The Risk of Lymphoma in Patients with Psoriasis

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Psoriasis is a common, chronic, inflammatory disease. Psoriasis has been hypothesized to be associated with an increased risk of lymphoma due to its pathophysiology, its treatments, or a combination of these factors. We performed a large population-based cohort study of the risk of lymphoma in psoriasis patients using the General Practice Research Database. We identified 153,197 patients with psoriasis and 765,950 corresponding subjects without psoriasis. Psoriasis patients who received a systemic treatment consistent with extensive disease were classified as severe ($N = 3,994$) and those who did not receive systemic therapies were classified as mild ($N = 149,203$). The analyses were adjusted for age, gender, and person–time using a Cox proportional hazards model. For mild and severe psoriasis patients, the respective adjusted relative risks for lymphoma and its subtypes were as follows: all lymphoma 1.34 (1.16, 1.54) and 1.59 (0.88, 2.89); non-Hodgkin's lymphoma 1.15 (0.97, 1.37) and 0.73 (0.28, 1.96); Hodgkin's lymphoma (HL) 1.42 (1.00, 2.02) and 3.18 (1.01, 9.97); cutaneous T-cell lymphoma (TCL) 4.10 (2.70, 6.23) and 10.75 (3.89, 29.76). Psoriasis is associated with an increased risk of lymphoma. The association is strongest for HL and CTCL. The excess risk of lymphoma attributed to psoriasis was 7.9/100,000 psoriasis patients per year. Although patients with psoriasis have an increased relative risk of lymphoma, the absolute risk attributable to psoriasis is low given that lymphoma is a rare disease and the magnitude of association is modest.

INTRODUCTION

Psoriasis is a common, chronic disease that affects approximately 2–3% of the adult population (Gelfand et al., 2005c). The extent of body surface area (BSA) affected by psoriasis is variable, ranging from limited (i.e., <2% body surface area) disease in approximately 80–85% of patients, to more extensive skin involvement in approximately 15–20% of patients (Gelfand et al., 2004, 2005b; Stern et al., 2004). Psoriasis has serious impacts on health-related quality of life, even in patients with limited body surface area involvement (Rapp et al., 1999; Gelfand et al., 2004). The pathophysiology of psoriasis involves an abnormal immune response characterized by increased activity of T cells, antigen-presenting (e.g., dendritic) cells, and Th-1 cytokines (Krueger and Bowcock, 2005). Other investigators have also demonstrated increased B lymphocyte activity in patients with psoriasis, which suggests broad immune activation (Muller et al., 1991; Jeffes et al., 1995; Mahmoud et al., 1999).

The immunologic nature of psoriasis has raised concern that its pathophysiology may be associated with an increased risk of lymphoma, as has been demonstrated previously for other Th-1 mediated diseases such as rheumatoid arthritis (Gridley et al., 1993; Ekstrom et al., 2003). Additionally, patients with extensive psoriasis may be treated with systemic therapies such as cyclosporine and methotrexate, which have been associated with the development of lymphoma in psoriasis patients treated with these medications (Koo et al., 1992; Kamel et al., 1996, 1997; Cliff et al., 1999; Mahe et al., 2003; Lelievre et al., 2005). Patients with psoriasis are increasingly treated with biologic therapies that target T cells (e.g., efazilumab, alefacept) or cytokines such as tumor necrosis factor-α (infliximab, etanercept, adalimumab). There is theoretical concern that biologic therapies may also increase the risk of lymphoma given their mechanism of action. Large, long-term observational studies of biologics therapies in psoriasis patients are not yet published. Epidemiologic studies in rheumatoid arthritis patients have found increased rates of lymphoma in patients treated with tumor necrosis factor inhibitors (Wolfe and Michaud, 2004; Geborek et al., 2005); however, it is unclear if this risk is due to the severity of rheumatoid arthritis or the tumor necrosis factor inhibition treatment (e.g., confounding by indication).

Lymphomas are divided into two broad categories, non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma (HL). The majority of lymphomas (88%) are NHL with the remaining 12% being HL (Fisher and Fisher, 2004). Studying the risk of lymphoma in psoriasis patients is challenging because lymphoma is statistically rare, and therefore large

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sample sizes need to be studied to yield robust findings. Although lymphoma is rare, it is of clinical and public health importance given that NHL is the fifth most common cause of cancer in the US, affecting 19/100,000 individuals per year (an incidence similar to melanoma) (Bierman *et al.*, 2004). The incidence of NHL has increased approximately 3–4% per year since 1973 and the current overall five year survival is only 53%. Approximately 85% of NHL is B cell in origin (Bierman *et al.*, 2004). Cutaneous T-cell lymphoma (CTCL) is the most common form of T-cell lymphoma, affecting approximately 0.5–1.0/100,000 individuals per year (Willemze *et al.*, 1997; Weinstock and Gardstein, 1999; Kim *et al.*, 2005). CTCL is of special interest given that it is a T-cell lymphoma of the skin, and therefore may be related to the pathophysiology of psoriasis.

There have been multiple previous studies of the risk of lymphoma in psoriasis patients from both the United States and Europe (Lindelof *et al.*, 1990; Doody *et al.*, 1992; Bhate *et al.*, 1993; Hannuksela *et al.*, 1996; Stern and Vakeva, 1997; Frentz and Olsen, 1999; Hannuksela-Svahn *et al.*, 1999, 2000; Tavani *et al.*, 2000; Boffetta *et al.*, 2001; Margolis *et al.*, 2001; Gelfand *et al.*, 2003; Morales *et al.*, 2003; Zhang *et al.*, 2004; Becker *et al.*, 2005). These studies have varied in their design,

sample size, population, and outcome (e.g., all lymphoma, NHL, HL, and CTCL) studied. Many of these studies did not report the relative risk of various forms of lymphoma, tended to concentrate on highly selected populations of patients with psoriasis such as those hospitalized for their disease or those treated with psoralen, and were not population-based. The results of these studies have been conflicting, and therefore additional studies are necessary to clarify this association, especially since patients with psoriasis are increasingly being treated on a long-term basis with systemic therapies that selectively target the immune system (i.e., biologics). The purpose of this investigation was to perform a broadly representative, population-based cohort study of the risk of all lymphoma, NHL, HL, and CTCL in patients with psoriasis.

RESULTS

We identified 153,197 patients with psoriasis and 765,950 corresponding subjects without psoriasis (Table 1). Psoriasis patients were older than control patients, and mild psoriasis patients were slightly more likely to be females. In unadjusted analyses, both mild and severe psoriasis patients were more likely to have a history of lymphoma at the time the study was initiated. Among psoriasis patients, 2.6% were classified as

Table 1. Description of study groups

Variable	Control	Mild psoriasis	Severe psoriasis
N (%)	765,950	149,203	3,994
Gender			
Male	366,238 (48%)	70,742 (47.4%)	1,937 (48.5%)
Female	399,712 (52%)	78,461 (52.6%)	2,057 (51.5%)
Odds ratio (95% CI)	—	0.98 (0.97, 1.00)	1.03 (0.97, 1.09)
		P=0.0045	*P*=0.3912
Age			
Mean (median, 25th, 75th percentile)	35.76 (33, 18, 53)	41.51 (40, 26, 57)	48.51 (48, 35, 62)
		P<0.001	*P*<0.001
History of lymphoma			
Yes	538 (0.07%)	179 (0.12%)	11 (0.28%)
No	765,412 (99.93%)	149,024 (99.88%)	3,983 (99.72%)
Odds ratio (95% CI)	—	1.71 (1.44, 2.03)	3.93 (1.95, 7.09)
		P<0.0001	*P*=0.0002
Systemic therapies (N (%))			
Methotrexate	—	—	2,314 (57.94%)
Psoralen/phototherapy	—	—	681 (17.05%)
Azathioprine	—	—	659 (16.50%)
Ciclosporine	—	—	414 (10.37%)
Etretinate or acitretin	—	—	351 (8.79%)
Hydroxyurea	—	—	224 (5.61%)
Mycophenolate mofetil	—	—	12 (0.30%)

CI, confidence interval.
Odds ratios and *P*-values refer to the comparison of the mild and severe psoriasis groups with the control group. Percentages for systemic therapies do not add to 100 because patients could have received more than one systemic therapy.

severe based on having received a systemic treatment for psoriasis. The frequency of use of oral therapies for psoriasis was similar to that reported in other population-based studies from the UK (Nevitt and Hutchinson, 1996). The majority of patients classified with severe psoriasis received methotrexate (58%). Documentation of psoralen and phototherapy use was low (17% of patients with severe disease) and may underrepresent the true use of these agents, as they are restricted to dermatologists and their use may not be well captured electronically by the general practitioner.

Psoriasis patients had an increased hazard ratio (HR) (i.e., risk) of lymphoma (Table 2) that persisted when adjusting for age and gender (HR 1.35, 95% CI 1.17, 1.55). The adjusted risk of lymphoma was elevated in mild (HR 1.34, 95% CI 1.16, 1.54) and severe psoriasis (HR 1.59, 95% CI 0.88, 2.89) patients; however, the association did not achieve conventional levels of statistical significance in the severe group. The risk of all lymphoma was slightly greater in our sensitivity analysis, which was restricted to subjects with at least 6 months of follow-up time and who did not have a history of lymphoma or a lymphoma in the first 6 months of observation.

The primary analysis for NHL (Table 3, excluding CTCL) found a small increased risk that was not statistically significant for all psoriasis patients (HR 1.14, 95% CI 0.96, 1.35) and for mild patients (HR 1.15, 95% CI 0.97, 1.37). There was no increased risk in the severe group (HR 0.73,

95% CI 0.28, 1.96). Sensitivity analyses slightly increased the degree of association leading to statistical significance in all psoriasis patients (HR 1.26, 95% CI 1.04, 1.52) and mild psoriasis patients (HR 1.27, 95% CI 1.05, 1.54), but not in severe psoriasis patients (HR 0.96, 0.36, 2.57).

The adjusted risk of HL (Table 4) was increased in all psoriasis patients (HR 1.48, 1.05, 2.08). The risk of HL was also increased in both the mild (HR 1.42, CI 1.00 2.02) and severe psoriasis (HR 3.18, 95% CI 1.01, 9.97) groups. In sensitivity analyses, the risk of Hodgkin's remained elevated but with borderline statistical significance in all psoriasis patients (HR 1.54, 95% CI 0.99, 2.40) and in patients with mild psoriasis (HR 1.53, 95% CI 0.98, 2.40); however, it was no longer statistically significant in the severe group (HR 1.79, 95% CI 0.25, 12.90).

The strongest association of lymphoma with psoriasis occurred for CTCL (Table 5). The adjusted risk of CTCL in all psoriasis patients was 4.34 (95% CI 2.89, 6.52). The adjusted risk of CTCL was substantially increased in both mild psoriasis (HR 4.10, 95% CI 2.70, 6.23) and severe psoriasis (HR 10.75, 95% CI 3.89, 29.76). Sensitivity analyses found a greater magnitude of association between CTCL and the psoriasis groups.

In all of the models described above, Poisson models resulted in very similar estimates for all of the observed effects. Additionally, tests for effect modification with respect to age and gender for all models in all psoriasis patients were nonsignificant.

Table 2. Incidence and relative risk (hazard) of lymphoma in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.18, 9.13)	4.50 (3.80, 1.64, 7.09)	5.77 (5.53, 2.70, 8.96)	4.54 (3.84, 1.67, 7.16)
Person years (N)	4,297,296	671,914	23,048	694,962
New lymphoma (N)	970	237	11	248
Incidence per 10,000 person years (95% CI)	2.26 (2.12, 2.40)	3.53 (3.09, 4.01)	4.77 (2.38, 8.54)	3.57 (3.14, 4.04)
Primary analysis				
Unadjusted hazard ratio	—	1.54 (1.33, 1.77)	2.12 (1.17, 3.85)	1.56 (1.35, 1.79)
		$P < 0.001$	$P = 0.013$	$P < 0.001$
Adjusted hazard ratio[1]	—	1.34 (1.16, 1.54)	1.59 (0.88, 2.89)	1.35 (1.17, 1.55)
		$P < 0.001$	$P = 0.124$	$P < 0.001$
Attributable risk (excess number of lymphoma cases related to psoriasis)	—	—	—	7.9/100,000 per year
Sensitivity analysis[2]				
New lymphoma (N)	711	183	9	192
Unadjusted hazard ratio	—	1.71 (1.45, 2.01)	2.37 (1.23, 4.57)	1.73 (1.48, 2.03)
		$P < 0.001$	$P = 0.010$	$P < 0.001$
Adjusted hazard ratio[1]	—	1.48 (1.25, 1.74)	1.78 (0.92, 3.44)	1.49 (1.27, 1.75)
		$P < 0.001$	$P = 0.085$	$P < 0.001$

CI, confidence interval.
[1]Adjusted for gender, age.
[2]Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first six months.

Table 3. Incidence and relative risk (hazard) of NHL in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.18, 9.13)	4.51 (3.81, 1.65, 7.09)	5.77 (5.53, 2.70, 8.96)	4.54 (3.84, 1.67, 7.16)
Person years (N)	4,298,107	672,168	23,061	695,230
New NHL (N)	759	159	4	163
Incidence per 10,000 person years (95% CI)	1.77 (1.64, 1.90)	2.37 (2.01, 2.76)	1.73 (0.47, 4.44)	2.35 (2.00, 2.73)
Primary analysis				
Unadjusted hazard ratio	—	1.33 (1.12, 1.58)	0.99 (0.37, 2.63)	1.32 (1.11, 1.56)
		$P=0.001$	$P=0.980$	$P=0.001$
Adjusted hazard ratio[1]	—	1.15 (0.97, 1.37)	0.73 (0.28, 1.96)	1.14 (0.96, 1.35)
		$P=0.103$	$P=0.539$	$P=0.134$
Sensitivity analysis[2]				
New NHL (N)	581	128	4	132
Unadjusted hazard ratio	—	1.47 (1.21, 1.78)	1.29 (0.48, 3.45)	1.47 (1.21, 1.77)
		$P<0.001$	$P=0.612$	$P<0.001$
Adjusted hazard ratio[1]	—	1.27 (1.05, 1.54)	0.96 (0.36, 2.57)	1.26 (1.04, 1.52)
		$P=0.015$	$P=0.939$	$P=0.018$

CI, confidence interval; NHL, non-Hodgkin's lymphoma.
[1]Adjusted for gender, age.
[2]Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first six months.

Table 4. Incidence and relative risk (hazard) of HL in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.19, 9.13)	4.51 (3.81, 1.65, 7.10)	5.77 (5.52, 2.70, 8.96)	4.54 (3.85, 1.67, 7.16)
Person years (N)	4,299,128	672,418	23,063	695,482
New Hodgkin's lymphoma (N)	160	39	3	42
Incidence per 10,000 person years (95% CI)	0.37 (0.32, 0.44)	0.58 (0.41, 0.79)	1.30 (0.27, 3.80)	0.60 (0.44, 0.82)
Primary analysis				
Unadjusted hazard ratio	—	1.48 (1.04, 2.10)	3.50 (1.12 10.96)	1.54 (1.10, 2.17)
		$P=0.029$	$P=0.032$	$P=0.012$
Adjusted hazard ratio[1]	—	1.42 (1.00, 2.02)	3.18 (1.01, 9.97)	1.48 (1.05, 2.08)
		$P=0.052$	$P=0.048$	$P=0.025$
Attributable risk (excess number of lymphoma cases related to psoriasis)				1.8/100,000 per year
Sensitivity analysis[2]				
New HL (N)	98	24	1	25
Unadjusted hazard ratio	—	1.58 (1.01, 2.47)	1.91 (0.27, 13.68)	1.59 (1.03, 2.47)
		$P=0.045$	$P=0.521$	$P=0.038$
Adjusted hazard ratio[1]	—	1.53 (0.98, 2.40)	1.79 (0.25, 12.90)	1.54 (0.99, 2.40)
		$P=0.063$	$P=0.561$	$P=0.055$

HL, Hodgkin's lymphoma; CTCL, cutaneous T-cell lymphoma.
[1]Adjusted for gender, age.
[2]Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first 6 months.

Table 5. Incidence and relative risk (hazard) of cutaneous T-cell lymphoma in psoriasis patients compared to controls

Variable	Control	Mild psoriasis	Severe psoriasis	All psoriasis
Mean follow-up time (median, 25th, 75th percentile)	5.61 (5.25, 2.19, 9.13)	4.51 (3.81, 1.65, 7.10)	5.77 (5.53, 2.70, 8.96)	4.54 (3.85, 1.67, 7.16)
Person years (N)	4,299,563	672,383	23,054	695,437
New CTCL (N)	51	39	4	43
Incidence per 10,000 person years (95% CI)	0.12 (0.09, 0.16)	0.58 (0.41, 0.79)	1.74 (0.47, 4.44)	0.62 (0.45, 0.83)
Primary analysis				
Unadjusted hazard ratio	—	4.78 (3.15, 7.27) $P<0.001$	14.60 (5.28, 40.40) $P<0.001$	5.08 (3.38, 7.64) $P<0.001$
Adjusted hazard ratio[1]	—	4.10 (2.70, 6.23) $P<0.001$	10.75 (3.89, 29.76) $P<0.001$	4.34 (2.89, 6.52) $P<0.001$
Attributable risk (excess number of lymphoma cases related to psoriasis)				4.0/100,000 per year
Sensitivity analysis[2]				
New CTCL (N)	32	31	4	35
Unadjusted hazard ratio	—	6.37 (3.88, 10.46) $P<0.001$	23.21 (8.21, 65.62) $P<0.001$	6.89 (4.26, 11.15) $P<0.001$
Adjusted hazard ratio[1]	—	5.42 (3.30, 8.89) $P<0.001$	17.18 (6.07, 48.58) $P<0.001$	5.84 (3.61, 9.44) $P<0.001$

CI, confidence interval; CTCL, cutaneous T-cell lymphoma.
[1]Adjusted for gender, age.
[2]Restricted to subjects with at least 6 months of follow-up time who did not have a history of lymphoma or a lymphoma in the first 6 months.

DISCUSSION

To our knowledge, this is the largest study to date to determine the risk of lymphoma in patients with psoriasis. Particular strengths of this study, in addition to its size, include its broadly representative nature and its population-based design, which helps minimize selection and information bias. We have also conducted detailed analyses of subtypes of lymphoma, and conducted sensitivity analyses to determine if the results were robust to different analytical approaches.

The risk of all lymphoma was increased in all psoriasis patients and mild psoriasis patients. The risk of all lymphoma was increased slightly in patients with severe psoriasis, but the finding was not statistically significant. The magnitude of association of all lymphoma in the current study is lower than in our previous study, in which we examined only patients who were 65 years of age or older in the General Practice Research Database (GPRD) from 1988 to 1996 (HR 2.94, 95% CI 1.82, 4.74) (Gelfand et al., 2003). The relative risk of lymphoma in psoriasis patients was similar across age groups in the current study, suggesting that the discrepancy may be due to statistical variability (the current study had approximately 70 times more person time in the psoriasis group than our previous study). Interestingly, a case–control study suggested that older psoriasis patients may have a higher relative risk of lymphoma than younger psoriasis patients

(Tavani et al., 2000); however, the relationships among age, psoriasis, and the risk of lymphoma are difficult to interpret due to sample size limitations. Additionally, the current study occurred over a longer time period, suggesting the possibility that lymphoma rates in older psoriasis patients may be changing over time.

The overall risk for lymphoproliferative malignancies was also increased in a study using an administrative Medicaid database, which found an increased risk for patients with psoriasis who received systemic therapies (RR 7.95, 95% CI 4.94, 12.79) and for those who did not receive systemic therapies (RR 2.11, 95% CI 1.63, 2.74) (Margolis et al., 2001). This study did not address subtypes of lymphoma and therefore it is unclear which form(s) of lymphoma accounted for the high relative risk in the severe group. In particular, CTCL is strongly associated with severe psoriasis (discussed below) and therefore may have accounted for much of this increased risk. Additionally, this study used an administrative database that covers an indigent patient population, which may have led to greater misclassification between psoriasis and CTCL, and concerns regarding the generalizability of the results. Other studies have not observed an increased risk for all lymphoma in psoriasis patients identified through general practitioners (Bhate et al., 1993) or in those treated with psoralen (Stern and Vakeva, 1997).

The strongest association of lymphoma and psoriasis occurred for CTCL. This finding is similar to the few previous studies that have specifically examined the risk of T-cell lymphoma and CTCL in psoriasis (Boffetta *et al.*, 2001; Morales *et al.*, 2003; Zhang *et al.*, 2004). Interestingly, those we classified as having severe psoriasis had the most strongly elevated relative risk of CTCL. Previous studies of patients with severe psoriasis have also found strongly increased relative risks of CTCL. For example, studies of patients hospitalized for psoriasis have found standardized incidence ratios of 19.3 (95% CI 6.22, 45) (Boffetta *et al.*, 2001) and 15.1 (95% CI 4.1, 38) (Frentz and Olsen, 1999) for the risk of developing CTCL. A population based study of lymphoma in the US, in which patients identified as having psoriasis are broadly representative and likely be similar to those in our current study, found an odds ratio of 3.7 (95% CI 1.3, 10.6) for T-cell lymphoma, which is similar in magnitude to our findings in all psoriasis patients (Zhang *et al.*, 2004).

The strong association between psoriasis and CTCL may be related to chronic lymphoproliferation in psoriasis which eventually leads to a dominant clone and evolution to CTCL in some patients. Alternatively, certain psoriasis therapies, misdiagnosis, or a combination of these factors may explain the association. The relative contribution of the pathophysiology of psoriasis, psoriasis treatment, and/or misdiagnosis to the increased risk of CTCL in psoriasis patients requires further study. We believe that is it unlikely that misdiagnosis completely explains this association as patients we classified as having severe psoriasis would have been seen by dermatologists based on the UK system of care (e.g., for initiation of treatment of their severe psoriasis). Additionally, it has been our clinical experience that some patients with well documented psoriasis have evolved into CTCL, and we have had patients who exhibit clinical and histological features of both psoriasis and CTCL. The risk of CTCL in patients with psoriasis is especially important because these patients are increasingly treated with immunologic therapies, which have the capacity to exacerbate lymphoma. For example, case reports have suggested that tumor necrosis factor inhibition may be associated with rapid progression of CTCL, resulting in extensive disease and death (Adams *et al.*, 2004).

The risk of HL was also increased in psoriasis patients. The magnitude of association between psoriasis and Hodgkin's was similar in patients with mild and severe psoriasis. In addition, our results were similar to those reported in patients hospitalized for psoriasis (standardized incidence ratio 3.3, 95% CI 1.4, 6.4) (Hannuksela-Svahn *et al.*, 2000). These results suggest that psoriasis patients have an increased risk of HL and that the degree of risk may be independent of psoriasis severity or systemic treatment for psoriasis. Other studies have not found an association between psoriasis and HL (Lindelof *et al.*, 1990; Tavani *et al.*, 2000; Boffetta *et al.*, 2001); however, these studies were limited by statistical power, as Hodgkin's is a very rare form of lymphoma.

NHL was found to only be slightly increased in the mild psoriasis group, and this finding did not reach conventional levels of statistical significance in our primary analysis. There was no evidence of an increased risk of NHL in patients with severe psoriasis. This finding is in contrast to studies in patients hospitalized for psoriasis (standardized incidence ratio 2.2, 95% CI 1.4, 3.4) (Hannuksela-Svahn *et al.*, 2000) or treated with psoralen plus UV light A (standardized incidence ratio 3.7, CI 1.2, 8.6) (Hannuksela-Svahn *et al.*, 1999), which demonstrated an increase in NHL. It is unclear if these studies excluded CTCL in their analysis of NHL, which may have led to an overestimation of the risk of NHL, given the strong association between psoriasis and CTCL demonstrated by the current study. Other large studies that investigated patients hospitalized for psoriasis (Frentz and Olsen, 1999; Boffetta *et al.*, 2001) or those deemed to have moderate to severe psoriasis (Lindelof *et al.*, 1990) did not find an increased risk of NHL. Finally, an additional population-based study did not find an increased risk of-B cell lymphoma, the most common form of NHL, in patients with psoriasis (Zhang *et al.*, 2004).

As with all studies, there are limitations to consider. First, we were unable to account for the extent of skin involvement of psoriasis in classifying the severity of psoriasis. Since the majority of the general population of psoriasis patients have limited disease, our analyses in the mild group are weighted towards patients with limited psoriasis (Nevitt and Hutchinson, 1996; Stern *et al.*, 2004; Gelfand *et al.*, 2005b, c). Additionally, since systemic therapies are used uncommonly in psoriasis patients, our severe group was relatively small, which reduced our statistical power when estimating the risk of lymphoma in this group. We also did not control for sun exposure, which has been implicated as a risk factor for lymphoma in some studies, but data on this potential association remain inconclusive with recent studies finding a protective effect (Fisher and Fisher, 2004; Smedby *et al.*, 2005).

In conclusion, we have demonstrated that psoriasis is associated with an increased risk of lymphoma. However, it is important to consider the subtype of lymphoma when investigating this association. The association between NHL (excluding CTCL) and psoriasis was small in this study and based on previously published data, this association is inconsistent. The emerging evidence suggests an association between HL and psoriasis; however, additional studies are necessary to confirm this finding. The relative risk of lymphoma in patients with psoriasis is greatest for CTCL, which may be strongly elevated in patients with severe disease. Although patients with psoriasis may have an increased relative risk of lymphoma, the absolute risk attributable to psoriasis is low given that lymphoma is a rare disease and the magnitude of association is modest.

MATERIALS AND METHODS
Study design
This was a retrospective cohort study with data collected prospectively from 1988 to 2002 by more than 500 general practitioners in the UK, who were unaware of the hypothesis to be tested. The data were collected as part of the patient's electronic medical record and are maintained in the GPRD. GPRD contains data on over 8 million persons with over 35 million person-years of follow-up time and is broadly representative of the UK population (Gelfand *et al.*, 2005a). General Practitioners receive specific training, financial induce-

ments, and penalties to ensure accuracy of the data. GPRD has been used extensively for epidemiologic studies. The validity of using the GPRD to study psoriasis and lymphoma has been demonstrated previously (Jick *et al.*, 1991; Walley and Mantgani, 1997; Lewis *et al.*, 2001; Gelfand *et al.*, 2003, 2005b, c). Additionally, the epidemiology of lymphoma in the GPRD is similar to population-based estimates in the US and UK (Parkin *et al.*, 1999; SEER, 2001).

The study population consisted of all psoriasis patients (i.e., exposed population, see *study groups* below) who had at least 1 day of observation time. Each psoriasis patient was matched to up to five control subjects (as available based on matching criteria) who did not have psoriasis (i.e., not exposed to psoriasis), who were seen in the same practice, and who had a date of observation in the practice (the maximum of the date when the patient registered with the practice and the date when the practice was designated ''up to standard'' (UTS)) within 60 days. Therefore, we assured that those with and without psoriasis were followed by the same practices during similar time periods. For control patients, observation start time was the maximum of the patient registration and UTS dates. For patients with psoriasis, observation start time was the maximum of the patient registration, UTS, and psoriasis diagnosis dates. For all patients, follow-up time ended when they developed a lymphoma, died, transferred out of the practice, or the practice was no longer UTS (whichever came earliest). Practices are designated UTS when audits demonstrate that at least 95% of relevant patient encounters are recorded and the data are determined to be of suitable quality for epidemiologic research.

Study groups

Diseases are classified in the GPRD using Oxford Medical Information System and Read codes. Oxford Medical Information System and Read codes are diagnostic codes that GPs use as part of the patient's electronic medical record. Patients were classified as having psoriasis if they ever received a diagnostic code for psoriasis, which has been previously validated as described above. Psoriasis patients were defined as having ''severe'' disease if they received a treatment code consistent with severe disease (e.g., psoralen, phototherapy, methotrexate, azathioprine, cyclosporine, etretinate, acitretin, hydroxyurea, and mycophenolate) prior to the first diagnostic code of lymphoma during the study period. Treatments consistent with severe psoriasis were determined by the British National Formulary and the opinion of two dermatologists (D.J.M., J.M.G.). Psoriasis was classified as ''mild'' if the patients never received a prescription code consistent with severe disease during the study period. Patients were classified as controls if they never received a diagnostic code consistent with psoriasis.

Outcomes

Patients were classified as having a new lymphoma if they received a medical code consistent with this diagnosis after the start date and on or before the end date. Lymphoma was classified as NHL, HL, and CTCL based on diagnostic codes. For patients who received more then one code for lymphoma after the start date, the most specific code was used to classify the lymphoma.

Statistical analysis

The data were summarized descriptively. Associations between the presence of psoriasis and age, gender, and history of lymphoma were tested using Fisher's exact test for categorical variables and *t*-test for continuous variables.

The rates of lymphoma in the psoriasis groups were compared to the rate of lymphoma in the control population using an unadjusted Cox proportional hazards model. The rates were then adjusted for age and sex. We also tested for effect modification by age or gender in all psoriasis patients on the relative risk of the various outcomes studied by incorporating interaction terms. Each dichotomous variable in the model was checked for proportionality while adjusting for the other covariates in the model by examining diagnostic log–log survival plots, which demonstrated adequate proportionality. We also performed Poisson regression to assess whether the modeling approach affected the results. In order to maximize the number of lymphoma outcomes available, we did not exclude patients with a history of lymphoma from the primary analysis based on the assumption that the onset of psoriasis likely predated the onset of lymphoma for most cases based on the epidemiology of the two diseases. To test this assumption, we performed a sensitivity analysis in which patients had to have at least 6 months of follow-up time and could not have had a history of lymphoma or a lymphoma in the first 6 months in order to ensure the capture of incident, not prevalent, lymphoma.

All statistical analyses were performed using Intercooled Stata 8.2 (Stata Corp, College Station, TX).

Protection of study subjects

Data utilized for this study were stripped of personally identifiable information. The study was approved by the Office of Regulatory Affairs of the University of Pennsylvania and by the Scientific and Ethical Advisory Group of the Medicines Control Agency, UK. The study was conducted in concordance with the Declaration of Helsinki Principles.

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