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Psoriasis and Risk of Incident Cancer: An Inception Cohort Study with a Nested Case–Control Analysis

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Psoriasis has been associated with lymphohematopoietic and solid cancers; however, reports have been inconsistent. Cancer incidence was compared between psoriasis and psoriasis-free patients, and the roles of psoriasis duration and treatment were explored in this observational study using the UK General Practice Research Database. Among 67,761 patients, 1,703 patients had incident cancer; of whom 54% had a history of psoriasis. Incidence rate ratios for lymphohematopoietic and pancreatic cancers were 1.81 (95% confidence interval (CI) 1.35–2.42) and 2.20 (95% CI 1.18–4.09), respectively. In a nested case–control analysis, adjusted odds ratios (ORs) for cancer overall were 1.50 (95% CI 1.30–1.74) for psoriasis of $\geqslant$4 years duration and 1.53 (95% CI 0.97–2.43) for patients receiving systemic treatment (marker of disease severity). Lymphohematopoietic malignancy risk was highest in patients with systemic treatment. The OR for patients without systemic treatment was 1.59 (95% CI 1.01–2.50) for psoriasis of $<$2 years and 2.12 (95% CI 1.45–3.10) for that of $\geqslant$2 years duration. Risks of bladder/kidney and colorectal cancers were increased with longer-duration psoriasis. Psoriasis patients may have an increased overall risk of incident cancer (mainly lymphohematopoietic and pancreatic). Longer-term psoriasis and more severe disease may increase the risk of some cancers. These observations need further confirmation, particularly because of the potential of findings by chance in observational studies with subgroup analyses.

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INTRODUCTION

Psoriasis is a chronic, inflammatory disease with an estimated prevalence of 1 to 3% in the general population (Stern *et al.*, 2004; Gelfand *et al.*, 2005a, b); its impact on the quality of life is considerable (Langley *et al.*, 2005). The disease is characterized by T-cell-mediated hyperproliferation of keratinocytes and inflammatory processes based on a complex genetic background. T cells and various other immune cells infiltrate the skin and activate each other and keratinocytes through cytokines, which appear to play a central role in the pathogenesis of psoriasis. This process leads to an increased proliferation of keratinocytes, as well as to the production of other cytokines and growth factors, thereby sustaining the inflammatory process (Sabat *et al.*, 2007).

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Abbreviations: BMI, body mass index; CI, confidence interval; CTCL, cutaneous T-cell lymphoma; GP, general practitioner; GPRD, General Practice Research Database; IR, incidence rate; IRR, incidence rate ratio; OR, odds ratio; PUVA, psoralen and ultraviolet A

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A derailed immune response is believed to be involved in the pathogenesis of psoriasis-associated comorbidities. Psoriasis has classically been associated with high physical and psychological morbidity. A better understanding of the underlying immunopathogenesis and intensified epidemiological research suggests that psoriasis is linked to additional comorbid conditions, such as psoriatic arthritis, Crohn's disease, atherosclerosis, myocardial infarction, and metabolic syndrome (Gulliver, 2008). The incidence of some cancers, in particular lymphoma, has been reported to be increased in patients with psoriasis. This is, in part, because of the use of immune-suppressive and potentially carcinogenic treatments, such as ciclosporin, methotrexate, and psoralen and ultraviolet A (PUVA) therapy (Kimball *et al.*, 2008).

Many published studies on the prevalence of cancer in patients with psoriasis have been hospital based or conducted in patients undergoing PUVA treatment, and results have been inconsistent or difficult to interpret (Stern and Lange, 1988; Lindelof *et al.*, 1990; Olsen *et al.*, 1992; Bhate *et al.*, 1993; Stern and Vakeva, 1997; Frentz and Olsen, 1999; Hannuksela-Svahn *et al.*, 1999, 2000; Boffetta *et al.*, 2001).

Among the population-based studies reported to date, two studies conducted using the General Practice Research Database (GPRD) focused on the risk of lymphoma (Gelfand *et al.*, 2003, 2006) and one, using an American claims records database (Margolis *et al.*, 2001), evaluated the risk of all cancers combined, but did not stratify the results by type of cancer.

The aim of this population-based, observational study was to further elucidate the association between psoriasis and the risk of developing cancer, and to provide baseline incidence rates (IRs) of different types of cancer in patients followed up for a maximum of 11 years after the diagnosis of psoriasis. The effect of disease duration and treatment received was also evaluated.

RESULTS

The study population consisted of 73,404 patients, including 36,702 with psoriasis (16,969 (46.2%) men and 19,733 (53.8%) women) and 36,702 matched psoriasis-free patients. Approximately 55% of the patients were below the age of 50 years at the time of psoriasis diagnosis. Compared with those in the comparison group, psoriasis patients were more likely to be current smokers (23.9 *vs* 18.8% for psoriasis and nonpsoriasis patients, respectively) and overweight (body mass index (BMI) 25–29.9 $kg\,m^{-2}$ in 22.7 *vs* 21.6% and BMI $\geqslant 30\,kg\,m^{-2}$ in 13.3 *vs* 10.6%, respectively). The average follow-up time was 4.6 years.

Incidence rates of cancer in the person-time analysis

After excluding patients with a history of cancer or HIV, the remaining study population consisted of 67,761 patients, including 33,760 with psoriasis (46.9% men and 53.1% women) and 34,001 psoriasis-free patients (46.8% men and 53.2% women). Within this population, we identified 1,703 patients with an incident cancer diagnosis. The IR was 5.83 (95% confidence interval (CI) 5.47–6.22) per 1,000 person-years in patients with psoriasis, and 5.18 (95% CI 4.83–5.55) per 1,000 person-years in patients without psoriasis. Among the 1,703 cancer cases, 927 (54%) had a history of psoriasis and 776 (46%) did not, resulting in a crude incidence rate ratio (IRR) of 1.13 (95% CI 1.02–1.24) for all cancers combined. IRs and IRRs for the different cancers are shown in Tables 1 and 2, respectively. Overall, the risk of developing lymphohematopoietic malignancies and cancers of the digestive tract (in particular, pancreatic cancer) was statistically significantly increased in patients with psoriasis, although this was not the case for other types of cancer (Table 2). Lymphohematopoietic malignancies included leukemia (including other myeloproliferative disorders) and lymphoma. All eight patients with cutaneous T-cell lymphoma (CTCL) had psoriasis; therefore, the IRRs for lymphohematopoietic cancers and lymphomas excluding CTCL were also calculated.

Nested case–control analysis—overall cancer risk

We included all 1,703 incident cancer cases and 6,812 matched controls without cancer in the nested case–control analysis; patient characteristics are summarized in Table 3. The psoriasis patients in the nested case–control analysis received the following treatments: emollients 36%, salicylic acid 1.0%, calcipotriol 36%, coal tar 33%, dithranol 4.9%, tazarotene 0.6%, topical corticosteroids 72%, methotrexate 1.6%, ciclosporin 0.2%, acitretin 0.2%, azathioprine 0.2%, hydroxyurea 0.1%, and UV therapy 0.2%. The adjusted odds ratio (OR) of developing cancer for patients with psoriasis was slightly over 1, relative to patients without psoriasis; this increased with duration of psoriasis (OR of 1.50 (95% CI 1.30–1.74) in patients with $\geqslant 4$ years psoriasis duration), mainly among patients $\geqslant 60$ years of age (Table 4 and Figure 1). A possible link with severity of psoriasis, using treatment as a proxy, was observed: OR was 1.53 (95% CI 0.97–2.43) for all patients receiving oral treatment and 2.48 (95% CI 1.08–5.72) for male patients receiving high-intensity oral treatment (Table 4). In total, 96 patients received oral psoriasis treatment, 72% of whom received methotrexate. In patients who did not receive oral treatment, the adjusted OR was 1.31 (95% CI 1.16–1.48) for psoriasis patients with $\geqslant 2$ years disease duration. The cancer risk also increased for patients with longer-term psoriasis duration in sensitivity analyses, (1) excluding all patients with a prescription for ciclosporin or methotrexate at any time and irrespective of indication, and (2) adjusting the main models for any use of ciclosporin and methotrexate. In a further analysis, including only case patients who developed cancer $\geqslant 6$ months after the start of follow-up ($n = 1{,}539$), an OR of 1.44 (95% CI 1.28–1.63) was observed for patients with psoriasis of $\geqslant 2$ years duration, compared with that in the psoriasis-free comparison group. Among those who had no benign neoplasms before the index date (372 cases and 1072 controls), OR was 1.30 (95% CI 1.13–1.49) for patients with psoriasis of $\geqslant 2$ years duration, compared with the psoriasis-free reference group.

Nested case–control analysis—stratified by type of cancer

Figure 1 shows the risks of different cancer types in patients with psoriasis in relation to duration of psoriasis and compared with psoriasis-free patients. The overall relative risk of developing a lymphohematopoietic malignancy was increased by about twofold for patients with psoriasis compared with that in the psoriasis-free control group. The risk was highest in patients who received oral treatment, resulting in an OR of 10.17 (95% CI 3.24–31.94) for any treatment and 16.79 (95% CI 3.23–87.22) for those with >2 prescriptions. An analysis restricted to patients without oral treatment yielded adjusted ORs of 1.59 (95% CI 1.01–2.50) for patients with psoriasis of <2 years duration and 2.12 (95% CI 1.45–3.10) for those with psoriasis of $\geqslant 2$ years duration. Stratification by age yielded increased overall risks for both age groups (OR 2.77 (95% CI 1.39–5.52) for patients aged <60 years and OR 1.84 (95% CI 1.24–2.73) for those aged $\geqslant 60$ years). When the risks of developing lymphoma (excluding CTCL) or leukemia were explored separately, the highest OR was 3.22 (95% CI 1.64–6.35) for leukemia in patients with psoriasis of $\geqslant 4$ years duration. The relative risk was increased for lymphoma in patients already with early psoriasis (Figure 1), particularly among patients <60 years of age (data not shown). In an analysis in which we excluded all patients who received any oral treatment, we still found an increased lymphoma risk overall in patients with $\geqslant 2$ years psoriasis duration (OR 1.67, 95% CI 1.05–2.66 and OR 1.86, 95% CI 1.10–3.14, respectively).

All eight patients with CTCL had a history of psoriasis, compared with only 34% of the 32 controls. Excluding the

Table 1. Cancer incidence rates stratified by cancer type in patients with or without psoriasis

	Non-psoriasis			Psoriasis		
	Cases	IR/1,000 py[1]	95% CI	Cases	IR/1,000 py[1]	95% CI
All cancer	776	5.18	4.83–5.55	927	5.83	5.47–6.22
Lymphohematopoietic malignancies	62	0.41	0.32–0.53	119	0.75	0.63–0.90
Lymphohematopoietic malignancies (excluding CTCL)	62	0.41	0.32–0.53	111	0.70	0.58–0.84
CTCL	0	NA	NA	8	0.05	0.03–0.10
Lymphoma overall	36	0.24	0.17–0.33	67	0.42	0.33–0.54
Lymphoma (excluding CTCL)	36	0.24	0.17–0.33	59	0.37	0.29–0.48
Leukemia/MD	26	0.17	0.12–0.25	52	0.33	0.25–0.43
Lung	101	0.67	0.55–0.82	85	0.53	0.43–0.66
Melanoma	33	0.22	0.16–0.31	29	0.18	0.13–0.26
Breast	139	1.71	1.45–2.02	153	1.79	1.53–2.10
Prostate	95	1.38	1.13–1.69	85	1.16	0.93–1.43
Digestive organs	107	0.71	0.59–0.86	159	1.00	0.86–1.17
Pancreas	12	0.08	0.05–0.14	28	0.18	0.12–0.25
Esophagus	16	0.11	0.07–0.17	23	0.14	0.10–0.22
Colorectal	55	0.37	0.28–0.48	79	0.50	0.40–0.62
Others	24	0.16	0.11–0.24	29	0.18	0.13–0.26
Female genital organs	35	0.43	0.31–0.60	51	0.60	0.45–0.79
Bladder/kidney	43	0.29	0.21–0.39	57	0.36	0.28–0.46
Brain	16	0.11	0.07–0.17	22	0.14	0.09–0.21
Other cancers[2]	97	0.65	0.53–0.79	126	0.79	0.67–0.94
Metastasis	48	0.32	0.24–0.42	41	0.26	0.19–0.35

CI, confidence interval; CTCL, cutaneous T-cell lymphoma; IR, incidence rate; MD, other myeloproliferative disorders; NA, not applicable; py, person-years.
[1]Person times in non-psoriasis patients: overall, 149,900.2 py; men, 68,843.7 py; women, 81,056.6 py; <60 years, 104,108.4 py; ⩾60 years, 45,791.9 py. In psoriasis patients: overall, 158,906.0 py, men 73,553.5 py; women, 85,352.5 py; <60 years, 111,945.2 py; ⩾60 years, 46,960.8 py.
[2]Other cancers: oral cavity, bone, male genital organs, parathyroid carcinoma, thymoma, and unspecified.

patients with CTCL from the analysis of developing lymphohematopoietic malignancies in patients with psoriasis yielded lower but still statistically significantly increased ORs overall, as well as for the various strata, by oral treatment, by duration in patients without oral treatment, and by age (data not shown).

For cancers of the colon/rectum, pancreas, and bladder/kidney, the risk increased with duration of psoriasis (see test for trend in Figure 1). Furthermore, an analysis restricted to patients with a normal BMI yielded an OR of 6.10 (95% CI 1.27–29.32) for pancreatic cancer in psoriasis patients, compared with that in psoriasis-free patients. The relative risk of melanoma tended to decrease in patients with psoriasis of longer duration (Figure 1). A tendency toward an increased risk of brain cancer was observed in male patients with a psoriasis duration of ⩾2 years (OR 3.38; 95% CI 0.92–12.45), although the number of cases of brain cancer was low overall (data not shown).

DISCUSSION

The findings of this large population-based study suggest that patients with psoriasis seem to be at an increased risk of developing certain cancers, especially patients with long psoriasis duration and possibly severe disease. Findings to date have been inconsistent, however, and, with the exception of evidence that is strongly suggestive of an increased incidence of lymphoma in this population (Gelfand *et al.*, 2003, 2006), no clear links between specific cancers and psoriasis have been identified. Some studies in which the overall cancer risk was not stratified by duration or severity of psoriasis reported an increased risk (Olsen *et al.*, 1992; Frentz and Olsen, 1999; Hannuksela-Svahn *et al.*, 2000; Boffetta *et al.*, 2001), but not all (Lindelof *et al.*, 1990; Bhate *et al.*, 1993; Gelfand *et al.*, 2003). The findings of the present population-based study, based on a follow-up of a large group of patients, provide evidence of an association between psoriasis and specific cancers, which increases with disease duration.

There is a suggestion in our data that the overall risk of developing cancer (excluding nonmelanoma skin cancers) is slightly increased in patients with psoriasis compared with that in psoriasis-free patients. Furthermore, patients with long-duration psoriasis seemed to be at an increased risk for colorectal, bladder, and kidney cancers, as well as for pancreatic and lymphohematopoietic cancers. Patients receiving oral treatment, which can be considered as a proxy

Table 2. Incidence rate ratios (IRRs) of cancer, stratified by type, sex, and age (reference group: patients without psoriasis)

	Overall		Men		Women		<60 years		⩾60 years	
Type	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
All cancer	1.13	(1.02–1.24)	1.11	(0.97–1.28)	1.14	(1.00–1.30)	1.19	(0.99–1.43)	1.13	(1.02–1.27)
Lympho-hematopoietic malignancies	1.81	(1.35–2.42)	2.45	(1.67–3.59)	1.24	(0.79–1.94)	2.17	(1.25–3.78)	1.74	(1.24–2.45)
Excluding CTCL	1.69	(1.25–2.27)	2.23	(1.50–3.31)	1.21	(0.77–1.90)	1.98	(1.12–3.52)	1.64	(1.16–2.32)
Lymphoma overall	1.76	(1.19–2.58)	2.15	(1.27–3.63)	1.40	(0.79–2.48)	2.38	(1.19–4.75)	1.59	(1.00–2.53)
Lymphoma (excluding CTCL)	1.55	(1.03–2.31)	1.76	(1.01–3.08)	1.35	(0.76–2.41)	2.07	(1.00–4.28)	1.41	(0.87–2.28)
Leukemia/ MD	1.89	(1.21–2.94)	2.88	(1.65–5.05)	1.02	(0.49–2.11)	1.86	(0.74–4.69)	1.95	(1.18–3.23)
Lung	0.79	(0.60–1.06)	0.80	(0.56–1.13)	0.78	(0.48–1.29)	0.74	(0.35–1.58)	0.83	(0.61–1.13)
Melanoma	0.83	(0.50–1.36)	0.73	(0.36–1.46)	0.95	(0.46–1.94)	0.83	(0.43–1.60)	0.84	(0.39–1.80)
Breast	1.04	(0.83–1.31)	NA	NA	1.04	(0.83–1.31)	0.98	(0.68–1.40)	1.11	(0.82–1.49)
Prostate	0.84	(0.63–1.12)	0.84	(0.63–1.12)	NA	NA	0.76	(0.32–1.83)	0.88	(0.65–1.20)
Digestive organs	1.40	(1.10–1.78)	1.25	(0.91–1.71)	1.64	(1.14–2.38)	1.80	(1.00–3.25)	1.38	(1.06–1.79)
Pancreas	2.20	(1.18–4.09)	2.43	(0.97–6.13)	2.03	(0.88–4.69)	NA	NA	2.11	(1.12–3.99)
Esophagus	1.36	(0.72–2.54)	1.40	(0.64–3.08)	1.27	(0.44–3.61)	2.48	(0.76–8.09)	1.13	(0.54–2.36)
Colorectal	1.35	(0.97–1.90)	1.30	(0.82–2.05)	1.42	(0.86–2.36)	1.21	(0.53–2.74)	1.43	(0.99–2.07)
Others	1.14	(0.67–1.95)	0.80	(0.42–1.52)	2.85	(1.07–7.59)	2.79	(0.70–11.17)	1.02	(0.57–1.83)
Female genital organs	1.38	(0.91–2.11)	NA	NA	1.38	(0.91–2.11)	1.93	(1.04–3.59)	1.06	(0.60–1.90)
Bladder/ kidney	1.25	(0.84–1.85)	1.11	(0.70–1.76)	1.71	(0.81–3.59)	0.78	(0.24–2.53)	1.37	(0.90–2.08)
Brain	1.30	(0.69–2.45)	1.74	(0.72–4.18)	0.95	(0.38–2.39)	1.70	(0.66–4.41)	1.07	(0.46–2.52)
Other cancers[1]	1.23	(0.94–1.59)	1.14	(0.77–1.67)	1.31	(0.91–1.88)	1.06	(0.68–1.67)	1.35	(0.98–1.87)
Metastasis	0.81	(0.53–1.22)	1.25	(0.64–2.42)	0.60	(0.35–1.03)	1.49	(0.50–4.42)	0.75	(0.48–1.17)

CI, confidence interval; CTCL, cutaneous T-cell lymphoma; IRR, incidence rate ratio; MD, other myeloproliferative disorders; NA, not applicable.
[1]Other cancers: oral cavity, bone, male genital organs, parathyroid carcinoma, thymoma, and unspecified.

for disease severity, were also at an increased risk of developing cancer, with the greatest effect observed in men receiving high-intensity treatment.

Other studies have reported that patients with psoriasis are at an increased risk of developing leukemia (Lindegard, 1986; Cooper *et al.*, 1996; Soderberg *et al.*, 2006) and other myeloproliferative disorders, in particular lymphoma (Hannuksela-Svahn *et al.*, 1999, 2000; Tavani *et al.*, 2000; Margolis *et al.*, 2001; Gelfand *et al.*, 2003, 2006; Zhang *et al.*, 2004; Mellemkjaer *et al.*, 2008). In this study, the increased risk was most prominent in male patients (as observed by Margolis *et al.*, 2001) and, in the case of lymphoma, in patients with psoriasis of shorter duration. The ORs for the various stratifications were statistically significantly increased when all lymphomas and lymphoma excluding CTCL were considered, but the ORs were slightly lower for the latter. This separate analysis allowed for the possibility of misclassification of psoriasis and CTCL. Furthermore, lymphoma risk was also increased in patients not receiving any oral psoriasis treatment, which suggests that patients who may receive biologicals also have an increased lymphoma risk. One explanation for the increase in these cancers may be the antigen-driven proliferation of lymphocytes in chronic inflammation caused by psoriasis (antigenic stimulation hypothesis) (Soderberg *et al.*, 2006).

Earlier studies have identified associations between psoriasis and a range of cancers, including those of the lung (Lindegard, 1986; Olsen *et al.*, 1992; Frentz and Olsen, 1999; Hannuksela-Svahn *et al.*, 2000; Boffetta *et al.*, 2001), liver (Boffetta *et al.*, 2001), oropharynx (Olsen *et al.*, 1992; Frentz and Olsen, 1999; Hannuksela-Svahn *et al.*, 2000; Boffetta *et al.*, 2001), colon (Stern and Lange, 1988; Olsen *et al.*, 1992; Frentz and Olsen, 1999), kidney (Lindelof *et al.*, 1990; Olsen *et al.*, 1992; Hannuksela-Svahn *et al.*, 1999; Boffetta *et al.*, 2001), breast (Stern and Lange, 1988; Lindelof *et al.*, 1990; Stern and Vakeva, 1997; Boffetta *et al.*, 2001), central nervous system (Stern and Lange, 1988; Stern and Vakeva, 1997), pancreas (Boffetta *et al.*, 2001), genital organs (Boffetta *et al.*, 2001), and thyroid (Stern and Vakeva, 1997). The results of the various studies were conflicting, possibly because of differences in study designs. With the exception of pancreatic and lymphohematopoietic cancers, we did not find an increased risk for these cancers in the overall psoriasis population. In the case of smoking-related cancers, this may be, at least in part, because of the fact that we adjusted for smoking, whereas a similar adjustment was not undertaken in earlier studies. For lung cancer, we found an increased risk neither before nor after adjustment for smoking. Our study population was rather young (more than half of all patients were below the age of 50 years at the time of start of follow-

Table 3. Characteristics of cancer cases and controls in the nested case–control analysis

Characteristics	No. of cases (%) (*n*=1,703)	No. of controls (%) (*n*=6,812)	OR adjusted[1] (95% CI)
Sex[2]			
Male	828 (48.6)	3312 (48.6)	—
Female	875 (51.4)	3500 (51.4)	—
Age group[2]			
<30 years	34 (2.0)	137 (2.0)	—
30–59 years	418 (24.5)	1687 (24.8)	—
⩾60 years	1251 (73.5)	4988 (73.2)	—
Smoking			
Non-smoker	726 (42.6)	3232 (47.4)	Reference
Current smoker	396 (23.3)	1361 (20.0)	1.31 (1.14–1.51)
Ex-smoker	418 (24.5)	1498 (22.0)	1.26 (1.10–1.45)
Unknown	163 (9.6)	721 (10.6)	1.07 (0.85–1.35)
BMI			
12–18.4 kg m^{-2}	46 (2.7)	95 (1.4)	1.71 (1.18–2.48)
18.5–24.9 kg m^{-2}	548 (32.2)	2092 (30.7)	Reference
25–29.9 kg m^{-2}	496 (29.1)	2173 (31.9)	0.87 (0.76–1.00)
30–60 kg m^{-2}	313 (18.4)	1149 (16.9)	1.05 (0.89–1.23)
Unknown	300 (17.6)	1303 (19.1)	0.89 (0.75–1.07)
Benign cancer	372 (21.8)	1072 (15.7)	1.53 (1.34–1.76)

BMI, body mass index; CI, confidence interval; OR, odds ratio.
[1]Adjusted for all covariates listed in the table.
[2]Matching variable.

up), and the mean follow-up was 4.6 years. This may explain why we did not find an increased lung cancer risk in psoriasis patients, as the lung cancer risk increases with advanced age and with duration of smoking history. The risk of cancers of the colon/rectum, pancreas, bladder, and kidney significantly increased in patients with psoriasis of long duration. As chronic inflammation influences initiation and progression of neoplastic growth (Krishnamoorthy and Honn, 2006), it is conceivable that the chronic inflammation sustained with psoriasis of longer duration may play a role in the development of cancer in patients with severe psoriasis. Similar to psoriasis, lupus erythematodes and rheumatoid arthritis are also chronic inflammatory diseases, and they have also been associated with certain types of cancer (Parikh-Patel *et al.*, 2008; Smitten *et al.*, 2008).

In this study, there was a tendency for an increase in risk of cancer with increasing disease severity. Other studies have also shown an association between the severity of psoriasis and increased cancer. In a study conducted using the Medicaid databases (Margolis *et al.*, 2001), patients with severe psoriasis had an increased cancer risk of 78% compared with that in the reference group of hypertensive patients. As patients with severe psoriasis may receive drugs, such as methotrexate, ciclosporin, or PUVA therapy, all of which have been associated with lymphoproliferative disorders (Koo *et al.*, 1992; Cliff *et al.*, 1999; Stern, 2006; Suzuki *et al.*, 2007) and malignancies (particularly nonmelanoma skin cancers) (Stern and Laird, 1994; Paquet and Pierard, 1998; Paul *et al.*, 2003; Shear, 2006), we conducted a number of sensitivity analyses in which patients with these treatments were excluded. A longer-term history of psoriasis (⩾2 years) remained associated with an increased relative cancer risk in this subset of patients, indicating that this effect was independent of the treatment received.

Our study has several limitations. First, in large observational studies, a certain degree of diagnosis misclassification cannot be ruled out. However, in earlier GPRD-based studies on psoriasis or cancer, the validity of these diagnoses has been high (Jick *et al.*, 1997; Gelfand *et al.*, 2003, 2005a, b). The epidemiology of psoriasis in the GPRD is similar to that in other population-based studies in the United Kingdom, 92% of patients with a psoriasis code received psoriasis treatment, and of a random sample of GPs, about 90% confirmed the psoriasis diagnosis after 4 years of follow-up. Furthermore, the IR of psoriasis in our study population (not shown) is closely similar to the rate of another study on GPRD with validated psoriasis patients (Huerta *et al.*, 2007). In contrast to the United States of America, most psoriasis patients in the United Kingdom are diagnosed and managed in primary care and are not referred to a specialist (Huerta *et al.*, 2007; Menter and Griffiths, 2007). Second, the initial recording of a psoriasis diagnosis by the general practitioner

Table 4. Relative cancer risk stratified by age, sex, and duration and severity of psoriasis in the nested case–control analysis

	Cases (%) (*n*=1,703)	Controls (%) (*n*=6,812)	OR adjusted[1] (95% CI)
No psoriasis	776 (45.6)	3394 (49.8)	Reference
Psoriasis	927 (54.4)	3418 (50.2)	1.13 (1.02–1.26)
Short-term disease (<2 years)	334 (19.6)	1517 (22.3)	0.91 (0.79–1.05)
Female	168 (9.9)	802 (11.8)	0.84 (0.69–1.03)
Male	166 (9.7)	715 (10.5)	0.98 (0.80–1.20)
<60 years	112 (6.6)	387 (5.7)	1.29 (0.99–1.68)
⩾60 years	222 (13.0)	1130 (16.6)	0.79 (0.66–0.93)
Long-term disease (⩾2 years)	593 (34.8)	1901 (27.9)	1.31 (1.17–1.48)
Female	309 (18.1)	991 (14.5)	1.29 (1.09–1.53)
Male	284 (16.7)	910 (13.4)	1.33 (1.13–1.58)
<60 years	142 (8.3)	533 (7.8)	1.14 (0.90–1.45)
⩾60 years	451 (26.5)	1368 (20.1)	1.37 (1.19–1.57)
Untreated psoriasis	48 (2.8)	245 (3.6)	0.81 (0.59–1.12)
Female	24 (1.4)	139 (2.0)	0.70 (0.45–1.09)
Male	24 (1.4)	106 (1.6)	0.95 (0.60–1.51)
Topical treatment	853 (50.1)	3103 (45.6)	1.15 (1.03–1.28)
Female	440 (25.8)	1613 (23.7)	1.12 (0.97–1.30)
Male	413 (24.3)	1490 (21.9)	1.18 (1.02–1.38)
Oral treatment (+/– topical)	26 (1.5)	70 (1.0)	1.53 (0.97–2.43)
High intensity	16 (0.9)	43 (0.6)	1.56 (0.87–2.80)
Female	13 (0.8)	41 (0.6)	1.25 (0.66–2.36)
High intensity	7 (0.4)	26 (0.4)	1.06 (0.45–2.46)
Male	13 (0.8)	29 (0.4)	1.99 (1.02–3.91)
High intensity	9 (0.5)	17 (0.2)	2.48 (1.08–5.72)
<60 years	7 (0.4)	21 (0.3)	1.56 (0.64–3.82)
⩾60 years	19 (1.1)	49 (0.7)	1.47 (0.85–2.54)

CI, confidence interval; OR, odds ratio.
[1]Adjusted for body mass index, smoking, and benign cancers.

(GP) is not the date of onset of the disease, but rather the point in time when the disease was brought to medical attention for the first time. Follow-up was started at the first recorded psoriasis diagnosis to increase the likelihood of beginning follow-up for all patients who are at a similar stage of the disease. Third, the number of psoriasis patients exposed to oral therapies was low in our study population, and therefore information on this subgroup, which may have the greatest disease severity, is limited. It is possible that some patients may have received oral or injectable treatment from a specialist, which was not recorded by the GP; such misclassification, if indeed present, may have diluted differences in risk caused by disease severity. Fourth, although we tested for a large number of potential confounding factors, we cannot exclude the possibility that unknown confounders or biases may have affected our results. Fifth, in observational research, we cannot exclude the potential of findings by chance because of the various subgroup analyses. The increased risk for certain types of solid cancers, mainly in patients with longer-term psoriasis, may be linked to chronic inflammation with various cytokines that are involved in the pathogenesis of psoriasis, but the findings need further confirmation in order to exclude findings by chance (type-α errors).

On the other hand, this study has an important strength: it reports the findings of a follow-up of a large population of people with psoriasis whose medical information was recorded before cancer diagnosis, thereby eliminating concerns regarding biased reporting of date of psoriasis diagnosis, treatments, and other potential confounders.

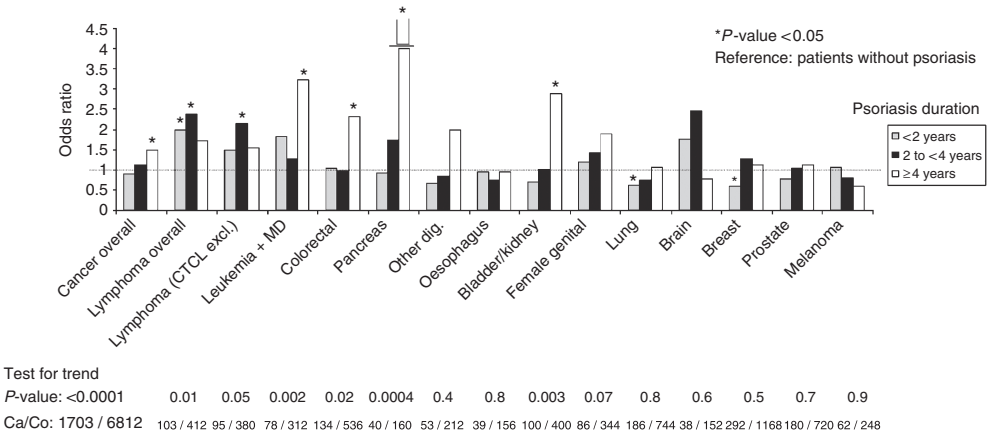

Figure 1. Psoriasis duration and risk of cancer by specific cancer type. Ca/Co, number of cases and controls on which the results are based; CTCL, cutaneous T-cell lymphoma; MD, other myeloproliferative disorders. Odds ratios are adjusted for age, sex, and calendar time, by matching, and for smoking, body mass index, presence of benign cancer (all cancers), presence of gastro-oesophageal reflux disease (digestive organ cancers), use of proton-pump inhibitors (digestive organ cancers), presence of chronic obstructive pulmonary disease (lung cancer), and for the use of estrogens, progestagens, or oral contraceptives (breast cancer).

In conclusion, this observational study conducted on a large population-based data resource explored the association between early psoriasis and the risk of incident cancers. Patients with psoriasis had an increased risk of developing lymphohematopoietic or certain types of solid cancers. The risk of solid cancers was increased primarily in psoriasis patients with a longer-term disease history. Further investigation into common mechanisms underlying psoriasis and the cancers identified in this study is warranted.

MATERIALS AND METHODS

This observational study with a nested case–control analysis was conducted to quantify the risk of various cancer types in patients with early psoriasis and to compare results with a matched population without psoriasis.

Data source

We used data from the GPRD, a large UK-based database established in 1987, which includes approximately five million patients who are actively enrolled with selected GPs. These GPs provide data for research purposes; they have been trained to record medical information in a standard manner and to supply it anonymously. Patients enrolled in the GPRD are representative of the UK population with regard to age, sex, geographical distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (for example, age, sex, height, weight, and smoking status), symptoms, medical diagnoses, referrals to consultants, hospitalizations, and all drug prescriptions, as the doctors generate prescriptions directly using the computer, by means of a coded drug dictionary. This database has been the source for numerous epidemiological studies (including those of psoriasis) published in peer-reviewed journals, and has been described in detail (Garcia Rodriguez and Perez Gutthann, 1998; Wood and Martinez, 2004) and validated extensively (Jick *et al.*, 2003).

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare products Regulatory Agency (MHRA) database research.

Study population

We included all patients with a first-time diagnosis of psoriasis between 1 January 1994 and 31 December 2005, along with a comparison group of the same number of patients without psoriasis. Patients in the control group were matched to the psoriasis patients on the basis of calendar time (follow-up for the matched patient started at the same date as for the psoriasis patient, that is, at the date of psoriasis diagnosis), age (same year of birth), sex, general practice, and years of history in the GPRD. Patients with <3 years of history in the database before first-time psoriasis diagnosis (or the corresponding date in the comparison group) were excluded. The validity of psoriasis diagnoses in the GPRD has been documented to be high (Gelfand *et al.*, 2003, 2005a, b), and as a result, all patients with a recorded psoriasis diagnosis were included in the analyses, as in earlier GPRD-based studies on psoriasis (Brauchli *et al.*, 2008a, b, c).

Follow-up and identification of incident cancer cases

We excluded patients if they had a history of cancer (malignant or *in situ*; except nonmelanoma skin cancer) or human immunodeficiency virus before psoriasis diagnosis or the corresponding date in the comparison group, and followed up all patients until one of the following events: a first-time diagnosis of cancer (malignant or *in situ*, other than nonmelanoma skin cancer); death; end of follow-up in the medical record; or end of the follow-up period. The date of cancer diagnosis will be referred to as the index date hereafter. We validated all potential patients with a recorded code for incident cancer using both a computer-based algorithm and a manual computer profile review. We included patients if they received cancer treatment (chemotherapy, endocrine therapy, or radiotherapy), were referred to a specialist, were hospitalized, underwent surgery, and/or died within 180 days after diagnosis. We excluded patients if they did not fulfill these criteria or if there was evidence that the cancer may have been preexisting rather than being newly diagnosed.

Nested case–control analysis

Each patient with cancer was matched with four control patients chosen at random from the study population based on age (same

year of birth), sex, and calendar time (same index date, that is, the date on which the patient was first diagnosed with cancer).

We compared the prevalence of diagnosed psoriasis before the index date between patients with cancer (overall and stratified by type) and matched controls. Psoriasis patients were classified by duration of disease (<2 years, $\geqslant 2$ years or <2 years, 2–<4 years, or $\geqslant 4$ years) and treatment (no treatment, topical treatment alone (emollients, salicylic acid, calcipotriol, coal tar, dithranol or tazarotene preparations, or corticosteroids), and/or oral treatment (azathioprine, ciclosporin, methotrexate, acitretin, hydroxyurea, mycophenolate mofetil, or UV/PUVA therapy)). Patients who received treatment were further classified by treatment intensity, defined as $\leqslant 4$ or >4 prescriptions per year for topical treatment, and $\leqslant 2$ or >2 prescriptions per year for oral treatment.

Statistical analysis

In the follow-up analysis, we assessed person-years for all patients in the study population from the date of first psoriasis diagnosis (or the corresponding date in the comparison group) until a patient developed an outcome of interest or died, or the follow-up in the medical record ended. We assessed crude IRs of a first-time cancer diagnosis (overall and stratified by cancer type) in patients with or without psoriasis, stratified by age and sex; crude IRRs were calculated with 95% CI.

In the nested case–control analysis, we carried out conditional logistic regression analyses using SAS (version 9.1; SAS Institute, Cary, NC) to calculate relative risk estimates as ORs with 95% CI. These analyses were controlled for the potential confounders of age, sex, and calendar time by matching, and were further adjusted for smoking status (none, current, past, or unknown) and BMI (<18.5, 18.5–24.9, 25.0–29.9, $\geqslant 30\,kg\,m^{-2}$, or unknown) in the multivariate model, as well as for the presence of benign cancer diagnoses before the index date. In addition, the analysis of digestive organ cancers was adjusted for gastroesophageal reflux disease and use of proton-pump inhibitors (none, 1–9, or $\geqslant 10$ prescriptions), the analysis of lung cancer was adjusted for chronic obstructive pulmonary disease, and the analysis of breast cancer was adjusted for the use of estrogens, progestagens, or oral contraceptives (none, 1–9, or $\geqslant 10$ prescriptions). The presence of other potential confounding covariates (including alcoholism) not included in the final model, because they were not materially associated with exposure or outcome, was also investigated. A test for trend was carried out in the conditional regression analysis to investigate the influence of psoriasis duration on the risk of the different types of cancer.

We did not carry out any sample size calculation because our main focus was on a high-quality analysis by, for example, excluding psoriasis patients with less than 3 years of active history before the psoriasis diagnosis date, by excluding patients with a history of cancer before psoriasis diagnosis, and by calculating cancer IRs only in patients with a first-time psoriasis diagnosis. Hence, we took all the information we could get within this large database.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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