

# Cancer Risk in a Population-Based Cohort of Patients Hospitalized for Psoriasis in Sweden

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Studies of clinical series of psoriasis patients have suggested an increased risk of nonmelanoma skin cancer and melanoma; the risk of other neoplasms has rarely been studied. In order to assess the incidence of cancer in a nationwide series of psoriasis patients from Sweden, we followed up, for the years 1965–89, 9773 patients with a hospital discharge diagnosis of psoriasis made during 1965–83, who were alive and free from malignancy 1 y after first discharge. We compared their incidence of neoplasms with that of the national population by computing standardized incidence ratios (SIR). We observed a total of 789 neoplasms [SIR 1.37, 95% confidence interval (CI) 1.28, 1.47]. There was an increase in the risk of cancers of the oral cavity and 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), skin (squamous

cell carcinoma, SIR 2.46, 95% CI 1.82, 3.27), female breast (SIR 1.27, 95% CI 1.00, 1.58), vulva (SIR 3.24, 95% CI 1.18, 7.06), penis (SIR 4.66, 95% CI 1.50, 10.9), bladder (SIR 1.43, 95% CI 1.03, 1.92), and kidney (SIR 1.56, 95% CI 1.04, 2.25). The risk of malignant melanoma was decreased (SIR 0.32, 95% CI 0.10, 0.74). Despite some limitations (possible diagnostic misclassification, lack of data on treatment, relatively short follow-up), our study provides evidence against an increased risk of melanoma among patients hospitalized for psoriasis. In addition to nonmelanoma skin and genital cancers, patients hospitalized for psoriasis were at increased risk of several malignancies, in particular those associated with alcohol drinking and tobacco smoking. **Key words:** alcohol drinking/epidemiology/malignant melanoma/psoriasis/skin neoplasms. *J Invest Dermatol* 117:1531–1537, 2001

Psoriasis is a chronic proliferative disease of the skin, with a variable and unpredictable clinical course characterized by exacerbations and remissions. The morphology is highly diverse, but the elemental lesion is an erythematous and squamous lesion characterized by inflammation and hypertrophy of the epithelium (Kerkhof, 1999). The etiology is unknown; a genetic component has been demonstrated, which might involve specific HLA haplotypes and possibly genes encoding for cytokines such as interleukin enhancer binding factor and tumor necrosis factor  $\alpha$ . Environmental exposures have been proposed as cofactors for psoriasis development: the evidence is strong for streptococcal infection in the case of childhood psoriasis, whereas data on tobacco smoking, alcohol drinking, diet, and use of medicaments such as  $\beta$ -blockers and corticosteroids are inconsistent. Psychogenic stress is likely to play a role in the exacerbation of the disease, but the evidence of an etiologic role is inadequate. Exposure to solar radiation reduces the lesions in a large proportion of patients, but a role in primary prevention is not demonstrated (Kerkhof, 1999).

Several agents used in psoriasis treatment are known or suspected carcinogens. Exposure to X-rays is a cause of cancer at many sites (IARC, 2000b). Nonmelanoma skin cancer, including genital

cancer, is caused by exposure to arsenic, coal-tar, and psoralen plus ultraviolet-A (PUVA) (IARC, 1987). Ingestion or inhalation of arsenic and inhalation of coal-tar fumes also cause cancers in other organs (e.g., lung, kidney, urinary bladder); it is unclear whether these effects are also present following dermal exposure. Exposure to UVA and UVB probably increases the risk of nonmelanoma skin cancer (IARC, 1992). Cyclosporin A and possibly methotrexate might also increase the risk of skin cancer (IARC, 1987; Arellano, 1997). A carcinogenic effect of Grenz rays has been suggested, although the risk is likely to be small if therapy recommendations are followed (Lindelöf, 1987). Some retinoid derivatives are suspected teratogens (IARC, 1999).

Studies of series of psoriasis patients have suggested an increased risk of nonmelanoma skin cancer and possibly of malignant melanoma (see for example Stern *et al*, 1997a, 1998; Frentz and Olsen, 1999; and see Lindelöf, 1999, for review). An increased risk of other neoplasms, such as cancers of the esophagus, lung, and kidney, and non-Hodgkin's lymphoma, has sporadically been reported in some of these investigations. The interpretation of the evidence on cancer risk among psoriasis patients is complicated by the small number of patients included in most series, precluding a full evaluation of rare neoplasms. Furthermore, the selection of patients in clinical series might result in the assessment of the effect of special types of therapies used in subsets of patients.

Population-based series of patients may overcome these limitations, as they tend to be large and to represent the experience of an unselected series of patients. Given the lack of detailed information

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on clinical and pathologic aspects of the disease, however, they cannot provide definite answers regarding pathologic pathways. To our knowledge, three such population-based studies have been reported, from Scotland (Alderson and Clarke, 1983), Denmark (Olsen *et al*, 1992; Frenzt and Olsen, 1999), and Finland (Hannuksela-Svahn *et al*, 2000). The first investigation, however, was based on a small number of patients.

We report the results of the follow-up of a large cohort of patients hospitalized for psoriasis in Sweden during 1965–83. We specifically aimed at testing the hypothesis that psoriasis (or its treatment) increases the risk of nonmelanoma skin cancer and of malignant melanoma. In addition, we wanted to assess the risk of other neoplasms in an unselected population of hospitalized psoriasis patients, as well as their mortality pattern.

## MATERIALS AND METHODS

**Materials** Since 1964, the Swedish National Board of Health and Welfare has collected computerized information on individual hospital discharges in the In-patient Register. The coverage of the population has increased steadily: in 1969, the Register covered 60% of the population of the country; by the end of 1983, the percentage was 85%. Each record of the Register includes the unique personal identification number of the patient, the dates of admission and discharge, up to eight discharge diagnoses, and data on hospital departments. The discharge diagnoses were coded using the seventh revision of the International Classification of Diseases (ICD-7) (WHO, 1955) until 1968, and the eighth revision (ICD-8) (WHO, 1965) thereafter.

We considered all records in the In-patient Register with a hospital discharge diagnosis of psoriasis (ICD-7 code 706; ICD-8 code 696) during the period 1965–83, and identified 14,421 such records. We linked this cohort to the nationwide Registers of Total Population, Cause of Death, and Population Migration to identify all patients who lived in Sweden during the study period (1965–89). This resulted in the exclusion of 1466 records with incomplete or incorrect registration numbers that did not correspond to any person. We also obtained the date and cause of death for the deceased patients or the date of emigration for those who emigrated. This linkage resulted in the exclusion of 211 patients who had died during the index admission. The causes of death were coded according to ICD-8 (WHO, 1965) until 1986 and according to the ninth revision (ICD-9) (WHO, 1975) thereafter. We finally linked the cohort to the Swedish Cancer Register, founded in 1958 and estimated to be 98% complete, including squamous cell carcinoma of the skin (Mattsson, 1977; Mattsson and Wallgren, 1984). The linkage with the Swedish Cancer Register covered again the period 1965–89 and aimed at identifying all cases of cancer that occurred among the cohort of psoriasis patients, either before (prevalent cases) or after (incidence cases) the first hospital discharge with a diagnosis of psoriasis. Although we did not assess the completeness and reliability of the linkage between the In-patient Register and the Swedish Cancer Register, a similar exercise conducted on the linkage between the Cancer Register and the 1960 Census revealed a completeness of 98.8% and a reliability of 99.5% (Wiklund and Eklund, 1986). We excluded at this stage 547 patients with a prevalent cancer. A further 241 patients were excluded at various steps of the linkage procedures because of inconsistencies between the dates used for the linkage. Finally, we restricted the cohort to patients with a diagnosis coded as 706.00 or 706.09 in ICD-7, or as 696.1 in ICD-8, thus excluding 1655 patients with psoriasis-related conditions such as parapsoriasis.

We excluded the first year of observation following the index admission in order to reduce selection bias, which could occur if psoriasis patients who develop a cancer or die within 1 y are more likely to be hospitalized than other psoriasis patients, as well as detection bias, which could occur if a cancer is diagnosed during the diagnostic and therapeutic procedures involved in the management of psoriasis. This resulted in the exclusion of 528 patients who developed a cancer, died, or emigrated within 1 y of the index admission. The final cohort of psoriasis patients, with valid data, who were alive and free from cancer 1 y after index admission, comprised 9773 individuals.

**Methods** The observed cancer cases in our analysis represent first cancers diagnosed in the cohort members. They were obtained from the Swedish Cancer Register, which codes malignant neoplasms according to the ICD-7 classification (WHO, 1955). Basal cell carcinomas of the skin are not recorded in the Cancer Register. We calculated the expected number of cancer cases by multiplying the gender-, 5-y-age-group- and

**Table I. Distribution of patients hospitalized for psoriasis and person-years by gender and selected characteristics**

Characteristic	Patients	Person-years
Total	9,773	93,775.6
Gender		
Men	5,306	49,138.3
Women	4,467	44,637.2
Duration of follow-up		
1–4 y	1,234 <sup>a</sup>	27,351.4
5–9 y	2,926 <sup>a</sup>	36,475.9
10–14 y	2,839 <sup>a</sup>	20,646.3
15+ y	2,774	9,302.0
Presence of other diagnoses		
Psoriasis as only diagnosis	5,164	55,512.7
Other diagnoses, psoriasis as primary	1,652	14,755.0
Other diagnoses, psoriasis as secondary	2,957	23,507.9

<sup>a</sup>Number of patients contributing up to each category.

calendar-year-specific incidence rates by the person-year distribution of the cohort. The rates used in the calculation were derived from the entire Swedish population, after excluding cancer cases first detected at autopsy.

All analyses are based on the standardized incidence ratio (SIR), defined as the ratio of the observed to the expected cases of cancer. We calculated the 95% confidence interval (CI) for each SIR on the assumption of a Poisson distribution of the number of observed cases. Similarly, we calculated standardized mortality ratios (SMR) and their 95% CI, using national mortality rates to calculate the expected numbers of deaths.

In separate analyses, person-years of observation were divided according to time elapsed since the index visit. No information was available on the severity or duration of psoriasis, nor on the treatment provided. The information available on other discharge diagnoses at the time of the index admission, however, allowed us to stratify the cohort by whether psoriasis was the only, the primary, or a secondary diagnosis, and by year of index hospitalization. Similarly, the information available on other diseases at the index or subsequent admissions enabled us to separate those psoriasis patients who also suffered from diseases that are possibly associated with psoriasis and that would also increase the risk of cancer such as alcoholism and liver cirrhosis.

## RESULTS

**Table I** provides summary information on the cohort used in the study. The patients in the cohort provided 93,776 person-years of observation (mean duration of follow-up, 10.6 y). Men comprised 54.3% of the cohort and contributed 52.4% of total person-years: they experienced on average a shorter follow-up (10.3 y) than women (11.0 y). The mean year of index admission was 1976 and the mean age at index hospitalization was 50.1; 25% of patients were 35 or younger and another 25% were over 65. There were 3004 patients with age at index hospitalization below 40: they contributed 37,125 person-years of observation.

The number of observed cases of cancer was significantly in excess of the expected number, resulting in an overall SIR of 1.37 (95% CI 1.28, 1.47). The excess risk was present in both genders. The analysis by specific neoplasm revealed a complex picture (**Table II**). A strong excess of mycosis fungoides was observed in men, based on five cases, but not in women. The risk of cancers of the oral cavity and pharynx, esophagus, liver, pancreas, lung, skin (squamous cell carcinoma), bladder, and kidney was significantly increased. A significant increase in risk was found in women for breast cancer and in men for cancer of the genital organs other than the prostate. Finally, an increased risk (SIR > 1.5), which did not reach statistical significance, was found for cancer of the female genital organs other than the uterus and ovary, and for nonlymphocytic leukemia. Skin melanoma was the only neoplasm for which a decreased risk was observed.

The six cases of cancer of the female genital tract were all vulvar cancers (SIR 3.24, 95% CI 1.18, 7.06). The eight cases of cancers of

**Table II. Standardized incidence ratio of selected neoplasms among patients hospitalized for psoriasis<sup>a</sup>**

	Men			Women			Both genders		
	N	SIR	95% CI	N	SIR	95% CI	N	SIR	95% CI
All cancers	444	1.34	1.22, 1.47	345	1.41	1.27, 1.57	789	1.37	1.28-1.47
Oral cavity, pharynx	25	2.60	1.68, 3.84	11	3.37	1.68, 6.04	36	2.80	1.96, 3.87
Oesophagus	13	3.00	1.59, 5.13	4	3.03	0.82, 7.76	17	3.01	1.75, 4.81
Stomach	22	1.07	0.67, 1.62	10	0.99	0.47, 1.82	32	1.04	0.71, 1.47
Colon	26	1.08	0.71, 1.59	26	1.25	0.81, 1.83	52	1.16	0.87, 1.52
Rectum	19	1.10	0.66, 1.71	17	1.62	0.94, 2.60	36	1.29	0.91, 1.79
Liver	18	2.52	1.49, 3.98	11	1.36	0.68, 2.44	29	1.91	1.28, 2.74
Pancreas	14	1.34	0.73, 2.24	14	1.82	0.99, 3.05	28	1.56	1.02, 2.23
Larynx	6	1.55	0.57, 3.37	0	[0.32]	0, 11.5	6	1.43	0.52, 3.12
Lung	65	1.91	1.48, 2.44	25	3.00	1.94, 4.43	90	2.13	1.71, 2.61
Connective tissue	1	0.47	0.01, 2.59	3	1.99	0.40, 5.81	4	1.09	0.29, 2.80
Melanoma	3	0.34	0.07, 1.00	2	0.29	0.03, 1.05	5	0.32	0.10, 0.74
SCC of the skin	35	2.75	1.92, 3.83	13	1.92	1.02, 3.28	48	2.46	1.82, 3.27
Breast	1	1.89	0.02, 10.5	78	1.27	1.00, 1.58	79	1.27	1.01, 1.58
Cervix	–	–	–	11	1.44	0.72, 2.57	11	1.44	0.72, 2.57
Endometrium	–	–	–	15	1.11	0.62, 1.84	15	1.11	0.62, 1.84
Ovary	–	–	–	19	1.38	0.83, 2.16	19	1.38	0.83, 2.16
Female genital organs	–	–	–	6	2.47	0.90, 5.37	6	2.47	0.90, 5.37
Prostate	77	0.96	0.76, 1.21	–	–	–	77	0.96	0.76, 1.21
Male genital organs	8	2.69	1.16, 5.30	–	–	–	8	2.69	1.16, 5.30
Bladder	33	1.37	0.95, 1.93	10	1.62	0.78, 2.98	43	1.43	1.03, 1.92
Kidney, pelvis	13	1.10	0.58, 1.88	15	2.45	1.37, 4.04	28	1.56	1.04, 2.25
Brain	4	0.49	0.13, 1.25	6	0.92	0.34, 2.00	10	0.68	0.33, 1.25
Thyroid	4	2.62	0.71, 6.71	3	1.00	0.20, 2.92	7	1.55	0.62, 3.19
Hodgkin's disease	1	0.58	0.01, 3.24	0	[1.04]	0, 3.53	1	0.36	0.01, 2.02
Non-Hodgkin's lymphoma <sup>b</sup>	15	1.56	0.87, 2.57	7	1.19	0.48, 2.45	22	1.42	0.89, 2.15
Mycosis fungoides	5	26.7	8.60, 62.3	0	[0.07]	0, 51.3	5	19.3	6.22, 45.1
Multiple myeloma	5	0.92	0.30, 2.14	6	1.70	0.62, 3.69	11	1.22	0.61, 2.19
Lymphocytic leukaemia	2	0.44	0.05, 1.58	4	1.89	0.51, 4.84	6	0.90	0.33, 1.96
Non-lymphocytic leukaemia	6	1.74	0.64, 3.79	5	2.18	0.70, 5.09	11	1.92	0.96, 3.43

<sup>a</sup>N, number of observed cases; SIR, standardized incidence ratio; CI, confidence interval; SCC, squamous cell carcinoma. When no cases were observed, expected cases are reported in square brackets.

<sup>b</sup>Excluding mycosis fungoides.

the male genital tract consisted of three cases of testicular cancer (SIR 1.67, 95% CI 0.33, 4.87) and five cases of penile cancer (SIR 4.66, 95% CI 1.50, 10.9). None of the cases was registered as scrotal cancer (0.04 cases expected).

Most kidney cancers were renal cell carcinomas (22 cases, SIR 1.48, 95% CI 0.92, 2.23). There was a nonsignificant increase in the incidence of cancer of the renal pelvis (three cases, SIR 1.59, 95% CI 0.32, 4.65). The SIR of primary liver cancer was 3.19 (95% CI 1.86, 5.11), and that of gallbladder cancer was 0.96 (95% CI 0.35, 2.09).

An increased risk of squamous cell carcinoma of the skin was present in all major anatomical regions (trunk: seven cases, SIR 5.12, 95% CI 2.05, 10.5; upper limbs: five cases, SIR 2.55, 95% CI 0.82, 5.94; lower limbs: 13 cases, SIR 9.15, 95% CI 4.87, 15.7), except for the head and neck (17 cases, SIR 1.33, 95% CI 0.77, 2.13).

The risk of cancer did not vary systematically according to time since index hospitalization: the SIR was 1.42 (95% CI 1.24, 1.61) at 1–4 y, 1.36 (1.21, 1.53) at 5–9 y, 1.33 (1.14, 1.55) at 10–14 y, and 1.36 (1.08, 1.68) at 15 y or more of follow-up. The SIR of mycosis fungoides was 37.9 (three cases) at 1–4 y and 20.3 (two cases) at 5–9 y of follow-up, whereas no cases occurred after 10 y or more (0.08 expected). In addition to mycosis fungoides, we conducted the analysis by time since index admission for those neoplasms with a significant increased risk and at least 20 observed cases (Fig 1). In the case of cancer of the oral cavity/pharynx, pancreas, or skin (squamous cell carcinoma), we found that the risk increased with duration of follow-up: the p-values of the test for linear trend of the SMR were 0.08, 0.23, and 0.03, respectively. No trend with duration of follow-up was apparent for cancers of the liver, lung,

and breast. The increase in risk of kidney cancer was restricted to the first period of follow-up and that of bladder cancer to the second period. The analysis on risk of melanoma by time of index hospitalization was hampered by the small number of cases: a decreased risk, however, was suggested throughout the entire follow-up.

The analysis of patients with age at hospitalization below 40 provided results consistent with those of the overall cohort: these patients experienced 54 cancers (SIR 1.44, 95% CI 1.08, 1.88) and had an increased incidence of squamous cell carcinoma of the skin (eight cases, SIR 15.8, 95% CI 6.82, 31.2) but not of malignant melanoma (two cases, SIR 0.59, 95% CI 0.07, 2.12).

For more than half of the patients included in the study, psoriasis was the only discharge diagnosis at index admission. The risk of cancer in this group was similar (SIR 1.31, 95% CI 1.18, 1.45) to that of patients with several discharge diagnoses including psoriasis as the primary diagnosis (SIR 1.34, 95% CI 1.13, 1.57, p-value of difference 0.9), but lower than that of patients with psoriasis as a secondary diagnosis (SIR 1.49, 95% CI 1.32, 1.68, p-value 0.11). The main primary diagnoses associated with a secondary diagnosis of psoriasis concerned erysipelas (3.9%), eczema (4.3%), other skin diseases (7.8%), rheumatoid arthritis (7.1%), other rheumatic and arthritic diseases (6.7%), in addition to highly prevalent diseases such as diabetes and ischaemic heart disease. The excess of liver cancer was present only among patients with a disease other than psoriasis as primary diagnosis (SIR 2.60, 95% CI 1.38, 4.44). In the case of cancers of the rectum, pancreas, and male genital organs, however, the SIR was highest among patients with psoriasis as the only diagnosis (rectum 1.37, 95% CI 0.81, 2.16; pancreas 1.75, 95% CI 0.98, 2.88; male genital organs 3.40, 95% CI 1.24, 7.39).

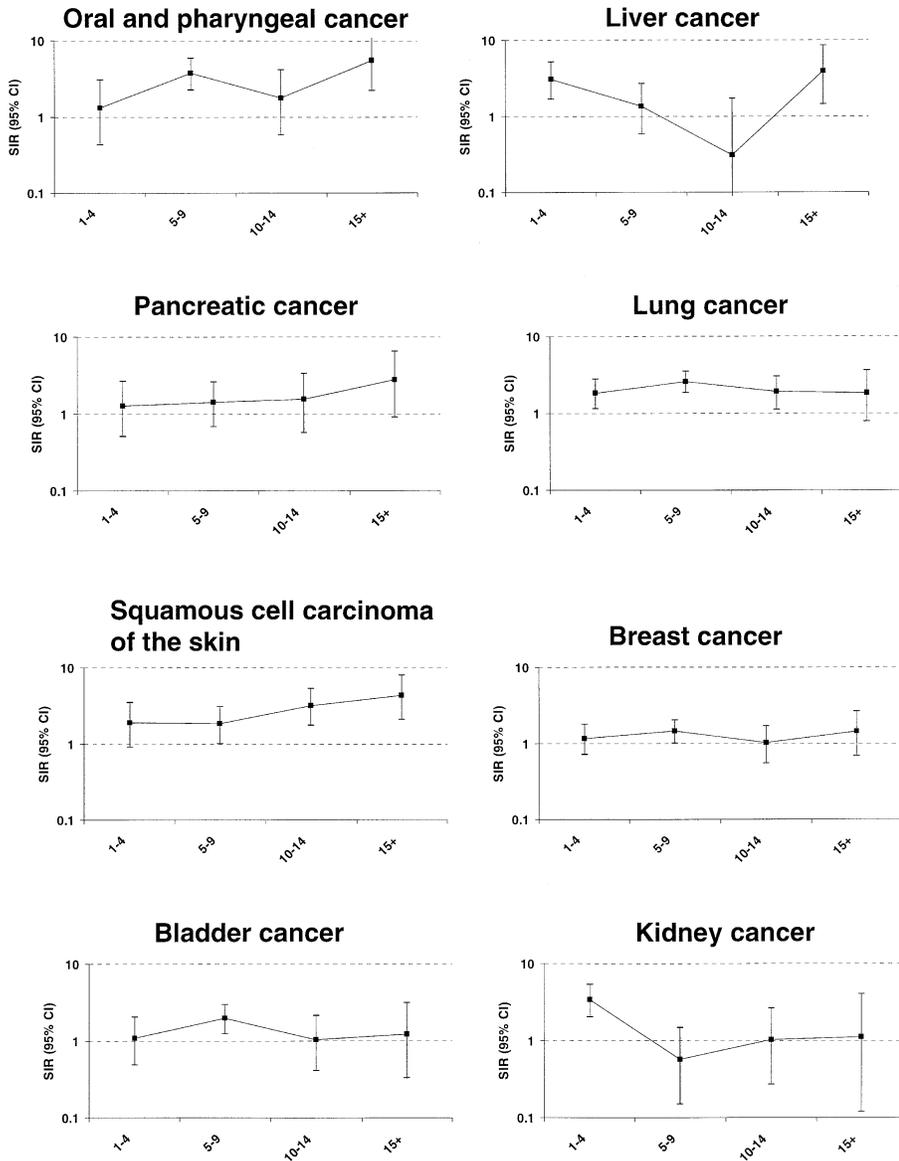


Figure 1. Risk of selected neoplasms among patients hospitalized for psoriasis by duration of follow-up.

Despite some fluctuation that might be attributed to chance, the results for the remaining neoplasms resulted in similar SIR in the three groups of patients with psoriasis as the only, the primary, or a secondary diagnosis (data not shown in detail).

For most neoplasms, there was no difference in the SIR according to whether the index hospitalization occurred before or after 1 January 1976. The only exceptions were kidney cancer, for which the SIR was only elevated during the first period (SIR 2.03, 95% CI 1.26, 3.10), and non-Hodgkin's lymphoma, which showed an opposite pattern (SIR for second period 1.96, 95% CI 1.07, 3.29). The increased incidence of alcohol-related diseases persisted when we excluded patients who also had a hospital discharge diagnosis for alcoholism or liver cirrhosis. In particular, the SIR of oral and pharyngeal cancer was 2.04 (95% CI 1.30–3.03), and that of primary liver cancer was 1.74 (95% CI 1.12–2.56).

The analysis of the mortality experience of patients hospitalized for psoriasis resulted in an overall SMR of 1.94 (95% CI 1.88, 2.00) (Table III). Among the non-neoplastic causes of death, the SMR was increased for infectious diseases, respiratory diseases (in particular pneumonia and chronic obstructive pulmonary disease), cardiovascular diseases (and all the major nosologic entities of this group), neurologic and psychiatric diseases, diabetes, digestive diseases (in particular liver cirrhosis), genitourinary diseases,

musculoskeletal diseases, and external causes (in particular wounds, intoxications, and internal and brain traumas). A strong increase was found in the SMR of non-neoplastic skin diseases. Restriction of the mortality analysis to patients with psoriasis as the only cause of hospitalization confirmed the increased mortality from respiratory diseases, cardiovascular diseases, mental disorders, liver cirrhosis, and external causes, although most increases in the SMR were less pronounced than in the analysis of the entire cohort.

### DISCUSSION

This large, population-based study of cancer occurrence among Swedish patients hospitalized for psoriasis provides no evidence for an increased risk of melanoma. In addition to squamous cell carcinoma of the skin, these patients were at increased risk of several malignancies, in particular those associated with alcohol drinking and tobacco smoking. It is important to stress, however, that these results are not directly applicable to all psoriasis patients, the majority of whom are not hospitalized because of their disease.

Two factors complicate the comparison of our results with previous investigations. The first problem is that most published studies are based on groups of psoriasis patients treated in one or several specialized centers. Although these studies contain import-

**Table III. Standardized mortality ratios for selected non-neoplastic causes among patients hospitalized for psoriasis\***

	Whole cohort			Psoriasis as only diagnosis		
	N	SMR	95% CI	N	SMR	95% CI
All causes	3813	1.94	1.88, 2.00	1392	1.56	1.48, 1.64
Infective diseases	28	2.25	1.49, 3.25	8	1.41	0.61, 2.77
Malignant neoplasms	616	1.48	1.36, 1.60	252	1.30	1.15, 1.47
Respiratory diseases	290	2.16	1.91, 2.42	94	1.58	1.27, 1.93
Pneumonia	169	2.02	1.73, 2.35	61	1.66	1.27, 2.14
Bronchitis	35	2.06	1.43, 2.86	8	1.06	0.46, 2.09
Emphysema	29	3.13	2.09, 4.49	6	1.44	0.53, 3.13
Asthma	24	2.46	1.58, 3.67	6	1.31	0.48, 2.85
Cardiovascular dis.	2066	1.87	1.79, 1.95	715	1.45	1.35, 1.56
Isch. heart dis.	1357	1.97	1.87, 2.08	479	1.55	1.42, 1.70
Cerebrovasc. dis.	334	1.60	1.43, 1.78	123	1.33	1.11, 1.59
Arterial diseases	134	1.83	1.54, 2.17	43	1.34	0.97, 1.80
Diabetes mellitus	88	3.14	2.52, 3.87	24	1.88	1.20, 2.79
Neurological dis.	33	1.77	1.22, 2.49	12	1.35	0.69, 2.35
Mental disorders	66	2.91	2.25, 3.70	33	3.03	2.08, 4.25
Alcoholism	51	7.19	5.35, 9.44	25	6.37	4.12, 9.39
Digestive diseases	246	3.86	3.39, 4.37	98	3.31	2.69, 4.03
Liver cirrhosis	133	8.13	6.81, 9.64	50	6.05	4.49, 7.97
Genito-urinary dis.	74	2.54	2.00, 3.19	20	1.56	0.96, 2.42
Skin/subcut. dis.	20	17.7	10.8, 27.3	4	7.87	2.11, 20.1
Musculoskeletal. dis.	27	3.34	2.20, 4.85	3	0.81	0.16, 2.35
External causes	213	2.29	2.00, 2.62	101	2.08	1.69, 2.53
Trauma to organs	21	7.13	4.42, 10.9	12	7.26	3.75, 12.7
Open wounds	66	2.19	1.69, 2.78	27	1.99	1.31, 2.89
Trauma of CNS	53	2.04	1.53, 2.67	28	1.91	1.27, 2.76
Adverse toxic eff.	39	3.81	2.71, 5.21	15	2.53	1.42, 4.18

\*N, number of observed cases; SMR, standardized mortality ratio; CI, confidence interval; CNS, central nervous system.

ant information on the clinical aspects of the disease and on its treatment, they are likely to reflect the experience of a selected group of patients whose cancer experience might be biased compared to the overall population of patients. Three investigations included a population-based series of psoriasis in-patients: they are from Scotland (Alderson and Clarke, 1983), Denmark (Olsen *et al*, 1992; Frentz and Olsen, 1999), and Finland (Hannuksela-Svahn *et al*, 2000). The second problem is the possibility of publication bias. Given the small size of most previous studies, it is possible that results that did not reach the significance level of 5% were not reported.

Two cohorts of Swedish psoriasis patients that partially overlap with our study population have been studied with respect to cancer risk: Lindelöf and colleagues (Lindelöf *et al*, 1990) studied over 20,000 members of the Swedish Psoriasis Association and found an excess of male breast cancer and of female kidney cancer. The same authors studied a group of nearly 5000 patients treated during 1974–85 with PUVA, 64% of whom for psoriasis, and reported an increased risk of respiratory cancer in both genders and of kidney cancer in women (Lindelöf *et al*, 1991, 1999). In addition, Lindgard (1986) studied 372 cases of psoriasis diagnosed during 1970–79 among the residents of Gothenburg and found an association with lung cancer in women born after 1922. The overlap of these populations with our cohort is unclear. It is likely, however, that the patients included in our study represent more severe cases, as they were all hospitalized and, for about 70% of them, psoriasis was the only or main discharge diagnosis.

Several biases might have operated in our study. Psoriasis patients, in particular those who underwent hospitalization, may have been subject to increased clinical surveillance, resulting in higher detection and diagnosis of neoplasms, compared to the national population. This is plausible in particular for skin neoplasms, and it may have accounted for at least part of the excess of squamous cell carcinoma of the skin, including cancer of the external genitals. It is less plausible, however, that this bias is

implicated in the increase in occurrence of cancers of other organs, in particular those with a severe clinical course.

A second possible bias concerns diagnostic misclassification between psoriasis and other dermatologic conditions. An erroneous diagnosis of psoriasis would result, on the one hand, in a false positive association if the misclassified condition were either a neoplasm (or a preneoplastic lesion) itself or a disease causally associated with cancer. Misdiagnosis of psoriasis as a disorder not associated with increased cancer risk, on the other hand, would reduce the strength of any association between psoriasis and cancer. The very strong increase in risk of mycosis fungoides in men can probably be explained by such bias. On the one hand, cases of this skin lymphoma, in particular in the initial stages, can be diagnosed as psoriasis (Elmer and George, 1999); on the other hand, large-plaque parapsoriasis is a lesion closely related to mycosis fungoides and, despite the fact that we excluded patients with a discharge diagnosis coded as parapsoriasis, it is possible that misclassification with psoriasis occurred. Other diseases that can be misdiagnosed as psoriasis, e.g., seborrheic dermatitis and other chronic dermatites, are not known to be associated with mycosis fungoides, lymphoma, or cancer. We did not validate the diagnoses obtained from the Inpatient Register.

Furthermore, the increased risk of all neoplasms might be due to a bias arising from the linkage of records from different registers. In a similar study of patients hospitalized for scleroderma, however, those with systemic sclerosis had an increased incidence of cancer, whereas the risk of cancer among patients with localized scleroderma was not different from that of the general population, arguing against such "registration" or "linkage" bias (Rosenthal *et al*, 1995).

For neoplasms for which bias can be excluded, explanations for the observed associations include a carcinogenic effect of treatment, and a role of cancer risk factors also associated with psoriasis. Given the known or suspected carcinogenicity of several agents used in psoriasis control, the lack of information on the treatment

experienced by the individual patients in the cohort is a major limitation of our study. Another important limitation is the lack of information on type of psoriasis and on the age at onset of the disease, including age at first hospitalization (as index hospitalization in our study might not correspond to first hospitalization, in particular among older patients).

The cohort of psoriasis patients experienced an increased risk of several neoplasms, resulting in an overall increase in cancer risk. Although each increase might have a different explanation (see detailed discussion below), one unifying hypothesis might be found in the increasing turnover of psoriatic cells, which might reflect a general alteration in cell proliferation and cell cycle control mechanisms. The increase in overall cancer incidence parallels the results of a similar study of psoriasis patients from Denmark (Frentz and Olsen, 1999) and might reflect, in addition to a systemic carcinogenic effect of treatment, a general proneness of psoriasis patients to carcinogenesis, possibly linked to increased cell proliferation beyond the epidermis. In addition, statistically significant results can be generated when many comparisons are performed, as in our study.

In particular, an increased risk of nonmelanoma skin cancer has been reported in many series of psoriasis patients (Alderson and Clarke, 1983; Stern *et al*, 1984, 1998; Tanew *et al*, 1986; Henseler *et al*, 1987; Forman *et al*, 1989; Lindelöf *et al*, 1991; Chuang *et al*, 1992; Hannuksela *et al*, 1996; McKennan *et al*, 1996; Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000). The association is attributed to the carcinogenic effect of PUVA (IARC, 1987). The interpretation of the data is complicated, however, by the fact that most patients treated with PUVA or similar regimens have also been treated with other drugs, including known or suspected skin carcinogens such as arsenic, coal-tar, cyclosporine A, and methotrexate. The available evidence is not consistent as to whether PUVA alone increases the risk of nonmelanoma skin cancer, as shown for example in a large prospective study from the U.S.A. (Stern *et al*, 1984, 1998), or whether only patients with exposure to skin carcinogens prior to treatment are at increased risk, as shown in a similar study from Europe (Forman *et al*, 1989). A recent meta-analysis, however, provided evidence of an increase in the incidence of nonmelanoma skin cancer following high-dose PUVA (Stern and Lunder, 1998). Among the other drugs used in psoriasis treatment, methotrexate *per se* does not seem to increase the risk of skin cancer (Stern *et al*, 1982; Nyfors and Jensen, 1983; Hannuksela-Svahn *et al*, 2000), whereas an effect of cyclosporine has been suggested (Arellano, 1997; Paquet and Pierard, 1998). If the association between psoriasis treatment and increased incidence of nonmelanoma skin cancer is well established, the magnitude of the excess might be difficult to establish because of possible surveillance bias (e.g., more complete reporting of cases of skin cancer among psoriasis patients compared to the general population).

Our result of a relative risk on the order of 2.5 for squamous cell carcinoma of the skin is in agreement with that of the population-based studies from Denmark and Finland (Olsen *et al*, 1992; Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000), whereas studies of selected groups of PUVA-treated patients resulted in higher risk estimates: relative risks of 18 in the U.S.A. and 4–6 in Sweden (Stern *et al*, 1998; Lindelöf *et al*, 1999). The lack of excess of nonmelanoma skin cancer in the cohort of members of the Swedish Psoriasis Association (Lindelöf *et al*, 1990) can be explained by the milder form of the disease experienced by many of these members, resulting in lower exposure to PUVA and other carcinogens. Arsenic was used in Sweden until the 1960s for severe forms of the disease and might be responsible for part of the excess. The excess of squamous cell carcinoma of the skin was greatest on the trunk and the lower limbs, as was also found in the study from Denmark (Frentz and Olsen, 1999). In addition, we detected a large excess risk of cancers of the penis and vulva, which would be worth investigating in other populations of psoriasis patients.

We found a decreased risk of malignant melanoma, which is unlikely to be due to artefact. Most previous studies reported no

increased risk of melanoma among psoriasis or PUVA-treated patients (Elwood *et al*, 1986; Olsen *et al*, 1992; Hannuksela *et al*, 1996; Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000). One notable exception is the latest follow-up of the multicenter cohort of American psoriasis patients treated with PUVA, which revealed an increased risk after 15 y of follow-up (Gupta *et al*, 1988; Stern *et al*, 1997a). In our study, no excess was found even 15 y or more after first hospital discharge (one observed and 2.2 expected cases). Although it is established that solar radiation increases the risk of malignant melanoma, intermittent exposure seems to play a bigger role than cumulative exposure (IARC, 1992; Armstrong and English, 1996). The evidence that exposure to artificial UV light increases the risk of melanoma is not conclusive (IARC, 1992). Our study offers no support to the hypothesis that PUVA (or other treatment for psoriasis), as experienced by patients hospitalized for this condition in Sweden, increases the risk of melanoma after a long latency period. Possible explanations of the apparent discrepancy of results on melanoma in studies of psoriasis patients from the U.S.A. and Northern Europe are as follows: (i) a role of background melanoma rate, which in men is higher in the U.S.A. than in Denmark, Finland, or Sweden; (ii) differences in frequency and modality of PUVA treatment; (iii) occurrence of psoriasis-linked melanoma before first hospitalization for psoriasis itself. The lack of an increase in risk of melanoma among patients with index hospitalization before age 40, however, speaks against the hypothesis of an elevated incidence of this neoplasm before hospitalization for psoriasis.

Apart from mycosis fungoides, the overall risk of non-Hodgkin's lymphoma was not increased in our cohort. There was an increased risk among patients with the first visit after 1975, however, which might reflect the effect of immunosuppressive drugs used in recent decades for the management of psoriasis. An increased risk of non-Hodgkin's lymphoma has been reported in cohorts of Finnish patients (Hannuksela *et al*, 1996; Hannuksela-Svahn *et al*, 2000), as well as in groups of psoriasis patients treated with cyclosporine A (Arellano, 1997). Further surveillance of the risk of lymphoma in our cohort is warranted.

We have detected an increased risk of breast cancer among the patients in our study. Although the magnitude of the excess is modest, it is consistently found throughout the follow-up. A similar modest increase in risk has been reported among PUVA-treated patients from the U.S.A. (Stern *et al*, 1997b), but not among psoriasis patients from Denmark or Finland (Frentz and Olsen, 1999; Hannuksela-Svahn *et al*, 2000). In a previous study of Swedish members of the Psoriasis Association, breast cancer risk was increased among men but not among women. Stern *et al* (1997b) evoked surveillance bias as a possible explanation for their findings (in their study, the excess risk was strongest in the first period of follow-up). This is not a likely explanation for our findings, as the risk is elevated 15 y or more after the first visit for psoriasis. In the American study, PUVA dose was not associated with breast cancer risk (Stern *et al*, 1997b). Other carcinogens used in the past for psoriasis treatment, like arsenic and tar, are not known to be active on the breast. A possible explanation of our findings is the therapeutic use of X-rays and radium (IARC, 2000b).

In addition to agents used for psoriasis treatment, lifestyle factors – in particular alcohol drinking and tobacco smoking – might have acted as confounders in our study. There is evidence of an increased risk of psoriasis among heavy smokers and drinkers (Kvali *et al*, 1985; Monk and Neil, 1986; Poikolainen *et al*, 1990; Naldi *et al*, 1992). In a survey from Gothenburg, there was an increased prevalence of alcoholism and liver cirrhosis, but not of chronic respiratory diseases, among psoriasis patients compared to the general population (Lindgard, 1986). Our cohort experienced a large increase in the risk of neoplasms known to be associated with alcohol drinking and tobacco smoking [cancers of the oral cavity, esophagus, liver, pancreas, lung, kidney (tobacco only), and breast (alcohol only)]. We have no information on the smoking and drinking habits of the patients in our study. The analysis of non-

neoplastic causes of death (**Table III**), however, reinforces the suspicion that alcohol drinking and tobacco smoking were highly prevalent among the patients included in our study.

The systematic analysis of mortality represents an original aspect of our investigation. The striking increase in mortality above expectation based on national mortality figures can be attributed, at least in part, to increased exposure to alcohol and tobacco. It is likely, however, that aggressive treatment given for psoriasis increased the risk of dying from chronic diseases other than cancer, such as cardiovascular diseases.

Despite several important limitations (possible diagnostic misclassification, lack of data on treatment, relatively short follow-up, possible false positive results resulting from multiple comparisons), our study has provided no evidence for an increased risk of melanoma among patients hospitalized for psoriasis. Our study has not confirmed previous reports of an increase in non-Hodgkin's lymphomas other than mycosis fungoides. Furthermore, our study has provided indirect (albeit strong) evidence that consumption of alcohol and tobacco is increased among patients with severe psoriasis. Future studies on cancer risk among psoriasis patients should include the strengths of this investigation (large study population, completed follow-up, population-based dimension), together with detailed and valid information on the clinical aspects of the disease, the treatment experienced by these patients, and their lifestyle habits.

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