Lymphoma Rates Are Low but Increased in Patients With Psoriasis

Results From a Population-Based Cohort Study in the United Kingdom

Joel M. Gelfand, MD, MSCE; Jesse Berlin, ScD; Abby Van Voorhees, MD; David J. Margolis, MD, PhD

Objective: To determine if the rate of lymphoma in patients with a history of psoriasis is different from the rate of lymphoma in patients without psoriasis.

Design: Cohort study.

Setting: Outpatient practices of general practitioners in the United Kingdom who contribute to the General Practice Research Database.

Patients: The population studied was a sample of 10% of the patients 65 years or older registered with a general practitioner contributing to the General Practice Research Database between 1988 and 1996.

Main Outcome Measure: The rate of lymphoma in patients with psoriasis compared with the rate of lymphoma in patients without psoriasis.

Results: There were 2718 patients who had psoriasis and 105,203 patients (the reference population) who did not have psoriasis. The median follow-up time was 46 months. We noted 276 lymphomas. Patients with psoriasis had a 2.95 relative rate of developing lymphoma (95% confidence interval, 1.83-4.76) compared with those without psoriasis. This estimate did not change after controlling for age and sex using the Cox multivariable proportional hazards model. The rate of lymphoma changed little when the patients treated with methotrexate or those who developed mycosis fungoides were excluded. Compared with the reference population, we found an additional 122 lymphomas per 100,000 patients annually among patients with psoriasis who were 65 years or older.

Conclusions: These results indicate that patients with psoriasis are at increased risk for developing lymphoma. Additional studies are necessary to determine if the increased rate of lymphoma is related to psoriasis severity, psoriasis treatment, or an interaction between these risk factors.

Arch Dermatol. 2003;139:1425-1429

Psoriasis is a common disease that affects about 1% to 2% of the general population.1-3 Psoriasis has dramatic effects on quality of life and adds significant costs to the health care system.4 For patients with extensive disease, systemic treatments that nonspecifically target the immune system, such as methotrexate or cyclosporine, are often used. The evolving treatments for psoriasis target specific areas of the immune system such as cytokines (eg, tumor necrosis factor α) and T cells.5

The pathophysiology of psoriasis is believed to be related to increased T-lymphocyte activity stimulated by antigen presentation.5 Other investigators have also demonstrated increased B-lymphocyte activity in patients with psoriasis, which suggests broad immune activation.6,6 Since psoriasis is a disease of immune activation, it has been hypothesized that patients with psoriasis may be at increased risk for developing lymphoproliferative malignancies.9 Furthermore, treatment with immunosuppressive medications used to treat psoriasis may be an independent risk factor for developing lymphoproliferative malignancies10, or it may be that having psoriasis and being exposed to immunomodulating medications results in an increased risk of developing lymphomas. There have been several case reports of patients with or without psoriasis who were treated with methotrexate11-14 or cyclosporine15-17 and later diagnosed with lymphomas.18,19 There is also an increasing number of reports of lymphomas developing in patients treated with tumor necrosis factor α inhibitors, which suggests that other treatments may also be associated with inducing lymphomas.20 Treatment-associated lymphomas are frequently of B-cell origin, are related to Epstein-Barr virus infection, and typi-
cally occur within the first year of immunosuppressive therapy. In some instances these treatment-associated lymphomas regress when the immunosuppressive agent is withdrawn. Several investigators have previously demonstrated that psoriasis is associated with an increased risk of lymphoproliferative disorders. Using a Medicaid administrative database, Margolis et al found a 7.8 relative rate of lymphoma in patients who had psoriasis and were treated with systemic agents and a 2.18 relative rate of lymphoma in patients who had psoriasis but were not treated with such agents. Hannuksela-Svahn et al found a 3.3 standardized incidence ratio for Hodgkin lymphoma and a 2.2 standardized incidence ratio for non-Hodgkin lymphoma among Finnish patients hospitalized for psoriasis, compared with expected rates based on the Finnish cancer registry. Other investigators, however, have not found an increased risk of lymphoproliferative disorders in psoriatic patients. The discrepancy in these findings may be due to variations in statistical power, the populations studied, and the use of nonpopulation-based methods.

Lymphoproliferative diseases such as non-Hodgkin lymphoma and Hodgkin lymphoma can be aggressive, requiring multagent chemotherapy and entailing significant morbidity and risk of death. These diseases are relatively rare forms of cancer (their incidence rates are similar to those for invasive melanoma), and to detect an increased risk for these diseases a large population of patients needs to be studied. The General Practice Research Database (GPRD), established in the United Kingdom in 1987, is a medical record database that holds data on more than 8 million ambulatory patients with more than 35 million person-years of follow-up. It includes about 5% of the UK population and is broadly representative of that population in terms of age, sex, and geographic distribution. The GPRD contains information on diagnoses and medications recorded by general practitioners (GPs) as part of patients’ medical records. The validity of specialists’ information and its capture by GPs in the GPRD has been well documented. The validity of using the GPRD to study a wide range of medical conditions, including lymphoma, has also been demonstrated in numerous studies.

The primary purpose of this study was to compare the risk of lymphoproliferative diseases developing in patients with and without psoriasis. In a secondary analysis we compared the rate of all internal malignancies in patients with and without psoriasis. We also performed a series of studies to assess the validity of using the GPRD for identifying patients who have psoriasis.

STUDY DESIGN

This was a retrospective cohort study, with data collected prospectively from 1988 to 1996 by GPs in the United Kingdom who were unaware of the hypotheses to be tested. The study population was a random sample of 10% of the entire GPRD population 65 years or older. This is a natural population in which to study malignancy outcomes since the incidence of cancer increases with age. For patients without psoriasis, follow-up time was counted from the patient’s registration with a GP and approval of the GP’s data as “up to standard” after review by the Epidemiology and Pharmacology Information Core (whichever came last). Such data are considered of a standard high enough to be used for epidemiologic research. The end of follow-up occurred when the patient experienced the outcome of interest, died, or left the GPRD. For patients with psoriasis, follow-up time was counted from the patient’s diagnosis with psoriasis, registration with the GP, and the approval of the GP’s data as up to standard (whichever came last) until the patient developed the outcome of interest, died, or left the database.

STUDY GROUPS

Diseases are classified in the GPRD database using Oxford Medical Information System (OMXIS) codes. Patients were defined as having psoriasis if they had an OMXIS code consistent with psoriasis. Patients were defined as not having psoriasis if they had no history of an OMXIS code consistent with psoriasis.

OUTCOMES

The primary outcome of our study was any OMXIS code consistent with a lymphoproliferative disease (eg, Hodgkin or non-Hodgkin lymphoma) that occurred after the patient qualified for the study. The secondary outcome of this study was the presence of any OMXIS code consistent with an internal malignancy that developed after the patient qualified for the study. The validity of using the GPRD for studying lymphoma has been previously established and the GPRD has been used to study a variety of internal malignancies. Details of the OMXIS coding algorithms are available from the first author (J.M.G.).

VALIDATION STUDY

The GPRD is a medical record database and GPs receive specific training and financial inducements and penalties to ensure the accuracy of the data. The GPRD has been shown to be a valid tool to study a variety of medical conditions. To further investigate the validity of the GPRD for studying psoriasis we evaluated the frequency of the disease in our population (ie, the percentage of patients with an OMXIS code consistent with psoriasis). We then randomly selected 100 patients with an OMXIS code consistent with psoriasis and prospectively evaluated their prescription medications. We expected a priori that at least 90% of patients with a diagnostic code for psoriasis would have treatments consistent with a common therapy for psoriasis. We defined any treatment with topical steroids of medium to high potency, tar, anthralin, or calcipotriene as consistent with psoriasis management. We defined these topical agents as our treatment outcomes algorithm because they are the most commonly used therapies for psoriasis. To further ensure that there were no systematic coding errors, we also reviewed the electronic medical records of the patients with psoriasis who developed lymphoma.

STATISTICAL ANALYSIS

The rate of the outcome of interest (lymphoma or internal malignancy) in patients with psoriasis relative to patients without psoriasis was evaluated using an unadjusted Cox proportional hazards model. The rate was then adjusted for age and sex to investigate possible confounding by these variables. Secondary analyses were performed to ensure capture of incident, rather than prevalent, outcomes of interest. These analyses excluded patients who had a history of one of the outcome
diseases prior to study entry, or who developed one of these diseases within 6 months of study entry. A cancer-free window of 6 months was selected because we believe that prevalent cancers would most likely be detected and documented by the GP within 6 months of the patient’s qualifying for the study. For the lymphoma outcome, an additional analysis excluding patients treated with methotrexate, or patients who developed mycosis fungoides as their lymphoma, was performed. The purpose of the latter analysis was to rule out potential bias that could be introduced if early mycosis fungoides had been incorrectly diagnosed as psoriasis. All statistical analyses were performed using the STATA statistical package 7.0 (Stata Corp., College Station, Tex).

INSTITUTIONAL APPROVAL

This study was approved by the institutional review board of the Office of Regulatory Affairs of the University of Pennsylvania and by the Scientific and Ethical Advisory Group of the GPRD.

RESULTS

There were 107921 patients followed up for 429847 person-years in our random sample of 10% of the GPRD population 65 years or older (Table 1 and Table 2). The frequency of psoriasis in this sample was 2.52% and there was no significant difference in the frequency of psoriasis based on sex (Table 1). Since psoriasis is a lifelong chronic condition, the frequency of psoriasis as documented by GPs in this study closely approximates the prevalence (ie, the number of existing cases divided by the entire population at a defined point in time) of the disease. The frequency of psoriasis that we determined in the GPRD population is similar to estimates of the prevalence of psoriasis using population-based methods.1-3 In agreement with our a priori hypothesis, 92% of patients with an OXMIS code for psoriasis received treatments consistent with a psoriasis diagnosis. These findings suggest that patients with psoriasis are accurately identified by the GPRD.

Patients with psoriasis had an almost 3-fold increased rate of lymphoma compared with patients without psoriasis (Table 3). Patients 65 years or older who had psoriasis developed an additional 122 lymphomas per 100000 patients annually. Review of the electronic medical record demonstrated that all patients with psoriasis who developed systemic lymphoma were treated with medications consistent with psoriasis and had outcomes consistent with the diagnosis of lymphoma (eg, referral to an oncology service). Kaplan-Meier analysis demonstrated that the rate of lymphoma was greater in patients with psoriasis than in patients without psoriasis at all time points during follow-up, suggesting proportional hazards (data not shown). The rate of lymphoma in patients without psoriasis (ie, the reference population) listed in the GPRD was similar to the age-adjusted rates of lymphoma in the UK and US populations37,38 (Table 2). The increased rate of lymphoma did not vary when adjusting for age and sex.

In secondary analyses (Table 3), the relative rate of lymphoma did not change meaningfully if patients with a history of lymphoma prior to study entry were excluded, or if patients diagnosed with a lymphoma within 6 months of follow-up were excluded. The relative rate of lymphoma also did not change substantially if patients treated with methotrexate were excluded from the analysis, and only decreased slightly if mycosis fungoides was excluded from the analysis. We did not evaluate the relative rate of lymphoma in patients treated with methotrexate, as this group was too small to yield interpretable findings. Furthermore, review of the electronic medical records showed that none of the patients who had psoriasis and developed lymphoma were treated with cyclosporine during the period of observation. The overall rate of internal malignancies was the same in patients with and without psoriasis (Table 3).

COMMENT

The results of this study indicate that the GPRD can be used to accurately identify patients who have psoriasis. The results demonstrate that no systematic errors occur when general practitioners use OXMIS codes to document that a patient has psoriasis. If systematic errors occurred when GPs coded patients as having psoriasis, the frequency of psoriasis in the GPRD population and the treatment outcomes of patients with psoriasis would be different from expected rates. The gold standard of comparing the patient’s medical record with the OXMIS code was not performed because of regulatory concerns about patient privacy. Nevertheless, the validation methods used (ie, the comparison of the frequency of psoriasis determined by this study with the frequency found in other population-based studies and the treatment outcomes approach) have been well accepted in epidemiologic

Table 1. Characteristics of the Study (With Psoriasis) and the Reference (Without Psoriasis) Populations†

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Psoriasis</th>
<th>Without Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>2718 (2.5)</td>
<td>105 203 (97.5)</td>
</tr>
<tr>
<td>Median age, y (25th, 75th percentile)</td>
<td>70.83 (66.0, 76.6)</td>
<td>71.08 (65.5, 78.4)</td>
</tr>
<tr>
<td>Women</td>
<td>1540 (56.7)</td>
<td>61 412 (58.4)</td>
</tr>
<tr>
<td>Men</td>
<td>1178 (43.3)</td>
<td>43 791 (41.6)</td>
</tr>
<tr>
<td>Patients treated with methotrexate</td>
<td>42 (1.6)</td>
<td>185 (0.2)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, values are given as number (percentage).

Table 2. Summary of Follow-up Time and Incidence Rate of Lymphoma for Patients With and Without Psoriasis

<table>
<thead>
<tr>
<th>Variable</th>
<th>With Psoriasis</th>
<th>Without Psoriasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, median, mo (25th, 75th percentile)</td>
<td>39.75 (19.1, 65.1)</td>
<td>46 (20.8, 73.1)</td>
</tr>
<tr>
<td>Person-years</td>
<td>9839</td>
<td>420 008</td>
</tr>
<tr>
<td>Lymphoma, No.</td>
<td>18</td>
<td>258</td>
</tr>
<tr>
<td>Incidence rate of lymphoma per 10 000 person-years</td>
<td>18.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Attributable risk (excess No. of lymphoma cases related to psoriasis)</td>
<td>122 per 100 000 per year</td>
<td>...</td>
</tr>
</tbody>
</table>

©2003 American Medical Association. All rights reserved.
studies. Therefore, the GPRD, which is estimated to include more than 120,000 patients with psoriasis, can be a valuable tool with which to perform population-based studies in these patients.

This study demonstrates that the rate of lymphoma among patients 65 years or older who have psoriasis is 3 times the rate found among patients without psoriasis. Lymphoma is not common, with incidence rates similar to those of melanoma; therefore, the absolute increase in lymphoma is small (an extra 122 cases of lymphoma per year per 100,000 patients who are 65 years or older and have psoriasis). Bias is unlikely to explain the increased rate of lymphoma, as a series of secondary analyses did not meaningfully change the results. In particular, ascertainment bias is unlikely to have explained our results; moreover, the overall rate of internal malignancies was not increased, and therefore the findings appear to be specific for lymphoproliferative diseases. These results are important in that they add psoriasis to the literature linking chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease to lymphoma. As novel immunosuppressive treatments are increasingly used in patients with psoriasis, it will be important to understand baseline rates of lymphoma in this population to determine if these treatments further increase the risk of lymphoproliferative diseases. For example, the results of this study and others suggest that it may be inappropriate to compare the rate of lymphoma in patients with psoriasis who are treated with a novel therapy with lymphoma rates found in the general population, as the baseline rate of lymphoproliferative diseases is greater in the former than in the latter.

Our results extend those of previous investigators who found an increased risk of lymphomas in patients with psoriasis because, being population-based, this study did not sample only hospitalized patients. For example, HannukseSa-Svahn and colleagues also found an increased rate of lymphoma in patients with psoriasis. However, they only studied patients who had been hospitalized. Since few individuals are hospitalized for psoriasis, they are unlikely to be representative of the full population of patients with psoriasis. Margolis and colleagues also found an increased rate of lymphoma in patients with psoriasis using an administrative Medicaid database. Our results add to these studies by demonstrating, with data generated from medical record rather than administrative claims, that the rate of lymphoma remains elevated among a socioeconomically diverse population of patients with psoriasis.

There are several important limitations to this study. Since it was performed only in patients 65 years or older, it is unclear if the results can be applied to younger patients with psoriasis in the United Kingdom and elsewhere. However, as studies using different populations and methods have consistently found an increased rate of lymphoma in patients with psoriasis, this finding is likely valid and generalizable. Second, we were not able to assess the effect of psoriasis severity and treatment on the rate of lymphoma. This study was population-based and therefore included patients with different degrees of psoriasis severity, only a small minority of whom (1.55%) received treatment with medications, such as methotrexate, that may relate to an increased risk of lymphoma. We did not plan to control for cyclosporine use in this study; as it was not approved in the United Kingdom for psoriasis until 1992, the number of psoriasis patients treated with cyclosporine during this study period was likely very low. In fact, none of the psoriasis patients who developed lymphoma were treated with cyclosporine during the study period. Additional studies are necessary to determine the effect of psoriasis severity and treatment on the risk of lymphoma. Finally, we did not look at the individual rate of internal malignancies other than lymphoma. Therefore, although the overall all rate of internal malignancy was not increased, it is possible that certain internal malignancies may be more or less common in patients who have psoriasis.

In summary, we have demonstrated a 3-fold increase in the rate of lymphoma in patients who have psoriasis and are 65 years or older. The increased rate of lymphoma observed in patients with psoriasis is important to consider when planning pharmacoepidemiologic studies of cancer outcomes. The overall rate of lymphoma in such patients is still very low. However, clinicians should consider the risks and benefits of long-term exposure to medications that may induce lymphomas in psoriasis patients who, at baseline, may have a higher incidence of lymphoproliferative malignancies.

Accepted for publication March 4, 2003.

This work was funded in part through grants F32-AR48100, R01-AR4695, and K24-AR22212 from the National Institutes of Health, Bethesda, Md, and through an unrestricted grant from the Herzig Foundation to the Trustees of the University of Pennsylvania.

We thank Jill Knauss for her expert assistance in creating the data analysis file for this study.

<table>
<thead>
<tr>
<th>Analyzed Malignancy</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Unadjusted</th>
<th>Adjusted for Age and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma, previous history of lymphoma excluded</td>
<td>2.95 (1.83-4.76)</td>
<td>2.94 (1.82-4.74)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma, excluding patients diagnosed within 6 mo of follow-up</td>
<td>3.39 (2.04-5.64)</td>
<td>3.38 (2.03-5.62)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma, excluding patients treated with methotrexate</td>
<td>3.04 (1.85-4.97)</td>
<td>3.02 (1.83-4.95)</td>
<td></td>
</tr>
<tr>
<td>Lymphoma, excluding mycosis fungoides</td>
<td>2.84 (1.74-4.64)</td>
<td>2.83 (1.73-4.64)</td>
<td></td>
</tr>
<tr>
<td>Internal malignancy</td>
<td>2.26 (1.29-3.95)</td>
<td>2.26 (1.29-3.94)</td>
<td></td>
</tr>
<tr>
<td>Internal malignancy, previous history of malignancy excluded</td>
<td>1.08 (0.93-1.24)</td>
<td>1.09 (0.94-1.26)</td>
<td></td>
</tr>
<tr>
<td>Internal malignancy</td>
<td>1.04 (0.88-1.23)</td>
<td>1.05 (0.89-1.24)</td>
<td></td>
</tr>
</tbody>
</table>


