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No Increased Risk of Cancer after Coal Tar Treatment in Patients with Psoriasis or Eczema

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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 with a reference category of patients treated with dermatocorticosteroids (assumed to carry no increased cancer risk). The median exposure to coal tar ointments was 6 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.

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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 (PAHs). 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 g pix lithantracis with 100 ml alcohol and addition of 5 g 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 PAHs, such as benzo(a)pyrene and benz(a)antracene, are carcinogenic (Bickers 1981; Boffetta *et al.*, 1997). Animal studies (IARC, 1985; Boffetta *et al.*, 1997; Marston *et al.*, 2001) and occupational studies (IARC, 1985; Partanen and Boffetta, 1994; Donato *et al.*, 2000; Tsai *et al.*, 2001) 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 (Maughan *et al.*, 1980; Stern *et al.*, 1980; Pittelkow *et al.*, 1981; Larko and Swanbeck, 1982; Jones *et al.*, 1985; Hannuksela-Svahn *et al.*, 2000). 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 (Roelofzen *et al.*, 2007; Paghdal and Schwartz, 2009). Some dermatologists even consider the use of coal tar obsolete (Mrowietz and Rott, 2007). 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 LAte effects of coal Tar treatment in Eczema and psoriasis; the Radboud study (LATER study).

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RESULTS

Characteristics of the cohort

In 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 eczema or date of diagnosis. One-third of the cohort consisted of patients with psoriasis and two-thirds with eczema. Over 60% of the patients with psoriasis had a severe form, i.e., >10% of their body was affected. In eczema, this applied to <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 for 4 months (range 1–300 months) and of liquor carbonis detergens for 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 tumors 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 (hazard ratio (HR) 1.09 and 95% confidence interval (CI) 0.69–1.72; and HR 0.92 and 95% CI 0.78–1.09, respectively). The risk of hematological malignancies seemed to be slightly decreased, especially in psoriasis, but these analyses only included a small number of tumors. In patients with eczema, the risk of gastrointestinal cancer after coal tar treatment was approximately 50% lower than in 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) when compared with 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 HR 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 groups. In patients with eczema, the risk of gastrointestinal cancer after liquor carbonis detergens was almost 50% lower when 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 3-fold increased risk of tumors of the female reproductive organs in patients with eczema (HR 2.90; 95% CI 1.31–6.43).

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 PAHs over a short period, whereas patients treated with liquor carbonis detergens were exposed to a lower dose of PAHs 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 PAHs (IARC, 1985; Partanen and Boffetta, 1994; Donato *et al.*, 2000; Tsai *et al.*, 2001).

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

Most of the studies that analyzed the risk of skin cancer after coal tar treatment did not find an increased risk of non-melanoma skin cancer (Maughan *et al.*, 1980; Pittelkow *et al.*, 1981; Larko and Swanbeck, 1982; Jones *et al.*, 1985; Hannuksela-Svahn *et al.*, 2000). Only Stern *et al.*, (1980) reported an increased risk of non-melanoma skin cancer in patients with psoriasis. 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. These patients had received coal tar therapy intermittently over a 10-year period and had never been exposed to ultraviolet B, PUVA, or cytotoxic therapies. The results indicated that coal tar treatment did not increase the risk of internal tumors. Hannuksela-Svahn *et al.* (2000) conducted a large cohort study to estimate the risk of cancer in 5,687 hospitalized patients with psoriasis. A nested case–control study within this cohort study showed a nonsignificant increase in the risk

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 years (0–95.7)	31.1 years (0–95.7)	27.2 years (0–91.4)
Calendar period of diagnosis			
1960–1969 (%)	2,476 (18.8)	931 (21.6)	1,545 (17.4)
1970–1979 (%)	4,160 (31.5)	1,575 (36.5)	2,585 (29.1)
1980–1989 (%)	6,564 (49.7)	1,809 (41.9)	4,755 (53.3)
Status at end of follow-up			
Diagnosed with cancer (%)	1,048 (7.9)	421 (9.8)	627 (7.1)
Deceased without cancer (%)	1,951 (14.8)	725 (16.8)	1,226 (13.8)
Censured at 31 December 2003 (%)	9,346 (70.8)	2,840 (65.8)	6,506 (73.2)
Lost to follow-up (%)	855 (6.5)	329 (7.6)	526 (5.9)
Median duration of follow-up (years)	21	22.5	20.5
1–9 years (%)	1,433 (10.9)	502 (11.6)	928 (10.5)
10–19 years (%)	4,634 (35.1)	1,219 (28.3)	3,414 (38.4)
20–29 years (%)	4,415 (33.4)	1,528 (35.4)	2,856 (32.5)
>30 years (%)	2,718 (20.6)	1,063 (24.6)	1,654 (18.6)
Severity of skin disease (% area affected)			
<1%	2,759 (20.9)	375 (8.7)	2,381 (26.8)
2–9%	4,528 (34.3)	1,290 (29.9)	3,234 (36.4)
10–30%	3,907 (29.6)	1,696 (39.3)	2,221 (25.0)
>30%	2,006 (15.2)	954 (22.1)	1,049 (11.8)
Use of coal tar ointments (%)			
Never[1]	5,138 (38.9)	1,234 (28.6)	3,904 (43.9)
Only liquor carbonis detergens, no pix lithantracis[1]	4,927 (37.3)	2,256 (52.3)	2,671 (30.1)
Pix lithantracis with/without liquor carbonis detergens[1]	3,135 (23.8)	825 (19.1)	2,310 (26.0)
Use of other therapies (%)			
Topical			
Local corticosteroids	96.6	96.6	96.5
Vitamin D3 analogs	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 prednisone	9.6	5.1	11.8

Table 1 continued on the following page

Table 1. Continued

Characteristic	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)
Photo(chemo)therapy			
PUVA	13.1	27.2	6.2
UVB	16.7	33.5	8.6
Goeckerman	3.5	9	0.9
Smoking status (%)[2]			
Never	1,499 (11.4)	400 (9.3)	1,099 (12.4)
Former	2,489 (18.9)	997 (23.1)	1,492 (16.8)
Current	1,526 (11.5)	559 (13.0)	967 (10.7)
Unknown	16 (0.1)	6 (0.1)	10 (0.1)
Missing (no data from questionnaire)	7,670 (58.1)	2,353 (54.5)	5,317 (59.8)
Alcohol (%)[2]			
<1 Days/week	2,561 (19.4)	859 (19.9)	1,702 (19.2)
1–2 Days/week	1,062 (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)	7,670 (58.1)	2,353 (54.5)	5,317 (59.8)
Skin type (%)[2]			
Type 1 (always burns, never tans)	426 (3.3)	167 (3.9)	259 (2.9)
Type 2 (burns easily, tans minimally)	1,764 (13.3)	555 (12.9)	1,209 (13.6)
Type 3 (burns moderately, tans to light brown	2,688 (20.4)	977 (22.6)	1,711 (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)	7,670 (58.1)	2,353 (54.5)	5,317 (59.8)

Abbreviations: PUVA, psoralen 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).

of non-Hodgkin's lymphoma after treatment with the Goeckerman regimen (odds ratio 1.2; 95% CI 0.1–16.8).

In the tumor-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 tumor risk site after coal tar treatment (in contrast with the bladder, lymphatic, and hematological system), a decreased risk was unexpected and we cannot think of a logical explanation. The study by Jones *et al.* (1985) reported an increased risk of colon cancer in men, but not in women. However, these results were based on very small numbers of tumors ($n=6$).

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 tumors 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 the 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

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

	Total cohort (13,200)	Psoriasis (4,315)	Eczema (8,885)	Coal tar (8,062)	No coal tar (5,138)
Tumor site	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Overall cancer	1,327 (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	1,192 (9.0)	444 (10.3)	748 (8.4)	707 (8.8)	485 (9.4)
Specific tumor groups					
Hematological	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	
Tumor	**Cases**	**HR (95% CI)[1]**	**Cases**	**HR (95% CI)[1]**	**Cases**	**HR (95% CI)[1]**
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[2]	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 tumor groups						
Hematological 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)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[1]All HRs were adjusted for age, gender, severity of skin disease, calendar period, use of psoralen plus UVA, use of systemic therapy, and smoking.
[2]Excluding basal cell carcinoma.
Patients treated with coal tar ($n = 8,062$) were compared with the reference group ($n = 3,705$ patients treated with dermatocorticosteroids alone).

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 (NCR; 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 NCR. Consequently,

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		
Tumor	Cases	HR LCD (95% CI)[1]	HR PL (95% CI)[1]	Cases	HR LCD (95% CI)[1]	HR PL (95% CI)[1]	Cases	HR LCD (95% CI)[1]	HR PL (95% CI)[1]
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[2]	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 tumor groups									
Hematological 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)

Abbreviations: CI, confidence interval; HR, hazard ratio; LCD, liquor carbonis detergens; PL, pix lithantracis.
[1]All HRs were adjusted for age, gender, severity of skin disease, calendar period, use of psoralen plus UVA, use of systemic therapy, and smoking.
[2]Excluding basal cell carcinoma.
Patients treated with LCD ($n=4,927$) and patients treated with PL ($n=3,135$) (with or without LCD) were compared with the reference group ($n=3,705$ patients treated with dermatocorticosteroids alone).

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 basal cell carcinoma (IARC, 1985; Partanen and Boffetta, 1994; Boffetta *et al.*, 1997; Donato *et al.*, 2000; Marston *et al.*, 2001; Tsai *et al.*, 2001).

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 (Enderlein *et al.*, 2005; Ring *et al.*, 2005). Until now, epidemiological studies have not shown any increased risk of (skin) cancer after the use of calcineurin inhibitors, and only short-term follow-up data are available (Ring *et al.*, 2005). 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 (Greaves and Weinstein, 1995; Lebwohl, 2003; Menter and Griffiths, 2007).

The risk of skin cancer after PUVA has been extensively studied and most studies showed an increased risk of skin cancer (Stern *et al.*, 1998; Lindelof *et al.*, 1999; Hannuksela-Svahn *et al.*, 2000; Nijsten and Stern, 2003). 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 (London *et al.*, 1995; Jensen *et al.*, 1999; Lindelof *et al.*, 2000; Ramsay *et al.*, 2000; Moloney *et al.*, 2006). Some of the studies that analyzed the risk of skin cancer after cyclosporine in psoriasis also showed an increased risk of skin cancer (Arellano, 1997; Marcil and Stern, 2001; Paul *et al.*, 2003). 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 hence 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 (Berger and Gottlieb, 2007; Menter *et al.*, 2008).

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.

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. This study was approved by the institutional review boards of all three hospitals

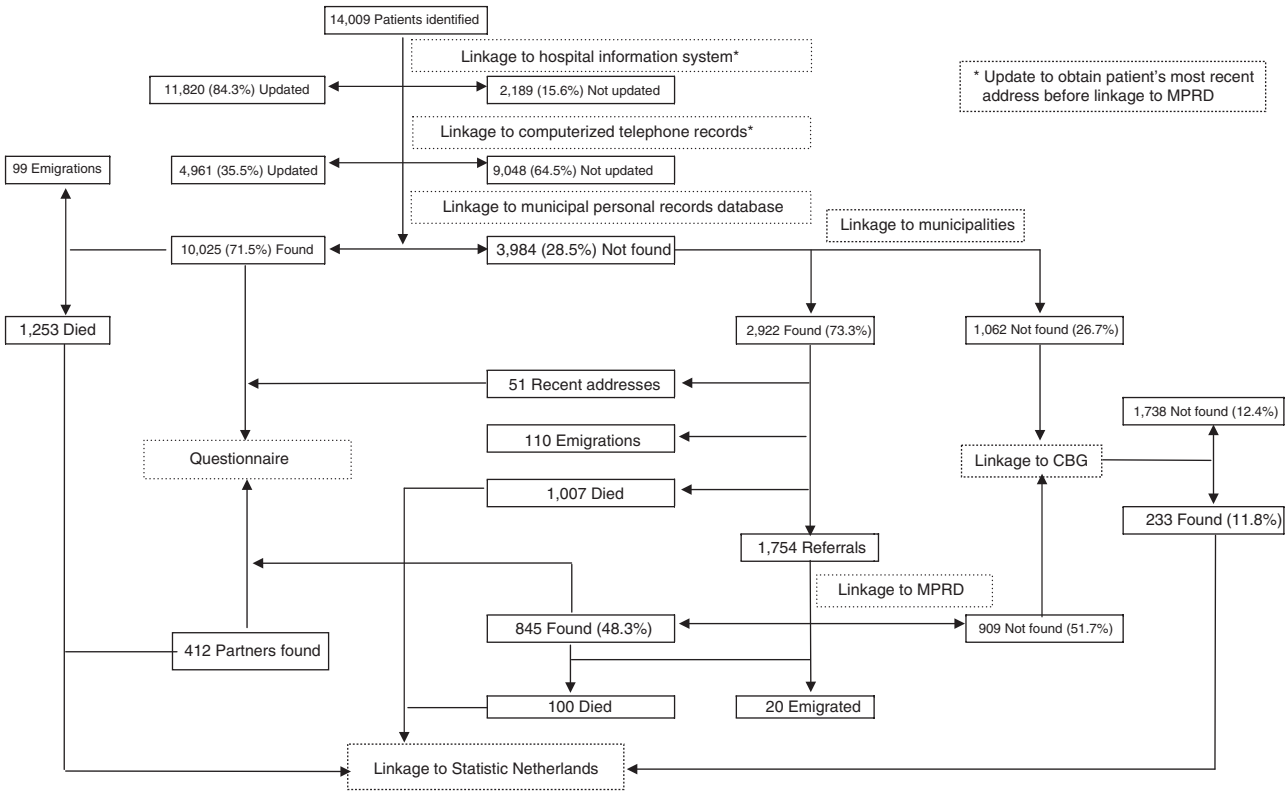

Figure 1. Process of updating personal data and vital status of patients in the cohort. CBG, Central Bureau of Genealogy; MPRD, municipal personal records database.

(Radboud University Nijmegen Medical Centre, Canisius-Wilhelmina Ziekenhuis, and University Medical Centre Groningen).

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 fulfill 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 the 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 NCR and Causes of Death Registry. Recent data on vital status were frequently unavailable in the medical files. This was supplemented by linkages with 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 labor-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. In addition, municipalities and the Central Bureau of Genealogy were consulted. By the end of these procedures, the addresses and vital status of 88% of the patients were 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 per 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, or >50 times per year) and residence in tropical areas (never, <1, 1–2, 3–5, or 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 3 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 the 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 to 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 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 nonresponders and deceased patients did not give explicit consent, linkage to the NCR is allowed using a strict privacy procedure (Ronckers, 2001). 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 diagnosis of cancer, date of death, date of loss to follow-up, or 31 December 2003, whichever came first. Separate analyses were conducted on specific outcomes: (1) overall cancer (total of all the tumors), (2) skin cancer (excluding basal cell carcinoma), (3) non-skin cancer, and (4) different (groups of) tumor sites. If a patient was diagnosed with multiple tumors, only the first tumor 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 alone (assumed to carry no increased risk of cancer) and an exposure category of patients treated with coal tar (including pix lithantracis and/or liquor carbonis detergens). As pix lithantracis contains far more carcinogenic PAHs than liquor carbonis detergens, 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 liquor carbonis detergens), and ''low exposure'' including patients treated with liquor carbonis detergens 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 (>10% body area affected vs <10%), an interaction term of coal tar and severity, calendar period of diagnosis (1960–1969, 1970–1979, and 1980–1989), 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 for assessing 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 was used (Donders *et al.*, 2006; Moons *et al.*, 2006; van der Heijden *et al.*, 2006). 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).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Arellano F (1997) Risk of cancer with cyclosporine in psoriasis. *Int J Dermatol* 36(Suppl 1):15–7

Berger EM, Gottlieb AB (2007) Developments in systemic immunomodulatory therapy for psoriasis. *Curr Opin Pharmacol* 7:434–44

Bickers DR. (1981) The carcinogenicity and mutagenicity of therapeutic coal tar: a perspective. *J Invest Dermatol* 77:173–4

Boffetta P, Jourenkova N, Gustavsson P (1997) Cancer risk from occupational and environmental exposure to polycyclic aromatic hydrocarbons. *Cancer Causes Control* 8:444–72

Donato F, Monarca S, Marchionna G *et al.* (2000) Mortality from cancer and chronic respiratory diseases among workers who manufacture carbon electrodes. *Occup Environ Med* 57:484–7

Donders AR, van der Heijden GJ, Stijnen T *et al.* (2006) Review: a gentle introduction to imputation of missing values. *J Clin Epidemiol* 59:1087–91

Enderlein E, Meller S, Rieker J *et al.* (2005) Current aspects of the therapy with topical calcineurin inhibitors. *Hautarzt* 56:937–41

Greaves MW, Weinstein GD (1995) Treatment of psoriasis. *N Engl J Med* 332:581–8

Hannuksela-Svahn A, Pukkala E, Laara E *et al.* (2000) Psoriasis, its treatment, and cancer in a cohort of Finnish patients. *J Invest Dermatol* 114:587–90

IARC (1985) Polynuclear aromatic compounds, part 4, bitumens, coal-tars and derived products, shale-oils and soots. *IARC, Monograph Eval Carcinog Risk Chem Humans* 35:83–159

Jensen P, Hansen S, Moller B *et al.* (1999) Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. *J Am Acad Dermatol* 40:177–86

Jones SK, Mackie RM, Hole DJ *et al.* (1985) Further evidence of the safety of tar in the management of psoriasis. *Br J Dermatol* 113:97–101

Larko O, Swanbeck G (1982) Is UVB treatment of psoriasis safe? A study of extensively UVB-treated psoriasis patients compared with a matched control group. *Acta Derm Venereol* 62:507–12

Lebwohl M (2003) Psoriasis. *Lancet* 361:1197–204

Lindelof B, Sigurgeirsson B, Gabel H *et al.* (2000) Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 143:513–9

Lindelof B, Sigurgeirsson B, Tegner E *et al.* (1999) PUVA and cancer risk: the Swedish follow-up study. *Br J Dermatol* 141:108–12

London NJ, Farmery SM, Will EJ *et al.* (1995) Risk of neoplasia in renal transplant patients. *Lancet* 346:403–6

Marcil I, Stern RS (2001) Squamous-cell cancer of the skin in patients given PUVA and ciclosporin: nested cohort crossover study. *Lancet* 358:1042–5

Marston CP, Pereira C, Ferguson J *et al.* (2001) Effect of a complex environmental mixture from coal tar containing polycyclic aromatic hydrocarbons (PAH) on the tumor initiation, PAH-DNA binding and metabolic activation of carcinogenic PAH in mouse epidermis. *Carcinogenesis* 22:1077–86

Maughan WZ, Muller SA, Perry HO *et al.* (1980) Incidence of skin cancers in patients with atopic dermatitis treated with coal tar. A 25-year follow-up study. *J Am Acad Dermatol* 3:612–5

Menter A, Gottlieb A, Feldman SR *et al.* (2008) Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *J Am Acad Dermatol* 58:826–50

Menter A, Griffiths CE (2007) Current and future management of psoriasis. *Lancet* 370:272–84

Moloney FJ, Comber H, O'Lorcain P *et al.* (2006) A population-based study of skin cancer incidence and prevalence in renal transplant recipients. *Br J Dermatol* 154:498–504

Moons KG, Donders RA, Stijnen T *et al.* (2006) Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol* 59:1092–101

Mrowietz U, Rott S (2007) Evaluating topical treatments in severe psoriasis. *Eur Dermatol Rev* 1:23–4

Nijsten TE, Stern RS (2003) The increased risk of skin cancer is persistent after discontinuation of psoralen+ultraviolet A: a cohort study. *J Invest Dermatol* 121:252–8

Paghdal KV, Schwartz RA (2009) Topical tar: back to the future. *J Am Acad Dermatol* 61:294–302

Partanen T, Boffetta P (1994) Cancer risk in asphalt workers and roofers: review and meta-analysis of epidemiologic studies. *Am J Ind Med* 26:721–40

Paul CF, Ho VC, McGeown C *et al.* (2003) Risk of malignancies in psoriasis patients treated with cyclosporine: a 5 y cohort study. *J Invest Dermatol* 120:211–6

Pittelkow MR, Perry HO, Muller SA *et al.* (1981) Skin cancer in patients with psoriasis treated with coal tar. A 25-year follow-up study. *Arch Dermatol* 117:465–8

Ramsay HM, Fryer AA, Reece S *et al.* (2000) Clinical risk factors associated with nonmelanoma skin cancer in renal transplant recipients. *Am J Kidney Dis* 36:167–76

Ring J, Barker J, Behrendt H *et al.* (2005) Review of the potential photococarcinogenicity of topical calcineurin inhibitors: position statement of the European Dermatology Forum. *J Eur Acad Dermatol Venereol* 19:663–71

Roelofzen JH, Aben KK, Khawar AJ *et al.* (2007) Treatment policy for psoriasis and eczema: a survey among dermatologists in the Netherlands and Belgian Flanders. *Eur J Dermatol* 17:416–21

Ronckers CM (2001) Long-term health effects of nasopharyngeal radium irradiation. Thesis, NKI, Amsterdam

Stern RS, Liebman EJ, Vakeva L (1998) Oral psoralen| and ultraviolet-A light (PUVA) treatment of psoriasis and persistent risk of nonmelanoma skin cancer. PUVA follow-up study. *J Natl Cancer Inst* 90:1278–84

Stern RS, Zierler S, Parrish JA (1980) Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. *Lancet* 1:732–5

Tsai PJ, Shieh HY, Lee WJ *et al.* (2001) Health-risk assessment for workers exposed to polycyclic aromatic hydrocarbons (PAHs) in a carbon black manufacturing industry. *Sci Total Environ* 278:137–50

van der Heijden GJ, Donders AR, Stijnen T *et al.* (2006) Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. *J Clin Epidemiol* 59:1102–9