Lymphoma Risk in Psoriasis

Results of the PUVA Follow-up Study

Robert S. Stern, MD

Objective: To assess the risk of lymphoma in patients with psoriasis.

Design: Prospective cohort study that spans 30 years and a systematic review of the literature.

Setting: Sixteen university medical centers.

Patients: A total of 1380 patients with psoriasis who were initially treated with psoralen–UV-A (PUVA) from 1975 through 1976 and who underwent periodic interviews and physician examinations irrespective of their use of any treatment.

Main Outcome Measure: Incidence of lymphoma relative to that expected in the general US population (original primary end point of the study).

Results: The incidence of lymphoma in patients who received PUVA and were not exposed to high levels of methotrexate was comparable to that expected in the general population (incidence rate ratio, 0.85; 95% confidence interval, 0.37-1.67) but was elevated among those exposed to high levels of methotrexate (≥36 months) (incidence rate ratio, 4.39; 95% confidence interval, 1.59-12.06).

Conclusion: Unless exposed to high levels of methotrexate, the risk of lymphoma among members of the PUVA Follow-up Study was comparable to that observed in the general population.

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With the advent of new treatments for psoriasis that may increase the risk of lymphoma, determining the innate risk of lymphoma in patients with psoriasis has become important both for clinical decision making and to ensure the robust evaluation of the risks of newer therapies. Most studies\(^1-15\) suggest that the risk of lymphoma in patients with psoriasis is comparable to that in the general population. However, 3 recent studies\(^16-18\) suggested an increased risk of lymphoma in persons with psoriasis. The PUVA [psoralen–UV-A] Follow-up Study provides a unique resource to establish the incidence of lymphoma among persons with moderate to severe psoriasis, both overall and in subgroups defined by their exposures to established treatments for psoriasis. This cohort study of 1380 persons first treated from 1975 through 1976 now includes nearly 30,000 person-years of follow-up of individuals with moderate to severe psoriasis whose major health events and use of treatments for psoriasis have been prospectively documented during a 30-year period. Determining the risk of lymphoma was an original primary end point for the study. Our data suggest that the innate risk of lymphoma among persons with moderate to severe psoriasis is unlikely to differ substantially from that in the general population.

METHODS

WHEN THE PUVA FOLLOW-UP STUDY

The PUVA Follow-up Study is a multicenter prospective cohort study. Its methods have been previously detailed.\(^1,19\) This study was approved by the Committee for Clinical Investigation of the Beth Israel Deaconess Medical Center. From 1975 through 1976, patients who had enrolled in a therapeutic study of PUVA were asked if they wished to be followed up long term to determine the safety and efficiency of PUVA. Of the 1450 patients participating in the clinical trial, 1380 (93%) enrolled in the long-term prospective study. In addition to baseline information collected from 1975 through 1976, during the subsequent 30 years, these patients were interviewed 22 times. Data collection for this study ended in 2005. Any patient who reported a serious health event, such as lymphoma, was asked to provide permission for us to obtain medical records that pertained to this event. In addition, we used the National Death Index to ascertain cause of death among individuals who were lost to follow-up.\(^20\)

The questionnaires administered at entry (1975-1976) and the 22 follow-up interviews...
administered during the subsequent 30 years included structured questions designed to determine exposure to systemic therapies for psoriasis and to PUVA and UV-B. On the basis of these data, for each calendar year we calculated the extent of exposure to methotrexate, UV-B, and PUVA. As in prior analyses, we defined high-dose exposure to methotrexate as 36 or more months of use and high-dose exposure to UV-B as at least 300 treatments.

### STATISTICAL ANALYSIS

We calculated the expected numbers of lymphoma cases based on data from the Surveillance Epidemiology and End Results (SEER) program of the National Cancer Institute. We used age- and sex-specific rates applicable to each year of follow-up. To calculate the expected number of lymphoma cases for 2003, 2004, and 2005, we used SEER incidence data for 2002, the most recent year available at the time of analysis (June 2005).

We compared the characteristics of cases to other cohort patients still being followed up (and alive) at the mean year at onset of lymphoma. For categorical variables, we used the chi-squared test to determine statistical significance with Yates correction when appropriate. For continuous variables, we used the t test. We compared observed and expected number of tumors to calculate the incidence rate ratios (IRRs) and used the Poisson distribution to calculate the 95% confidence intervals (CIs). We compared observed and expected numbers of lymphoma cases for the cohort as a whole and for cohort subgroups as defined by demographic and exposure characteristics.

In calculating expected numbers of tumors based on age-, sex-, and year-specific incidence data from SEER, our analyses were standardized for age, sex, and calendar year. Our multivariate models were Poisson regression models and included all exposures and attributes that were related to lymphoma risk with P ≤ .20 in the univariate analyses. We also tested for possible interactions among exposures that were related to lymphoma risk with P ≤ .20 in the univariate analysis using 2-way interaction terms. In addition, we performed analyses for each significantly associated exposure that were stratified according to level of exposure to other factors that were also significantly associated with lymphoma risk in the univariate analysis.

### RESULTS

Of the 1380 patients originally enrolled in the study (1975-1976), at the time of the 22nd and final follow-up interviews (2003-2005), we successfully interviewed 526 (83%) of the 636 who were still alive and participating in the study. As detailed in Table 1, the attrition rate, except because of death, was low until after 1995. In 28,554 person-years of prospective follow-up, we detected 16 persons with lymphoma, of which 14 had non-Hodgkin lymphoma and 2 had Hodgkin disease. We did not include cutaneous T-cell lymphoma. Of the 16 incident lymphomas, 13 were ascertained through our normal follow-up procedures and 3 from our search of the National Death Index database. Compared with our last report, which spanned 1975 through 1996, the incidence of lymphoma was significantly higher from 1997 through 2005 than in prior years (1975-1996) (IRR, 4.38; 95% CI, 1.60-12.06).

Table 2 compares the characteristics of the cases at the time of detection of lymphoma (mean year of detection, 1995) and the 848 other cohort patients still alive and being followed up in 1995. Patients with lymphoma were significantly older. Except for a significantly higher proportion of patients with high-dose exposure to methotrexate but not PUVA or UV-B, those who developed lymphoma and other active cohort members had similar characteristics and exposures.

Table 3 provides the univariate and multivariate analysis results of associations of various patient exposures and attributes with lymphoma risk. The incidence of lymphoma was significantly higher after 1996 compared with that for the cohort from 1975 through 1996 (Table 3) and for those who had used methotrexate for at least 36 months (Table 3). There was an apparent interaction between the follow-up year and level of exposure to methotrexate. Beginning in 1997, persons who had used methotrexate for at least 36 months had a risk of lymphoma that was more than 7 times that of cohort members earlier in the study and with less exposure to methotrexate (IRR, 7.77; 95% CI, 2.83-21.39).

In the univariate analysis, more than 300 UV-B treatments were significantly associated with lymphoma risk, but this association was no longer significant in the multivariate analysis (Table 3). Because UV-B use and methotrexate exposure were associated, we performed an analysis of the relationship between level of UV-B exposure and lymphoma risk limited to patients with less than 3 years of exposure to methotrexate (ie, low-dose exposure). Patients with high-dose exposure to UV-B but lacking high-dose exposure to methotrexate had no increased risk of lymphoma (IRR, 1.02; 95% CI, 0.21-5.04). Level of exposure to PUVA and having had ionizing radiation therapy for psoriasis were not significantly associated with increased lymphoma risk (Tables 2 and 3). After we adjusted for level of exposure to methotrexate, risk of lymphoma in patients with 400 or more PUVA treatments was nearly identical to that of patients with fewer than 200 PUVA treatments (IRR, 1.12; 95% CI, 0.23-5.38). The frequency of exposure to oral reti-

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**Table 1. Follow-up Status, by Decade, of 1380 Patients Enrolled From 1975 Through 1976**

<table>
<thead>
<tr>
<th>Follow-up Cycle†</th>
<th>No. of Patients (% Enrolled/Alive)*</th>
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<tbody>
<tr>
<td>1985</td>
<td>1192 (86/98)</td>
</tr>
<tr>
<td>1994-1995</td>
<td>84 (61/89)</td>
</tr>
<tr>
<td>2003-2005‡</td>
<td>526 (38/69)</td>
</tr>
</tbody>
</table>

*Percentages are rounded; therefore, totals may not equal 100.
†Follow-up data in that cycle or in subsequent follow-up.
‡Final follow-up cycle.

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Results.

applicable; PUVA, psoralen–UV-A; SEER, Surveillance Epidemiology and End
genic therapies with the passage of time or that only in
lymphoma risk. Risk in the cohort was higher in later years,
possible; PUVA, psoralen–UV-A; SEER, Surveillance Epidemiology and End
level of exposure to methotrexate was nearly identical to that in the general popu-
ment members who lacked substantial exposures to metho-
the PUVA cohort, the risk of lymphoma observed in co-
After nearly 30 000 person-years of prospective study of
noids, cyclosporine, and biologics (all <2.5% of person-
other agents that increase lymphoma risk. When patients with exposure to
niectomy an average of 2.5 times during 10 years observed a
"The large case-control study of non-
the risk of lymphoma is not significantly different in pa-
Patients with high levels of exposure to metho-
treatments had a lymphoma risk comparable to that based on
SEER data (8 observed, 9.40 expected; IRR, 0.85; 95% CI, 0.37-1.67). In contrast, we observed 8 lymphoma cases in those with exposure to high levels of methotrexate (8 observed, 2.14 expected; IRR, 3.74; 95% CI, 1.61-7.36).

After nearly 30 000 person-years of prospective study of the PUVA cohort, the risk of lymphoma observed in cohort members who lacked substantial exposures to methotrexate was nearly identical to that in the general popu-
lation. In persons with high levels of exposure to methotrexate, a significant increase in lymphoma risk was noted. Level of exposure to PUVA was not associated with lymphoma risk. Risk in the cohort was higher in later years, which may reflect either greater exposure to carcino-
genic therapies with the passage of time or that only in later years of the study had a sufficiently long period elapsed for the effect of such exposures to be manifested.

In the univariate analysis, high levels of UV-B were signif-
icantly associated with lymphoma risk. However, the results of both the multivariate model and a stratified analy-
A Finnish study16 of patients hospitalized for pso-
immunosuppression, our data suggest that long-term and even inter-
stitutive exposure at more modest doses of some psoriasis therapies may, after many years, increase lymphoma risk.

Others have noted that a higher likelihood of greater exposure to treatments used for more severe psoriasis is also associated with increased risk of lymphoma. In a Medicare population, Margolis et al17 noted that those with psoriasis who had used systemic therapies had a risk of lymphoma that was almost twice that of Medicare enrollees with psoriasis who had no record of using these treatments. Paul et al14 noted that the risk of melanoma was more than 3-fold higher among patients with psoriasis exposed to 2 years of low-dose, often intermittent cyclosporine treatment compared with other cohort mem-
bers also treated with cyclosporine but for shorter periods. A Finnish study16 of patients hospitalized for psoriasis an average of 2.5 times during 10 years observed a modest and significant increase in lymphoma risk. How-
however, similarly designed studies in Sweden and Den-

Table 3. Univariate and Multivariate Estimates of IRR for Lymphoma Among Persons With Psoriasis, Adjusted for Age and Sex, Based on SEER Incidence Rates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td>Year, 1997-2005</td>
<td>4.38 (1.60-12.06)</td>
<td>3.49 (1.25-9.79)</td>
</tr>
<tr>
<td>Methotrexate use for ≥36 mo</td>
<td>4.39 (1.59-12.06)</td>
<td>3.65 (1.34-9.90)</td>
</tr>
<tr>
<td>High U-VB exposure (&gt;300 treatments)</td>
<td>2.77 (1.04-7.39)</td>
<td>2.13 (0.79-5.73)</td>
</tr>
<tr>
<td>Skin type 1 or 2</td>
<td>1.90 (0.71-5.11)</td>
<td>2.28 (0.84-6.17)</td>
</tr>
<tr>
<td>PUVA (≥200 treatments)</td>
<td>1.38 (0.52-3.71)</td>
<td>NA</td>
</tr>
<tr>
<td>High tar exposure</td>
<td>0.74 (0.21-2.58)</td>
<td>NA</td>
</tr>
<tr>
<td>X-ray treatment for psoriasis</td>
<td>0.83 (0.28-2.39)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; NA, not applicable; PUVA, psoralen–UV-A; SEER, Surveillance Epidemiology and End Results.
*Based on Poisson regression analysis.21

noids, cyclosporine, and biologics (all <2.5% of person-years of follow-up) was too low to assess the relationship between these substances and lymphoma.

Patients without high levels of exposure to methotrexate had a lymphoma risk comparable to that based on
SEER data (8 observed, 9.40 expected; IRR, 0.85; 95% CI, 0.37-1.67). In contrast, we observed 8 lymphoma cases in those with exposure to high levels of methotrexate (8 observed, 2.14 expected; IRR, 3.74; 95% CI, 1.61-7.36).

COMMENT
cyclosporine.14 However, our data and those of other studies suggest an elevated incidence of lymphoma in persons with psoriasis receiving methotrexate and of systemic agents other than PUVA and methotrexate. Furthermore, the higher incidence of lymphoma noted since 1996 suggests that there may be a long latency between causative exposure and the detection of cancer. Clearly, if we are to exclude a substantial increase in risk of lymphoma among persons hospitalized for psoriasis.5,13,19

Our findings are potentially important for evaluating the relationship between extent of exposure to PUVA and lymphoma risk, as well as the lack of association of UV-B to lymphoma risk, in both multivariate and stratified analyses argues against increased severity of psoriasis.

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Correspondence: Robert S. Stern, MD, Department of Dermatology, Beth Israel Deaconess Medical Center, 330 Brookline Ave, Room GZ-522, Boston, MA 02215 (rstern@bidmc.harvard.edu).

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Acknowledgment: Since its inception in 1975, more than 100 dermatologists and nurses have collected data for the PUVA Follow-up Study. Without their skilled work, this study would not have been possible. The 16 original centers that enrolled patients in the study are Stanford University School of Medicine, University of California Medical School, Baylor College of Medicine, Washington Hospital Center, University of Michigan Medical School, Columbia University College of Physicians and Surgeons, Mayo Graduate School of Medicine, University of Miami, Mount Sinai Medical Center, Temple University School of Medicine, Beth Israel Deaconess Medical Center, Dartmouth Medical School, Yale University School of Medicine, Duke University Medical Center, University of Pennsylvania Hospitals, and Massachusetts General Hospital. In addition, Jane Unaeze, MD, helped with use of the SEER data.