthy volunteers, and from 1.0 (0.6-2.9) to 3.6 (2.1-18.9) in patients. At 96 h, PAH-DNA adduct levels were almost 6-fold higher in healthy volunteers than in patients ($p < 0.05$).

The percentage of BPDE-like DNA adducts to the sum of PAH-DNA adducts were comparable in both groups (38% versus 31%). At t = 96 h the sum of PAH-DNA and BPDE like DNA adducts were strongly correlated in both volunteers and patients (Pearson's correlation coefficients of 0.70 and 0.96, respectively). DNA adduct levels were not affected by cigarette smoking in both study groups.

Table 1 Median levels of the sum of PAH-DNA and BPDE-like DNA adducts in volunteers and patients before and after CTO application. Adduct levels are expressed in adducts per 10^8 nucleotides.

		N	Before CTO application (t = 0 h)		After CTO application (t = 96 h)	
			BPDE-DNA adducts	Sum of PAH-DNA adducts	BPDE-DNA adducts	Sum of PAH-DNA adducts
Volunteers	All	10	< 0.1	3.5 (1.0-5.2)	8.2 (3.9-13.3)	21.1 (12.9-29.2)
	Non smokers	7	< 0.1	3.5 (1.0-5.2)	7.3 (3.9-13.3)	21.0 (12.9-27.4)
	Smokers	3	< 0.1	3.5 (3.4-5.1)	10.2 (8.0-10.5)	21.2 (16.6-29.1)
Patients	All	10	< 0.1	1.0 (0.6-2.9)	1.1 (0.5-6.7)	3.6 (2.1-18.9)
	Non-smokers	8	< 0.1	0.8 (0.6-1.6)	1.1 (0.5-3.7)	11.3 (2.1-10.5)
	Smokers	2	< 0.1	2.0 (1.1-2.9)	3.0 (1.1-6.7)	3.6 (3.7-18.9)

Discussion

In this study several biomarkers of bioavailability and bioactivation of PAH in CTO were investigated in patients with psoriasis and in healthy volunteers. PAH-DNA adducts were studied in skin biopsies and additionally the excretion of urinary 1-OHP was analyzed, reflecting the result of both local and systemic metabolism. Substantial differences were observed in patients compared to healthy volunteers. Both urinary 1-OHP as well as DNA adduct levels were lower in patients with psoriasis, compared to healthy volunteers, indicating a reduction in absorption or bioactivation in psoriatic skin. Possible mechanisms that could explain the observed differences between patients and volunteers will be discussed.

The most straightforward explanation could be that the structural changes of the psoriatic skin are such that it becomes more difficult for the PAH to permeate the skin. Psoriatic skin is less lipophilic and therefore less permeable for PAH that have a high octanol-water partition coefficient (Log $P_{o/w}$ of 6) .[45] Also, slow uptake could be explained by an increased rate of renewal of stratum corneum, resulting in increased peeling off flakes of dead cells, including incorporated PAH.[46] If the total amounts of cells in psoriatic skin is greater compared with healthy skin cellular dose in patients may be lower due to distribution of the same amount of administered PAH over a larger number of cells. This hypothesis could be tested by also taking biopsies from healthy skin in patients. In the study we only looked at the effects in biopsies of psoriatic skin.

After dermal uptake the lung is the site of second pass metabolism after the skin (ACGIH, 2009). This leads to a higher probability that 1-OHP is excreted in urine as a glucuronide conjugate (compared with oral uptake of pyrene, which leads to liver metabolism and subsequent excretion primarily via bile because of the relative high molecular weight of the glucuronidated 1-OHP). 1-OHP should therefore be interpreted as an indicator of dermal uptake and bioavailability rather than of (local) biotransformation in the skin. Therefore, the observed pattern of urinary excretion supports the reduced dermal absorption in patients as the most plausible explanation of the differences observed between patients and healthy volunteers.

Urinary 1-OHP excretion shows a 2-fold difference, whereas the difference in DNA-adducts was 6- to 8-fold (for the sum of PAH and BPDE like DNA adducts, respectively), suggesting that other factors than reduced absorption, bioavailability and bioactivation may be involved to explain lower biomarker levels in patients.

A difference may exist in conjugation pathways such as the glutathione-S-transferase (GSH) activity. We studied the activity of GSH in the biopsy tissues, but were not able to find any differences (results not presented).

Another possible explanation is an increased activity of DNA repair systems in patients, resulting in removal of adducts from DNA bases, e.g. by nucleotide excision repair. We suppose that stress-activated protein kinases like the c-Jun-N-terminal kinase (JNK) signal transduction pathway could be involved in activation of the AP1 proteins that mediate a physiological response to DNA-damage, including induction of DNA repair enzyme activity. This pathway is not active in normal skin, but is activated in psoriatic epidermis.[47;48] However, in our opinion, this is not a very plausible explanation since bulky DNA adducts have a life span that goes beyond the duration of the study period of 96 h.[49]

Some methodological issues and limitations of this study will be addressed. The number of included study persons is relatively small: ten patients with psoriasis and ten healthy volunteers. Nevertheless, results of PAH-DNA adducts and urinary 1-OHP excretion point to the same reduction in absorption and bio-activation, indicating that the number of subjects in the current study provided sufficient power for these biomarkers.

The age distribution of the subjects in the patient and volunteer groups was different: the mean age was 2-fold higher in the patients compared to the volunteers. For PAH it has been reported that exposure accumulates over time and age was found to be associated with the level of excreted 1-OHP in some studies.[50] We cannot rule out the possibility that age interfered with the study outcome, but these age differences do not explain the observed reduced level of 1-OHP excretion in patients.

In healthy volunteers all punch biopsies were taken from the lower back. This region was chosen for cosmetic reasons, because punch biopsies could result in scar formation. In patients with psoriasis punch biopsies were taken from a psoriatic plaque: forearm in five patients, lower leg in four patients and abdomen in one patient. This is not a likely explanation for the observed differences between volunteers and patients, since the uptake of PAH between different regions of the body is similar.[27] Six patients were topically treated with ointments, of which three patients with corticosteroid or calcipotriol ointments. To eliminate the possible effects of these therapies on the study results, a washout period of two weeks was applied.

Our study was limited to benzo(a)pyrene and pyrene as chemical markers of a complex PAH mixture that involves several hundred different substances. Although these substances are often used as markers for physicochemical and toxicological evaluations for this mixture, we cannot rule out the possibility that our findings may not reflect the uptake and bioactivation patterns of other relevant and carcinogenic substances.

In this study, 1-hydroxypyrene was used as a biomarker of exposure to CTO and reflects both dermal uptake and bioavailability of PAH. No specific marker was used to measure only absorption of CTO because attempts to quantitatively extract benzo(a)pyrene and pyrene from skin biopsy materials was unsuccessful. In our study it was not possible to make a clear distinction between the contribution of local and systemic metabolism, but for the formation of DNA-adducts it is likely that local bioactivation and repair mechanisms are primarily responsible for the observed adduct levels.

Smoking is a known contributor to formation of DNA adducts.[51] The number of smokers was small (three volunteers and two patients) and the differences in DNA-adduct levels between smokers and non-smokers were not statistically significant. It would be worthwhile to study the influence of smoking on the effect of skin therapy in psoriasis patients in more detail. With regard to the excretion of 1-OHP, however, at most time points after the start of the treatment, smokers had on average higher levels of 1-OHP excretion (results not shown). However, this could not be attributed to differences in background excretion of 1-OHP, because no differences were found before the start of CTO treatment. A more likely explanation is the induction of enzyme activity involved in PAH-metabolism, such as CYP1A1 and CYP1B1, which is a known effect in cigarette smokers.[52;53]

In conclusion, in a controlled topical dermal exposure trial comparing psoriasis patients with healthy volunteers, we observed coherent differences in biomarkers reflecting uptake and metabolic activation of PAH, consistent with local and systemic bioactivation. These results may suggest a possible reduced carcinogenic risk for development of tumors in the skin of psoriasis patients. This experimental finding is consistent with and supports a recent finding that patients treated for psoriases and eczema with CTO are not subject to an increased risk of skin cancer.[54] It would be interesting to study other PAH than pyrene and benzo(a)pyrene in a similar study and also include patients with other diseases that are treated with CTO such as eczema. Future research is also needed to elucidate the involved cellular mechanisms that contribute to the observed reduced absorption, bioavailability and bio-activation of PAH in patients with psoriasis.

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General discussion

7

Later-studie

General discussion

This thesis presents the results of the LATER-research project: the LAte effects of coal Tar treatment in Eczema and psoriasis; the Radboud study. The main objective of this project was to assess the risk of cancer after coal tar treatment in patients with psoriasis or eczema. We also aimed to evaluate whether the risk of cancer in patients with psoriasis or eczema differs from the general population. Finally, we planned to conduct a side study to investigate dermal absorption and metabolism of PAH after dermal application of coal tar in psoriasis patients and healthy volunteers. In this general discussion the overall results that are presented in this thesis will be evaluated and some methodological issues will be addressed. In the last part of this chapter possible clinical implications and recommendations for future research will be presented.

Evaluation of study results

Risk of cancer after dermatological application of coal tar

The use of coal tar in dermatological practice has diminished over the past decades. Pharmacists are more reluctant to produce coal tar preparations because of stringent regulations by the government. Also, dermatologists prescribe coal tar ointments less frequent, because of their assumed potential carcinogenic effect (Chapter 3). However, substantial scientific evidence is lacking; only a few studies on the risk of cancer after coal tar treatment in dermatological patients are available.[1-5] These studies included only a small number of patients or were not designed to address specifically the risk of cancer after coal tar treatment (e.g. patients were also treated with UVB or PUVA phototherapy). The LATER-study included 13,200 patients with psoriasis or eczema and had sufficient power to investigate the risk of cancer after coal tar treatment in these patients.

We showed that the use of coal tar ointments was not associated with an increased risk of non-melanoma skin cancer (Chapter 4.1). We also analyzed the risk of non-melanoma skin cancer after coal tar exposure in a high exposure category (pix lithantracis) and a low exposure category (liquor carbonis detergens). The risk of skin cancer was not significantly increased after the use of liquor carbonis detergens, whereas a non-statistically significantly decreased risk was observed in the group of patients treated with pix lithantracis. The concentration of PAH in pix lithantracis is much higher compared to liquor carbonis detergens. However, the intensity of PAH exposure is not only determined by the PAH concentration, but also by the duration of exposure. In general, the use of pix lithantracis is largely restricted to a hospital

setting and therefore, used for a shorter period of time compared to the use of liquor carbonis detergens. This was confirmed by our study, showing that patients applied liquor carbonis detergens for a longer period of time compared to pix lithantracis.

Overall, the risk of non-skin cancer after coal tar was not increased in patients with psoriasis or eczema. No differences in cancer risk were observed when stratifying by skin disease, except for the increased risk of cancer of the female reproductive organs in patients with eczema. In contrast, no increased risk was observed in female psoriasis patients.

In the literature it is suggested that patients with psoriasis and eczema may have an increased risk of hematological malignancies, because of the hyperreactive immune status in these skin diseases.[6-9] Therefore, we considered this type of malignancy a tumor risk 'site' for coal tar exposure. However, no association between hematological malignancies and coal tar treatment was observed in our cohort of patients with psoriasis or eczema.

We did not expect the gastrointestinal tract to be a tumor risk site, but the decreased risk of gastrointestinal cancer, most pronounced in patients with eczema, was unexpected. The observed number of gastrointestinal tumors in our cohort was fairly large (n= 203), so there may be another reason than just chance. In the literature, very little is known about the risk of gastrointestinal cancer after coal tar exposure. Jones reported an increased risk of colon cancer in men, but not in women after coal tar treatment in patients with psoriasis. However, these results were based on small numbers of gastrointestinal tumors (n=6).[1]

No increased risk of bladder cancer was observed after dermatological exposure to coal tar. In our case-control study no association was found between bladder cancer and the use of coal tar preparations as well (Chapter 4.2). It is known that PAH are absorbed and metabolized in the skin after application. Consequently, several studies have shown increased 1-hydroxypyrene (1-OHP) levels in urine of patients with psoriasis[10-12] or eczema[13-15] after coal tar application. In our toxicology study, we investigated the uptake and bio-activation of PAH in psoriatic patients and healthy volunteers after coal tar application (Chapter 6). Increased levels of urinary 1-OHP and PAH-DNA levels in skin were observed after coal tar application in both study groups. However, 1-OHP levels and PAH-DNA adduct levels were lower in patients with psoriasis compared to healthy volunteers, suggesting a reduced absorption and activation in psoriatic skin. Hyperkeratosis of the epidermis and alterations in the intracellular lipid composition of psoriatic skin changes the barrier function of the skin. As a result, the permeability of the skin is changed and this may explain the

lower levels of urinary 1-OHP and PAH-DNA adducts in patients with psoriasis. The barrier function of the skin is also disturbed in patients with eczema, but these changes have a different pathophysiology compared to psoriasis. For future research it would be very interesting to study absorption and metabolism after coal tar application in patients with eczema to investigate whether the differences in pathophysiology between these two skin diseases will lead to differences in absorption and metabolism.

Risk of cancer in patients with psoriasis or eczema

The risk of cancer in patients with psoriasis and eczema has been studied by many authors.[6;7;9;16-28] Our results are consistent with the majority of previous studies, showing a slightly increased risk of cancer in patients with eczema and psoriasis compared to the general population (Chapter 5).

The majority of patients in these reported studies of cancer risk have been treated with several therapies and therefore, it is not possible to exclude the effect of treatment on the risk of cancer. Theoretically, it may be possible that patients with psoriasis or eczema have an increased risk of cancer, independent of treatment. The chronic state of inflammation in these skin diseases could lead to chronic stimulation of cells of the immune system, which may lead to randomly occurring pro-oncogenic mutations in actively dividing cells.[29;30]

In our study we were able to select a subgroup of patients treated with dermatocorticosteroids only (of which no increased risk of cancer is assumed). Therefore, we were able to study the treatment-independent risk of cancer in patients with psoriasis or eczema.

For both psoriasis and eczema, the overall risk of cancer in patients treated with dermatocorticosteroids only was borderline increased. These results suggest that patients with psoriasis or eczema have a slightly increased risk of cancer, independent of therapy. Our results also pointed to an increased risk of lymphomas in patients with psoriasis and eczema who were treated with dermatocorticosteroids only. An increased risk of lymphomas in psoriasis has been suggested previously, but studies that investigated the risk of lymphomas in psoriasis showed conflicting results.[6;7;17;20;22;23] Studies that investigated the association between atopic eczema and the risk of lymphomas also showed conflicting results.[9;16;21;26;28] It is difficult to compare the results of these studies, because the effect of treatment cannot be excluded in these studies. In our study, we also included patients with allergic contact eczema and irritant contact eczema. These subtypes of eczema have a different pathophysiology and therefore, our study and studies in atopic dermatitis are not completely comparable.

Besides the selection of an 'untreated' group of patients, we also selected patients who were treated with PUVA and systemic therapies. Our results show that some of the observed increased cancer risks may be therapy-related. The risk of non-bcc skin cancer was increased in patients with psoriasis (SIR 2.0), but was not significantly increased in the subgroup of untreated psoriasis patients, suggesting that the increased skin cancer risk can be explained by treatment. This was supported by our results showing an increased risk of non-bcc skin cancer in psoriasis patients who had been treated with PUVA and systemic therapies. An association between non-melanoma skin cancer and long-term use of PUVA and systemic therapies, such as cyclosporine, has been shown in several studies before.[31-34]

Also, the risk of cancer of the female reproductive organs in patients with eczema that we reported may be therapy-related, because no increased risk of cancer was observed in eczema patients treated with dermatocorticosteroids only, while a significantly increased risk was found in eczema patients treated with systemic therapies.

However, it is possible that the increased cancer risks in patients treated with PUVA or systemic therapies cannot be completely explained by these treatments. Patients treated with systemic therapies and phototherapy will have a more severe skin disease compared to the untreated group of patients. It may be possible that patients with severe psoriasis or eczema have a more disturbed immune system and therefore, may have a higher intrinsic risk of cancer compared to patients with less severe skin disease.

Psoriasis and eczema often require years of treatment and therefore, it is important to consider the efficacy and safety profile when prescribing a therapy. We found an increased risk of non-melanoma skin cancer associated with the use of PUVA and systemic therapies. In the past years, the use of PUVA has largely been replaced by UVB. This was confirmed in our survey among Dutch dermatologists showing that for both eczema and psoriasis UVB is more often used than PUVA. The Dutch guidelines also advise UVB as first line phototherapy in the treatment of psoriasis and eczema.[35;36] Systemic therapies are often used in the treatment of moderate or severe psoriasis or eczema. To reduce cumulative toxicity of these therapies, several treatment strategies, such as rotation therapy (in which different therapies with different safety profiles are alternately prescribed) have been used. Combination therapies (simultaneously prescribing multiple medications to allow dose reduction of each therapeutic modality), or intermittent use (introducing drug-free periods) have also been proposed.[37-40] However, liver and kidney damage caused by methotrexate, cyclosporine or retinoids cannot be completely prevented by these treatment strategies. The introduction of the biologic agents about a decade ago has provided more options for the short- and long-term treatment of patients with psoriasis. In the Netherlands four biologics are registered for the treatment of psoriasis: adalimumab, etanercept, infliximab (tumour necrosis factor-α(TNF-α) antagonists) and ustekinumab (interleukin 12/23 monoclonal antibody).[36] These therapies have a favorable short-term safety profile, but long-term safety data are not yet available.

Methodological considerations

Study design

The study design of the LATER-study is a historic cohort study. There is a long time between exposure and development of cancer and this makes a prospective study not feasible. A cohort design was chosen because we were not only interested in the occurrence of overall cancer, but also in many site-specific cancers. Therefore, the most feasible study design to answer our research questions was a historic cohort study.

Because of the study-design, data in the LATER-study were retrospectively collected. Approximately 50% of the patients in the LATER-study were diagnosed with psoriasis or eczema in the calendar period 1960-1979. As a consequence, these patients had to remember information on their skin diseases and diagnosis of cancer more than 25 years ago when filling out the questionnaire. However, detailed information was collected from the medical files and this was supplemented with information from the questionnaires.

Clear eligibility criteria for inclusion in the cohort were formulated before start of the study, and therefore, selection probably not occurred during the initial inclusion of patients in the cohort. The amount of information on the occurrence of cancer was not the same for all patients in the cohort. For the deceased patients no information on cancer was available from the questionnaires. In addition, no information from the Netherlands Cancer Registry was available for patients who deceased before 1989 (introduction of the NCR). This could have caused an underestimation of cancer occurrence in the cohort. However, information on cancer occurrence was obtained in the same way for patients who were and who were not treated with coal tar, so information bias will be unlikely. Also, not all information from the questionnaires may be exactly correct, because patients had to remember information on their skin disease from the past. However, we assume that this is similar in the coal tar exposed and non-exposed patients, i.e. the misclassification will be non-differential.

Use of self reported data from questionnaires

Data on the variables used in our analyses (cancer occurrence, use of coal tar and other therapies and several confounders) were recorded from medical files and

registries, but also self-reported information from the questionnaires was used. We checked whether information on cancer occurrence from the responders to the questionnaire correlated with the data on cancer occurrence from the Netherlands Cancer Registry. Only 54 patients (<1%) did not report a diagnosis of cancer in the questionnaire, but were diagnosed with a tumor in the Netherlands Cancer Registry. Almost 5% of the patients reported a diagnosis of cancer in the questionnaire, but were not registered with a tumor in the NCR. However, for patients who reported a diagnosis of cancer before 1989 (3.3%) this is possible, because the NCR data are only complete since 1989. We therefore, think that information on cancer occurrence from the self-administered questionnaires is reliable. In the literature, several studies have been published in which the validity of self reported diagnosis of cancer was investigated.[41-44] Data from questionnaires were compared to data from medical records or population-based cancer registries. These studies showed differences in sensitivity, depending on the type of cancer. In general, breast cancer has the highest sensitivity and bladder cancer, colorectal cancer and cancer of the cervix uteri and corpus uteri showed the lowest sensitivity. Propably, in case of these latter types of cancer doctors often tell patients that they have a 'benign' type of cancer and therefore, these patients don't report these forms of cancer. Other factors associated with a correct self reported diagnosis of cancer are age, sex and level of education.[42;43] Also, differences have been observed across countries, with the highest level of ability to self report cancer in the USA, followed by Europe and lowest in Japan.[41-44]

Data on the use of coal tar ointments were collected from the medical records and postal questionnaires. Based on information from the medical files, patients were included in the study. Therefore, all information on the use of coal tar ointments available through these medical files was recorded for all included patients. In addition, information on the use of coal tar ointments was collected from the questionnaires. Because of the typical color, odor and staining of coal tar ointments, it can be assumed that patients will remember the use of coal tar ointments. However, only a minority of responders of the questionnaire (20%), filled out the questions on the duration of coal tar use. This was analogue to the questions on the duration of all other therapies that patients received (local, photo- and systemic therapies). From these data we concluded that patients remembered which therapies were prescribed, but were not able to remember the duration of these therapies.

Data on smoking habits were only available from the patients with a completed questionnaire and were therefore missing in a large proportion of the cohort (58%). To handle these missing data, we used a multiple imputation technique.[45] This technique is preferred over simple techniques for handling missing data, such as complete case analysis, overall mean imputation, and the missing-indicator method, because

these techniques often produce biased results.[45-47] We used self-reported data on smoking habits from the questionnaire, because no information on smoking was available from the medical files. A recent study of Wong et al, assessing the validity of self-reported cigarette smoking in Canadians, showed high concordance estimates (91.6%) between self-reported smoking and urinary cotinine (nicotine-metabolite) concentrations.[48] However, a systemic review on this topic reported highly variable sensitivities (30-100%), depending on the population studied and the medium in which the biological sample was measured (urine, saliva or blood).[49]

Coal tar: past, present and future

Before the introduction of topical corticosteroids, coal tar ointments were frequently used in the treatment of psoriasis and eczema. Coal tar ointments were used as monotherapy, in combination with UVB as the Goeckerman therapy or as the Ingram regime; a combination of coal tar, dithranol and UVB. Since the introduction of more cosmetically accepted ointments such as topical corticosteroids, vitamin D analogues and calcineurin inhibitors, the use of coal tar ointments has diminished. However, from the results of our survey we can conclude that coal tar ointments still have a position in the treatment of eczema, and to a lesser extent in psoriasis. Coal tar ointments can be used as an alternative in carefully selected cases for the (long-term) use of systemic drugs as prednisone and cyclosporine. Long-term use of prednisone can cause osteoporosis, hypertension and corticosteroid-induced diabetes[50], whereas long-term use of cyclosporine is associated with nephrotoxicity and an increased risk of non-melanoma skin cancer and hematological malignancies.[32-34] In addition, tapering or stopping these systemic therapies often causes an exacerbation of the skin disease.

We realize that the application of coal tar ointments is much more time consuming compared to the intake of systemic therapies. However, skin diseases as eczema and psoriasis are chronic skin diseases requiring long-term treatment. Besides therapy, education of patients with a skin disease must be an important treatment goal. If patients are well informed on their skin disease and treatment, the acceptance of the skin disease will be better, leading to a higher compliance of therapies. In our hospital or day care setting, patients can be trained in coal tar treatment by specialized nurses. They provide information on the basic concepts of treatment, advice on coping with a chronic skin disease and answer questions of the patients. In our opinion, this concept of education and support is very important in the feasibility of coal tar treatment.

In the current guidelines of the Dutch Association for Dermatology and Venereology coal tar preparations have a minor position in the treatment of atopic dermatitis[35]. Topical corticosteroids and calcineurin inhibitors are first choice therapies. The opinion of the experts is that coal tar preparations can be used when dermatocorticosteroids or calcineurin inhibitors are not effective or can be added to pulse therapy with dermatocorticosteroids. In many international guidelines coal tar no longer has a position in the treatment of atopic dermatitis.[51;52] In the current national and international guidelines, the role of coal tar ointments in the treatment of psoriasis is limited.[36;53;54] Although coal tar ointments don't have an important position in the treatment of eczema and psoriasis nowadays according to the guidelines, we think that coal tar ointments still are a second line therapy for many dermatologists. This was confirmed by the data from our survey showing that the majority of dermatologists in the Netherlands and Belgian Flanders still prescribe coal tar ointments (Chapter 3).

Future perspectives

Despite the fact that coal tar ointments have been used for decades for the treatment of several skin diseases, the mechanism of action on the cellular level is still unknown. Coal tar ointments are a mixture of more than 10,000 components and therefore, it is very hard to identify which components are responsible for the biological effect and which for carcinogenic effect. Theoretically, it is possible that some components have anti-carcinogenic effects and some components have a pro-carcinogenic effect. It would be very interesting to disentangle the pathways that are responsible for the mechanism of action of coal tar ointments.

PAH are metabolized by cytochrome P450 enzymes to diol epoxides. These reactive metabolites are able to bind with DNA to form PAH-DNA adducts, which are pro-mutagenic.[55;56] Detoxification pathways are competing with the activation pathways. These pathways include direct hydroxylation to phenols by cytochrome P450 isoenzymes (CYP), conjugation of epoxides and diol epoxides with glutathione by glutathione S-transferases and glucuronidation of diols by UDP-glucuronosyltransferases.[22;57] Many studies have investigated the role of polymorphisms in these enzymes as modifiers of cancer risk in people exposed to PAH. The results of these studies have been inconsistent[58;59], but certain genotypes may lead to a higher risk of cancer.[60;61]

In future research it would be interesting to study the effect of these polymorphism on the levels of several biomarkers of PAH after coal tar application, such as 1-hydroxypyrene in urine and PAH-DNA in skin. These studies must include very large numbers of study objects, because many combinations of polymorphisms of

the genes in the activation and detoxification pathways are possible. This will possibly complicate the feasibility of such studies.

Clinical implications of this project

The main objective of the LATER-study was to investigate the risk of cancer after coal tar treatment in patients with psoriasis or eczema. So far, the LATER-study is the largest study on this topic and therefore, we were able to estimate the risk of cancer after coal tar treatment reliably. Our results did not show an association between the use of coal tar and an increased risk of non-melanoma skin cancer or internal malignancies. This indicates that coal tar has been proven to be a safe treatment in dermatological practice. We believe that the LATER-study provided enough evidence to take away doubts on the carcinogenicity of coal tar with dermatological use. Therefore, coal tar ointments should not be abandoned as a therapeutic option, but should be maintained as a second line treatment option for eczema and psoriasis in selected patients.

A second objective of this project was to evaluate whether the risk of cancer in patients with psoriasis or eczema differs from the general population. Psoriasis and eczema are two chronic skin diseases that require long-term treatment. Therefore, it is important that patients with these skin diseases are treated as effective and safely as possible. An association between non-melanoma skin cancer and PUVA and systemic therapies was observed in our study. These results suggest that these therapies should be used with care as long-term therapies. With the introduction of biologics in the treatment of psoriasis, an alternative for long-term use of classic systemic treatments has become available. The risk of cumulative toxicity associated with long-term use of biologics may be less compared to classical systemic therapies. However, the costs of treatment with biologics are high and long-term safety data are not yet available. When considering topical treatment like tar ointments or systemic therapy, such as the biologics, efficacy, cost-effectiveness and safety profiles of the therapies should be taken into account.

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Summary

Summary

The efficacy of topical treatment with coal tar in patients diagnosed with psoriasis or eczema has been well established. However, coal tar ointments contain numerous polycyclic aromatic hydrocarbons (PAHs), which are transformed by the cytochrome P450 system into reactive metabolites capable of interaction with DNA. Concern has been raised about the carcinogenicity of coal tar treatment in the dermatological practice. Treatment of skin disorders by coal tar, however, is effective and probably safer than its immunosuppressive topical and oral alternatives and should therefore not be banned before proper risk assessment. To study the risk of cancer after coal tar treatment, the LATER-study (LAte effects of coal Tar treatment in patients with Eczema or psoriasis; the Radboud study) was initiated. Within this research project, several sub-studies were conducted.

Position of coal tar in the treatment of psoriasis and eczema

Chapter 1 gives a short general introduction on the subject of this thesis. *Chapter 2* provides a review of coal tar in dermatology. An overview of the production of dermatological coal tar, mechanism of action and indications in dermatological practice is presented. Possible short-term and long-term side effects are described. Short-term side effects include folliculitis, irritation of the skin, contact allergy and phototoxic reactions. Long-term side effects focus on the possible carcinogenicity of coal tar. An overview of the literature published so far on this topic is discussed.

Coal tar has been used for decades in the treatment of various skin diseases, but over the past years, the use of coal tar ointments in dermatological practice has diminished. One of the reasons for the decreased use is the presumed carcinogenicity of coal tar ointments, although empirical data for an increased risk of cancer are lacking. Another reason is the difficulty to obtain coal tar preparations from the pharmacies, because many governments have developed stringent rules for the preparation of coal tar ointments. To evaluate the current position of coal tar in the treatment of psoriasis and eczema, a survey was conducted. In *Chapter 3* we present the results of this study. A postal survey was conducted among Dutch and Flemish dermatologists. The study was performed in The Netherlands and Belgium to get an impression concerning the variation between the two countries with respect to the use of coal tar ointments. The results showed that almost all dermatologists prescribed topical corticosteroids, vitamin D3 analogues and calcineurin inhibitors, but also coal tar was still used by the majority of the dermatologists. From this study we concluded that coal tar still is an important second line therapy for psoriasis and eczema.

Risk of cancer after coal tar treatment

Despite the lack of clear evidence of an increased risk of cancer, many dermatologists have abandoned the use of coal tar. However, it not justified to abandon this therapy before a valid assessment of the risk of cancer has been made. In order to assess the risk of cancer after coal tar treatment in patients with psoriasis or eczema, we initiated a large historical cohort study, the LATER study (LAte effects of coal Tar treatment in Eczema and psoriasis; the Radboud study). *Chapter 4.1* describes the results of this study in which 13,200 patients diagnosed with psoriasis or eczema between 1960 and 1990 were included. Information on skin disease and treatment, possible risk factors and cancer occurrence was retrieved from medical files, postal questionnaires and medical registries (Netherlands Cancer Registry and Causes of Death registry held by Statistics Netherlands). Patients treated with coal tar were compared with a reference category of patients treated with dermatocorticosteroids only (assuming to carry no increased risk of cancer). Coal tar did not increase the risk of skin cancer or internal organ malignancies. From these results we concluded that coal tar can be maintained as a safe therapy in the treatment of psoriasis and eczema.

After absorption and metabolisation, several metabolites of coal tar are excreted in urine and therefore, an increased risk of bladder cancer may be plausible. The risk of bladder cancer in patients treated with coal tar was investigated in a few studies, but none of the earlier studies was specifically aimed at the association between dermatological application of coal tar ointments and the risk of bladder cancer. In a population-based case-control study, addressed in *chapter 4.2,* we studied the association between bladder cancer and the use of coal tar. The study included 1,387 cases diagnosed with bladder cancer and 3,527 population controls. Information on the use of coal tar, occurrence of skin disease and known risk factors for bladder cancer was obtained through postal questionnaires. No association was found between the use of coal tar ointments and an increased risk of bladder cancer.

Risk of cancer in patients with psoriasis and eczema

Psoriasis and eczema are common, inflammatory skin diseases in which a hyperreactive immune system leads to chronic inflammation. Because of the chronic stimulation of cells of the immune system, patients may have an intrinsic increased risk of malignancies. So far, many studies have investigated the risk of cancer in psoriasis and eczema. Many of the patients in these studies were treated with carcinogenic therapies, such as cyclosporine and PUVA and as a result, it was not possible to exclude the effect of treatment on the risk of cancer in patients with psoriasis or eczema in these studies.

Chapter 5 describes our cohort study in which the risk of cancer was assessed by comparing the number of observed cancers in the cohort of patients with psoriasis

or eczema to the expected numbers of cancer in the general population. In order to obtain the expected number of cancer cases, the national incidence rates stratified by sex, 5-year age groups and calendar year groups from the Netherlands Cancer Registry were used. We collected data on all therapies that patients received, and therefore, it was possible to select a group of patients who were only treated with emollients or dermatocorticosteroids. By selecting this group of patients, we were able to exclude the effect of treatment on the risk of cancer.

The overall risk of cancer was slightly increased in the total cohort of patients with psoriasis and eczema. Also, in the subgroup of patients treated with dermatocorticosteroids only, a slightly increased risk of cancer was observed. This study shows that patients with psoriasis and eczema have a slightly increased risk of cancer, independent of treatment.

Toxicology

Coal tar ointments contain high concentrations of polycyclic aromatic hydrocarbons (PAH). The skin is an important route of uptake of these PAH after coal tar application. After exposure *via* the skin, 1-hydroxypyrene (1-OHP), the principal metabolite of pyrene, can be used as a biomarker for the assessment of dermal uptake and bio-availability of PAH. Psoriasis is characterized by hyperproliferation of the epidermis, leading to thickening of the epidermis and by disturbance of the barrier function. As a consequence, the permeability of the skin is altered. In addition, metabolism of PAH may be changed in patients with psoriasis. If the permeability of the skin and the metabolism of PAH in psoriasis are altered, this could have implications for the carcinogenic potential of coal tar ointments.

To evaluate possible differences in dermal absorption and metabolism of PAH after dermal application of coal tar, we conducted a study in ten patients with psoriasis and ten healthy volunteers. In *Chapter 6* we report the results of this toxicology study. DNA was isolated from skin biopsies before and after 96 hours of coal tar application and urine was collected during and after the exposure period. 48 hours after application of coal tar, a statistical significantly higher 1-OHP excretion was observed in volunteers compared to psoriasis patients. At baseline PAH-DNA adduct levels were comparable, but after removal of coal tar, PAH-DNA levels were higher in healthy volunteers. These results implicate reduced absorption and bio-activation of PAH in patients with psoriasis, suggesting a lower risk of carcinogenic effects of coal compared to healthy skin. Future research is needed to explore the cellular mechanism that can explain the observed results.

Conclusions

The main conclusions of this thesis can be summarized as follows:

- Coal tar still is an important second line treatment for psoriasis and eczema. (Chapter 3)
- The most important reasons for the diminished use of coal tar are difficulties to obtain coal tar preparations from pharmacies and the possible carcinogenicity of coal tar. (Chapter 3).
- Patients with psoriasis or eczema treated with coal tar preparations have no increased risk of cancer. (Chapter 4)
- The use of coal tar ointments in dermatological practice is not associated with an increased risk of bladder cancer (Chapter 4)
- Patients with psoriasis or eczema have a slightly increased risk of cancer, independent of treatment (chapter 5)
- Uptake, bioavailability and bio-activation of PAH in patients with psoriasis differ from healthy volunteers (Chapter 6).

Samenvatting

Samenvatting

Koolteerzalven zijn in de afgelopen decennia vaak toegepast als behandeling van psoriasis en eczeem. Echter, koolteer bevat vele polycyclische aromatische koolwaterstoffen (PAKs) die door het cytochroom P450 systeem worden omgezet in reactieve metabolieten die kunnen reageren met DNA. Daarom is de afgelopen jaren ongerustheid ontstaan over de mogelijke carcinogeniteit van koolteerzalven als behandeling van huidziekten. Belangrijk hierbij is wel dat een aantal van de alternatieve topicale en systemische behandelingen voor psoriasis en eczeem potentieel carcinogeen zijn. Omdat koolteerzalf wel een effectieve therapie is, moet eerst grondig onderzoek worden gedaan naar de mogelijke risico's bij dermatologisch gebruik van koolteer voordat deze uit het therapeutisch arsenaal worden geschrapt. Om het risico op kanker na het gebruik van koolteerzalf te onderzoeken, is de LATER-studie (Late effecten van koolteer behandeling in patiënten met eczeem of psoriasis; de Radboud studie) gestart. Binnen dit onderzoeksproject zijn diverse substudies uitgevoerd.

Plaatsbepaling van koolteer in de behandeling van psoriasis en eczeem

Hoofdstuk 1 geeft een korte introductie over het onder het onderwerp van dit proefschrift.

Vervolgens wordt in **hoofdstuk 2** een review over koolteer beschreven. Er wordt een overzicht gegeven van de productie van koolteer, het werkingsmechanisme en indicaties in de dermatologische praktijk. Ook wordt aandacht besteed aan de korte- en lange termijn bijwerkingen die als gevolg van koolteer behandeling kunnen optreden. Bijwerkingen die na korte tijd kunnen ontstaan zijn folliculitis, huidirritatie, contactallergieën en fototoxische reacties. De belangrijkste bijwerking die op lange-termijn zou kunnen optreden is het ontstaan van kanker. In het laatste deel van het review wordt een overzicht gegeven van de studies die tot dusver over dit onderwerp werden gepubliceerd.

Koolteer wordt al decennia gebruikt bij de behandeling van huidziekten, maar het gebruik van deze zalven is in de afgelopen jaren verminderd. Eén van de redenen hiervoor is de veronderstelde carcinogeniteit alhoewel overtuigend bewijs hiervoor ontbreekt. Een andere reden voor het afgenomen gebruik is de moeizame verkrijgbaarheid van koolteer bij apotheken. De overheid heeft regels opgesteld voor het bereiden van koolteerzalven waarbij strenge voorzorgsmaatregelen getroffen moeten worden. Dit heeft als gevolg dat de zalven niet meer door alle apothekers worden bereid. Om de huidige rol van koolteer in de behandeling van psoriasis en eczeem te evalueren, hebben we onder alle Nederlandse en Vlaamse dermatologen een

enquête uitgevoerd. In hoofdstuk 3 worden de resultaten van deze studie beschreven. De enquête werd uitgevoerd onder Nederlandse en Vlaamse dermatologen om een indruk te krijgen over mogelijke verschillen en overeenkomsten in voorschrijfgedrag tussen deze twee landen. Uit de resultaten van deze studie bleek dat bijna alle dermatologen topicale corticosteroïden, vitamine D3 analogen en calcineurine-inhibitoren voorschrijven. De meerderheid van de dermatologen schrijft daarnaast ook nog steeds koolteerzalven voor. Wij concludeerden uit deze resultaten dat koolteerzalven nog steeds een plaats hebben in de behandeling van psoriasis en eczeem.

Risico op kanker na behandeling met koolteer

Ondanks het ontbreken van goed bewijs op een verhoogd risico op kanker na het gebruik van koolteer, wordt het minder voorgeschreven door dermatologen. Het zou echter voorbarig zijn om het gebruik van koolteer uit te bannen voordat dat het risico op kanker na koolteer goed is onderzocht. Daarom werd in 2003 de LATER-studie (Late effecten van koolteer behandeling in patiënten met eczeem of psoriasis; de Radboud studie) gestart. In **hoofdstuk 4.1** worden de resultaten van deze studie beschreven waarin 13.200 patiënten, gediagnosticeerd met psoriasis of eczeem tussen 1960 en 1990, werden geïncludeerd. Informatie over de huidziekte, behandelingen, risicofactoren voor kanker en het voorkomen van kanker werden verzameld met behulp van medische dossiers, vragenlijsten en medische registraties (Nederlandse Kankerregistratie en de Doodsoorzaken Registratie van het Centraal Bureau voor de Statistiek). Patiënten die werden behandeld met koolteer werden vergeleken met patiënten die alleen met lokale corticosteroïden of emollientia werden behandeld. Voor deze referentiegroep werd gekozen omdat het gebruik van lokale corticosteroïden en emollientia niet geassocieerd is met kanker. Er werd geen verhoogd risico gevonden op huidkanker of interne tumoren na het gebruik van koolteer. Uit deze resultaten concludeerden wij dat het gebruik van koolteer bij de behandeling bij psoriasis en eczeem veilig is.

Nadat koolteer op de huid is aangebracht, wordt het geabsorbeerd en gemetaboliseerd. Tijdens dit proces worden diverse metabolieten van koolteer in de urine uitgescheiden waardoor er theoretisch een verhoogd risico op blaaskanker zou kunnen zijn. Het risico op blaaskanker bij patiënten met psoriasis en eczeem is in enkele studies onderzocht, maar in geen enkele studie werd de relatie tussen behandeling met koolteer en blaaskanker specifiek onderzocht. In een case-controle studie, beschreven in **hoofdstuk 4.2**, werd de associatie tussen het dermatologisch gebruik van koolteer en blaaskanker bestudeerd. 1387 patiënten met blaaskanker en 3527 controles werden geïncludeerd. Vragenlijsten werden gebruikt om informatie te verzamelen over het gebruik van koolteer, het voorkomen van huidziekten en

risicofactoren voor blaaskanker. Er werd geen associatie gevonden tussen het gebruik van koolteer en blaaskanker.

Risico op kanker bij patiënten met psoriasis of eczeem

Psoriasis en eczeem zijn veel voorkomende, inflammatoire huidziekten waarin een hyperreactief immuunsysteem tot chronische inflammatie leidt. Door de chronische stimulatie van cellen van het immuunsysteem, hebben deze patiënten mogelijk een verhoogd risico op kanker. In veel studies is het risico op kanker bij patiënten met psoriasis en eczeem onderzocht waarbij in de meerderheid van deze studies een verhoogd risico op kanker werd gevonden. In deze studies waren veel patiënten behandeld met carcinogene middelen zoals cyclosporine en PUVA waardoor het niet mogelijk was om het aandeel van het effect van deze behandelingen op het risico op kanker uit te filteren.

In **hoofdstuk 5** wordt de cohort studie beschreven waarin het risico op kanker werd onderzocht bij patiënten met psoriasis en eczeem. Het aantal gediagnosticeerde tumoren in het cohort werd vergeleken met de algemene bevolking. Om het aantal tumoren in de algemene bevolking te berekenen, werden incidentiecijfers (gestratificeerd voor geslacht, leeftijd en kalenderperiode) van de Nederlandse Kankerregistratie gebruikt. Doordat informatie werd verzameld over alle middelen waarmee patiënten werden behandeld, was het mogelijk om een groep patiënten te selecteren die alleen werden behandeld met emollientia en/of lokale corticosteroïden. Hierdoor was het mogelijk om het intrinsieke (therapieonafhankelijke) risico op kanker in deze subgroep te onderzoeken.

Het risico op kanker in het gehele cohort van patiënten met psoriasis en eczeem was licht verhoogd. Ook werd er een licht verhoogd risico op kanker gevonden in de subgroep van patiënten die alleen met lokale corticosteroïden werden behandeld. Deze studie heeft laten zien dat patiënten met psoriasis en eczeem een licht verhoogd risico op kanker hebben, onafhankelijk van behandeling. Een mogelijke verklaring hiervoor is de chronische stimulatie van het immuunsysteem bij deze patiënten.

Metabolisatie van PAKs in de huid

Koolteerzalven bevatten hoge concentraties polycyclische aromatische koolwaterstoffen (PAKs). Bij dermatologisch gebruik is de huid één van de belangrijkste opnameroutes van deze PAKs. 1-hydroxypyreen (1-OHP), de belangrijkste metaboliet van pyreen, kan worden gebruikt als biomarker voor dermale opname en omzetting van PAKs.

Psoriasis wordt gekenmerkt door hyperproliferatie van de epidermis waardoor deze verdikt is. De barrière functie raakt hierbij verstoord en er treedt verandering op van de permeabiliteit van de huid. Hierdoor zou de metabolisatie van PAKs in de huid bij psoriasis kunnen verschillen van gezonde huid. Het carcinogene effect van

koolteer zou door de verstoorde permeabiliteit van de huid en een mogelijk andere metabolisatie van PAKs anders kunnen zijn bij patiënten met psoriasis ten opzichte van gezonde vrijwilligers.

Om mogelijke verschillen in dermale absorptie en metabolisatie van PAKs na koolteer blootstelling te onderzoeken, werd een studie uitgevoerd bij tien patiënten met psoriasis en tien gezonde vrijwilligers. **Hoofdstuk 6** beschrijft de resultaten van deze toxicologische studie. Huidbiopten werden afgenomen vóór het aanbrengen van koolteer en nadat de koolteerzalf na 96 uur blootstelling werd verwijderd. Uit de biopten werd DNA geïsoleerd om het gehalte aan PAK-DNA adducten te bepalen. Urinemonsters werden verzameld vóór het aanbrengen van de koolteerzalf, tijdens de onderzoeksperiode en na 96 uur blootstelling. In de urinemonsters werd het gehalte aan 1-hydroxypyreen bepaald. 48 uur na blootstelling aan koolteerzalf werd een statistisch significant hogere 1-OHP excretie gevonden bij de gezonde vrijwilligers ten opzichte van de patiënten met psoriasis. Vóór het aanbrengen van koolteer was het PAK-DNA adducten gehalte in beide onderzoeksgroepen gelijk, maar na 96 uur blootstelling was het gehalte aan PAK-DNA adducten hoger bij de gezonde vrijwilligers dan bij de psoriasis patiënten. Deze resultaten suggereren een lager carcinogeen risico bij psoriasis door een verminderde absorptie en bio-activatie van PAKs. Er is meer onderzoek nodig om de gevonden resultaten op cellulair niveau te kunnen verklaren.

Conclusies

De belangrijkste conclusies van dit proefschrift zijn:

- Koolteer is nog steeds een belangrijke therapeutische optie bij de behandeling van psoriasis en eczeem (hoofdstuk 3)
- De belangrijkste redenen voor het verminderd gebruik van koolteer zijn de moeizame verkrijging van koolteer bij apotheken en de mogelijke carcinogeniteit van koolteer (hoofdstuk 3)
- Patiënten met psoriasis en eczeem hebben geen verhoogd risico op kanker na behandeling met koolteer (hoofdstuk 4)
- Dermatologisch gebruik van koolteer is niet geassocieerd met een verhoogd risico op blaaskanker (hoofdstuk 4)
- Patiënten met psoriasis of eczeem hebben een licht verhoogd risico op kanker, onafhankelijk van behandeling (hoofdstuk 5)
- Opname, beschikbaarheid en bio-activiteit van PAKs in patiënten met psoriasis verschilt van gezonde vrijwilligers (hoofdstuk 6)

Dankwoord

Dankwoord

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Op de afdeling Epidemiologie, Biostatistiek en HTA, inmiddels Department for Health Evidence, heb ik een hele fijne onderzoekstijd gehad. Er werd hard gewerkt, maar er was ook tijd voor gezelligheid. De cake-van-de week, de gezellige lunchpauzes en sociale activiteiten hebben zeker positief bijgedragen aan mijn promotietijd. Hans en Marijn, het was erg gezellig om met jullie in de SoA-commissie te zitten. We hebben vele leuke borrels en andere activiteiten georganiseerd. Reini, bedankt voor de gezellige tijd en fijn dat we elkaar nog steeds een paar keer per jaar zien om bij te praten tijdens een gezellig etentje. Hans, we hebben een beetje hetzelfde tempo aangehouden. Nu mijn “project” is afgerond, is jouw renovatieproject ook afgerond. Erik, dank voor je hulp bij het programmeren van de SPSS- en SAS-programma’s die ik nodig had voor de statistische analyses. Voor mij soms onbegrijpelijk hoe je het voor elkaar kreeg, maar het werkte altijd! Wim, als dorpsgenoten hebben we vaak samen gereden naar het werk. Op je werkplek aan het begin van de gang op de 3e verdieping had je altijd tijd voor mijn vragen en een gezellig praatje. Ook toen ik was “verhuisd” naar de afdeling Dermatologie kon ik nog altijd bij jou terecht als mijn SPSS- of SAS programma’s weer eens kuren hadden. Alle andere collega’s van de afdeling wil ik ook bedanken voor de prettige werksfeer op de afdeling.

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List of publications

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Curriculum vitae

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Judith Roelofzen werd op 17 augustus 1977 geboren in Doetinchem. In 1995 behaalde zij haar VWO diploma aan het Isala College te Silvolde. Zij begon in datzelfde jaar met haar studie geneeskunde aan de Universiteit van Antwerpen. Als onderdeel van de co-schappen liep zij twee maanden stage op de afdeling gynaecologie en verloskunde in het Diakonesse ziekenhuis in Paramaribo. In de zomer van 2002 heeft zij gedurende twee maanden haar keuze co-schap gedaan op de afdeling Dermatologie van het UMC St Radboud. Ook haar wetenschappelijke stage werd gelopen op deze afdeling waarbij onder leiding van prof. dr. dr. P.C.M. van de Kerkhof en dr. P.G.M. van der Valk twee onderzoeken werden uitgevoerd.

Na het behalen van het arts-examen in 2003, begon zij met haar promotie-onderzoek op de afdeling Epidemiologie en Biostatstiek (inmiddels afdeling Health Evidence). Onder leiding van prof. dr. L.A.L.M. Kiemeney, prof. dr. dr. P.C.M. van de Kerkhof, dr. K.K.H. Aben en dr. P.G.M. van der Valk werd het in dit proefschrift beschreven onderzoek verricht. In november 2007 ving zij aan met haar opleiding tot dermatoloog in het UMC St Radboud. Vanaf 1 december 2012 is zij werkzaam als dermatoloog in het Streekziekenhuis Koningin Beatrix in Winterswijk.